ADULTS WITH CHILDHOOD ONSET DISABILITIES: A LIFESPAN APPROACH

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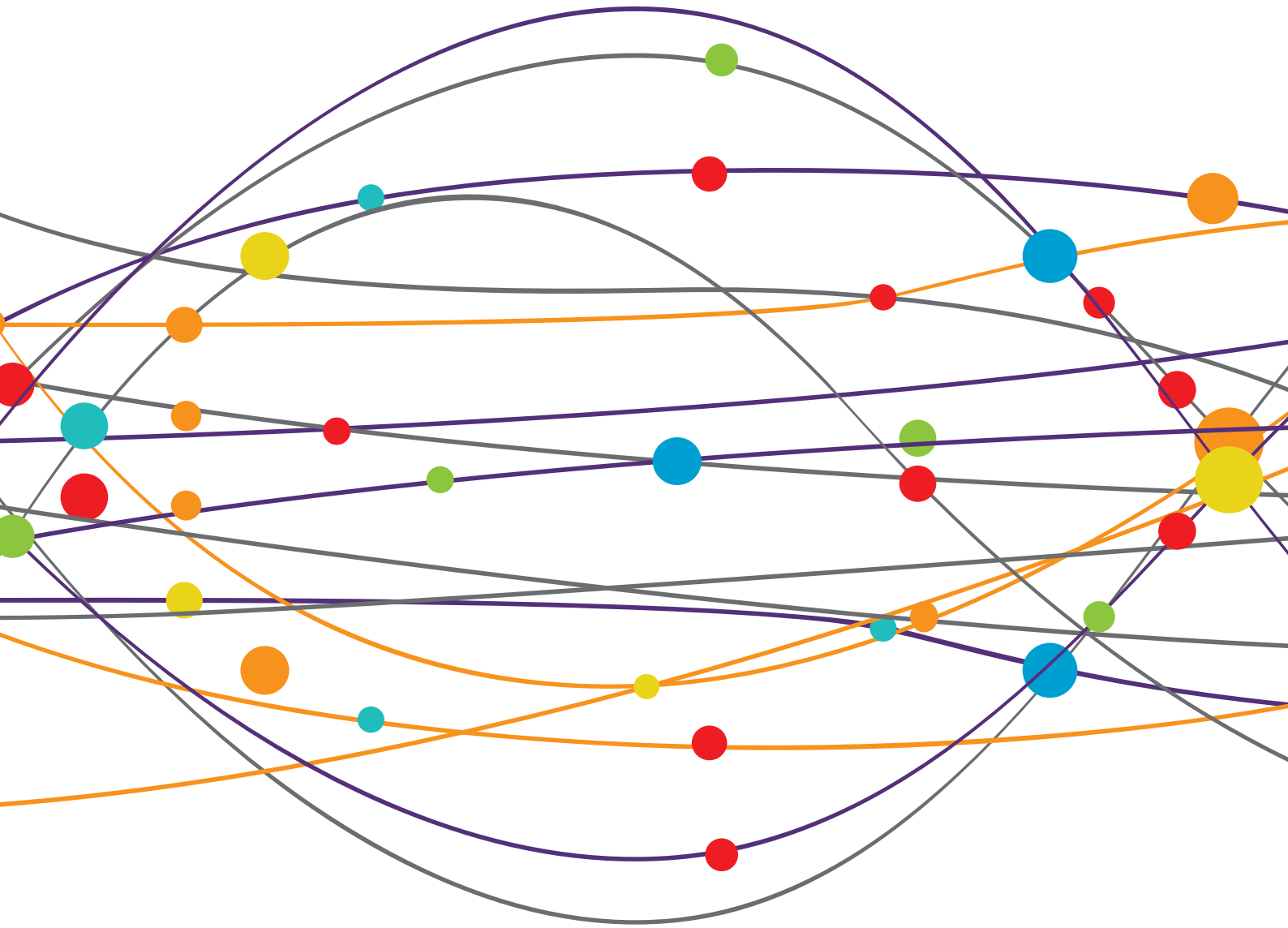

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ADULTS WITH CHILDHOOD ONSET DISABILITIES: A LIFESPAN APPROACH

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Editorial: Adults with childhood onset disabilities: A lifespan approach

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Editorial on the Research Topic
Adults with childhood onset disabilities: A lifespan approach

Introduction

Many individuals with a childhood onset disability (COD) such as cerebral palsy or spina bifida may experience near-normal life expectancies; however, healthcare coordination, clinical interventions, and research efforts remain largely focused on children with these conditions. For many individuals living with a COD, adult life comes with challenges in housing, employment, relationships, family life, and overall participation (Imms et al.; Pettersson and Rodby-Bousquet; Shrader et al.). The ability to participate in society without restrictions and a sense of belonging is rated as an important aspect of "meanings of citizenship" (van Heijningen et al.). This requires access to person-centered rehabilitation, social services and in many cases access to personal assistance (Pettersson and Rodby-Bousquet; van Heijningen et al.). Adults with CODs may experience higher risk for developing secondary conditions such as musculoskeletal morbidity (Dayanidhi; Won and Jung), pain (Jersak and Noritz; Jonsson et al.; Jacobson et al.), cardiometabolic diseases (Shin and Jung; Whitney et al.), kidney diesase (Whitney and Oliverio), dysphagia [Jonsson et al.; (1)], and mental health outcomes such as depression and anxiety (Jonsson et al.; Cohen et al.; Nguyen et al.) that may develop or be influenced by the disability, the presence of impairment, and/or the possibly accelerated process of aging. Consequently, there is a need for approaching health care delivery for adults with COD within the context of a life course health development model.

The goal of this Research Topic was to increase clinical and public health awareness of the unique healthcare needs facing adults living with cerebral palsy and other CODs, and to expand upon the social determinants of health (e.g., environmental, socioeconomic conditions, public policies, and etc.) that may contribute to disparities in or enhance the access, coordination, and continuity of clinical care for these populations.

Experts from multiple countries have documented a similar lack of clinical follow-up for individuals after they transition from pediatric to adult care, and inadequate longitudinal data to determine the natural history of CODs across a lifespan (Shrader et al.; Cornec et al.; Duncan et al.; Hurvitz et al.; Kingsnorth et al.; Ryan et al.; Starowicz et al.). Despite the increasing number of people living with CODs, there is also a lack of coordinated services and trained specialists and primary care providers who understand their unique medical needs, as these patients are still viewed collectively as having a "pediatric" medical condition. These problems exist at the level of the health care system, the clinician, and the individual (Hurvitz et al.). This is unquestionably troubling for youth with disabilities as they transition to adulthood and are left to navigate their confusing and disjointed options for continued healthcare services. The lack of coordinated care and access to services from adults with COD seems to be a global problem. In particular improved access to physiotherapy services for adults are urgently needed, and perceived as important to maintain physical activity and deal with the impact of aging on daily activities (van Heijningen et al.; Cornec et al.; Ryan et al.).

Sedentary behavior is increased in adults with cerebral palsy, particularly those with low functional capacities, as compared to adults without cerebral palsy, and they are less physically active than adolescents with cerebral palsy (Salie et al.). In fact, adults unable to change position independently are likely to spend around 23 h daily either in a sitting or lying position, and few use standing devices more than 1 h/day (Rodby-Bousquet and Agustsson). Finding strategies to keep adolescents and adults with CODs physically active and try to reduce sedentary behavior is important (Salie et al.).

Several clinical assessments, tests, and biomarkers are recommended for systematic follow-up of adults with COD to improve their care. These vary from cognitive assessments (Stadskleiv et al.), to screening for bone health (Won and Jung), body composition (Shin and Jung), pain (Jersak and Noritz), respiratory conditions (Jonsson et al.), kidney disease (Whitney and Oliverio), bladder and bowel function (Starowicz et al.), mental health (Cohen et al.; Nguyen et al.), physical activity and sedentary behavior (Salie et al.), asymmetric postures (Rodby-Bousquet and Agustsson), and IGF-1 involved in cognitive decline and dementia (Ng et al.).

Challenges with housing, employment, relationships, and participation in society for adults with CODs are apparent across countries and continents (Imms et al.; Pettersson and Rodby-Bousquet; Shrader et al.; van Heijningen et al.). Even though many adults with CODs have similar levels of education as the general population, they tend to have lower rates of employment and long term relationships (Shrader et al.). Better targeted societal resources and access to personal assistance for adults with CODs are urgently needed to allow equitable access to employment, independent living, enable full participation in society, and best possible outcomes in all aspects of life (Pettersson and Rodby-Bousquet; Shrader et al.; van Heijningen et al.).

In addition, adults with CODs face several barriers to health care at different levels, and have unique needs. The ability to initiate and coordinate their own care is sometimes complicated by challenges with cognitive function and communication (Hurvitz et al.; Stadskleiv et al.). They need continuity of care, and access to medical and health care professionals with expertise in these conditions and we need to develop evidence-based guidelines for health surveillance and provide appropriate interventions (van Heijningen et al.; Whitney et al.; Cornec et al.; Hurvitz et al.; Ryan et al.; Starowicz et al.). Thus, transition programs are desperately needed to bridge the gap from pediatric to adult care (Duncan et al.; Kingsnorth et al.).

Conclusion

Despite the increasing number of adults living with CODs, there is a lack of coordinated services and adequately trained specialists to identify and treat preventable chronic conditions in these patients, as they are still viewed collectively as having a pediatric medical condition. Thought leadership is thus essential to increase research and promote best practices in preventive care, diagnosis, and disease management in these growing populations, as well as seamless transition and continuity of care as individuals with CODs grow up. This Research Topic is the first of its kind to assimilate research evidence regarding the unique healthcare needs facing individuals with CODs across the lifespan, and highlights the need for appropriate healthcare coordination and policies designed to enhance health and quality of life for all adults living with CODs.

Author contributions

Both authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Patterns of Health Service Use Among Young People With Cerebral Palsy in England

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Background: Although the provision of healthcare for people with cerebral palsy (CP) is typically focussed on childhood, many people with CP require access to services periodically throughout their life. Few studies have examined patterns of health service use among young people with CP in England. Understanding patterns of use may inform future service development.

Objective: To describe patterns of visits to rehabilitation and medical professionals among ambulatory young people with CP living in England, and identify factors associated with service use.

Methods: Sixty-two young people with CP aged 10–19 years [mean (SD) age 13.7 (2.5) years] in Gross Motor Function Classification System (GMFCS) levels I-III reported visits to a range of health professionals, hospital admissions and visits to the emergency department over a median duration of 34 weeks (min–max: 12–34 weeks). Negative binomial models were used to examine factors associated with number of visits.

Results: Physiotherapists were the most commonly used professional, with 67.7% of participants visiting a physiotherapist at least once, followed by dentists (66.1%), general practitioners (48.4%), occupational therapists (40.3%) and orthopaedic surgeons (40.3%). Physiotherapists were also the most frequently visited professional with a total of 473 visits (13.3 visits per person-year). Speech and language therapists (5.0 visits per person-year), occupational therapists (4.5 visits per person-year) and nurses (4.3 per person-year) were the next most frequently visited professionals. Age, GMFCS level, and speech impairment were associated with rate of visits to a physiotherapist.

Conclusions: The proportion of young people who visited medical and rehabilitation professionals during the study period varied considerably depending on the profession. Generally, the proportion of young people using services was low. In the context of limited resources, data on service use in combination with data on unmet need, may support the reorganisation of services to maximise benefits to young people with CP.

Keywords: cerebral palsy, health services, adolescent, rehabilitation, neurological disorders

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BACKGROUND

Cerebral palsy (CP) is a lifelong condition, with the majority of people with CP surviving to at least 60 years (1). Although impaired motor function is the core feature, people with CP can experience a range of associated impairments, such as epilepsy and intellectual disability (2). The type and severity of impairment experienced varies significantly between individuals. People with CP are intensive users of healthcare. Between 2000 and 2014, children and young people with CP in Northern Ireland accounted for 1.6% of total hospital admissions and 1.6% of total outpatient appointments, despite representing just 0.3% of the population (3). Although there is evidence that service use declines from childhood to adolescence and through to adulthood (4, 5), this may be because of difficulties accessing services rather than lack of need (6). Adults with CP have an increased risk of chronic physical health conditions, mental health conditions, and falls compared to adults without CP (7–10). Further, between 18 and 63% of young people with CP aged 14–18 years report needs in areas such as epilepsy, bone or joint problems, and control of movement, with between 10 and 45% reporting that their needs are not met (11).

Understanding patterns of health service use and predictors of service use is essential for planning service delivery. However, despite a significant proportion of young people with CP in the UK reporting healthcare needs (11), there is limited information available regarding service use in this group. A recent report found that, between 2004 and 2014, the rate of GP consultations was ∼200 per 100 person-years among people with CP aged 10–14 years and 250 per 100 person-years among those aged 15–19 years in England (12). Rate of outpatient appointments were approximately 450 per 100 person-years among people aged 10–14 years and 350 per 100 person-years among those aged 15–24 years (12). Rate of inpatient visits were ∼50 per 100 person-years among people aged 10–19 years (12). Another recent study of children and young people with CP aged 0–24 years in Northern Ireland reported that 68.4% had at least one hospital admission between 2004 and 2014 and 32.6% had at least one outpatient appointment between 2010 and 2014 (3). While providing important information using population based datasets, these studies do not describe the range of services used by young people with CP.

A survey of young people in Northern Ireland in 2008 identified the percentage of 12–18 year olds who visited a range of professionals during a 6-month period, which ranged from 3% for a psychologist to 92% for a physiotherapist (5). This study however was limited to non-ambulatory individuals with CP [i.e., those in Gross Motor Function Classification System (GMFCS) levels IV and V]. As people with CP in GMFCS levels IV and V typically have greater needs and are more frequent users of health services than people in levels I-III (4, 13–15), findings may not be applicable to ambulatory people with CP who constitute ∼75% of the CP population (16).

While these studies provide essential information about service use among young people with CP, there remains gaps in our knowledge about the range of professionals used by young people with CP in the UK. In this paper, we aim to add to current knowledge by describing patterns of visits to rehabilitation and medical professionals among ambulatory young people with CP living in England, and identifying factors associated with service use.

METHODS

Sample

Young people with CP who participated in a randomised controlled trial examining the effects of a 10-week progressive resistance training programme were included in this study (17). Participants were recruited from eight National Health Service (NHS) trusts in England, a special education needs school, a University, a primary care organisation in London, national organisations for people with disabilities, and by word of mouth. Young people aged 10–19 years with spastic CP and the ability to walk independently with or without a mobility aid [i.e., Gross Motor Function Classification System (GMFCS) levels I-III] were included in the study. The GMFCS is a five-level classification system (18). Those in GMFCS level I are able to walk and run and climb stairs without assistance. Those in level II are able to walk in most settings but may use a hand-held mobility device indoors or wheeled mobility to travel long distances. Those in level III can walk using a hand-held mobility device but use a wheelchair or powered mobility outdoors. Young people were excluded if they had orthopaedic surgery of the lower limbs in the past 12 months, botulinum toxin type A injections or serial casting in the past 6 months, or insufficient cognition to comply with assessment procedures and the training programme. Approval was obtained from Brunel University London's College of Health, Medicine and Life Sciences Research Ethics Committee and the Surrey Borders Research Ethics Committee (ref: 15/LO/0843). Participants 16 years and over provided written consent. Participants under 16 years provided assent, and parents of participants under 16 years provided written consent.

Assessments were conducted at baseline, 10 and 22 weeks. Demographic and CP-related information was collected at baseline using a standardised questionnaire. Anatomical distribution was described as unilateral or bilateral. Functional mobility was classified according to the GMFCS. Participants selected a statement that best described their mobility based on descriptors of each GMFCS level. Two physiotherapists retrospectively cross-referenced subjective ratings of GMFCS level against video recordings of participants, obtained as part of the baseline assessment. Participants were also asked if they had autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), behavioural problems, speech problems, epilepsy, or learning difficulties. We combined those with ASD, ADHD or behavioural problems into one category as less than five people reported having ASD and ADHD, respectively.

Outcomes

The primary outcome in this study was the binary outcome of whether or not an individual used a health service. Secondary outcomes were number of visits, service provider and setting. At each assessment, participants completed a modified Client

Service Receipt Inventory (CSRI) to assess health service use (19). At the baseline assessment, participants were asked to state the number of times they visited a range of professionals, number of visits to the emergency department, and number of hospital admissions in the past 12 weeks. They were also asked to state if the service was provided by the NHS, school or privately, and they were asked to state the setting they saw the professional in (i.e., clinic, home or school). At the 10 and 22 week assessment, participants were asked to provide the same information considering the time-period since their last assessment (i.e., the previous 10 and 12 weeks). Assistance was provided by the researcher to read the questions if required. Further, the young person was allowed to ask their parent/guardian or researcher for assistance to answer the questions if required.

Analysis

The distribution of data was examined using histograms, Q-Q plots, and cross-tabulations. Participant characteristics were described as mean and standard deviation (SD), minimum, maximum, frequencies and percentages, as appropriate. We reported the number and percentage of people with at least one visit to each professional, with at least one visit to the emergency department, and at least one hospital admission. Some participants did not complete the CSRI at 10 or 22 weeks. Therefore, to account for the fact that participants were observed for varying lengths of time, we calculated the incidence rate of at least one visit as the number with at least one visit divided by total person-weeks under observation. We also calculated the rate of visits as total number of visits to each professional divided by total person-weeks. For each service, we examined associations between participant characteristics (i.e., age, sex, GMFCS level, distribution, behavioural problems, speech problems, epilepsy, learning difficulties and type of school) and having at least one visit using separate Cox proportional hazards models. For each service, we also examined associations between participant characteristics and number of visits using separate negative binomial models including an offset for person-time. Where there was evidence that the independent variable was associated with the outcome at the level of $\alpha = 10\%$ (i.e., $p < 0.10$) in unadjusted analyses, we included these variables together in an adjusted model. Where type of school was not associated with the outcome, we additionally included it in adjusted models as we identified that it confounded the association between a number of participant characteristics and service use. We combined visits to a psychologist and psychiatrist when examining associations because only three people reported visiting a psychiatrist. We did not examine associations with visits to a social worker, chiropodist or audiologist because five or fewer young people reported visiting these professionals. Similarly, we did not examine associations with hospital admissions because less than five children were admitted to hospital. Analyses were performed using Stata version 13.

RESULTS

Sixty-four participants were recruited to the study. Two participants did not complete the CSRI at any assessment and were therefore excluded from analysis. Sixty-two participants provided data at baseline, 51 participants provided data at 10 weeks, and 50 participants provided data at 22 weeks. Seventy-four percent of participants provided data at all assessments. Participants were observed for a total of 1,854 person-weeks, with a median of 34 weeks per person (min–max: 12–34 weeks). Characteristics of included participants are presented in **Table 1**. Participants were aged 10–19 years. The majority were male, with bilateral CP, and in mainstream education.

TABLE 1 | Participant characteristics.

	n (%)	Mean (SD); min, max
Age, yr	62	13.7 (2.5); 10, 19
Female	26 (41.9)	
Male	36 (58.1)	
GMFCS level		
I	28 (45.2)	
II	25 (40.3)	
III	9 (14.5)	
Distribution		
Unilateral	30 (48.4)	
Bilateral	32 (51.6)	
Type of school		
Mainstream education	50 (80.6)	
SEN	12 (19.4)	
Presence of additional impairment		
Epilepsy	7 (11.3)	
Speech impairment	14 (22.6)	
Learning difficulties	20 (32.3)	
ASD/ADHD/Behaviour impairment	9 (14.5)	

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; GMFCS, Gross motor function classification system; SD, Standard deviation; SEN, Special education needs.

Patterns of Service Use

Participants' use of each service is described in **Table 2**. Physiotherapists were the most commonly visited professional with 67.7% of participants visiting a physiotherapist at least once, followed by dentists (66.1%), general practitioners (GPs) (48.4%), occupational therapists (40.3%) and orthopaedic surgeons (40.3%). Physiotherapists were also the most frequently visited professional with a total of 473 visits (13.3 visits per person-year). Speech and language therapists (5.0 visits per person-year), occupational therapists (4.5 visits per person-year), and nurses (4.3 visits per person-year) were the next most frequently visited professionals. Nine participants (14.5%) attended the emergency department at least once. The rate of emergency department visits was 0.31 per person-year. Only three participants (4.8%) had a hospital admission, resulting in an admission rate of 0.08 per person-year. For all services except for counselling and social work, the majority of participants accessed the service through the NHS (**Table 2**). The majority of participants

TABLE 2 | Description of visits to each professional, emergency department visits, and hospital admissions.

	≥1 visit, *n* (%)	Incidence rate (95% CI), per person-year	Visits, n	Rate of visits (95% CI*), per person-year	Provider, *n*[a]				Setting, *n*[a]		
					NHS	Private	School	Other	Clinic	School	Home
Physiotherapist[e]	42 (67.7)	1.18 (0.87, 1.59)	473	13.27 (8.82, 19.96)	36	4	2	0	25	19	5
Dentist[c,f]	41 (66.1)	1.15 (0.85, 1.56)	84	2.36 (1.82, 3.06)	34	6	0	0	37	1	0
General practitioner[d]	30 (48.4)	0.84 (0.59, 1.20)	74	2.08 (1.41, 3.06)	30	0	0	0	29	1	1
Occupational therapist[d]	25 (40.3)	0.70 (0.47, 1.04)	160	4.49 (2.38, 8.48)	25	2	1	0	10	13	4
Orthopaedic surgeon[e]	25 (40.3)	0.70 (0.47, 1.04)	43	1.21 (0.80, 1.81)	25	1	0	0	22	0	0
Orthotist	24 (38.7)	0.67 (0.45, 1.00)	44	1.23 (0.82, 1.84)	23	1	0	0	18	1	0
Optician[c,g]	24 (38.7)	0.67 (0.45, 1.00)	36	1.01 (0.71, 1.43)	16	7	0	1	22	0	0
Nurse[b,e]	18 (29.0)	0.50 (0.32, 0.80)	152	4.26 (0.89, 20.44)	17	0	0	0	13	4	0
Paediatrician	18 (29.0)	0.50 (0.32, 0.80)	33	0.93 (0.52, 1.65)	18	0	0	0	17	0	0
Speech and language therapist[d]	13 (21.0)	0.36 (0.21, 0.63)	179	5.02 (1.54, 16.35)	13	0	2	0	3	12	0
Other medical specialist[b]	12 (19.4)	0.34 (0.19, 0.59)	17	0.48 (0.28, 0.82)	10	1	0	0	12	0	0
Neurologist	9 (14.5)	0.25 (0.13, 0.49)	14	0.39 (0.18, 0.88)	9	0	0	0	9	0	0
Psychologist[c,g]	8 (12.9)	0.22 (0.11, 0.45)	27	0.76 (0.30, 1.90)	5	0	0	1	4	3	0
Counsellor	7 (11.3)	0.20 (0.09, 0.41)	32	0.90 (0.41, 1.96)	3	0	4	0	3	4	0
Social worker	5 (8.1)	0.14 (0.06, 0.34)	9	0.25 (0.10, 0.63)	2	0	0	3	2	0	4
Chiropodist	4 (6.5)	0.11 (0.04, 0.30)	4	0.11 (0.04, 0.29)	3	1	0	0	3	1	0
Psychiatrist[b]	3 (4.8)	0.08 (0.03, 0.26)	4	0.11 (0.03, 0.36)	2	0	0	0	3	0	0
Audiologist	1 (1.6)	0.03 (0.004, 0.199)	2	0.06 (0.01, 0.40)	0	1	0	0	1	0	0
Emergency department	9 (14.5)	0.25 (0.13, 0.49)	11	0.31 (0.16, 0.59)							
Hospital admission	3 (4.8)	0.08 (0.03, 0.25)	3	0.08 (0.03, 0.25)							

**Calculated using robust sandwich estimator of variance; [a]person may select more than one category; [b]data on provider missing for one person; [c]data on provider missing for two people; [d]data on setting missing for one person; [e]data on setting missing for three people; [f]data on setting missing for four people; [g]data on setting missing for two people.*

attended a clinic for most services (**Table 2**). However, many young people received rehabilitation services in school. Thirteen of 25 participants received occupational therapy in school, 12 of 13 participants received speech and language therapy in school, four of seven participants received counselling in school, and 19 of 42 participants received physiotherapy in school.

Participant Characteristics Associated With at Least One Visit to a Professional

Unadjusted Analyses

Unadjusted associations between participant characteristics and having at least one visit to each professional are reported in **Tables 3**, **4**. In unadjusted analyses, there was some evidence that GMFCS level was positively associated with at least one visit to an occupational therapist ($p = 0.030$), speech and language therapist ($p = 0.022$), nurse ($p = 0.078$) and paediatrician ($p = 0.033$). People with bilateral CP were more likely to visit a paediatrician than people with unilateral CP (HR: 3.43, 95% CI 1.13, 10.43; $p = 0.030$). People with ASD/ADHD/behaviour impairment were more likely to visit the emergency department (HR: 3.84, 95% CI 1.03, 14.31; $p = 0.045$). People with epilepsy were more likely to visit an occupational therapist (HR: 2.60, 95% CI 1.04, 6.50; $p = 0.042$) and speech and language therapist (HR 3.70, 95% CI 1.14, 12.00; $p = 0.030$). People with learning difficulties were more likely to visit an occupational therapist (HR: 2.79, 95% CI 1.27, 6.15; $p = 0.011$), speech and language therapist (HR: 3.57, 95% CI 1.17, 10.90; $p = 0.026$), psychologist or psychiatrist (HR: 4.49, 95% CI 1.12, 17.97; $p = 0.034$) and optician (HR: 2.26, 95% CI 1.02, 5.03; $p = 0.046$). People with a speech impairment were more likely to visit a speech and language therapist (HR: 7.70, 95% CI 2.37, 25.04; $p = 0.001$). People attending a SEN school were more likely to visit a speech and language therapist than those attending a mainstream school (HR: 4.19, 95% CI 1.41, 12.46; $p = 0.010$).

Adjusted Analyses

As presented in **Table 5**, in adjusted analyses, people in GMFCS level III remained more likely to visit an occupational therapist (adjusted HR: 4.23, 95% CI 1.25, 14.30; $p = 0.020$) and nurse (adjusted HR: 4.32, 95% CI 1.17, 16.00; $p = 0.028$) than those in level I. There was also weak evidence that people with learning difficulties were more likely to visit an occupational therapist (adjusted HR: 2.35, 95% CI 1.00, 5.48; $p = 0.049$) and people with a speech impairment were more likely to visit a speech and language therapist (adjusted HR: 4.14, 95% CI 0.97, 17.62; $p = 0.055$).

TABLE 3 | Unadjusted associations with at least one visit to a physiotherapist, occupational therapist, speech and language therapist, psychologist/psychiatrist, orthotist, counsellor, optician.

	Physiotherapist unadjusted HR (95% CI)	Occupational therapist unadjusted HR (95% CI)	SALT unadjusted HR (95% CI)	Psychologist/ Psychiatrist unadjusted HR (95% CI)	Orthotist unadjusted HR (95% CI)	Counsellor unadjusted HR (95% CI)	Optician unadjusted HR (95% CI)
Age	0.95 (0.84, 1.08)	1.02 (0.87, 1.20)	0.98 (0.78, 1.22)	0.90 (0.68, 1.19)	0.91 (0.76, 1.08)	1.02 (0.76, 1.37)	1.02 (0.87, 1.19)
Sex							
Female	0.83 (0.45, 1.54)	1.31 (0.60, 2.88)	1.40 (0.47, 4.18)	0.98 (0.26, 3.63)	0.87 (0.38, 1.95)	2.98 (0.58, 15.36)	1.20 (0.54, 2.67)
GMFCS							
Level II	1.39 (0.71, 2.73)	**2.66 (1.01, 7.00)**	**4.40 (0.91, 21.20)**	1.26 (0.25, 6.24)	1.49 (0.64, 3.45)	2.49 (0.46, 13.59)	1.03 (0.43, 2.49)
Level III	2.04 (0.87, 4.78)	**4.06 (1.31, 12.61)**	**8.50 (1.55, 46.50)**	4.26 (0.86, 21.15)	0.83 (0.18, 3.81)	2.16 (0.20, 23.88)	1.61 (0.51, 5.07)
Distribution							
Bilateral	1.18 (0.64, 2.17)	0.90 (0.41, 1.97)	2.20 (0.68, 7.16)	3.45 (0.72, 16.59)	1.16 (0.52, 2.58)	0.39 (0.08, 2.03)	1.39 (0.62, 3.13)
Behaviour impairment	0.67 (0.26, 1.71)	0.94 (0.32, 2.73)	1.45 (0.40, 5.29)	2.46 (0.61, 9.83)	0.70 (0.21, 2.35)	1.92 (0.37, 9.90)	0.96 (0.33, 2.81)
Epilepsy	1.37 (0.58, 3.25)	**2.60 (1.04, 6.50)**	**3.70 (1.14, 12.00)**	1.03 (0.13, 8.24)	0.36 (0.05, 2.65)	3.28 (0.64, 16.90)	1.17 (0.35, 3.92)
Learning difficulties	1.50 (0.81, 2.79)	**2.79 (1.27, 6.15)**	**3.57 (1.17, 10.90)**	**4.49 (1.12, 17.97)**	1.33 (0.58, 3.04)	0.89 (0.17, 4.59)	**2.26 (1.02, 5.03)**
Speech impairment	1.72 (0.91, 3.27)	1.91 (0.84, 4.33)	**7.70 (2.37, 25.04)**	1.74 (0.44, 6.97)	1.15 (0.46, 2.90)	0.58 (0.07, 4.83)	1.19 (0.47, 2.99)
School							
SEN	1.30 (0.65, 2.59)	1.71 (0.74, 3.96)	**4.19 (1.41, 12.46)**	2.92 (0.78, 10.88)	0.52 (0.15, 1.74)	2.70 (0.60, 12.06)	1.21 (0.48, 3.04)

Bold text indicates $p < 0.010$.

CI, confidence interval; GMFCS, Gross motor function classification system; SALT, speech and language therapist; SEN, Special education needs.

Participant Characteristics Associated With Number of Visits to a Professional

Unadjusted Analyses

Unadjusted associations between participant characteristics and number of visits to each professional are reported in **Tables 6**, **7**. Age was negatively associated with visits to a GP (IRR: 0.84, 95% CI 0.72, 0.97; $p = 0.019$) and positively associated with visits to a nurse (IRR: 1.58, 95% CI 1.13, 2.22; $p = 0.008$). Compared to people in GMFCS level I, people in GMFCS level II had more visits to a physiotherapist (IRR: 2.80, 95% CI 1.17, 6.68; $p = 0.020$), occupational therapist (IRR: 4.99, 95% CI 1.48, 16.80; $p = 0.009$), speech and language therapist (IRR: 31.52 (95% CI 4.69, 211.97; $p < 0.001$), nurse (IRR: 24.64, 95% CI 5.11, 118.80; $p < 0.001$), dentist (IRR: 0.45, 95% CI 0.26, 0.79; $p = 0.005$) and paediatrician (IRR: 3.71, 95% CI 1.12, 12.26; $p = 0.032$). People in GMFCS level III also had more visits to a paediatrician than people in level I (IRR: 7.70, 95% CI 1.94, 30.50; $p = 0.004$). People with bilateral CP had more visits to a physiotherapist (IRR: 3.15, 95% CI 1.42, 6.99; $p = 0.005$), an occupational therapist (IRR 3.82, 95% CI 1.22, 11.92; $p = 0.021$), and a paediatrician (IRR: 3.95, 95% CI 1.32, 11.83; $p = 0.014$) and less visits to a nurse (IRR: 0.17, 95% CI 0.04, 0.78; $p = 0.022$) than those with unilateral CP. People with epilepsy had more visits to a speech and language therapist (IRR: 72.61, 95% CI 16.69, 315.89; $p < 0.001$), nurse (IRR: 36.97, 95% CI 7.19, 189.99; $p < 0.001$) and neurologist (IRR: 5.58, 95% CI 1.12, 27.71; $p = 0.035$). People with learning difficulties had more visits to an occupational therapist (IRR: 4.25, 95% CI 1.32, 13.62; $p = 0.015$), psychologist or psychiatrist (IRR: 7.60, 95% CI 1.38, 41.99; $p = 0.020$), and nurse (IRR: 14.71, 95% CI 3.43, 61.13, $p < 0.001$). People with a speech impairment had more visits to a physiotherapist (IRR: 3.48, 95% CI 1.38, 8.78; $p = 0.008$), speech and language therapist (IRR: 72.61, 95% CI 16.69, 315.89; $p < 0.001$), GP (IRR: 2.24, 95% CI 1.02, 4.89; $p = 0.044$), and nurse (IRR: 21.01, 95% CI 4.93, 89.60; $p < 0.001$). People attending a special educational needs school had more visits to a speech and language therapist (IRR: 19.03, 95% CI 2.40, 145.16; $p = 0.004$) and nurse (IRR: 19.52, 95% CI 4.16, 91.54; $p < 0.001$) than those in mainstream education.

Adjusted Analyses

Results from adjusted analyses are reported in **Table 8**. In adjusted analyses, people with learning difficulties had more visits to an occupational therapist (adjusted IRR: 5.6, 95% CI 1.7, 18.0; $p = 0.004$). People with a speech impairment (adjusted IRR: 19.5, 95% CI 3.9, 97.7; <0.001) and epilepsy (IRR: 6.3, 95% CI 1.2, 34.4; $p = 0.032$) had more visits to a speech and language therapist. Age remained negatively associated with rate of GP visits (adjusted IRR: 0.85, 95% CI 0.74, 0.99; $p = 0.035$). People with epilepsy had more visits to a nurse (adjusted IRR: 18.1, 95% CI 2.0, 167.0; $p = 0.010$) and people in GMFCS level II had more visits to a nurse than people in GMFCS level I (adjusted IRR: 5.4, 95% CI 1.1, 26.6; $p = 0.040$).

DISCUSSION

We aimed to describe patterns of visits to rehabilitation professionals, medical professionals, emergency department visits and hospital admissions among ambulatory young people with CP living in England, and identify factors associated with service use. In our sample, physiotherapists were the most commonly visited professional, with 68% of young people visiting a physiotherapist at least once, and also the most frequently visited professional, with a visit rate of 13.3 per person-year. A similar proportion of young people visited a dentist at least once.

TABLE 4 | Unadjusted associations with at least one visit to a general practitioner, nurse, dentist, paediatrician, orthopaedic surgeon, neurologist, other medical specialist and emergency department.

	GP unadjusted HR (95% CI)	Nurse unadjusted HR (95% CI)	Dentist unadjusted HR (95% CI)	Paediatrician unadjusted HR (95% CI)	Orthopaedic surgeon unadjusted HR (95% CI)	Neurologist unadjusted HR (95% CI)	Other medical specialist unadjusted HR (95% CI)	ED unadjusted HR (95% CI)
Age	0.98 (0.85, 1.14)	1.04 (0.86, 1.24)	0.97 (0.86, 1.10)	0.93 (0.76, 1.13)	0.92 (0.78, 1.08)	0.88 (0.66, 1.17)	0.90 (0.70, 1.15)	0.88 (0.66, 1.17)
Sex								
Female	1.05 (0.51, 2.15)	0.96 (0.38, 2.42)	0.86 (0.46, 1.60)	1.51 (0.59, 3.81)	0.69 (0.30, 1.56)	2.42 (0.61, 9.69)	0.40 (0.11, 1.47)	0.96 (0.26, 3.57)
GMFCS								
Level II	0.91 (0.40, 2.04)	**2.00 (0.65, 6.12)**	0.76 (0.39, 1.47)	**2.84 (0.87, 9.23)**	1.24 (0.52, 2.98)	0.76 (0.18, 3.16)	1.53 (0.47, 5.02)	0.43 (0.09, 2.11)
Level III	1.90 (0.73, 4.96)	**4.31 (1.25, 14.92)**	0.73 (0.25, 2.11)	**5.34 (1.43, 19.90)**	2.06 (0.70, 6.05)	0.88 (0.10, 7.52)	0.90 (0.10, 7.67)	0.74 (0.09, 6.15)
Distribution								
Bilateral	1.49 (0.72, 3.09)	1.55 (0.60, 3.99)	0.77 (0.41, 1.42)	**3.43 (1.13, 10.43)**	1.25 (0.57, 2.75)	3.48 (0.72, 16.73)	1.99 (0.60, 6.60)	1.24 (0.33, 4.61)
Behaviour impairment	0.74 (0.26, 2.12)	9.96 (0.28, 3.33)	1.08 (0.45, 2.27)	0.97 (0.28, 3.35)	0.94 (0.32, 2.75)	1.39 (0.29, 6.69)	0.96 (0.21, 4.37)	**3.84 (1.03, 14.31)**
Epilepsy	1.27 (0.44, 3.63)	2.35 (0.77, 7.15)	1.14 (0.45, 2.90)	*	1.12 (0.33, 3.74)	2.33 (0.48, 11.22)	*	1.04 (0.13, 8.28)
Learning difficulties	1.31 (0.62, 2.76)	**2.23 (0.88, 4.62)**	1.28 (0.68, 2.43)	1.79 (0.71, 4.53)	1.25 (0.55, 2.83)	1.81 (0.49, 6.75)	1.62 (0.51, 5.11)	1.81 (0.49, 6.75)
Speech impairment	1.77 (0.83, 3.78)	2.21 (0.86, 5.70)	0.98 (0.47, 2.05)	1.71 (0.64, 4.56)	1.35 (0.56, 3.23)	1.79 (0.45, 7.16)	1.76 (0.53, 5.86)	1.00 (0.21, 4.82)
School								
SEN	1.10 (0.47, 2.56)	1.38 (0.49, 3.88)	0.75 (0.33, 1.69)	1.38 (0.49, 3.87)	0.92 (0.34, 2.45)	1.04 (0.22, 5.03)	1.20 (0.32, 4.43)	0.45 (0.06, 3.59)

Bold text indicates $p < 0.010$.

**Unable to calculate.*

CI, confidence interval; ED, Emergency department; GMFCS, Gross motor function classification system; GP, General practitioner; SEN, Special education needs.

TABLE 5 | Adjusted associations with at least one visit to an occupational therapist, speech and language therapist, nurse, optician, paediatrician.

	Occupational therapy adjusted HR (95% CI); *p*-value	SALT adjusted HR (95% CI); *p*-value	Nurse adjusted HR (95% CI); *p*-value	Paediatrician adjusted HR (95% CI); *p*-value
GMFCS				
Level II	2.18 (0.80, 5.92); 0.126	2.40 (0.43, 13.31); 0.315	1.93 (0.63, 5.93); 0.253	2.14 (0.61, 7.50); 0.234
Level III	4.23 (1.25, 14.30); 0.020	4.54 (0.56, 36.57); 0.155	4.32 (1.17, 16.00); 0.028	3.05 (0.65, 13.23); 0.156
Distribution				
Bilateral	–	–	–	2.33 (0.66, 8.18); 0.188
Behaviour impairment	–	–	–	–
Epilepsy	2.12 (0.73, 6.15); 0.165	2.09 (0.35, 12.63); 0.420	–	
Learning difficulties	2.35 (1.00, 5.48); 0.049	1.97 (0.59, 6.53); 0.270	2.24 (0.80, 6.24); 0.123	–
Speech impairment	–	4.14 (0.97, 17.62); 0.055	–	–
School				
SEN	0.77 (0.30, 1.99); 0.585	0.84 (0.15, 4.75); 0.847	0.71 (0.21, 2.36); 0.574	1.17 (0.39, 3.50); 0.776

CI, confidence interval; GMFCS, Gross motor function classification system; SALT, speech and language therapist; SEN, Special education needs.

TABLE 6 | Unadjusted associations with number of visits to a physiotherapist, occupational therapist, speech and language therapist, psychologist/psychiatrist, orthotist, counsellor, optician.

	Physiotherapist unadjusted IRR (95% CI)	Occupational therapist unadjusted IRR (95% CI)	SALT unadjusted IRR (95% CI)	Psychologist/ Psychiatrist unadjusted IRR (95% CI)	Orthotist unadjusted IRR (95% CI)	Counsellor unadjusted IRR (95% CI)	Optician unadjusted IRR (95% CI)
Age	**0.85 (0.71, 1.01)**	0.89 (0.70, 1.14)	0.74 (0.44, 1.26)	0.72 (0.44, 1.19)	**0.87 (0.73, 1.03)**	0.95 (0.63, 1.45)	1.03 (0.90, 1.18)
Sex							
Female	1.11 (0.47, 2.59)	2.64 (0.73, 9.51)	3.44 (0.47, 24.99)	2.14 (0.34, 13.56)	1.08 (0.47, 2.49)	2.39 (0.26, 21.89)	1.02 (0.50, 2.05)
GMFCS							
Level II	**2.80 (1.17, 6.68)**	**4.99 (1.48, 16.80)**	**31.5 (4.7, 212.0)**	0.78 (0.11, 5.75)	1.87 (0.81, 4.29)	1.47 (0.14, 15.08)	0.93 (0.44, 1.99)
Level III	**3.22 (0.97, 10.66)**	**4.33 (0.82, 22.75)**	**5.4 (0.4, 72.8)**	0.61 (0.03, 10.72)	0.43 (0.08, 2.25)	0.24 (0.01, 9.74)	0.99 (0.34, 2.88)
Distribution							
Bilateral	**3.15 (1.42, 6.99)**	**3.82 (1.22, 11.92)**	0.47 (0.06, 3.45)	1.10 (0.17, 7.04)	0.96 (0.42, 2.21)	0.25 (0.03, 2.18)	1.17 (0.58, 2.35)
Behaviour impairment	0.72 (0.22, 2.38)	2.57 (0.50, 13.11)	1.8 (0.1, 31.3)	6.22 (0.68, 56.61)	0.67 (0.20, 2.29)	4.12 (0.22, 76.47)	1.28 (0.53, 3.12)
Epilepsy	1.38 (0.37, 5.19)	**5.28 (0.96, 29.04)**	**26.5 (2.3, 306.6)**	3.94 (0.28, 55.60)	0.98 (0.27, 3.61)	4.34 (0.17, 111.7)	1.03 (0.34, 3.15)
Learning difficulties	2.01 (0.84, 4.83)	**4.25 (1.32, 13.62)**	1.04 (0.12, 9.12)	**7.60 (1.38, 41.99)**	1.80 (0.79, 4.11)	1.50 (0.13, 15.98)	1.67 (0.84, 3.34)
Speech impairment	**3.48 (1.38, 8.78)**	**3.62 (0.96, 13.62)**	**72.6 (16.7, 315.9)**	0.66 (0.07, 6.28)	1.21 (0.47 (3.13)	0.46 (0.03, 7.03)	0.93 (0.40, 2.15)
School							
SEN	1.72 (0.61, 4.90)	3.08 (0.74, 12.83)	19.0 (2.5, 145.2)	1.39 (0.14, 13.99)	0.82 (0.29, 2.36)	2.92 (0.20, 42.74)	1.27 (0.56, 2.85)

Bold text indicates p < 0.010.

CI, confidence interval; GMFCS, Gross motor function classification system; SALT, speech and language therapist; SEN, Special education needs.

All other professions were visited by less than half of participants during the study period. Despite only 21% of young people visiting a speech and language therapist and only 40% visiting on occupational therapist, these were the second and third most frequently visited professionals, with visit rates of 5.0 and 4.5 per person-year, respectively. In adjusted analyses, GMFCS level, age and presence of epilepsy, learning difficulties and speech impairment were associated with having at least one visit and number of visits to a range of professionals.

Few studies that report service use among young people with CP have examined the range of services examined in this study. Estimates for the proportion of young people visiting an occupational therapist (44%) and speech and language therapist (19%) in the Netherlands (4) were almost identical to estimates

TABLE 7 | Unadjusted associations with number of visits to a general practitioner, nurse, dentist, paediatrician, orthopaedic surgeon, neurologist, other medical specialist and emergency department.

	GP unadjusted IRR (95% CI)	Nurse unadjusted IRR (95% CI)	Dentist unadjusted IRR (95% CI)	Paediatrician unadjusted IRR (95% CI)	Orthopaedic surgeon unadjusted IRR (95% CI)	Neurologist unadjusted IRR (95% CI)	Other medical specialist unadjusted IRR (95% CI)	ED unadjusted IRR (95% CI)
Age	**0.84 (0.72, 0.97)**	**1.58 (1.13, 2.22)**	0.98 (0.88, 1.09)	0.92 (0.74, 1.14)	0.89 (0.74, 1.07)	0.80 (0.54, 1.19)	0.87 (0.68, 1.11)	0.88 (0.66, 1.18)
Sex								
Female	1.35 (0.64, 2.81)	**0.11 (0.02, 0.53)**	0.71 (0.42, 1.20)	2.30 (0.82, 6.41)	1.01 (0.44, 2.31)	2.98 (0.67, 13.18)	0.53 (0.16, 1.75)	1.08 (0.29, 3.95)
GMFCS								
Level II	1.24 (0.56, 2.73)	**24.6 (5.1, 118.8)**	**0.45 (0.26, 0.79)**	**3.71 (1.12, 12.26)**	1.16 (0.47, 2.82)	0.48 (0.10, 2.36)	0.97 (0.29, 3.26)	0.29 (0.06, 1.42)
Level III	1.12 (0.36, 3.44)	**3.4 (0.4, 30.7)**	**0.64 (0.30, 1.36)**	**7.70 (1.94, 30.50)**	1.34 (0.40, 4.50)	0.35 (0.02, 4.54)	0.81 (0.13, 4.95)	0.43 (0.05, 3.72)
Distribution								
Bilateral	**1.85 (0.89, 3.85)**	**0.17 (0.04, 0.78)**	0.91 (0.54, 1.53)	**3.95 (1.32, 11.83)**	1.24 (0.54, 2.83)	1.32 (0.30, 5.87)	1.30 (0.42, 4.06)	0.79 (0.22, 2.88)
Behaviour impairment	1.15 (0.42, 3.17)	0.17 (0.02, 1.90)	1.51 (0.79, 2.87)	0.53 (0.11, 2.64)	1.72 (0.62, 4.74)	3.87 (0.77, 19.53)	1.14 (0.25, 5.18)	3.03 (0.80, 11.45)
Epilepsy	**2.62 (0.99, 6.95)**	**37.0 (7.2, 190.0)**	0.62 (0.24, 1.61)	*	1.43 (0.43, 4.67)	**5.58 (1.12, 27.71)**	*	0.80 (0.09, 7.37)
Learning difficulties	1.72 (0.82, 3.64)	**14.7 (3.5, 61.1)**	0.97 (0.55, 1.69)	1.88 (0.66, 5.36)	1.41 (0.61, 3.26)	2.56 (0.60, 11.00)	1.42 (0.45, 4.50)	1.18 (0.31, 4.51)
Speech impairment	**2.24 (1.02, 4.89)**	**21.0 (4.9, 89.6)**	0.76 (0.40, 1.45)	2.15 (0.70, 6.61)	0.62 (0.22, 1.75)	0.86 (0.14, 5.10)	1.34 (0.38, 4.74)	0.74 (0.14, 3.87)
School								
SEN	1.77 (0.75, 4.17)	**19.5 (4.2, 91.5)**	0.68 (0.34, 1.36)	2.15 (0.67, 6.91)	0.60 (0.20, 1.81)	0.63 (0.09, 4.55)	1.57 (0.44, 5.66)	0.38 (0.05, 3.25)

Bold text indicates $p < 0.010$.

**Unable to calculate.*

CI, confidence interval; ED, Emergency department; GMFCS, Gross motor function classification system; GP, General practitioner; SEN, Special education needs.

TABLE 8 | Adjusted associations with number of visits to a physiotherapist, occupational therapist, speech and language therapist, general practitioner, nurse, paediatrician.

	Physiotherapist adjusted IRR (95% CI); *p*-value	Occupational therapist adjusted IRR (95% CI); *p*-value	SALT adjusted IRR (95% CI); *p*-value	GP adjusted IRR (95% CI); *p*-value	Nurse adjusted IRR (95% CI); *p*-value	Paediatrician adjusted IRR (95% CI); *p*-value
Age	0.82 (0.66, 1.01); 0.067	–	–	0.85 (0.74, 0.99); 0.035	1.05 (0.77, 1.42); 0.760	
Sex						
Female	–	–	–	–	0.24 (0.06, 0.96); 0.043	
GMFCS						
Level II	1.57 (0.61, 4.05); 0.353	3.3 (0.8, 14.7); 0.113	1.9 (0.3, 11.3); 0.481	–	5.4 (1.1, 26.6); 0.040	2.92 (0.86, 9.90); 0.086
Level III	2.23 (0.56, 8.85); 0.254	7.2 (0.9, 56.9); 0.060	0.9 (0.1, 10.3); 0.926	–	8.8 (0.5, 142.6); 0.124	3.9 (0.8, 19.5); 0.104
Distribution						
Bilateral	1.64 (0.65, 4.15); 0.298	0.81 (0.17, 3.78); 0.787	–	1.69 (0.84, 3.40); 0.145	0.95 (0.16, 5.54); 0.950	2.45 (0.75, 8.04); 0.140
Behaviour impairment	–	–	–	–	–	
Epilepsy	–	3.8 (0.6, 22.3); 0.142	6.3 (1.2, 34.4); 0.032	2.08 (0.76, 5.66); 0.153	18.1 (2.0, 167.0); 0.010	
Learning difficulties	–	5.6 (1.7, 18.0); 0.004	–	–	1.53 (0.35, 6.63); 0.568	
Speech impairment	2.38 (0.87, 6.46); 0.090	2.43 (0.60, 9.91); 0.215	19.5 (3.9, 97.7); <0.001	1.38 (0.58, 3.28); 0.465	1.8 (0.3, 10.7); 0.493	
School						
SEN	1.31 (0.41, 4.26); 0.649	0.75 (0.17, 3.24); 0.697	3.0 (0.7, 13.8); 0.156	1.21 (0.45, 3.30); 0.703	0.44 (0.05, 3.63); 0.443	1.45 (0.44, 4.80); 0.546

CI, confidence interval; GMFCS, Gross motor function classification system; GP, General practitioner; SALT, speech and language therapist; SEN, Special education needs.

from this study. The proportion of young people visiting a physiotherapist was higher than that reported among 13–18 year olds in the United States (59.4% over 12 months) (13) and 12–19 year olds in the Netherlands (51.8% over 6 months) (4). In contrast, the proportion visiting a physiotherapist, occupational therapist and speech and language therapist was lower in this study than in a study of young people aged 12–18 years in GMFCS levels IV and V in Northern Ireland (92, 62, and 39%, respectively) (5).

Less than half of young people visited a medical professional during the study period. The proportion visiting an orthopaedic surgeon, at 40%, was lower than that reported among young people in GMFCS levels IV and V in Northern Ireland (64% over 6 months) (5). While the difference may be partly explained by difference in GMFCS level, this study also excluded individuals who had received orthopaedic surgery of the lower limbs in the past year, which may have resulted in a biased sample. A third of ambulatory young people in France visited a neurologist (20), which is much higher than the 14.5% of our sample. The higher proportion of people visiting a neurologist in France may partly be explained by a higher prevalence of epilepsy in the sample. Compared to other professions, the number of young people visiting a psychologist or psychiatrist was small. Only 5% of young people in this study visited a psychiatrist, which is identical to the proportion of ambulatory young people who visited a psychiatrist in France (20). Thirteen percent visited a psychologist, which is similar to the 15% who visited a psychologist in the study in the Netherlands (4) but higher than the 3% reported in the study in Northern Ireland (5).

The relatively small number of people visiting a paediatrician or neurologist suggests that a medical professional is not co-ordinating their care. Only 15% of young people with CP in the UK reported having a person they can easily contact to support with co-ordination of care (21). Further, in the UK, nearly half of young people with CP are discharged from paediatric services to their GP, in the absence of dedicated adult services (11). In this study, the rate of visits to GPs, at approximately 2 per person year, is nearly identical to that reported from a recent analysis of primary care data of children aged 10–14 years in England (12). The same analysis indicated that the rate of visits increased to approximately 2.5 per person year at age 15–19 years and 3.5 per person year at 20–24 years (12), which corresponds with the GP becoming the co-ordinator of care. We however, found that the rate of visits to GPs declined with age. This may be because we included those in GMFCS levels I-III, who potentially do not report health issues until adulthood, and thus there may be a delay between being discharged from paediatric services and requiring access to adult services via their GP. A study in France similarly observed that the proportion of ambulatory young people visiting a GP was lower in those aged 12–17 years

compared to those aged 6–11 years but increased in the group aged 18 years and older (20). This potential decline in visits to a GP in adolescence may result in the GP being unfamiliar with the young person's medical history and contribute to the lack of continuity of care reported by young adults with CP (6).

We found limited data on service use among young people with other long-term conditions in the UK or internationally. A report from the UK Cystic Fibrosis Registry indicated that 96% of people with cystic fibrosis received an annual review in 2019 (22). Seventy-eight percent of people with cystic fibrosis under 18 received any form of positive expiratory pressure and 66% received an exercise intervention from a physiotherapist (22). Among 175 children with attention deficit/hyperactivity disorder (ADHD) in the UK, use of medical services was higher compared to that in our study, with 59% visiting a hospital, 69% visiting a doctor, and 47% visiting a psychologist in the past 6 months (23). Not unlike our findings, a study of 122 young people aged 12–17 years with autism spectrum disorder in Germany found that the dentist/orthodontist was the most commonly visited professional over 12 months (24). However, unlike our study, the paediatrician was the second most commonly visited professional, with 50% visiting the paediatrician at least once in the past year. Nearly 30% of young people also reported visiting a ASD outpatient clinic in the past year. The higher proportion of young people visiting specialist services may explain why only 27% visited the GP in the past year (24), in contrast to 48% of our sample. Conversely, use of physiotherapy, speech and language therapy, and occupational therapy was higher among young people with CP than ASD (24), which concurs with a study that directly compared therapy use between children with CP and ASD in the United States (25).

In unadjusted analyses, we found that GMFCS level was positively associated with having at least one visit to an occupational therapist and speech and language therapist, and having more visits to a physiotherapist and occupational therapist. This is consistent with previous studies that found severity of motor impairment was positively associated with using physiotherapy, occupational therapy, and speech and language therapy (4, 13). However, in adjusted analyses GMFCS level was only associated with visiting an occupational therapist and nurse. In contrast to a previous study (4), we did not find that children in specialist education settings were more likely to receive services. However, this may be because a relatively low proportion of people in this study attended a special educational needs school. In agreement with a study from the Netherlands (4), unadjusted analyses indicated that young people with learning difficulties were more likely to visit a psychologist or psychiatrist. However, in our adjusted analyses, learning difficulties were only associated with visiting an occupational therapist, and not a psychologist or psychiatrist.

While this study shows the proportion of young people with CP using services is generally low, it does not indicate the needs of young people or unmet need. However, some findings do align with needs reported by a group of young people with CP from the UK, the majority of whom were in GMFCS levels I-III (11). Twenty-two percent of young people reported needs relating to speech (11), 42% report needs relating to bone and joint problems, and 45% report needs relating to eyesight. In this study 21% of young people used speech and language therapy, 40% visited an orthopaedic surgeon, and 38% visited an optician. Although the findings may be used to support future service planning, a significant proportion of ambulatory young people with CP in the UK report unmet health needs, which also need to be considered when allocating resources (11). In particular, between 35 and 60% of young people and parents report that needs are not being met in relation to bone and joint problems, pain, and speech (11). There is also a trend toward an increase in unmet health needs with age, highlighting that people with CP continue to require access to services as they transition to adulthood (11).

Understanding existing service use and factors associated with service use is pertinent in order to identify gaps in health care, and to develop services. Despite the relatively high incidence of CP compared to other childhood-onset conditions, there is limited information regarding service use among young people with CP in the NHS. The breadth of health services accessed by young people with CP demonstrates the complexity of the condition and the need for a co-ordinated approach to developing services. In particular, it highlights the lack of condition-specific specialist services available for young people with CP. Combining this data with currently available and future data on the unmet needs of young people with CP is warranted to inform service development that meets the needs of people with CP throughout their life.

A limitation of this study is that participants were recruited largely through the physiotherapists in the NHS, hence potentially biasing the sample toward individuals who visit physiotherapists frequently. However, not all participants were recruited through the NHS. Further, participants recruited through the NHS received information about the study even if they were not currently attending physiotherapy. Importantly our study has a cross-sectional design and therefore we cannot make inferences regarding the change in service use among young people with CP over time. Findings are also limited to young people with spastic CP in GMFCS levels I-III without severe intellectual disability. For context, ∼92% of people have spastic CP and ∼75% are in GMFCS levels I-III in the UK (16). As the data for this study were collected as part of a trial examining the effects of resistance training, young people were excluded if they had orthopaedic surgery of the lower limbs in the past 12 months, botulinum toxin type A injections or serial casting in the past 6 months. Individuals in receipt of these interventions are likely more frequent users of health services than individuals included in our study, and therefore service use in our sample may be an underestimation of use in the population. Finally, we may not have found associations between participant characteristics and service use because the number of people who visited some services was relatively small.

Despite the relatively high prevalence of CP, there is a stark lack of data on health service use. Data on patterns of use may be helpful for planning future services. Generally the proportion of young people with CP using services was low. In the context of limited resources, data on service use in

combination with data on unmet health needs, may support the reorganisation of services to maximise benefits to young people with CP.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the datasets generated during and/or analysed during the current study are not expected to be made available publicly, as consent was not obtained to publish the anonymised data. Requests to access the datasets should be directed to Jennifer Ryan, jenniferryan@rcsi.com.

ETHICS STATEMENT

Approval was obtained from Brunel University London's College of Health and Life Sciences Research Ethics Committee and the Surrey Borders Research Ethics Committee (ref: 15/LO/0843). Participants 16 years and over provided written consent. Participants under 16 years provided assent, and parents of participants under 16 years provided written consent.

AUTHOR CONTRIBUTIONS

JR, CK, and GL conceived and designed the analysis. JR, GL, NT, and MN collected the data. JR and GL performed the analysis and drafted the manuscript. NT, CK, and MN provided critical feedback and contributed to the final manuscript. All authors contributed to the article and approved the submitted version.

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frontiers in Neurology

CLINICAL TRIAL
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A First Clinical Trial on Botulinum Toxin-A for Chronic Muscle-Related Pain in Cerebral Palsy

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Objective: To test if botulinum toxin-A (BoNT-A) is effective in reducing chronic muscle-related pain in adults with spastic cerebral palsy (CP), as compared to placebo.

Design: A single-center, double-blind, parallel, randomized placebo-controlled trial. The design included an interim analysis to allow for confirmatory analysis, as well as pilot study outcomes.

Setting: Tertiary university hospital.

Participants: Adults with spastic CP and chronic pain associated with spastic muscle(s).

Intervention: Treatment was one session of electromyographically guided intramuscular injections of either BoNT-A or placebo normosaline.

Main Study Outcomes: The primary outcome was the proportion who achieved a reduction of pain intensity of two or more steps on the Numerical Rating Scale 6 weeks after treatment.

Results: Fifty individuals were screened for eligibility, of whom 16 were included (10 female, 6 male, mean age = 32 years, SD = 13.3 years). The randomization yielded eight participants per treatment arm, and all completed the study as randomized. The study was stopped at the interim analysis due to a low probability, under a preset threshold, of a positive primary outcome. Four individuals were treatment responders in the BoNT-A group for the primary outcome compared to five responders in the placebo group ($p = 1.000$). Adverse events were mild to moderate. In exploratory analysis, the BoNT-A group had a trend of continuing reduction of pain at the last follow-up, after the primary endpoint.

Conclusions: This study did not find evidence that BoNT-A was superior to placebo at the desired effect size (number needed to treat of 2.5) at 6 weeks after treatment.

Trial registration: ClinicalTrials.gov: NCT02434549

Keywords: cerebral palsy, spasticity, adult, pain, randomized controlled trial, Botulinum Toxin-A

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STRENGTHS AND LIMITATIONS OF THE STUDY

- Researcher-initiated and academically funded, randomized, placebo-controlled double-blind clinical trial.
- The trial was stopped at the interim analysis due to a low probability of a positive primary outcome (i.e., stopped for futility) resulting in a small sample size.
- This study presents the first data on effect sizes in pain treatment trials in adults with CP.

INTRODUCTION

One particularly important health issue in adults with cerebral palsy (CP) is pain. Pain, often chronic in character, is reported to affect up to 76% of adults with CP (1). Despite the high prevalence of pain, very little, if any, is known on how to address this issue. To the best of our knowledge, no clinical trial has been published where pain reduction has been the primary outcome in adults with CP and in only one case as an exploratory variable (2). The need for studies primarily focused on pain management in CP has been requested as a top research priority by individuals with CP and the involved community (3).

The etiology of the pain in CP is incompletely understood and, most likely, diverse in nature (4). Common clinical explanatory causes include arthropathy, postsurgical pain, neuropathic pain, and muscle-tone abnormalities. Spasticity, a commonly proposed causative factor (4, 5), is present in 9 of 10 individuals with CP (6). Spasticity is characterized by a velocity-dependent resistance of a muscle to stretch (7) and could, hypothetically, cause mechanical stresses on musculoskeletal structures with secondary development of chronic pain. Although spasticity is a quite frequent finding in neurological disorders, many aspects of spasticity differ because of the etiology. These include, but are not limited to, the onset of spasticity after an event, the development or change of spasticity over time, and the possible neuroradiological findings that are considered to correlate with the spasticity. Thus, findings from studies on spasticity reduction in multiple sclerosis or traumatic brain injury, for example, cannot be directly extrapolated onto CP.

For over 30 years, botulinum toxin-A (BoNT-A) has been used extensively to treat spasticity in CP owing to its muscle-relaxing effects (8). After intramuscular injection, BoNT-A acts by blocking the presynaptic release of acetylcholine at the neuromuscular junction causing dose-dependent levels of muscle paralysis (9).

Overall, common indications for BoNT-A have been disorders characterized by muscle hyperactivity such as spasticity and dystonia. There is, however, also high-level evidence for its efficacy in several pain conditions not associated with increased muscle tone including chronic migraine, postherpetic neuralgia, and trigeminal neuralgia (10, 11). Proposed mechanisms of analgesia include altered neurotransmitter release of sensory nerves and central modulatory effects (9–11).

There is clinical experience that some children and adults with CP and pain related to spastic muscle can respond to BoNT-A treatment (12). The evidence base is, however, minimal (13). In the literature, there are two trials in children with CP, comparing BoNT-A with placebo, with pain reduction as the primary outcome. Barwood et al. reported significant advantages in pain reduction, the need for other analgesics, and duration of hospital stay in children with spastic CP who received BoNT-A before soft-tissue hip surgery (14). Will et al., however, reported no differences in pain reduction, quality of life, need for other analgesics, or hospital stay in children with spastic CP who received BoNT-A before skeletal hip surgery (15). Overall, there is a scarcity of studies systematically evaluating interventions for pain in CP including the use of BoNT-A (13).

This study was designed in light of the burden that pain poses to individuals with CP and the lack of evidence-based interventions, as well as the theoretical therapeutic potential of BoNT-A. Given the limited existing information on expected efficacy, the trial incorporated an interim analysis. The sole purpose of this midtrial analysis was to determine whether the trial was likely to fail given its preset parameters. This allowed the study to serve a dual purpose. If the interim analysis recommended continuation of the trial, it would fulfill its confirmatory purpose; if the recommendations was to stop, the trial would provide pilot study data for future trials without subjecting unnecessarily many participants to inclusion in a futile trial.

METHODS

Design

This was an academically initiated and funded single-center, double-blind, parallel, randomized, placebo-controlled trial with an even randomization ratio. The study was approved by the Stockholm Regional Ethical Review Board (2015/271-31/2) and the Swedish Medical Products Agency (2015-000095-10) and was preregistered at ClinicalTrials.gov (NCT02434549).

Study Participants and Setting

The study was conducted at a tertiary referral center in Stockholm, Sweden. Adults with CP were recruited through referrals from clinicians at all care levels in Stockholm and adjacent counties and through public advertisements in newspapers, on patient organization websites and in medical facilities. Inclusion criteria were age $\geq$18 years, spastic type of CP according to Surveillance of Cerebral Palsy in Europe guidelines (16), chronic pain related to spastic muscle [duration $\geq$3 months, intensity $\geq$3 on Numerical Rating Scale (NRS)], and signed informed consent. Exclusion criteria were hypersensitivity to BoNT-A, pregnancy, breastfeeding, treatment with BoNT-A within the last 5 months, changes in muscle-tone–altering medications within the last 2 weeks, clearly degenerative pain mechanisms, and/or intellectual disability or communication impairments that disabled the individual from independently giving informed consent.

Study Timeline

The screening and baseline visit and follow-ups were performed by one team (D.J., K.L.) at the Karolinska University Hospital,

TABLE 1 | Overview of study time points.

Time point	Baseline	Treatment	Posttreatment		
			1 week	6 weeks	10 weeks
Location	**Karolinska hospital**	**Danderyd hospital**	**Telephone**	**Karolinska hospital**	**Telephone**
Team	**D.J., K.L.**	**K.K., B.M.R.**	**D.J., K.L.**	**D.J., K.L.**	**D.J., K.L.**
Variable					
NRS	x		x	x	x
Analgesics	x			x	x
BPI	x			x	x
SF-36v2	x			x	
PGIC				x	
FSS	x			x	
MAS	x			x	
ROM	x			x	
AE	x	x	x	x	x

NRS, Numerical Rating Scale (of pain intensity); BPI, Brief Pain Inventory–Short Form; SF-36v2, Short Form 36 version 2 (Health-Related Quality of Life); PGIC, Patient Global Impression of Change scale; FSS, Fatigue Severity Scale; MAS, Modified Ashworth Scale according to Bohannon and Smith (spasticity); ROM, range of motion; AE, adverse events.

Stockholm. Each participant was interviewed and assessed for muscle-related pain and examined for regional spastic muscles to be targeted for injection. The treatment was given between 0 and 21 days after the baseline visit at Danderyd Hospital, Stockholm, by another team (K.K., B.M.R.). A telephone contact was made 1 week after treatment (D.J., K.L.), and at 6 weeks, there was a return visit to the team where primary and secondary outcomes were assessed (D.J., K.L.). A final telephone follow-up occurred 10 weeks after the treatment (D.J., K.L.). See **Table 1** for a summary of study time points.

Intervention

The treatment consisted of one session of electromyographically guided intramuscular injections of either BoNT-A (abobotulinumtoxin-A, Dysport®, 100 U/mL, up to a maximal total dose of 1,500 U), or normosaline in the corresponding volume (placebo). For treatment details, see **Table 2**, and for injected muscles, see **Table 3**.

Outcomes

Selection of outcomes adhered to guidelines from IMMPACT (Initiative on Methods, Measurement and Pain Assessment in Clinical Trials) (18).

The primary outcome was the proportion of treatment responders, defined as a reduction of pain intensity of two or more steps on the NRS, at 6 weeks after treatment, compared to baseline.

Secondary outcomes were

1) Categories of change in the use of analgesic treatments compared to baseline. This was defined as either increased, unchanged, or decreased at 6 weeks after treatment.
2) The proportion of responders derived as a reduction in the mean pain interference score of ≥1 on the Brief Pain Inventory (19) at 6 weeks after treatment. The pain interference items capture the consequences of pain on general activities, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.

Exploratory outcomes were self-reported health status using the Short Form-36 version 2 (SF-36v2) (20), participant overall satisfaction with the treatment using the Patient Global Impression of Change (PGIC) scale (21), and severity of mental

TABLE 2 | Participant characteristics and treatment details.

	Group allocation	
	BoNT-A	**Placebo**
Participant characteristics		
Participants, *n*	8	8
Age, median (range), years	24 (18–60)	33 (21–50)
Female sex, *n* (%)	5 (63%)	5 (63%)
Subtype of spastic CP, bilateral/unilateral	4/4	7/1
GMFCS levels, I–II/III–IV	6/2	3/5
BoNT-A treatment ≤12 months, *n*	1	2
NRS baseline, median (range)	5 (4–7)	5 (4–9)
Pain interference baseline, [a]mean (SD)	4.7 (1.6)	5.5 (2.6)
Opioid treatment at baseline, *n*	1	1
Treatment		
Target, LE/LE and UE	7/1	8/0
No. of muscles, median (range)	2.5 (1–4)	4 (1–4)
No. of injections, median (range)	13 (8–24)	15 (8–24)
Dose, [b]median (range), U	920 (660–1,500)	—
Dose, [b]median (range), mL	9.2 (6.6–15)	10.2 (4–13.9)

[a] *As assessed on the BPI.*
[b] *Units (U) of Dysport®, 100 U/mL, per participant, as actually given in the BoNT-A group; given as the equivalent volume of normosaline only in the placebo group.*
CP, cerebral palsy; GMFCS, Gross Motor Function Classification System (17); BoNT-A, botulinum toxin-A; NRS, Numerical Rating Scale of pain intensity; SD, standard deviation; BPI, Brief Pain Inventory–Short Form; LE, lower extremity; UE, upper extremity.

TABLE 3 | Injected muscles per participant, with treatment allocation.

Participant	Group allocation	
	BoNT-A	**Placebo**
1	Adductor magnus R Adductor brevis R Adductor longus R Medial hamstrings R	
2		Adductor brevis R and L Medial hamstrings R and L
3		Gastrosoleus R
4	Gastrosoleus R	
5	Medial hamstrings R and L Rectus femoris R and L	
6		Adductor magnus R Adductor brevis R Adductor longus R Rectus femoris R
7	Gastrosoleus L	
8	Gastrosoleus L	
9		Medial hamstrings R and L Gastrocnemius R and L
10		Adductor magnus R and L Adductor brevis R and L Adductor long R and L Medial hamstrings R and L
11		Medial hamstrings L Lateral hamstring L Gastrocnemius L
12	Medial hamstrings R and L Gastrocnemius R and L	
13	Gastrosoleus R and L	
14		Medial hamstrings R and L Gastrocnemius R and L
15		Medial hamstrings R and L
16	Medial hamstrings R Gastrosoleus R Biceps brachii R	

fatigue (e.g., lacking energy and/or feeling of tiredness not restituted by rest) using the Fatigue Severity Scale (FSS) (22). Spasticity was assessed using the Modified Ashworth Scale according to Bohannon and Smith (MAS) (23) and passive joint range of motion (ROM) measured with a goniometer in standardized positions. There were no changes in outcomes or eligibility criteria after trial commencement. See **Table 1** for time points and variables. Any adverse events were recorded continuously.

Sample Size and Interim Analysis

There were no prior data on the expected efficacy of pain reduction in adults with CP. The sample size was calculated with the goal of detecting a proportion of 70% treatment responders in the group receiving BoNT-A and 30% treatment responders in the placebo group. This corresponds to a number needed to treat (NNT) efficacy of 2.5. Statistical power $(1 - \beta)$ was set at 0.8 and α at 0.05. This yielded a sample size of $n = 42$ ($n = 21$ per group).

The interim analysis, performed by an independent Data Monitoring Committee, was included in the protocol with evaluation of one criterion: *stop for futility* (defined as <20% probability of showing treatment superiority). The rationale for the interim analysis was (1) very limited prior data on expected efficacy and (2) limited data on expected inclusion rate. This design allowed the study to fulfill two different purposes: if the study was not stopped at the interim analysis, it would fulfill its confirmatory design of accepting or rejecting efficacy of BoNT-A or, if the study was stopped at the interim analysis, it would be a pilot study for future confirmatory studies.

Randomization, Treatment Allocation, and Blinding

The study statistician prepared a computer-generated treatment allocation randomization list with random block sizes. Participants were entered on the list sequentially at enrollment and identified through their sequential study ID. The study nurse preparing the injections was the only individual (except for the statistician) with access to this list. The study nurse was not involved in any other part of patient care or data collection. At the treatment session, the study nurse prepared the syringes, marked these with study ID only, and brought these to the physician positioned in an adjacent room. Reconstituted BoNT-A is a clear, water-like solution indistinguishable from normosaline on inspection. The treatments were performed in an identical fashion regardless of allocation. Treatment allocation was altogether double-blind: allocation was unknown to study participants, to the screening and evaluating team, and to the team performing the treatment.

Statistical Analyses

The primary and secondary outcomes were analyzed using Fisher exact test of proportions on the categories of response by treatment. Exploratory analysis of magnitude of pain reduction by treatment arms was tested using independent *t*-test with unequal variance. The independent *t*-test was also used to test pretreatment and posttreatment differences in FSS and SF-36v2, whereas spasticity (MAS) and PGIC were tested using Wilcoxon rank-sum test. Differences in proportion of significant improvement in ROM (>10 degrees) were tested using Fisher exact test. Adverse events were prepared descriptively. The significance level was set at $p \leq 0.05$.

RESULTS

A total of 50 individuals were screened for eligibility (**Figure 1**). Sixteen participants were included and randomized (10 female and 6 male participants, mean age = 32 years, SD = 13.3 years), with eight participants in each treatment arm. The most common causes for exclusion were that the individual presented with pain that appeared only infrequently (not daily as per the definition of chronic pain) or that the pain was unrelated to regional spasticity. Other common pain types during the screening process were neuropathic pain and joint pain. The inclusion process is illustrated in **Figure 1**. Baseline characteristics are shown in **Table 2**. There were no significant differences in age,

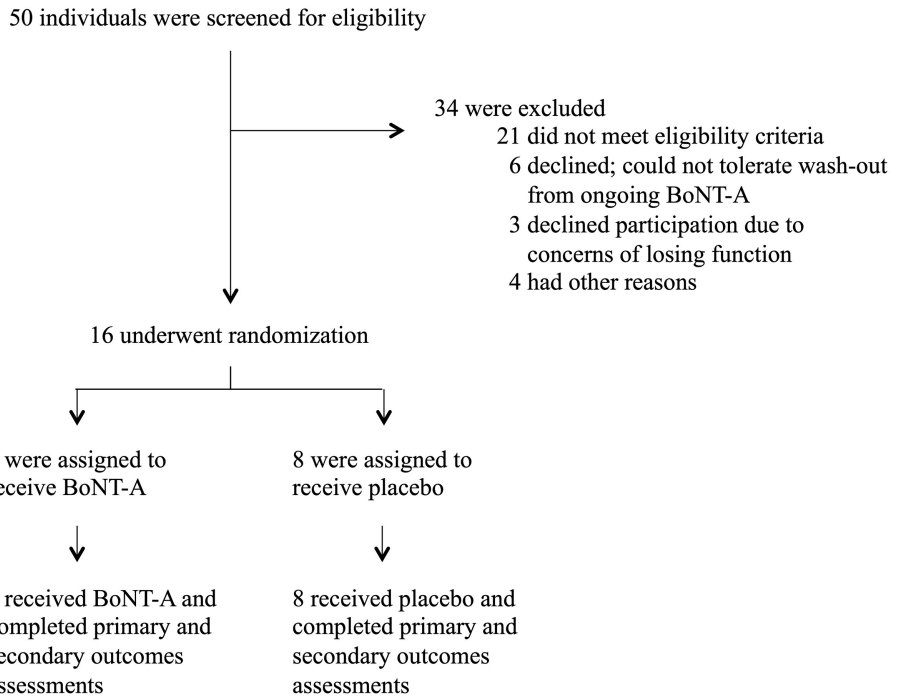

FIGURE 1 | Study patient flowchart. BoNT-A, botulinum toxin-A.

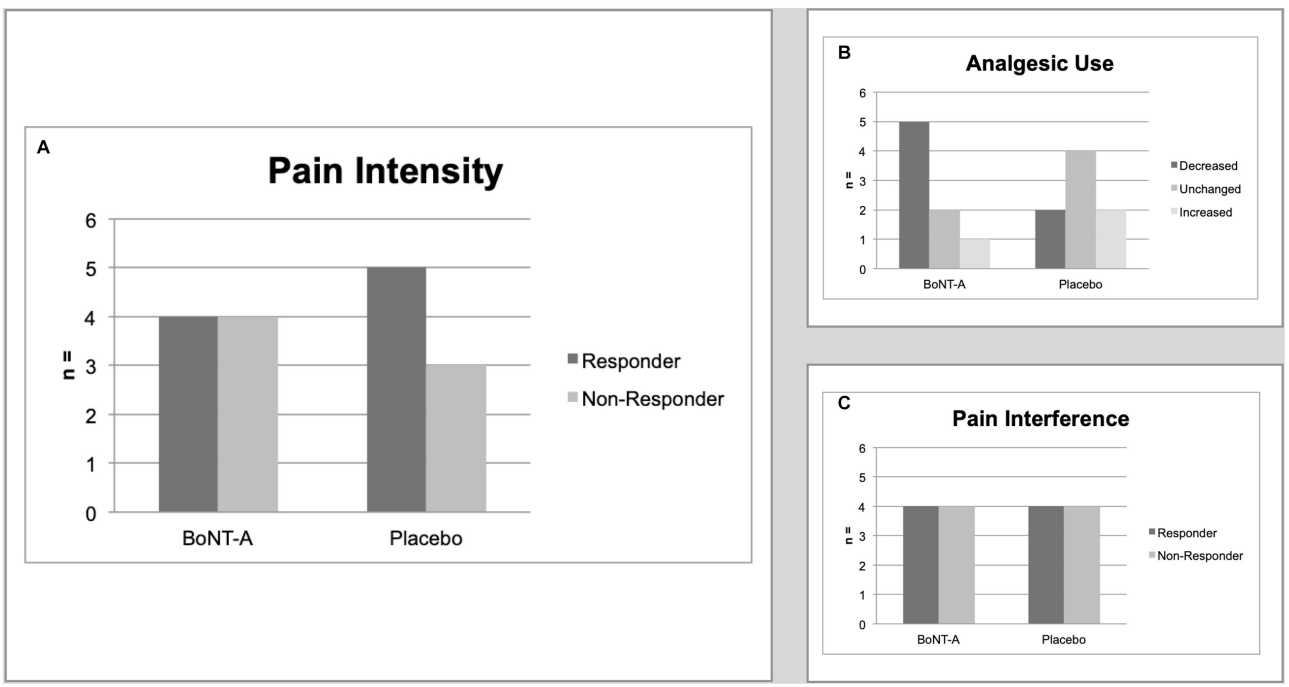

FIGURE 2 | Main study outcomes. **(A)** Primary outcome. The number of treatment responders (defined as a reduction of ≥2 scale steps on the NRS) at 6 weeks after treatment, by treatment group. Test of proportions, $p = 1.000$. **(B)** Secondary outcome. The number of treatment responders (defined as change in categories of analgesics use) at 6 weeks after treatment, by treatment group. Test of proportions $p = 0.429$. **(C)** Secondary outcome. The number of treatment responders (defined as a reduction of mean interference score of ≥1 on the BPI) at 6 weeks after treatment, by treatment group. Test of proportions $p = 1.000$. BPI, Brief Pain Inventory; NRS, Numerical Rating Scale.

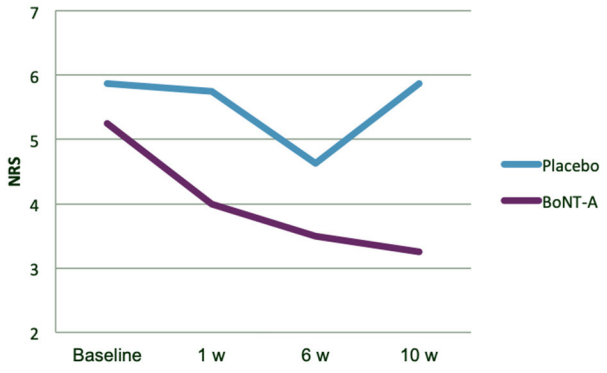

FIGURE 3 | Exploratory analysis of mean pain intensity, by treatment group. BoNT-A, botulinum toxin-A; NRS, Numerical Rating Scale.

sex, pain intensity, or any other baseline characteristic between groups. Inclusion began in September 2015 and was stopped in October 2018. The study was terminated at the interim analysis due to futility of the primary outcome. All randomized participants received the intended treatment and were assessed for the primary and secondary outcomes.

There were four treatment responders and four non-responders in the group receiving BoNT-A for the primary outcome of pain intensity at 6 weeks after treatment as compared to five treatment responders and three non-responders in the placebo group (test of proportions $p = 1.000$) (**Figure 2**).

In the group receiving BoNT-A, five participants had decreased their concomitant analgesic use at 6 weeks after treatment, two were unchanged, and one had an increased use. In comparison, in the placebo group two participants had decreased their analgesic use, four were unchanged and two had increased their use ($p = 0.429$) (**Figure 2**).

Four participants in each treatment arm reported a reduction of $\geq$1 score points on mean pain interference ($p = 1.000$) (**Figure 2**).

Exploratory Analyses

The magnitude of change in pain intensity was subject to *post-hoc* analysis (**Figures 3**, **4**). There was a trend for a continuing reduction of pain intensity in the group receiving BoNT-A not seen in the placebo group (**Figure 3**). At 10 weeks after treatment, the mean and median pain reduction was 2.0 NRS scale steps in the BoNT-A group and 0.0 NRS scale steps in the placebo group (difference $= -2.0$, 95% CI $= -0.60$ to 4.60, $p = 0.121$). Data on individual pain intensity over time are shown in **Figure 4**. There were no significant group differences in pain interference (as assessed with the BPI) at 10 weeks after treatment (data not shown).

There were no significant differences when comparing treatment differences on PGIC, FSS, or SF-36v2 physical component score, mental component score, or bodily pain (**Table 4**).

Muscle spasticity was reduced one or more scale steps in 80% of muscles treated with BoNT-A and in 50% of muscles treated with placebo (**Table 5**). There were no significant group differences in changes in MAS or ROM. There was no apparent correlation (Spearman correlation coefficient $= 0.11$, $p = 0.709$) between being a treatment responder at the primary endpoint and having a significant reduction of spasticity (MAS reduction $\geq$1).

Adverse Events

There was one serious adverse event in which a participant in the placebo group was diagnosed with lymphoma during the study period, a diagnosis that was interpreted as unrelated to study treatments or events. Study-related adverse events were mild to moderate: the most common adverse event was mild pain and discomfort during and immediately after the intramuscular injections, which was reported by five of eight participants (75%) in the BoNT-A group and seven of eight (88%) in the placebo group. Two participants (38%) in the BoNT-A group reported transient focal weakness in treated muscles, which in one case briefly interfered with activities of daily living (moderate severity), whereas no such event occurred in the placebo group.

DISCUSSION

This study is the first randomized controlled trial aimed at reducing pain in adults with CP. As such, the results are of significant value for future interventional studies within this largely unexplored field.

As a general reminder, pain is a complex phenomenon with an often multifactorial background. Pain does not become less complex when it is combined with a childhood-onset disability such as CP. Establishing anchoring points for "zero" pain on the NRS can be difficult if the individual has had lifelong pain and discomfort. Likewise, setting inclusion cutoff values for pain intensity (or pain interference) can be difficult, as adults with CP and pain could have adapted their lives to minimize painful activities. Notwithstanding these difficulties, it is important to find effective treatments through randomized trials.

The primary outcome of responder analysis at 6 weeks after treatment failed to show a difference between BoNT-A and placebo at the effect size corresponding to an NNT of 2.5. This is a reasonable effect size to strive for when comparing with the efficacy of common, less expensive, non-opioid analgesics in other disorders (24). The results obtained do not exclude that smaller effect sizes are possible at 6 weeks after treatment. More interesting is the fact that the results indicate that the (possible) analgesic effect of BoNT-A comes later than what was initially assumed. The mean pain intensity in the BoNT-A group continued to trend downward at the last follow-up (10 weeks). When BoNT-A is used to treat spasticity in CP, the onset of therapeutic effect is within a few days, peaking ~4 weeks after injection, typically with a sustained effect for 3–5 months (8, 25). This was the main basis for the timing of the primary outcome at 6 weeks after injection. Will et al. had the same preconception (primary outcome at 6 weeks) in their recently published trial on preoperative BoNT-A for bony surgery–related pain in children with CP, which failed to show superiority compared to placebo (15). Our results lead to a hypothesis that the supposed effect

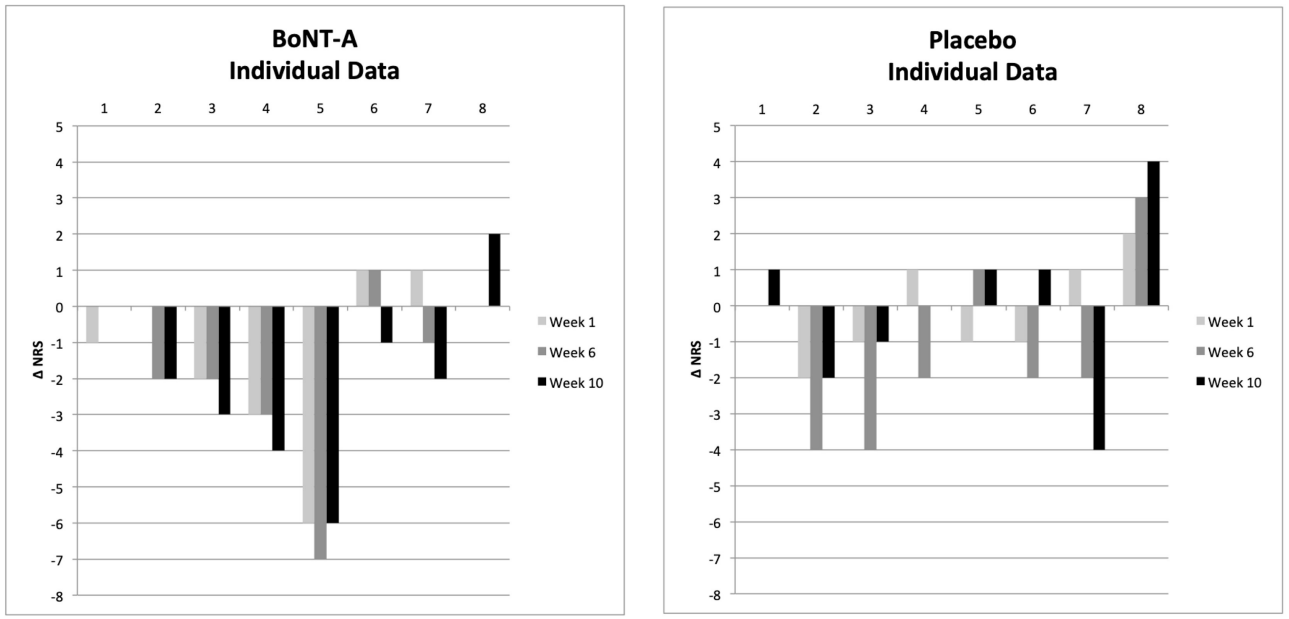

FIGURE 4 | Exploratory analysis of individual patient pain intensity, by treatment group. Δ NRS represents change in pain intensity as compared to baseline. BoNT-A, botulinum toxin-A; NRS, Numerical Rating Scale.

TABLE 4 | Exploratory analyses of patients' global impression of change, fatigue severity, and self-reported physical and mental health at 6 weeks after treatment.

	BoNT-A $n = 8$	Placebo $n = 8$	Statistical test p
PGIC			0.499
Very much improved	0	0	
Much improved	2	1	
Minimally improved	4	4	
Unchanged	1	1	
Minimally worsened	0	1	
Much worsened	1	1	
Very much worsened	0	0	
FSS			
Baseline, mean (SD)	4.0 (1.2)	5.1 (1.6)	
Difference after treatment, mean (SE)	+0.2 (0.4)	−0.2 (0.2)	0.401
SF-36v2			
PCS			
Baseline, mean (SD)	41.2 (7.4)	36.9 (6.5)	
Difference after treatment, mean (SE)	+4.1 (2.5)	+2.4 (2.0)	0.602
MCS			
Baseline, mean (SD)	46.6 (8.6)	39.8 (16.1)	
Difference after treatment, mean (SE)	+3.4 (4.6)	+4.6 (2.8)	0.832
Bodily pain			
Baseline, mean (SD)	37.4 (6.3)	34.1 (8.5)	
Difference after treatment, mean (SE)	+8.2 (3.6)	+3.2 (3.5)	0.329

SF-36v2 results are norm-based scores, normalized to center on 50 for the referral population, with 1 standard deviation = 10. For SF-36v2 norm-based scores, higher scores are better, and lower scores are worse, e.g., an increase in bodily pain scores signifies an improvement.
BoNT-A, botulinum toxin-A; FSS, Fatigue Severity Scale; MCS, mental component score; PCS, physical component score; PGIC, Patient Global Impression of Change Scale; SD, standard deviation; SE, standard error; SF-36v2, Short Form 36 version 2.

TABLE 5 | Differences in spasticity (MAS) and joint range of motion (ROM) after treatment, compared to baseline.

	BoNT-A	Placebo	Statistical test *p*
MAS (scale steps)			0.078
Min	0	0	
Max	−2	−3	
Median	−2	−0.5	
Mode	−2	0	
Proportion ≥-1	80%	50%	
Proportion ≥-2	60%	30%	
ROM (degrees)			
Proportion ≥+10	42%	38%	0.788

The results refer to injected muscles, and ROMs associated with the injected muscles. For MAS, results are presented both as treatment group median, minimum, maximum, and mode difference and the proportion of muscles in each treatment group achieving more than 1 and 2, scale steps reduction on the MAS scale. For ROM, results represent the proportion of ROMs where an improvement of 10 degrees or more was seen, per treatment group.
MAS, Modified Ashworth Scale according to Bohannon and Smith; ROM, (joint) range of motion; BoNT-A, botulinum toxin-A; Min, minimum value; Max, maximal value.

of BoNT-A could be through other mechanisms than spasticity reduction. Pain relief does not necessarily coincide with muscle relaxation when BoNT-A is used for established pain indications (26). For example, compared to placebo, the effect of BoNT-A was more pronounced 3 months after a single injection in one of the first trials on migraine (27). Other than muscle relaxation, modulation of peripheral neurotransmitter release, anti-inflammation, and central nervous system modulatory effects have been proposed as alternative modes of action in BoNT-A–mediated pain relief (9, 26). These modes of action could potentially modulate painful secondary musculoskeletal effects associated with spasticity, mentioned in the introduction. If these are the pathways in play in spastic muscle-related pain in CP, then future research should incorporate longer follow-up with later endpoints. Additionally, it is possible that the placebo effect, which is considerably large in chronic pain trials (28), wanes off before the pharmacological effects of BoNT-A do, also prompting longer follow-up. The placebo effect was apparent on MAS and ROM, where improvements could be seen in both groups with a slight, but not statistically significant, added effect in the BoNT-A group. At the primary endpoint (6 weeks), 80% of the treated muscles in the BoNT-A group showed a significant reduction of spasticity compared to 50% in the placebo group. The distribution of treatment responders at this time point (in slight favor of the placebo group) further puts into question the role of pure spasticity reduction in pain relief in this setting.

Another finding from this study is that certainly not all adults with CP and chronic pain who were screened for eligibility had muscle-related pain associated with spastic muscle. This was the main reason for non-eligibility in the screening process. Other pain modalities were also seen such as intra-articular pain and neuropathic pain, which indicate the need for further investigations on the epidemiology of, and mechanisms behind, chronic pain in adults with CP.

Adverse events were generally mild and related to the injection procedure. Two participants in the BoNT-A group experienced transient focal weakness, a well-recognized possible side effect of this drug.

Study limitations include study size, a consequence of the termination of the trial at the interim analysis. Another limitation is that there are few or no instruments and questionnaires specific to adults with CP. Some items in the generic questionnaires are poorly suited for individuals with childhood-onset disability. This has the potential of causing non-differential misclassifications on those items, which could make the study results less accurate. Development of condition-specific outcome measures would be of value for future studies. Also, the validity of the often-used MAS as a measurement of spasticity has been questioned (29).

CONCLUSIONS

This study was stopped at the interim analysis as there were no indications that BoNT-A was more effective than placebo in reducing chronic muscle-related pain in adults with spastic CP at 6 weeks after treatment. Further trials of longer duration are nevertheless warranted, as the BoNT-A group displayed a trend of continuous pain reduction at the last follow-up. This study can be used as a pilot study in the design of chronic pain trials in adults with CP.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Stockholm Regional Ethical Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DJ coordinated the study, drafted the manuscript, and contributed to the design and the data collection. KL contributed to the design, the data collection, reviewed, and approved the final manuscript for publication. KK and B-MR contributed

to the design, the data collection, and approved the final manuscript for publication. KT conceptualized the design and had senior responsibility for the study, reviewed, and approved the final manuscript for publication. No other individual fulfilled criteria for authorship. All authors contributed to the article and approved the submitted version.

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Aging With Cerebral Palsy: A Photovoice Study Into Citizenship

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Background: Adults with cerebral palsy (CP) may experience an increasing impact of their disability on daily life and this may interfere with their citizenship. Citizenship is a layered construct. Next to formal and theoretical significations, and civil rights acts such as the UN Convention on the Rights for Persons with Disabilities (CRPD), the meaning of citizenship is formed by the person themselves. The present study aimed to gain insight into what citizenship means for adults with CP 40 years or older and what is needed to support and pursue their citizenship to improve person-centered rehabilitation which can facilitate this process.

Methods: Adults with CP (>40 years) without intellectual disability were recruited from medical records of a large rehabilitation center to participate in a qualitative study using the photovoice method. Participants were asked to take photos of objects or life situations that constituted citizenship for them; these photos were then the prompts for the semi-structured interviews that were held face-to-face at their homes. Background and clinical characteristics were gathered using a short face-to-face questionnaire. Data were analyzed through inductive thematic analysis.

Results: Nineteen adults participated [mean age (SD) 57.8 (9.4) years (range 44–79), six men]. From the analysis four themes emerged: (a) Meanings of citizenship; (b) Citizenship: Facilitator and barriers; (c) Paradoxes of support and participation; and (d) Future. Furthermore, next to the ability to participate in society without restrictions, sense of belonging was reported to be an important aspect of "meanings of citizenship." The physiotherapist was perceived as an important health professional to maintain physical activity and deal with the impact of aging with CP on daily activities. Complex healthcare and support services regulations and aging affected citizenship negatively.

Conclusion: Middle-aged and older adults with CP view citizenship as the ability to participate and belong in society. To optimize their citizenship the challenges and individual needs must be seen and supported by person-centered rehabilitation and support services. Simplification of complex healthcare and services regulations can further improve citizenship.

Keywords: cerebral palsy, citizenship, aging, adults, photovoice, qualitative research

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INTRODUCTION

Cerebral palsy (CP) is the largest population in pediatric rehabilitation (1) and has an estimated incidence of 2.0–3.5 per 1,000 live births (2, 3). Seventy-five percent of persons with CP are adults, of which approximately 60% is older than 40 years (4). In the past two decades increasing attention has been paid to the adolescents and (young) adult population with CP, research in the middle-aged and older adult population with CP is scarce (5).

Fatigue and increasing pain are the most common problems reported by adults with CP (2, 6–10). As a result, the perceived impact of CP on daily activities increases with age with mobility and self-care declining (7), and community participation becoming more difficult (11, 12). This increasing impact of aging with CP complicates the delicate balance between demands of daily life and available energy levels and makes demands on the adaptability of adults with CP. This process also affects one's citizenship.

In 2006, the United Nations adopted the Convention on the Rights of Persons with Disabilities (CRPD) (13). The CRPD "is intended as a human rights instrument with an explicit, social development dimension. It adopts a broad categorization of persons with disabilities and reaffirms that all persons with all types of disabilities must enjoy all human rights and fundamental freedoms" (14). As such, it is a civil rights act, advocating equal citizenship for persons with disabilities in terms of autonomy and respect for human diversity. Citizenship is a layered construct: it refers to (the ability to exercise) civil rights, (15) making a contribution to society (often narrowed to paid employment), (16) and to democratic practice and identity (17). These aspects concur with the review by Waldschmidt and Sépulchre, (18) who described three ambivalent citizenship roles for persons with disabilities: social citizenship, autonomous citizenship and political citizenship. The social citizenship role stresses the value of making a contribution to society; those citizens who cannot meet this value can rely on the solidarity of the welfare state. This solidarity, however, can result in stigmatization (e.g., high social control and minimum income) and increases the risk of marginalization. The autonomous citizenship role conflicts with the practice that all citizens are interdependent (i.e., dependent on one another), but in the case of disability, this interdependence is more pronounced and labeled as dependence. This mechanism hampers the autonomous citizenship role. Lastly, the political citizenship role refers to representation and involvement in decision-making. Still, those citizens who utilize healthcare and support services often have little influence in how this support is legislated, implemented and operationalized; hence their political citizenship role is restrained (18). The way in which adults with disabilities experience their citizenship – and how policy environments impact this – may vary internationally due to differences in support and healthcare systems. Dutch adults with disabilities define citizenship as equality and diversity (19). Australian young adults with CP identify four aspects of citizenship: contribution to society, inclusion, equal opportunities, and a context without barriers (20). Yet the lived experiences of older adults with CP regarding their citizenship are unknown.

Citizenship is closely related to rehabilitation outcomes such as community participation and fulfilling social roles (21, 22). However, rehabilitation and support services are not always sensitive to the context, expertise and autonomy of adults with CP (12). Person-centered rehabilitation addresses patients' needs, preferences, experiences or knowledge and cultural values, as well as their history and biography (23). To optimize person-centered rehabilitation and support services for adults with CP, the present study aims to gain insight into what constitutes citizenship for middle-aged and older adults with CP and how they experience their citizenship.

METHODS

Design

This study used a qualitative design, based on the photovoice method applying photos and semi-structured interviews. Wang and Burris described photovoice as "a process by which people can identify, represent, and enhance their community through a specific photographic technique" [(24), p.369]. Photovoice offers an opportunity to share experiences and viewpoints with others whose decisions affect their lives, (25) captures the non-verbal experiences of participants (26) and allows participants to set the interview agenda to ensure that the interview connects with their lived experiences. **Box 1** shows how the photovoice method was applied in the present study. The local Medical Research Ethics Committee Leiden The Hague Delft in the Netherlands granted ethical approval (NL72958.058.20). All participants signed informed consent themselves.

Participants

Adults with CP were recruited at a large rehabilitation center. Eligibility was checked via the electronic medical records. The following inclusion criteria were applied: (1) a documented diagnosis of CP; (2) aged $>$ 40 years; and (3) good comprehension of the Dutch language. The ability to communicate verbally was not an inclusion criterium. Adults were excluded in case of: (1) a documented severe learning disability (IQ$<$70); and (2) severe comorbidity (including depression, severe somatic disorders). On behalf of the research group, an invitation was sent by the participating rehabilitation center to eligible participants. This invitation included an explanation of the study and an informed consent form. The first author was available by phone to answer any questions regarding the study. After the participant signed the informed consent, the first author made an appointment for the interview.

Data Collection

Prior to the interviews, participants were asked during a telephone call to take photos of places, people, situations, objects, or activities expressing their meanings, opinions and/or experiences of citizenship. Participants could also use existing photos, images from the internet, or ask others to take photos for them. These photos were used only as prompts for the interview and were not included in the analyses. In the face-to-face interview lasting 60–90 minutes, participants showed their photos and related them to their meanings of and experiences

BOX 1 | The application of the Photovoice method in the present study.

To understand how middle-aged and older persons with CP experience their citizenship, the photovoice method was used. Photovoice studies are often conducted with persons who belong to traditionally marginalized groups, who are seldom heard. With photovoice, persons become involved and have the chance to share their knowledge and views (25). The first author conducted the interviews, prior to data collection she tested the photovoice method and interview with the last author to become familiarized with this method. In this study, the photographs formed the prompt for the interview and were not included in the thematic analyses.

After receiving the signed informed consent to participate in the study, participants were contacted by telephone to explain and clarify the method, to answer questions and to schedule an interview. Participants had two to four weeks to take these photos. The researcher also signed the informed consent form and sent a copy to the participant.

Participants were asked to take 4–10 photographs of: (1) places, people, situations or objects, activities that were important in their life and that showed how they perceived the world; and (2) examples/situations of how they shaped their citizenship, e.g. in what ways they participated in society.

When it was not possible for a participant to take photographs themselves, it was allowed to use photos or images from magazines or from the Internet, or ask another person to take photos. It was stressed that the images should depict what the participant would have photographed.

Participants were asked to mail the photos to the researcher by email. When received, the photographs were printed and labeled so the participant could easily choose the photos they wanted to talk about in the interview. To avoid any influence of the labeling on the participant's choice for the ranking of the photos during the interview, each photo was assigned to a color. Not all photos were discussed during the interviews, participants were free to say if they had used enough photos to tell their story.

The face-to-face interview took place at their home (one interview was held online due to Covid-19 safety measures). At the start of the interview, all photo were spread out on the table and the participant was invited to choose a photo with which he/she wanted to start. Participants were asked: (1) "What is your story with this photo?"; and (2) "Can you tell me more about how this photo relates to citizenship?."

During the interviews the participants were encouraged to tell more about it by asking open-ended questions about the photo and following the story, to reveal a more in-depth look at what the photo meant to them.

of citizenship. Participants were asked what they would need to optimize their citizenship in the present and in the future. Citizenship was introduced to the participants as a multi-layered construct (**Appendix I**). The interviews were conducted by the first author and were audio-recorded, transcribed verbatim and anonymized for analysis. The interviews were conducted from September 15 to December 9, 2020.

To describe the sample, a short face-to-face questionnaire assessed background characteristics (sex, age, educational level, work / daily activities, living situation, marital status, having children, support at home). Educational level was classified as low (prevocational practical education or lower), medium (prevocational theoretical education and upper secondary vocational education), or high (secondary education, higher education, and university) (27). Work/daily activities were assessed by the question: Do you have a job? [(1) yes, paid; (2) yes, unpaid; (3) no, daycare facility; and (4) no, no job or daycare facility]. Participants were asked if they received support or care at home (no/yes). The first author assessed the clinical characteristics of CP, including gross motor function (Gross Motor Function Classification System; GMFCS), (28) manual ability (Manual Ability Classification System; MACS), (29) and CP type (spastic, non-spastic) and laterality (unilateral, bilateral). Both GMFCS and MACS are a five-level classification system (I = least severely affected to V = most severely affected).

Data Analysis

Thematic analysis was applied. Thematic analysis is a practical, step-by-step tool for recognizing patterns in qualitative data (30). Transcriptions were read and re-read to become familiar with the data. The data were then divided into fragments and inductively analyzed and coded. The codes were organized into groups and a potential theme was formed for each group. It was then verified that the themes and groupings worked for the coded fragments and for the complete data set as well. Saturation was reached when an interview did not reveal new codes. As a final step, the main themes and sub-themes were defined, named and linked. To illustrate the themes, quotes made by the participants that corresponded to the specific theme were used. The first four interviews were analyzed by two authors (VvH, JS), codes were compared, and differences were discussed and converged with the second author (MC). The other interviews were analyzed by one author (VvH), under supervision of JS and SH. Final codes and relations between codes were discussed between VvH, SH and MC. Data were analyzed using Atlas.ti version 9.0 for Windows.

Development of Implementation Materials

Six adults with CP, who did not participate in the study, were asked in three meetings, to reflect on the study results to help future adults with CP and (rehabilitation) professionals with these themes. They proposed how to translate the findings into easily accessible formats. They recommended developing an infographic and making a short YouTube video. Although the development of these implementation materials goes beyond the scope of this study and therefore is not described in this publication, the developed infographic can be found in **Appendix II**.

RESULTS

Twenty-two (35%) of the 63 invited adults with CP (44% men) responded. Three did not participate; one declined, one could not be contacted and one was not able to take photos nor had access to the internet or was willing to ask others to take photos, resulting in 19 participants (32% male) who signed informed consent. They had a mean age of 57.8 years (SD 9.4) and about half of them (47%) had followed higher education. Nine participants (47%) lived with a partner and seven (37%) had children. Twelve participants (63%) had GMFCS and MACS levels I-II. The minority of the participants (37%) had unilateral CP (**Table 1**).

A total of 146 photos were received (mean (SD) 7.7 (2.6); range 4–15). Photos included mobility issues,

TABLE 1 | Characteristics of the sample ($n = 19$) of adults with CP.

	***n* (%) or mean (SD; range)**
Man	6 (32%)
Age in years	57.8 (mean) [9.4 (SD); 44–79 (range)]
40–49 years	5 (26%)
50–59 years	6 (32%)
60–69 years	6 (32%)
70–79 years	2 (10%)
Educational level	
Low	4 (21%)
Medium	6 (32%)
High	9 (47%)
Marital status	
Single/widowed	10 (53%)
Married/cohabiting	9 (47%)
Having children	7 (37%)
Support at home	
No support	8 (42%)
Support	11 (58%)
Employment status	
Paid	7 (37%)
Volunteer	2 (11%)
Daycare facility	2 (11%)
None	8 (42%)
GMFCS	
I	4 (21%)
II	8 (42%)
III	4 (21%)
IV	2 (11%)
V	1 (5%)
MACS	
I	4 (21%)
II	8 (42%)
III	4 (21%)
IV	2 (11%)
V	1 (5%)
CP type	
Spastic	18 (95%)
Unilateral	6 (32%)
Bilateral	12 (63%)
Non-spastic (unilateral)	1 (5%)

GMFCS, Gross Motor Classification System; MACS, Manual Ability Classification System; I - least severely affected, V - most severely affected.

(facilitating or hampering) physical environments, activities at the physiotherapy practice, social activities and hobbies, assistive technology devices (ATD) (e.g., walker, orthopedic shoes, sit ski) and situations or objects at home. Thematic analysis revealed four themes: (a) Meanings of citizenship; (b) Citizenship: Facilitator and barriers; (c) Paradoxes of support and participation; and (d) Future (**Table 2**). Analysis of interview 19 revealed no new codes with saturation in codes reached in interview 18.

TABLE 2 | Summary of the themes and subthemes found in this study of adults with CP.

Themes	Subthemes
Meanings of citizenship	a. ability to participate in society (e.g., work, social activities/relationships) b. a sense of belonging (e.g., reciprocity, caring for others, family life, proud of life-achievements)
Facilitator to citizenship	a. independence and autonomy in support (e.g., agency in support and assistance, independence in mobility, physical activities)
Barriers to citizenship	a. the impact of aging (e.g., physical deterioration, needing more time to accomplish tasks) b. stigmatization (e.g., not being regarded as full) c. life-events (e.g., divorce, incapacitated for work) d. complex and time-consuming laws and regulations (e.g., difficult and multiform application processes, extended processing time)
Paradox of support and participation	a. (in)accessible contexts b. (in)sensitivity of healthcare providers (e.g., (not) listening to their needs, giving standard/personalized advices) c. (un)supportive effects of using devices (e.g., solving the pre-existing problem but sometimes provoking social exclusion and stigmatization) d. pushing on to participate and exhaustion (e.g., social roles take more effort which increases fatigue and exhaustion)
Future	a. not really thought of, yearly check up by rehabilitation specialist

"Meanings of Citizenship"

The meaning of citizenship appeared to be ambiguous. Two participants associated citizenship with laws or social norms such as paying taxes or taking out the garbage. For others, citizenship related to their place in society. Analyses revealed two mutually influencing subthemes of what constituted citizenship for adults with CP: (a) the ability to participate and contribute to society, and (b) a sense of belonging.

> *"And Agenda 22* [of the United Nations] *actually states that everyone, regardless of their disability, has the right to equal treatment. One should be able to participate in society and yes, also be fully mobile. And that's where the Netherlands lags behind quite a bit." (Male, 53 years)*

Ability to Participate and Contribute to Society

Participants valued being able to participate and contribute to society in various ways (e.g., paid work and/or volunteering, sports activities and social activities); this strengthened their sense of belonging. Most participants had or have had paid employment, whether sheltered or not, or attended daycare services. This was considered to be meaningful and contributing to citizenship. Nine participants worked (or had worked) in the health, education or government sectors, three participants worked at utility companies (either banking or telecom) and one was a journalist. Participants felt responsible for their performance in work and/or volunteering and considered their efforts being meaningful for others.

Paid and unpaid work was fulfilling and attributed to citizenship. If one was not able to be involved in paid and unpaid work anymore, due to their handicap or retirement, it took time and energy to adjust to a life without work and find new meaningful daytime activities.

"When I used to work, I was mostly focused on my work. I often did things in the evening, but not every night. And now I have a different life, I don't have to go to work anymore. Well, I found it REALLY hard to stop working." (Female, 79 years)

Employed participants, when energy levels sufficed, were often volunteers as well. A range of voluntary activities was seen, from ad hoc community activities to regular participation in programs or projects. Both being among other people and sharing experiences and joy, but also being able to help and support others in their lives, were the main reasons for volunteering.

"I do the phone circle helpline on Wednesday mornings and it takes three quarters of an hour, which usually works out. And it's nice work." (Female, 65 years)

Sense of Belonging

Being part of social groups (colleagues, friends) was found to be important for participants. It contributed to their life and how they identified themselves. Longtime friendships, sometimes since high school, meant a shared biography. Participants experienced a sense of belonging by caring for others, such as their partner, children, nephews and nieces, or in community activities such as church, Lesbian Gay Bisexual Transgender (LGBT) groups, patient organizations or in a group of former rehabilitation patients.

Sense of belonging also consisted of one's biography, especially the achievements in life related to feelings of pride and self-esteem. Examples of life achievements were having a partner, (still) being able to drive a car, owning a home, sports achievements, but also having made the right choices in life. In general, participants felt that they had a vibrant personality and that they managed to have a good life.

"Well then, if you look back at the ten years since I stopped working, those have flown by for me. In retrospect, then I've done well because that's what this whole choice was about, to have this. So if you may look back, then I think I'll give myself a pat on the back and partly thank my ex who also hammered on it very much to point of annoyance. So then I can also be grateful to him." (Female, 49 years)

Citizenship: Facilitator and Barriers

Citizenship could be both facilitated and hampered. Independence and agency in support formed one facilitator. The following barriers were found: (a) the negative impact of aging, (b) stigmatization, (c) life-events, and (d) complexity of laws and regulations. Some of these subthemes were interrelated (**Figure 1**).

Independence and Agency in Support

Participants indicated that when they felt heard and seen, this contributed to having agency, such as having control over how they were supported and by whom. Independence in mobility (e.g., not being dependent on adapted transport or taxi, and being allowed to go wherever one wanted to go whenever one wanted) allowed participants to socialize with others and attend events with few or no restrictions, resulting in having agency. Agency was also felt when one needed support from their partner, family or friends. However, it seemed in a lesser degree than in situations when no support was required.

"Yes, you are different. Or you walk differently. But am I different? Do I have a problem? No. I don't see it that way. You have to make of it what you want. You have it all in your own hands. One of my hobbies is motorcycling. Well, that's all doable. But you have to do it in your own way, it might be just a little different, just like climbing stairs. You run up stairs, but I use my arms a bit more." (Male, 48 years)

Citizenship was something that required physical effort and it was therefore important to maintain the current level of physical functioning. For most participants, this was the motivation to exercise regularly. Examples of physical activity were cycling and walking. Exercising was performed either individually independently, organized individually, in group form in a gym, or under the guidance of a physiotherapist. Some mentioned that they were fearful of losing walking skills which would then hamper their independence.

Negative Impact of Aging

With aging comes physical deterioration, as manifested in problems with walking and increased spasticity. As a result, participants needed more time to accomplish their daily activities or tasks and had an increased risk of falling. As a consequence, these participants hesitated to join social events and were less confident to move around outdoors. For some participants this led to feelings of loneliness.

"But I absolutely can't complain. At that moment it's a small moment when you see other grannies going to the playground with a grandchild. I think, well, I can't do that. Not just with him. I can't say, I'll take the bike or I'll walk to the playground and I'll let him play." (Female, 62 years)

For several participants increased spasticity impacted speech. One participant experienced that this complicated striking up a conversation with neighbors. If the neighbor himself was hard of hearing, social contact would be even more difficult. Speech impediments complicated being part of the local community.

Stigmatization

The majority of participants felt they were sometimes labeled based on their disability (e.g., spasticity, impaired speech) which then resulted in prejudices about their capabilities. Stigmatization hampered citizenship, for example when participants were not being regarded as normal. Participants were frequently approached by strangers giving them unsolicited advice. These situations felt alienating and marginalizing.

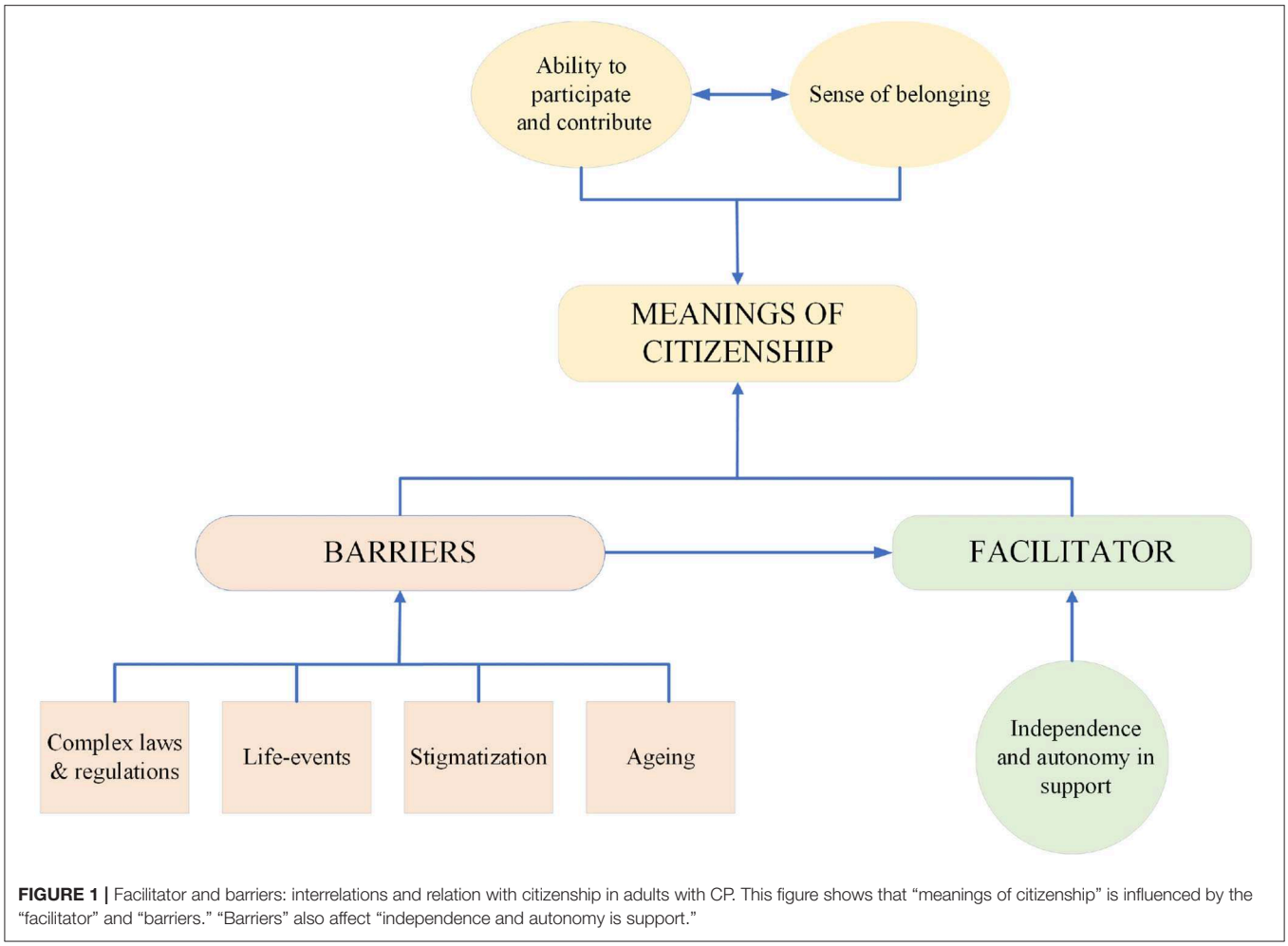

FIGURE 1 | Facilitator and barriers: interrelations and relation with citizenship in adults with CP. This figure shows that "meanings of citizenship" is influenced by the "facilitator" and "barriers." "Barriers" also affect "independence and autonomy is support."

"They think when I walk, well, oh, he must have been drinking again or something. You're being shrugged off, you've been drinking. But they never look past appearances to the inside. But I don't admit to anything either. But I don't know what to say at that moment. It's hard to explain. Yes, if I could I would, but I can't find my words either. But nobody says what I'm good at." (Male, 64 years)

Life Events

Major life events (such as being forced to stop working, death of one's spouse, divorce) were disruptive and significantly affected participants' lives (e.g., reducing their self-esteem or feeling estranged. Life events also impacted the way participants' organized their support; it forced them to apply for more support which combined with a sense of losing control over their lives. At the time of conducting the interviews, the COVID-19 pandemic was present and associated rules (e.g., keeping distance between individuals, closing communal buildings and offices, not receiving visitors) led to increased feelings of loneliness and, in some cases, even feelings of isolation.

"A few years ago I was volunteering at [name company] *and really needed to recover from 4 hours of volunteer work. Then I got a letter from the UWV* [Dutch benefits organization] *that stated that I had to find work because of the new Participation Act. Well, I got so angry because for 20 years I had been doing everything I was able to do, I physically can't do it anymore and now I am required to work. So I phoned them. I explained that I have volunteer work and have to do my daily naps. I'm going to talk to the occupational physician.* [UWV said then:] *You don't have to search anymore and said I would get a benefit* [instead of having to find work]. *And that was a very mixed feeling. Then I really had the feeling of failure in my life, very much so!" (Female, 44 years)*

Complexity of Laws and Regulations

Finally, the complex and time-consuming laws and regulations to apply for assistive technology devices (ATD), healthcare and support services were frustrating for participants. While waiting for ATD, participants felt losing agency over the situation and being at the mercy of the people who granted the approvals as well as the suppliers.

"My work has moved to another building, how stupid can it be, with no parking spaces, ZERO. I had thought, well, two for the management, one for me and one or two for visitors, something like that, but no, ZERO! So I'm now waiting for a parking space from the city council. They've been working on that for over six months

now. There is still no parking space so I go back and forth by cab. That costs me a lot of time." (Female, 58 years)

Paradoxes of Support and Participation

Analyses revealed some paradoxes in the role of support and participation in the way participants experienced citizenship: (a) (in)sensitivity of healthcare providers, (b) (un)supportive effects of using devices, (c) (in)accessible contexts, and (d) pushing on to participate what leads to exhaustion. These subthemes related to citizenship directly as well as via the facilitator and barriers.

(In)sensitivity of Healthcare Providers

Many participants indicated that healthcare providers did not respond to their needs or gave just standard advice. Often this made participants feel unheard and unseen; they felt they were not recognized and that they were stonewalled. On the other hand, participants valued "sensitive" healthcare providers who listened to their needs and pursued an equal relationship. The physiotherapist appeared to be important in the participant's life, not only for guidance to deal with the impact of aging, but also as a life coach. The physiotherapist often had a long-term supportive relationship with participants by listening to the participant's story, empathizing with them and giving advice regarding daily challenges. About half of the participants had both positive and negative experiences with healthcare providers.

"Well no, they didn't seem to care much about what I said. Because I remember that the orthopedist said afterwards 'You were right, so sorry I didn't listen to that'. So they were probably using some kind of protocol or something. I hate that in healthcare.... they thought they knew what I needed."(Female, 56 years)

"When the shoes didn't give the right results, he said, "then we'll go into surgery." He had come up with a plan for that. Then I went to see a neurologist. She saw the plan, we talked about it and she said "I think the orthopedist is looking too much at the foot and not at the whole person." So she recommended that I have a gait analysis. The gait analysis showed that the intended surgery would be counterproductive. I am intensely grateful."(Female, 56 years)

(Un)supportive Effects of Using Devices

Many participants used some form of ATD in their daily lives. ATD (e.g., orthopedic shoes, walker, (electric) wheelchair) improved participants' mobility, which was supportive in engaging in community activities. ATD also positively affected the relationship with the partner, for example, an adapted electric twin bed enabled the participant to sleep with her spouse again. On the other hand, participants were sometimes reluctant to implement ATD in their daily lives to avoid possible stigmatization. For one participant, an ATD improved mobility outdoors, but she was not yet emotionally ready to be seen with this device. Others said they did not want to stand out in society using an ATD. In addition, using an ATD could result in new problems. For example, the use of a walker contributed to stability during walking, but also resulted in a crouched posture while walking which eventually caused back pain. Pain was also caused by an ankle foot orthosis: it improved walking, but hindered bicycling due to chafing of the skin when pedaling.

(In)accessible Contexts

The accessibility of the physical environment affected citizenship. An obstacle free physical environment allowed participants to be active in society without spending too much energy. So, accessibility not only meant *access*, it was also helping participants to maximize the degree of *engagement*.

"…. In Spain they are everywhere in the street, well, every 50 to 100 meters there is a bench. Just a bench. So when I'm in Spain with my brother, he says, 'oh, you want walk to the boulevard?'. Well that's about 10 to 15 minutes. That would be impossible for me to do here." (Female, 62 years)

Conversely, inaccessible physical environments hindered the participants in taking part in society. Participants regularly experienced poor accessibility of public buildings, shops, restaurants and public transport; for example, staircases without handrails, too small toilets or absence of train boarding assistance staff. When confronted with unexpected barriers, some felt disappointed, others felt they were not important enough or felt left out.

"Once there was a very good film we had seen on TV, which was to be shown in the cinema. So I said 'we are going to the cinema' and I call and I say "we use wheelchairs." "Oh, well then it's going to be a bit different. It's not allowed." I say "why not?' Well because of the fire hazard." (Male, 53 years)

Pushing on to Participate and Exhaustion

The pursuit of living a 'normal' life was sometimes accompanied by hard work and intrinsically driven perseverance. In childhood, one was encouraged by parents to both try out and persevere to achieve the next level. Because of the increased impact of CP over time, participants needed more effort to keep up with their life ambitions (e.g., social activities, work) which consequently resulted in even more strain. For some participants, this resulted in burn-out, depression or quitting their job.

"It's okay to say "hey I'm having a bad day or my body hurts", but yeah, I wasn't raised that way. I'm always like, let's put our shoulders to the wheel, I might not always say the right thing now. No, I think I just work harder. I notice that I never cancel an appointment or when I'm so sick or in such pain, I always go, yes, always.... So I think that my drive is even higher than a healthy person."(Female, 49 years)

Future

The participants indicated that they would in the future like to live as independently as possible. This theme related directly to citizenship, as well as via the facilitator and barriers, as well as paradoxes of support and participation. Almost all of the participants said they did not think through what they needed in the future to constitute their citizenship. Several participants said they would probably need more help such as using ATD, and increased use of healthcare and support services. One participant, who had not seen a rehabilitation specialist since his teenage years, had recently consulted a rehabilitation specialist. This consultation provided insight into how CP affects aging (back

pain due to reduced muscular strength and degeneration of spinal vertebrae). It raised awareness that pain was a signal that needed to be addressed to be able to maintain (social) functioning.

> *"And so all of a sudden I came back into the picture. And for me actually, like, I never thought about it because of* [the disability being in] *my legs that my back is wearing out or something. I mean, it turned out that there was joint wear in two vertebrae, this had also been diagnosed years earlier in another hospital with in the lower part of the back,* [lumbar] *four and five I believe it was, and the intervertebral disc, that had joint wear. And in the rehab center here I had a gait analysis done." (Male, 48 year)*

It was also mentioned that the current single family home may eventually become unsuitable, which would mean modifying the house or moving. However, being occupied with daily hassles meant that many participants had not really thought about future needs yet, and were unaware of what to expect.

> *"Yes it's hard to foresee. I tend to put blinders on for a while for that and think "I'll see when it comes." There's no point in worrying about something that might not be necessary." (Female, 56 years)*

DISCUSSION

The present study aimed to gain insight into what constitutes citizenship for middle-aged and older adults with CP and how they experience their citizenship. Findings identified the ability to participate and the sense of belonging as important aspects of citizenship for these persons. Independence and agency in support contributed to citizenship, while aging, stigmatization, life events and the complexity of laws and regulations were perceived as barriers. The paradoxes, such as (in)accessible contexts and using ATD, could either facilitate or hamper citizenship.

Participants sometimes viewed citizenship as an abstract construct. Two participants referred explicitly to civil rights or democratic practices (15, 17, 18). Other aspects, such as contributing to society (16, 18) and identity, (17) were brought up by the vast majority. This partly corresponds to how persons without disability in the Netherlands conceptualize citizenship: [(31), p.221] '"taking responsibility" or "showing responsible behavior," "caring for others," and "being a member of society." They [persons without disability] took citizenship to mean all kinds of social rather than political things." In addition, citizenship was associated with "solidarity", "involvement" and "responsibility" (31). The participants in our study also referred to conditions and situations in which citizenship taking place.

Our findings are in line with Yeung, Passmore and Packer (20) who reported that barrier-free contexts and belonging to society were aspects of citizenship according to young adults with CP. Interestingly, when asked to define participation adults with lifelong conditions report similar themes (32, 33). This raises the question how citizenship and participation relate, both in theory as in the lived experiences. Our results show that middle-aged and older adults with CP consider participation ("ability to participate") as one aspect of citizenship. The International Classification of Functioning, Disability and Health (ICF) (34) defines participation as "involvement in a life situation." Adults with lifelong disabilities consider participation to go beyond life situations: participation is also meaningful contribution, belonging, reciprocity/equality and having agency or being independent (32, 33). However, participation emphasizes the involvement in regular productive activities, (33) which may vary internationally. The adults in our study indicated that they weighed their CP in valuing citizenship, they were proud of what they had achieved in life and were aware that their CP and support services and/or use of ATD were sometimes extra barriers. Citizenship appears to be less normative than participation for adults with CP. The lived experiences of these adults also resonate the various layers of citizenship that relate to the guiding principles of the CRPD (35). Therefore, a citizenship perspective might help health and support service providers to better align with the experiences of their clients.

Taking the lived experiences as a starting point, the citizenship perspective on participation makes sense. For example, a study on the use of ATD reflected on its inclusive and exclusive consequences (36). To better understand these consequences, the concept of "passing as normal" is helpful (37). Passing as normal can be summarized as an adaptive strategy to strive for normality, and in this way to belonging. For example, one participant reflected on the use of an ankle foot orthosis (adaptive strategy) that improved walking (normality) and facilitated citizenship (inclusive consequence). Simultaneously, the use of the ankle foot orthosis hampered riding a bike and caused pain (exclusive consequences). The adults in our study gave many examples of both inclusive and exclusive consequences of support and participation. This, in combination with other barriers such as stigmatization and physical deterioration due to aging, significantly affected the ability to participate and influenced their sense of belonging.

With regard to social citizenship, autonomous citizenship and political citizenship roles, (18) middle-aged and older adults with CP provided diverse examples of how these roles were either facilitated or hampered. Some were politically active or volunteered in patient organizations while others contributed to the local community by organizing festivities or taking part in charity committees. Social and autonomous citizenship roles were frequently hindered by stigmatization, inaccessible contexts, unsupportive healthcare and support services. Contextual factors may be more important than individual characteristics in defining citizenship roles (38).

Because of the increasing impact of CP, (7, 38, 39) healthcare utilization increases with age (40). Nevertheless, health needs often remain unmet (41–43). Adults in this study had mixed experiences with healthcare and support services. Professionals who were sensitive to needs and questions were highly appreciated; these professionals took time to listen to what mattered for the participants. Sensitivity not only resulted in appropriate care delivery (supporting the ability to participate), but also acknowledged the person behind the needs (supporting the sense of belonging) (i.e., person-centered care). The adults in our study appreciated the physiotherapist as a professional to minimize physical deterioration. The physiotherapist also provided coaching in how to deal with the impact of CP on

daily life. A possible explanation for this is that physiotherapy is offered in the community in the Netherlands and that many adults thus have a long-term relationship with the practitioner. In line with other studies, the adults in this study encountered healthcare providers who were not responsive to their needs. Adults with CP often experience incompetence in healthcare providers (12, 39, 44, 45) or experience stigma when they seek support (46). More generally, citizenship of adults with lifelong disabilities has been contested by changes in long-term care policies and accompanied austerities, resulting in fragmentation of healthcare and support services (18, 35, 47). Consequently, people must do more themselves and/or rely on unpaid care (48). Adults with CP are challenged to participate in their community and to find adequate healthcare and support (11, 12, 44).

Strengths and Limitations

The present study included middle-aged and older adults with CP with a wide age range and GMFCS and MACS levels. However, females and highly educated adults were overrepresented. As a consequence, we did not fully capture the lived experiences of males and of adults with lower levels of education, which may be due to the subject matter of the study. In a representative cohort of adults with CP 42% were women, (49) however, of the 63 invited adults for this study about 56% were women. A second limitation of the study is that the explanation to the participants of the different "meanings of citizenship" may have been too directive. In a preliminary study, however, we found that the explanation was necessary because the concept of citizenship was too abstract for the participants making it difficult to take pictures of what citizenship meant to them. By summing up the many layers of citizenship in the explanation, we tried to minimize this influence. Thirdly, differences between background (sex and age) and clinical characteristics (GMFCS and laterality) regarding the found themes could not be explored because of our sample size. Lastly, we did not compare the lived experiences of middle-aged and older adults with and without CP. Therefore it remains unclear whether some findings (i.e., the impact of life events) specifically relate to living with CP or are common for the general population. Our study was not designed to compare adults with and without CP, but to gain insight into the lived experiences of middle-aged and older adults with CP. It is clear that these experiences are not only limited to the CP itself.

Implications for Clinical Practice

Middle-aged and older adults with CP are often confronted with a lack of expertise in health providers, which stresses the need for specialized rehabilitation care for adults with CP. On the one hand there is a need for more centers of expertise, while on the other hand a health provider in the community (e.g., a physiotherapist) can help these adults to deal with the impact of CP and daily hassles. These findings highlight the importance of person-centered rehabilitation care, in which a life-course perspective (50) is adopted and that acknowledges the experiential knowledge of these adults. Person-centered rehabilitation services are encouraged to consider the three citizenship roles (18), to proactively assess contextual barriers, and to assist adults with CP in finding solutions that work for them.

Apart from clinical implications for rehabilitation, municipal services and long-term care policymakers should develop a better sensitivity to the needs of adults with disabilities (including CP). As long-term care systems vary internationally, there are differences in equity in access to support services, (51) resulting in variations in the impact on citizenship of adults with disabilities. Services should aim at better accessible contexts to facilitate the opportunities to contribute to society (social citizenship) and to tailored and person-oriented approaches with short processing times to give room for the diversity of support needs (autonomous citizenship). Political citizenship can be better supported by including persons with disabilities (including CP) in legislation and policy making and support and healthcare delivery. All these recommendations are in line with the UN Convention on the Rights of Persons with Disabilities (CRPD) (34). The reported barriers to citizenship indicate that the implementation of the CRPD requires ongoing attention.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because Transcripts are in Dutch. Although all transcripts are anonymized, Participants' stories contain personal information. Requests to access the datasets should be directed to s.r.hilberink@hr.nl.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Research Ethics Committee Leiden The Hague Delft. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SH and MC contributed to conception and design of the study. VH, MH, and SH wrote the Medical Research Ethical Committee study protocol. VH conducted the interviews. VH, MC, and JS performed the analysis. VH and SH wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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APPENDIX I

Explanations of the multiple meanings of citizenship

Citizenship is a multi-layered construct.

Citizenship means being part of society. Being part of society can be done in different ways. Participating in society can mean working, but also having and maintaining social contacts, sports, clubs, theater, visiting neighbors. Recognizing and feeling a connection with others and society is an important part of citizenship.

Another aspect of citizenship is more juridical. Every person has rights and duties. These rights and duties determine what is allowed and how we behave.

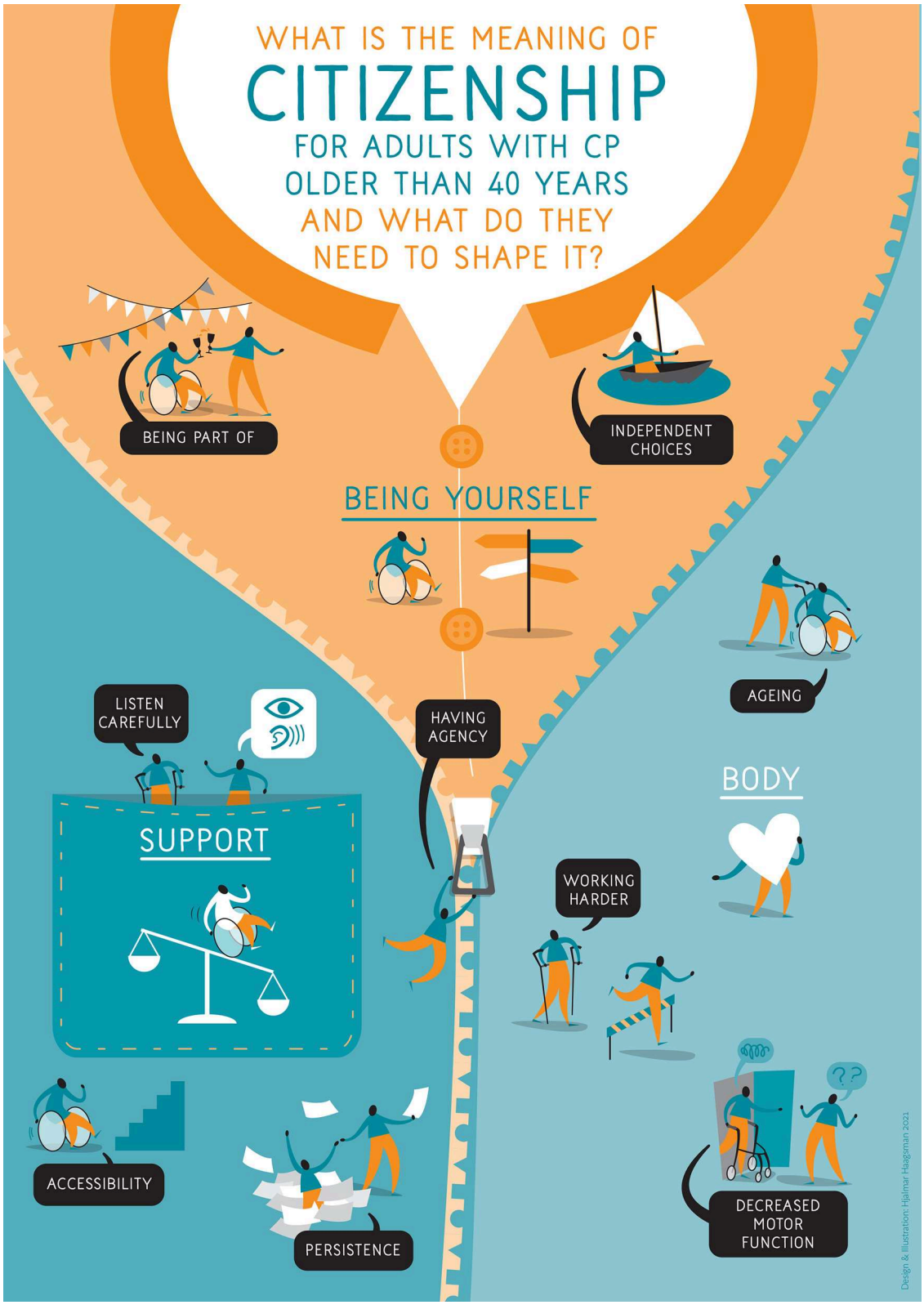
It is also important that ethical origin, religion and physical functioning can result in both differences and similarities in our norms and values. This is your own identity. Because people have different customs, have been brought up differently or do not speak the same language, every person is different. Here, citizenship means dealing with differences.

Finally, people (with and without disabilities) are encouraged to live independently and participate in society in a good way for as long as possible.

We want to study how adults with CP describe their citizenship; what it means to them. We also want to investigate what it takes to keep shaping citizenship. How does being part of society work, what does it make you or how do you feel connected to society. How do you contribute to society, how do you fulfill your civic rights and obligations? How do you deal with being different in today's diverse society. We are interested in how you experience your citizenship and how you have shaped your citizenship throughout your life. For this, we would like to have a conversation with you. The interview can take place at the rehabilitation center or at your home, whichever is most convenient for you.

APPENDIX II

Infographic in English.


WHAT IS THE MEANING OF
CITIZENSHIP
FOR ADULTS WITH CP
OLDER THAN 40 YEARS
AND WHAT DO THEY
NEED TO SHAPE IT?
BEING PART OF
INDEPENDENT CHOICES
BEING YOURSELF
LISTEN CAREFULLY
HAVING AGENCY
AGEING
BODY
SUPPORT
WORKING HARDER
ACCESSIBILITY
PERSISTENCE
DECREASED MOTOR FUNCTION
Design & Illustration: Hjalmar Hagsman 2021

CEREBRAL PALSY

BEING YOURSELF

Citizenship means being in control of your own participation in society. This includes having equal relationships with others. Having ownership over your life. Having opportunities to belong to and take part in society.

BODY

Ageing with CP comes with increasing health issues. Taking part in society demands greater effort. Greater effort may be effective, but could also cause additional challenges to one's health, such as increased fatigue. A balance between keeping the body active and not overstepping its limits is important to continue participation in society.

SUPPORT

Citizenship requires various forms of support. Accessibility (of society, public spaces, stores, restaurants and healthcare services) is supportive. This ranges from an extra handrail in a staircase and wheelchair-accessible restrooms to accessible healthcare and support services. Instead of sticking to regulations and protocols, health professionals should listen to the questions of clients and attend to their needs. The knowledge and experiences of clients must be taken seriously.
Support should be focused on the client and on what the client wants and is able to do.

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The Association Between Kidney Disease and Mortality Among Adults With Cerebral Palsy—A Cohort Study: It Is Time to Start Talking About Kidney Health

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Objective: Recent evidence shows that adults with cerebral palsy (CP) have an increased risk for kidney disease, but nothing is known about how kidney disease integrates with their overall health. To begin understanding the importance of kidney health, the objective was to determine if kidney disease is associated with mortality among adults with CP after accounting for comorbidities common to CP and kidney disease.

Methods: Data from 2016 to 2018 from adults ≥18 years with CP were used from a random 20% sample fee-for-service Medicare database. Kidney disease in 2016 was ascertained as chronic kidney disease (CKD) stages 1–4, end stage kidney disease (ESKD), nephritic and nephrotic syndrome, and renal osteodystrophy. A modified version of the Whitney Comorbidity Index (modWCI) was used, which includes 24 comorbidities relevant to CP and kidney disease. Mortality rate ratio (MRR) through the year 2018 was estimated for each kidney disease and Cox regression estimated the hazard ratio (HR) of mortality after adjusting for demographics, co-occurring neurological conditions, and the modWCI.

Results: Prevalence of kidney disease was 7.3% among 16,728 adults with CP. MRR was elevated for any kidney disease (MRR = 3.14; 95%CI = 2.76–3.58) and most subtypes (MRR = 2.21–3.56; all $p < 0.05$). The adjusted HR of mortality remained elevated for any kidney disease (HR = 1.25; 95%CI = 1.09–1.45) and ESKD (HR = 1.38; 95%CI = 1.10–1.74).

Discussion: Kidney disease, especially ESKD, is associated with mortality among adults with CP independent of comorbidities that are relevant to CP and kidney disease. Findings suggest that nephrology care should be considered as part of routine clinical care for this population.

Keywords: cerebral palsy, kidney disease, mortality, chronic kidney disease, clinical epidemiology

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INTRODUCTION

Cerebral palsy (CP) and kidney disease can have shared etiology, and the CP-related sequela can lead to or exacerbate kidney dysfunction. Pre-mature birth (1), stunted body and organ growth (2, 3), low activity and fitness levels (3, 4), altered body composition (5), and poor hydration status (6) are common among children with CP and are known risk factors for kidney disease. Furthermore, adults with CP have an increased risk for pre-mature development of hypertension, cardiometabolic diseases, and polypharmacy (7–11), which are well-established risk factors for chronic kidney disease (CKD) in the general population (12) and adults with CP (13, 14). Despite the shared etiologic and pathophysiologic pathways, little is actually known about kidney health in CP, especially as children with CP age into and throughout their adult years.

The burden of CKD is immense. Much of CKD is progressive, comes with a high degree of morbidity and mortality, and can lead to end stage kidney disease (ESKD). ESKD treatment and management is incredibly costly and time consuming, and can significantly hinder quality of life (15). Hemodialysis, the most common treatment for ESKD in the US, typically requires ∼4 h per treatment, 3 days per week. Recent epidemiologic studies have begun to document just how common CKD and ESKD are for adults with CP. CKD stages 1–4 and ESKD were found to be 2.4-fold more prevalent for adults with vs. without CP (16). The 4-year incidence rate of advanced CKD (stages 4+) was 83% higher for adults with vs. without CP, which was not explained by their higher prevalence of cardiometabolic diseases (17). While these and other recent studies shed new light on the elevated risk of kidney disease and its risk factors unique to CP (13, 14, 16–18), nothing is known about how kidney disease integrates with overall health or influences unhealthful aging for adults with CP.

A grand challenge in developing clinical care pathways for adults with CP is understanding the appropriate timing for treatment and prioritization, due to the complexity of sorting through the array of diseases that pre-maturely afflict adults with CP (19). It is therefore unknown if treating and managing kidney disease should be prioritized over other health problems, which is in part complicated by clinical assessment of kidney function. For example, cardiovascular disease is 2.5-fold more prevalent for young adults with vs. without CP (20), and cardiovascular-related mortality is 3.2-fold higher for adults with vs. without CP (21). Kidney disease not only gives rise to or exacerbates cardiovascular disease, but many patients with CKD and ESKD will die from cardiovascular disease (22, 23).

However, as kidney disease is often clinically assessed by creatinine-based methods, the low muscle mass in CP leads to the erroneous interpretation that their kidney function is better than it is (18). This false negative can create a masked pathway of unhealthful aging, where the undetected kidney dysfunction over time may be driving, in part, the elevated cardiovascular-related morbidity and mortality burden in CP. Understanding the etiology of multimorbidity will help to develop more targeted prevention and treatment strategies, as well as clinical care guidelines for aging persons with CP.

A recent report found that kidney disease was associated with an increased risk of 2-year mortality among adults with CP (24). However, the association between kidney disease with mortality could not be examined independent of other comorbidities. This calls into question if kidney disease is independently associated with mortality among adults with CP beyond the influence of other comorbidities, or if kidney disease is a "downstream" consequence of aging with CP unrelated to mortality and benign to exacerbating multimorbidity profiles. Addressing this knowledge gap could assist in prioritizing clinical care for adults with CP. Therefore, the objective of this study was to determine if kidney disease is associated with mortality among adults with CP after accounting for comorbidities common to CP and kidney disease.

METHOD

Data Source

Data came from a 20% random sample from the Medicare fee-for-service administrative claims data source including the calendar years 2016–2018. Medicare is a U.S. federal program providing health insurance to adults ≥65 years of age or individuals of any age with ≥1 chronic disability, including CP, or ESKD. Administrative claims data are used for billing reimbursement from healthcare-related visits. Medical conditions can be identified by specific International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes that are attached to claims. A description of data ascertainment of this cohort, variables, and the ICD-10-CM codes used to identify each medical condition, as well as a flow chart of inclusion/exclusion criteria for this cohort have been reported previously (19, 24, 25). Data are de-identified and the University Institutional Review Board approved this study as non-regulated.

Timeline and Sample Selection

The full calendar year 2016 was used to identify adults with CP ≥18 years of age (≥1 inpatient claim or ≥2 outpatient claims in 2016 for CP) that had continuous health plan enrollment in Part A and B from January 1, 2016 to January 30, 2017 to obtain a full 1-year baseline period and at least 30 days of follow-up for mortality, and without missing data for demographics. Data for all medical conditions and demographics were collected from the year 2016, and mortality data were collected from January 31, 2017 to December 31, 2018. The start date of follow-up for all participants was January 1, 2017. This allows for a 1-year baseline period and 2 years of follow-up for mortality.

Mortality

All-cause mortality was ascertained as the number of days from January 31, 2017 to the date of death. Medicare has validated >99% of deaths (26). Participants that did not die during the follow-up were right-censored as the date of drop in health plan enrollment or the end of the study period (December 31, 2018)—whichever came first.

Kidney Disease

Kidney disease was identified by CKD stages 1–4 (ICD-10-CM codes: I12.9, I13.0, I13.10, N18.1-N18.4); ESKD (including CKD stage 5), dialysis, or kidney transplant, hereafter referred to as "ESKD" (ICD-10-CM codes: I12.0, I13.11, I13.2, N18.5, N18.6, N19.x, Z49.x, Z94.0, Z99.2); CKD stage unspecified (ICD-10-CM code: N18.9); nephritic syndrome (ICD-10-CM codes: N03.x, N05.x); nephrotic syndrome (ICD-10-CM codes: N04.x); and renal osteodystrophy (ICD-10-CM code: N25.0). Nephritic and nephrotic syndrome and renal osteodystrophy are not mutually exclusive from one another and CKD or ESKD, but are examined separately in this study. Furthermore, renal osteodystrophy is a complication of CKD, but was included in this early phase of research to understand the association between kidney diseases and CP given the pervasive and profound bone fragility in this population (27, 28).

Comorbidities

A modified version of the Whitney Comorbidity Index (WCI) was used to account for comorbidities relevant to CP and kidney disease. The WCI was recently developed in a privately insured cohort of adults with CP (24) and validated in this Medicare cohort with CP (25) and captures the unique morbidity profiles for adults with CP better than other commonly used comorbidity indices. The WCI is a single variable with a score ranging from 0 to 27 based on the number of WCI comorbidities present. However, the original WCI includes kidney disease, which was removed in this study as kidney disease is the exposure variable. Epilepsy and intellectual disabilities often co-occur with CP and may complicate the association between kidney disease and mortality. The WCI includes epilepsy and intellectual disabilities. However, these were removed from the modified version of the WCI and a new variable was constructed to isolate the effect of these co-occurring neurological conditions on the associations examined in this study. Specifically, mutually exclusive subgroups were assessed by stratifying the cohort as CP only, CP with co-occurring epilepsy but without intellectual disabilities (CP + EP), CP with co-occurring intellectual disabilities but without epilepsy (CP + ID), and CP + EP + ID. Therefore, the modified WCI in this study ranged from 0 to 24.

Statistical Analysis

Baseline descriptive characteristics were summarized for the whole cohort with CP and for subgroups with or without kidney disease. Group differences between those with vs. without kidney disease for descriptive characteristics were tested using the Chi-square test for categorical variables and the independent *t*-test for continuous variables.

Crude mortality rate (MR) with 95% confidence intervals (CI) was estimated for any kidney disease and the specific conditions (e.g., CKD stages 1–4, renal osteodystrophy) separately as the number of deaths divided by the number of person-years, and expressed as per 100 person years. Crude MR ratio (MRR with 95% CI) was estimated for any kidney disease and the specific conditions separately using the group without that kidney disease as the reference. Cox proportional hazards regression models were developed to estimate the hazard ratio (HR with 95% CI) of mortality for any kidney disease and the specific conditions after adjusting for two groups of covariates: model 1—age (as continuous), sex, race, U.S. region of residence, and co-occurring epilepsy and/or intellectual disabilities; model 2—model 1 covariates plus the modified WCI. Clinically relevant interactions were examined for each exposure variable with age, sex, race, and co-occurring epilepsy and/or intellectual disabilities by separate analyses for the main effect and including the product term in the Cox model.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and $p \leq 0.05$ (two-tailed) was used to determine statistical significance.

RESULTS

Of the 16,728 adults with CP, 7.3% ($n = 1{,}215$) had kidney disease, with the majority having any stage of CKD (7.2%) and 2.0% having ESKD. To put that into perspective, the prevalence in 2015 of ESKD for the general population ≥45 years of age was ∼0.5% (29).

Baseline descriptive characteristics for the whole cohort with CP ($n = 16{,}728$) and for the subgroups without ($n = 15{,}513$) and with ($n = 1{,}215$) kidney disease are presented in **Table 1**. Adults with CP with kidney disease were on average 10.1 years older, had a slightly higher proportion of Black adults and CP only, and a higher modified WCI score that was more than double on average (7.2 vs. 3.5) compared to adults with CP without kidney disease (all $p < 0.01$). Adults with CP with vs. without kidney disease had a higher prevalence of all comorbidities in the modified WCI ($p < 0.001$), except for the lower prevalence of epilepsy and intellectual disabilities ($p < 0.05$; **Supplementary Table 1**).

During the 2-year follow-up for a mean (SD) of 696 (126) days and a median [interquartile range (IQR)] of 730 (730–730) days, a total of 1,486 (8.9%) died with a mean (SD) age at death of 61.9 (15.0) years, while 27 (0.1%) were right-censored owing to a drop in health plan enrollment and 15,215 (91.0%) were right-censored owing to being alive by the end of the study period. The follow-up time was similar for the subgroups: without kidney disease, 7.8% (1,213) died with a mean (SD) age at death of 61.0 (15.1) years; with kidney disease, 273 (22.5%) died with a mean (SD) age at death of 65.5 (13.9) years.

Association Between Kidney Disease and Mortality

Any kidney disease (**Figure 1**) and each subtype was associated with an elevated crude MR and MRR (**Table 2**). After adjusting for all covariates, any kidney disease was associated with an elevated HR of mortality (HR = 1.25; 95% CI = 1.09–1.45) (**Table 2**). Among the specific conditions, ESKD was associated with an elevated HR of mortality (HR = 1.38; 95% CI = 1.10–1.74), as was CKD stages 1–4, but this was not statistically significant (HR = 1.16; 95% CI = 0.98–1.38; $p = 0.092$). The other specific conditions had too few outcome cases to perform adjusted analyses.

TABLE 1 | Baseline descriptive characteristics and prevalence of kidney disease for adults with cerebral palsy (CP) with or without kidney disease.

	Entire group (*n* = 16,728)	CP without kidney disease (*n* = 15,513)	CP with kidney disease (*n* = 1,215)
Descriptive characteristics			
Age, mean (SD)	51.0 (15.3)	50.3 (15.1)	60.4 (14.9)*
18–40 years, % (*n*)	27.7 (4,633)	29.0 (4,491)	11.7 (142)
41–64 years, % (*n*)	51.6 (8,631)	52.0 (8,067)	46.4 (564)
≥65 years, % (*n*)	20.7 (3,464)	19.0 (2,955)	41.9 (509)
Sex, % (*n*)			
Male	51.8 (8,662)	51.6 (8,001)	54.4 (661)
Female	48.2 (8,066)	48.4 (7,512)	45.6 (554)
Race, % (*n*)			*
White	80.5 (13,471)	80.5 (12,492)	80.6 (979)
Black	13.0 (2,180)	12.9 (1,993)	15.4 (187)
Hispanic	3.4 (560)	3.5 (535)	2.1 (25)
Asian	1.0 (167)	1.0 (162)	0.4 (5)
North American Native	0.9 (142)	0.9 (137)	0.4 (5)
Other	1.2 (208)	1.3 (194)	1.2 (14)
U.S. region of residence, % (*n*)			
Midwest	27.7 (4,639)	27.7 (4,292)	28.6 (347)
Northeast	21.7 (3,631)	21.9 (3,399)	19.1 (232)
South	34.4 (5,756)	34.3 (5,313)	36.5 (443)
West	16.2 (2,702)	16.2 (2,509)	15.9 (193)
Co-occurring neurological conditions			*
CP only	45.1 (7,542)	44.7 (6,927)	50.6 (615)
CP + EP	15.6 (2,607)	15.7 (2,433)	14.3 (174)
CP + ID	16.6 (2,781)	16.8 (2,610)	14.1 (171)
CP + EP + ID	22.7 (3,798)	22.8 (3,543)	21.0 (255)
Modified Whitney comorbidity index			*
Mean (SD)	4.5 (3.2)	3.5 (2.8)	7.2 (3.6)
Median (IQR)	4.0 (2–6)	3 (1–5)	7 (4–10)
Kidney disease, % (*n*)			
Any kidney disease	7.3 (1,215)		
Chronic kidney disease (CKD)	7.2 (1,202)		
CKD stages 1–4	4.3 (712)		
End stage kidney disease (including CKD stage 5)	2.0 (333)		
CKD stage unspecified	0.9 (157)		
Nephritic syndrome	0.2 (25)		
Nephrotic syndrome	0.1 (10)		
Renal osteodystrophy	0.2 (25)		

SD, standard deviation; IQR, interquartile range.
**p < 0.01 compared to adults with CP without kidney disease.*

Interactions

While there was an interaction between ESKD and race (p for interaction, <0.001) and between ESKD and age (p for interaction, 0.001), the crude MR was similar between White and Black adults with CP with ESKD (interaction due to racial difference for adults with CP without ESKD) (**Table 3**). There were too few mortality cases to perform analyses for adults with ESKD that were Hispanic ($n = 2$), Asian ($n = 2$), North American Native ($n = 0$), and other race ($n = 2$). While the crude MR was higher for older age groups, the relative mortality risk (i.e., MRR) was higher for younger age groups when age was stratified as young, middle-aged, and elderly (**Table 3**).

DISCUSSION

This study found that kidney disease among adults with CP, especially ESKD, was associated with mortality above the influence of other comorbidities relevant to CP and kidney disease. Furthermore, while the mortality rate was

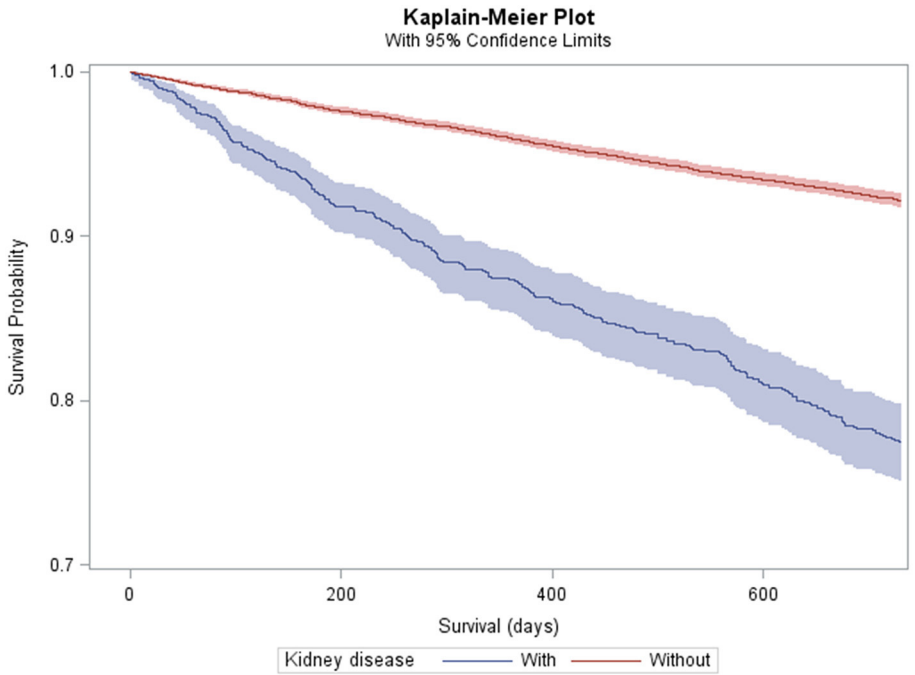

FIGURE 1 | Kaplan–Meier plot and 95% confidence limits (shaded area) of mortality among adults with cerebral palsy with (n = 1,215) and without (n = 15,513) kidney disease.

TABLE 2 | Mortality rate (MR), MR ratio (MRR)*, and adjusted hazard ratio (HR)* of mortality for each kidney disease among adults with cerebral palsy (n = 16,728).

	Mortality cases (n)	MR per 100 person years (95% CI)	MRR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Any kidney disease	273	12.8 (11.3, 14.3)	3.14 (2.76, 3.58)	2.04 (1.78, 2.34)	1.25 (1.09, 1.45)
CKD 1–4	156	12.4 (10.5, 14.4)	2.87 (2.43, 3.38)	1.72 (1.45, 2.04)	1.16 (0.98, 1.38)
ESKD	86	15.1 (11.9, 18.3)	3.38 (2.72, 4.20)	2.54 (2.04, 3.16)	1.38 (1.10, 1.74)
CKD stage unspecified	29	10.2 (6.5, 13.9)	2.21 (1.53, 3.20)	1.54 (1.06, 2.22)	**
Nephritic syndrome	7	16.6 (4.3, 28.8)	3.56 (1.70, 7.49)	**	**
Nephrotic syndrome	2	**	**	**	**
Renal osteodystrophy	6	13.9 (2.8, 25.0)	2.99 (1.34, 6.68)	**	**

CI, confidence interval; CKD, chronic kidney disease; ESKD, end stage kidney disease.
**Reference is the group without that disease; e.g., reference for any kidney disease includes those without any kidney disease.*
***Too few mortality cases for analysis.*
Model 1 adjusted for: age (continuous), sex, race, U.S. region of residence, and co-occurring epilepsy and intellectual disabilities. Model 2 adjusted for: model 1 covariates and the modified Whitney Comorbidity Index.

higher for older adults, the relative mortality risk was higher for younger adults with CP with vs. without ESKD. The latter finding may be due to the higher mortality rate observed among individuals with more vs. less severe forms of CP, who also have an earlier and elevated burden of disease (30).

Inconsistent with the general population (23), this study found that Black and White adults with CP and ESKD had a similar MR (14.5 and 14.8, respectively). A previous study found that race and sex were not associated with incidence of advanced stages of CKD among adults with CP (13), which is also inconsistent with the general population (12). The mechanisms for the lack of race and sex effects on CKD risk and the associated mortality is not clear. One possible explanation is that the biological, socioeconomic, and health disparity differences between race and sex strata may be less disparate in the context of CP, possibly due to the complex unhealthful aging process "over-riding" any biological and/or environmental or social differences that would arise from race and sex, although more research is needed.

The clinical challenge for the field is not so much wrestling with the notion that kidney disease can be deadly for adults

TABLE 3 | Mortality rate (MR), MR ratio (MRR), and adjusted hazard ratio (HR)* of mortality for those with and without end stage kidney disease (ESKD) by race and age group.

	Mortality, % (*n*)	MR per 100 person years (95% CI)	MRR (95% CI)	HR (95% CI)
Race				
White (*n* = 13,471)				
Without ESKD	9.1 (1,196)	4.8 (4.5, 5.0)	Reference	Reference
With ESKD	25.3 (64)	14.8 (11.1, 18.4)	3.11 (2.42, 3.99)	1.29 (0.99, 1.68)
Black (*n* = 2,180)				
Without ESKD	6.4 (136)	3.3 (2.8, 3.9)	Reference	Reference
With ESKD	25.0 (16)	14.5 (7.4, 21.6)	4.35 (2.59, 7.31)	**
Age				
Young, 18–40 years (*n* = 4,633)				
Without ESKD	3.0 (135)	1.5 (1.3, 1.8)	Reference	Reference
With ESKD	13.8 (8)	7.4 (2.3, 12.6)	4.95 (2.42, 10.10)	**
Middle-aged, 41–64 years (*n* = 8,631)				
Without ESKD	7.3 (614)	3.8 (3.5, 4.1)	Reference	Reference
With ESKD	26.5 (45)	15.5 (10.9, 20.0)	4.10 (3.03, 5.54)	1.83 (1.32, 2.54)
Elderly, ≥65 years (*n* = 3,464)				
Without ESKD	18.8 (651)	10.8 (10.0, 11.6)	Reference	Reference
With ESKD	31.4 (33)	19.4 (12.8, 26.0)	1.80 (1.27, 2.56)	0.92 (0.64, 1.33)

CI, confidence interval.

**Model adjusted for age (continuous), sex, race (only for the age group analysis), U.S. region of residence, co-occurring epilepsy and intellectual disabilities, and the modified Whitney Comorbidity Index.*

***Too few mortality cases for analysis.*

with CP, which is well-known in the general population, but rather, a lack of awareness that kidney disease may be a pervasive problem carrying a high mortality risk for adults with CP, which may be masked by the high cardiovascular-related mortality burden (21). Primary care physicians, neurologists, and rehabilitation clinicians are typically the clinical disciplines that frequently interface with adults with CP for their healthcare management. Unfortunately, many clinicians are unaware of the medical complexities of aging with CP, or how to interpret clinical tests that may be altered in CP for appropriate treatment or medical referrals, leading to suboptimal care (31). For example, routine blood work estimates glomerular filtration rate (eGFR), a marker of kidney function, using serum creatinine and equations established from samples without CP. Due to the low muscle mass in CP resulting in low creatinine, the creatinine-based method overestimates eGFR, leading to the interpretation that kidney function is higher than it actually is (18). Clinicians that treat adults with CP are generally unaware of this issue. The clinical consequence is a missed opportunity for a nephrology referral, or early recognition and intervention by primary care physicians to reduce the risk of CKD progression (e.g., controlling hypertension, limiting nephrotoxic drugs). This calls into question just how common and deadly CKD actually is for adults with CP, which may be underestimated in previous studies (13, 14, 17) and this study.

Cystatin c is another biomarker that can be used for eGFR (32), and is less impacted by age, sex, diet, and muscle mass (33). In a non-CP cohort with significant muscle deficits, cystatin c-based eGFR was a better predictor of kidney function than creatinine-based eGFR (34). Although since cystatin c is expressed by adipose tissue (35), more work is needed to identify whether cystatin c or creatinine may be a better biomarker to estimate kidney function in populations with low muscle and high body and regional fat stores, such as CP (3, 5, 36, 37).

Nephrologists are aware of the issues in interpreting eGFR and assessing kidney function in the context of low muscle mass conditions, such as CP. However, nephrology is currently not a routine part of clinical care for individuals with CP at any age. Importantly, advanced stages of CKD are irreversible, costly, and fatal (15), so delaying the onset of CKD and mitigating the progression to advanced stages is essential. Therefore, while more work is needed to deliver targeted clinical recommendations, we urge the clinical community to consider nephrology referrals whenever feasible, which may serve at least as preventive care, so that adults with CP can get the provision of services they may need. We also recommend utilizing albuminuria values in addition to eGFR for CKD prognosis when determining a nephrology referral, as outlined by the KDIGO guidelines (Kidney Disease: Improving Global Outcomes) (38).

It is important to note that CKD and ESKD appeared in this study as the more pervasive kidney issues. While nephritic and nephrotic syndrome and renal osteodystrophy appeared to be rare in this cohort, we felt it was necessary to initially examine these non-CKD kidney conditions, to determine future directions; i.e., whether to focus

future research efforts into CKD and/or other kidney conditions, although some of the non-CKD kidney conditions examined in this study can be acute and comorbid with CKD.

This study has identified for the first time an independent association between kidney disease and mortality in adults with CP; yet, there remains a number of questions in regard to how integrative and deleterious kidney disease is for aging and quality of life for this population. For example, does kidney disease lead to or exacerbate cardiovascular-related morbidity and mortality among adults with CP? Are there distinct etiologies of kidney disease for different segments of the population with CP, such as those born pre-mature, or those with normal birth but develop cardiometabolic disease early in life? If there are different etiologies of kidney disease in CP, does clinical care differ in its approach to prevention and treatment? To address these and other questions, studies are first needed to identify new methods or refinements to existing methods that more accurately capture kidney function for adults with CP (18), which will need to account for the severity of CP.

The limitations of this study must be discussed. First, claims data do not contain information on how diagnoses were made or by whom (e.g., nephrologist). It is possible that many adults with CP that have kidney disease are not being diagnosed, many of which may have died in the current study, leading to conservative estimates of mortality risk associated with kidney disease. Second, each kidney disease was examined separately for those with vs. without that condition, which may have led to more conservative estimates. For example, those with ESKD were compared to those without ESKD, but the non-ESKD group included those with CKD stages 1–4 and the other specific kidney conditions. Third, this study examined prevalent rather than incident kidney disease, which does not provide a sense of the time-related factor of having kidney disease and its impact on organ-specific or overall pathophysiology. It is difficult to make an assumption of how this impacts the mortality risk estimates in this study in conjunction with the first two stated limitations. Fourth, claims data do not contain information on the cause of death. Fifth, severity of CP cannot be reliably ascertained in claims data. Therefore, study findings can be viewed as empirical evidence to contribute to a more general discussion on the need for more nephrology services and research for adults with CP as a whole. However, the WCI estimates the overall disease status, and can be a proxy of severity of CP, which was adjusted for in the analyses. This provides some indication that findings may be present across the CP severity spectrum, but still likely differs in the magnitude and timing by severity of CP. Lastly, as data come from a single, nationwide insurance database, although large, findings may not be generalizable to all adults with CP.

In conclusion, kidney disease is associated with an increased risk of mortality for adults with CP, independent of other comorbidities relevant to CP and kidney disease. Findings provide preliminary evidence for the need to consider incorporating nephrology care as part of routine clinical care for adults with CP. Future research is needed to determine if adopting nephrology care as part of routine clinical care for adults with CP improves detection, increases preventive strategies, and improves kidney and overall health for this underserved population.

DATA AVAILABILITY STATEMENT

The data analyzed in this study was obtained from the Centers for Medicare and Medicaid Services, the following licenses/restrictions apply: The dataset analyzed in this study may be accessed through a contractual agreement with the Centers for Medicare and Medicaid Services following the payment of an administrative fee. Information about these datasets and requests for dataset access can be found at: https://www.cms.gov/Research-Statistics-Data-and-Systems/Research-Statistics-Data-and-Systems.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Michigan Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

DW analyzed the data and wrote the first draft of the manuscript. DW and AO conceptualized, designed the study, approve the final version of this manuscript, and agree to be accountable for the content of the work. AO edited the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.732329/full#supplementary-material

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Bone Mineral Density in Adults With Cerebral Palsy

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Low bone mineral density (BMD) is an emerging health issue in adults with cerebral palsy (CP). This cross-sectional study aimed to describe the characteristics of BMD in adults with CP, and to elucidate the risk factors for low BMD in this population. People aged ≥20 years and diagnosed with CP were recruited from February 2014 to November 2014. We assessed BMD using dual-energy X-ray absorptiometry (DXA) for the lumbar spine, femoral neck, and total femur. Moreover, the body composition was assessed using DXA. We included a total of 87 adults with CP (mean age 42.01 years; 52 men). The prevalence of low BMD was 25.3%. Male sex and age were associated with lower BMD. BMD was significantly lower in the non-ambulatory group than that in the ambulatory group for both lumbar spine and femoral neck. The total fat mass demonstrated a positive correlation with the *Z*-score and BMD for the femur neck and total femur. Body mass index (BMI) and total fat mass were positively correlated with BMD in the lumbar spine, femoral neck, and total femur. However, the Gross Motor Function Classification Scale levels were negatively correlated with BMD at the aforementioned three sites. In conclusion, adults with CP revealed decreased BMD, which was associated with male sex, age, decreased gross motor function, loss of ambulatory function, low BMI, decreased total fat mass, and decreased total fat-free mass.

Keywords: cerebral palsy, osteoporosis, bone density, adult, cerebral palsy - complications

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INTRODUCTION

Low bone mineral density (BMD) is a common health issue in cerebral palsy (CP) (1, 2). Children with CP have lower BMD than their non-disabled counterparts (2). Several causes, including decreased ambulation, insufficient vitamin D or calcium, or anticonvulsants, supposedly induce low BMD in children and adolescents with CP (3). In addition, individuals with CP demonstrate a higher prevalence of fracture (4) and increased risk of fracture with minor stress (5). Fracture impedes ambulation and affects their quality of life (6). This necessitates BMD assessment in adults with CP.

There is little evidence for BMD and its associated factors in adults with CP. Adults with CP are more likely to experience reduced physical activities throughout their lives. Therefore, decreased mechanical force on the bone could decrease the anabolic influence on bone metabolism, besides causing low BMD (7). Several studies have reported on low BMD in young adults with CP. Young adults with CP demonstrate relatively low bone mass in the lumbar spine, hip, and femur (7, 8). In addition, BMD of young adults with CP is associated with ambulatory status (9), types of CP (7), and the Gross Motor Function Classification Scale (GMFCS) scores (10). However, these studies were either confined to non-ambulatory participants (8) or young populations (9–11). Despite

previous reports on correlation between the body mass index (BMI) and higher BMD (9–11), researchers have not investigated the association between body composition and BMD in adults with CP.

Therefore, we aimed to investigate BMD in adults with CP and to investigate the factors related to BMD, including body composition variables.

METHODS

Study Design and Population

A total of 243 adults with CP were identified from outpatient rehabilitation clinics of the participating hospitals and were referred to our clinic. All participants were aged ≥20 years. The exclusion criteria were as follows: (i) inability to understand or respond to our written questionnaire even with the aid of an interviewer, (ii) failure to complete dual-energy X-ray absorptiometry (DXA), or (iii) participation withdrawal prior to data collection. Data were collected between February 1, 2014, and November 31, 2014. All procedures were approved by the institutional review boards of the participating institutions and were in compliance with the guidelines for good clinical practice. All procedures were in accordance with the ethical standards of the institutional and national research committees, and with the tenets of the 1964 Declaration of Helsinki.

Assessment Procedure

We requested the participants to complete questionnaires on their demographics, physical function, and socioeconomic background. A registered nurse measured basic body anthropometries, such as height, weight, and waist circumference. A physiatrist with 15 years of clinical experience in CP (S.H.J.) conducted structured interviews. Clinical variables, such as the GMFCS level and manual muscle strength, were assessed by a physiatrist.

The body composition was assessed using a single DXA machine (GE Lunar Prodigy, Bedford, MA, USA). The lumbar spine and hip joints were imaged and analyzed using the software of the manufacturer. BMD was measured in grams per square centimeter and was represented using *Z*-scores and *T*-scores. The *Z*-score refers to the number of standard deviations, compared with age- and sex-matched individuals. The *T*-score refers to those compared with sex-matched individuals aged 30 years. If the bone mineral density of an individual is lower than the average of the reference group, the *T*-score, and *Z*-score are smaller than 0. A *Z*-score below −2.0 at any of the lumbar spine (LS), total femur (TF), and femur neck (FN) regions was classified "below the expected range for age" (low BMD) (12). Based on the *T*-score, we classified BMD into the following three categories according to the World Health Organization criteria: ≥−1.0, normal; > −2.5 and < −1.0, osteopenia; and ≤ −2.5, osteoporosis. Clinicians recommend treatment for subjects classified as having low BMD or osteoporosis to reduce the risk of fracture and morbidity. *Z*-scores are recommended for adolescents and young adults (12), and most studies have previously reported on *Z*-scores for BMD of adults with CP (7, 9, 10). Therefore, we reported on *Z*-scores as the major outcome. However, we also reported on the *T*-score because ∼ half of the participants were older than 40 years. The total fat mass and total fat-free mass were also assessed using DXA. The availability and cost-effectiveness of analyzing body composition by DXA scans have been reported in previous studies (13, 14).

Statistical Analyses

To identify the difference in *Z*-scores and the proportion of low BMD between groups, we performed a univariate analysis for nominal variables, including sex, ambulatory function, and involvement site. We compared BMD across the GMFCS levels using an analysis of variance. We analyzed the correlation between *Z*-scores and BMD for each site and other clinical information using Pearson correlation analysis. A stepwise selection of variables was conducted using multiple linear regression analysis. The independent variables were those that significantly correlated with BMD. In contrast, BMD of the LS, TF, and FN regions were the dependent variables. All statistical analyses were conducted using SPSS ver. 25.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Study Population

A total of 87 adults with CP were included in this study. The mean age was 42.01 ± 8.29 years (age range, 23–68 years). Of these

TABLE 1 | Characteristics of the study population.

		Total (*N* = 87)
Age	≤40	43 (49.4%)
	>40, ≤50	33 (38.0%)
	>50	11 (12.6%)
Sex	Male	52 (59.8%)
	Female	35 (40.2%)
BMI	<20	24 (27.6%)
	≥20, <25	40 (46.0%)
	≥25	23 (26.4%)
Type	Spastic	31 (35.6%)
	Mixed	28 (32.2%)
	Dystonic	13 (14.9%)
	Dyskinetic	8 (9.2%)
	Ataxic	1 (1.1%)
	Others	6 (6.9%)
Involvement	Bilateral	64 (73.6%)
	Unilateral	20 (23.0%)
	Not known	3 (3.4%)
GMFCS	I	10 (11.5%)
	II	21 (24.1%)
	III	4 (4.6%)
	IV	46 (52.9%)
	V	6 (6.95%)
Ambulation	Ambulatory	35 (40.2%)
	Non-ambulatory	52 (59.8%)

BMI, body mass index; GMFCS, Gross Motor Function Classification System.

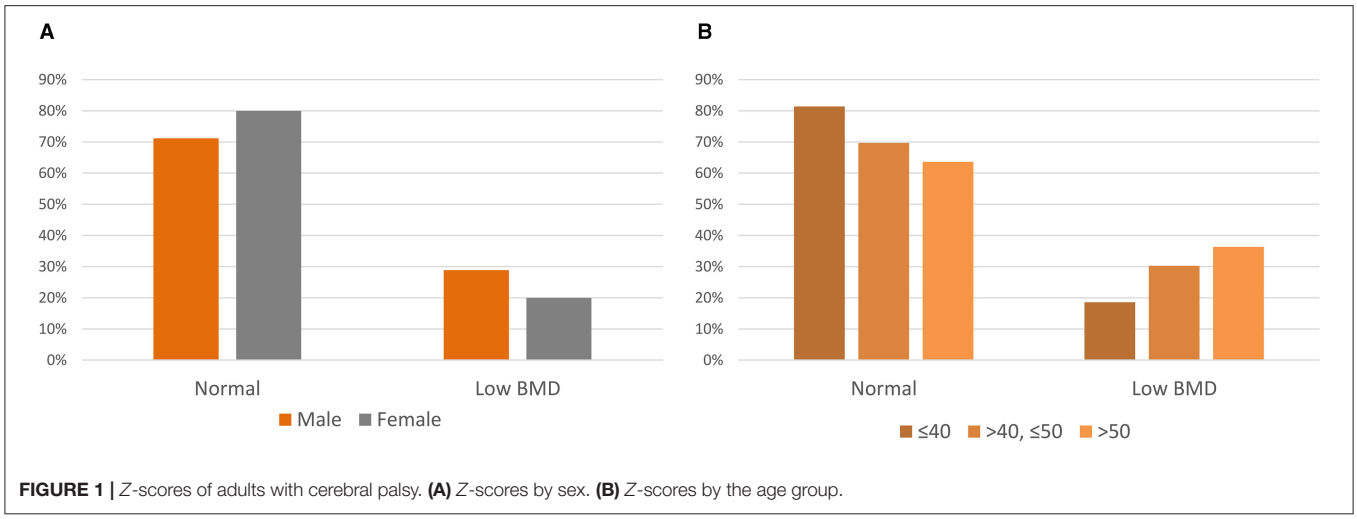

FIGURE 1 | *Z*-scores of adults with cerebral palsy. **(A)** *Z*-scores by sex. **(B)** *Z*-scores by the age group.

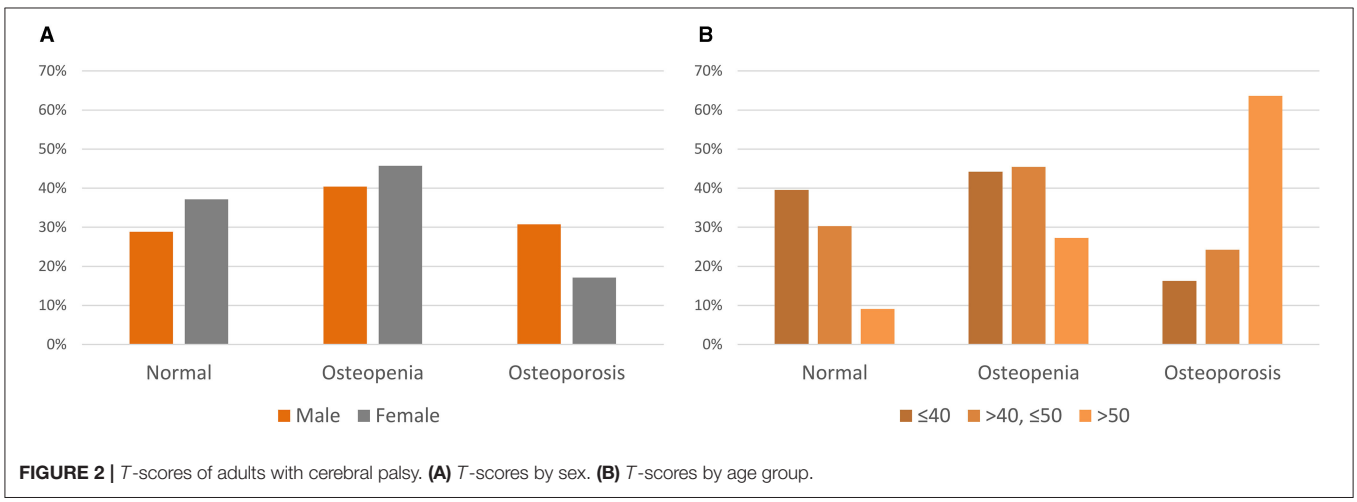

FIGURE 2 | *T*-scores of adults with cerebral palsy. **(A)** *T*-scores by sex. **(B)** *T*-scores by age group.

participants, 49.4% were 40 years old or younger, 38.0% were aged between 41 and 50 years. There were 52 men (mean age: 42.63 ± 9.33 years) and 35 women (mean age: 41.09 ± 6.46 years). The spastic type was the most common type of CP (31 subjects; 35.6%), followed by the mixed type (28 subjects; 32.2%). **Table 1** summarizes the detailed characteristics of the study population.

BMD of the Study Population

The average *Z*-scores were −0.64 ± 1.49, −0.76 ± 1.13, and −0.45 ± 1.21 for the LS, TF, and FN regions, respectively. Twenty-two subjects (25.3%) revealed *Z*-scores below −2.0 at any of the LS, TF, and FN regions. A *Z*-score below −2.0 was observed in 29% of the men and 20% of women (**Figure 1A**). By age group, 19% of subjects were 40 years or younger, 30% were 50 years or younger, and 36% were older than 50 years and had a *Z*-score below −2.0 (**Figure 1B**).

The average *T*-scores were −0.91 ± 1.74, −1.03 ± 1.25, and −1.17 ± 1.37 for the LS, TF, and FN, respectively. Thirty-four (39.1%) and 21 (24.1%) subjects were classified as having osteopenia and osteoporosis, respectively. Osteopenia and osteoporosis were prevalent in 40.0 and 30.8% men and 45.7, and 17.1% women, respectively (**Figure 2A**). Osteopenia and osteoporosis accounted for 44 and 16% of the subjects aged ≤40 years, 45 and 24% in subjects aged ≤50 years, and 27 and 64% in subjects aged >50 years, respectively (**Figure 2B**).

Factors Associated With BMD in Adults With CP

The mean LS *Z*-score was significantly lower in men than that in women ($p < 0.001$). However, *Z*-scores in the FN and TF regions did not display significant differences by sex. There was no significant difference in *Z*-scores between bilateral CP and unilateral CP. Subjects with bilateral involvement had a significantly higher prevalence of *Z*-score below −2.0 than those with unilateral involvement. The *Z*-score was insignificantly different between those with non-ambulatory and ambulatory CP. Non-ambulatory subjects had a significantly higher prevalence of *Z*-score below −2.0 in the LS and FN

TABLE 2 | *Z*-scores and "low BMD" group for sex, involvement site, and ambulatory status.

	N	Lumbar spine		Femoral neck		Total femur	
		Mean ± SD	*Z*-score below −2.0	Mean ± SD	*Z*-score below −2.0	Mean ± SD	*Z*-score below −2.0
Total	87	−0.64 ± 1.49	13 (15.0%)	−0.78 ± 1.21	12 (13.8%)	−0.76 ± 1.13	11 (12.6%)
Sex							
Male	52	−1.09 ± 1.35*	12 (23.1%)*	−0.77 ± 1.22	7 (13.5%)	−0.56 ± 1.08	5 (9.6%)
Female	35	0.04 ± 1.45*	1 (2.9%)*	−0.79 ± 1.21	5 (14.3%)	−1.04 ± 1.17	6 (17.1%)
Involvement site							
Bilateral	64	−0.67 ± 1.63	11 (17.2%)	−0.71 ± 1.30	11 (17.2%)*	−0.69 ± 1.21	10 (15.6%)
Unilateral	20	−0.48 ± 0.98	1 (5.0%)	−0.99 ± 0.81	0 (0%)*	−0.98 ± 0.86	1 (5.0%)
Ambulatory status							
Ambulatory	35	−0.39 ± 1.32	2 (5.7%)*	−0.46 ± 0.95	1 (2.9%)*	−0.57 ± 0.89	2 (5.7%)
Non–ambulatory	52	−0.82 ± 1.64	11 (21.1%)*	−1.00 ± 1.33	11 (21.2%)*	−0.88 ± 1.26	9 (17.3%)
GMFCS							
I	10	−0.15 ± 0.58	1 (10.0%)	−0.04 ± 0.35	0 (0.0%)	−0.06 ± 0.28	0 (0.0%)
II	21	−0.41 ± 0.24	1 (4.8%)	−0.77 ± 0.17	1 (4.8%)	−0.90 ± 0.18	2 (9.5%)
III	4	−0.91 ± 0.42	0 (0.0%)	−0.08 ± 0.46	0 (0.0%)	−0.08 ± 0.19	0 (0.0%)
IV	46	−0.72 ± 0.25	9 (19.6%)	−0.83 ± 0.18	8 (17.4%)	−0.68 ± 0.18	6 (13.0%)
V	6	−1.89 ± 0.33	2 (33.3%)	−1.70 ± 0.86*	3 (50.0%)	–2.40 ± 0.46*	0.5 (50.0%)

SD, standard deviation; GMFCS, Gross Motor Function Classification System.
**p-value < 0.05.*

TABLE 3 | Pearson correlation and *p*-values for *Z*-scores, and bone mineral density.

	Lumbar spine		Femur neck		Total femur	
	Z-score	BMD	*Z*-score	BMD	*Z*-score	BMD
Age	0.046 (0.681)	−0.173 (0.121)	−0.047 (0.67)	−0.283 (0.009)*	−0.021 (0.846)	−0.229 (0.035)*
BMI	0.119 (0.289)	0.447 (<0.001)*	0.083 (0.453)	0.301 (0.005)*	0.218 (0.047)*	0.439 (<0.001)*
WC	−0.045 (0.707)	0.099 (0.410)	−0.028 (0.811)	0.049 (0.676)	0.085 (0.470)	0.159 (0.172)
Total fat-free mass	−0.185 (0.115)	0.028 (0.814)	0.333 (0.003)*	0.332 (0.003)*	0.418 (<0.001)*	0.312 (0.006)*
Total fat mass	0.145 (0.219)	0.4770 (<0.001)*	0.05 (0.665)	0.330 (0.003)*	0.109 (0.346)	0.429 (<0.001)*
Percent body fat	0.337 (0.004)*	0.558 (<0.001)*	0.048 (0.678)	0.306 (0.007)*	0.067 (0.566)	0.401 (<0.001)*

BMD, bone mineral density; BMI, body mass index; WC, waist circumference.
**p-value < 0.05.*

regions. The mean *Z*-score was significantly different between subjects with GMFCS level I and GMFCS level V in the FN ($p = 0.03$) and TF regions ($p = 0.005$). **Table 2** summarizes the *Z*-scores and low BMD.

Table 3 outlines the factors correlated with BMD and *Z*-score of each region. Subjects with a higher body fat percentage displayed higher *Z*-scores in the LS region. In contrast, subjects with higher total fat-free mass and those with a lower GMFCS demonstrated higher *Z*-scores in the FN region. Moreover, those with higher BMI, higher total fat-free mass, and lower GMFCS displayed higher *Z*-scores in the TF region. The waist circumference did not display any correlation with the *Z*-scores in the aforementioned three regions.

Multiple linear regression using stepwise selection revealed total fat-free mass as a significant factor associated with BMD in the TF and FN regions. In addition, sex was significantly associated with BMD in the LS and TF regions (**Table 4**).

DISCUSSION

BMD by *Z*- and *T*-scores of adults with CP was lower than that of the age- and sex-matched general population. Moreover, ∼25% of the participants had a *Z*-score below normal in either the LS, FN, or TF regions. Based on the *T*-scores, 24% of the participants and 64% of those older than 50 years were classified as having osteoporosis. Men, non-ambulators, and bilateral CP were more likely to have lower *Z*-scores. In addition, adults with lower BMI, lower total fat-free mass, lower percent body fat, and higher GMFCS levels had a lower *Z*-score.

This is the first study to investigate the association between BMD and body composition, including BMI, total fat mass, and fat-free mass, in adults with CP. BMI was identified as a significant factor for BMD in the entire region and for the *Z*-scores in the TF region. Total fat mass was another significant factor for BMD in the LS, FN, and TF regions. BMI was

TABLE 4 | Multiple linear regression analysis for *Z*-scores in subjects with cerebral palsy.

	Lumbar spine			Femur neck			Total femur		
	Coefficient	**SE**	***p*-value**	**Coefficient**	**SE**	***p*-value**	**Coefficient**	**SE**	***p*-value**
Intercept	−1.069	1.757	0.545	−3.621	1.343	0.009	−2.841	1.281	0.03
Age	0.025	0.021	0.234	−0.007	0.016	0.667	0	0.015	0.993
Sex[a]	−1.315	0.546	0.019	−0.974	0.42	0.023	−0.178	0.401	0.658
Involvement site[b]	0.131	0.419	0.755	−0.242	0.319	0.45	−0.073	0.304	0.812
GMFCS	−0.38	0.393	0.337	0.157	0.296	0.599	−0.236	0.283	0.407
Ambulatory status[c]	0.873	0.924	0.349	−0.495	0.706	0.485	0.402	0.673	0.553
Total fat mass	0.015	0.023	0.511	−0.025	0.017	0.145	−0.001	0.016	0.936
Total fat-free mass	0.016	0.037	0.676	0.099	0.028	<0.001	0.068	0.027	0.012

SE, standard error; GMFCS, Gross Motor Function Classification System.
[a]Nominal variable (male = 1, female = 0).
[b]Nominal variable (bilateral = 0, unilateral = 1).
[c]Nominal variable (ambulatory = 0, non-ambulatory = 1).
**p-value < 0.05.*

previously reported as an important determinant of BMD in the general population (15), and in subjects with CP (9–11). In the general population, BMD increases with BMI in weight-bearing bones (16). A study reported on a correlation between lower triceps skin-fold measurement, and a lower BMD (17). The triceps skin-fold measurement is an indirect measurement of body fat mass. Thus, our results provided more direct evidence for the association between total fat mass and BMD. Another possible explanation is nutritional status. Individuals with higher total fat mass and BMI supposedly have better nutritional status than those with lower total fat mass or BMI (18). Total fat-free mass was correlated with both *Z*-scores and BMD of the FN and TF regions. Moreover, it was significantly associated with higher BMD in the multiple linear regression analysis of the FN and TF regions. Total fat-free mass could also affect BMD by increasing weight loading. Moreover, it is considered a predictor of muscle strength (19). The force exerted against the bone could affect bone mass and BMD. In addition, a larger total fat-free mass could be interpreted as being of greater physical activity level. A meta-analysis reported that both fat mass and fat-free mass were positively correlated with BMD in the general population (18). Our findings provided similar evidence in individuals with CP. Therefore, BMD maintenance might necessitate maintaining proper fat mass and fat-free mass through nutrition support and physical therapy.

The non-ambulatory subjects displayed a significantly higher prevalence of low *Z*-scores in the LS and FN regions. Bilateral CP revealed a significantly higher prevalence of low *Z*-scores than unilateral CP. In addition, individuals with higher GMFCS levels demonstrated lower *Z*-scores in the FN and TF regions. Ambulatory status is one of the best indicators of weight-bearing status. Several studies reported that BMD of the weight-bearing bone in the CP population is associated with their ambulatory status and GMFCS level. Fowler et al. mentioned that *Z*-scores of the LS, TF, and FN regions were significantly lower in non-ambulatory adults with CP (10). Yoon et al. reported that ambulatory subjects had higher *T*-scores in the hip region, but not in the LS region (11). Our data are consistent with those of previous studies. Higher GMFCS levels and non-ambulatory status were not only associated with lower BMD but also with a higher risk of fractures in children with CP (20). This necessitates regularly assessing BMD in non-ambulatory adults with CP to prevent fractures.

Previous reports on the relationship between age and BMD in adults with CP are inconsistent. According to Fowler et al., *Z*-scores of the LS and hip increased with age in adults with CP (10). However, two other studies reported on no association between BMD and age (8, 11). Our findings shed light on a negative association between BMD and age in adults with CP. However, this correlation is relatively small, thus warranting a larger cohort to elucidate these relationships.

The mean *Z*-score was −0.64 and ∼25% of adults with CP had *Z*-scores below the expected range for age and sex. In previous studies, the prevalence of low *Z*-scores was reportedly >58% (8) and 50% (9) in the LS region. Fowler et al. (10) mentioned that the average *Z*-scores were −1.40, −1.36, and −1.02 for the LS, TF, and FN regions, respectively. Other studies reported average *Z*-scores of −2.37 (8) and −1.69 (9) in the LS region. The average *Z*-score in this study was higher than that in other studies. Our findings also revealed a higher average *T*-score. Yoon et al. (11) reported an average *T*-score of −1.08 and −1.50 for the LS and TF regions, respectively, by investigating 35 subjects with CP (mean age, 35.18 ± 1.87 years). This difference might account for the differences in the study cohort. Considering the enrollment of adults in nationwide organizations for disabled people, the study population might have had a higher level of physical activity, and better medical status than those in other studies.

This study had several limitations. First, the study population did not represent the entire CP population in South Korea. Second, considering the cross-sectional design, we could not investigate the causal relationship between the clinical characteristics and low BMD. Third, we did not investigate the longitudinal course of BMD and events, including falls and fractures after recruitment. Lastly, we could not collect medication histories from the participants, such as anticonvulsive medications. Therefore, we could not establish a direct association between each factor and the risk of fracture.

In conclusion, adults with CP had a lower BMD than the sex- and age-matched general population. Those with CP and lower BMI, lower total fat-free mass, and lower total fat mass were more likely to have lower *Z*-scores. Decreased BMD in adults with CP was associated with male sex, age, decreased gross motor function, and the loss of ambulatory function.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the datasets generated during and/or analysed during the current study are not expected to be made available publicly, as consent was not obtained to publish the anonymised data. Requests to access the datasets should be directed to Se Hee Jung, ideale1@snu.ac.kr.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Seoul National University Boramae Medical Center Institutional Review Board. All subjects provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SJ conceived and designed the study, collected the data, interpreted the data, and revised the manuscript for intellectual content. JW performed the analysis and drafted the manuscript. Both authors contributed to the article and approved the submitted version.

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Prioritizing a Research Agenda of Transitional Care Interventions for Childhood-Onset Disabilities

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Transitional care interventions have the potential to optimize continuity of care, improve health outcomes and enhance quality of life for adolescents and young adults living with chronic childhood-onset disabilities, including neurodevelopmental disorders, as they transition to adult health and social care services. The paucity of research in this area poses challenges in identifying and implementing interventions for research, evaluation and implementation. The purpose of this project was to advance this research agenda by identifying the transitional care interventions from the scientific literature and prioritize interventions for study. A modified-Delphi approach involving two rounds of online surveys followed by a face-to-face consensus meeting with knowledge users, researchers and clinician experts in transitional care (n = 19) was used. A subsequent virtual meeting concluded the formulation of next steps. Experts rated 16 categories of interventions, derived from a systematic review, on importance, impact, and feasibility. Seven of the 16 interventions categories received a mean score rating of ≥7 (out of 10) on all three rating categories. Participants then rank ordered the reduced list of seven interventions in order of priority and the top four ranked interventions advanced for further discussion at a consensus meeting. Using the Template for Intervention Description and Replication (TIDieR) checklist as a guide, the participants identified that a study of a *peer system navigator* was worthy of future evaluation. This study highlighted that transitional

care interventions are complex and multifaceted. However,the presence of a peer to support system navigation, advocacy and individual and family education was considered the most ideal intervention addressing the current gap in care. Future research, which aims to engage patients and families in a co-design approach, is recommended to further develop this intervention.

Keywords: transitional care, intervention prioritization, childhood, disability, modified Delphi

INTRODUCTION

Youth living with childhood-onset disabilities may experience challenges during the transition process from pediatric to adult health and social services. Adolescence in itself is an important period of transition involving multiple changes and choices related to identity, sexuality, education and work (1). Living with chronic disabilities can further complicate this developmental period. The process of transition to adult care is often complex, multifaceted and maintaining continuity of care requires considerations beyond the medical needs and preparation for new healthcare environments (2, 3). Adolescents and young adults with disabilities are at higher risk of poor mental health outcomes such as anxiety disorders, depression, suicidal ideation, and suicide attempts (4–9). As adults, they face the risk of restricted participation in many aspects of community integration such as housing, intimate relationships and employment (10). Psychosocial, educational, residential, vocational and recreational needs are therefore important factors to consider during transition, and have more recently been recognized as important determinants of health and critical components of a holistic strategy for healthcare transition (2, 11). Without multi-faceted and multi-disciplinary approaches, negative outcomes can include diminished quality of life and unnecessary stress on healthcare systems (12–14).

Transitional care interventions (TCIs) are a wide range of services and interventions known to promote continuity of care, reduce significant detrimental physical and mental health outcomes, and improve the quality of life of adolescents and young adults living with childhood-onset disabilities as they age. Examples of TCIs include preparing patients and families for transition readiness, promoting information continuity amongst health professionals or case management services through the transition process (15). The paucity of research in this area poses challenges in terms of identifying and prioritizing interventions to implement and evaluate. Where evidence does exist on TCIs, most evaluation studies are descriptive in nature (15), and are lacking in rigorous design (16), valid and reliable instruments for evaluation (17) and external validity (18). Additionally, the high variability across practice settings and the siloed nature of health and social services have led to issues with reliability and transferability across settings and contexts (15). These considerations leave researchers and clinicians struggling to identify the best next steps in the selection, implementation and evaluation of TCIs for adolescents and young adults with childhood-onset disabilities. To address this gap in knowledge, our objective was to prioritize the TCIs found in the literature and then identify one intervention best suited for a future relevant, high-quality, and holistic research agenda.

METHODS

We conducted a modified Delphi (19) with knowledge users, researchers, and clinician experts in transitional care to narrow a set of previously identified TCIs (15). Specifically, our process included two rounds of online surveys, one large group face to face consensus meeting and a virtual planning meeting to prioritize TCIs for future evaluation and create a plan for execution. This study was approved by the University Health Network Research Ethics Board (REB 19-5746) and all participants provided informed consent prior to taking part in the study.

Participant Recruitment

A snowball sampling approach (20) was used to recruit local, national and international experts in transitional care for youth with childhood onset disabilities. Following recommended practices in Delphi methodology for size of expert groups (21), and to account for potential attrition, we recruited participants on a rolling basis with an aim of approximately 20 and achieved participant diversity in discipline, role and region.

Modified Delphi Approach

The Delphi method is a process whereby multiple rounds of feedback from a group of experts are solicited (22). Repeated surveys are conducted and after each round, responses are aggregated and shared with the group before the next round. This allows experts to adjust their answer based on how they interpret the group response, and the final outcome is meant to reflect a true group consensus (22). The *modified* Delphi mirrors the regular Delphi in using repeated surveys to arrive at consensus. Where it differs from convention is that it begins the process with pre-selected items drawn from earlier work, rather than using the experts to brainstorm on a particular subject (23). In our modified Delphi approach, two rounds of feedback were conducted. The surveys were informed by a systematic review conducted by the research team, predominantly focused on neurodevelopmental disorders and their associated complexities (15). The face-to-face consensus meeting was convened to prioritize one intervention for future evaluation. A core research group met virtually to further plan the implementation of a future evaluation.

Modified Delphi Surveys

Both survey rounds were conducted using *Hosted in Canada Surveys* (https://www.hostedincanadasurveys.ca). Consistent with healthcare-oriented modified-Delphi processes, the multi-round surveys employed rating and ranking exercises (24).

In Round 1, experts were presented with a list of 16 categories of TCIs, based on a systematic review conducted by the research team (15). Experts were asked to rate their level of agreement on a Likert-scale from 0 = strongly disagree to 10 = strongly agree on statements related to importance, impact of the intervention, and feasibility of the intervention for a future evaluation. We deemed these criteria as central to developing an actionable research agenda. Experts were also given the option to comment on the particular interventions listed and add intervention categories not identified in the list. Mean scores out of 10 for each statement, under each of the interventions were calculated and open-ended answers were scanned to identify any new interventions. An a-priori cut-off mean score of >7 on each rating category was set to narrow the list and move a subset of interventions to Round 2.

In Round 2, experts were presented with the condensed list of interventions and asked to rank order from most to least important. As with Round 1, experts were asked to comment on the particular interventions listed and add any other intervention categories not identified. A total score for each intervention listed in the Round 2 survey was calculated by assigning a reverse weighting. Each experts' rank order was scored and all scores for a particular intervention were summed to create an overall score for that intervention (25). Open-ended answers were scanned to identify new intervention categories as well as identify issues to consider regarding the prioritization of particular interventions.

Consensus Meeting

We then hosted a face-to-face, 1.5-day consensus meeting to serve as an opportunity to deliberate and finalize the top priorities for TCIs identified from the modified Delphi, as well as to support discussion in developing a research agenda. A facilitator with expertise in group facilitation and extensive knowledge of healthcare delivery systems supported the consensus meeting. A research assistant captured all key discussion points in meeting notes.

The meeting commenced with a presentation of the results of the systematic review that informed the modified Delphi process followed by a presentation of the results of the two rounds of surveys for the modified Delphi. A recorded presentation from a young adult with cerebral palsy and lived experience with transitional care challenges was shared to highlight the importance of first-person considerations.

Experts discussed and developed consensus for the most significant TCIs. Specifically, the meeting focused on defining the top four TCIs identified in the modified Delphi, discussing the implementation considerations of these interventions, and devising a priority research agenda and key steps for its advancement. Specifically, the Template for Intervention Description and Replication (TIDieR) checklist and guide (26) was used as a tool to structure discussions and ensure the components of the interventions were comprehensively documented. In small groups, meeting participants described items 1 to 7 on the TIDieR checklist of one intervention. These components were then presented back to the larger group for discussion. The small groups then switched interventions and further described items 8 to 12 on the TIDieR checklist of the intervention. Large group discussions were repeated followed by reflecting on optimal research questions for their assigned intervention based on the four interventions. The consensus meeting concluded with discussing a focused research agenda based on one intervention.

Virtual Research Planning Meeting

Lastly, with a priority TCI identified, a virtual meeting was held amongst experts who indicated an interest in further discussing and refining the proposed research including study focus and methods. The experts were provided with a summary of the consensus meeting and then participated in a consensus discussion around next steps for a study of the prioritized intervention.

RESULTS

In total, 19 out of 29 invited experts in TCIs consented to participate in the modified Delphi process. This included individuals working within pediatric and adult specialty care medicine, psychology, social work, occupational therapy, physical therapy, kinesiology, therapeutic recreation and nursing; individuals working in appropriate health, social, and non-governmental organizations; and, researchers with expertise in transitional care for adolescents and young adults with childhood-onset disabilities, health services research and knowledge translation. The majority of experts were female (84%) and included healthcare professionals, researchers, and those with a combined role of researcher and healthcare professional. More than half of the experts (63%) indicated 20 or more years of experience in their area of expertise, with over one third of respondents (42%) specifying expertise in pediatrics.

In the Round 1 rating survey, all interventions received a mean score rating of ≥7 on importance and impact; however, only seven of the interventions received a mean score rating of ≥7 on the third rating category related to feasibility. See **Supplementary Table 1** for a list of the interventions, components and their associated scores. The experts did not add any new interventions to the list for consideration.

In the Round 2 ranking survey, participants were asked to rank and prioritize the 7 TCIs identified in Round 1. See **Supplementary Table 2** for these results.

Consensus Meeting

The experts indicated that it was important to focus on the top four TCIs identified in the surveys. See **Supplementary Table 3** for the specific TCI descriptions developed by the smaller working groups through the TIDieR checklist. As evident in the descriptions of the four TCIs, there was a great deal of overlap in terms of content and approach between these interventions. Although the consensus meeting sought to address the ambiguity amongst the various TCIs, the large group discussions highlighted that it was difficult to consider

each intervention in isolation. Participants emphasized various reasons for not focusing on just one of the interventions under consideration; such as, the siloed nature of health and social systems, the complexity of patient and family needs and issues with communication between child and adult systems. Additionally, participants demonstrated highly varied views on the key drivers of success in transitional care, such as supportive family, naturally integrated systems and health professionals' readiness to support the transitional process. Despite efforts to converge and focus the discussion, participants often had "just one more comment" or other important items for consideration. The large group consensus was that addressing the key/active components of TCIs is like asking "what's in the stew" and that high flexibility amongst approaches is required. Medical complexity and social determinants of health were most referenced as issues that complicate the transition process.

After in-depth consultation and facilitated discussion, it became apparent that "case management" continued to arise as the most significant construct, as it was represented in all of the top four TCIs. While this was an intervention that scored low on the feasibility criteria in Round 1, after discussion, the participants agreed that the presence of a "coach," "peer" or "system navigator" should be the key intervention of a future research study. Specifically, participants agreed that evaluating the impact of "a person" who would act as an educator, advocate and system navigator to support patients and families through the transition into the adult system would best serve the population. Issues of concern remained about comparison groups, population, geography and identity of the case manager.

Virtual Research Planning Meeting

Although not initially planned as part of the modified Delphi process, we added a final, brief virtual meeting with interested participants who held research roles and expertise to build a more focused evaluation plan. While the consensus meeting was successful at prioritizing one TCI for future research, a focused research discussion to plan an optimal future evaluation was warranted.

It was agreed upon by all the researchers that a targeted intervention using peers with lived experience of transitioning into the adult system as peer navigators offered a promising approach and a unique future evaluation opportunity. A proposed intervention described using the TIDieR checklist, was developed during this discussion (see **Supplementary Table 4**).

The researchers also determined that this research agenda would benefit from input and participation from patients and families. This notion initially arose during the consensus meeting; however, was reinforced in the final research discussion. It was determined that the next steps in the research development plan would require a co-design approach with these partners.

DISCUSSION

Using the modified Delphi approach, we sought the opinions of experts on TCIs for adolescents and young adults with childhood-onset disabilities, including neurodevelopmental disorders, with the intention of prioritizing key components for future implementation and evaluation. The results of our previous systemic review identified a list of 16 interventions (15) that were prioritized by transitional care experts to four interventions after two survey rounds and then one intervention of "peer system navigator" after two consensus meetings.

Collaborative discussions with experts highlighted that TCIs for adolescents and young adults with childhood-onset disabilities are complex and multifaceted. Using the TIDieR framework to focus the discussions, experts indicated that the presence of an individual playing the role of system navigator, educator, advocate, coach and case manager would be an ideal intervention for further evaluation. More specifically, a focused evaluation of trained peer transitional coaches is needed to advance the evidence in TCIs for youth and young adults with childhood-onset disabilities. The notion of a peer system navigator is still unique to this population.

Our findings are consistent with other researchers in the field of pediatric TCIs. Dimitropoulos et al. (27) previously highlighted that children with complex health needs benefit from a care coordinator to promote transition but indicated that the title and scope of this navigator is varied in the literature and practice. Through interviews with health professionals in the field, the researchers identified that the process of transitional navigation should embrace a four-stage process including: "(1) identification of young people with special healthcare needs and families requiring support, (2) preparation for transfer, (3) health system navigation and (4) post-transfer support." In general, we recognize that a transitional care coordinator can have benefits for patients, their families and the entire healthcare system; however, we also recognize that healthcare providers have traditionally assumed these roles.

Our study had many strengths. First, to our knowledge, there are no studies assessing the impact of a peer transition coach to assist the population of youth with childhood-onset disabilities as they transition to the adult system. The role of a "peer" has gained increasing recognition in the literature and practice amongst other populations. The literature on peer support suggests that peers can help patients develop improved well-being while decreasing symptoms and hospitalizations (28). Furthermore, peers are known to provide valuable support across varying conditions such as diabetes (29), mental health (30), and cancer (31). Lastly, findings from more recent evidence have demonstrated that peers can also play an impactful role in supporting the system navigation process (32–34).

Based on these findings, we propose that peers could potentially fulfill an important role as transitional care coaches within the population of youth with childhood-onset disabilities transitioning to the adult care system and community. The collective results of the systematic review, modified Delphi process and consensus meetings have culminated in an emergent understanding that system navigation lead by peers is a potential impactful intervention worthy of further investigation for this population, and that there is a unique opportunity to train adults who have successfully transitioned to the

adult system to support patients and their families with this same process. We anticipate that peers may be well-suited for the provision of "health system navigation" and "post-transfer support" (27), yet further systematic examination is needed.

Before proceeding to such an investigation, key considerations seem warranted. Firstly, prior to potentially considering specific activities, processes and competencies to be integrated in the role of peer navigator, the perspectives and preferences of patients and families need to be sought. As such, a co-design approach is needed to elicit the perspectives of patients' and families' and ensure that they inform the nuanced elements of the implementation and evaluation protocols. Additionally, the need to create core competencies of a peer system navigator has been emphasized in the literature (30, 32), and this will need to be addressed and outlined before an evaluation begins. Baumann and Christophilakis (unpublished data), conducted semi-structured interviews with young adults with childhood onset disabilities and determined that some of the components of this training should include advocacy, empathy, interpersonal communication, motivation and goal setting and self-management skills.

With a concrete construct identified, and clear vision on the next steps of building the research protocol with a co-designed approach, we are confident that a solid evaluation structure is being established. Both quantitative and qualitative approaches will be necessary to evaluate the efficacy/effectiveness of such a targeted intervention. We are optimistic that this essential evaluation will be attractive to future granting agencies.

STUDY LIMITATIONS

We acknowledge study limitations. Although we followed modified Delphi practices based on the precedent of previous authors (25), real time adjustment of modified Delphi practices were required to reach our objective of developing a focused evaluation plan for one TCI. The complexity of TCIs and the variability in the population's health, social and geographic considerations are thought to be the reason for these necessary methodological adjustments. We are unaware of other researchers who have articulated struggles with group consensus at the final stage of the modified Delphi process; however, we speculate that we are not the first research group to experience this phenomenon. Acknowledging this challenge was therefore judged to be an important addition to the current paper. However, we also acknowledge that a different mix of stakeholders, a different set of activities for the consensus meeting or an alternate approach to facilitation may have led to a different result.

CONCLUSIONS

This study commenced with 16 potential TCIs for adolescents and young adults who have a childhood-onset disability and are transitioning to the adult healthcare system. Using a modified Delphi process, we were able to prioritize one key intervention and research agenda which involves the development and evaluation of a peer transitional coach. The next steps of our research agenda will be to engage patients and families in a co-design approach to optimize its function in the lives of the individuals it will endeavor to enable.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This study involved human participants and was reviewed and approved by University Health Network Research Ethics Board (REB 19-5746). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AD and DL: led the creation of this manuscript. SM: research project and manuscript creation. All authors contributed to the creation of the grant, study methodology, data analysis, and review and feedback of the manuscript.

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SUPPLEMENTARY MATERIAL

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Skeletal Muscle Mitochondrial Physiology in Children With Cerebral Palsy: Considerations for Healthy Aging

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Skeletal muscle contractile proteins require a constant supply of energy to produce force needed for movement. Energy (ATP) is primarily produced by mitochondrial organelles, located within and around muscle fibers, by oxidative phosphorylation that couples electron flux through the electron transport chain to create a proton gradient across the inner mitochondrial membrane that is in turn used by the ATP synthase. Mitochondrial networks increase in size by biogenesis to increase mitochondrial abundance and activity in response to endurance exercise, while their function and content reduce with constant inactivity, such as during muscle atrophy. During healthy aging, there is an overall decline in mitochondrial activity and abundance, increase in mitochondrial DNA mutations, potential increase in oxidative stress, and reduction in overall muscular capacity. Many of these alterations can be attenuated by consistent endurance exercise. Children with cerebral palsy (CP) have significantly increased energetics of movement, reduced endurance capacity, and increased perceived effort. Recent work in leg muscles in ambulatory children with CP show a marked reduction in mitochondrial function. Arm muscles show that mitochondrial protein content and mitochondria DNA copy number are lower, suggesting a reduction in mitochondrial abundance, along with a reduction in markers for mitochondrial biogenesis. Gene expression networks are reduced for glycolytic and mitochondrial pathways and share similarities with gene networks with aging and chronic inactivity. Given the importance of mitochondria for energy production and changes with aging, future work needs to assess changes in mitochondria across the lifespan in people with CP and the effect of exercise on promoting metabolic health.

Keywords: skeletal muscle, mitochondria, cerebral palsy, oxidative phosphorylation, energetics

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INTRODUCTION

Skeletal muscles are highly organized structures composed of bundles of multinucleated muscle cells, myofibers, made up of sarcomeres along the length and girth of fibers (1). Sarcomeres are the contractile proteins, made up of actin and myosin, whose interaction *via* the cross-bridge cycle is responsible for muscle force generation. This force generation is highly energetic and requires the constant replenishment of ATP for the cross-bridge cycle. Evolutionarily conserved metabolic pathways are utilized to break down carbohydrates, fats, and proteins systemically (2).

The substrates from this then enter cells such as muscles, where glucose and fatty acids are oxidized to create metabolites for majority of energy production within mitochondria (3). Human skeletal muscle fibers have three primary fiber types, namely, type I, type IIA, and type IIX (slowest to fastest/oxidative to more glycolytic), associated with different isoforms of myosin heavy chain, which demonstrates differing metabolic properties (4), with majority of energy production being dependent on mitochondria (**Figure 1**).

SKELETAL MUSCLE MITOCHONDRIA, AGING, AND CEREBRAL PALSY

Mitochondrial Physiology

Mitochondria are subcellular organelle networks located around and within muscle fibers (5). Two key processes of energy production in muscles and other tissues under aerobic conditions occur within the mitochondria: the trichloroacetic acid (TCA) cycle (for breaking down food substrates) and the electron transport chain (ETC)-ATP synthase (for creating ATP) (**Figure 2**). Carbohydrates and fatty acids are partly broken down outside the mitochondria and then broken further down within the mitochondria using the TCA cycle to nicotinamide adenine dinucleotide hydride (NADH), and succinate. For example, (anaerobic) glycolysis occurs within the cells, outside of the mitochondria, and yields a small fraction of ATP and pyruvate. Pyruvate, in the presence of oxygen, is then broken down to acetyl Co-A that enters the mitochondrial TCA cycle and generates some ATP, NADH, and succinate that then feed into the ETC-ATP synthase to generate the majority of ATP by oxidative phosphorylation (**Figure 1**). Each mitochondrial network has numerous ETC-ATP synthase units that have five complexes: CI (NADH-ubiquinone oxidoreductase), CII (succinate-ubiquinone oxidoreductase), CIII (ubiquinol-cytochrome c oxidoreductase), CIV (cytochrome c oxidase), and the ATP synthase (6), located along the inner mitochondrial membrane, and intermediaries coenzyme Q (ubiquinone), cytochrome c. The transport of the electron passes through CI–CIII–CIV or CII–CIII–CIV with NADH and succinate being the starting substrates, respectively. The electron transport flux through the complexes creates a proton gradient across the inner mitochondrial membrane. The ETC is indirectly coupled to the ATP synthase such that the proton difference facilitates energy production at the ATP synthase to provide energy to the working muscle (7). This uses oxidative phosphorylation, i.e., ATP phosphorylation from ADP by the ATP synthase requires oxidation by the ETC (**Figure 2**).

Skeletal muscles are remarkably adaptive tissue that respond positively to activity and exercise over weeks by increasing their mitochondrial content and function needed to maintain appropriate energy levels during exercise (5, 8). The primary processes involved in this increase are improved ETC capacity, mitochondrial biogenesis (9), and mitochondrial dynamics of fusion to increase the size of the mitochondrial network (10). Unlike nuclei of cells that have one copy of nuclear (or genomic) DNA, each mitochondrion has multiple copies of their own sparse circular DNA [mitochondrial DNA (mtDNA)] but, as an evolutionary mechanism, depend on nuclear DNA for generating 99% of the 1,000+ mitochondrial proteins (11, 12). Consequently, during biogenesis to create new ETC and ATP synthase, the 37 genes of mitochondrial DNA can only encode 13-core protein subunits (13–15). Dual-genetic coordination and control is required so that nuclear DNA can encode the remaining 75 subunits of the ETC and ATP synthase. The only electron transport complex that is not coded by mtDNA and is entirely coded using nuclear DNA is complex II, which also does not have a proton pump to contribute to the ETC gradient. In contrast, mitochondrial function is dramatically reduced due to prolonged inactivity by the loss of mitochondrial content and fragmentation (fission) of the mitochondrial network (16–18). Consequently, a high level of quality control is required to ensure that functional subunits are maintained and dysfunctional units are removed by mitophagy and replaced with newer functional units by mitochondria biogenesis.

Cerebral Palsy

Cerebral palsy (CP), caused by a non-progressive brain injury around birth, is the leading cause of movement disability in children (19). Most children develop spasticity, have impaired muscle growth, contractures, weakness, and increased energy cost of movement (20). They have a continuum of functional abilities broadly classified using the Gross Motor Function Classification System (GMFCS) (21), with lower GMFCS levels ambulating independently and higher GMFCS levels being minimally ambulatory and requiring wheelchairs. Children show significant impairments in their energetics of movements and decreased endurance capacity (22, 23) compared to children with typical development (TD), associated with increasing GMFCS levels. Increased energy expenditure has been attributed to cardiorespiratory factors (24) and to inefficient muscle activation (22).

Energetics is dependent on muscle metabolic factors such as oxidative potential and mitochondrial function (8, 25) and cannot be explained purely due to gait alterations and presence of spasticity (26, 27). As children approach adulthood, their capacity for movement can decline particularly during the transition from adolescence to adulthood (28–31). Consequently, individuals with CP have a high risk for cardiometabolic diseases (32–34) and comorbidities (35–39), and, in general, physical activity induces numerous health benefits (40, 41). It is essential to understand the interaction and potential benefits of physical activity on muscle energetics of movement during childhood into adulthood. Even ambulatory children with CP have considerably low level of activity compared to kids with TD (42, 43), and there is a need to promote physical activity for lifelong well-being.

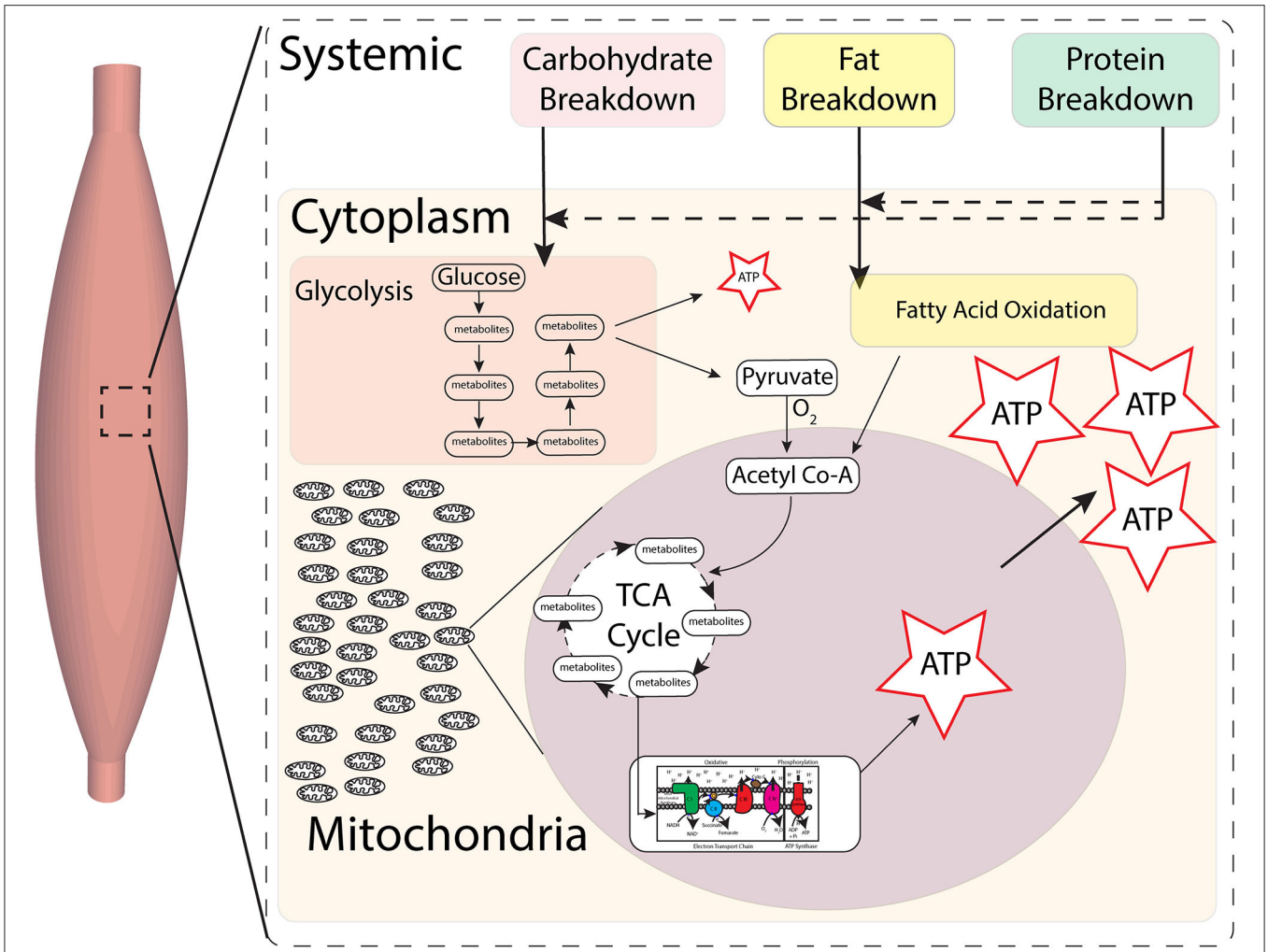

FIGURE 1 | Skeletal muscle metabolic pathways for energy. Carbohydrates, fats, and proteins foods are broken down systemically, substrates of which then enter cells. Production of energy by final breakdown of food occurs primarily within cells by glycolysis and fatty acid oxidation. Anaerobic glycolysis in the cytoplasm can only create small amounts of energy (ATP) in the short term. Substrates from glycolysis then enter mitochondria and, in the presence of oxygen, go through the tricarboxylic acid (TCA) cycle, whose substrates then feed into the electron transport chain (ETC), which in turn is indirectly coupled to ATP synthase to create ATP. Most energy (ATP) production occurs in the presence of oxygen within the mitochondria by breakdown of metabolites *via* the TCA cycle and oxidative phosphorylation at the ETC-ATP synthase.

Changes in Skeletal Muscle Mitochondria With Healthy Aging and Impact of Exercise

Muscle oxidative capacity can be measured non-invasively for whole muscle kinetics (phosphorus-P31 magnetic resonance spectroscopy or near-infrared spectroscopy) (44). Direct measurements of mitochondrial physiology can only routinely be measured from muscle biopsies for mitochondrial function (respiration capacity, maximal activity assays, membrane potential, ATP production) (45) and/or mitochondrial content (electron microscopy morphology, protein abundance, mitochondrial DNA) (46). With aging, mitochondrial function (47) and abundance decline (48), mitochondrial DNA mutations increase (49), and overall muscular capacity reduces (50). In sedentary elderly subjects, muscle oxidative capacity (51) and mitochondrial respiration and content are lower by 30–50% (52). Mitochondria produce reactive oxygen species, which, if not cleared, can lead to increased oxidative stress (53). Mitochondrial quality control is maintained by mitophagy, such that dysfunctional electron transport chain components are removed and updated with newer functional components (49). Within mitochondria, there is an age-associated increase in oxidative stress and reactive oxygen species, particularly at complex I and III proton pumps, leading to mitochondrial dysfunction (53, 54). Mitochondria are important not just for energy production but also for a myriad of other sensing functions (55). In young, healthy individuals, endurance exercise programs such as cycling or running over the course of 6–8 weeks

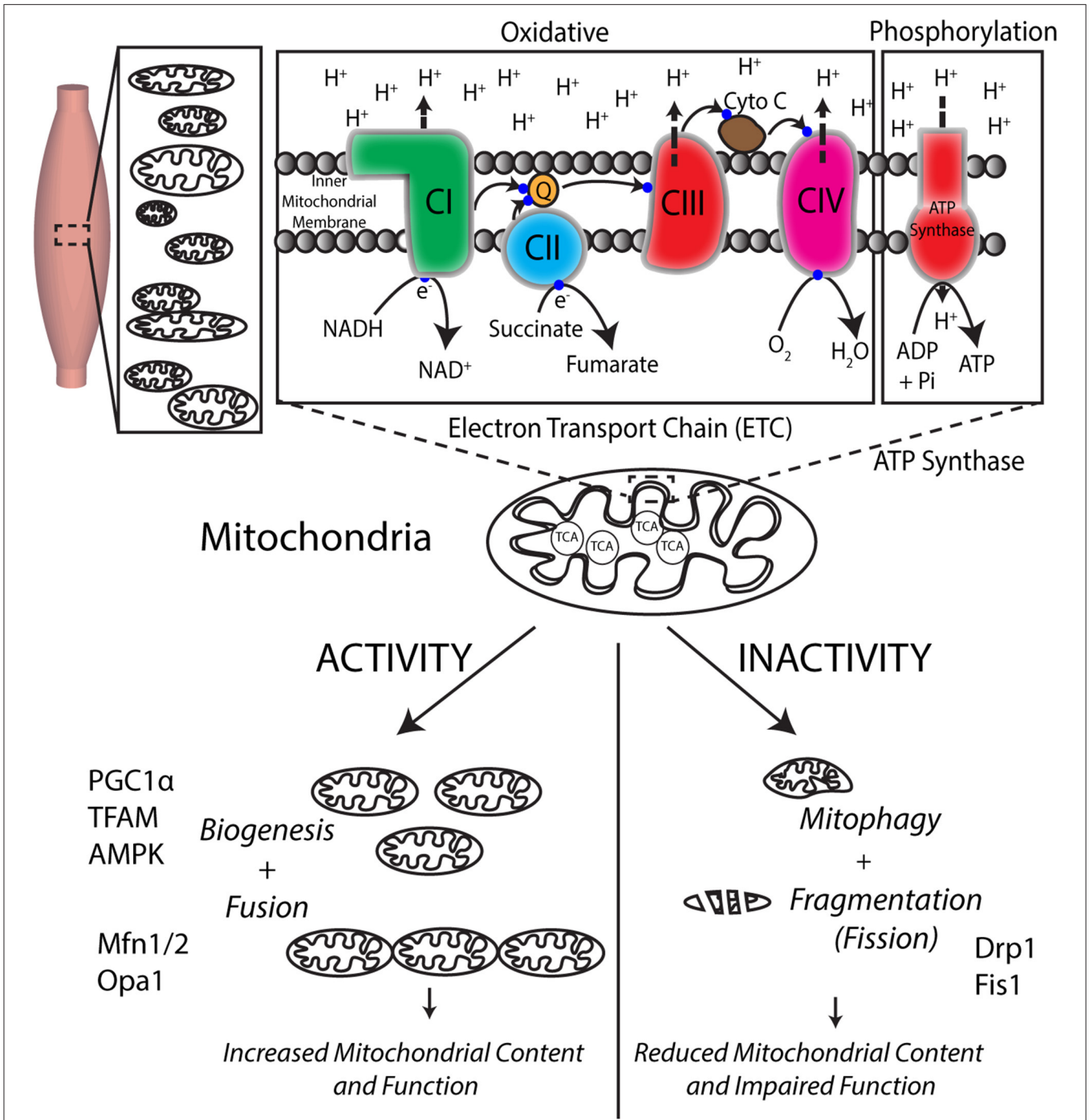

FIGURE 2 | Mitochondria are responsible for energy production *via* cellular respiration and are dynamically regulated by exercise. Skeletal muscles have numerous mitochondria for the production of energy required for force production. The TCA cycle within the mitochondria helps break down food to create substrates that feed into the numerous electron transport system (ETC) units located in the mitochondrial inner membrane. The flux of electrons through the four protein complexes of ETC uses the substrates coupled with oxygen utilization to create a proton (H^+) gradient across the inner mitochondrial membrane, which drives energy generation at the ATP synthase. Mitochondria respond positively to consistent exercise by creating new mitochondria by mitochondrial biogenesis, while inactivity negatively impacts their function and morphology.

can stimulate mitochondrial biogenesis (49) to increase mitochondrial content and function by 40%, measured by activity assays or electron microscopy (5, 56). Even during aging, with consistent endurance exercise, muscles can maintain mitochondrial content and function (57). Importantly, even in aged sedentary individuals, endurance exercise can improve

mitochondrial health (57), although it might not restore it completely (49, 58).

Changes in Skeletal Muscle Metabolism and Mitochondria in Children With Cerebral Palsy

Direct measurements of skeletal muscle mitochondrial physiology in children with CP have only recently been reported (59, 60). Previously, our understanding of metabolic capacity in children with CP were primarily based on fiber-type capacities. Prior to the discovery of individual myosin heavy chain isoforms, fiber types were classified on the basis of myofibrillar adenosine triphosphatase (ATPase) activity, which distinguishes between slow (type I) and fast (type II) contracting muscle fibers. Lower extremity muscles from children with CP show a strong preference for one or the other fiber type, with a shift toward type I muscle fibers (61), whereas TD children show a greater balance between fiber types (62). Similar changes in having a predominance of one fiber type, with a shift toward type 2X, has been observed in upper extremity muscles in young adults with contractures using classification based on the newer techniques of myosin heavy chain isoforms (63). However, there are significant alterations in myofiber size, heterogeneity, and fiber type distributions in the muscles from children with CP, and even the newer techniques of purely measuring fiber type percentages do not capture their metabolic capacity. Our recent work using simple histochemical succinate dehydrogenase (SDH-ETC complex 2) staining shows that while the hamstring muscles in children with CP are significantly smaller than in TD children, the metabolic activity per unit of both type I and type IIA muscle fibers are similar between the two groups, i.e., greater for type I (64). Gene expression of oxidative metabolic genes is significantly reduced in both wrist flexor and hamstring muscles of children with CP (65, 66), suggesting alterations in mitochondrial capacities. The metabolic machinery within the muscle also depends on the appropriate delivery of oxygen to the mitochondria through appropriate development of the capillary network. Reduced capillary density has been reported in wrist flexor contractures in young adults compared to control subjects, suggesting that it may have a role to play in reduced metabolic capacity (63). Exercise studies have shown that young adults with cerebral palsy do get exhausted at lower exercise intensities, but they are able to dynamically increase muscle vascularization in response to exercise (67). Overall, while some information exists at the level of fiber types, metabolic capacities by fiber types, gene expression, vascularization, and response to exercise, these are not informative of mitochondrial oxidative phosphorylation capacities, the driver of energy production.

A recent small study ($n = 12$) directly measured mitochondrial electron transport capacity using spectrophotometric assays (68) in gracilis muscle biopsies obtained during surgery from independently ambulatory children (CP, $n = 6$; mean age, 13 years; GMFCS I–II) (59). Maximal enzyme activity assays were performed for CI, CII, CIII, and CI + III by using specific substrates with associated electron acceptors, and reduction/oxidation rates of either substrate or electron acceptor, depending on the assay, were measured. Maximal rate of individual electron transport complexes CI, CII, CIII, and CI + CIII combined were 45–80% lower in children with CP compared to TD children. Citrate synthase activity, a mitochondrial matrix enzyme and part of the TCA cycle, is considered a robust marker of mitochondrial content, at least in healthy young adults (46). Skeletal muscles in children with CP had similar citrate synthase rate as that in TD children. mtDNA: genomic DNA, also referred to as mtDNA copy number, was increased four-fold in children with CP, although this was not significant ($p = 0.061$). These data suggest that, at least in the hamstring, muscle alterations in mitochondrial function are not simply due to a reduction in content but are probably reflective of poorly functioning electron transport chain, similar to what has been reported with aging. A more mechanistic study in a larger cohort of children, where more measures of content are performed, is needed to understand if and how the mitochondrial physiology is altered in these children.

In a complementary, comprehensive, and larger study ($n = 29$), von Walden et al. (60) measured mitochondrial electron transport chain and ATP synthase complexes protein abundance and gene expression of mitochondrial biogenesis genes, performed secondary analysis of transcriptomics in CP, and compared it to aging and chronic inactivity using publicly available gene expression datasets. They obtained biceps biopsies during surgery from children with CP ($n = 19$, mean age of 15 years, 12 GMFCS I–II, 7 GMFCS IV–V), along with typical developing control samples, obtained post-mortem. Protein abundance for mitochondrial electron transport chain complexes CI, CIII, CIV, and ATP synthase was 20–40% lower in children with CP but not significantly lower for CII ($p = 0.07$). Correspondingly, the mtDNA copy number was ∼25% lower in children with CP, suggesting an overall reduction in mitochondrial content in these muscles. They then evaluated for any changes in gene expression of peroxisome-proliferator-activated receptor gamma coactivator (PGC1) α, considered a "master regulator" of mitochondrial biogenesis (9), although, as mentioned previously, mitochondrial biogenesis is complicated and requires multiple pathways, players from both mtDNA and genomic DNA, and transporter proteins into the mitochondria, since mtDNA by themselves are unable to create the whole of any of the complexes. Interestingly, they report that the total PGC1α gene expression was ∼25% lower in children with CP, along with 35–65% reduction in splice-variants PGC1α1 and PGC1α4. Although this is not a measurement in response to a single bout or a program of exercise, this does suggests that capacity for mitochondrial biogenesis may be reduced in children with CP. A secondary transcriptomic analysis of publicly available gene expression data set (66) was performed to evaluate any changes in gene ontology and pathways in the hamstrings (gracilis and semitendinosis) muscles between children with TD and CP. Their analyses revealed that both glycolytic and mitochondrial transcriptomic networks were significantly altered, and associated gene sets were downregulated. Their experimental and secondary analysis results indicate that there is a significant downregulation of

mitochondrial physiology in children with CP. To further test if these alterations are metabolically similar to conditions known to reduce mitochondrial capacity—chronic inactivity or aging—they compared the transcriptomics across these three conditions, namely, CP, aging, and bed rest data sets. Downregulated genes were in common between CP and aging (332 genes), between CP and inactivity (109 genes), and across all three (28 genes). Overall, these data show that muscles in children with CP have a significant reduction in metabolic capacity, which cannot purely be explained by disuse and might have more in common with aging, secondary to living with a chronic disability.

DISCUSSION

These two recent papers show that skeletal muscle mitochondrial physiology is negatively altered in adolescent children with CP. Mitochondrial function, content, and markers for mitochondrial biogenesis are reduced. More concerningly, at the level of gene expression, children with CP appear to have a large number of genes in common with aged skeletal muscle than muscles after chronic bedrest or inactivity. Many adolescent children with CP are at risk for losing their functional ability to move, and adults with CP have a higher risk of developing cardiometabolic conditions and comorbidities. Since mitochondrial alterations are also negatively associated with aging, it would be important to understand how mitochondrial physiology changes such as in ETC-ATPase function, abundance, biogenesis, mtDNA mutations, reactive oxygen species occur in people with CP across the lifespan from childhood through adulthood. Importantly, more direct experimental studies are required to understand if the well-documented positive impact of exercise on mitochondrial physiology is maintained or altered in children and adults with CP and if that translates to maintained or improved capacity for movement across the lifespan.

AUTHOR CONTRIBUTIONS

SD wrote the complete manuscript and designed the figures for this article.

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Navigating the Pathway to Care in Adults With Cerebral Palsy

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As individuals with cerebral palsy (CP) age, they face unique challenges which complicate their ability to access and receive appropriate health care. These problems exist at the level of the health care system, the clinician, and the individual. At the system level, there is an inadequate number of professionals who are informed of and interested in the care of adults with CP. Pediatric clinicians prefer treating children, and adult caregivers are not knowledgeable about and may feel less competent about CP. Pediatric care does not translate well to the adult population, and information about best practices for adults is just starting to develop. Differences in the physiologic development of individuals with CP render well-established clinical protocols for risk screening of chronic diseases less effective. Moreover, lack of supportive resources decreases a caregiver's sense of self-efficacy in treating this population. The patient's ability to navigate these barriers is complicated by the high prevalence of comorbid cognitive impairment and mental health issues including anxiety, depression, and other psychiatric disorders; a bidirectional relationship between challenges in navigating care/needs and comorbid mental health conditions appears likely. Many patients have additional barriers related to social determinants of health, such as access to transportation, accessible health care facilities, and other personal and environmental factors that may impede health maintenance and wellness. Increasing and disseminating knowledge, harnessing the power of new technologies such as telemedicine, and addressing mental health issues are some of the methods that are available to help adults with CP navigate this road.

Keywords: cerebral palsy, health systems, care coordination, telemedicine, mental health

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INTRODUCTION

Cerebral palsy (CP) arises early in life and is historically viewed as a non-progressive pediatric condition affecting movement, muscle tone, or posture. With improvements in care, individuals with CP are living well into adulthood (1). It follows, then, that there are more adults than children with CP, indicating that CP is also an adult condition. In health care systems, however, CP is often confined to pediatric hospitals and ambulatory care services, while adults with CP struggle to receive appropriate care, even for the most common disorders such as musculoskeletal morbidities (2). As individuals with CP age, they face unique challenges which make their medical care complex. Models of care and interventions that worked for them as children do not exist and may not be appropriate for them as adults, owing in part to new problems that arise with aging.

Consequently, medical care for adults with CP requires different expertise and coordinated approaches. The complex health care pathway that adults with CP must navigate poses challenges at the level of the health care system, the clinical provider, and within the individuals themselves.

Health Care Systems

There are an inadequate number and network of health care providers who have both the interest and the expertise to provide appropriate care for adults with CP. Adults with CP have complex issues requiring longer appointments which are hard to fit into busy clinical schedules and make care for this population less appealing for a health system. Additionally, there is a significant knowledge gap about the unique issues facing this population. Most professional schools provide little training in the care of individuals with disabilities. People who grow up with pediatric-onset disabilities form an even smaller "niche" population, and even less exposure within curriculums. Compounding this problem is the general lack of published scientific guidance in this area. The literature on adults with CP has grown significantly in the past several years (1), and has focused on identifying and defining problems across the lifespan; however, few studies have informed the implementation for proper screening and intervention protocols.

Adults with CP often find themselves in pediatric models of care. Many receive care in pediatric hospitals (3) or in pediatric clinical settings that have, at best, an "adult day." Finding the right specialists to staff these clinics is a conundrum: many pediatric providers do not want to deal with the complex medical and psychosocial issues of adults, while adult providers are not comfortable with a diagnosis that they were exposed to briefly during their medical school pediatric rotation. The pediatric clinic model with the typical multidisciplinary milieu (physiatry, orthopedics, neurosurgery, therapies) does not address some of the most pressing issues of the adult CP population, which may include multimorbidity (4, 5) across organ systems spanning cardiac, renal, pulmonary, musculoskeletal and mental health issues (6). In general adult care, multidisciplinary clinics are less common because there are so many varied needs, and because busy, independent adults don't have the time for the typical multidisciplinary 4 hour appointment.

Clinical Providers

Providers with these knowledge gaps will have poor self-efficacy related to the care of adults with CP. Even physiatrists, who are trained to care for individuals with disabilities, struggle with trying to apply information from their pediatric and stroke rotations to a population who represents neither of those. For surgical providers, care provision is more complicated due to a lack of experience and resultant lack of knowledge of potential risks, outcomes, and best post-operative protocols. Knowledge development is greatly needed in several areas related to preventive care and the treatment of medical and rehabilitation needs of adults with CP.

Preventive care is a high priority for adults with CP, but there are several differences from the general population which are most likely not known by most providers. Adults with CP are at risk for multimorbidity at a much younger age than their non-CP peers. Among young adults with CP (i.e., 18–30 years), 1 in 4 has multimorbidity (5). Despite this, adults with CP are less likely to receive preventive care (7). A large, nationwide study examining the natural history of several morbidities across the adult lifespan recommended: "Broadly speaking, whenever feasible, preventive and monitoring measures should be adopted early in the lifespan and not later than age 50 years for adults with cerebral palsy" (8). To achieve a successful systematic approach for earlier screening of comorbidity risk, considerable efforts will be needed to reform primary prevention for adults with CP with investments from a variety of stakeholders (e.g., clinical systems, insurance providers, clinicians, patients, policy makers, etc.).

As a result of living with a lifelong physical disability, individuals with CP have alterations in muscle and bone development. The smaller and unique body sizes and heterogeneity in muscle deficits across the body (9) can result in erroneous interpretation of commonly used approaches [e.g., body mass index (BMI)] when assessing body habitus and obesity risk (10, 11). Clinical interpretation of obesity risk from body fat, whether total body or regional fat depots, can be misleading and inconsistent based on the approach used and anatomical site examined in persons with CP [e.g., normal BMI but high visceral fat found with imaging (12)]. BMI can underestimate total body fat, with the degree of underestimation being greater for more severe forms of CP (13). This is largely due to the lower fat-free mass in CP, which reduces the numerator in the BMI ratio-thus lowering the BMI value independent of fat mass. Additionally, fat may accumulate disproportionately among visceral and musculoskeletal depots (14, 15), despite "normal" subcutaneous fat stores and even normal BMI-calling into question the utility of subcutaneous-derived methods to assess body fat, such as skinfold measurements. Therefore, clinicians may miss opportunities for detection of obesity risk and its associated disease sequela. Adults with CP have significantly higher rates of risk factors for metabolic syndrome with resultant risk of cardiovascular disease, stroke, and other chronic diseases related to excess body fat (16–18), and low levels of fitness and physical activity (19), so appropriate screening is critical.

Another example is screening for chronic kidney disease, which is prevalent in adults with CP (16, 20–23). Kidney disease is assessed by glomerular filtration rate (GFR), which is a measure of kidney function. Measuring GFR is the gold-standard for GFR assessment, but is cumbersome, so GFR is often estimated using serum biomarkers (eGFR), including creatinine and/or cystatin c (24–26). The problem for interpreting eGFR in CP is that creatinine and cystatin c are influenced by the amount of muscle and fat mass, respectively, which can lead to inaccurate interpretation of kidney function and risk of kidney disease (27–29). Creatinine-based eGFR is more commonly performed clinically and is typically part of routine blood work. Individuals with CP have lower levels of creatinine due to reduced muscle, which artificially inflates eGFR values and leads to a false interpretation of healthier kidney function.

Bone fragility and fractures are common in CP due to a variety of interacting factors (30–34), and are associated with significant morbidity and early mortality (35). Bone strength

is often monitored clinically by the sole interpretation of bone mineral density (BMD) from dual-energy x-ray absorptiometry. However, BMD alone may not be sufficient to assess bone strength or bone fragility for adults with CP. BMD is a ratio of bone mineral content relative to bone area. The smaller bones in CP (36, 37) can inflate BMD independent of bone mineral content, presenting clinically as a bone that is stronger than it actually is. Further, bone size is itself an independent determinant of fracture risk (38, 39), which is missed when assessing BMD alone.

In addition to these complexities of health screening, the adult with CP brings many unique challenges into the clinic to providers unfamiliar with this population. A major one is early functional loss. Mobility decreases early in adulthood for many individuals with CP, sometimes in the fourth decade for those with bilateral involvement (40). This functional loss is often attributed to pain and fatigue. Many adults with CP are told that their "CP is getting worse." Clinicians (and patients) must understand that functional loss is not a "progression of CP," nor just a result of pain and fatigue, but rather a product of several factors, many of which are treatable, including poor fitness levels, new neurologic problems, and the effects of aging and chronic disease. As an example, there is a higher incidence of myelopathy and stroke in CP which may go undiagnosed and contribute to functional loss (41).

Pain is common in adults with CP. Recent studies showed that up to 70% of adults with CP experience pain, which can affect life activities and sleep, and increase risk for psychiatric disorders (42–44). However, pain cannot be addressed and treated as it is in the general population. First, it is most likely under-reported in individuals with communication difficulties, making it complex to assess (42). In addition, most practitioners would assume that adults with CP have nociceptive (i.e., peripheral) pain based on their history of poor biomechanics, joint dysplasias, muscle spasticity, and prior surgeries. They may easily miss the fact that many adults with CP have a heterogeneous pain phenotype, which could also include nociplastic pain or a mixed picture (45, 46). Prescription of opioids for pain is significantly higher in this population, an indication that their healthcare providers struggle with finding appropriate treatment options (45). Thus, increasing clinical awareness of the pain phenotypes, improving clinical pain screening strategies, and developing efficient referral resources for appropriate pain management may help reduce the burden of opioid addiction and overdose in these population.

Physical and occupational therapists working with adults with CP must adapt as well. Adults with CP is that they have never moved "normally" in their lifetime, which creates a challenge for their therapists who typically focus on helping patient's return to "normal" or near-normal function. Throughout life, persons with CP have had to overcome some amount of weakness and/or hypertonicity whenever they move, which has resulted in movement patterns that are not biomechanically appropriate or efficient. Adults with CP may not know how to volitionally contract a single muscle or isolate a muscle contraction without utilizing a spasticity pattern in the entire limb. Additionally, abnormal joint reaction forces as a consequence of muscle spasticity and atypical movement patterns accelerate the "aging" process of the joints, resulting in increased incidence of orthopedic conditions such as osteoarthritis (47).

Finding an appropriate rehabilitation plan for this complex patient population can be challenging. Pain, spasticity, and multiple musculoskeletal problems interfere with therapy. Many of these patients require orthotics and/or use wheelchairs, so deep knowledge of these assistive devices is necessary when treating this population. Unfortunately, insurance coverage limitations often interfere with maximizing rehabilitation interventions. Many adults with CP may only get 6–12 visits for physical and occupational therapy for an entire year, regardless of their functional limitations and potential to benefit from rehabilitation intervention. Insurance companies commonly only cover a new wheelchair or orthotic every 5 years; thus, it is very important that the correct, most useful device be ordered initially. Given the importance of accurate and timely care, it is vital for primary care physicians to collaborate with physical therapists or physiatrists who specialize in assistive devices prior to ordering equipment to ensure that the patient's needs are met.

The Individual

Several individual factors related to the diagnosis of CP in adults can function as barriers to optimizing physical health and accessing appropriate care. Many secondary health complications occur in adults with CP due to immobility. Despite their physical impairments, many patients may try to exercise and improve their physical activity but then encounter equipment that is logistically or financially inaccessible, resulting in decreased engagement in proactive positive health behaviors such as exercise. Similarly, logistical barriers exist (e.g., transportation, flexible scheduling) to accessing optimal physical health care. Even for patients who want to do the right thing, there are many obstacles to negotiate.

Mental health challenges can also function as barriers to optimal health care and, subsequently, health related quality of life (although, it is important to note that the associations between mental health challenges with medical co-morbidities, function, societal and psychosocial factors can be bidirectional and complex) (48). Adults with CP have a greater prevalence of mental health disorders including mood and anxiety disorders as well as thought disorder, personality or behavioral disorders, and substance use disorders, as compared to the general population (49, 50). In the context of reported declines in mobility status in persons with CP as they reach adulthood, mobility decline has been linked to worse mental health status, with potential mechanisms including functional loss, pain, fatigue, and reduced participation (51).

Although most research has focused on the influence of physical function on mental health, it is also important to consider the potential influence of mental health functioning on self-care and self-management of chronic physical challenges. The broad mental health literature clearly demonstrates that mental illness can negatively impact compliance with the plan of care and recommended interventions (52, 53). Negative influence of mental health disorders on individual's engagement in self-management is well-acknowledged in the rehabilitation literature (54, 55). Over time, mental health factors may cause or exacerbate

a learned helplessness associated with chronic difficulties and may be associated with lower levels of resilience. Addressing mental health needs may result in health re-prioritization and subsequent deference of some aspects of physical care as emotional needs become primary.

An additional barrier to optimal care of persons with CP is the well-established fact that persons with various types of disabilities are at a disadvantage broadly within our healthcare system. This disadvantage is related to both understanding of health needs and socioeconomic and community-based factors that influence access to and utility of healthcare approaches (56, 57). Equitable access for persons with CP to meet their needs can include accessible transportation, housing, and health care facilities, and employment opportunities that are flexible enough to accommodate the varied practical and medical needs of persons with disabilities. Adults with CP may lack the resources needed to acquire greater resources, resulting in a cycle of inadequate support that perpetuates ongoing health and functional declines.

Navigating the Path Forward

The first step in addressing the many roadblocks on the way to appropriate health care for adults with CP is knowledge development, transfer, and translation. Individuals with CP need greater knowledge about the complexities and unique aspects of their care to increase their self-efficacy in their self-management. Healthcare providers in multiple medical, therapy, and other disciplines need access to training in evidence-based care, and that evidence must continue to be developed. Long-term studies and health surveillance of CP using registries are critical for this goal (58). On a system-wide level, there is a need for greater knowledge translation aimed at advocacy services such as coordinated care options, patient navigators, and value-based care models that would make care for adults with CP efficient and more attractive to providers (1).

New technologies bring options for models of care that differ from pediatric clinics and address the unique needs of this population. Issues related to health promotion can be addressed through telemedicine. Knowledgeable clinicians can connect with patients who live at a distance from their center and work virtually with their local providers on issues that need to be addressed in person, contributing expertise and guidance. The medical home for an adult with CP needs a provider network that incorporates many specialists beyond those classically attending the "CP clinic," including cardiologists, endocrinologists, nephrologists, psychiatrists, and many others trained in adult CP care. Telemedicine can bring together patients and specialists, creating virtual medical homes. Clinicians reported high satisfaction with telemedicine in a study looking at its use in children with CP (59). It has been used successfully in many neurologic conditions for adults (60) and to provide care for several problems common in adults with CP (61, 62).

Importantly, mental health care is a clear need in the adult CP population, but access to adequate mental health care is not universal and is often contingent upon factors outside of the patient's control-including insurance coverage, availability within a geographical area, and fit between patient and provider. Increased capacity for mental health services, in part via implementation of telemedicine, is essential to even begin to address the need for support. Certain approaches to mental health care are likely to be differentially effective in adults with CP, although this has not yet been systematically studied. Use of a transdiagnostic treatment approach would appear to be an appropriate first line treatment, but future work is needed to assess efficacy and effectiveness.

CONCLUSION

Adults with CP face barriers to health care at many levels, including the health system, the clinician, and the individual. They have many unique needs based on the changes in physiology that accompanied their growth and development, as well as social determinants of health common to them and many others with disabilities. Mental health issues are a prominent concern that will contribute to learned helplessness and interfere with self-management. More knowledge needs to be developed and disseminated in the form of evidence-based guidelines for health surveillance and appropriate interventions. Adults with CP should never be told "your CP is getting worse." Rather, they are entitled to knowledge about the process of aging with CP and related risk factors, as well as coordinated care that leads to wellness, full participation, and excellent quality of life.

AUTHOR CONTRIBUTIONS

EH, DW, and MP conceived the concept of the review. EH, DW, BW-P, HH, MS, DR, and MP drafted the manuscript. CG provided critical feedback and contributed to the final manuscript. All authors contributed to the article and approved the submitted version.

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Bridging Pediatric and Adult Rehabilitation Services for Young Adults With Childhood-Onset Disabilities: Evaluation of the LIFEspan Model of Transitional Care

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Background: LIFEspan ("Living Independently and Fully Engaged") is a linked transition service model for youth and young adults with childhood-onset disabilities offered via an inter-agency partnership between two rehabilitation hospitals (one pediatric and one adult) in Toronto, Canada.

Objective: The objective was to evaluate healthcare outcomes (continuity of care and healthcare utilization) for clients enrolled in LIFEspan.

Methods: A prospective, longitudinal, observational mixed-method study design was used. The intervention group comprised youth with Acquired Brain Injury (ABI) and Cerebral Palsy (CP) enrolled in LIFEspan. A prospective comparison group comprised youth with Spina Bifida (SB) who received standard care. A retrospective comparison group comprised historical, disability-matched clients (with ABI and CP) discharged prior to model introduction. Medical charts were audited to determine continuity of care, i.e., whether study participants had at least one visit to an adult provider within 1 year post-discharge from the pediatric hospital. Secondary outcomes related to healthcare utilization were obtained from population-based, health service administrative datasets. Data were collected over a 3-year period: 2 years pre and 1 year post pediatric discharge. Rates were estimated per person-year. Fisher's Exact Test was used to examine differences between groups on the primary outcome, while repeated measures GEE Poisson regression was used to estimate rate ratios (post vs. pre) with 95% confidence intervals for the secondary outcomes.

Results: Prospective enrolment comprised 30 ABI, 48 CP, and 21 SB participants. Retrospective enrolment comprised 15 ABI and 18 CP participants. LIFEspan participants demonstrated significantly greater continuity of care (45% had engagement with adult services in the year following discharge at 18 years), compared to the prospective SB group (14%). Healthcare utilization data were inconsistent with no significant changes in frequency of physician office visits, emergency department visits, or hospitalizations for clients enrolled in LIFEspan in the year following discharge, compared to the 2 years prior to discharge.

Conclusion: Introduction of the LIFEspan model increased continuity of care, with successful transfer from pediatric to adult services for clients enrolled. Data on longer-term follow-up are recommended for greater understanding of the degree of adult engagement and influence of LIFEspan on healthcare utilization following transfer.

Keywords: continuity of care (COC), inter-agency partnership, pediatric healthcare providers, adult healthcare providers, Canada (MeSH), disability, healthcare utilization, transition to adult care

INTRODUCTION

Advances in technology and healthcare practice have significantly increased survival rates for individuals with childhood-onset disabilities, with most now living well into adulthood (1, 2). In Canada, these young adults must transition from pediatric to adult healthcare systems at 18 years of age to manage their lifelong rehabilitation needs (3). In this transition, healthcare delivery should be a coordinated and uninterrupted provision of developmentally appropriate and comprehensive services (4). Transition from the pediatric to adult healthcare system is a complex process, however; and there is significant evidence that healthcare systems are not yet designed to effectively meet lifelong rehabilitation needs (2, 5, 6). Adolescents with childhood-onset disabilities are often significantly under-serviced as young adults, while some receive no care at all (2). Recurring themes related to barriers experienced during this transition include poor links between pediatric and adult rehabilitation services, insurance coverage restrictions, inadequate access to adult providers because of narrow criteria focused on adult-onset disabilities, and a general lack of specialized training and expertise related to aging with a disability or chronic illness (7, 8). In the absence of adequate services, health issues can go unmonitored and/or untreated, increasing the risk of preventable complications, an inappropriate reliance on emergency health services, and increased hospital admissions (9, 10).

Responding to calls for action, there has been a surge in transition models and activities, with a growing body of literature seeking to understand "what works" for young adults with specialized healthcare needs. Numerous systematic reviews of transition interventions that address transition planning, transfer assistance, and integration into adult services demonstrate positive outcomes from such interventions related to population health, continuity or adherence to care, healthcare utilization, and satisfaction with care (11–13). Examples of transition models range from dedicated young adult clinics within adult services, pediatric clinics with structured processes, and "bridge programs" where components of pediatric and adult care are included, e.g., dual visit models where adult and pediatric providers are both present (12, 14). An additional distinguishing feature is whether transition models are built around a dedicated facilitator, or are based on a multi-disciplinary team approach (15). To a large extent, transition services have predominantly focused on chronic illness, such as diabetes, heart disease, kidney transplant and juvenile idiopathic arthritis (11, 13, 16, 17). In comparison, fewer studies have examined service models and outcomes for young people with childhood-onset disabilities (18–21).

The LETS study ("Longitudinal Evaluation of Transition Services") aims to contribute to this emerging evidence base by examining healthcare outcomes for youth and young adults with childhood-onset disabilities enrolled in a linked transition service delivery model (22). In Toronto, Ontario, two hospitals partnered to develop LIFEspan ("Living Independently and Fully Engaged"). This inter-agency collaboration was designed to formally link pediatric and adult rehabilitation services for youth with a diagnosis of childhood Acquired Brain Injury (ABI) or Cerebral Palsy (CP). The linkage was reflected in cross-appointed staff, a multi-disciplinary allied health team and standardized care processes, supporting a 2-year transition preparation at the pediatric hospital followed by a coordinated transfer to the adult hospital for ongoing care. The model reflects key principles outlined in a Canadian national guideline for transitioning from pediatric to adult care (23). Prior publications have reported on healthcare provider perspectives and experiences within the LIFEspan model and perceived successes related to enhanced transition preparation (18, 24, 25). The objective of this study was to quantitatively examine the impact of the LIFEspan model on healthcare outcomes, specifically continuity of care and healthcare utilization. It was hypothesized *a priori* that clients in

Abbreviations: ABI, acquired brain injury; CP, cerebral palsy; ED, emergency department; SB, spina bifida.

the LIFEspan model would have better continuity of care and a reduced reliance on emergency services for their care, compared with prospective, and historical controls.

METHODS

Study Design

The LETS Study was a prospective, longitudinal, observational mixed-method study evaluating the LIFEspan model of transition care. This study was completed before the COVID-19 pandemic. The full protocol has previously been published (22). This manuscript addresses the primary outcome of continuity of care through medical record audit; as well as secondary outcomes of healthcare utilization (physician office visits, emergency department visits, and hospitalization) through health services administrative dataset review. Diagnostic study groups included three childhood-onset neurological conditions: Acquired Brain Injury (ABI), Cerebral Palsy (CP) and Spina Bifida (SB).

Intervention

LIFEspan

The LIFEspan program is a coordinated, client-centered model of linked healthcare offered through a collaborative partnership between a pediatric rehabilitation centre (Holland Bloorview Kids Rehabilitation Hospital, Toronto, Canada) and an adult rehabilitation centre (Toronto Rehabilitation Institute, Toronto, Canada). Supported by multi-disciplinary healthcare teams, clients engage in a 2-year period of healthcare transition preparation from 16 to 18 years of age and are seen 2–4 times depending on individual need. During this period, they are medically followed (by pediatric physician/ambulatory care nurse or nurse practitioner) and work on transition-related goals (e.g., social participation, community involvement) with support from a youth facilitator, life skills facilitator and/or social worker. This preparation is followed by discharge from the pediatric hospital and a coordinated transfer to adult care around the age of 18 led by cross-appointed LIFEspan staff – nurse practitioner, youth facilitator and life skills facilitator – in the context of a formal linkage between the two rehabilitation centres. In addition to the cross-appointed roles, the adult LIFEspan team includes a physiatrist, social worker, occupational therapist, physiotherapist and speech language pathologist. Continued transition supports in the adult clinic focus on interventions to address goals set by the young adults and their families, and establishing linkages to community services, and allied and primary care resources. Details of the LIFEspan model have previously been described (24, 25).

At the time of this study, two pediatric clinics at Holland Bloorview serving clients with ABI and CP streamed into a single adult ABI/CP clinic at Toronto Rehabilitation Institute. Alternatively, clients could opt out of the LIFEspan service model pathway and make other choices for adult care provision.

Standard of Care

The Spina Bifida clinic at Holland Bloorview is supported by a multi-disciplinary team including nursing, occupational therapy, social work, psychology, physiotherapy and a life skills facilitator, as well as a pediatric physician (neonatology and developmental pediatrics), and consulting specialists in urology and orthopedics. Clients are seen annually, with intervention and consultation services as required. Around 18 years of age, these clients were referred to a local tertiary hospital (Sunnybrook Health Sciences Centre, Toronto, Canada) or other adult care provision of their choosing on discharge.

Recruitment and Sample

Study participants were recruited from Holland Bloorview; a large, urban, pediatric academic health sciences center supporting inpatient and outpatient rehabilitation needs of children and youth from birth to 18 years of age with physical disabilities and complex medical needs. Institutional policy mandated that all clients with ABI and CP received LIFEspan services. Thus, eligible participants for the "prospective" arm of the study were clients 16 years of age with a diagnosis of ABI or CP and enrolled in the LIFEspan model.

The LIFEspan program had no "waitlist" of clients from which to select a comparison group as all eligible clients were enrolled in the program. Therefore, alternative comparison groups were identified. First, clients 16 years of age in the Spina Bifida clinic at Holland Bloorview were selected as a prospective comparison group receiving "standard of care." In general, people with SB face the same challenges as those with ABI and CP with respect to complexity of care, the need for ongoing monitoring, and holistic support to maximize their health and wellness, social participation and community involvement. Individuals with SB also experience the same gaps in obtaining adult health services with the attendant consequences (5, 26). There are often, however, significant differences between these diagnostic groups with respect to baseline health status, clinical management, and health care utilization.

In addition to the prospective SB comparison group, data were also collected on a "retrospective" historical comparison group, consisting of past clients with ABI and CP at Holland Bloorview who had transitioned to adult care services without participating in the LIFEspan model. Data were collected over the same 3-year period for the comparison groups, i.e., for each client from 16 to 19 years of age.

Recruitment lists were generated by health data services based on date of birth (i.e., 16 years of age at enrolment) and diagnosis, with 88 ABI, 128 CP, and 43 SB clients identified for the prospective arm; and 61 ABI and 71 CP former clients for the retrospective arm. Prospective participants were recruited in-person. Retrospective participants were recruited via mailed information packages and follow-up phone calls. All participants provided written informed consent or written informed assent with parental/guardian consent. Ethics approval for the study was granted by Holland Bloorview Kids Rehabilitation Hospital, Toronto Rehabilitation Institute and Sunnybrook Health Sciences Centre.

Outcome Measures

Demographic Factors

Demographic and clinical information were collected on participants: sex, ethnicity and diagnostic details. The general health of prospective participants was self-rated using a global

health question ["In general, would you say your health is: excellent (5), very good (4), good (3), fair (2) or poor (1)?"] (27).

Primary Outcome Measure

The primary outcome of interest was the maintenance of *continuous care,* given that the published literature suggests that the core indicator of transition success is the minimization of loss of patients from pediatric discharge to adult follow-up (28). Lotstein et al. defines continuity of care as "ongoing access to age- and disease-appropriate health care" (29). In a systematic review of continuity of care during transfer to adult services, attendance at an adult clinic visit and/or time between last pediatric clinic visit and first adult clinic visit were the most common measures of engagement in adult care (17).

Medical charts at the adult hospitals (Toronto Rehabilitation and Sunnybrook) were audited to determine whether prospective participants had at least one visit to an adult provider within 1 year post-discharge (at around 18 years) from the pediatric rehabilitation hospital.

Secondary Outcome Measures

Healthcare utilization data were also collected on physician visits, emergency department visits, and hospitalizations determined from population-based, health services administrative datasets held by ICES, using participants' unique Ontario Health Insurance Plan (OHIP) number. ICES is an independent, non-profit research institute funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). As a prescribed entity under Ontario's privacy legislation, ICES is authorized to collect and use healthcare data for the purposes of health system analysis, evaluation, and decision support. Secure access to these data is governed by policies and procedures that are approved by the Information and Privacy Commissioner of Ontario. These datasets were linked using unique encoded identifiers and analyzed at ICES.

Statistical Analyses

For the primary outcome, Fisher's Exact Test was used to test for differences in the proportion of clients with continuous care between the prospective LIFEspan group and the prospective SB comparison group. For the secondary outcomes, the frequency of physician office visits, emergency department visits, and hospitalizations over the 3-year period of study were calculated per person-year. Each of the three groups—the LIFEspan group, the prospective SB group, and the retrospective historical comparison group—acted as their own control. In other words, the frequency of healthcare utilization in the year following discharge from the pediatric rehabilitation hospital (post) was compared with healthcare utilization in the 2 years prior to discharge (pre). Repeated measures GEE Poisson regression was used to estimate rate ratios (post vs. pre) along with 95% confidence intervals for the prospective LIFEspan group, the prospective SB group, and the retrospective historical (ABI+CP) group.

RESULTS

Participants

In total, 132 clients participated in the study: the prospective arm included 78 clients in the LIFEspan group (30 ABI and 48 CP) and 21 SB clients in the prospective comparison group. The retrospective "historical" comparison group consisted of 33 participants (15 ABI and 18 CP). Recruitment rates based on eligible clients were 30% for the prospective arm and 25% for the retrospective arm.

Table 1 shows the demographic characteristics of the participants in the prospective arm; most were male (64%) and born in Canada (88%). With respect to ratings of global health, both ABI and CP participants reported a median rating of 4 ("very good") and SB reported a median rating of 3 ("good").

Primary Outcome Measure

Of the 78 clients enrolled in LIFEspan, 35 (45%) had formal engagement with healthcare services in the adult hospitals within 1 year post-discharge (i.e., after 18 years of age), compared with only three of 21 (14%) SB clients ($p = 0.012$) during this window.

Secondary Outcome Measures

Of note, several participants in the prospective arm (5 ABI, 2 SB) did not consent to providing OHIP numbers and therefore population-based, health services administrative data could not be collected on these participants. Physician office visits, emergency department (ED) visits, and hospitalization data are presented in **Table 2**.

Physician Office Visits

On average, participants in the LIFEspan group had 4.82 physician office visits per person-year (1,056 total over the 3 years). The rate ratio for the LIFEspan group (post vs. pre) was 0.95 (95% CI: 0.77–1.17), $p = 0.626$. The prospective SB group had 7.18 physician office visits per person-year (409 total over 3 years), with a rate ratio (post vs. pre) of 1.13 (95% CI: 0.86–1.50), $p = 0.373$. The retrospective historical (ABI+CP) group had 7.07 physician office visits per person-year (700 total over the 3 years), with a rate ratio (post vs. pre) of 0.78 (95% CI: 0.59–1.04), $p = 0.096$.

In summary, the LIFEspan group had fewer physician office visits in the year after discharge from Holland Bloorview, compared with pre-discharge; however, this difference was trivial and not statistically significant. Likewise, there were no significant differences in physician office visits post- vs. pre-discharge for the prospective SB group and the retrospective historical (ABI+CP) group.

Emergency Department Visits

On average, participants in the LIFEspan group had 0.32 ED visits per person-year (70 total over the 3 years). The rate ratio for the LIFEspan group (post vs. pre) was 1.59 (95% CI: 0.98–2.58), $p = 0.060$. The prospective SB group had 0.74 ED visits per person-year (42 total over 3 years), with a rate ratio (post vs. pre) of 0.80 (95% CI: 0.41–1.54), $p = 0.505$. The retrospective historical (ABI+CP) group had 0.35 ED visits per person-year (35 in total

TABLE 1 | Clinical and demographic characteristics of (prospective) participants at study enrolment (16 years of age).

	ABI *N* (%)	CP *N* (%)	SB *N* (%)
Sex			
Male	19 (63)	30 (62)	10 (48)
Female	11 (37)	18 (38)	11 (52)
Diagnostic details	Injury: 20 (67)	GMCFS I: 12 (25)	Lipomyelomingocele: 17 (81)
	Medical: 10 (33)	GMCFS II: 5 (10)	Myelomeningocele: 2 (9.5)
		GMCFS III: 8 (17)	Not reported: 2 (9.5)
		GMCFS IV: 4 (8)	
		GMCFS V: 10 (21)	
		Other/Not reported: 9 (19)	
Canadian born*	17 (81)	32 (88)	14 (93)
Ethnicity*			
Caucasian	11 (52)	17 (47)	8 (53)
Black	6 (29)	7 (19)	2 (13)
Asian	2 (9)	6 (17)	4 (27)
Other	1 (5)	2 (6)	1 (7)
Prefer not to answer	1 (5)	4 (11)	0 (0)
Global health rating*	Median: 4	Median: 4	Median: 3
	Min: 1	Min: 2	Min: 2
	Max: 5	Max: 5	Max: 5

**Data not provided for 9 ABI, 12 CP and 6 SBI.*

TABLE 2 | Secondary outcomes: physician office visits, emergency department (ED) visits, and hospitalizations by study groups.

	Pre* events	Rate/person-year	Post^ events	Rate/person-year	Rate ratio# (post vs. pre)	95% CI
Office visits						
LIFEspan	716	4.90	340	4.66	0.95	0.77–1.17
SB	261	6.87	148	7.79	1.13	0.86–1.50
Historical	503	7.62	197	5.97	0.78	0.59–1.04
ED visits						
Lifespan	39	0.27	31	0.42	1.59	0.98–2.58
SB	30	0.79	12	0.63	0.80	0.41–1.54
Historical	25	0.38	10	0.30	0.80	0.36–1.76
Hospitalizations						
LIFEspan	10	0.07	3	0.04	0.60	0.17–2.16
SB	13	0.34	1	0.05	0.15	0.02–1.38
Historical	8	0.12	0	0	N/A	

**Two years prior to discharge.*
^One year post-discharge.
#Repeated Measures GEE Poisson Regression Analysis.

over the 3 years), with a rate ratio (post vs. pre) of 0.80 (95% CI: 0.36–1.76), $p = 0.580$.

In summary, the LIFEspan group had more ED visits in the year after discharge from Holland Bloorview, compared with pre-discharge; however, this difference was modest and not statistically significant. Similar findings, i.e., no significant difference in ED visits post- vs. pre- discharge for the prospective SB group and the retrospective historical (ABI+CP) group were also noted.

Hospitalizations

On average, participants in the LIFEspan group had 0.06 hospitalizations per person-year (13 total over the 3 years). The rate ratio for the LIFEspan group (post vs. pre) was 0.60 (95% CI: 0.17–2.16), $p = 0.434$. The prospective SB group had 0.25 hospitalizations per person-year (14 total over 3 years), with a rate ratio (post vs. pre) of 0.15 (95% CI: 0.02–1.38), $p = 0.095$. The retrospective historical (ABI+CP) group had 0.08 hospitalizations per person-year (8 in total over the 3 years).

There were no hospitalizations, however, in this group in the year following discharge, which made calculation of a post vs. pre rate ratio unfeasible.

In summary, the LIFEspan group had fewer hospitalizations in the year following discharge from Holland Bloorview, compared with pre-discharge; however, this difference was modest and not statistically significant. Likewise, there was no significant difference in hospitalizations post- vs. pre-discharge for the prospective SB group.

DISCUSSION

Introduction of the LIFEspan model of linked transitional care led to increased continuity of care (as measured by engagement with adult services within 1 year of pediatric discharge) for clients with ABI and CP, compared to clients with SB who were not enrolled in the model. Healthcare utilization data were inconsistent and showed no significant changes in physician office visits, ED visits, or hospitalizations for clients in the LIFEspan program in the year following discharge from the pediatric rehabilitation hospital, compared to the 2 years prior to discharge. Previously published Canadian research on childhood disabilities shows high rates of urgent care use by these specific clinical populations (26, 30).

This finding of successful transfer from pediatric to adult services aligns with previous qualitative evaluations of the LIFEspan model, based on provider reflections of increasing caseloads in the adult clinic following model launch (25) and positive transition experiences described by clients with ABI and their parents (18). In contrast to the comparison SB clinic that offered "standard of care," specific design features of the LIFEspan model may have fostered relational continuity through the cross-appointed staff roles as well as management continuity through the formal partnership between a pediatric and an adult rehabilitation hospital (31).

From a service delivery perspective, several studies have examined a variety of transition outcomes for "bridging" models, also described in the literature as "integrated" (32), "concurrent" (33), "intra-agency" (34), "co-located" (35) or "inter-agency" (19). For example, Harden et al. described an integrated joint multi-disciplinary pediatric-adult transition clinic and care pathway for youth with kidney failure (32). In this approach, patients were seen jointly by two teams from 15 to 18 years of age and then transferred by the age of 18 years to adult services. Enhanced engagement with healthcare providers and improved adherence to medication were noted, leading to reduced transplant failure rates compared with historical controls (32). Semalulu et al. described a similar joint transition program for youth with juvenile idiopathic arthritis and systematic lupus erythematosus (33). From 14 to 18 years of age, patients had concurrent pediatric and adult rheumatologist visits as part of a multi-disciplinary pediatric team; provision of care by the adult rheumatologist continued till 22 years of age following transfer to the young adult clinic. The study described trust as a key component of transition preparedness, with favorable perceptions of patient-provider relationships increasing with age (33). Van Pelt et al. conducted a longitudinal observational study of an intra-agency nurse facilitator model for youth with juvenile idiopathic arthritis with pediatric and adult clinics within the same medical centre (34). Patterns of drop-out during the transfer window of 16–18 years relative to other age windows—pediatric (10–13 years) and adult (18–27 years)—were examined. Relative to the comparison windows, drop-out rates were higher for the facilitator model during this period of upheaval, but still lower than rates noted in the literature in the absence of structured transition processes (34).

Nolan et al. further describe a co-location model distinguished by overlap in pediatric and adult care for young adults with sickle cell disease (35). In the model, young adults (18–25 years) were seen by an adult internist, in addition to a cross-appointed pediatric hematologist and a pediatric transition nurse coordinator, in monthly clinics within the adult setting. Nursing transition case management began at age 17 years in the pediatric setting. Continuity of care was maintained after transfer for the 59 participants enrolled in the model (35). Specific to childhood-onset disability, Lindsay et al. examined an inter-agency transition model for spina bifida (19, 36). Analogous to LIFEspan, the model comprised a formal linkage between a pediatric and an adult hospital, and included a cross-appointed nurse practitioner and life skills coach as members of the transition teams at each site (19, 36). Care experiences were examined qualitatively for parents, youth and young adults with SB (14–21 years) at varying stages of healthcare transfer, relative to a cohort that had transitioned prior to model introduction. Whilst few of the intervention group had transferred out of pediatric care, experiential narratives described enhanced perceptions of support related to accessing adult care. Cross-sectoral linkages were identified as required in the model to fully address extensive social, educational and vocational needs (19).

Our study had several strengths. First, the use of comparison groups, contemporaneous and historical, allowed a direct comparison of healthcare outcomes across time and clinical conditions. Second, there was minimal loss to follow-up of participants. We also had a diverse sample in terms of race and ethnicity. Last, data were extracted from an established, population-based, administrative data source. With respect to study limitations, many potentially eligible pediatric clients were not interested in participating in the study; a lack of data made comparison of those who agreed to participate and those who did not unfeasible. In addition, proficiency in English was an inclusion criterion, which meant that the experiences of clients from other cultural and linguistic backgrounds were not captured. Medical records and administrative databases may also have inherent limitations, depending on the accuracy and completeness of information collected. Last, the evaluation of healthcare utilization was limited by small sample sizes, relatively few events, and a short follow-up period of 1 year. These limitations may explain the inconsistent and statistically non-significant results related to healthcare utilization. Our findings on continuity of care, however, are consistent with previous systematic reviews that have examined continuity of care following participation in structured healthcare transition processes (11, 13). We believe our study is particularly important,

because of its emphasis on childhood-onset disabilities, given the previous predominant focus of evaluation studies on chronic illness (11–13, 16, 17).

Taken collectively, the current literature suggests that bridging models, such as LIFEspan, are particularly relevant for clients with childhood-onset disabilities, for whom multidisciplinary clinics are ideal for lifelong care (35). This necessity was highlighted in a 2016 survey of 11 nationally recognized US pediatric multi-disciplinary CP clinics. Survey respondents identified the limited number of adult providers willing to accept CP patients, concerns about the level of care in the adult healthcare system, and lack of financial resources as significant barriers that remained very "real and problematic." Of all the participating clinics, only one had transitioned 100% of its clients to adult providers by 22 years of age (37).

CONCLUSIONS

Clients who participated in the LIFEspan model were more likely to be *linked* to adult healthcare services following discharge from the pediatric hospital. Not all participants in the LIFEspan model were engaged with the adult healthcare system 1 year after discharge; however, the program appears to foster and enhance continuity of care outcomes for young adults with childhood-onset disabilities as they navigate the pediatric and adult service divide. With regards to future research, longer-term follow-up would provide a more in-depth understanding of the degree of adult engagement (specifically retention in the system) as well as long-term impacts on healthcare utilization. In this context, evaluation of outcomes three or more years after transition to adult care has been suggested (3, 37).

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because data from this study are held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification. Requests to access the datasets should be directed to das@ices.on.ca.

ETHICS STATEMENT

The study protocol was reviewed and approved by the Registered Ethics Board at each of the partnering hospitals: Holland Bloorview Research Ethics Board (Approval #09-036), University Health Network Research Ethics Board (Approval #10-009); and Sunnybrook Research Institute Ethics Office (Approval #251-2011). Written informed consent to participate was provided by participants, or assent to participate with consent by the participants' legal guardian/parent. The LETS Study is registered as a clinical trial: ID NCT00975338 with information available at www.clinicaltrials.gov.

AUTHOR CONTRIBUTIONS

SK, CM, MB, JM, SL, YH, and AC conceived the study design, obtained funding and contributed to execution of the project. SK, CM, and JZ performed data analysis and interpretation. SK and CM drafted the initial manuscript. SL, JM, YH, AC, JZ, and MB critically revised and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Well-Being of Ambulatory Adults With Cerebral Palsy: Education, Employment, and Physical Function of a Cohort Who Received Specialized Pediatric Care

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Introduction: The transition from pediatric health care and school systems presents enormous challenges for young adults with cerebral palsy (CP). The lack of strong societal support during this seminal life event is well-documented and leads many adults with CP to struggle with independence, higher education, and employment. Despite the relatively high prevalence of CP, information about the experiences and function of adults with CP in our society continues to be limited. The purpose of this project was to describe well-being by assessing education, employment, physical function, walking activity, and utilization of health care in an ambulatory adult cohort with CP who received specialized pediatric care at our center.

Method: In this Institutional Review Board-approved prospective study, we invited former patients from our tertiary care pediatric CP center to complete a set of patient-reported outcomes including (1) the Patient-Reported Outcomes Measurement Information System domains of physical function and pain interference, (2) the Satisfaction with Life Scale, and a project-specific demographic questionnaire about education, employment, income, independence, pain, and health care utilization. Participants also wore a pedometer for 8 days to monitor community walking activity. Chi-squared pairwise or *t*-tests were used as appropriate to compare survey responses and walking activity data between three groups: participants who self-reported, those who reported by proxy, and published normative data from age-matched typically developing adult (TDA) samples.

Results: One hundred twenty-six adults with CP consented to participate; 85 self-reported [age 29.7 ± 4.3 years; Gross Motor Function Classification System: I (28%), II (47%), and III, (25%)] and 41 reported by proxy [age 29.7 ± 4.1 years; Gross Motor Function Classification System: I (10%), II (68%), and III (22%)]. For the group who self-reported, high school graduation rate (99%) was similar to TDA (92%; $p = 0.0173$) but bachelor's degree achievement rate (55%) was higher than TDA (37%; $p < 0.001$). Despite more advanced education, the unemployment rate in this group was higher than national levels at 33% and was associated with high utilization of Social Security Disability

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Insurance (33%). Within the self-reporting group, 13% required a caregiver. For the group who reported by proxy, educational levels (73% high school graduates, 0 bachelor's degree) were lower than the general population ($p < 0.001$) and unemployment was higher than the national level, at 64%. Unemployment in this group was associated with high utilization of Social Security Disability Insurance (85%). Within the proxy-reporting group, 71% required a caregiver. The full cohort demonstrated lower levels of physical function according to the Patient-Reported Outcomes Measurement Information System and less community walking activity compared with TDA references ($p < 0.001$). This cohort of adults with CP reported significantly higher frequency of chronic pain (48 vs. 12% for TDA; $p < 0.001$), but less pain interference with daily activities than TDA based on Patient-Reported Outcomes Measurement Information System results ($p < 0.001$). This cohort reported good to excellent overall health (93%) and high utilization of primary care (98%), but limited utilization of specialty care, specifically orthopedic care (21%) and physical therapy (15%).

Discussion: This cohort of adults with CP had similar levels of education as the general population, but had relatively high rates of unemployment, caretaker need, and Social Security Disability Insurance utilization. Although chronic pain was frequent, the impact of pain on work and independent living did not exceed reports from a typically developing reference. Better targeted societal resources for adults with physical disabilities are urgently needed to allow equitable access to employment, promote opportunities for independence, and enable full participation in community life.

Keywords: cerebral palsy, adults, health, education, employment, independence

INTRODUCTION

Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, which cause activity limitation and are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior; by epilepsy; and by secondary musculoskeletal problems (1). Cerebral palsy is known to cause motor dysfunction leading to impairments that persist throughout the lifespan (2). These impairments can have an impact on mobility and a variety of factors that influence overall quality of life and well-being. With appropriate medical and supportive care, life expectancies for ambulatory adults with CP can approach that of typically developing adults (TDA). Hence, understanding trajectories of well-being and function for adults with CP is important to determine barriers that prevent individuals from achieving their maximum societal potential.

Currently, limited research is available on self-reported outcomes of adults with CP, whether functional in nature or related to quality of life (2, 3). From a functional standpoint, orthopedic surgery is widely applied during childhood to help improve long-term mobility and participation. These treatments, however, may only prevent or retard the development of further functional deterioration and relative gains that may not affect a patient's independence, education goals, or levels of employment as adults (4). As such, more research throughout the lifespan of individuals with CP is needed to identify barriers and develop solutions that serve to improve long-term outcomes–both functional and societal–for adults with CP.

Conflicting evidence exists related to achievements in education and employment for adults with CP (5–11). Reports of university degree completion varied widely at 2% (6), 5% (7), and 24% (8). A study from South Africa found that 50% of adults with CP had enrolled in post-secondary education, but the main source of income for 37% of the participants was governmental disability benefits (9). Employment rates for adults with CP also vary, reported at 79% (10), 68% (5), 45% (11), and 36% (6).

Access to primary and specialized health care is important for well-being. There is conflicting evidence in the literature regarding adequate access to health care for adults with CP in the United States. For instance, a study by Gannotti et al. (4) found that over half of adults with CP reported having "easy" to "very easy" access to health care with only a small number classifying their access to health care as being difficult. Orlin et al. identified several barriers for adults with CP to access specialized health care, including relying on family or caregivers for transport, communication difficulties, and issues relating to follow-up (12).

A few studies have investigated quality of life (QoL) in adults with CP (13–16). Similar to studies focused on functional

Abbreviations: CP, cerebral palsy; GMFCS, Gross Motor Function Classification Scale; TDA, non-disabled adults; PR, proxy-reported; PROMIS, Patient-Reported Outcomes Measurement Information System; SR, self-reported.

mobility, findings relating to life satisfaction, depression, and well-being have been inconsistent. One study suggested that adults with CP maintain childhood levels of mobility function in young adulthood, are satisfied with social roles, and have minimal pain (3). In their population-based study, Morgan et al. reported that health status and well-being in adults with CP is below average compared with TDA (14). By contrast, Jarl et al. reported high health-related QoL in adults with CP overall, with reduced QoL only for those with severe motor dysfunction and pain (13). Others reported that limited functional mobility is not associated with mental health impairment (3, 15, 16). Pain, which has been linked to decreased QoL, is highly prevalent in CP (30–80% of adults) (17–19).

The purpose of this project was to assess independence, education, employment, walking activity, pain, utilization of health care, and physical function in an adult cohort of former patients from a pediatric CP specialty center.

MATERIALS AND METHODS

Potential study participants were identified from a historical database from the authors' institution. Inclusion criteria were individuals who (a) were between the ages of 25 and 45 years; (b) had a diagnosis of CP; and (c) were functioning at Gross Motor Function Classification System (GMFCS) level I, II, or III. The study was approved by our institutional review board (# 1115672).

Patient-Reported Outcomes

Participants were asked to complete, with or without caregiver assistance, an online demographic survey and two domains of the Patient-Reported Outcomes Measurement Information System (PROMIS) tool, including (1) physical function v2.0 and (2) pain interference v1.1. The PROMIS is a rigorously constructed, generalizable, and clinically relevant set of patient-reported outcomes developed by the National Institutes of Health (20). Additionally, the survey consisted of questions that collected demographic data (such as sex, age, ethnicity, race, etc.), highest level of education, employment, personal and household income levels, frequency of pain, health care provider utilization, and life satisfaction (21, 22).

Walking Activity

To monitor community-based walking activity, participants were given a Food and Drug Administration approved class-2 activity monitoring device (Modus StepWatch, Edmonds, WA USA), to track the participant's walking activity for 8 consecutive days. The device was calibrated to each adult's specific gait pattern in our gait analysis laboratory following the guidelines of the manufacturer to verify accuracy (23).

Normative Comparison

Whenever possible, we compared our data with published results for age-matched TDA in the United States. Education was compared with data collected through the United States Census in 2017 (24) for adults aged 25–34 years. Information on employment and the rate of Social Security Disability Insurance was compared with the United States Bureau of Labor Statistics report (25). Income levels for TDA from 2017 were obtained from the Income and Poverty in the United States: 2019 report (26). An age-matched (30–39 years old) cohort of 193 TDA living in the United States was used for comparison with the average strides per day collected from adults with CP (27). In 2012, pain was self-reported in a study population consisting of over 8,000 adults in the United States, where 11.2% of the adults reported chronic pain occurring on a daily basis (28). Normative values for PROMIS pain interference and physical function were obtained from a published data bank source of 1,700–15,903 TDA adults (20). Satisfaction with Life Scale results were compared with published TDA data (22).

Statistics

Pairwise comparisons, chi square, or *t*-tests were used as appropriate to compare responses between self-reporting adults ($n = 85$), proxy-reporting adults ($n = 41$), and normative data for TDA. Statistical significance was set at $p < 0.0167$ to account for multiple (three-way comparisons). All statistical analyses were performed using R-Studio version 1.4.1106 (29).

RESULTS

A total of 645 adults who met the inclusion criteria were identified from historical databases and invited to participate in the study. Of these, we successfully contacted 171, and a total of 152 adults with CP agreed to participate in the study (see **Figure 1**). Twenty-six respondents were excluded due to having incomplete survey responses or not functioning at GMFCS level I, II, or III. Participants were placed in two groups, those who completed the survey/questionnaire by themselves (self-reported) and those who used an assistant to answer the questions (proxy-reported). A total of 85 participants were included in the self-reported (SR) group (41 female, 29.7 ± 4.3 years old). This group self-identified ethnically as 88% White, 9% Black or African American, 1% Japanese, and 1% as "Other." The GMFCS distribution was I (28%), II (47%), and III (25%), and was not significantly different compared with the 645 eligible participants ($p > 0.1$).

A total of 41 participants were included in the proxy-reported (PR) group [15 females (37%), 29.7 ± 4.1 years old]. This group self-identified ethnically as 73% White, 20% Black or African American, 2% Korean, and 5% as "Other." The GMFCS distribution was I (10%), II (68%), and III (22%).

Socioeconomic Factors

Participants in the SR group were found to have similar or higher levels of education compared with the TDA population, in contrast with the PR group who were found to have lower levels of academic achievement (see **Table 1**). Eighty-four participants in the SR group (99 vs. 92% of TDA; $p = 0.0173$) graduated from high school and 48 (57 vs. 37% of TDA; $p < 0.001$) obtained a bachelor's degree or higher. Only 30 participants in the PR group (73%) were found to have graduated from high school and none

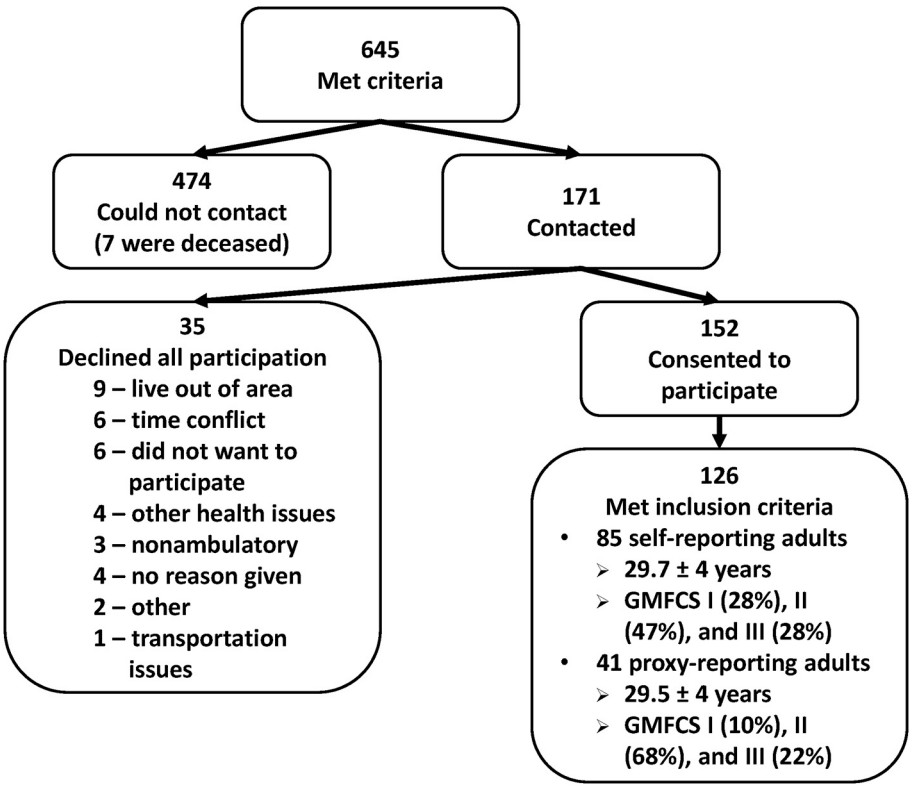

FIGURE 1 | Breakdown of 645 adults who met the inclusion criteria and were invited to participate in the study. GMFCS, Gross Motor Function Classification System.

TABLE 1 | Socioeconomic factors: education, employment, and income of adults with cerebral palsy compared with non-disabled adult populations.

Outcome	Self-report (n = 85)	Proxy-report (n =41)	TDA	SR vs. PR p-value	SR vs. TDA p-value	PR vs. TDA p-value
Graduated high school, %	99	73	92	<0.001	0.0173	<0.001
Attained bachelor's degree or higher, %	57	0	37	<0.001	<0.001	<0.001
Employment, %	68	37	96	<0.001	<0.001	<0.001
Full-time/part-time, %	68/32	27/73	80/20	<0.001	0.003	<0.001
Personal income [Mean (SD)]	$36,743 ($32,308)	$14,193 ($23,169)	$35,001	<0.001	–	–
Household income [Mean (SD)]	$86,394 ($58,185)	$73,451 ($60,876)	$86,992 ($892)	0.259	0.925	0.154
Utilization of SSDI, %	32	85	–	<0.001	–	–

– indicates not applicable. TDA, typically developing adults; PR, proxy-report; SD, standard deviation; SR, self-report; SSDI, Social Security Disability Insurance.

had attained a level of higher education (bachelor's degree or higher; $p < 0.001$ compared with the SR group and TDA).

Similarly, participants in the SR group were found to have a comparable level of personal and household income as TDA, while participants in the PR group had significantly reduced personal income compared with the SR group ($p < 0.001$). In terms of unemployment rate, both groups in this study showed higher levels of unemployment compared with the 4.4 ± 0.2% unemployment rate reported for adults in the United States through 2017 ($p < 0.001$) (25). Additionally, adults with CP in the PR group showed higher levels of Social Security Disability Insurance use than the SR group ($p < 0.001$).

Independence and Physical Capacity

Regarding levels of functional independence, the PR group showed a greater need for a caregiver than the SR group ($p < 0.001$) (see **Table 2**). Adults with CP showed significantly higher levels of chronic pain, 47.1% (SR) and 53.7% (PR), compared with 11.2% found in TDA ($p < 0.001$), but demonstrated less pain interference in daily activities than TDA reported according to PROMIS results ($p < 0.001$).

In terms of walking activity, 75 individuals from the SR group and 39 from the PR group had valid data from the StepWatch device. Walking activity was significantly lower in both groups compared with a published cohort of 193 TDA

TABLE 2 | Independence and physical capacity.

Outcome	Self-report ($n = 85$)	Proxy-report ($n = 41$)	TDA	SR vs. PR p-value	SR vs. TDA p-value	PR vs. TDA p-value
Need a caregiver, %	13	71	–	<0.001	–	–
Spasticity, %	66	66	–	1.00	–	–
Joint/muscle pain, %	72	61	–	0.214	–	–
Chronic pain, %	47	54	11	0.487	<0.001	<0.001
SWLS [Mean (SD)]	26.2 (7.0)	22.5 (7.5)	20–24 (Range)	0.009	–	–
PROMIS pain interference [Mean (SD)]	50.7 (9.3)	49.2 (8.1)	55.9 (10.8)	0.356	<0.001	<0.001
PROMIS physical function [Mean (SD)]	44.5 (9.7)	35.5 (8.9)	50 (10)	<0.001	<0.001	<0.001
Walking activity [strides/day; Mean (SD)]	2,679 (1,992)	1,727 (269.7)	5,127 (2,834)	<0.001	<0.001	<0.001

– indicates not applicable. TDA, typically developing adults; PR, proxy-report; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation; SR, self-report; SWLS, Satisfaction with Life Scale.

TABLE 3 | Primary and specialty care utilization by adults with cerebral palsy.

Outcome	Self-report ($n = 85$)	Proxy-report ($n = 41$)	P-values
Visit an orthopedic specialist, %	20.0	19.5	0.947
Visit a physical therapist, %	15.3	14.6	0.918
Visit a primary care physician, %	97.6	100	0.317
Visit a dentist, %	75.3	87.8	0.104
Visit an obstetrician-gynecologist (females), %	67.3	53.3	0.335
Good to excellent health, %	92.9	87.8	0.343

in the United States (p-value < 0.001) (27). These results were in keeping with lower scores on the PROMIS physical function domain observed in both groups compared with TDA ($p < 0.001$).

Primary and Specialty Care Utilization

There were no significant differences in primary and specialty care use between groups of people with CP ($p > 0.1$) (see **Table 3**). Our results indicate that adults with CP had relatively low utilization of orthopedic specialists (∼20% in both groups) or physical therapists (∼15% in both groups). Women's responses indicated that slightly over half visited an obstetrician-gynecologist. Nevertheless, around 90% of both groups classified their overall health as "good to excellent."

DISCUSSION

The transition from adolescence to adulthood is a seminal life event. For youth with CP, the loss of pediatric health care and school-based support systems presents enormous challenges. A lack of strong societal support mechanisms is well-documented for people with disabilities and leads many young adults with CP to struggle with independence, higher education, and employment (2, 5–11, 30). These observations have been documented in other countries, such as Norway where individuals with CP had lower odds of completing upper secondary education and had higher odds of receiving a disability pension (31). Similarly, a study from Latvia showed only 9% of adults having a paid job whereas 44% were still financially dependent as adults (32). This is consistent with several other studies reporting low employment rates in adults with CP (5, 6, 10, 11). Despite the relatively high prevalence of CP, information on the life experiences and function of adults with this condition in our society is limited. Conflicting and limited evidence is available related to mobility, quality of life, and the factors that influence these issues in adults with CP (3, 13–16). Such knowledge could inform both comprehensive transition programs and better targeted societal mechanisms to support adults with childhood onset conditions such as CP.

From a socioeconomic perspective, there were clear differences in this cohort between those who self-reported and those who did not. Educational achievement and employment rates were higher in the SR group compared with the PR group. In terms of work "quantity," full-time employment was more prevalent than part-time in the SR group, whereas part-time employment was more commonly reported in the PR group.

When compared with the TDA reference, both the SR and PR groups had significantly lower employment rates. While adults with CP in the SR group had similar high school and higher post-secondary education attainment rates as TDA, there was a significantly lower employment rate than in the TDA reference. This suggests the presence of societal barriers to employment opportunities for adults with CP.

Our results on educational attainment compared with the TDA population are in contrast with other studies where lower levels of advanced educational attainment were found (7, 9). Some of the variability in education and employment reports could be related to the frequency of cognitive involvement in each study sample. Many of the differences between the SR and PR groups are thought to be related to comorbid cognitive impairments that we did not fully capture in the demographic survey.

It has been reported that adults with CP face declining health with aging related to increased levels of pain (2, 30, 33, 34). For

instance, a study on self-reported health outcomes found that 63% of adults with CP report chronic pain (35). This is consistent with the current study findings where, compared with a cohort of TDA, both groups of adults with CP (SR and PR) demonstrated higher frequency of chronic pain, with lower levels of physical function and community-based walking activity. Despite the high incidence of chronic pain, this cohort of adults with CP reported less pain interference with daily activities compared with TDA and had average to above average satisfaction with life. Similar findings on pain interference levels were reported by Flanigan et al. for a group of adults with CP (36).

Utilization of specialized musculoskeletal care by the young adults with CP in this study was much lower compared with the highly specialized pediatric services provided during childhood, specifically, orthopedics, and physical therapy. While we could not confirm that low utilization was related to lack of access, participants frequently reported that they could not find adult providers specializing in CP care.

It has been hypothesized in the literature that access to specialty health care for adults with CP is limited because CP is considered to be a static condition with a focus on care during childhood (2, 30, 37). There is conflicting information in the literature about the accessibility to specialized health care for adults with CP. Roquet et al. found that adults with CP have low utilization of rehabilitative physical health care (37), whereas Gannotti et al. found that most adults with CP had easy access to general health care (4).

Children with CP have higher utilization of specialty care, the focus of which is optimizing mobility function and musculoskeletal health, compared with typically developing youth. The lack of quality rehabilitation and orthopedic care for adults with CP could hinder the maintenance of functional mobility since orthopedic sequelae persist throughout the lifespan and continue to impact motor performance. Compounding this on the medical side, a high prevalence of comorbidities in persons with CP is associated with decreased overall health in adulthood (2, 30, 33, 34).

Limitations

This study was not population-based and included ambulatory adults with CP who were previously treated at the authors' institution. Therefore, our results should be interpreted with caution when extrapolating to adults with CP in other locales. GMFCS scores were given at the adult visit, but the classification has not been validated in that population. Another limitation in this study was the inability to distinguish between participants in the PR group who had a substantial cognitive or fine motor skill impairment as the reason for a proxy requirement and those who did not. Future research into the health-related outcomes and community participation of adults with CP should focus on identifying and removing barriers as well as developing effective care and support mechanisms throughout the lifespan for people with CP.

CONCLUSION

The cohort of young adults with CP in this study had similar levels of higher education as the general population and had good access to primary health care. Despite this, there were relatively high rates of unemployment, caretaker need, and SSDI utilization. Although reports of pain were frequent, the pain did not interfere with physical activities and did not limit satisfaction with life compared with an age-matched reference. Improvements in societal and medical resources for adults with childhood onset physical disabilities such as CP are urgently needed to allow equitable access to employment and independent living opportunities and promote full societal integration.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Nemours Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MS, CC, NL, JH, and FM contributed to the conception and design of the study. MS, CC, NL, TS, JS-T, JH, and FM contributed to the methodology of the study. JS-T and JH contributed to software design and procurement for the study. CC, NL, TS, JS-T, and JH participated in the validation of the data. MS, CC, NL, TS, JS-T, and FM participated in the formal analysis of the data. MS, CC, TS, JS-T, and FM participated in investigation of the data and provided resources for the study. MS, CC, TS, JS-T, and JH curated the data for the study. MS and TS wrote the original draft of the manuscript. MS, CC, NL, and FM provided visualization for the study and acquired the funding for the study. MS, CC, and FM provided supervision for the study. CC provided project administration for the study. All authors contributed to manuscript revision, read, and approved the submitted version.

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METHODS
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Systematic Monitoring of Cognition for Adults With Cerebral Palsy—The Rationale Behind the Development of the CP*Cog*-Adult Follow-Up Protocol

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Cerebral palsy (CP) comprises a heterogeneous group of conditions recognized by disturbances of movement and posture and is caused by a non-progressive injury to the developing brain. Birth prevalence of CP is about 2–2.5 per 1,000 live births. Although the motor impairment is the hallmark of the diagnosis, individuals with CP often have other impairments, including cognitive ones. Cognitive impairments may affect communication, education, vocational opportunities, participation, and mental health. For many years, CP has been considered a "childhood disability," but the challenges continue through the life course, and health issues may worsen and new challenges may arise with age. This is particularly true for cognitive impairments, which may become more pronounced as the demands of life increase. For individuals with CP, there is no one-to-one correlation between cognition and functioning in other areas, and therefore, cognition must be individually assessed to determine what targeted interventions might be beneficial. To facilitate this for children with CP, a systematic follow-up protocol of cognition, the CP*Cog*, has been implemented in Norway and Sweden. However, no such protocol currently exists for adults with CP. Such discontinuity in healthcare services that results from lack of follow-up of cognitive functioning and subsequent needs for adjustments and interventions makes transition from pediatric to adult healthcare services challenging. As a result, a protocol for the surveillance of cognition in adults with CP, the CP*Cog*-Adult, has been developed. It includes assessment of verbal skills, non-verbal reasoning, visual–spatial perception, and executive functioning. It is

recommended to perform these assessments at least once in young adulthood and once in the mid-fifties. This report describes the process of developing the CP*Cog*-Adult, which has a three-fold purpose: (1) to provide equal access to healthcare services to enable the detection of cognitive impairments; (2) to provide interventions that increase educational and vocational participation, enhance quality of life, and prevent secondary impairments; and (3) to collect systematic data for research purposes. The consent-based registration of data in the well-established Swedish and Norwegian national CP registries will secure longitudinal data from childhood into adulthood.

Keywords: cerebral palsy, cognition, assessment, intelligence, transitioning, life-span, health service access

INTRODUCTION

Cerebral palsy (CP) is a condition that comprises a heterogeneous group of individuals with motor impairments due to a congenital brain malformation or an early acquired brain lesion. The motor disability is often accompanied by other impairments, of which cognitive functioning is one of the areas frequently affected (1). Cognitive impairments can have far-reaching consequences, and affect academic learning, social functioning, self-care skills, and participation in society. There is a large variability in the type and severity of cognitive impairments among individuals with CP, ranging from challenges affecting functioning in just one area to severe and global impairments (2, 3). Although cognition and motor functioning are associated, there is not a one-to-one relationship (4) and individual assessment of cognition is therefore recommended (5).

CP has for many years been regarded as a "childhood disability" in the sense that interventions have been mainly targeting children and adolescents. To ensure that all children with CP are offered individual assessments of cognition, a protocol of cognition for children with CP (the CP*Cog*) was developed in Scandinavian countries (i.e., Sweden, Denmark, and Norway) (6). Research emerging over the last decades has shown, however, that challenges continue into adulthood, when pre-existing problems worsen and new challenges may arise (7, 8). Despite this, there is no systematic follow-up of cognition in adults with CP in Scandinavian countries. In addition to challenges experienced by most young adults, such as gaining independence, completing an education or a training, gaining employment, and starting a family, adults with CP also report specific challenges, including increased experiences of pain, mental fatigue, and loss of functioning. Thus, although the initial brain lesion is non-progressive, the consequences may change over time (9–18). This is also true for cognitive impairments (11). Specific cognitive impairments, such as executive dysfunctioning (19) and visual–perceptual impairments (20), play a larger role as expectations of academic functioning and independence increase. Adults with CP are less likely to be employed than their adult counterparts without CP, even after completing regular education and having normal intelligence (21). Sometimes, the reason is lack of physically accessible workplaces or sufficient adaptation to perceptual problems, but mental fatigue, pain, and lack of compensatory aids may also contribute. Being excluded from employment has ramifications other than the obvious financial ones, as work not only is a source of income, but also provides companionship, purpose, and feelings of being able to contribute and participate (22). For society, it is preferable that people who are capable of employment are working, and necessary adaptations should therefore be put in place to enable employment for as many as possible (23). Moreover, in 2006, the United Nations published the *Convention on the Rights of Persons with Disabilities* (CRPD), which mandates in-home, residential, and community support services, including personal assistance necessary to prevent isolation and segregation by supporting living and inclusion in the community (24). Scandinavian countries have all ratified the CRPD (25).

Scandinavian countries have public health and welfare systems that are available for all at low costs. In Sweden and Norway, services to children and adults with congenital and early acquired brain injuries are offered through the habilitation centers, while adults who acquire brain injuries are offered services through rehabilitation hospitals and centers (26). The habilitation centers for adults are a part of the specialized healthcare services, and as each serves a limited geographical cohort of inhabitants, together they provide national coverage in each country. In Sweden, there are a total of 137 habilitation centers for adults throughout the 21 hospital regions (27). In Norway, there are 20 hospital trusts that offer habilitation services to adults, with a total of 31 teams/locations (28). Denmark does not have a system of habilitation centers, neither for children nor for adults, but follow up individuals with disabilities in the municipalities.

The first systematic Scandinavian surveillance program for CP was established in Sweden in 1994, and during the next 16 years, it spread to Norway and Denmark (29). The Swedish Cerebral Palsy Follow-up Program (CPUP), the Norwegian Quality and Surveillance Registry for Cerebral Palsy (NorCP), and the Danish Cerebral Palsy Follow-up Program (CPOP) are combined quality registries and surveillance programs (30, 31) [The NorCP in Norway includes the former Cerebral Palsy follow-up program (CPOP) and the Cerebral Palsy Registry of Norway (CPRN), which were combined in 2020 (32)]. The surveillance programs have primarily focused on motor functioning. The cognitive follow-up protocol for children, the CP*Cog*, was first introduced in Norway in 2012 and in Sweden in 2015 (33). In Denmark, the need for cognitive follow-up of children with CP has been recognized, but implementation of CP*Cog* has been challenging

partly due to the organization of the healthcare services, which lack a similar structure to Swedish and Norwegian habilitation centers. In Norway, the introduction of the CP*Cog* has led to more children with CP being offered assessments of cognition. Before the introduction, only 29% of children with CP had been assessed with a standardized test of intelligence (30). After increasing knowledge about the CP*Cog* protocol in the pediatric habilitation centers through a quality improvement project in 2019, this number increased to 54% (34). In Sweden, over the last 5 years, 14 of the 21 regions have started to record cognitive data in the CPUP database, and by December 2020, 292 children (∼7% of all children with CP in Sweden) had undergone cognitive assessments [unpublished results].

For persons with disabilities, it is vital to have proper knowledge and understanding about personal strengths and challenges in order to be able to describe the type of adaptations that are required (10, 35). These adaptations pertain not only to physical accessibility, but also to adaptations necessary to handle the cognitive demands of education, work, or of meaningful and fulfilling activities if employment is not an option. For instance, the appropriate type of communication aid is central for adults with CP who have speech impairments (17, 23, 36). This implies that adults with CP need to have detailed knowledge about their cognitive functioning and needs.

Despite the vast impact cognitive impairments might have on the possibilities of independent living, employment, communication, and general wellbeing among adults with CP, very few studies have focused on cognitive functioning or on interventions aimed at increasing the management of cognitive impairments (37–39). The only exceptions being some studies that highlight the executive difficulties adults with dyskinetic CP might experience (40, 41). In addition, there are very few longitudinal studies following cognition in cohorts of children with CP (2), and as far as we are aware, there is only one longitudinal study that includes adults (8). In this study, however, cognition was not assessed, but was included as one of several dimensions in a questionnaire on quality of life on which the adults reported functioning.

Given the identified clinical needs and the lack of studies of cognitive functioning in adults with CP, the decision was made to extend the current systematic surveillance program for cognition in children and youths, the CP*Cog*, to adults with CP. The aim of this article is to describe the rationale behind the protocol for the systematic assessment of cognition in adults with CP—henceforth referred to as the CP*Cog*-Adult—and how this protocol may enhance access to healthcare services in Norway and Sweden.

MATERIALS AND EQUIPMENT

Participants

All persons 18 years or older living in Norway and Sweden with a diagnosis of CP (42) are eligible for inclusion. The prevalence of CP is now ∼2–2.5 per 1,000 live births in Scandinavian countries, which implies that, per birth year, there is ∼140–165 living with CP in Norway and Denmark and 200–220 in Sweden (31, 43–45). However, for adults, the prevalence is probably lower. Based on Swedish registry data, it was recently reported to be as low as 1.1 per 1,000 (46).

Instruments

The core battery of instruments chosen to assess cognitive functioning was selected based on the following criteria: (1) equivalence to instruments included in the pediatric surveillance protocol CP*Cog*, (2) their current use and availability in the habilitation centers, and (3) availability of national or Scandinavian norms. The core battery therefore consists of a standardized test of intelligence, the Wechsler Adult Intelligence Scale (47, 48), a test of visual–spatial abilities, the Beery-Buktenica Developmental Test of Visual-Motor Integration (49), and the questionnaire Behavior Rating Inventory of Executive Function (50, 51) for self- and proxy report on executive functioning in daily life (see **Table 1**).

In addition to the core instruments in CP*Cog*-Adult, it is recommended to use instruments for more thorough assessments of attention, executive functioning, and memory, if challenges in these areas are detected. For this purpose, tasks from the Delis-Kaplan Executive Function System (53, 54), such as the Trail Making Test and the Color–Word Interference, the California Verbal Learning Test (55), the Rey Complex Figure Test (56), and the Wisconsin Card Sorting Test (52) are recommended. If participants report, or mental health issues are noted, it is recommended to administer the Hospital Anxiety and Depression Scale (63), and that referrals are provided to receive professional help, as appropriate. If a diagnosis of intellectual impairment is suspected, it is recommended to use instruments such as the Vineland Adaptive Behavior Scale (57, 58).

Cognitive assessments of individuals with the most severe motor impairment include adaptations, such as substituting finger pointing with gaze pointing on a computer screen using tests with a multiple-choice format (64). It is therefore recommended that cognitive assessments of adults with the most severe speech and motor impairments are offered at habilitation centers with specialized knowledge about the use of assistive technology and augmentative and alternative communication (AAC) and that funding is applied to develop this knowledge when necessary.

In Norway, it is recommended to use instruments for assessment of fatigue, pain, self-care abilities and activities of daily living, as this might affect participation in everyday life and employment. Suggested instruments are the Fatigue Severity Scale (FSS) (59) or the Modified Mental Fatigue Scale, which is developed particularly for adults with CP (60), the section on pain from the Short Form Health Survey-36 (SF-36) (61), and the 12-item version of the World Health Organizations Disability Assessment Schedule 2.0 (WHODAS 2.0) (62). The FSS, WHODAS 2.0, and pain questions from SF-36 are already part of CPUP for adults in Sweden.

Assessment Time Points

The CP*Cog*-Adult includes two recommended assessment points, and two additional time points, which are proposed to be

TABLE 1 | Instruments in the CP*Cog*-Adult for assessing cognition and adaptive functioning: core battery (recommended for all) and supplemental tests (administered on indication).

Area	Test	Task	Type of instrument	Included in
Cognition	Wechsler Adult Intelligence Scale (47, 48)	At minimum tasks necessary for a IQ score	Test	Core battery
	The Beery-Buktenica Developmental test of Visual-Motor Integration (49)	Copy, visual perception, and motor integration	Test	Core battery
Attention and executive functioning	Behavior Rating Inventory of Executive Function—Adult (50, 51)	Self-report and informant report	Questionnaire	Core battery
	Wisconsin Card Sorting Test (52)		Test	Supplemental battery
	Delis-Kaplan Executive Function System (D-KEFS) (53, 54)	Trail Making Test and the Color–Word Interference	Test	Supplemental battery
Memory	California Verbal Learning Test (55)		Test	Supplemental battery
	Rey Complex Figure Test (56)		Test	Supplemental battery
Adaptive functioning	Vineland Adaptive Behavior Scales (57, 58)	Informant report	Informant interview/questionnaire	Supplemental battery
Fatigue	Fatigue Severity Scale (59)		Questionnaire	Supplemental battery*
	Modified Mental Fatigue Scale (60)		Questionnaire	Supplemental battery
Pain	Short Form Health Survey-36 (SF-36) (61)	Section about pain	Questionnaire	Supplemental battery*
	World Health Organization Disability Assessment Schedule (WHODAS 2.0) (62)	The 12-item version	Questionnaire	Supplemental battery*
Mental health	Hospital Anxiety and Depression Scale (63)		Questionnaire	Supplemental battery

**Already included in the follow-up program (CPUP) for adults with CP in Sweden.*

TABLE 2 | Recommended time points for the assessment of cognition and adaptive functioning in adults with cerebral palsy.

Age	Rationale	Status
18–19 years	Knowledge of cognitive functioning may aid in planning education and housing. Recommend assessment if not done during adolescence.	Optional
24 years	Aid in transitioning from education to employment. First time during adulthood that all with CP are scheduled for follow-up as part of CPUP-Adult in Sweden.	Highly recommended
42 years	Approximately midway through employment. Highly recommended for adults with bilateral CP, to prevent late adverse effects with respect to pain and fatigue, which might be particularly prevalent in this group.	Optional
54 years	Knowledge of cognitive functioning may be beneficial to prevent early retirement or transition to disability benefits due to health reasons.	Highly recommended

optional (see **Table 2**). This assessment schedule will enable long-term follow-up of the participants, as well as longitudinal studies.

These time points are guidelines and might need to be adjusted somewhat for feasibility. Furthermore, if an adult has recently (i.e., within the last 5 years) been cognitively assessed as part of their clinical follow-up, assessment should not be repeated for the mere sake of following the CP*Cog*-Adult protocol. For example, if a 24-year-old adult has already been assessed sometime between 19 and 23 years of age, he/she should not be reassessed at 24 years of age unless it is deemed appropriate for another reason.

METHODS

The initiative to develop the CP*Cog* protocol for children was taken by the umbrella organization for the user organizations in the Nordic countries (CP Norden) and the subsequent development was described as the result of a natural experiment (6). Based on our experiences from this (34) and the development of procedures to systematically follow-up adults with CP in other domains (65, 66), professionals in Scandinavia involved in the development of the CP*Cog* took the initiative to develop the CP*Cog*-Adult (In 2012, an initiative was taken to include the other two Nordic countries, Iceland and Finland, in the development of the CP*Cog* protocol, but was unfortunately not successful at that time).

The development process started in the spring of 2019. Initially, meetings and discussions were country-specific. Next, professionals from Scandinavian countries met at Lund University, Sweden, in April 2019, after which a first draft of the protocol was sent out to professionals and user representatives in all three Scandinavian countries. This draft was then discussed in a meeting consisting of representatives, both professionals and users, from Scandinavian countries at the CPUP conference in Stockholm, Sweden, in October 2019. Further amendments of the protocol were discussed *via* email, until consensus

was reached. The proposed protocol is therefore the result of discussions and joint collaboration between users, clinicians, and researchers (i.e., the authors of this manuscript).

ANTICIPATED RESULTS

The protocol has a threefold purpose: (1) to provide equal access to healthcare services that will enable the detection of cognitive impairments; (2) to provide interventions that increase educational and vocational participation, enhance quality of life, and prevent secondary impairments; and (3) to collect systematic data for research purposes.

Access to Healthcare Services

The sample has the potential to constitute large geographical cohorts in the two countries. The habilitation centers for adults are part of the public health services, and as such, the costs for the individuals using them are minimal. This ensures that the CP*Cog*-Adult protocol will be accessible to all adults with CP, regardless of their socio-economic background, once the protocol is implemented.

It is recommended that the habilitation centers for adults take the primary responsibility of recruiting participants, as they are the part of the public healthcare systems who sees the largest number of adults with CP. This, however, depends on the habilitation centers' resources and willingness to implement the protocol. We have reason to believe that many centers will regard this initiative positively, given that all pediatric habilitation centers in Norway volunteered to be part of the quality improvement project in 2019, aimed at implementing the CP*Cog*-protocol for children (34). Also, the vast majority of healthcare regions in Sweden participate in the protocol for children.

Recruitment might initially be somewhat challenging, since many adults with CP are currently not followed regularly by the adult habilitation centers. These individuals are not always known to the specialized healthcare system, and will therefore not receive invitations for cognitive assessments. Instead, they will be approached and enrolled on a consecutive basis in the follow-up protocol as soon as they get in contact with the healthcare system. This challenge is expected to particularly affect assessments for individuals at 54 years of age, and to be less of concern at 24 years of age. The reason for this is that the younger adults have been enrolled in the follow-up programs for children that cover over 95% of children with CP. When transitioning into adult services, the habilitation centers for children can inform participants about the possibility of continued follow-up in adulthood. As such, the introduction of the CP*Cog*-Adult protocol will secure the continuity of clinical care when transitioning from pediatric to adult services. Over time, the aim is therefore that the protocol will be offered to all adults with CP.

Enabling Interventions

The rationale for the areas investigated and the recommended assessment time points in the CP*Cog*-Adult protocol are related to securing appropriate interventions with regard to education and employment. Due to lack of longitudinal studies, it was not possible to base recommendations on developmental trajectories of cognitive functioning in adults with CP. However, the suggested time points are harmonized with the existing follow-up protocol for adults with CP in Sweden (CPUP for adults). The time points are, however, only guidelines and data for individuals who are assessed at other ages can still be entered into the national databases, provided consent.

Around 18–19 years of age, there is a transition from the school system where everybody is included and everyday life is structured, into a more uncertain, less structured future that requires more active choices by the individual. Many go on to higher education, some start work, either in regular or in sheltered employment, others are enrolled in day service centers, whereas some do not gain access to further education or employment. The education, employment, and everyday activities people are offered should reflect their cognitive, communicative, and social skills, and not be limited by lack of knowledge about each individual's potential. However, many of the younger adults with CP will have been included in the follow-up programs for children, where an assessment of cognition is recommended at 15 years of age as an optional part of the CP*Cog* (6). This time point is only considered necessary for the young adults who have not been assessed as teens and is therefore listed as optional.

The first age at which all adults with CP should be offered cognitive assessment is around 24 years of age. At this age, those who have been enrolled in higher education usually transition to employment. However, even for those who have successfully completed higher education, transitioning to employment can still be challenging (21). Subtle cognitive deficits that may not have been as noticeable when living at home and attending school may have serious consequences when transitioning to employment and being expected to manage independent living. Offering a cognitive assessment at this age, and thereby detecting subtle deficits (for example, in the ability to initiate, plan, organize, and juggle a number of tasks at the same time), will make it possible to put in place the necessary adjustments in the workplace and at home. Moreover, 24 years of age fits with the continuous follow-up in other areas offered to adults within the CPUP program in Sweden. In Sweden, the follow-up of adults is scheduled annually, every second year, or every third year based on their functional level according to the Gross Motor Function Classification System (67). Therefore, 24 years of age will be the first time point after turning 18 years when all adults with CP will be seen by the habilitation centers in Sweden.

Another optional assessment time point is suggested at 42 years of age. At this age, many are approximately halfway through their working years. The purpose of having an assessment at this time point is to prevent adverse late effects with respect to pain and fatigue, which might be particularly relevant for adults with bilateral CP (15).

At 54 years of age, the last quartile of work-life is approaching. Many with chronic disabilities, who have managed to stay employed over the years, are forced into early retirement or to

transition to disability benefits due to health reasons (9, 68). It is therefore suggested that all adults with CP are offered an assessment of cognition in their mid-fifties, and 54 years of age is recommended, as this is an age when all will be seen as part of the CPUP for adults. The purpose of this is to implement, if necessary, interventions that will enable adults with CP to stay connected to the workforce as long as possible or to transition gradually to early retirement.

Data Registry

The CP*Cog*-Adult protocol aims to ensure that all adults with CP in Norway and Sweden are offered cognitive assessments around 24 and 54 years of age, at a minimum. Inclusion into the CP*Cog*-Adult will be based on participants' informed consent, according to national standards. With consent, data from their clinical cognitive assessment can be entered into the national CP registries. It may be valuable to register any adaptations to testing procedures that are made, as this will aid in interpreting the results and provide unique epidemiological data on assessment procedures. It will be possible to consent to only participation in the cognitive assessment, and not to registration of data, but experience from the pediatric protocols indicates that the vast majority consent to registration of data (31).

Moreover, it will be possible to merge data from assessments in childhood with assessment in adulthood. Therefore, over time, the national CP registries will provide unique longitudinal data on the developmental trajectories of individuals with CP.

DISCUSSION

The CP*Cog*-Adult protocol has a threefold purpose: (1) to allow for systematic clinical follow-up of cognition in adults with CP, (2) to provide equal access to health services, and (3) to strengthen research on CP in adulthood.

The primary goal of the CP*Cog*-Adult protocol is to increase the quality of life of adults with CP, i.e., that their strengths and challenges will be recognized, interventions that may prevent dropout from education and employment may be implemented, and the development of secondary impairments resulting from unrecognized cognitive challenges can be prevented. Failing to gain employment and falling out of the workforce can lead to social isolation, depression, and secondary somatic problems (22). Cognitive functioning is not only important for learning to live with and managing challenges related to daily life both at home and work, but awareness of cognitive impairments may also contribute in the prevention of fatigue, mental distress, and reduced quality of life, by allowing necessary interventions to be implemented.

Studies of cognitive functioning in children with CP indicate that not all children keep their level of cognitive functioning over time compared to their peers who do not have CP (69, 70). A larger proportion of youths with CP have intelligence quotient (IQ) scores in the low range, compared to children in the younger age cohorts. This cannot be explained by worsening of motor functioning, as the same finding is also seen for tests placing very low demands on motor functioning (5). Even if children with CP improve their skills, the gap between their level of functioning and that of their peers without disability may increase (2). This illustrates the necessity to assess cognition not only in childhood, but also in adulthood.

Transitioning from child to adult healthcare services is a vulnerable time, and for the transition to be successful, it must be well-planned (71). All children with CP are followed by the local pediatric habilitation centers until they are between 16 and 18 years of age, and thereafter, they transition into adult services. Some of the older participants in the CP follow-up programs/registries, born between 1994 and 2001, have now reached adulthood and may be expecting the same systematic follow-up as they received as children and adolescents. However, this is currently not guaranteed for all geographical areas. In Sweden, adults with CP are followed by the CPUP program, but this program does not focus on cognition. In Norway, adults with CP who have an intellectual disability or recognized cognitive deficits are traditionally those most likely to be followed by the adult habilitation centers. In addition, they will also often be offered community services like housing and sheltered work. The rest of the adult CP population is usually followed by a family physician or a primary healthcare clinic. Healthcare for adults tends to be less multidisciplinary and more fragmented and requires more personal responsibility in terms of arranging and getting to appointments and coordinating different types of services. Many adults with CP or other disabilities thus report that they feel left to cope on their own (65, 72).

An additional reason to develop a follow-up protocol for cognitive monitoring is therefore to facilitate equal access to health services, which focus on cognition and the possible consequences of cognitive impairments for all adults with CP. For this purpose, the follow-up protocol only has value if it is widely implemented. The results from the CP*Cog* for children illuminate that offering assessments in a systematic manner to all increases the numbers reached, but it also illustrates that changing clinical practice takes time. Comprehensive projects in other countries have shown that managing a successful transition from child to adult health services requires an organization-wide approach to implementation (71). Introducing the CP*Cog*-Adult protocol, which builds on the CP*Cog* protocol for children, is an important part of such a multidisciplinary intervention approach. However, implementation of the CP*Cog*-Adult will depend on securing support for the protocol among relevant stakeholders, including the managers in charge of the adult habilitation centers and the psychologists. Therefore, the proposed protocol is comprehensive enough to yield meaningful results, while at the same time not requiring more resources than deemed absolutely necessary. It is difficult to estimate the time needed for assessments, due to the large heterogeneity of the CP population. However, the majority of assessments are expected to be completed in two sessions lasting from 1 to 2 h each time.

In Norway and Sweden, the adult habilitation centers already provide services to some adults with CP. In Sweden, there are regions where all adults with CP are offered follow-up as part of the CPUP, and where transitioning from pediatric to adult services therefore is already handled well. In Norway, follow-up by the adult habilitation centers, which are run by 20 hospitals spread throughout the country (28), is typically

dependent on referral and not part of systematic follow-up of the whole cohort (66). In Norway, to secure the referral of adults with CP to the adult habilitation centers, the pediatric habilitation centers will be encouraged to inform adolescents about the protocol when they turn 18 years of age. Professionals at other rehabilitation institutions that provide more specific and time-limited rehabilitation services to adults with CP will also be encouraged to refer, and the protocol will be made known to adults with CP through the user organization's journal, webpage, and annual user conference. Currently, the centers are not staffed to implement a systematic cognition follow-up protocol for adults with CP; thus, additional funding needs to be secured (73). Offering assessments to all adults with CP at two time points implies that, for Norway with ∼80–90 adults with CP per birth year (46), 160–180 assessments are to be conducted nationally per year (43), which, in turn, implies an average of 8–9 assessments annually per hospital. This does not imply that there will be a need for 180 assessments in addition to what the centers are already conducting, as many of the adults with CP will already have been scheduled for assessment or have been assessed within the last 5 years. Furthermore, the adult habilitation centers may cooperate with other services offering neuropsychological assessments of adults with CP, like the Sunnaas Rehabilitation Hospital in Norway. However, it is still likely that implementation of the CP*Cog*-Adult protocol will lead to an increase in the number of assessments offered, thus indicating a need for increased resources allocated to the adult habilitation centers.

The primary aim of the CP*Cog*-Adult is clinical; to detect challenges in the assessed areas so that more in-depth assessments, interventions, or referrals might be undertaken as needed. However, it is also an aim to create a better knowledge base for research related to cognitive functioning in adults with CP. On a consent basis, information from the individual assessments, coupled with information about diagnosis, functioning, type of brain lesions, and associated impairments, will be entered into the national CP registries (CPUP and NorCP). The national CP registries can be merged with other national health registries, pending ethical approval. A Nordic research project based on the Nordic CP registries and other national registries, "CP-North—Living life with cerebral palsy in the Nordic countries?," is ongoing, funded by Nordforsk (https://rdi.arcada.fi/cpnorth). There is also an ongoing research program, MOVING ON with CP, which is funded by the Swedish Research Council for Health, Working Life and Welfare, where the development and implementation of CP*Cog* and CP*Cog*-Adult are included (74). As multiple assessments spanning across many years are planned, longitudinal studies on cognitive functioning from childhood into adulthood will also be possible. Studies revealing more comprising descriptions of cognitive function in light of other clinical and socio-demographic data of the adult population with CP at various points across adult life will be conducted. Linking the clinical follow-up protocol CP*Cog*-Adult with the national CP registries will therefore be beneficial for research, which in turn will lead to quality improvement of services.

Strength and Limitations

The initiative to establish the CP*Cog* for children came as a joint initiative from the user organizations in the Nordic countries, illustrating that families recognize that cognition is a concern that has traditionally been overlooked. A strength to this initiative is that the CP*Cog*-Adult protocol has been discussed and finalized together with representatives from the user organizations, in collaboration with representatives from the national CP registries and follow-up programs (CPUP and NorCP) and the specialized health services in Sweden and Norway.

The CP*Cog*-Adult protocol outlines a systematic manner of assessment, detailing both assessment time points and instruments to be used. A limiting factor is that the protocol only details assessment, not the interventions that should follow from the results or a plan for psychoeducational follow-up. The aim is to, over time, expand the protocol, so that it, in the future, also includes suggestions for interventions. An additional limitation is that the protocol likely will be implemented at different time points in Sweden and Norway and that funding is not yet fully secured. It is a strength that the battery of neuropsychological tests also includes tests that can be administered to adults with severe motor impairments and that cognition is assessed together with adaptive skills in adults where a diagnosis of adaptive functioning is possible. Furthermore, it is a limitation that only two time points are recommended and that the interval between these (i.e., 24 and 54 years of age) is large. The rationale for recommending only two time points is to propose a protocol with a limited enough scope to make it feasible for implementation. The drawbacks of this approach are that each adult with CP will been seen by a psychologist very seldom, that the follow-up might end too early to detect any neurodegenerative changes that adults with brain lesions are potentially more at risk for, and that it will take a long time to collect longitudinal data. A final potential limitation is that the number of instruments suggested is rather large, especially if administering both the core and the supplemental battery. It is therefore necessary to investigate the feasibility of the protocol in a real-life clinical situation, and the plan is therefore to apply for funding for a pilot project to investigate this further.

Clinical Implications

Adults with CP have an increased risk of cognitive impairments, which are not always recognized but may have negative consequences. A systematic follow-up of cognition in adults with CP is therefore needed. This need for follow-up led to the development of the CP*Cog*-Adult protocol, which comprises a battery of instruments to assess cognition, and will be offered to all adults with CP at specified time points (around 24 and 54 years of age). This protocol is brief by design, and only two time points are highly recommended while a further two time points are listed as optional. This is done to maximize the likelihood that the protocol will be implemented. Representatives from user organizations have collaborated with clinicians and researchers to develop the protocol, and will collaborate also in disseminating experiences at workshops and training courses

for relevant professionals, at scientific conferences, in written publications, on the websites of the user organizations, and in relevant scientific journals. Implementation of the CP*Cog*-Adult protocol will be carried out in close collaboration with the leaders of the adult habilitation centers in Norway and Sweden.

In addition to securing better follow-up of cognition in adults with CP, the protocol is also designed to increase our knowledge about cognitive impairments and the consequences, which may follow. To enable the best possible data collection in Scandinavian countries, the protocol builds on the CP*Cog* protocol for children, and will be harmonized with follow-up in other areas of adults with CP.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work and approved it for publication.

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BRIEF RESEARCH REPORT
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Shared Physiologic Pathways Among Comorbidities for Adults With Cerebral Palsy

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Objective: Aging with cerebral palsy is accompanied by a declining health and function status across neurological and non-neurological systems. There is a need to understand the shared pathophysiology among comorbidities for adults with cerebral palsy, to inform clinical assessment and guidelines for interventions to improve healthful aging. To begin defining multimorbidity, this study identified the most common comorbidity combinations and their association with mortality among a representative sample of adults with cerebral palsy.

Methods: Data from 2016 to 2018 were used from a random 20% sample from the fee-for-service Medicare database. Adults ≥18 years with cerebral palsy and 25 neurological and non-neurological comorbidities were obtained from 2016. Principal component (PC) analysis identified the most common comorbidity combinations, defined as individual PCs. Cox regression estimated the hazard ratio (HR) of 2-year mortality including all PCs and demographics in a single model. To facilitate comparisons, PC scores were transformed into quintiles (reference: lowest quintile).

Results: Among the 16,728 adults with cerebral palsy, the most common comorbidity combinations (PCs) in order were: cardiorespiratory diseases, dysphagia, and fluid/electrolyte disorders; metabolic disorders (e.g., diabetes, renal disease, hypertension); neurologic-related disorders (e.g., dementia, cerebrovascular disease); gastrointestinal issues; and orthopedic-related disorders. During the 2-year follow-up, 1,486 (8.9%) died. In the adjusted model, most PCs were associated with an elevated mortality rate, especially the first PC (5th quintile HR = 3.91; 95%CI = 3.29–4.65).

Discussion: This study identified the most common comorbidity combinations for adults with cerebral palsy, many of them were deadly, which may inform on the underlying pathophysiology or shared characteristics of multimorbidity for this population.

Keywords: cerebral palsy, comorbidities, mortality, multimorbidity, clinical epidemiology

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INTRODUCTION

Neurological, functional, metabolic, and psychosocial aspects can manifest in multiple ways for children with cerebral palsy, and collectively increase risk for a variety of morbidities as these children become adults. The declining health and function with age can further complicate neurologic status in cerebral palsy (1–7), underscoring the importance of increasing knowledge of

multimorbidity regarding the shared pathophysiology among neurological and non-neurological morbidities (8, 9).

Multimorbidity, defined as ≥2 morbidities, is a major burden for adults with cerebral palsy, and contributes to their greater healthcare utilization and costs (10). For example, 1 out of 4 adults with cerebral palsy aged 18–30 years have multimorbidity, which is >3 times more prevalent than the general population of young adults (11), and continues to get worse with older age (12). Recent work suggests that multimorbidity for adults with cerebral palsy is a robust risk factor for premature mortality (13, 14).

Importantly, many morbidities can be prevented, delayed, or better clinically managed; yet, the field lacks evidence-based approaches to monitor morbidities for adults with cerebral palsy. To address this need, the Whitney Comorbidity Index (WCI) was recently developed (15) and validated (14), which is a simple, clinical-friendly tool designed to monitor health status for adults with cerebral palsy. The WCI score is calculated by summing the presence of 27 morbidities across neurological and non-neurological systems, which captures the unique multimorbidity profiles for adults with cerebral palsy better than other currently available methods (15). However, while the WCI provides a novel basis to inform clinical decision making, it is a quantitative approach to defining multimorbidity profiles, and provides no evidence on the shared pathophysiology among comorbidities.

As the field progresses, there is a need to understand the shared etiologies and characteristics among groups of comorbidities for adults with cerebral palsy, to ultimately inform clinical assessment and guidelines for interventions. For example, a WCI of 3 identifies those at risk for premature mortality (14). However, if one person's multimorbidity is defined by hypertension, diabetes, and renal disease (WCI = 3), which are commonly comorbid in the general population (16), treatment strategies would be very different than someone with a multimorbidity defined by dysphagia, pneumonia, and mal-nutrition (WCI = 3). Given the difference in physiologic development for individuals with cerebral palsy, there may be unique combinations of comorbidities that may inform on the underlying shared pathophysiology across neurological and non-neurological systems.

Principal component analysis (PCA), a data reduction technique, is an excellent analytic approach to identify comorbidity combinations as it explains the variance within a dataset based on inter-correlations among variables. In the context of multimorbidity, PCA allows for meaningful analysis and clinically-relevant interpretation of the most common combinations of comorbidities. Accordingly, using a large, nationwide sample, the primary objective of this study was to perform PCA to identify the most common comorbidity combinations from the WCI present in adults with cerebral palsy. The secondary objective was to determine how each of these comorbidity combinations associated with mortality.

METHOD

Data Source

Data for this retrospective cohort study came from a random 20% sample of the Medicare fee-for-service claims database. Demographics and the WCI comorbidities were obtained from the year 2016. Death date was obtained from the years 2017 and 2018. As described previously (15), Medicare is a U.S. federal program providing health insurance coverage to adults ≥65 years or individuals across any age that have end-stage renal disease or one or more chronic disabilities, including cerebral palsy. While administrative claims data are primarily used for healthcare billing reimbursement, medical conditions can be identified by searching for unique International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes that are attached to individual claims, allowing for the possibility of health-related research. The ICD-10-CM codes used to identify cerebral palsy and WCI comorbidities have been presented elsewhere (14).

Study Timeline and Sample Selection

The start date of follow-up was January 1, 2017 for all participants, which allows for a 1-year baseline period (17) and 2-years of follow-up for mortality. A flow diagram of the inclusion/exclusion criteria has been presented previously (14). Individuals that were 18 years of age or older at baseline with cerebral palsy were identified using an algorithm that required meeting at least one of the following criteria: one or more inpatient claims in 2016 for cerebral palsy; two or more outpatient claims in 2016 for cerebral palsy. Further inclusion criteria included: continuous enrollment in Part A and B from January 1, 2016 to January 30, 2017 (1 year + 30 days) to obtain a full 1-year baseline period and ≥30 days of follow up for mortality; complete data on demographics, including age, sex, race, and U.S. region of residence.

As epilepsy and intellectual disabilities often co-occur with cerebral palsy and can complicate the individual's medical needs (18, 19), a subgroup analysis was performed. For the subgroups, epilepsy and intellectual disabilities were identified in the same manner as cerebral palsy, and mutually exclusive groups were created: cerebral palsy only (CP only), cerebral palsy and co-occurring epilepsy but without co-occurring intellectual disabilities (CP+EP), cerebral palsy and co-occurring intellectual disabilities but without co-occurring epilepsy (CP+ID), and cerebral palsy and co-occurring epilepsy and intellectual disabilities (CP+EP+ID).

Mortality

All-cause mortality up to December 31, 2018 (2-year period) was derived from the Medicare database. Medicare has >99% of deaths validated (20).

WCI Comorbidities

The WCI comorbidities were previously identified using an iterative process that harmonized *a priori* clinical knowledge of relevant comorbidities for adults with cerebral palsy, use of established and validated measures, and data-driven approaches to select the final 27 WCI comorbidities (15). For the current study, two sets of two comorbidities were merged into a single comorbidity given the potential for considerable overlap, which may alter PCA interpretation: "any cancer" included the

presence of "metastatic cancer" or "any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin"; "type 2 diabetes" included the presence of "diabetes with chronic complication" or "diabetes without chronic complication" ($n = 25$ WCI comorbidities). Since the WCI includes epilepsy and intellectual disabilities as individual comorbidities, these were removed for the subgroup analysis, thereby totaling 23 comorbidities. All comorbidities were identified in the same manner as cerebral palsy.

Statistical Analysis

PCA is a multivariable data reduction technique that operates in a highly correlated environment to identify inter-correlated variables. In the context of multimorbidity, PCA allows for meaningful analysis and interpretation of comorbidity data by reducing the number of comorbidities into a few inter-correlated combinations. Each comorbidity combination corresponds to a specific principal component (PC) (21, 22), which is independent of other PCs. To derive the PCs, the models included each of the WCI comorbidities (25 for the entire group; 23 for the subgroups). The PCA models used a varimax rotation to facilitate interpretation of the loading factors. Loading factors are derived from the correlation matrix and provides a numerical interpretation of the PCs. Comorbidities with a loading factor of $\geq|0.40|$ were included for interpretation, which has been suggested previously (23). PCs with eigenvalues of ≥ 1.00 were retained and analyzed, as this is common practice for PCA (24).

The resulting PCs for the group analysis provides information on the most common comorbidity combinations. This group-level analysis also provides information on how much of the total variance of the data is explained for each PC, and when more than 1 PC, the cumulative variance explained. In this context, the explained variance provides indirect evidence of the heterogeneity of comorbidity profiles for adults with cerebral palsy, where a low cumulative percent for all identified PCs is indicative of a greater number of ways in which comorbidities are inter-related. PCA also provides individual-level data in a standardized manner, where each person is assigned a PC score for each PC separately with a mean of 0 and standard deviation of 1. For example, if a PC is defined by 4 comorbidities, individuals with 3 or 4 of those comorbidities would have a higher PC score compared to those with 2 or fewer.

Cox proportional hazards regression was used to determine the association between each of the identified PCs with mortality. Models were developed to estimate the hazard ratio [HR with 95% confidence intervals (CI)] of 2-year mortality after including all PCs in a single model, while controlling for age, sex, race, and U.S. region of residence. To facilitate comparisons across PCs and enhance clinical interpretation, individual-level PC scores were transformed into quintiles and the lowest quintile (lower likelihood of having the PC's comorbidities) was set as the reference. Interpretation of the HR is the risk of mortality per increase in a comorbidity profile that is more exemplary of that PC.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and $P \leq 0.05$ was considered statistically significant.

RESULTS

Baseline descriptive characteristics and prevalence of the WCI comorbidities for the entire group of adults with cerebral palsy ($n = 16{,}728$) and the subgroups, CP only ($n = 7{,}542$), CP+EP ($n = 2{,}607$), CP+ID ($n = 2{,}781$), and CP+EP+ID ($n = 3{,}798$), is presented in **Table 1**.

PCs

For the entire group, there were 6 PCs (**Figure 1**) that explained 39.8% of the total variance. PC1 generally includes cardiorespiratory diseases, as well as fluid/electrolyte disorders and dysphagia, explaining 9.4% of the variance. PC2 includes neurological disorders, explaining 8.0% of the variance (cumulative, 17.4%). PC3 generally includes metabolic disorders, specifically type 2 diabetes, hypothyroidism, renal disease, hypertension, anemias, and liver disease, explaining 6.6% of the variance (cumulative, 23.9%). PC4 generally includes brain-related disorders, specifically dementia, cerebrovascular disease, and depression, as well as osteoarthritis, explaining 6.1% of the variance (cumulative, 30.0%). PC5 includes gastrointestinal issues and neurogenic bowel or bladder, explaining 4.9% of the variance (cumulative, 34.9%). Finally, PC6 includes orthopedic-related disorders, specifically bone fragility and rheumatoid arthritis and other inflammatory polyarthropathies, explaining 4.9% of the variance (cumulative, 39.8%).

For the subgroups, there were 6 PCs for CP only (**Figure 2**), 7 PCs for CP+EP (**Figure 3**), 7 PCs for CP+ID (**Supplementary Figure 1**), and 7 PCs for CP+EP+ID (**Supplementary Figure 2**), that explained 40.5, 45.2, 43.9, and 44.2%, respectively, of the total variance. Notably, all subgroups had a similar PC1 as the entire group (explaining 8.8–10.8% of the variance), generally including cardiorespiratory diseases, and fluid/electrolyte disorders, and dysphagia. Renal disease, type 2 diabetes, hypertension, and hypothyroidism were included in PC2 for CP only and CP+EP, whereas PC2 for CP+ID included type 2 diabetes, hypertension, and blood loss and deficiency anemias, and PC2 for CP+EP+ID included type 2 diabetes, hypertension, and hypothyroidism. Dementia and cerebrovascular disease were together in PC3, among other morbidities, for each subgroup.

Association Between PCs With Mortality

During the follow-up period for a mean (SD) of 696 (126) days (median, 730 days), 1,486 (8.9%) died from the entire group, 27 (0.1%) were right-censored due to loss of follow-up, and 15,215 (91.0%) were right-censored due to the end of the study period. The follow-up time was similar for the subgroups. In total, 602 (8.0%) died from CP only, 203 (7.8%) died from CP+EP, 260 (9.4%) died from CP+ID, and 421 (11.1%) died from CP+EP+ID.

The adjusted HR of 2-year mortality after including all PCs in the model as quintiles (reference: lowest quintile) is presented in

TABLE 1 | Baseline descriptive characteristics and prevalence of comorbidities for the entire group of adults with cerebral palsy (CP) and for mutually exclusive subgroups based on co-occurring epilepsy (EP) and intellectual disabilities (ID).

	Entire group (*n* = 16,728) (%)	CP only (*n* = 7,542) (%)	CP+EP (*n* = 2,607) (%)	CP+ID (*n* = 2,781) (%)	CP+EP+ID (*n* = 3,798) (%)
Descriptive characteristics					
Age, mean (SD)	51.0 (15.3)	53.0 (16.2)	47.2 (15.2)	52.2 (14.3)	49.0 (13.3)
18–40 years	27.7	25.2	38.8	23.2	28.3
41–64 years	51.6	48.1	45.5	56.4	59.2
≥65 years	20.7	26.7	15.7	20.4	12.5
Sex					
Women	48.2	51.2	52.1	51.1	53.3
Men	51.8	48.9	47.9	48.9	46.7
Race					
White	80.5	80.7	77.6	82.0	81.2
Black	13.0	13	13.6	13.1	12.7
Hispanic	3.3	1.1	1.4	1.4	1.3
Asian	1.0	1.0	1.4	0.8	0.8
North American Native	0.8	3.3	4.6	2.3	3.3
Other	1.2	0.9	1.4	0.5	0.7
U.S. region of residence					
Midwest	27.7	27.5	26.0	29.1	28.4
Northeast	21.7	19.2	16.4	27.6	26.0
South	34.4	36.0	39.0	29.9	31.4
West	16.2	17.3	18.6	13.5	14.2
Comorbidities					
Hypertension (Un)complicated	45.0	51.3	39.6	43.6	37.3
Intellectual disabilities	39.3	-	-	-	-
Epilepsy	38.3	-	-	-	-
Other neurological disorders	35.8	15.4	54.6	26.8	69.9
Depression	28.2	30.2	27.3	31.1	22.8
Fluid and electrolyte disorders	25.5	19.7	24.6	23.4	39.0
Gastrointestinal issues	23.8	19.3	20.9	28.1	31.7
Dysphagia	20.9	13.5	18.1	24.3	34.8
Hypothyroidism	20.7	16.5	17.7	22.3	30.0
Bone fragility	20.7	16.1	18.2	21.6	31.1
Osteoarthritis and allied disorders	19.6	23.7	17.2	16.9	15.1
Cardiac arrhythmias	18.5	15.8	18.1	18.7	24.1
Type 2 diabetes	17.6	19.7	14.8	18.5	14.9
Pneumonia	14.7	9.2	13.7	15.4	25.8
Chronic pulmonary disease	14.0	14.0	14.6	12.5	14.5
Blood loss and deficiency anemias	12.7	11.2	11.9	13.7	15.4
Cerebrovascular disease	9.8	9.0	13.9	6.2	11.1
Congestive heart failure	8.3	8.5	6.9	8.4	8.9
Neurogenic bowel or bladder	7.5	8.1	7.3	6.7	7.3
Renal disease	7.1	8.0	6.7	6.0	6.4
Dementia	6.4	5.0	6.3	7.5	8.5
Any cancer	6.0	7.2	5.5	5.6	4.4
Mild to severe liver disease	4.8	4.7	4.8	4.8	4.9
Myocardial infarction	2.3	3.1	2.2	1.5	1.6
Rheumatoid arthritis and other inflammatory polyarthropathies	1.6	1.8	1.3	1.5	1.5

SD, standard deviation.

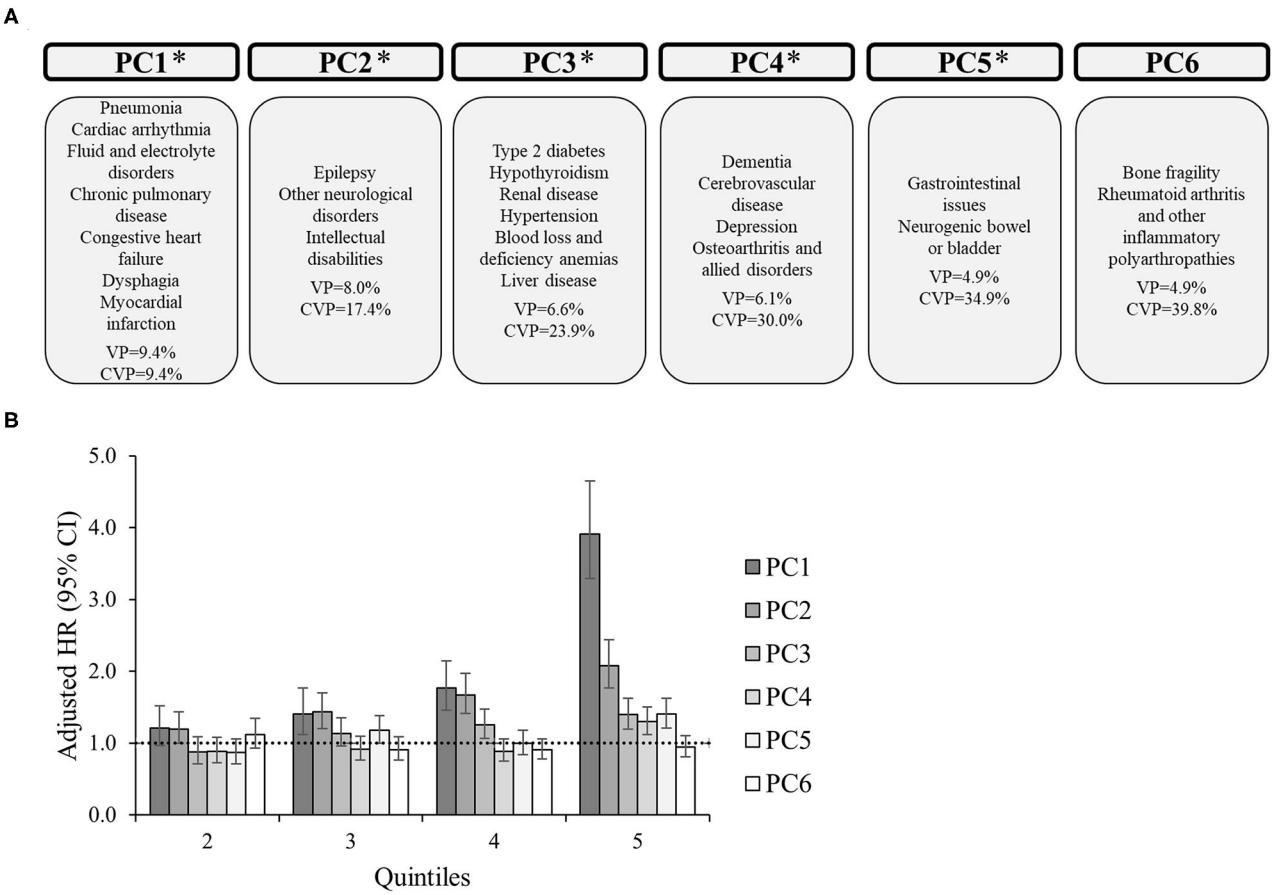

FIGURE 1 | Principal component analysis among 16,728 adults with cerebral palsy. **(A)** Principal components (PC) represent the comorbidity combinations in order of the amount of variance percent (VP) explained and the cumulative VP (CVP) explained. *$P < 0.05$ for the association of that PC with 2-year mortality. **(B)** The association between each PC with 2-year mortality after PC scores were transformed into quintiles to facilitate comparisons across PCs (reference: lowest quintile). The bars represent the hazard ratio (HR) and the vertical lines represent the 95% confidence interval (CI) for 2-year mortality after adjusting for all PCs, age, sex, race, and U.S. region of residence. The dotted horizontal line represents a HR of 1.0. If the 95% CI crosses the dotted line, the association is not statistically significant at $P = 0.05$.

Figures 1–**3** and **Supplementary Figures 1**, **2** alongside the PC comorbidity grouping. For the entire group (**Figure 1**), PC1-PC5 were significantly associated with an elevated HR of mortality, especially PC1. For example, the adjusted HR (95% CI) for the 5th quintile for PC1 (reference: 1st quintile) was 3.91 (3.29–4.65), which was higher than the HRs of the 5th quintile from PC2-PC5 (HR range, 1.21–2.08, all $P < 0.05$).

PC1 was significantly associated with an elevated HR of mortality for each subgroup, which included similar comorbidities (e.g., cardiorespiratory diseases) across subgroups. Additionally, PC1 had the highest HR for the 5th quintile compared to other PCs for each subgroup. There were unique associations between PCs with mortality for each subgroup.

DISCUSSION

This study identified the most common comorbidity combinations among adults with cerebral palsy with and without co-occurring epilepsy and/or intellectual disabilities, advancing the knowledge of what multimorbidity looks like for this population, and additionally, what it may mean for survival. These findings inform on the potential underlying shared set of etiologies or characteristics among these combinations of comorbidities unique to adults with cerebral palsy. Some comorbidity combinations were more obvious given what is known in the field, such as dysphagia and pneumonia in PC1. Some comorbidity combinations were less obvious, and may inform on new shared pathophysiologic pathways among comorbidities not previously regarded as established knowledge in the field, such as dysphagia and myocardial infarction, or the comorbidities present in PC3 for the entire sample.

It is important to note that the most common comorbidity combinations in the entire sample explained ∼40% of the total variance. The total variance explained for defining multimorbidity profiles in this study is between that previously

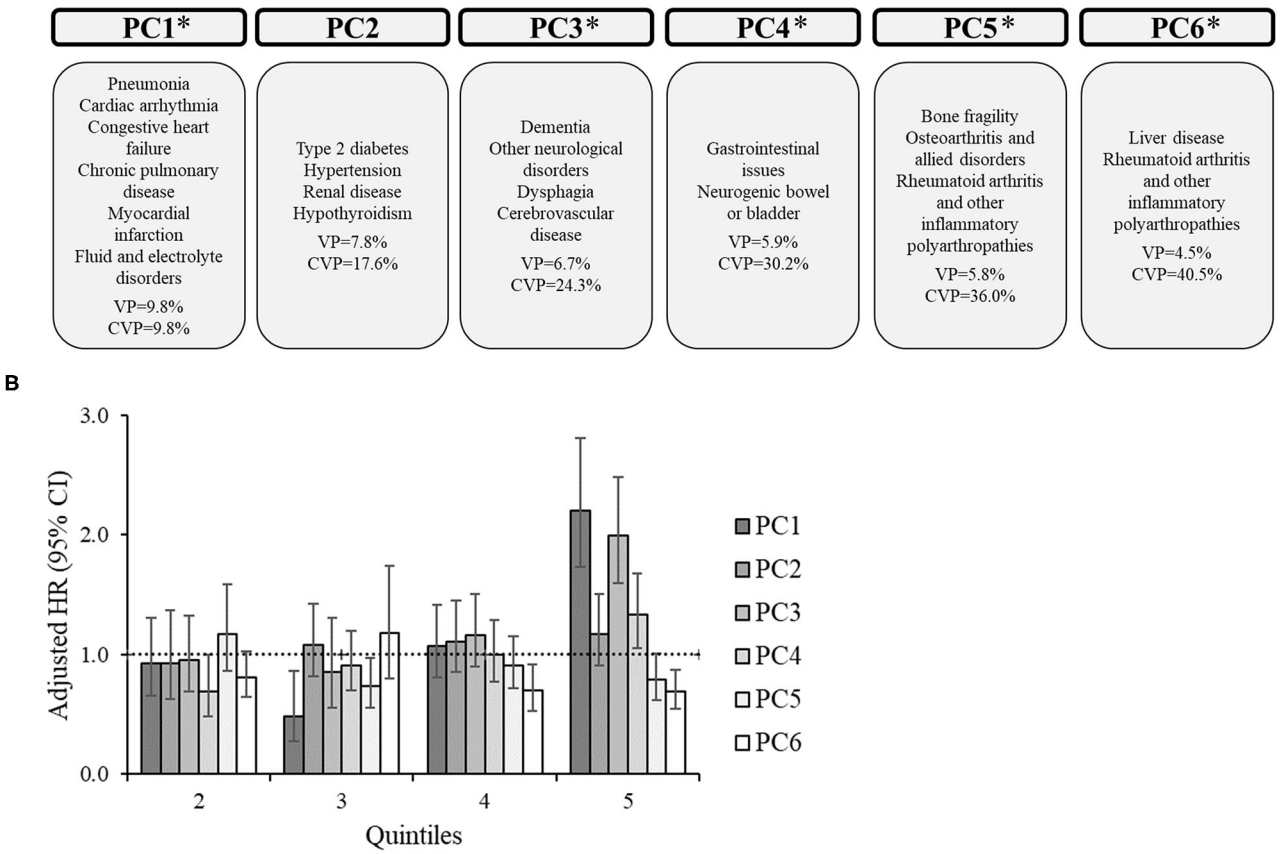

FIGURE 2 | Principal component analysis among 7,542 adults with cerebral palsy without co-occurring epilepsy and intellectual disabilities. **(A)** Principal components (PC) represent the comorbidity combinations in order of the amount of variance percent (VP) explained and the cumulative VP (CVP) explained. *$P < 0.05$ for the association of that PC with 2-year mortality. **(B)** The association between each PC with 2-year mortality after PC scores were transformed into quintiles to facilitate comparisons across PCs (reference: lowest quintile). The bars represent the hazard ratio (HR) and the vertical lines represent the 95% confidence interval (CI) for 2-year mortality after adjusting for all PCs, age, sex, race, and U.S. region of residence. The dotted horizontal line represents a HR of 1.0. If the 95% CI crosses the dotted line, the association is not statistically significant at $P = 0.05$.

reported from other studies among adults without cerebral palsy (15–65%) (24–26). The difference between studies may be due to differences in the number of morbidities examined and criteria used, among other factors. The current study examined an extensive list of clinically relevant morbidities (15) and applied more stringent criteria (e.g., factor loading) to minimize the possibility of type I error. Nevertheless, the 40% of total variance explained could suggest significant heterogeneity of multimorbidity profiles for adults with cerebral palsy, which is likely confirming what many in the field have suspected. Further, the heterogeneity may be in part due to the different multimorbidity profiles associated with co-occurring intellectual disabilities and/or epilepsy. When these subgroups were stratified, their most common comorbidity combinations explained slightly more of the total variance (∼45%) compared to the entire sample (∼40%). Indeed, while many of the same comorbidities were present in PCs across subgroups, unique comorbidity combinations emerged for each of the subgroups, providing more personalized information for the broader adult population with cerebral palsy.

As expected, the PCs had general themes, with PC1 including several cardiorespiratory diseases along with dysphagia and fluid/electrolyte disorders. PC1 was also the deadliest for the entire sample and all subgroups. This finding may be in part driven by those with more severe forms of cerebral palsy, as severity of cerebral palsy is associated with a greater risk of respiratory diseases, dysphagia, and premature mortality, as well as mal-nourishment contributing to fluid/electrolyte disorders (27, 28). The quintile pattern of the association of PC1 with mortality suggests that, after full adjustments, those that have a moderate profile of PC1 have an increased rate of mortality (e.g., entire sample 3rd quintile HR = 1.41), but those with a more exemplary profile of PC1 have a substantially increased rate of mortality (e.g., entire sample 5th quintile, HR = 3.91). This could suggest that cardiorespiratory diseases are deadly for adults with cerebral palsy, which is consistent with previous

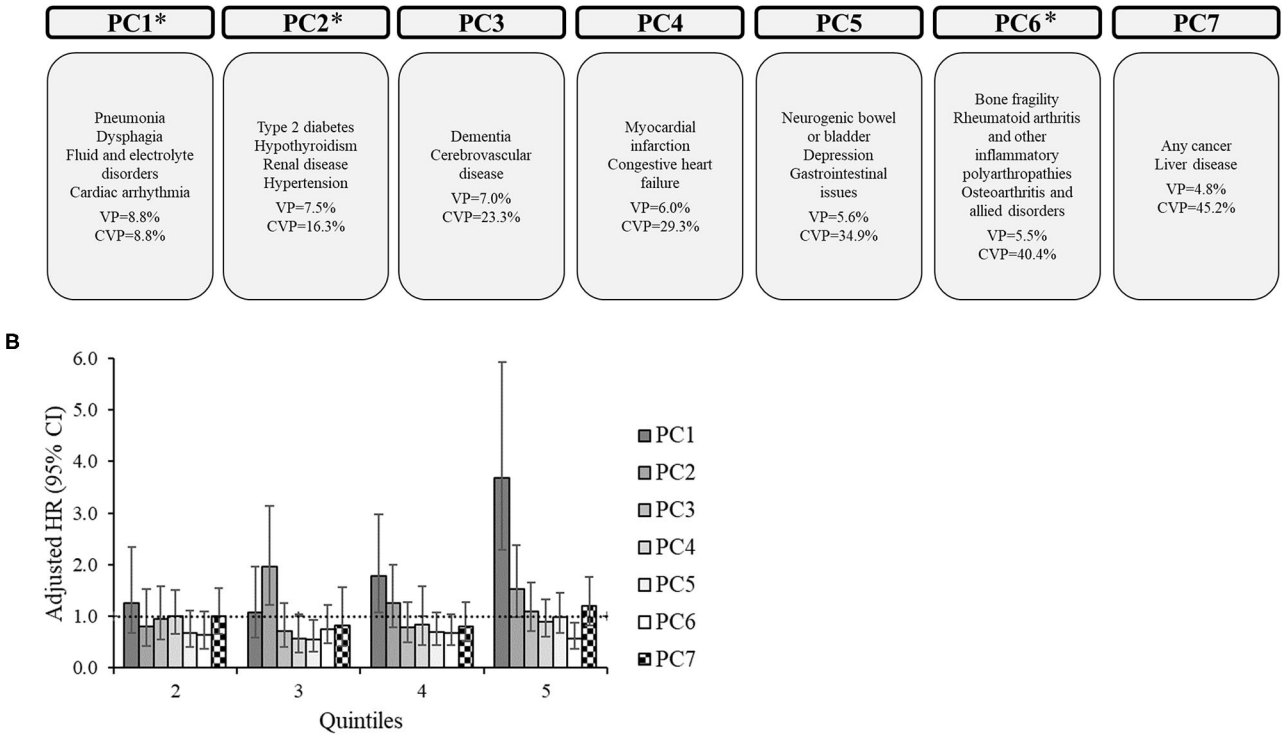

FIGURE 3 | Principal component analysis among 2,607 adults with cerebral palsy with co-occurring epilepsy, but without co-occurring intellectual disabilities. **(A)** Principal components (PC) represent the comorbidity combinations in order of the amount of variance percent (VP) explained and the cumulative VP (CVP) explained. *$P < 0.05$ for the association of that PC with 2-year mortality. **(B)** The association between each PC with 2-year mortality after PC scores were transformed into quintiles to facilitate comparisons across PCs (reference: lowest quintile). The bars represent the hazard ratio (HR) and the vertical lines represent the 95% confidence interval (CI) for 2-year mortality after adjusting for all PCs, age, sex, race, and U.S. region of residence. The dotted horizontal line represents a HR of 1.0. If the 95% CI crosses the dotted line, the association is not statistically significant at $P = 0.05$.

studies (29), but that the combination with dysphagia and possibly fluid/electrolyte disorders are especially deadly, making this finding unique to cerebral palsy. Importantly, dysphagia and fluid/electrolyte disorders can both be clinically managed, but are likely overlooked due to lack of clinicians familiar with these problems when treating adults with cerebral palsy, thus exacerbating a preventable health disparity that may be associated with an excess risk of mortality.

Notably, this study identified that in the entire sample and each subgroup, dementia and cerebrovascular disease were together in a PC. Further, for the entire group and subgroups with ID, depression was included in the PC with dementia and cerebrovascular disease. There is growing interest in the neurological field in examining dementia risk for adults with cerebral palsy (6, 8). However, it can be challenging to identify dementia risk using the currently available methods. Clinically, this study may provide an indirect path for assessment of dementia, by considering that those with cerebrovascular disease (and depression) may also be likely to have dementia; although, this is speculation and more work in this area is needed (8). Biologically, this novel finding may suggest an underlying etiology or shared characteristics among dementia, cerebrovascular disease, and depression in cerebral palsy. Early life stressors are known to alter epigenetic modifications leading to later-life brain-related abnormalities, cardiometabolic disease, and mental health disorders, providing a biologically embedded link between childhood adversity and adult health (30–32). Crowgey et al. (33) found distinct altered epigenetic patterns in peripheral blood cells in adolescents with vs. without cerebral palsy. More research is certainly needed into the role of early life stressors (e.g., damage to brain causing cerebral palsy, psychosocial stressors) as a biologically plausible link to poor health in adults with cerebral palsy.

Interestingly, for the entire sample and for CP+EP+ID, but not the other subgroups, osteoarthritis loaded onto the factor containing cerebrovascular disease, dementia, and depression. While often regarded as an orthopedic or peripheral pain condition, osteoarthritis has been shown to modify brain activity over time, and increase risk of dementia, stroke, and mental health disorders through several pathways, and can also re-direct pain experience and symptoms among centralized brain networks (34–37). This could suggest that osteoarthritis can act as both a peripheral and central nervous system condition, which may uniquely manifest and integrate with other health problems

for people with cerebral palsy. However, more work is needed to understand these pathways and why this was more relevant to the subgroup with CP+EP+ID.

This study also identified that diabetes and hypertension were present in PC2 in all subgroups, where renal disease was additionally combined in CP only, CP+EP, and the entire sample (for PC3), indicating that these comorbidity combinations are relatively common among adults with cerebral palsy (based on the position of the PC). This is consistent with previous studies that have shown that these 3 morbidities often co-occur in the general population (16, 24) and adults with cerebral palsy (38). Further, diabetes and hypertension have been found to be robust risk factors for developing advanced stages of chronic kidney disease among adults with cerebral palsy (39). In the current study, the PC that was defined in part by diabetes, renal disease, and hypertension for the entire sample and subgroups was associated with an elevated rate of mortality. The duality of these comorbidity combinations presenting as (1) relatively common and (2) deadly could provide a basis for clinical monitoring and justification to insurance providers for additional testing.

For the entire sample, PC6, defined by bone fragility and rheumatoid arthritis, was not associated with mortality. This may shed some light on a newly forming concept in the field that bone fragility is implicated in the pathogenesis of unhealthful aging for adults with cerebral palsy. A recent epidemiologic study have found that sustaining a fragility fracture is a robust risk factor for premature mortality for adults with cerebral palsy, even after accounting for demographics, cardiorespiratory diseases, diabetes, cancer, and kidney disease (40). Additional epidemiologic studies have also found that fragility fractures are a robust risk factor for incidence of several cardiorespiratory diseases for adults with cerebral palsy (41–44). Fractures therefore may have an "up-stream" effect on mortality risk by orchestrating a cascade of events (e.g., altered biology, loss of function) that contributes in part to the increased risk of cardiorespiratory diseases, which in turn drives premature mortality, as cardiorespiratory diseases are among the primary causes of premature mortality for adults with cerebral palsy (29). Since this study identified comorbidities in a cross-sectional manner, the temporal sequence of fracture longitudinally leading to cardiorespiratory disease would not be captured, helping to explain why these conditions were not present together in a PC.

Limitations of this study based on the use of administrative claims data for adults with cerebral palsy has been reported previously (10, 38, 45–47). It is worth re-mentioning the potential issue for healthcare providers in accurately detecting and diagnosing mental health disorders and dementia, especially for individuals that have intellectual disabilities or trouble communicating. As a result, mental health disorders and dementia may be under-represented in this study. It is also worth re-mentioning that many cerebral palsy-related characteristics are not available in administrative claims data, such as severity of cerebral palsy. In some research contexts studying multimorbidity, this is not a major limitation, as the number of comorbidities is associated with severity of cerebral palsy (11, 12). However, the accumulation and combinations of comorbidities may differ by severity of cerebral palsy due to the differences in body development, biology, and medical needs. Future research is needed to identify comorbidity combinations by severity of cerebral palsy. Along these lines, claims data do not contain information about nutrition or body composition measures, such as body mass, waist circumference, or body mass index, preventing the ability to examine the influence by body composition. Claims data do not contain information as to the cause of death, so it is unknown what that actual cause of deaths were in this study. This study was also focused on morbidities and not medications. The number of and composition of medications may promote drug interactions creating new medical problems or exacerbating current medical problems. Future studies are needed to understand the role of medications along with morbidities in the context of aging with cerebral palsy. Finally, as there is a lack of general consensus on best methodologies for PCA using dichotomous variables to define multimorbidity profiles, this study opted for more stringent criteria to provide a simpler and more robust conclusion. However, the cost can be lack of placement of comorbidities in certain combinations, providing an incomplete assessment of comorbidities that may further inform on the underlying shared pathophysiology.

This study provides empirical evidence of the most common comorbidity combinations among adults with cerebral palsy with and without co-occurring epilepsy and/or intellectual disabilities, thus enhancing interpretations for the broader adult population with cerebral palsy. This study also observed that many of the comorbidity combinations were associated with an elevated mortality rate, but to a differing degree. Taken together, study findings provide a comprehensive qualitative assessment of multimorbidity, informing on the potential underlying shared etiologies or characteristics of comorbidities unique to adults with cerebral palsy.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: the data analyzed in this study was obtained from the Centers for Medicare & Medicaid Services, the following licenses/restrictions apply: The dataset analyzed in this study may be accessed through a contractual agreement with the Centers for Medicare & Medicaid Services following the payment of an administrative fee. Information about these datasets and requests for dataset access can be found at: https://www.cms.gov/Research-Statistics-Data-and-Systems/Research-Statistics-Data-and-Systems.

AUTHOR CONTRIBUTIONS

DW designed the study, analyzed the data, and wrote the first draft of the manuscript. MS and EH edited the manuscript. All authors conceptualized the study, approve the final version of this manuscript, and agree to be accountable for the content of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.742179/full#supplementary-material

Supplementary Figure 1 | Principal component analysis among 2,781 adults with cerebral palsy with co-occurring intellectual disabilities, but without co-occurring epilepsy. **(A)** Principal components (PC) represent the comorbidity combinations in order of the amount of variance percent (VP) explained and the cumulative VP (CVP) explained. $^*P < 0.05$ for the association of that PC with 2-year mortality. **(B)** The association between each PC with 2-year mortality after PC scores were transformed into quintiles to facilitate comparisons across PCs (reference: lowest quintile). The bars represent the hazard ratio (HR) and the vertical lines represent the 95% confidence interval (CI) for 2-year mortality after adjusting for all PCs, age, sex, race, and U.S. region of residence. The dotted horizontal line represents a HR of 1.0. If the 95% CI crosses the dotted line, the association is not statistically significant at $P = 0.05$.

Supplementary Figure 2 | Principal component analysis among 3,798 adults with cerebral palsy with co-occurring epilepsy and intellectual disabilities. **(A)** Principal components (PC) represent the comorbidity combinations in order of the amount of variance percent (VP) explained and the cumulative VP (CVP) explained. $^*P < 0.05$ for the association of that PC with 2-year mortality. **(B)** The association between each PC with 2-year mortality after PC scores were transformed into quintiles to facilitate comparisons across PCs (reference: lowest quintile). The bars represent the hazard ratio (HR) and the vertical lines represent the 95% confidence interval (CI) for 2-year mortality after adjusting for all PCs, age, sex, race, and U.S. region of residence. The dotted horizontal line represents a HR of 1.0. If the 95% CI crosses the dotted line, the association is not statistically significant at $P = 0.05$.

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Corrigendum: Shared Physiologic Pathways Among Comorbidities for Adults With Cerebral Palsy

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Keywords: cerebral palsy, comorbidities, mortality, multimorbidity, clinical epidemiology

A Corrigendum on

Shared Physiologic Pathways Among Comorbidities for Adults With Cerebral Palsy
by Whitney, D. G., Schmidt, M., and Hurvitz, E. A. (2021). Front. Neurol. 12:742179. doi: 10.3389/fneur.2021.742179

In the original article, there was an error in the reporting of one of the statistical approaches in the Methods section. The original reporting stated that the principal component analysis model used a tetrachoric correlation matrix, but the model did not use this matrix. Specifically, the error was in the section *Methods*, *Statistical Analysis*, *Paragraph 1*, which stated: "The PCA models used a tetrachoric correlation matrix due to the dichotomous nature of the variables, and a varimax rotation was used to facilitate interpretation of the loading factors."

A correction has been made to *Methods*, *Statistical Analysis*, *Paragraph 1*. The corrected paragraph is shown below.

PCA is a multivariable data reduction technique that operates in a highly correlated environment to identify inter-correlated variables. In the context of multimorbidity, PCA allows for meaningful analysis and interpretation of comorbidity data by reducing the number of comorbidities into a few inter-correlated combinations. Each comorbidity combination corresponds to a specific principal component (PC) (21, 22), which is independent of other PCs. To derive the PCs, the models included each of the WCI comorbidities (25 for the entire group; 23 for the subgroups). The PCA models used a varimax rotation to facilitate interpretation of the loading factors. Loading factors are derived from the correlation matrix and provides a numerical interpretation of the PCs. Comorbidities with a loading factor of $\geq|0.40|$ were included for interpretation, which has been suggested previously (23). PCs with eigenvalues of ≥ 1.00 were retained and analyzed, as this is common practice for PCA (24).

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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MINI REVIEW
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Evaluation of Pain in Adults With Childhood-Onset Disabilities and Communication Difficulties

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Adults with childhood-onset disabilities, particularly those with central nervous system impairment, commonly experience pain. Because many such individuals have difficulties in communication, caregivers and medical professionals must identify and interpret non-verbal behaviors as indicators of pain. This process is challenging and can lead to poor outcomes through delayed or incorrect diagnosis and treatment. Most research in the evaluation of pain in individuals with neurologic impairment has focused on the pediatric population, and evidence-based guidelines do not exist for adults. The purpose of this paper is to review current recommendations for pain assessment in adults with communication impairment. This approach includes guidance for history-taking, pharmacologic review, physical examination, and the judicious use of laboratory and imaging tests. Finally, we discuss adult-specific diagnoses to consider when evaluating pain in adults with childhood-onset disabilities and communication difficulties.

Keywords: cerebral palsy, neurologic impairment, childhood-onset disability, adults, pain assessment, palliative care

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INTRODUCTION

Because of advancements in medicine, people with childhood-onset disabilities commonly live into adulthood (1, 2). One of the most common childhood-onset disabilities is cerebral palsy (CP), a group of movement disorders caused by a disturbance to the fetal or infant brain (2, 3). Because cerebral palsy is highly prevalent, with ∼2–3 per 1,000 live births affected (3, 4), we will use this condition as an exemplar of childhood-onset disabilities related to neurologic impairment.

Although the brain disorder causing cerebral palsy is not progressive, the manifestations of CP can change over time, and this population experiences numerous physical and psychological challenges, such as pain, that can change and persist into adulthood (2, 5, 6).

In children and young adults with cerebral palsy, prevalence of pain ranges from 14 to 76% (2, 7). More specifically, pain is more common in non-ambulatory adults with cerebral palsy, with a prevalence of 79% (8).

There are several other common childhood-onset disabilities in which pain is commonly experienced (9–11). Spina bifida has a prevalence of pain in young adults ranging from 34 to 40% (9). Additionally, childhood CNS cancer survivors have a prevalence of pain in young adults of 36% (11), and a relative risk of pain of 7.9 compared to unaffected siblings (12).

Despite pain being common in adults with childhood-onset disabilities, it is frequently underrecognized and undertreated (6). Diagnosing the underlying etiology of pain is difficult, particularly in individuals with communication difficulties who are unable to identify and relay

the location, severity, or pattern to their pain. Common sources of pain in adults with CP and other CNS disorders include musculoskeletal abnormalities, spasticity, gastrointestinal dysmotility, feeding tube dysfunction, tooth decay, and acute injuries (2, 7, 8). There are no standardized tools recommended for measurement of pain in adults with childhood-onset disabilities or with barriers to communication. Research is limited for both adults and children. We will review the available literature of pain assessment in individuals with communication impairment and then describe an approach for evaluation of pain in adults with childhood-onset disabilities.

CURRENT LITERATURE

Pediatric Literature

Children with neurologic impairment commonly experience pain, and pain is notably more common in individuals with dyskinetic and mixed cerebral palsy types, with a prevalence estimate of 85% (13). The frequency with which children with moderate to severe cerebral palsy experience pain is high, with 44% of parents reporting pain in their children "once or twice" to "a few times" over the course of 4 weeks (14).

The evaluation of pain in children with neurologic impairment is also complex due to having multiple potential sources of pain, as well as frequent barriers to communication. Common sources of acute pain in children with cerebral palsy may be directly related to the underlying cerebral palsy (e.g., hip dislocation), secondarily associated with CP (e.g., nephrolithiasis related to immobility), or not related at all (e.g., appendicitis). Acute exacerbations of chronic pain from neuropathic etiologies and spasticity are also important to consider (7, 13–15). The most common locations of pain in children with cerebral palsy are the lower extremities, back, and abdomen, though this population has numerous other locations that should be evaluated as well (7).

Complicating this process is that many children with neurologic impairment are unable to verbally describe the location or characteristics of their pain. Some individuals may also express atypical behaviors to indicate pain, such as altered mental status, self-injurious behaviors, and laughter (14). In these situations, health care providers must rely on history provided by other informants, such as relatives or other caregivers, to evaluate pain and create a differential diagnosis.

There have been numerous assessment tools developed to evaluate pain in children with neurologic impairment and communication difficulties (14–19). Several tools that have been validated for use in the pediatric population, though none of the tools have been proven to be more effective and accurate than the others, and none have been validated in adults (14, 16, 18, 19).

Most recently, the Guidelines for Ruling Out and Assessing Source of Pain (GRASP) was developed as an assessment tool to evaluate pain in children with medical complexity, including cerebral palsy, who are unable to verbally express pain (15). The tool helps to provide a systematic approach to guide clinicians through the history, physical examination, and initial workup of a pain evaluation. The GRASP uses a flowsheet to guide the history and physical exam. If the child is not at their baseline, or there are any concerns in the history and physical exam, the flowsheet provides suggestions for an initial diagnostic workup. The GRASP also includes a broad differential diagnosis, considering common neurologic, infectious, respiratory, gastrointestinal, genitourinary, musculoskeletal, and other etiologies that may cause pain in this population. A mixed-methods study provided initial content and face validation of the tool (15).

Adult Literature

Children with neurologic impairment now commonly live into adulthood and make up an increasing percentage of the general population. Increasing age is related to higher levels of pain, and, similar to findings in the pediatric population, adults with cerebral palsy who are non-ambulatory experience more frequent pain (8). Importantly, pain is associated with a reported lower quality of life in adults with cerebral palsy, highlighting the need to effectively evaluate and treat their pain (8).

Despite pain being highly prevalent in adults with cerebral palsy, research is limited in this population (2). Most literature on this topic discusses the prevalence and characteristics of pain in adults with cerebral palsy and neurologic impairment. Prevalence of pain in individuals with cerebral palsy is similar between adolescents and adults, suggesting that pain starts early in life and continues, especially as neuromuscular complications change and progress (2). For example, pain in the upper extremities increases as the aging process occurs, possibly due to overuse of arms over time and with increased dependence on mobility devices. The most commonly reported sites of pain in adults with cerebral palsy include the back (most common), lower extremities, and upper extremities. Interestingly, this distribution of pain differs slightly from children, whose most common source of pain is primarily the lower extremities (6). Other common sources of pain to consider include bladder distension or irritation, constipation, kidney stones, gastroesophageal reflux, subluxed or broken bones, and dental caries (3).

Additionally, pain is underrecognized in individuals who cannot verbally communicate or who rely on reports by others (6). This finding is especially concerning, given that pain is prevalent in all patients with CP regardless of the severity of the motor disability (2, 20). Because of the recognition that many people with cerebral palsy have communication barriers, one study compared the pain ratings between individuals with cerebral palsy and observers. Although there was moderate agreement between observers, there were major differences between patient and observer ratings (21). Although pain is an important and prevalent problem in adults with childhood-onset disabilities, there are no tools validated for use in non-verbal adults with neurologic impairment to evaluate pain.

DISCUSSION

Given the paucity of evidence-based recommendations for evaluation of pain in adults with childhood-onset disabilities, we will describe the approach taken in our program to evaluate pain in this population.

Take a Systematic History

There are several considerations to obtain a thorough and accurate history. The most important feature is to recognize the value of the history provided by the person's caregivers, as they spend the most time with individual and can notice slight changes in patterns and behavior before most others, especially health care providers. These changes are often the best clues to the diagnosis. We ask about the duration and pattern of the behavior, such as if it is worse before or after meals, before or after stooling, in certain positions, or temporally related to menses.

It is well-known that individuals with medical complexity may express pain using non-verbal signs or atypical expressions (14). Caregivers are familiar with the persons' patterns of verbal and non-verbal communication, and can detect a change. The caregiver may also be able to relay what similar symptoms have meant in the past and we often ask the caregivers what they suspect based on their previous experiences. Often, recurrent urinary infections, kidney stones, or ventricular shunt malfunction may present similarly to previous episodes, what we call the "recapitulation of symptoms"[1]. Asking the caregivers for their diagnostic thoughts also helps us understand their areas of concern. This highlights the importance of developing a longitudinal relationship with individuals and their caregivers.

Comprehensive Physical Examination

A comprehensive physical examination is the next step in evaluation of pain. Special attention should be paid to the vital signs, joints, teeth, dependent areas, and any medical devices such as a ventricular shunt, implanted pump, tracheostomy, and feeding tube. It is important to relate each physical exam finding back to the person's baseline, as this may not be the same baseline as others.

Diagnostic Testing

Findings in the history and physical examination should guide the diagnostic testing. The initial workup typically includes a complete blood count with differential, comprehensive metabolic panel, urinalysis, cultures, and inflammatory markers to delineate pain sources. Imaging is also commonly useful to detect specific areas and organs that may be causing pain, including *x*-ray, ultrasound, and sometimes CT scan. Based on results of the initial workup, further testing may be indicated to identify the etiology of pain more specifically. If this first round of testing is unrevealing and symptoms persist, it is often useful to image the abdomen because intra-abdominal pathology is commonly difficult to detect with physical examination.

Special Considerations for Adults With Childhood-Onset Disabilities and Communication Difficulties

Although it is recognized that having a standardized approach is important to evaluate and diagnose the cause of pain in individuals with communication difficulties, many current assessment tools are validated only for use in children (15). Many diagnoses that lead to pain apply to both children and adults, such as bowel obstruction, kidney stones, and fractures, and the use of a pediatric assessment tool may be helpful to guide initial workup. However, there are several diagnoses that are relatively common in adults and uncommon in children. **Table 1** illustrates findings in the history and physical examination that could be possible indicators of pain in adults (1, 15, 22–24). The diagnoses associated with these findings should also be considered in the evaluation of behavior change in adults with childhood-onset disabilities and communication impairment.

Cervical spine stenosis, causing spinal cord compression, may lead to changes in mobility, strength, and incontinence (1). These outcomes disproportionately affect adults with cerebral palsy and other neurologic syndromes and may have irreversible consequences if not identified early (1). Adults with Down Syndrome are also at risk for cervical myelopathy from atlanto-axial instability (25). Adults presenting with rapid decline in mobility, gait changes, new weakness below the C4–C5 level, or new onset incontinence should be evaluated with x-ray and CT or MRI of the spine (1).

Cardiovascular disease, including coronary artery disease and congestive heart failure, affects a higher prevalence of adults with cerebral palsy than other adults (24). Adults with cerebral palsy are also three times more likely to die from cardiovascular disease (23). Further workup for cardiac sources of pain is indicated, especially for adults with exertional pain, change in exercise capacity, tachypnea, orthopnea, lower extremity swelling, rapid weight gain, and personal or family history of atherosclerosis, hyperlipidemia, or diabetes (22–24). Diagnostic testing may include electrocardiogram, echocardiogram, and lab testing, such as brain natriuretic peptide, blood chemistry, and troponin.

Adults with cerebral palsy also have a higher prevalence of diseases affecting a person's respiratory status, including asthma (24). It is unclear if there is an increased prevalence of venous thromboembolism in adults with CP, but this might be investigated if there are signs such as increased work of breathing, pain or discomfort with exertion, or unilateral leg swelling. If these signs or symptoms are present, initial workup should include pretest probability testing and diagnostic imaging (24). While asthma also leads to increased respiratory distress, it commonly is associated with wheezing on exam and is evaluated with a chest x-ray and trial of bronchodilators, such as albuterol (24). Pulmonary function testing is helpful if the patient is able to complete it.

Low bone mineral density and osteoporotic fractures are common in children and young adults with CP, Down Syndrome, and other disorders that reduce independent mobility, such as spina bifida (3, 24, 26–30). There should be high suspicion for an occult fracture, particularly if they have reduced mobility or inability to bear weight, prolonged use of anticonvulsants, steroids, or proton pump inhibitors, and may have bruising or swelling noted on physical examination (3, 24). Initial imaging includes x-ray of the affected area, as well as a bone density scan.

Osteoarthritis is also more commonly seen in adults with cerebral palsy compared to other adults (3). History will typically describe pain in the person's hands, shoulders, hips,

[1]Originally attributed to Robert M. Bilenker, MD.

TABLE 1 | Findings in history and physical examination that may indicate pain as source of behavior change in adults with childhood-onset disabilities and communication impairment.

Source of pain	Common findings in history	Physical examination findings	Diagnostic considerations
Neurologic	Altered mental status/acting withdrawn Rapid decline in mobility or change in gait Recurrent vomiting, regurgitating, or feeding refusal New onset incontinence Increase or change in pattern of self-injurious behavior or others signs of pain	Diaphoresis Increased spasticity Increased weakness Signs of increased intracranial pressure (bradycardia, hypertension, irregular breathing, cranial nerve palsies, etc.)	CT/MRI of brain X-ray of spine CT/MRI of spine
Cardiovascular	Increased fatigability Pain or discomfort with exertion Rapid changes in weight	Lower extremity swelling Signs of respiratory distress Orthopnea Tachycardia Hepatomegaly	ECG Echocardiogram Brain natriuretic peptide Comprehensive metabolic panel Troponin
Respiratory	Signs of respiratory distress Dyspnea with exertion	Unilateral lower extremity swelling Cough or wheezing Increased work of breathing Tachypnea	Pretest probability testing (Wells score, D dimer) Diagnostic imaging Trial of bronchodilator Pulmonary function testing
Gastrointestinal	Nausea/vomiting Feeding intolerance	Diarrhea/constipation Abdominal distension Coughing with feeding	X-ray of abdomen Abdominal ultrasound CT of abdomen Comprehensive metabolic panel Amylase/Lipase
Genitourinary	Pain signs with urination Colicky abdominal pain Pain around menstruation Malodorous urine	Urinary retention Abdominal distension Hematuria	Ultrasound of kidneys and bladder Urinalysis Basic metabolic panel
Musculoskeletal	Pain with movement of joints or extremities Pain with repositioning Prolonged use of anticonvulsants, steroids, or proton pump inhibitors	Joint swelling or deformity Bruising	X-ray of affected joint or extremity Bone density scan

or knees, and is evaluated initially with *x*-ray of the painful joint (3).

CONCLUSION

Although pain is both common and associated with a lower quality of life in adults with childhood-onset disabilities, it is frequently underrecognized and undertreated. Additionally, there are no standardized tools for measurement of pain in adults with childhood-onset disabilities or for those with communication difficulties and research is limited.

We propose an approach to pain evaluation that consists of a systematic history, comprehensive physical examination, and judicious use of diagnostic testing to help formulate an appropriate differential diagnosis for adults with childhood-onset disabilities. We also recommend additional consideration of adult-specific diagnoses to include for this population.

In future studies, it will be important to adapt assessment tools for use in adults with childhood-onset disabilities or create new tools with a focus on adult-specific diagnoses. This type of research is vital to improve outcomes such as time-to-diagnosis and accuracy of diagnosis and treatment. By improving these outcomes through increased research, the goal is to provide high-quality, patient-centered, and comprehensive care for all adults with childhood-onset disabilities and communication difficulties.

AUTHOR CONTRIBUTIONS

TJ and GN confirm their individual contributions to the paper. Both authors reviewed and approved the submitted manuscript.

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Living Conditions and Social Outcomes in Adults With Cerebral Palsy

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Objectives: To analyse the living conditions and social outcomes (housing, engagement in employment or higher education, access to personal assistance and having a partner) in adults with cerebral palsy (CP) relative to their age, sex, communication ability, and motor skills.

Methods: Cross-sectional registry-based study of 1,888 adults (1,030 males/858 females) with CP in the Swedish CP follow-up programme, median age 25 years (range 16–78 y). Type of housing, occupation, access to personal assistance and having a partner were analysed relative to their age, sex, and the classification systems for Gross Motor Function (GMFCS) and Communication Function (CFCS). Binary logistic regression models were used to calculate odds ratios (OR) for independent living, competitive employment, and having a partner.

Results: Most of the 25- to 29-year olds (55.6%) lived independently, increasing to 72.4% in 40- to 49-year olds, while the majority (91.3%) of those under 20 years lived with their parents. Independent living was almost equal in adults at GMFCS levels I (40.2%) and V (38.6%). This parity was explained by access to personal assistance, which increased with higher GMFCS and CFCS levels. Personal assistance of >160 hours/week was associated with a high probability of independent living (OR 57). In the age span 20–64 years, 17.5% had competitive employment and 45.2% attended activity centres for people with intellectual disabilities. In the younger age group up to 24 years old, 36.9% went to mainstream/higher education and 20.5% went to special schools. In total, 13.4% had a partner and 7.8% lived together. Slightly more women than men had a partner, and most individuals were classified at CFCS level I.

Conclusion: Only one in eight adults with CP has a partner, and one in six has competitive employment. Access to personal assistance is the single most important factor for independent living. It is vital to support adults with CP throughout their lifespan to achieve the best possible outcomes in all aspects of life.

Keywords: cerebral palsy, adults (MeSH), domestic partners, employment, housing, occupation, personal assistance, social security

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INTRODUCTION

Today, most adults with cerebral palsy (CP) have a full life expectancy (1). The prevalence of CP is estimated to be 17 million individuals worldwide (2). Those with the most severe impairments have poor survival, but the surviving adults have significantly fewer impairments, particularly regarding severe motor impairment, intellectual disability and epilepsy (3). Even so, our knowledge of their living conditions and social outcomes is sparse.

Qualitative studies of young adults with CP show that living arrangements, occupation, personal care and interpersonal relationships are among the most important issues to address (4–6). According to the World Health Organisation, social well-being is an important aspect of health (7). Individuals with neurodevelopmental conditions such as CP are less likely to pursue post-secondary education. They also experience lower employment rates and participate in fewer leisure and social activities. In daily life, they rely more on their families for living arrangements, and adults with CP experience poorer health than their peers without disabilities. There is still a great need to understand better the development of individuals with CP through their lifetime (8). Population-based studies may increase our understanding of the living conditions of adults with CP, leading to knowledge that facilitates the distribution of resources (3).

To improve the continuity of care throughout life and bridge the gap between paediatric and adult care, a follow-up programme for adults with CP (CPUP) was initiated as a pilot project in Sweden in 2009. The programme has expanded and since 2019, all 21 health-care regions in Sweden offer ongoing follow-up within this programme. The transition from child- to adult services within the programme is flexible from 16 up to 19 years. The programme originally started in 1994 as hip surveillance of children (9) and over the years has developed into a National multiprofessional health-care programme and quality registry. Now, the programme involves orthopaedic surgeons and hand surgeons, neuropaediatricians, physical and occupational therapists, speech and language pathologists, psychologists and certified prosthetists and orthotists. Since 1994, Swedish law has decreed that certain physically disabled people over the age of 20 years have the right to services by specialists and to rehabilitation in special units. Before then, only individuals over the age of 20 years with learning disabilities were guaranteed services and rehabilitation (10).

An early study of the adult population with CP within the follow-up programme showed that most individuals lived at home with their parents. They either studied or had their occupation at activity centres; 34 out of 70 young adults had personal assistance. The study included 102 individuals in their early twenties, explaining the high number of individuals living at home and in higher education (11). A Danish study showed that 55% of Danish adults with CP (aged 29–35 years) were unemployed, did not cohabit with a partner and did not have children, compared with only 4% of the control population (12). Andersson and Mattsson (10) reported results from a Swedish population of 121 adults with CP (20–58 years) with most adults living independently and in single households, with or without home services and that 24% worked full time. A study from the Netherlands reported employment rates of 49% in 74 young adults (20–years) with spastic CP without intellectual disabilities (13), which is slightly higher than the 18% recently reported in a Swedish study of 61 young adults with CP (20–22 years old) (6).

The aim of this study was to analyse the living conditions and social outcomes (housing, engagement in employment or higher education, access to personal assistance, and having a partner) in adults with CP relative to their age, sex, communication ability and motor function.

MATERIALS AND METHODS

Participants

This cross-sectional registry-based study included all adults followed within the Swedish CP follow-up program from 2012 until 2019. The age ranged from 16 to 78 years and a majority of those included in the program were enrolled as adults and have not previously been followed as children. All participation was voluntary, and all participants gave their consent, even if they previously had participated in the follow-up as children. The male/female ratio corresponded to the CP prevalence in children with slightly more males than females.

The adults were examined regularly by their local adult specialist team, (usually a physical therapist, an occupational therapist and a speech and language pathologist), according to a schedule based on their level of the Gross Motor Function Classification System (GMFCS). Adults classified at levels III to V are offered examinations every year and those at levels II and I are examined every second or third year. The examinations are accompanied by several patient-reported outcome measures and information about living conditions and social outcomes.

Classifications and Measurements

The CP definition used was that of Rosenbaum et al. (14). The inclusion and exclusion criteria for CP was defined according to the Surveillance of Cerebral Palsy in Europe as a brain injury before the age of 2 years, with subtypes divided into unilateral spastic CP, bilateral spastic CP, ataxic CP, dyskinetic CP or mixed type/unclassifiable CP (15). Functional levels were classified by the local specialist team according to the expanded and revised version of the GMFCS, describing gross motor performance (16), and the Communication Function Classification System (CFCS), which describes the effectiveness of communication as a sender and receiver of information including all types of communication such as facial expressions and alternative communication (17).

Sex and Age

Sex was based on the legal gender, male or female. Age at examination was calculated based on the date of birth and date of examination. Age was grouped into seven categories: 16–19, 20–24, 25–29, 30–39, 40–49, 50–64, and 65–78 years. The rationale for this grouping was the skewed distribution due to an excess of younger people, where people in the transition years are more likely to attend school and live with their parents. The formative years, where many are moving into higher education, starting to

work and moving away from home were divided into several age categories. There is no fixed retirement age in Sweden, but the age for the guaranteed pension is 65 years, therefore adults 65 years and older were grouped together. Guaranteed pension includes people with disabilities and those who never worked.

Having a Partner

Having a partner was categorised as (1) Single, (2) Partner who lives elsewhere, or (3) Domestic partner (reside together with partner or spouse).

Type of Housing

The participants' type of housing was categorised as (1) independent living (own housing, with or without assistance); (2) living with parents; (3) assisted-living facilities (e.g., group homes and service housing provided by the municipality); or (4) other living arrangements.

Personal Assistance

Data on personal assistance were collected and divided into the following categories, depending on the hours of assistance per week (h/w): (1) <60, (2) 60–160, (3) >160 h/w, or (4) no assistance. The Swedish Personal Assistance act is demand-driven and entitles personal assistance (part-time or full time) to individuals with certain disabilities who need help more than 20 h/w for activities of daily living. The personal assistants are carers paid for by the state and the costs are fully covered. The need for assistance is expressed as h/w, and the needs are assessed by tax-funded Social Security. Eligibility is independent of income, property or housing of the person or their family. The individual is free to buy services from any provider or employ their own assistants (18).

Occupation

Occupation status was classified as (1) mainstream education; (2) special school (schools for individuals with intellectual disabilities, the intelligence quotient (IQ) for such schooling is an IQ of <70); (3) competitive employment; (4) supported employment (for example, ventures stipulated by the government to offer an occupation to individuals outside the labour market); (5) activity centre (according to the Swedish law on special support and service for certain disabled people, daily activity can be provided to adults, 18–65 years old, with a developmental disorder, autism or autism-like condition or significant and permanent intellectual disability [IQ < 70]. Activity centres are intended to give a meaningful work life and contribute to the development of the adult during weekdays, at so-called "day centres". The activity offered is based on the individual's functional ability and interests and organised by the municipality); or (6) No occupation. The different categories of occupation were divided into full time (>30 h/w), or part-time (≤30 h/w).

Ethics

This study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans (19). The study was approved by the Medical Research Ethics Committee at Lund (no. 2009/341).

Statistical Analyses

Frequencies and percentages were used to describe the data. The chi-squared test was used to detect any differences between categorical data. Binary logistic regression models were used to predict independent living, competitive employment and having a partner based on other variables such as age, sex, and functional levels. Age was used as a continuous variable. The results were presented as adjusted odds ratios (ORs) with 95% confidence intervals (CI). All values were adjusted for all other variables in the models. The significance level was set to 0.05. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp was used for all analyses.

RESULTS

Participants

Data from 1,888 adults with CP born between 1941 and 2003 were reported into the database, made up of 1,030 males (54.6%) and 858 females (45.4%), at a median age of 25 years (range 16–78 y) (**Table 1**). Four out of five individuals were younger than 40 years of age. Most adults were either classified at GMFCS level I (22.9%) or GMFCS level V (23.0%), with the fewest individuals at GMFCS level III (14.8%). Many of the adults had better communication than gross motor skills, and the majority were classified at CFCS level I (43.4%) or evenly distributed among CFCS levels II to V ranging from 11.8 to 14.3%. Spastic CP was the most frequent neurological subtype, with 983 (52.1%) having spastic bilateral CP and 444 (23.5%) spastic unilateral CP. Only 76 adults (4%) had ataxic CP and 233 (12.3%) had dyskinetic CP (**Table 1**).

Having a Partner

Most adults with CP were single (86.6%). Of the 13.4% who had a partner, 7.8% had a domestic partner and 5.6% had a partner who lived elsewhere (**Table 2**). More females (17.5%) than males (10%) had a partner, both a domestic partner (10.6 vs. 5.5%) and a partner living elsewhere (6.9 vs. 4.5%). Having a partner ranged from 2.1% of the youngest age group to 24.8% of all adults 50 years and older. A slightly higher proportion of the 50- to 64-year olds lived together with a partner or spouse (17.7%). Adults at CFCS level I more often lived with a partner (14.6%), than those at CFCS levels II–V. Having a more severe disability was associated with a decreased probability of having a partner. Only 4.9% of the individuals at GMFCS levels IV and V, and 1.3% at CFCS levels IV and V had a partner (**Table 2**).

Age increased the likelihood of having a partner (OR 1.03, 95% CI 1.01–1.04), and women were almost twice as likely to have a partner as men (OR 1.89, 95% CI 1.36–2.63), when adjusted for GMFCS, CFCS, housing and occupation (**Table 3**). Adults at GMFCS level III were almost half as likely to have a partner (OR 0.45, 95% CI 0.27–0.74) compared with adults at GMFCS level I, and those at GMFCS level V were much less likely to have a partner (OR 0.12, 95% CI 0.04–0.31). Having more severe challenges with communication decreased the likelihood of having a partner, CFCS levels IV (OR 0.15, 95% CI 0.05–0.49), and V (OR 0.18; 95% CI 0.05–0.65) compared with adults

TABLE 1 | Characteristics of the 1,888 adults with CP.

		Participants	
		N	%
Total		1,888	100
Sex			
	Male	1,030	54.6
	Female	858	45.4
Age groups			
	16–19 y	355	18.8
	20–24 y	556	29.4
	25–29 y	344	18.2
	30–39 y	328	17.4
	40–49 y	165	8.7
	50–64 y	127	6.7
	65–78 y	13	0.7
GMFCS			
	I	432	22.9
	II	401	21.2
	III	279	14.8
	IV	341	18.1
	V	435	23.0
CFCS			
	I	819	43.4
	II	226	12.0
	III	225	11.9
	IV	222	11.8
	V	270	14.3
	Missing	126	6.7
CP Subtype			
	Spastic unilateral	444	23.5
	Spastic bilateral	983	52.1
	Ataxic	76	4.0
	Dyskinetic	233	12.3
	Mixed type/unclassifiable	121	6.4
	Missing	31	1.6

CFCS, Communication Function Classification System; GMFCS, Gross Motor Function Classification System; Y, years.

at CFCS level I. Independent living (OR 5.01, 95% CI 3.30–7.59), and having a competitive employment (OR 1.67, 95% CI 1.15–2.43) increased the likelihood of having a partner (**Table 3**).

Type of Housing

Most adults either lived with their parents (43.3%) or in independent living (41.3%), whereas 13.1% had assisted-living facilities. Females more often lived independently than males (44.9 vs. 38.4%), while males more often lived with their parents (45.5 vs. 40.7%) (**Table 4**). Housing differed significantly between age groups ($p < 0.001$). Most of the 25- to 29-year olds (55.6%) lived independently, increasing up to 72.4% of the 40- to 49-year olds. Most of the younger adults lived at home with their parents (91.3% of those under 20 years and 63.4% of the 20- to 24-year olds). There was also a relatively large number of individuals, 27.8% aged 25–29 years, who still lived at home. The number of individuals living in assisted-living facilities increased with age, ranging from 2% for those under 19 years, up to 31.2% for those over 50 years of age (**Table 4**).

Type of housing differed between adults at different GMFCS and CFCS levels ($p < 0.001$). Most adults at CFCS level I lived independently (51.3%), while the majority of those at CFCS levels II to V lived with their parents (44.4–48.9%). Assisted-living facilities were most frequent in adults at GMFCS levels II (17.5%), and V (15.5%). Most individuals at GMFCS level I either lived with their parents (51.3%) or in independent living (40.2%). The proportion of adults living independently was almost equal at GMFCS levels I (40.2%) and V (38.6%), despite the differences in motor functioning and ability to manage daily life (**Table 4**).

The single most important factor for independent living was access to personal assistance (**Table 5**). Personal assistance for >160 h/w increased the likelihood of independent living over 50 times (OR 57.07, 95% CI 32.35–101). In addition, increasing age, having a partner, and being employed increased the probability of independent living (**Table 5**).

Personal Assistance

In total, 807 adults (45%) had personal assistance, at similar levels for males and females (**Table 4**). Most individuals had assistance >160 h/w (23.2%), ranging from 10.5% of those over 50 years, up to 37.6% of the 25- to 29-year olds. The proportion of adults who received personal assistance increased with increasing GMFCS and CFCS levels ($p < 0.001$). Most adults at GMFCS levels I (97.6%) and II (79.5%) had no assistance. The amount of assistance increased proportionally for both GMFCS levels IV and V, such that 59.7% at level V had assistance over 160 h/w. More individuals at CFCS levels I received assistance at all assistance levels, compared with GMFCS levels I. Those with fewer communication skills also had personal assistance for more hours per week than those with more ability, with 59.4% of the adults at CFCS level V having assistance more than 160 h/w, compared with 35.4% at CFCS level III and 6.2% of those at CFCS level I (**Table 4**).

Occupation

The majority had their primary occupation at an activity centre for people with intellectual disabilities (36.7%). Because of the high number of young adults in the population, many individuals either went to mainstream education/higher education or attended special school (19.4 vs. 10.1%) (**Table 6**). In the age span 20–64 years, 17.5% had competitive employment, 3.7% had supported employment and 45.2% attended activity centres. In the younger age group up to 24 years old, 36.9% went to mainstream education and 20.5% to special schools. Individuals at activity centres were found in all age groups. Competitive employment ranged from 0.6% of those under 19 years, up to 26.1% of the 40- to 49-year olds, then declined (**Table 6**).

Occupation also differed significantly between adults at different GMFCS and CFCS levels (**Table 6**). The majority of individuals in mainstream education were classified at GMFCS levels I (39.2%) or II (18.0%), with the same tendency for CFCS levels, with individuals at levels I (29.1%)

TABLE 2 | Adults who are single or have a partner, relative to their sex, age, GMFCS and CFCS levels.

		Single	Partner who lives elsewhere	Domestic partner	*p*-value
		n = 1551	*n* = 101	*n* = 140	
		N (%)	*N* (%)	*N* (%)	
Sex					
	Male	874 (90.0)	44 (4.5)	53 (5.5)	<0.001
	Female	677 (82.5)	57 (6.9)	87 (10.6)	
	Total	1,551 (86.6)	101 (5.6)	140 (7.8)	
Age					
	≤ 19 y	318 (97.8)	6 (1.8)	1 (0.3)	<0.001
	20–24 y	468 (89.8)	28 (5.4)	25 (4.8)	
	25–29 y	278 (84.5)	15 (4.6)	36 (10.9)	
	30–39 y	259 (81.4)	29 (9.1)	30 (9.4)	
	40–49 y	125 (77.2)	13 (8.0)	24 (14.8)	
	50–64 y	93 (75)	9 (7.3)	22 (17.7)	
	≥ 65 y	10 (76.9)	1 (7.7)	2 (15.4)	
	Total	1,551 (86.6)	101 (5.6)	140 (7.8)	
GMFCS					
	I	308 (76.8)	36 (9.0)	57 (14.2)	<0.001
	II	316 (82.1)	26 (6.8)	43 (11.2)	
	III	225 (84.0)	19 (7.1)	24 (9.0)	
	IV	296 (91.4)	15 (4.6)	13 (4.0)	
	V	406 (98.1)	5 (1.2)	3 (0.7)	
	Total	1,551 (86.6)	101 (5.6)	140 (7.8)	
CFCS					
	I	588 (76.1)	72 (9.3)	113 (14.6)	<0.001
	II	200 (91.7)	11 (5.0)	7 (3.2)	
	III	201 (91.8)	8 (3.7)	10 (4.6)	
	IV	212 (98.6)	1 (0.5)	2 (0.9)	
	V	252 (98.8)	2 (0.8)	1 (0.4)	
	Total	1,453 (86.5)	94 (5.6)	133 (7.9)	

CFCS, Communication Function Classification System; GMFCS, Gross Motor Function Classification System; y, years.

and II (24.7%). The opposite was seen for those attending a special school, mostly including individuals at GMFCS levels IV (11.8%) and V (15.5%) and also at CFCS levels IV (19.4%) and V (16.5%). Competitive employment was more common in individuals at GMFCS level I (27.4%) and CFCS level I (28.4%), thereafter decreasing proportionally for increasing GMFCS/CFCS levels. Having no occupation was evenly distributed among the different GMFCS and CFCS levels (**Table 6**).

Independent living (OR 5.51, 95% CI 3.78–8.63) and having a partner (OR 1.65, 95% CI 1.12–2.42) increased the likelihood of having competitive employment, whereas women were half as likely to have employment as men (OR 0.54, 95% CI 0.39–0.76). Reduced communication ability seemed to be the highest risk factor for not having employment, ranging from CFCS level II (OR 0.36, 95% CI 0.2–0.65) to level IV (OR 0.07, 95% CI 0.02–0.32). No individual at CFCS V had a competitive employment (**Table 5**).

Full or Part-Time Occupation

Most individuals (54.8%) worked full time (>30 h/w). There were no significant differences between males and females in worked h/w. A full-time occupation was most common for the youngest age group of 16 to 19 years attending school (91.3%). Considering individuals of working age (20–64-year olds), full-time occupation gradually decreased from 59.1% in the 20- to 24-year olds to 31.2% of the 50- to 64-year olds, whereas part-time work increased successively for 20- to 24-year olds, to peak at 50 to 64 years of age. Two individuals over 65 years worked part-time (**Table 6**).

Full-time and part-time occupation differed significantly between GMFCS ($p < 0.001$) and CFCS levels ($p = 0.015$). Most individuals at GMFCS level I, (70.5%) had a full-time occupation. More individuals at CFCS level I (42.7%) worked part-time than those at GMFCS level I (29.5%). The largest groups having a part-time occupation were adults at GMFCS level V and CFCS level V (54.3 vs. 52%) (**Table 6**).

TABLE 3 | Binary logistic regression analyses for having a partner presented as odds ratios (ORs) with 95% confidence intervals (CIs).

		Having a partner			
		OR	95% CI		*p*-value
			Lower	Upper	
	Age	1.03	1.01	1.04	<0.001
Sex	Male	*ref*			
	Female	1.89	1.36	2.63	<0.001
GMFCS	I	*ref*			
	II	0.61	0.40	0.94	0.026
	III	0.45	0.27	0.74	0.002
	IV	0.31	0.18	0.55	<0.001
	V	0.12	0.04	0.31	<0.001
CFCS	I	*ref*			
	II	0.48	0.27	0.85	0.012
	III	0.66	0.37	1.21	0.179
	IV	0.15	0.05	0.49	0.002
	V	0.18	0.05	0.65	0.009
Housing	No independent living	*ref*			
	Independent living	5.01	3.30	7.59	<0.001
Occupation	No competitive employment	*ref*			
	Competitive employment	1.67	1.15	2.43	0.008

All values are adjusted for all other variables in the model.
CFCS, Communication Function Classification System; GMFCS, Gross Motor Function Classification System.

DISCUSSION

This study describes the living conditions and social outcomes in 1,888 adults with CP, aged 16–78 years old. Only one in eight had a partner, and one in six of the 20- to 64-year olds had competitive employment, revealing that reduced communication ability seemed to be the highest risk factor for not having employment. Access to personal assistance was the single most important factor for independent living and explained why independent living was almost as common in adults with the least and the most severe motor impairments.

Having a Partner

To have support, but also help from family and friends, is considered the main core for gaining quality of life (20). We found that only one in eight people in our study had a partner (12.7%). This is slightly lower than a previous report that found 22% had a partner (10). The higher prevalence might be explained by different inclusion criteria because the authors excluded individuals with learning disabilities and those living in assisted-living facilities (10). In a recent Danish study (12), as much as 28% of the 416 adults with CP had a partner. The population in that study had a slightly higher mean age of 32 years, than the mean age of 25 years in our cohort. We found that older age increased the likelihood of having a partner. Another study of 61 young adults with CP (20–22 years), reported that 5% lived with a partner (6). This is in line with our findings, where 4.8% (20–24 y), lived with a partner or spouse.

A novel but unexpected finding was that women were almost twice as likely to have a partner as men, either a domestic partner or a partner living elsewhere. Adults at CFCS level I and more often lived with a partner than those with less communication ability. This is in line with previous findings where better CFCS has been associated with having experience of intimate relationships, although, unlike our study, the authors found no association with the GMFCS (6). We found that the severity of CP, both in terms of communication and gross motor function decreased the likelihood of having a partner. The difference in findings can perhaps be explained by their smaller sample size, slightly different outcomes, and analyses of data. The link between the quality of life and social relations (family, friends, and others), affects an individual's life, both positively and negatively depending on the characteristic of the relationship (20). Our findings also reinforce the crucial need for good communication abilities, particularly important for social functioning in young adults with CP (6, 12). Unfortunately, having a partner seems to be less common in adults with CP than in the general population.

Type of Housing

To have independent living is a prioritised goal for young adults (5). We found that most adults either lived with their parents (43.3%) or in independent living (41.3%), whereas only 13.1% lived in assisted-living facilities. There was a clear association between age and type of housing. We found that many younger adults in the transition years still lived with their parents, which agrees with other studies (21, 22), whereas as many as 72.4% in

TABLE 4 | Type of housing and personal assistance (hours/week) for all adults relative to their sex, age, GMFCS and CFCS levels.

		Housing					Personal assistance, h/w				
		Independent *N* (%)	With parents *N* (%)	Assisted living *N* (%)	Other *N* (%)	*p*-value	No *N* (%)	<60 *N* (%)	60–160 *N* (%)	>160 *N* (%)	*p*-value
Sex						0.018					0.993
	Male	386 (38.4)	457 (45.5)	134 (13.3)	28 (2.8)		539 (55.3)	59 (6.1)	151(15.5)	225 (23.1)	
	Female	372 (44.9)	337 (40.7)	107 (12.9)	13 (1.6)		448 (54.6)	51 (6.2)	129 (15.7)	192 (23.4)	
	Total	758 (41.3)	794 (43.3)	241 (13.1)	41 (2.2)		987 (55.0)	110 (6.1)	280 (15.6)	417 (23.2)	
Age						<0.001					<0.001
	≤ 19 y	7 (2.0)	315 (91.3)	7 (2.0)	16 (4.6)		181 (56.4)	41 (12.8)	61 (19.0)	38 (11.8)	
	20–24 y	136 (25.5)	338 (63.4)	44 (8.3)	15 (2.8)		302 (57.3)	33 (6.3)	95 (18.0)	97 (18.4)	
	25–29 y	184 (55.6)	92 (27.8)	48 (14.5)	7 (2.1)		151 (45.8)	14 (4.2)	41 (12.4)	124 (37.6)	
	30–39 y	224 (69.1)	41 (12.7)	58 (17.9)	1 (0.3)		162 (50.3)	11 (3.4)	46 (14.3)	103 (32.0)	
	40–49 y	118 (72.4)	6 (3.7)	38 (23.3)	1 (0.6)		89 (56.3)	4 (2.5)	24 (15.2)	41 (25.9)	
	50–64 y	83 (66.4)	2 (1.6)	39 (31.2)	1 (0.6)		91 (73.4)	7 (5.6)	13 (10.5)	13 (10.5)	
	≥ 65 y	6 (46.2)	0	7 (53.8)	0		11 (91.7)	0	0	1 (8.3)	
	Total	758 (41.3)	794 (43.3)	241 (13.1)	41 (2.2)		987 (55.0)	110 (6.1)	280 (15.6)	417 (23.2)	
GMFCS						<0.001					<0.001
	I	167 (40.2)	213 (51.3)	27 (6.5)	8 (1.9)		414 (97.6)	6 (1.4)	1 (0.2)	3 (0.7)	
	II	158 (40.6)	151 (38.8)	68 (17.5)	12 (3.1)		302 (79.5)	27 (7.1)	28 (7.4)	23 (6.1)	
	III	127 (47.0)	92 (34.1)	41 (15.2)	10 (3.7)		138 (53.5)	35 (13.6)	57 (22.1)	28 (10.9)	
	IV	142 (42.4)	147 (43.9)	39 (11.6)	7 (2.1)		69 (21.2)	31 (9.5)	105 (32.3)	120 (36.9)	
	V	164 (38.6)	191 (44.9)	66 (15.5)	4 (0.9)		64 (15.7)	11 (2.7)	89 (21.9)	243 (59.7)	
	Total	758 (41.3)	794 (43.3)	241 (13.1)	41 (2.2)		987 (55.0)	110 (6.1)	280 (15.6)	417 (23.2)	
CFCS						<0.001					<0.001
	I	413 (51.3)	314 (39.0)	54 (6.7)	24 (3.0)		642 (80.9)	43 (5.4)	60 (7.6)	49 (6.2)	
	II	74 (33.2)	101 (45.1)	41 (18.4)	7 (3.1)		128 (59.0)	15 (6.9)	41 (18.9)	33 (15.2)	
	III	75 (33.6)	109 (48.9)	37 (16.6)	2 (0.9)		61 (29.2)	20 (9.6)	54 (25.8)	74 (35.4)	
	IV	66 (30.3)	102 (46.8)	48 (22.0)	2 (0.9)		57 (27.1)	15 (7.1)	61 (29.0)	77 (36.7)	
	V	93 (34.7)	119 (44.4)	53 (19.8)	3 (1.1)		52 (20.3)	9 (3.5)	43 (16.8)	152 (59.4)	
	Total	721 (41.5)	745 (42.9)	233 (13.4)	38 (2.2)		940 (55.8)	102 (6.0)	259 (15.4)	385 (22.8)	

CFCS, Communication Function Classification System; GMFCS, Gross Motor Function Classification System; y, years.

the age group 40–49 years lived independently. Other studies report that between 13 and 95% live with their parents, and between 28 and 86% of adults with CP live independently (10, 12, 21–24). It is important to note that the selection criteria, sample sizes, age and degree of severity often differ substantially among these studies, making it difficult to compare the results.

Almost half of the young adults with CP rely on family members for help with ADL on a daily basis (6) and this may be one of the reasons why we found that almost one-third of individuals aged 25–29 years still lived at home. Our data represent a nationwide cohort, and this may be another reason for the differences related to housing. The 61 young adults in the study by Jacobson et al. (6) live in a large city, with a tough housing market. This may explain why only 20% of young adults had moved away from their parents, compared with 44% of age-matched adults from official statistics (6). Today, as a young adult (with or without a disability), financial constraints can make entering the housing market a challenge, which may explain the higher number of young individuals still living at home. Access to, and quality of, assisted-living facilities can also play a part in why young adults remain so long in the parental home, especially when the parents want to find a facility that matches their expectations. Instead, young adults remain with their parents (12). To care for a person with impairments can be stressful, particularly for the parents and especially as challenging behaviour often occurs in the context of cognitive impairment and mental health problems, in addition to the individuals' physical impairments (25). In addition, the parents' health and well-being are of great importance when planning for youth transition into adulthood (4).

We found that males more often live with their parents or in assisted-living facilities than females who more often lived independently, while others did not find any differences between males and females regarding the type of housing (12). This difference might be explained by our larger cohort (1,888 vs. 416). In line with previous studies (11, 12, 21, 26), we found that one in five adults lived in assisted-living facilities, most frequently for adults at GMFCS

TABLE 5 | Binary logistic regression analyses for independent living and competitive employment presented as odds ratios (ORs) with 95% confidence intervals (CIs).

		Independent living				Competitive employment			
		OR	95% CI		*p*-value	OR	95% CI		*p*-value
			Lower	Upper			Lower	Upper	
	Age	1.12	1.10	1.13	<0.001	1.02	1.00	1.03	0.074
Sex	Male	*ref*				*ref*			
	Female	1.21	0.93	1.59	0.160	0.54	0.39	0.76	<0.001
GMFCS	I	*ref*				*ref*			
	II	1.05	0.68	1.62	0.834	0.73	0.48	1.12	0.147
	III	0.51	0.30	0.86	0.011	0.54	0.33	0.87	0.013
	IV	0.32	0.18	0.58	<0.001	0.43	0.25	0.75	0.003
	V	0.36	0.19	0.68	0.002	0.17	0.06	0.51	0.002
CFCS	I	*ref*				*ref*			
	II	0.31	0.19	0.50	<0.001	0.36	0.20	0.65	0.001
	III	0.15	0.09	0.25	<0.001	0.13	0.05	0.34	<0.001
	IV	0.13	0.07	0.22	<0.001	0.07	0.02	0.32	<0.001
	V	0.14	0.08	0.24	<0.001	0.00	–	–	0.994
Partner	Single	*ref*				*ref*			
	Partner	6.21	3.96	9.74	<0.001	1.65	1.12	2.42	0.011
Housing	No independent living	–	–	–	–	*ref*			
	Independent living	–	–	–	-	5.51	3.78	8.63	<0.001
Occupation	No competitive employment	*ref*				–	–	–	–
	Competitive employment	5.21	3.42	7.93	<0.001	–	–	–	–
Personal assistance	No assistance	*ref*							
	<60 h/w	1.11	0.53	2.34	0.780	–	–	–	–
	60–160 h/w	10.03	5.89	17.08	<0.001	–	–	–	–
	>160 h/w	57.07	32.25	101.0	<0.001	–	–	–	–

All values are adjusted for all other variables in the models.
CFCS, Communication Function Classification System; GMFCS, Gross Motor Function Classification System.

levels II and V. This observation is most likely explained by the higher proportion of individuals attending special schools or activity centres for these two groups, indicating cognitive disabilities.

Like the findings by Michelsen et al. (12), we found that the type of housing also differed between adults at different levels of motor function and communication ability. An unexpected finding was that independent living levels were almost equal in adults at GMFCS levels I and V. When adjusting for several factors in the regression analysis, adults at GMFCS V were much less likely to live independently than adults at GMFCS I. However, this seemed to be compensated by their access to personal assistance. We identified personal assistance as the single most important factor for independent living. Access to personal assistance for >160 h/w, increased the likelihood of independent living more than 50-fold. In addition, increasing age, having a partner and employment increased the probability of independent living. Obtaining personal assistance opens possibilities and increases social integration and participation for adults with CP, giving reason to live an independent life in the community.

Personal Assistance

Some form of personal assistance is currently available in all Nordic countries, most Western European countries, Australia, parts of Asia, the U.S. and Canada (25). In 2017 there were 19,690 persons receiving personal assistance in Sweden. For the last three decades, quality of life has increased, for those gaining assistance. Today, the future is uncertain, as the state in many cases reduces, or denies assistance hours (27).

We found that 45% of our adult population with CP received personal assistance, and one out of five had assistance more than 160 h per week. In a study from 2014, 49% of 102 young adults had personal assistance (11) and in a study from 2001, 55% received assistance. These studies included individuals with CP, but without cognitive disabilities (10). The actual difference in access to personal assistance over these 20 years may be even more pronounced, considering that those with cognitive disabilities were included in our study but excluded in the study from 2001.

The access to personal assistance was similar for males and females (44.7 vs. 45.4%). This differs from Sweden as a whole, where a slight predominance of males (54%) had personal assistance (27). The reverse is seen in the U.S. where there is a

TABLE 6 | Primary occupation and full-time or part-time occupation for all adults with CP relative to their sex, age, GMFCS, and CFCS levels.

		Education		Employment		Activity	No		Full or part-time		
		Mainstream	Special	Competitive	Supported	Centre	Occupation	*p*-value	Full time	Part-time	*p*-value
		n = 355	*n* = 184	*n* = 261	*n* = 55	*n* = 672	*n* = 299		*n* = 795	*n* = 656	
		N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)		*N* (%)	*N* (%)	
Sex								0.372			0.323
	Male	181 (18.1)	103 (10.3)	156 (15.6)	29 (2.9)	371 (37.2)	158 (15.8)		446 (56.0)	351 (44.0)	
	Female	174 (21.0)	81 (9.7)	105 (12.7)	26 (3.1)	301 (36.3)	141 (17.0)		349 (53.4)	305 (46.6)	
	Total	355 (19.4)	184 (10.1)	261 (14.3)	55 (3.0)	672 (36.8)	299 (16.4)		795 (54.8)	656 (45.2)	
Age								<0.001			<0.001
	≤ 19 y	181 (52.6)	140 (40.7)	2 (0.6)	0 (0.0)	6 (1.7)	15 (4.4)		283 (91.3)	27 (8.7)	
	20–24 y	142 (26.7)	39 (7.3)	65 (12.2)	20 (3.8)	187 (35.2)	78 (14.7)		253 (59.1)	175 (40.9)	
	25–29 y	20 (6.0)	2 (0.6)	64 (19.3)	11 (3.3)	182 (54.8)	53 (16.0)		98 (36.6)	170 (63.4)	
	30–39 y	9 (2.8)	2 (0.6)	61 (18.9)	13 (4.0)	175 (54.3)	62 (19.3)		95 (38.2)	154 (61.8)	
	40–49 y	2 (1.2)	0	42 (26.1)	9 (5.6)	70 (43.5)	38 (23.6)		42 (35.9)	75 (64.1)	
	50–64 y	1 (0.8)	1 (0.8)	27 (22.0)	2 (1.6)	50 (40.7)	42 (34.1)		24 (31.2)	53 (68.8)	
	≥ 65 y	0	0	0	0	2 (15.4)	11 (84.6)		0	2 (100)	
	Total	355 (19.4)	184 (10.1)	261 (14.3)	55 (3.0)	672 (36.8)	299 (16.4)		795 (54.8)	656 (45.2)	
GMFCS								<0.001			<0.001
	I	162 (39.2)	20 (4.8)	113 (27.4)	16 (3.9)	57 (13.8)	45 (10.9)		251 (70.5)	105 (29.5)	
	II	70 (18.0)	33 (8.5)	70 (18.0)	11 (2.8)	152 (39.1)	53 (13.6)		164 (51.6)	154 (48.4)	
	III	40 (14.9)	26 (9.7)	45 (16.8)	9 (3.4)	91 (34.0)	57 (21.3)		104 (52.3)	95 (47.7)	
	IV	48 (14.5)	39 (11.8)	29 (8.8)	12 (3.6)	134 (40.6)	68 (20.6)		126 (50.4)	124 (49.6)	
	V	35 (8.2)	66 (15.5)	4 (0.9)	7 (1.6)	238 (55.9)	76 (17.8)		150 (45.7)	178 (54.3)	
	Total	355 (19.4)	184 (10.1)	261 (14.3)	55 (3.0)	672 (36.8)	299 (16.4)		795 (54.8)	656 (45.2)	
CFCS								<0.001			0.015
	I	234 (29.1)	26 (3.2)	228 (28.4)	37 (4.6)	126 (15.7)	153 (19.0)		359 (57.3)	268 (42.7)	
	II	54 (24.7)	21 (9.6)	17 (7.8)	7 (3.2)	89 (40.6)	31 (14.2)		105 (57.7)	77 (42.3)	
	III	25 (11.2)	27 (12.1)	5 (2.2)	5 (2.2)	132 (58.9)	30 (13.4)		90 (50.3)	89 (49.7)	
	IV	13 (6.0)	42 (19.4)	2 (0.9)	1 (0.5)	132 (61.1)	26 (12.0)		95 (53.4)	83 (46.6)	
	V	13 (4.9)	44 (16.5)	0	2 (0.7)	158 (59.2)	50 (18.7)		98 (48.0)	106 (52.0)	
	Total	339 (19.6)	160 (9.2)	252 (14.6)	52 (3.0)	637 (36.8)	290 (16.8)		747 (54.5)	623 (45.5)	

CFCS, Communication Function Classification System; GMFCS, Gross Motor Function Classification System; y, years.

predominance of assistance for females (65%) (25). In addition, younger adults received more hours of assistance than older adults, with a peak for those aged 25–29 years. Age may be an explaining factor for the reduced assistance frequency (11), because the current population is older than in 2014. Another scenario could be that government-granted funds for assistance have decreased (27) for the population of adults with CP.

More individuals at CFCS levels I received assistance than those at GMFCS levels I. A plausible explanation is that even those with severe motor disabilities can have better communication skills than gross motor skills. Assistance increased with higher GMFCS levels, and to gain access to assistance, the individual had to fulfil certain criteria. In addition to the medical diagnoses that are required, they also needed assistance for more than 20 h/w for activities of daily living, on at least one of the following basic needs: personal hygiene, eating, dressing, and undressing, communicating with others and other help. Limited participation in activities may negatively impact the quality of life, health and family functioning (25), which reinforces the need to find means to continue providing assistance to people with disabilities such as CP.

Occupation, and Full or Part-Time Occupation

It has been stated that we need to identify factors for accessibility regarding occupation to minimise the negative effect of impairment, such as CP (12). Almost one in five adults in the age range of 20–64 years had competitive employment, which is the same as in young adults in 2014 (11). This figure is much lower than that reported for 416 Danish adults with CP, (29–35 years), where 33% had competitive employment (12). According to Mesterman et al. (21), 23% had competitive employment while two out of three received monthly disability support. A large systematic review and meta-analysis by van Gorp et al. (23) concluded that on average, 40% had remunerative employment. The difference in employment rates could be due to the difference in populations studied, sample sizes, social constructs, and regulations. Even so, the low number of Swedish adults with CP and employment is discouraging.

Reduced communication ability was the highest risk factor for not having competitive employment. Living with a partner almost doubles the likelihood of having competitive employment, whereas women were half as likely to have employment as men. Most individuals worked full time. We found no significant differences between men and women regarding full- or part-time occupation, while Dutch women with CP showed a strong decline in working hours, especially when becoming a mother (22). Looking at all types of work and sexes for those in working age (20–64-year olds), full-time occupation gradually decreased, whereas part-time work successively increased, with older age (12). Having a more severe disability increased the likelihood of individuals with CP working part-time, with GMFCS/CFCS level V as the largest group. More individuals at CFCS level I worked part-time than those at GMFCS level I. As mentioned earlier, several adults at higher GMFCS levels (lower motor function), had good communication abilities (CFCS level I).

The majority aged 20–64 years had their primary occupation at activity centres (45.2%). This is similar to the 41% reported by Jacobson et al. (6). but contrasts with the findings from a Dutch longitudinal study (22), where only one in five had their occupation at activity centres. Even though Benner et al. (22) describe the Dutch labour market as having, "high density of sheltered employment and financial resources", numbers are still lower than in our study. A postal survey in Israel by Mesterman et al. (21), revealed that only 15% had their occupation at activity centres. As both the current study and that of Jacobson et al. (6) originate from Sweden, the explanation may lie in the different social systems. Perhaps the Swedish welfare system offers sheltered work (activity centres), to a much higher extent than in other countries.

Because of the high number of young adults in the population, many individuals either went to mainstream education or attended a special school. Full-time occupation was most common for the youngest age group of 16–19 years that attended school. Lack of social competence (28), physical fatigue (29) and increased ageing (30) are different factors mentioned when discussing the lack of individuals with CP engaged in competitive employment, or employment overall. Addressing psychosocial issues and educational and vocational needs is necessary when considering social outcomes. It is important to open the debate with medical experts, legislators, and politicians to make some changes.

Limitations

There are several limitations to this study. The cross-sectional design was used to document the status of a group at a particular point in time, which means that we can show association but not any causal relationships. Another limitation is the skewed distribution of ages because four out of five individuals were younger than 40 years of age, also mentioned earlier in an initial study of a smaller cohort in 2014 (11). The GMFCS levels are also skewed because the study mostly included individuals at GMFCS levels I and V. In children, GMFCS level I usually represents up to 40% of the population (9). This could be explained by the premature decline in gross motor function seen in adults with CP (31), or a selection bias where more adults with severe motor impairments agree to participate in the continuous follow-up programme. Another limitation is that we had no access to data on individual social competence, potentially affecting cohabitation (28) or factors influencing personal assistance, such as behavioural problems, autism disorders and visual impairment.

Nevertheless, the strength of this study is the large study population, which allows for differentiation and comparisons of all levels of gross motor function and communication ability, and between sexes and age groups. Regular systematic and uniform assessments assure high accountability.

CONCLUSIONS

Only one in eight adults with CP have a partner, and one in six have competitive employment. Access to

personal assistance is the single most important factor for independent living.

The opportunity for equality is an important issue regarding living conditions and social outcomes such as independent living, having employment and finding a partner. However, for adults with CP, the possibility to be active and to participate, and the contextual factors in the individual's life, may affect all aspects of their life. Our primary goal should be to support adults with CP throughout their lifetime to allow them to achieve the best possible outcomes in all aspects of life.

DATA AVAILABILITY STATEMENT

The data analysed in this study was obtained from the Cerebral Palsy Follow-Up Program (CPUP) registry, the following licences/restrictions apply: requests to access the datasets are subject to ethical approval and must first be granted by KVB Region Skåne. Requests to access these datasets should be directed to https://vardgivare.skane.se/kompetens-utveckling/forskning-inom-region-skane/utlamnande-av-patientdata-samradkvb/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Ethical Review Board, Lund, Sweden. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

ER-B collected the data and supported the analysis and interpretation of data and actively revised the manuscript. KP performed the analysis and drafted the manuscript. Both authors designed the study and contributed to the article and approved the submitted version.

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Behavioral Symptoms May Correlate With the Load and Spatial Location of Tubers and With Radial Migration Lines in Tuberous Sclerosis Complex

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Objective: Tuberous sclerosis complex (TSC) is a multisystem neurocutaneous genetic disorder. The clinical manifestations are extensive and include neurological, dermatological, cardiac, ophthalmic, nephrological, and neuropsychiatric manifestations. The prediction and pathophysiology of neuropsychiatric disorders such as emotional symptoms, conduct problems, hyperactivity, and poor social behavior are poorly understood. The aim of the study was to diagnose neuropsychiatric symptoms in individuals with TSC, and to examine their possible correlations with quantity, magnitude, and spatial location of tubers and radial migration (RM) lines.

Methods: The cohort comprised 16 individuals with TSC, aged 5–29 years, with normal or low normal intelligence. The participants or their parents were requested to fill Strengths and Difficulties Questionnaire (SDQ) and the TAND (TSC-associated neuropsychiatric disorders) Checklist for assessment of their neuropsychiatric symptoms. Correlations were examined between these symptoms and the magnitude, quantities, and locations of tubers and white matter RM lines, as identified in T2/FLAIR brain MRI scans.

Results: The SDQ score for peer relationship problems showed correlation with the tuber load ($r = 0.52$, $p < 0.05$). Tuber load and learning difficulties correlated significantly in the temporal and parietal area. Mood swings correlated with tubers in the parietal area ($r = 0.529$, $p < 0.05$). RM lines in the temporal area correlated with abnormal total SDQ ($r = 0.51$, $p < 0.05$). Anxiety and extreme shyness were correlated with RM lines in the parietal area, $r = 0.513$, $p < 0.05$ and $r = 0.593$, $p < 0.05$, respectively. Hyperactive/inattention correlated negatively with RM lines in the parietal area ($r = -707$, $p < 0.01$).

Conclusions: These observations may lead to future studies for precise localization of neuropsychiatric symptoms, thereby facilitating directed therapy.

Keywords: tuberous sclerosis complex, behavioral symptoms, cortical tubers, radial migration lines, Strengths and Difficulties Questionnaire (SDQ)

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INTRODUCTION

Tuberous sclerosis complex (TSC) is a multisystem neurocutaneous genetic disorder caused by mutations in the tumor suppressor genes *TSC1* and *TSC2*, located on chromosomes 9 and 16, respectively. The protein products of *TSC1* and *TSC2* (hamartin and tuberin) function together within the cell and have an inhibitory effect on the mammalian target of rapamycin (mTOR), a protein kinase that influences cell growth and division, and on the synthesis of proteins and other cell components (1). About two-thirds of the occurrences of TSC are sporadic. The clinical manifestations are extensive, including neurological, dermatological, cardiac, ophthalmic, nephrological, and neuropsychiatric (2). These manifestations vary between patients and between genetic mutations, and the expression is age-dependent. About 85% of individuals with TSC exhibit neuropsychiatric manifestations, which include behavioral, psychiatric, intellectual, academic, neuropsychological, and psychosocial impairments (3). Genetic predisposition with *TSC2* mutations (4) and early-onset seizures such as infantile spasm are associated with increased risks of neurodevelopmental and cognitive problems, including autism spectrum disorder (ASD) (5). Structural brain abnormalities such as a higher number of dysplastic lesions on MRI were also shown to predict adverse mental and clinical outcomes (6). The predictors and the etiology of TSC, of behavioral difficulties such as anxiety, depressed mood, learning difficulties, attention deficit hyperactivity disorder (ADHD), and psychosis, have been less investigated. Our aim was to diagnose the neuropsychiatric symptoms in individuals with TSC and to examine their possible correlations with the quantity, magnitude, and spatial location of tubers and radial migration (RM) lines.

METHODS

The Participants and Brain MRI Evaluation

All patients with TSC who attended our institute between May 2019 and March 2020 with normal or low normal intelligence and brain MRI performed <1 year before evaluation were included. The clinical diagnosis of TSC was made by a senior pediatric neurologist based on the 2012 International Tuberous Sclerosis Complex Consensus Group (7). Individuals with TSC who had motor or moderate–severe intellectual disabilities or intractable epilepsy were excluded. The local ethics committee approved the study. Signed informed consent was obtained from the parents or guardians of each participant before enrollment. The most recent T2-weighted fluid-attenuated inversion recovery (T2-FLAIR) brain MRI scans (<1 year before) of the participants were evaluated by a senior pediatric neuroradiologist. Tubers and white matter RM lines were identified, measured, and classified by their characteristics, location, and size.

Evaluation of Neuropsychiatric Symptoms

The neuropsychiatric profile was evaluated using the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), in addition to the TAND (TSC-associated neuropsychiatric disorders) Checklist that was translated to Hebrew. This checklist is generally used during meetings with a neurologist in order to assess patients' problems and to help guide a conversation between the clinician and the family or the person with TSC. It consists mainly of a series of YES/NO items in six domains: behavioral, psychiatric, intellectual, academic, neuropsychological, and psychosocial.

The Strengths and Difficulties Questionnaire (SDQ) was used to evaluate children's behavioral and attentional problems. It is an internationally accepted behavioral screening questionnaire for 3- to 16-year-olds (8). Brann et al. (9) support its use also for adolescents (aged 12–17 years) and young adults (aged 18–25 years). We used the American norms. The SDQ consists of 25 items, each rated on a three-point Likert scale (0 = not true, 1 = somewhat true, 2 = true). The items are scored according to five subscales: emotional symptoms (scored from 0 to 5), behavioral problems (from 0 to 3), hyperactivity/inattention (from 0 to 5), peer problems (from 0 to 3), and prosocial behavior (from 6 to 10). The scores for the first four scales are summed to a total difficulty score ranging from 0 to 40, which indicates the likelihood of a psychiatric disorder. In the current study, patients, and/or their parents filled out the questionnaires. If there were differences between their answers, the abnormal results were considered. The results were compared with values in the general population, as reported in the official SDQ site (American norms, https://www.sdqinfo.org).

Statistical Analysis

All statistical analyses were conducted using IBM-SPSS v.27 (IBM-SPSS, Armonk, NY, USA). Associations were calculated for the scores of the SDQ elements with the numbers and areas of tubers and with RM lines using Spearman's correlation. A $p \leq 0.05$ was considered significant.

RESULTS

Clinical Characteristics

The study group consisted of 16 patients with TSC, aged 5–29 years (mean age = 13 years). Nine (56%) were males. Eleven patients (68%) had epilepsy, and seizures were controlled in 90% of them with oxcarbazepine, carbamazepine, lacosamide, levetiracetam, and valproic acid. Five patients (31%) had a history of infantile spasm, which was treated with vigabatrin. All

TABLE 1 | Demographic and clinical characteristics of 16 individuals with tuberous sclerosis complex.

Characteristic	Number or number (%)
Male	9 (56%)
Mean age at the brain MRI evaluation, years	13
SEGA	1 (6%)
SEN	16 (100%)
Epilepsy	11 (68%)
Infantile seizures	5 (31%)
Seizure control (of those with seizures)	10 (90%)

TABLE 2 | Characteristics of the tubers and radial migration (RM) lines in individuals with tuberous sclerosis complex.

	Mean	Minimum	Maximum
No. tubers per patient	17.2	2	39
Cystic tubers only	2.3	0	22
Tuber area (cm^3): Right	8.5	1	25
Tuber area (cm^3): Left	9.9	1	24
Tuber area (cm^3): Frontal	6.1	0	15
Tuber area (cm^3): Parietal	4.2	0	9
Tuber area (cm^3): Temporal	2.9	0	8
Tuber area (cm^3): Occipital	4.0	0	10
Tuber area (cm^3): Cerebellum	0.3	0	2
Tuber load (cm^3)	18.0	1.5	53
No. RM lines per patients	7.2	1	15
Area of RM lines (cm^3): Right	3.3	0	8
Area of RM lines (cm^3): Left	3.8	0	11
Area of RM lines (cm^3): Frontal	2.8	0	9
Area of RM lines (cm^3): Parietal	2.4	0	5
Area of RM lines (cm^3): Temporal	0.9	0	5
Area of RM lines (cm^3): Occipital	1.0	0	3
Area of RM lines (cm^3): Cerebellum	0.1	0	1
RM lines <0.5 cm^3	2.1	0	13
RM lines >0.5 cm^3	5.1	0	14

patients had subependymal nodules (SEN) and one patient had subependymal giant cell astrocytoma (SEGA) (**Table 1**).

Quantity, Magnitude, and Spatial Location of Tubers

In total, the patients had 273 tubers. The mean number of tubers per patient was 17.2, the minimum number was 2, and the maximum was 39. The range of cyst-like cortical structures detected per patient was 0–22. Fourteen (5.1%) tubers were calcified; none of these were in patients younger than 8 years. The overall quantity, magnitude, and spatial location of the tubers are summarized in **Table 2**. The mean overall area of the tuber load was 18.0 cm^3. More tubers were found on the left than on the right hemisphere (mean area = 9.9 vs. 8.5 cm^3). The area of tubers on the frontal area was the highest (mean area = 6.1 cm^3), followed by the parietal (4.2 cm^3), occipital (4.0 cm^3), temporal (2.9 cm^3), and the cerebellum areas (0.3 cm^3). The mean number of RM lines per patient was 7.2 and the range was 1–15. A mean number of 2.1 RM lines was smaller than 0.5 cm^3, and a mean number of 5.2 was larger than 0.5 cm^3. The mean areas of RM lines were almost equal on the right and left hemispheres: 3.31 and 3.8 cm^3, respectively. The mean areas of the RM lines were the largest on the frontal (2.81 cm^3) and parietal areas (2.4 cm^3), followed by the occipital (1.0 cm^3), temporal (0.94 cm^3), and the cerebellum areas (0.1 cm^3).

The TAND Checklist and Correlations With Tubers and RM Lines

Psychiatric diagnoses were made according to the DSM-V criteria and were collected by the TAND Checklist. Fourteen (87%) had psychiatric disorders. ADHD, diagnosed in nine (57%) patients, was the most common diagnosis, followed by learning disabilities in eight (50%). Anxiety disorder was diagnosed in three patients, schizophrenia in two, major depressive disorder in two, obsessive compulsive disorder in one, and ASD in one patient. Behaviors of concern were reported in all but one patient (93%). For 10 (63%), the concern was regarding emotional behavior such as anxiety and depressive mood. Nine reported hyperactive behavior, 7 reported aggressive behavior, 7 peer problems, 4 eating problems, and 19 had sleeping problems. The correlations of the tubers and radial migration lines with the TAND Checklist are presented in **Table 3**.

Learning difficulties were correlated with the number of tubers per patient ($r = 0.611$, $p < 0.05$) and the tuber load ($r = 0.569$, $p < 0.05$). Tubers in the right and left hemispheres were correlated with learning difficulties ($r = 0.54$, $p < 0.05$, and $r = 0.57$, $p < 0.01$, respectively); the correlation coefficient relating to the left hemisphere was highly significant. Learning problems were also correlated with tuber area in the parietal ($r = 0.54$, $p < 0.01$) and temporal areas ($r = 0.55$, $p < 0.05$). The presence of RM lines in the right hemisphere was correlated with learning difficulties ($r = 0.12$, $p < 0.05$).

ADHD was negatively correlated with RM lines in the left hemisphere ($r = -0.50$, $p < 0.05$) and in the frontal area ($r = -0.53$, $p < 0.05$) and with RM line area >0.5 cm^3 ($r = -0.52$, $p < 0.05$).

Sleep problems were correlated with tuber area in the cerebellum ($r = 0.61$, $p < 0.05$) and with the area of the RM lines in the right hemisphere ($r = 0.54$, $p < 0.05$) and in the cerebellum ($r = 0.537$, $p < 0.01$). RM lines with an area >0.5 cm^3 were correlated with sleep problems ($r = 0.50$, $p < 0.05$).

Mood swings correlated with tubers in the parietal area ($r = 0.529$, $p < 0.05$). Anxiety and extreme shyness were correlated with RM lines in the parietal area ($r = 0.513$, $p < 0.05$, and $r = 0.593$, $p < 0.05$, respectively).

SDQ and Correlation With Tubers and RM Lines

Half of the participants (8/16) scored in the abnormal range of the SDQ for total difficulty. The data elicited from the respondents were tested for normality using the Kolmogorov–Smirnov statistic. The mean (SD) score for total SDQ was significantly higher than that in a normative population [14.44 ($SD = 7.14$), $p < 0.001$]. The mean score for peer problems was also significantly higher, with a mean of 3.5 ($SD = 2.06$, $p < 0.001$). The mean scores for emotional symptoms, conduct problems, hyperactivity, and prosocial behavior were outside the norm, but without statistical significance (**Table 4**). One of the two patients with SEGA had abnormal SDQ scores in the

TABLE 3 | Correlations of tubers and radial migration lines with scores on the TAND Checklist.

		Tuber load Tot	No. tubers Per patient	Tuber area RT (cm^3)	Tuber area LT (cm^3)	Tuber area Parietal (cm^3)	Tuber area Temporal (cm^3)	Tuber area Cerebellum (cm^3)	Area of RML LT (cm^3)	Area of RML Frontal (cm^3)	Area of RML Parietal (cm^3)	Area of RML Cerebellum (cm^3)	RML >0.5cm^3
Anxiety	Correlation coefficient	0.054	0.027	0.123	0.095	0.428	0.041	0.478	0.164	−0.014	0.513*	0.258	−0.095
	Sig. (2-tailed)	0.842	0.92	0.651	0.726	0.098	0.879	0.061	0.543	0.959	0.042	0.334	0.725
	N	16	16	16	16	16	16	16	16	16	16	16	16
Extremely	Correlation coefficient	−0.188	−0.235	−0.173	0.255	0.255	−0.08	0.069	0.221	−0.112	0.593*	−0.149	−0.142
Shy	Sig. (2-tailed)	0.486	0.348	0.521	0.34	0.34	0.789	0.8	0.41	0.678	0.015	0.562	0.601
	N	16	16	16	16	16	16	16	16	16	16	16	16
Mood	Correlation coefficient	0.068	0.027	0.096	0.529*	0.529*	0.195	0.06	−0.207	−0.407	0.308	0.228	−0.371
Swing	Sig. (2-tailed)	0.801	0.92	0.723	0.035	0.035	0.489	0.825	0.442	0.118	0.245	0.396	0.157
	N	16	16	16	16	16	16	16	16	16	16	16	16
ADHD	Correlation coefficient	−0.25	−0.298	−0.252	0.175	0.175	−0.16	−0.138	0.506*	0.530*	0	0.149	0.520*
	Sig. (2-tailed)	0.349	0.262	0.347	0.516	0.516	0.555	0.081	0.046	0.035	1	0.582	0.039
	N	16	16	16	16	16	16	16	16	16	16	16	16
Sleep	Correlation coefficient	0.365	0.33	0.279	0.283	0.283	0.46	0.612*	0.175	0.285	0.267	0.537*	0.507*
Problem	Sig. (2-tailed)	0.165	0.211	0.295	0.283	0.283	0.073	0.012	0.516	0.284	0.318	0.032	0.045
	N	16	16	16	16	16	16	16	16	16	16	16	16
Learning	Correlation coefficient	0.589*	0.611*	0.545*	0.566**	0.566**	0.566*	0.179	0.11	0.32	0.333	0.258	0.068
Difficulties	Sig. (2-tailed)	0.021	0.012	0.029	0.022	0.022	0.021	0.506	0.686	0.227	0.207	0.334	0.045
	N	16	16	16	16	16	16	16	16	16	16	16	16

*$p < 0.05$ and **$p < 0.01$. ADHD, attention deficit hyperactivity disorder.*

TABLE 4 | Scores of individuals with tuberous sclerosis complex on the Strength and Difficulties Questionnaire (SDQ).

	Emotional problems	Behavioral problems	Peer relationship problems	ADHD	Prosocial behavior	Total SDQ
Mean	3.56	2.88	3.50	4.75	6.63	14.44
SD	2.68	2.58	2.06	2.38	2.60	7.14
P-value	0.043	0.07	<0.001	0.02	0.006	<0.001

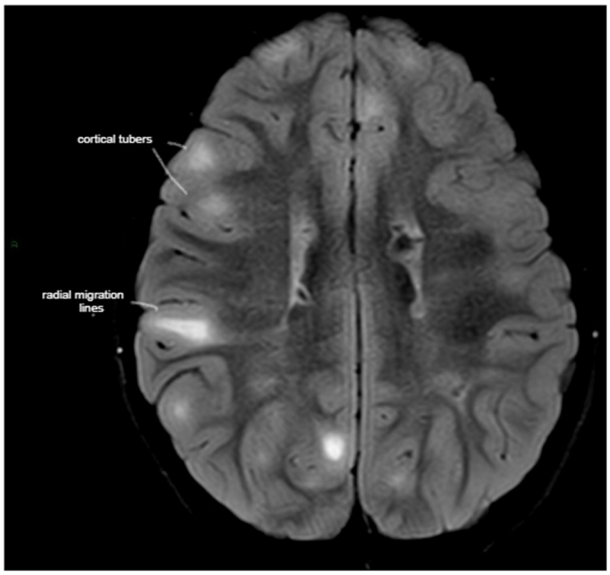

FIGURE 1 | Axial T2-weighted fluid-attenuated inversion recovery (T2-FLAIR) MRI demonstrating high tuber load and radial migration (RM) white lines in a 7-year-old boy with tuber sclerosis complex, normal intelligence, peer relationship problems, and hyperactive/inattention, which correlated negatively with RM lines in the parietal area.

hyperactive/inattention domain and in prosocial behavior. Both patients with SEGA had abnormal SDQ scores regarding peer problems and also total SDQ scores. Of the 11 patients with epilepsy, two had abnormal emotional SDQ, three had abnormal conduct SDQ scores, five had abnormal hyperactive/inattention SDQ scores, six had abnormal SDQ scores regarding peer problems (**Figure 1**), and seven had abnormal prosocial behavior scores. Five patients with epilepsy had abnormal total SDQ scores. Two of four patients with a history of infantile spasm had abnormal scores on the emotional, hyperactive/inattention, and conduct domains of SDQ. Three of the four patients had abnormal prosocial behavior scores, and all four had abnormal peer problem behavior. All four of the patients with a history of infantile spasm had abnormal total SDQ scores. **Table 5** presents the correlations between the SDQ scores and the tubers and RM lines. The SDQ score for peer relationship problems correlated with the tuber load ($r = 0.52$, $p < 0.05$). The SDQ score of hyperactive/inattention correlated negatively with RM lines in the parietal area ($r = -707$, $p < 0.01$). RM lines in the temporal area correlated with abnormal total SDQ ($r = 0.51$, $p < 0.05$).

DISCUSSION

Neuropsychiatric features of TSC present in up to 90% of individuals with TSC (10) and cause great burden to patients and their families (11). Due to the presumed associations of the development of intellectual disability with early and severe epilepsy, efforts have been invested to detecting abnormal background activity in individuals with TSC by routine EEG. The goal is to promote the early initiation of antiepileptic drugs, even before seizures appear (12). In contrast, the prediction, the pathophysiology, and the treatment of neuropsychiatric disorders, such as emotional symptoms, conduct problems, hyperactivity, and poor social behavior, are poorly understood. In this study, we examined the associations of these parameters with cortical tubers and white matter abnormalities. We assessed behavioral problems using the SDQ, a validated questionnaire, and the TAND Checklist, which was designed for the routine examination of individuals with TSC. Total SDQ was significantly higher in our patients with TSC than that in a normative population.

Cortical tubers are focal malformations that consist of various cellular abnormalities, including astrogliosis, dysmorphic neurons, and immature glial cells (13). These tubers are very common in TSC and present in at least 80% of affected patients (14). The wide age range suggests that the associations found are not related to age. The association of tuber load with intellectual disabilities is well-established (6, 14). However, whether this association is due to the severe epilepsy caused by a high tuber load or due to the tuber load itself remains unclear. According to Gipson et al., patients with self-injurious behavior-associated TSC have higher frequencies of tubers in quadrants other than the left posterior neuroanatomical region (15). We found that tuber load and its localization correlate with certain neuropsychiatric symptoms. The SDQ domain for peer relation problems was correlated with cortical tuber load in this study; in some studies, the latter correlated with ASD (16, 17), but others failed to find a correlation (18). Since, in our study, epilepsy was controlled and cognition was normal, the results support the possibility that the tubers interrupt the brain structure and affect peer relation problems directly. Learning difficulties were associated with tuber load in the left hemisphere, mainly in the parietal but also in the temporal area—areas involved in language processing. This is consistent with previous studies (6, 19, 20) that showed associations of significantly high densities of tubers in the inferior parietal lobe and middle temporal lobe with lower IQ scores and learning difficulties. In our study, the somatosensory cortex function

TABLE 5 | Correlations of tubers and radial migration (RM) lines with scores on the Strength and Difficulties Questionnaire (SDQ) in individuals with tuberous sclerosis complex.

SDQ domain		Tuber load	Area of RM lines (cm^3): Parietal	Area of RM lines (cm^3): Temporal
Emotional	Correlation coefficient	0.218	−0.149	0.222
Problems	Sig. (2-tailed)	0.417	0.581	0.409
	N	16	16	16
Behavioral	Correlation coefficient	0.119	−0.489	0.135
Problems	Sig. (2-tailed)	0.662	0.055	0.619
	N	16	16	16
Peer relationship	Correlation coefficient	0.520*	−0.048	0.337
Problems	Sig. (2-tailed)	0.039	0.86	0.202
	N	16	16	16
Hyperactive/	Correlation coefficient	0.199	−0.707**	0.222
Inattention	Sig. (2-tailed)	0.46	0.002	0.409
	N	16	16	16
Prosocial	Correlation coefficient	−0.42	0.129	0.122
Behavior	Sig. (2-tailed)	0.105	0.634	0.653
	N	16	16	16
Total	Correlation coefficient	−0.005	−0.052	0.511*
	Sig. (2-tailed)	0.985	0.85	0.043
	N	16	16	16

*$p < 0.05$ and **$p < 0.01$.

correlated with emotional regulation (21), whereas tubers in this location correlated with shyness and mood disorder. Sleep problems correlated with tubers in the cerebellum and also in the right hemisphere. The cerebellum is involved in sleep stage-dependent activity, and its malfunctions can lead to changes in the sleep–wake cycle, resulting in sleep disorders (22). The right hemisphere mediates vigilance and might also affect sleep.

White matter abnormalities have emerged as another important mechanism for brain dysfunction in TSC. Such abnormalities are associated with an overall decrease in measures of functional connectivity, such as a reduced interhemispheric synchrony, between the different regions of the brain (23, 24). The latter appears critical for a variety of brain symptoms of TSC, including intellectual disability, autism, epilepsy, and other psychiatric and behavioral disorders (25). RM lines refer to linear bands seen on MRI radiating from the periventricular white matter to the subcortical region. In our study, RM lines presented more in the frontal area, and their location in the temporal area was correlated with total abnormal SDQ. This supports the possibility that abnormal behavioral symptoms may be related to abnormalities in white matter (25). Specifically, anxiety correlated with RM lines in the parietal area, an area where anxiety increased after stimulation (26). ADHD negatively correlated with RM lines in the left hemisphere and in the frontal area and with RM lines larger than 0.5 cm^3. Associations have been reported between ADHD and weaker function and structure of prefrontal cortex circuits, especially in the right hemisphere. The prefrontal association cortex plays a crucial role in regulating attention, behavior, and emotion; the right hemisphere is especially associated with behavioral inhibition (27). Both RM lines located in the cerebellum and RM lines larger than 0.5 cm^3 were found to correlate with sleeping disorders (21). By interfering with the development of neural circuitry, RM lines could impair neurotransmission, thus resulting in deficits in intelligence, communications, and social skills, in seizures (28), and probably also in difficulties in learning, attention, and sleep. The limitation of our study was the relatively small population. Although the genetics analysis was available for only 60% of the patients, since individuals with moderate to severe intellectual disability were excluded, such data were less important. This is the first report of a correlation between behavioral symptoms and RM lines and tuber load in various brain areas. These observations may lead to future studies for precise localization of neuropsychiatric symptoms, thereby facilitating directed therapy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Helsinki Committee, Rabin Medical Center. Written

informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

RC and JG examined the patients and participated in revising the article. LK revised the brain MRI's and participated in revising the article. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.673583/full#supplementary-material

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Physical Activity Levels of Adolescents and Adults With Cerebral Palsy in Urban South Africa

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Background: Research in high income countries shows that people with cerebral palsy (CP) are less physically active than typically developing (TD) peers, but less is known regarding physical activity (PA) in those with CP in low-to-middle income countries. The aim of this study was to determine daily step count and levels of PA in adolescents and adults with CP living in urban South Africa, compared to TD peers, and to determine associations with sex, Gross Motor Function Classification System (GMFCS) level, body mass index and socio-economic status.

Materials and Methods: This case–control study included 26 adolescents and 22 adults with CP (GMFCS Level I-V) and matched TD peers (25 and 30, respectively). Participants wore an ActiGraph GT3X for 7 consecutive days to determine step count and time (minutes per hour) spent in PA levels, including sedentary (SED), low physical activity (LPA) and moderate to vigorous physical activity (MVPA).

Results: The daily step count and PA levels for ambulant adolescents with CP (GMFCS level I-III) were similar to TD peers, while this was less for adolescents classified in GMFCS level IV-V. Daily step count, SED and MVPA were similar for adults classified in GMFCS level I-II compared to TD adults, while all parameters were lower for adults using assistive devices (GMFCS level III) and non-ambulant adults (GMFCS level IV-V) compared to TD peers. Daily step count and PA levels were inversely associated with GMFCS, while no other associations were found.

Conclusion: People with CP who were more mobile dependent (higher GMFCS level) were less active. However, adolescents and adults with CP classified as GMFCS levels I-II living in urban South Africa recorded similar step count and PA levels as their TD peers. This was also the case for adolescents using assistive devices, though not for those in the adult group (GMFCS level III). Furthermore, it was apparent that even the ambulant individuals with CP and TD cohorts were relatively inactive. Intervention programs for CP and TD adolescents should be aimed at finding strategies to keep adolescents physically active well into adulthood, in order to promote physical health, social and emotional well-being and independence.

Keywords: cerebral palsy, lifespan, accelerometry, GMFCS, low-to-middle income country

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INTRODUCTION

Cerebral palsy (CP) is the one of the most common motor disabilities in children (1), with a reported prevalence of 2–3 cases per 1,000 live births. However, these figures are largely drawn from studies in high income countries (HIC). The prevalence is estimated to be as high as 10 cases per 1,000 in low-to-middle income countries (LMIC) (2). According to the World Health Organization (3), the number of adolescents is expected to increase through to 2050, especially in LMIC where close to 90% of the 10–19 year old population live. This, together with improved survival of children with CP into adulthood (1), highlights the importance of preparing the healthcare system to address important challenges faced by people with CP.

It is widely understood that CP is a permanent disorder of posture and movement, attributed to a non-progressive disturbance that occurred in the developing fetal or infant brain (4). Motor disturbances in CP such as impaired motor planning, coordination, motor learning and fine motor skills may lead to the limitation of activities and activity levels starting before adulthood (5). Evidence suggests that developing healthy patterns of physical activity (PA) as an adolescent with CP greatly increases the probability of maintaining healthy PA levels as an adult (6). Exercise, however, is often poorly utilized in populations with CP (7), despite the positive effects it has on physical function (8).

Compared to the typically developing (TD) general population, individuals with CP are frequently reported to have reduced physical fitness levels (7) and to be less physically active (9, 10). Reasons for this inactivity could be due to different factors like physical impairments, but probably the lack of knowledge and life skills, limited availability of transport and professional guidance as well as social support plays a role (11). McKenzie et al. (12) concluded in a systematic review that (young) adults struggle to find the right balance to be physically active because of their social and physical environment. However, since these studies are mainly focused on HIC, little is known about the influence of cultural and socio-economic factors on the level of an individual's PA in resource-limited settings such as South Africa.

A recent systematic review by Malek and colleagues (13) regarding research on CP in LMICs, reported that research studies focused on the impairments of individuals with CP, rather than their functioning. In other words, the literature mainly comprises research addressing issues of body structure and function as conceptualized in the International Classification of Functioning, Disability and Health (ICF) (14) framework, while there is a lack of published work with a focus on the level of activities, participation and contextual factors. These authors also acknowledged that the research in Africa is mainly focused on children with CP, with few studies focusing on adolescents and adults with CP (13).

Very little has been reported on PA levels in adolescents and adults with CP or TD peer groups living in LMIC settings. Based on the knowledge gained from studies conducted in HIC and recognizing that there might be additional barriers in LMIC, it is hypothesized that adolescents and adults with CP will be less active than their TD peers. Understanding the complete picture, particularly regarding levels of PA in individuals with CP, may support strategies to address the possible challenges faced during transition as well as to promote healthy aging for individuals with CP living in LMIC. Therefore, the aim of this study was to determine the levels of PA in adolescents and adults with CP living in urban South Africa, compared to TD peers, and to determine whether there are associations between PA levels and contextual factors sex, Gross Motor Function Classification System (GMFCS) level, Body Mass Index (BMI) and socio-economic status (SES).

METHODS

Study Design and Participants

This case-control study is a sub-study of a bigger research project (15) focusing on the challenges, needs and well-being of adolescents and adults with CP (GMFCS Levels I-V) and TD peers (matched for sex, age and SES) living in urban South Africa. The cohorts were based on a convenience sample, where the adolescents with CP were recruited from three different schools for Learners with Special Education Needs (LSEN) in Cape Town South Africa, where they were in one of the last 3 years of school (grades 10–12). The TD adolescents were recruited from a mainstream school in Cape Town, and matched for age, sex and SES. Adults with CP were recruited from databases of previous studies (16, 17), referrals, word of mouth suggestions and social media. They were included if they had a medical diagnosis of CP, had attended a special school at least 5 years prior to the study, and were aged between 23 and 40 years. Adults in the TD cohort were similarly matched for age, sex, and SES to the adults with CP. Adolescent and adult participants were excluded if they had any neuromuscular or physical disorders unrelated to CP, and if they were unable to effectively understand and communicate in English or Afrikaans.

Each adolescent and adult who showed interest in participating in the study and met the selection criteria was contacted to make an appointment. During this meeting the procedure for the study was explained, the written informed consent form was signed by the participants (and when appropriate their caregivers), instructions were given on how to use the Actigraph and a date was set to collect the device after testing.

This study was approved by the Human Research Ethics Committee at the University of Cape Town, South Africa. Permission was also granted by the Western Cape Education Department and as well as by the principals of the three LSEN schools. The study was conducted in line with the principles set out in the Declaration of Helsinki (18).

Background Information

Participant's characteristics including age, sex, CP subtype, and SES were obtained. The latter was estimated based on housing density, which was calculated by dividing the number of people living in the house by number of rooms within the house (excluding kitchen and bathroom). The housing density was then categorized as low SES (housing density score >1.5), average SES

(score 1–1.5) and high SES (score < 1) (19). In addition, height and weight were measured to determine BMI, which was then categorized into underweight (BMI < 18.5), healthy (BMI 18.5–24.9), overweight (BMI 25–29.9) and obese (BMI > 30) (20). Adolescents and adults with CP were also classified for gross motor function with the GMFCS (21), manual ability according to the Manual Ability Classification System level (MACS) (22), as well as the participant's ability to communicate using the Communication Function Classification System (CFCS) (23).

Accelerometry

The tri-axial ActiGraph GT3X accelerometer (ActiGraph, Shalimar, FL, USA; mass: 19 g, dimensions: 4.6 x 3.3 x 1.5 cm) was used for this study, which is a waist-worn accelerometer used to objectively measure the daily step count and levels of PA. In this manner, PA was divided into time spent sedentary (SED), in low physical activity (LPA), moderate physical activity (MPA) and vigorous physical activity (VPA). Different cut-points [counts per minute (cpm)] have been validated (24) but for the current study cut-points defined by Freedson (25) (developed for adults) and Evenson (26) (developed for children) were chosen. Therefore, the following cut-points were utilized: SED: Freedson 0 to 99 cpm, Evenson 0 to 100 cpm; LPA: Freedson 100 to 1,951 cpm, Evenson 101 to 2,295 cpm; MPA: Freedson 1,952 to 5,724 cpm, Evenson 2,296 to 4,011 cpm; and VPA: Freedson > 5,725 cpm, Evenson > 4,012 cpm. The ActiGraph has been used in individuals with CP as well as the TD population (27–31), and research showed evidence to support its reliability (32) and validity in children (30, 31, 33) adolescents (30, 32) and adults with CP (27, 28).

Data Collection and Analyses

The ActiGraph was placed on the participant's non-dominant hip (27, 28, 34) and secured around the waist. The accelerometer was set and initialized to record magnitudes of movement triaxially in epochs of 5 s with a sampling frequency of 30 Hz (default setting). Participants were asked to wear the ActiGraph consecutively for 7 days, and only to removed it prior to bathing/showering or swimming.

The ActiLife software (Pensacola, FL, USA) was used to process the recordings and transform epoch lengths to 60 s (35). Sleep time was set at non-wear time. Valid wear time per day was determined by using similar protocols as also applied in other studies with adolescents (31) as well as adults (27, 36). First a valid day was set at a minimum of 5 h per day (300 min), excluding sleep time. Participant's data were considered for further analysis when a minimum of 3 valid weekdays were recorded and a minimum of 1 valid weekend day. The valid days of wear time did not have to be consecutive.

For each participant, an average of daily step count and SED, LPA and MVPA (MPA plus VPA) were determined. Thereafter step count and PA data was reported for weekdays and weekend days together ("whole week") as well as separately ("weekdays" and "weekend days").

Statistical Analysis

Shapiro-Wilk tests were conducted to determine the normality of the data. This resulted in the use of non-parametric statistical analyses for the description of the personal and environmental factors, as well as daily step count and PA data (time spent in SED, LPA and MVPA) for the adolescents and adults with CP and matched TD cohorts. Based on GMFCS, adolescents and adults with CP were subdivided into 3 groups including: CP I-II: independently ambulant and classified as GMFCS levels I and II; CP III: required assistive devices for ambulation and classified as GMFCS level III; and CP IV-V: non-ambulant and classified in GMFCS levels IV and V.

Kruskal-Wallis tests were used to determine differences in daily step count and PA data between the CP and TD groups. If Kruskal-Wallis showed a significant group effect, post-*hoc* testing was performed to analyse the differences between the 4 groups (i.e., CP I-II, CP III, CP IV-V, and TD). Spearman rho correlations were calculated to determine any associations between PA data with sex, GMFCS, BMI and SES. A Bonferroni correction was applied to correct for multiple analyses. This means for determining differences in physical activity levels the significance was set at $p < 0.0167$ (0.05/3) (SED, LPA and MVPA), for daily step count at $p < 0.05$ (Step count), and for the associations at $p < 0.0167$ (0.05/4) (Step count/SED/LPA/MVPA). Statistical analyses were conducted using SPSS (version 25; IBM SPSS Inc, Chigago, IL, USA).

RESULTS

Participant Characteristics

Thirty-one adolescents with CP and 31 TD peers, together with 30 adults with CP and 30 TD peers were included in the research project. However, due to invalid wear time of the ActiGraph, 5 adolescents with CP, 6 TD adolescents and 8 adults with CP were excluded for further data analyses. The personal characteristics of the remaining participants were similar to the original cohorts as described in Salie et al. (15). In the current study 26 adolescents with CP (84% inclusion rate), 25 TD adolescents (81%), 22 adults with CP (73%) and 30 TD adults (100%) participated. In the adolescents with CP cohort, 8 (31%) were diagnosed with unilateral spastic CP, 14 (54%) with bilateral spastic CP, and 4 (15%) with dyskinesia. The adults with CP consisted of 2 (9%) who were diagnosed with unilateral spastic CP, 17 (77%) with bilateral spastic CP and 3 (14%) with dyskinesia. **Table 1** provides an overview of the characteristics of all participants included in this study. Due to the purposeful matching of the CP and TD cohorts for age, sex and SES, there were no statistical differences between the two cohorts. Step count data from two adolescents with CP who were classified as GMFCS level V were identified as outliers and excluded from analysis, while PA data for these adolescents were retained.

Wear Time

Of the 26 *adolescents* with CP, 19 (73%) recorded valid PA data for 7 days and 7 (27%) for 6 days, while of the 25 TD adolescents, 22 (88%) recorded PA data for 7 days, 1 (4%) for 6 days and 2 (8%) for 5 days. Calculated over the valid days, on average the

TABLE 1 | Overview of participant's characteristics expressed in median [interquartile ranges] or *n* (%).

	Adolescents		Adults	
Parameters	**CP (*n* = 26)**	**TD (*n* = 25)**	**CP (*n* = 22)**	**TD (*n* = 30)**
Age (years)	17.8 [16.8–18.5]	17.3 [16.9–18.0]	34.9 [30.9–36.3]	34.0 [29.3–35.6]
Sex				
Male	13 (50)	11 (44)	7 (32)	10 (33)
Female	13 (50)	14 (56)	15 (68)	20 (67)
GMFCS				
Level I	4 (15)	n/a	6 (27)	n/a
Level II	7 (27)		4 (18)	
Level III	6 (23)		5 (23)	
Level IV	4 (15)		4 (18)	
Level V	5 (19)		3 (14)	
MACS				
Level I	18 (69)	n/a	16 (73)	n/a
Level II	3 (12)		4 (18)	
Level III	2 (8)		1 (5)	
Level IV	2 (8)		1 (5)	
Level V	1 (4)		0 (0)	
CFCS				
Level I	19 (73)	n/a	18 (82)	n/a
Level II	6 (23)		3 (14)	
Level III	0 (0)		0 (0)	
Level IV	1 (4)		1 (5)	
Level V	0 (0)		0 (0)	
BMI	19.8 [18.1–25.5]	21.2 [19.0–25.0]	26.6 [23.1–36.8]	28.1 [22.9–32.9]
Underweight	8 (31)	4 (16)	1 (5)	1 (3)
Healthy	11 (42)	14 (56)	9 (41)	9 (30)
Overweight	4 (15)	6 (24)	4 (18)	11 (37)
Obese	3 (12)	1 (4)	8 (36)	9 (30)
SES	1.3 [1.0–1.8]	1.3 [0.9–1.6]	1.4 [1.0–1.7]	1.3 [1.0–1.7]
Low	3 (12)	6 (24)	4 (18)	3 (10)
Average	16 (62)	13 (52)	12 (55)	18 (60)
High	7 (27)	6 (24)	6 (27)	9 (30)

CP, Cerebral Palsy; TD, Typically Developing; IQR, interquartile ranges; n/a, not applicable; GMFCS, Gross Motor Function Classification System; MACS, Manual Ability Classification System; CFCS, Communication Function Classification System; BMI, Body Mass Index; and SES, Socio Economic Status.

recorded wear time (duration that the ActiGraph was worn for the day) had a median [IQR] of 14 h 30 m [13 h 51 m−15 h 18 m] for the adolescents with CP and 15 h 30 m [14 h 12 m−16 h 9 m] for the TD adolescents.

With regards to the *adults*, of the 22 adults with CP, 14 (64%) recorded PA data for 7 days, 6 (27%) for 6 days, and the remaining 2 (9%) recorded data for 5 and 4 days each. Of the 30 TD adults, 26 (86%) recorded PA data for 7 days, 2 (7%) for 6 days and 2 (7%) for 5 days. The actual valid median [IQR] time the adults wore the ActiGraphs per day (calculated as an average over all days) had a median [IQR] of 14 h 36 m [13 h 4 m−15 h 36 m] for adults with CP and 14 h 54 m [14h29m−16 h 21 m] for TD adults.

Step Count

With regards to the adolescents, on average over the "whole week," no differences were reported in daily step count between the ambulant adolescents with CP (CP I-II and CP III) compared to the TD peers. On the other hand, the non-ambulant adolescents with CP (CP IV-V) showed lower step counts to the TD peers and the other CP groups. These results were the same for "weekdays" and "weekend days" only (**Figure 1A, Appendix I**).

With regards to the adult groups, the average step count calculated over the "whole week" was similar for the ambulant adults with CP (CP I-II) and TD peers, while it was lower for the other CP groups (CP III and CP IV-V) compared to the TD adolescents. The step count was also lower in the non-ambulant group (CP IV-V) compared to the independently ambulant adults with CP (CP I-II). Overall, the results were similar calculated over the "whole week," "weekdays" and "weekend days," except with the step count between the adults with CP who walked with assistive devices (CP III) and TD peers which was not significant different during the "weekend days" (**Figure 1B, Appendix I**).

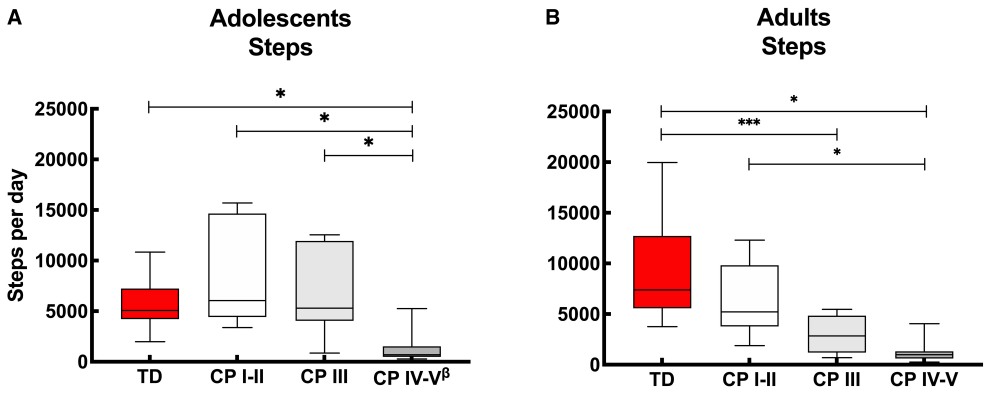

FIGURE 1 | Box and whisker plots for daily step count of **(A)** adolescents and **(B)** adults with cerebral palsy (CP) and typically developing (TD) peers. CP groups include CP I-II, participants with CP classified in Gross Motor Functional Classification System (GMFCS) level I and II; CP III, participants with CP classified in GMFCS level III; CP IV-V, participants with CP classified in GMFCS level IV and V. [β]Data of 2 adolescents excluded: $n = 24$. *Significant difference found for "whole week," "weekdays" and "weekend days;" ***significant difference found for "whole week" and "weekdays" ($p < 0.05$).

Levels of Physical Activity

The results of PA are recorded in appendices, including data from the adolescent's groups using Freedson (**Appendix IIa**) and Evenson (**Appendix IIb**) cut-point, as well as the adult's groups with Freedson (**Appendix IIIa**) and Evenson cut-points (**Appendix IIIb**). For clarity, the results described below are based on the data calculated with the Freedson cut-points. Despite the fact that Freedson cut-points (25) were only validated in adult population, the data is very similar to outcomes where Evenson cut-points (26) were utilized.

Figure 2 shows the proportion of time the participants of the different groups spent in SED, LPA and MVPA. Overall, adolescents with CP (classified in GMFCS level I-V) spend on average 74% of their day in SED, 24% in LVPA and 1% in MVPA, while their TD peers spend 70% of the time in SED, 28% in LPA and 3% in MVPA. With regards to the adults with CP, all adults with CP together (GMFCS level CP I-V) spend on average 75% of their time in SED, 23% in LPA and 2% in MVPA, while the TD peers spend 62% of the time in SED, 36% in LPA and 3% in MVPA.

Figure 3A provides insight into the actual time (minutes per hour) the adolescents spend in SED, LPA and MVPA. Calculated over the "whole week," the PA levels of adolescents with CP who are ambulant (CP I-II and CP III) were similar to the TD peers. Adolescents with CP who were non-ambulant (CP IV-V) spent more time SED and less time in LPA and MVPA compared to adolescents with CP who were independently ambulant (CP I-II) and TD adolescents. In addition, adolescents with CP who were non-ambulant (CP IV-V) spent less time in MVPA than adolescents with CP who were using assistive devices (CP III) (**Figure 3A, Appendix IIa**). Overall, similar results were observed when interpreting the data for the "whole week," "weekdays" and "weekend days." The only difference found was that the adolescents with CP who used assistive devices (CP III) spent more time in MVPA than non-ambulant adolescents with CP (CP IV-V) during the "whole week" and "weekend," but this was not the case for "weekdays" (**Figure 3A, Appendix IIa**).

The results of the *adults* with CP and TD peers are shown in **Figure 3B**. When considering the "whole week," then no differences were found in PA levels between independently ambulant adults with CP (CP I-II) and TD peers for SED and MVPA, while the level of PA (based on SED, LPA and MVPA) was lower in the other CP groups (CP III and CP IV-V) compared to TD peers. In addition, MVPA was higher in the CP I-II group compared to CP III and CP IV-V groups. Results of 'whole week' were quite similar to the outcomes calculated over "weekdays" and "weekend days." The exception being LPA levels, which were not lower in CP I-II compared to TD during the "weekend days" and MVPA was not lower in CP III and CP IV-V compared to TD adults when the results of the weekend days only were considered (**Figure 3B, Appendix IIIa**).

Associations

As shown in **Table 2**, adolescents and adults with CP both showed an association between daily step count and GMFCS levels, which indicates that adolescents and adults who were less independently mobile showed a lower daily step count. In line with this, higher GMFCS levels in adolescents and adults with CP was associated with greater time spent SED and a lower time spent in MVPA. No associations were found between daily step count or PA with sex, BMI and SES.

DISCUSSION

Despite what has been previously reported in well-resourced environments (HIC), as well as the hypothesis for the current study conducted in LMIC, not all adolescents and adults with CP were less active than their peers. This study demonstrated that PA in adolescents and adults with CP classified in GMFCS level I-II are no different to their TD peers when considering

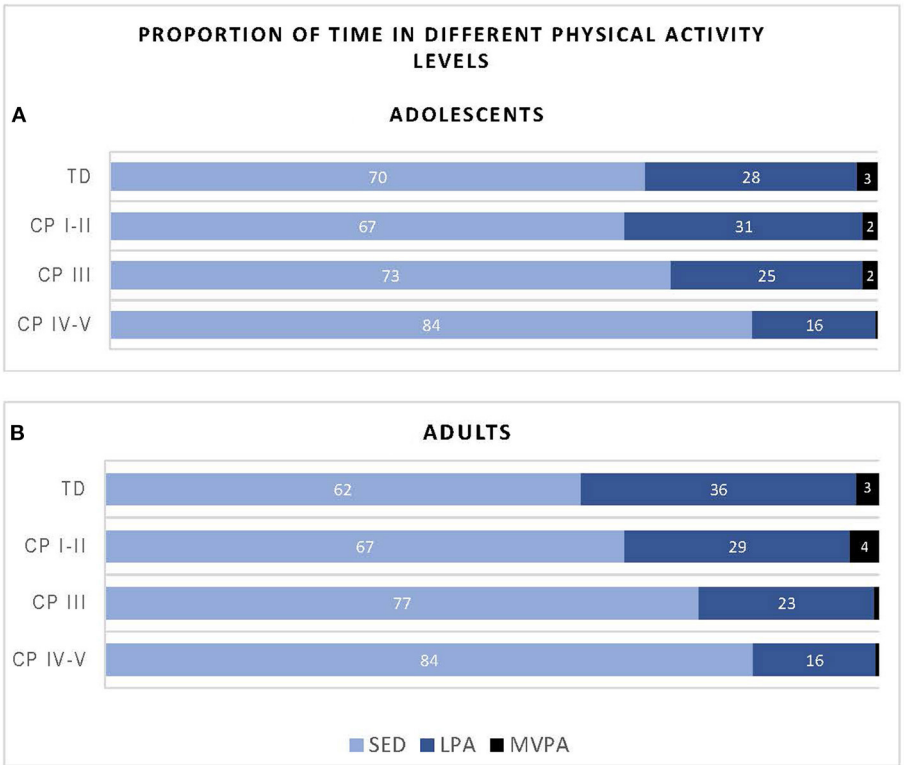

FIGURE 2 | Proportion of time adolescents **(A)** and adults **(B)** with cerebral palsy (CP) and typically developing (TD) peers spend in sedentary (SED), low physical activity (LPA) and moderate to vigorous physical activity (MVPA) based on data recorded over the "whole week" using Freedson cut-points. CP groups includes CP I-II, participants with CP classified in Gross Motor Functional Classification System (GMFCS) level I and II; CP III, participants with CP classified in GMFCS level III; CP IV-V, participants with CP classified in GMFCS level IV and V.

the whole week. Outcomes were similar for adolescents with CP who walked with assistive devices (GMFCS level III), however, *adults* with CP classified in GMFCS level III showed a lower daily step count and less PA than TD adults. Understandably, both adolescents and adults with CP who are non-ambulant (GMFCS level IV-V), showed lower daily step counts as well as lower PA levels compared to the TD cohorts. These results confirm the inverse relationship between participant's GMFCS levels and PA, indicating that adolescents and adults with CP who are less independently mobile show reduced physical activity.

Valid Data

In the current study, accelerometry data was captured with ActiGraph GT3X (worn around the waist). The ActiGraph has been considered the gold standard for PA research in individuals with CP as well as the TD population (27–31). The protocol we used was based on a systematic review (24) and other similar studies (27, 28, 34), which led to a relatively good succession rate with 73–100% of the CP and TD cohorts having valid data and included in the study. This data was based on 7 days of the week in 79% of all cases (6 days: 16; 5 days: 5; and 4 days: 1%), which corresponded with a real presentation of PA for a week.

Step Count

No differences were found between the daily step count for ambulant adolescents with CP (classified in GMFCS levels I-II and III) and TD peers (**Figure 1A, Appendix I**). This contrasts with previous findings from studies conducted in HIC (37, 38) reporting adolescents with CP to have a lower daily step count than TD adolescents. A possible reason for the lack of consistency of findings across these studies may include the relatively low daily step count of the TD peers in the current study (median: 5,075 steps), compared to the other studies with average step counts of 10,100 (38) and 6,812 (37). An alternative explanation is that the ambulant adolescents with CP in the current study had a relatively high daily step count. The adolescents with CP who used an assistive device (GMFCS level III), in particular, had a relatively high median daily step count of 5,310 steps, while the other studies reported 2,574 (9) and 2,606 (38) steps. These differences could be due to the use of other accelerometers ActivPal 3 (9, 38) and Orthocare SAM (37) or may be explained by social and physical environment factors (12). The fact that the adolescents with CP who reside in a LMIC have a relative high step count, may be due to challenges they face with accessing transport, whether private or public, and may have to resort to walking in order to get to their destination. Financial challenges

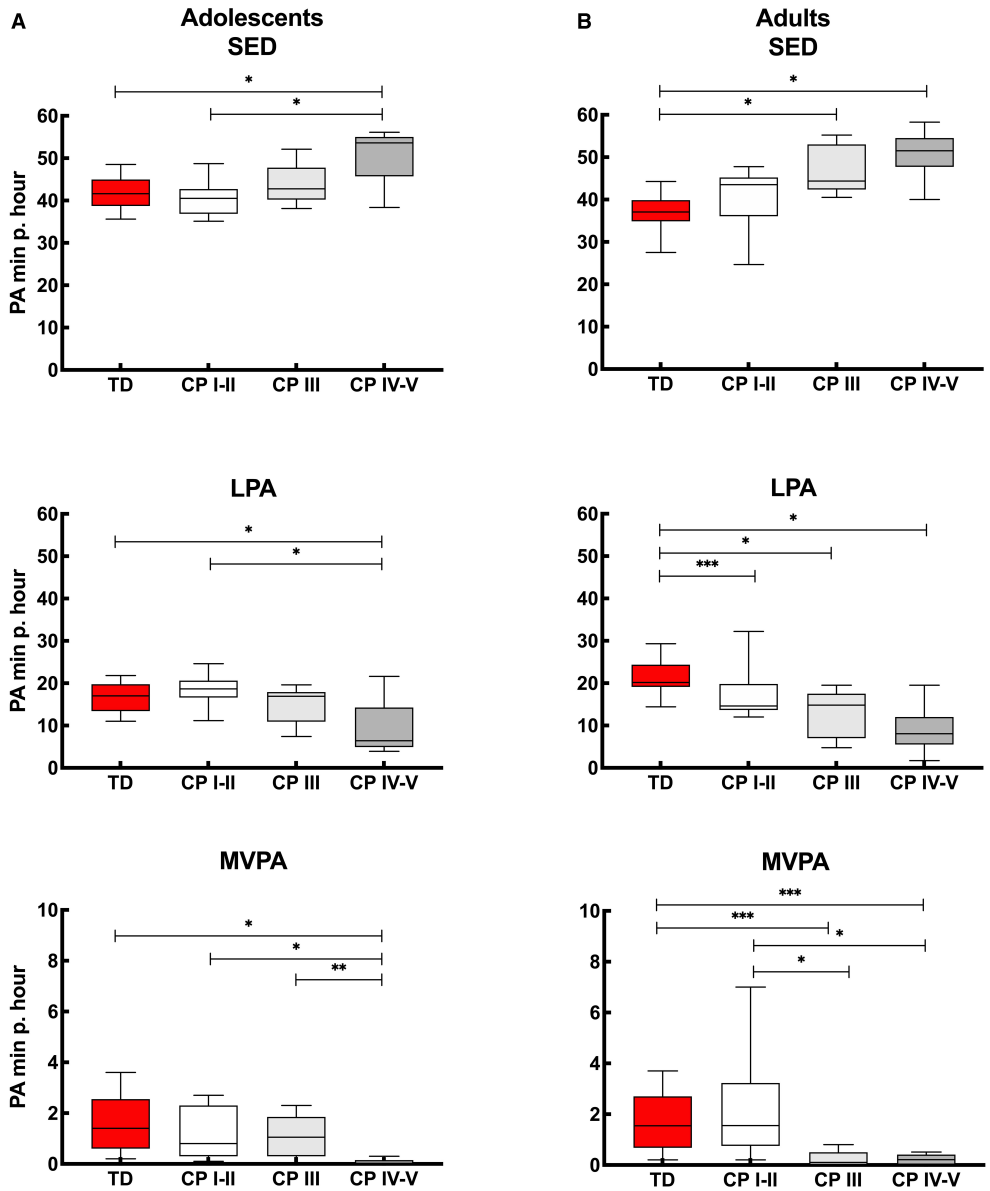

FIGURE 3 | Box and whisker plots for time spent in sedentary (SED), low physical activity (LPA) and moderate to vigorous physical activity (MVPA) using Freedson cut-points of **(A)** adolescents and **(B)** adults with cerebral palsy (CP) and typically developing peers (TD). CP groups include CP I-II, participants with CP classified in Gross Motor Functional Classification System (GMFCS) level I and II; CP III, participants with CP classified in GMFCS level III; CP IV-V, participants with CP classified in GMFCS level IV and V. *Significant difference found for "whole week," "weekdays" and "weekend days;" **significant difference found for "whole week" and "weekend days;" ***significant difference found for "whole week" and "weekdays" ($p < 0.0167$).

may also play a role in choosing to walk instead of taking a bus or taxi for transportation.

In line with the adolescents, considering the whole week, independent ambulant adults with CP (GMFCS level I-II) had a similar step count to TD adults, though adults who walked with assistive devices (GMFCS level III) had a lower step count than their TD peers. Step count for this group was different for whole week and weekdays, with no differences between adults with GMFCS level III and their TD peers in daily step count during the weekend. This suggests that these adults are capable of a typical daily step count but were not achieving this during the week. This is in contrast to the non-ambulant adults with CP (GMFCS level IV-V), who understandably did not achieve a daily step count similar to TD peers (**Figure 1B, Appendix I**).

Physical Activity

In line with the daily step count results, the current study showed that PA levels for *adolescents* with CP who are ambulant as well

TABLE 2 | Overview of the associations between step count and level of physical activity (minutes per hour)[#] and contextual factors for adolescents ($n = 26$) and adults ($n = 22$) with cerebral palsy.

Parameters		Contextual factors			
		Sex	GMFCS	BMI	SES
Adolescents					
Step count[ß]	rho	−0.260	-0.614	−0.202	0.179
	p	0.220	0.001*	0.344	0.402
SED	rho	0.241	0.574	0.145	0.006
	p	0.235	0.002*	0.479	0.978
LPA	rho	−0.159	-0.536	−0.197	0.004
	p	0.438	0.005*	0.334	0.984
MVPA	rho	−0.477	-0.636	0.204	−0.109
	p	0.014	<0.001*	0.319	0.598
Adults					
Step count	rho	0.315	-0.765	−0.440	0.373
	p	0.153	<0.001*	0.041	0.087
SED	rho	−0.331	0.572	0.375	−0.264
	p	0.133	0.005*	0.085	0.235
LPA	rho	0.331	-0.528	−0.354	0.166
	p	0.132	0.012*	0.106	0.460
MPA	rho	0.355	-0.746	−0.311	0.522
	p	0.105	<0.001*	0.159	0.013

[#]*Average physical activity measured over the "whole week" using Freedson cut-points. GMFCS, Gross Motor Classification System; BMI, Body Mass Index; SES, socio-economic status; SED, sedentary; LPA, Low physical activity; MVPA, Moderate to vigorous physical activity.* [ß]*Data of 2 adolescents excluded: n = 24. *Significance set at p < 0.0125.*

as those who used assistive devices, residing in a LMIC such as South Arica, are similar to TD peers (**Figure 2A, Appendix IIa**). These findings differ from previous studies conducted among adolescents with CP who reside in HICs, who reported more sedentary behavior in adolescents with CP compared to TD adolescents (10, 37, 38).

A more obvious finding of the current study was the difference in time spent in SED, LPA and MVPA in non-ambulant adolescents with CP compared to ambulant participants. More specifically, the current study showed that adolescents classified in GMFCS level IV-V reported less physical activity than TD adolescents and adolescents with CP classified in GMFCS level I-II and level III. The difference in MVPA between adolescents classified in GMFCS level III compared to GMFCS level IV-V was not found during the weekdays only, explained by a relatively low MVPA in this group. This highlights the fact that those adolescents with CP who used assistive devices in the current study are capable of being more active (evident on the weekends). A perceived barrier for reduced PA during the weekdays could be ignorance, due to lack of knowledge and active-living skills (11). Adolescents should be encouraged to be active to prevent long-term health issues (8, 11).

When comparing the PA outcomes of the adolescents with CP of current study with the work from Gorter and colleagues (31), who used a similar protocol (also including the Actigraph), but conducted in Canada, similar findings were reported. Gorter and colleagues (31) also showed lower LPA and MVPA for non-ambulant adolescents (GMFCS level IV) compared to independently ambulant adolescents (GMFCS level I and level II). However, it seems that the adolescents in the latter study (27) spent more time in MVPA (mean time per GMFCS level I/II/III/IV: 4.5/2.2/1.5/0.5 minutes per hour), compared to the current study (median time per GMFCS level I-II/III/IV-V: 0.8/1.1/0.0 minutes per hour). This shows that overall, the CP cohort living in urban South Africa was less active than the Canadian cohort.

Similar to the findings reported in the adolescent group, the independently ambulant *adults* with CP (GMFCS level I-II) showed similar PA levels (SED and MVPA) to their TD peers (**Figure 3, Appendix IIIa**). This is in contrast to adults with CP classified in GMFCS level III and level IV-V, who were less active than the TD adults. Nieuwenhuijsen and colleagues (39) similarly reported that adults with CP living in the Netherlands were relatively inactive compared to their peers, especially for those classified in GMFCS level III and IV (GMFCS level V was not included in the study), in agreement with our findings.

The difference in time spent in MVPA for adults with CP who used assistive devices and the non-ambulant adults with CP compared to TD peers was not seen on the weekends. This was because a relatively short time was spent in MVPA by the TD adults in the current study during the weekend. This highlights the fact that not only should adults with CP be motivated to spend more time in MVPA, but also the TD population. Therefore, TD adults may need to be encouraged to be more active during the weekend as they are also at risk for non-communicable disease (NCD) such as stroke, heart disease or diabetes (40).

When comparing the level of PA within the CP groups, then the current study reported no differences in SED and LPA between ambulant adults with CP (GMFCS level I-III) with non-ambulant adults (GMFCS level IV-V). On the other hand, differences between CP groups were found for MVPA as also previously reported in the literature. Ryan and colleagues (41) reporting on a cohort from Ireland and using a RT3 accelerometer, found differences between ambulant adults with CP classified in GMFCS level I compared to GMFCS levels II and level III. In addition, Claridge and colleagues (27) in a study conducted in Canada which also used the ActiGraph in ambulant and non-ambulant adults with CP, reported differences between ambulant adults with CP (GMFCS levels I, II and III) to non-ambulant adults (GMFCS level IV and level V).

The latter (27) was in contrast to the current study, with no differences found between adults who walk with an assistive device (GMFCS level III) and non-ambulant adults (GMFCS level IV-V). This finding could possibly be explained by the fact that relatively more time was spent in MVPA by adults classified in GMFCS level III in the Canadian study (MVPA GMFCS level I/II/III/IV/V: 3.8 / 1.6 / 0.7 / 0.1 / 0.1 minutes per hour) compared to the current study (MVPA per GMFCS level I-II/III/IV-V: 1.6 / 0.1 / 0.2 minutes per hour).

The differences between the outcomes of the adolescents and adults with CP, particularly those who used assistive devices, compared to their peers may suggest that as individuals with CP

grow into adulthood, they tend to be less physically active. This is in line with the decline in walking ability which was shown especially for those who are less independent in gait (42) and started as early as mid-30's in individuals with CP (43). Intrinsic (e.g., pain, fatigue) and extrinsic factors (e.g., environment) could be the cause of walking restrictions (44) and should try to be prevented. Walltersson and colleagues (6) suggest that when adolescents with CP are physically active in their youth, that this increases the likelihood of having higher PA levels in adulthood. Therefore, participation in regular exercise programs from an early age must be educated and encouraged in order to promote increased PA in adulthood so that the challenges and secondary complications of aging with a disability could be minimized. PA programs with theoretical and practical knowledge about the benefits of PA will help developing life-skills, which is of value for the whole lifespan (11). Though the barriers during the transition phase and thereafter are not only experienced by the individual with CP, there are also challenges for the health care system and clinicians, which needs to be addressed (45).

Regular PA not only benefits physical fitness but also cardiometabolic health (blood pressure, diabetes), bone health, mental health (anxiety and depression), maintain healthy body weight as well as cognitive function (40). Therefore, the World Health Organisation (WHO) 2020 guidelines (46), recommend adolescents, whether or not disabled, to engage in a minimum of 60 min per day on average of moderate- to- vigorous intensity, aerobic physical activity. Furthermore, the guidelines for adults, with or without a disability, are similar and include a recommendation to spend a minimum of 150 to 300 min of moderate intensity or 75 to 150 min vigorous intensity aerobic physical activity per week. Data from current study provides PA results based on minutes per hour and not per day, and therefore does not allow one to determine whether the CP and TD cohorts fulfill these criteria. However, with all cohorts spending only 1–3% of an h in MVPA (adolescents: CP 1 and TD 3%, adults: CP 2 and TD 3%) (**Figure 1**), it is clear that on average the adolescents and adults with CP and TD peers living in urban South Africa do not meet the WHO PA criteria.

Associations

As expected, the daily step count and all levels of PA were associated with GMFCS levels for both adolescents and adult with CP, indicating that participants with CP who were less independently mobile (higher GMFCS level) took fewer steps and spent less time being physically active (**Table 2**). This is corroborated by previous studies conducted with adolescents (9, 31) and adults (39) with CP. In line with the findings of Nieuwenhuijsen and colleagues (39), no associations were found for sex, BMI and SES, between PA levels and personal or environmental factors, with the exception of GMFCS levels.

Limitations

Several limitations should be considered when interpreting the results of this study. Although the small sample size for the different adolescent and adult CP groups (based on GMFCS levels) was relatively small, the groups were well distributed (**Table 1**) and personal characteristics were similar to the original cohorts (15). Another point of discussion is the use of cut-points to determine PA levels. The results presented are based on the data created with outcomes using Freedson cut-points. As mentioned, Freedson cut-points are developed for adults (25), while Evenson cut-points for children (26). Despite the differences in cut-points, especially for time spent in MVPA, we found minimal differences in the outcomes when interpretating the data with Freedson (**Appendices IIa**, **IIIa**) and Evenson (**Appendices IIb**, **IIIb**) cut-points. In addition, Freedson and Evenson cut-points have been validated in the general population and this may have underrepresented activity levels in those with lower gross motor function (e.g., GMFCS levels III to V). Likewise, because the ActiGraph was worn around the waist, activity in the upper limbs may not have been accounted for when determining PA, which may have affected PA levels of individuals with CP who walked with assistive devices (GMFCS level III) or those who were non-ambulant (GMFCS level IV and level V) but have been self-propelling their wheelchairs. No logbook or other questionnaire was completed, which could have been used to check the reliability of the data. Another limiting factor is that this is not a longitudinal study, where adolescents with CP were followed into adulthood, but rather based on different cohorts during adolescence and adulthood. Future follow-up studies will provide more insight into a possible trajectory although we can anticipate and plan for future challenges faced during the transition phase. In addition, the current study has been conducted in urban South Africa and one can hypothesize that the outcomes might differ for adolescents and adults living in rural communities with a different distribution of resources. Therefore, the outcomes cannot be generalized for all individuals with CP living in LMICs who may have different cultural norms and regulations or policies in place.

CONCLUSION

The current study showed that daily step count and PA levels of ambulant adolescents with CP, classified as GMFCS levels I to III, were similar to TD peers when considering the whole week. In contrast, ambulant *adults* with CP who used assistive devices (GMFCS level III) were less physically active than TD peers. Adolescents and adults with CP who were non-ambulant (GMFCS level IV-V) reported less daily step count and levels of PA compared to their peers. In addition, this study confirmed an inverse relationship between participant's GMFCS levels and PA, while the contextual factors of sex, BMI and SES were not related.

Since the level of PA in adolescence might be a predictor for PA in adulthood (6), providing support and intervention to this group during transition would be critical to maintain function (not only in the weekends as seen in the current study, but also during the week) in order to promote physical health, social and emotional well-being and independence. Even though physical challenges may hamper participation in PA, individuals with CP should be encouraged, assisted and supported to meet the PA recommendations by the WHO (40, 47). These should be developmentally appropriate, enjoyable, and involve a variety

of activities (11, 48). While this is a global aspiration, it seems that adolescents and adults with CP living in a LMIC such as South Africa, spend relatively less time in MVPA than peers living in HIC. It is also important to note that the overall PA level of the TD population in the current study was lower than expected, especially during the weekend days, and this group may also benefit from encouragement to engage in regular PA. This indicates that activity promotion programs should not only be focused on the individuals with CP (as rehabilitation), but rather be part of a general healthy aging program for the whole community.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town, South Africa. Written informed consent to participate in this study was provided by the participants or participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

NL and RS conceived and designed the analysis. RS and ME collected the data. RS, NL, and ME performed the analysis and drafted the manuscript. RS, NL, ME, KD, and AF provided critical feedback and contributed to the final manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.747361/full#supplementary-material

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Health Conditions in Adults With Cerebral Palsy: The Association With CP Subtype and Severity of Impairments

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Aim: To determine the prevalence of common health conditions in adults with cerebral palsy (CP) and to identify associations with the CP subtype or the severity of impairments.

Methods: A population-based, cross-sectional study of 153 adults with CP born from 1959 to 1978 (87 males, 66 females; median age 48 years 3 months, range 37–58 years; 41% with unilateral spastic, 36% bilateral spastic, 19% dyskinetic, and 4% with ataxic CP). Data was gathered through interviews, physical assessments, and medical record reviews.

Results: The most common health conditions in adults with CP were pain 65%, upper gastrointestinal disorders 33%, dysphagia 29%, epilepsy 29%, and depression 27%. Cerebral palsy subtype was significantly associated with the presence of pain ($p = 0.029$), gastrointestinal ($p < 0.001$), and respiratory disorders ($p = 0.006$). A more severe physical impairment was associated with a higher prevalence of gastrointestinal disorders ($p < 0.001$), respiratory disorders ($p < 0.001$), and pressure ulcers ($p < 0.001$). Intellectual disability was associated with a higher prevalence of gastrointestinal disorders ($p < 0.001$), pneumonia ($p = 0.001$) epilepsy ($p = 0.001$), and pressure ulcers ($p < 0.001$), but with a lower prevalence of pain ($p < 0.004$) and hypertension ($p = 0.043$).

Conclusion: The prevalence of several common health conditions is related to the CP subtype and severity of impairments, indicating that CP plays a role in the development of these health conditions. Follow-up of adults with CP needs to include not only impairments, but general health as well. Increased attention directed toward signs of gastrointestinal and respiratory disorders in individuals with either dyskinetic CP, gross motor function classification system (GMFCS) levels IV–V, or intellectual disability, is recommended.

Keywords: cerebral palsy, health conditions, CP subtype, intellectual disability, prevalence, gross motor function classification system, comorbidities

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INTRODUCTION

Adults with cerebral palsy (CP) have a higher prevalence of many different health conditions, compared to the general population (1–4). Musculoskeletal problems such as musculoskeletal pain, contractures, and scoliosis have long been recognized as complications of CP, but recent studies have broadened the focus to also include medical and mental health. Several reports have shown that adults with CP have a higher prevalence of cardiovascular and respiratory disease, including health conditions such as heart failure, ischemic heart disease, stroke, hypertension, obesity, diabetes, and asthma, and an increased prevalence of mental health disorders such as depression and anxiety compared to the general population (1–5).

However, CP is a condition with marked variations in symptoms and severity between individuals, ranging from independent to totally dependent in all daily activities. These individual variations are often described using classification systems such as the gross motor function classification system (GMFCS) (6) and the communication function classification system (CFCS) (7). The type and localization of the neurological symptoms can be described using the CP subtype classification (8). In addition, intellectual disability is diagnosed based on standardized intelligence testing and evaluation of adaptive skills (9).

The leading cause of death in both children and adults with CP is respiratory disorders (10, 11). Both the CP subtype and the severity of impairments in childhood have been shown to be related to survival in both childhood and adulthood (10, 11). Hence, it is likely that the background of CP, the subtype and the impairments, play a role in the development of the respiratory disorders causing early mortality. These mechanisms have been well-described in children with CP (12). However, the health conditions in adults with CP might differ from those in children, as health conditions related to CP might be amalgamated with other health conditions affecting adults.

The links between the functional impairments, the co-occurring health conditions, and the causes of death in adults with CP has only recently begun to be investigated. For example, the increased prevalence of cardiovascular disease and stroke might be explained by an increased prevalence of known risk factors such as lower aerobic fitness, less muscle mass, and higher percentages of body fat. These risk factors in turn could be caused by combinations of pain, fatigue, and physical inactivity, originating from the motor impairments (13). Other links between impairments, health conditions, and causes of death in adults with CP remain to be explored, and evidence-based interventions to be established.

It is possible that early detection and treatment of several of the co-occurring health conditions could not only improve health and well-being, but also improve survival. The ideal would be for preventive measures to be tailored to the health risks of the individual, based on known characteristics, such as the CP subtype and the severity of specific impairments.

Recent studies have provided important knowledge about the prevalence of numerous health conditions in adults with CP (1–5, 14, 15). However, many of these studies are based on health care registers or claims registers that provide data on diagnostic codes, but rarely include data on CP subtype or impairment severity classifications. The association between each health condition and the CP subtype or severity of impairments in adults, is therefore largely unknown. Moreover, health conditions that are not treated, or not relevant to the reason for the consultation may not always be given a diagnostic code. Therefore, the prevalence of the various health conditions experienced by adults with CP are likely to be underreported in health care registers. Additionally, a recent review of health conditions in adults with CP, noted that individuals with intellectual disability were excluded in as many as 27% of the samples (14). Considering the increased mortality associated with intellectual disability (10, 11, 16), this should be a prioritized population to study, and excluding them is likely to affect the prevalence of the studied health conditions.

The aim of this population-based study was to look beyond the musculoskeletal aspects of CP and determine the prevalence of other common health conditions, in adults with CP in western Sweden. A second aim was to identify associations with the CP subtype, the gross motor function, the communication function, or the presence of intellectual disability.

MATERIALS AND METHODS

The present study was a population-based cross-sectional study based on interviews, physical assessments, and a manual review of medical records. The study was part of a more extensive project surveying health and participation in adults with CP in western Sweden. The method for identifying and inviting participants has been described in a previous study (17). The follow-up assessments, consisting of a thorough medical history, a physical examination, and questionnaires, were conducted during 2015–2019. Medical records were then obtained from the hospitals and habilitation units in the area. The follow-up assessments were conducted by a multiprofessional team with extensive clinical experience of patients with CP. All medical interviews were conducted by authors UJ or KH, and all medical records were reviewed by author UJ. For the purpose of facilitating the participation of individuals with intellectual disability or communication impairments, various individual adaptations, regarding for example communication methods, assistance, scheduling, and location of the assessment, were made to accommodate for the needs of each participant. In the instances where a participant was still unable to understand or answer a question, a proxy answer was recorded. All participants or their legal guardian gave informed consent. The study was approved by the Regional Ethics review board in Gothenburg 2014-01-16 No. 777-13 and the Swedish Ethical Review Authority 2019-11-05 No. 2019-05518.

Participants

All adults included in the 20 oldest birth cohorts in the CP register of western Sweden (18), born 1959–1978 and still residing in the Region of Västra Götaland ($n = 417$), were invited to a follow-up assessment. Region Västra Götaland, on the west coast of Sweden, with 1.6 million inhabitants distributed

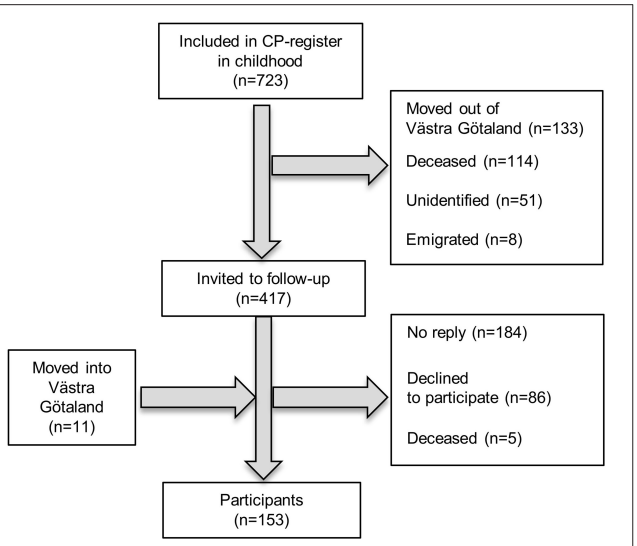

FIGURE 1 | Flow-chart of the inclusion process.

over both rural and urban areas, makes up two-thirds of the population included in the CP register of western Sweden. Adults with CP, born 1959–1978, who had moved into the area and thus were not in the register, were invited through patient organizations and habilitation units. A total of 153 adults with CP participated (**Figure 1**).

Definitions

Cerebral palsy subtype was classified according to the Surveillance of CP in Europe, as unilateral spastic, bilateral spastic, dyskinetic, or ataxic CP (8). Gross motor function classification system and CFCS levels were assessed (6, 7). Intellectual disability was defined as an intellectual quotient (IQ) of <70 with deficits in adaptive skills (9). Weight (kg) and height (m) was measured and body mass index (BMI) (kg/m^2) was calculated. Obesity was defined as having a BMI ≥30 kg/m^2. Blood pressure was measured three times using a digital, automatic inflation device with properly sized cuffs, and a mean value was calculated. Hypertension at assessment was defined as having a mean systolic blood pressure ≥140 or diastolic blood pressure ≥90, according to the NICE guidelines (19). However, a single visit with a high blood pressure is not sufficient for a diagnosis of hypertension, and therefore only participants taking medication for hypertension were classified as having a diagnosis of hypertension.

The medical history was gathered through a semi-structured interview, covering all health concerns, both past and present. Additionally, the medical records from the children's hospital, from birth to age 18, and from adult hospitals and habilitation units from year 2000 to 2019, were reviewed. All health conditions, except pain, were classified as present if a participant self-reported having had the condition at some time, or if it was mentioned in the medical records. In order to detect all health conditions experienced by the participants, not only diagnoses and treatments were noted. Symptoms such as phlegm in airways, heartburn, or pain that were untreated or symptomatically treated without any extensive work-up, or with non-prescription medicines, were also included. Pain mentioned in medical records was often related to an acute illness, trauma, or operation and was not the persistent pain that we aimed to study. Pain was therefore defined as current or recurring pain of any type at the time of the assessment. Participants were asked to describe pain intensity, (mild, moderate, or severe), frequency (daily, weekly, monthly, or more seldom), and duration (more or less than 3 months). When participants reported several different pain sites, with different frequency, intensity, or duration, the highest intensity and frequency, and the longest duration was recorded.

Gastrointestinal tract (GI) disorders included for example: gastroesophageal reflux disease, dysphagia, gastritis, peptic ulcers, gastrostomy, constipation, diarrhea, or irritable bowel syndrome. All participants reporting either gastroesophageal reflux disease, gastritis, or peptic ulcers, or taking proton pump inhibitors, were classified as having an upper GI disorder. Psychiatric disorders were defined as any type

TABLE 1 | Characteristics of participants (n = 153).

Age		
median (range)	48 years 3 months	(37–58 years)
IQR		42–55 years
Age categories		
37–44 years	50	(33)
45–52 years	52	(34)
53–60 years	51	(33)
Sex		
Female	66	(43)
Male	87	(57)
CP subtype		
Unilateral spastic	63	(41)
Bilateral spastic	55	(36)
Dyskinetic	29	(19)
Ataxic	6	(4)
GMFCS level		
I	60	(39)
II	32	(21)
III	18	(12)
IV	26	(17)
V	17	(11)
CFCS level		
I	109	(71)
II	16	(11)
III	10	(7)
IV	10	(6)
V	8	(5)
Intellectual disability		
IQ < 70	34	(22)
IQ > 70	119	(78)

Values are n (%). CP, cerebral palsy; GMFCS, gross motor function classification system; CFCS, communication function classification system; IQ, intelligence quotient.

TABLE 2A | Health conditions in adults with CP, by CP subtype, GMFCS level, CFCS level, and ID ($n = 153$).

	Total		Pain		Gastrointestinal						Psychiatric					
					GI total		Upper GI		Dysphagia		Constipation		Psychiatric total		Depression		Anxiety	
Total	153	(100)	100	(65)	94	(61)	50	(33)	45	(29)	39	(26)	60	(39)	41	(27)	18	(12)
CP subtype			$p = 0.029$*		$p < 0.001$*		$p < 0.001$*		$p < 0.001$*		$p < 0.001$*		$p = 0.378$		$p = 0.066$		$p = 0.021$*	
Unilateral	63	(41)	36	(57)	19	(30)	6	(10)	8	(13)	2	(3)	20	(32)	15	(24)	3	(5)
Bilateral	55	(36)	43	(78)	43	(78)	27	(49)	20	(36)	14	(26)	24	(44)	13	(24)	12	(22)
Dyskinetic	29	(19)	19	(66)	26	(90)	16	(55)	16	(55)	18	(62)	14	(48)	13	(45)	2	(7)
Ataxic	6	(4)	2	(33)	6	(100)	1	(17)	1	(17)	5	(83)	2	(33)	0	(0)	1	(17)
GMFCS level			$p = 0.407$		$p < 0.001$*		$p < 0.001$*		$p < 0.001$*		$p < 0.001$*		$p = 0.488$		$p = 0.142$		$p = 0.931$	
I	60	(39)	37	(62)	20	(33)	9	(15)	5	(8)	2	(3)	21	(35)	14	(23)	6	(10)
II	32	(21)	21	(66)	21	(66)	10	(31)	8	(25)	7	(22)	12	(38)	6	(19)	4	(13)
III	18	(12)	12	(67)	12	(67)	5	(28)	6	(33)	5	(28)	9	(50)	5	(28)	3	(17)
IV	26	(17)	18	(69)	24	(92)	16	(62)	12	(46)	11	(42)	12	(46)	11	(42)	4	(15)
V	17	(11)	12	(71)	17	(100)	10	(59)	14	(82)	14	(82)	6	(17)	5	(29)	1	(6)
CFCS level			$p = 0.021$*		$p < 0.001$*		$p = 0.006$*		$p < 0.001$*		$p < 0.001$*		$p = 0.092$		$p = 0.282$		$p = 0.067$	
I	109	(71)	76	(70)	53	(49)	27	(25)	17	(16)	12	(11)	45	(41)	28	(26)	15	(14)
II	16	(11)	11	(69)	14	(88)	9	(56)	7	(44)	8	(50)	9	(56)	9	(56)	3	(19)
III	10	(7)	5	(50)	9	(90)	5	(50)	7	(70)	5	(50)	2	(20)	2	(20)	0	(0)
IV	10	(6)	5	(50)	10	(100)	4	(40)	9	(90)	6	(60)	3	(30)	2	(20)	0	(0)
V	8	(5)	3	(38)	8	(100)	5	(63)	5	(63)	8	(100)	1	(13)	0	(0)	0	(0)
ID			$p = 0.004$*		p <0.001*		p <0.061		p <0.001*		p <0.001*		$p = 0.692$		$p = 0.826$		$p = 0.365$	
IQ<70	34	(22)	15	(44)	32	(94)	16	(47)	21	(62)	23	(68)	12	(35)	8	(24)	2	(6)
IQ>70	119	(78)	85	(71)	62	(52)	34	(29)	24	(20)	16	(13)	48	(40)	33	(28)	16	(13)

*Values are n (%). *Significant, $p < 0.05$. p-values refer to Fisher's exact test, for variation across subtypes or presence of ID and to Linear-by-linear Association across GMFCS or CFCS-levels. Percentages are the proportion of participants with the given subtype of CP, GMFCS level, CFCS level or ID, with a certain health condition. Missing data for hypertension at visit ($n = 7$). CP, cerebral palsy; GMFCS, gross motor function classification system; CFCS, communication function classification system; ID, intellectual disability; IQ, intelligence quotient; pain, recurring or consistent pain; GI, gastrointestinal tract; GI total, includes upper GI, dysphagia, constipation, and miscellaneous GI disorders; upper GI, gastroesophageal reflux and gastritis, psychiatric total includes depression, anxiety and miscellaneous psychiatric disorders.*

TABLE 2B | Health conditions in adults with CP, by CP subtype, GMFCS level, CFCS level, and ID ($n = 153$).

	Respiratory								Other									
	Respiratory total		Phlegmy		Pneumonia		Asthma		Hypertension at visit		Hypertension diagnosis		Diabetes		Epilepsy		Pressure ulcers	
Total	46	(30)	19	(12)	15	(10)	9	(6)	63	(41)	27	(18)	12	(8)	44	(29)	14	(9)
CP subtype	$p = 0.006$*		$p < 0.001$*		$p = 0.023$*		$p = 0.354$		$p = 0.240$		$p = 0.245$		$p = 0.838$		$p = 0.122$		$p = 0.048$*	
Unilateral	10	(16)	0	(0)	4	(6)	2	(3)	24	(39)	9	(14)	4	(6)	23	(37)	2	(3)
Bilateral	20	(36)	9	(16)	3	(6)	6	(11)	28	(54)	13	(24)	6	(11)	11	(20)	6	(11)
Dyskinetic	14	(48)	9	(31)	6	(21)	1	(3)	10	(37)	3	(10)	2	(7)	7	(24)	6	(21)
Ataxic	2	(33)	1	(17)	2	(33)	0	(0)	1	(20)	2	(33)	0	(0)	3	(50)	0	(0)
GMFCS level	$p < 0.001$*		$p < 0.001$*		$p = 0.013$*		$p = 0.907$		$p = 0.133$		$p = 0.972$		$p = 0.918$		$p = 1.000$		$p < 0.001$*	
I	8	(13)	1	(2)	3	(5)	2	(3)	33	(55)	8	(13)	4	(7)	17	(28)	1	(2)
II	9	(28)	2	(6)	2	(6)	5	(16)	8	(26)	8	(25)	4	(13)	10	(31)	0	(0)
III	6	(33)	1	(6)	3	(17)	0	(0)	8	(47)	4	(22)	1	(6)	6	(33)	1	(6)
IV	13	(50)	9	(35)	2	(8)	1	(4)	10	(40)	6	(23)	2	(8)	3	(12)	5	(19)
V	10	(59)	6	(35)	5	(29)	1	(6)	4	(31)	1	(6)	1	(6)	8	(47)	7	(41)
CFCS level	$p = 0.030$*		$p = 0.003$*		$p < 0.001$*		$p = 0.199$		$p = 0.043$*		$p = 0.028$*		$p = 0.715$		$p < 0.001$*		$p < 0.001$*	
I	26	(24)	7	(6)	5	(5)	8	(7)	52	(48)	24	(22)	9	(8)	23	(21)	5	(5)
II	8	(50)	4	(25)	3	(19)	1	(6)	4	(27)	2	(13)	1	(6)	4	(27)	0	(0)
III	4	(40)	3	(30)	2	(20)	0	(0)	5	(56)	0	(0)	1	(10)	5	(25)	3	(30)
IV	4	(40)	3	(30)	2	(20)	0	(0)	2	(22)	1	(10)	1	(10)	6	(60)	3	(30)
V	4	(50)	2	(25)	3	(38)	0	(0)	0	(0)	0	(0)	0	(0)	6	(75)	3	(38)
ID	$p = 0.056$		$p = 0.015$*		$p = 0.001$*		$p = 0.685$		$p < 0.035$*		$p = 0.043$*		$p = 0.302$		$p = 0.001$*		$p < 0.001$*	
IQ<70	15	(44)	9	(27)	9	(27)	1	(3)	7	(25)	2	(6)	1	(3)	18	(53)	12	(35)
IQ>70	31	(26)	10	(8)	6	(5)	8	(7)	56	(48)	25	(21)	11	(9)	26	(22)	2	(2)

*Values are n (%). * = significant, $p < 0.05$. p-values refer to Fisher's exact test, for variation across subtypes or presence of ID and to Linear-by-linear Association across GMFCS or CFCS-levels. Percentages are the proportion of participants with the given subtype of CP, GMFCS level or ID, with a certain health condition. Missing data for hypertension at visit (n = 7). CP, cerebral palsy; GMFCS, gross motor function classification system; CFCS, communication function classification system; ID, intellectual disability; IQ, intelligence quotient; Respiratory total includes Phlegmy, pneumonia, asthma and miscellaneous respiratory disorders; Hypertension at visit ≥140/≥90 mmHg; hypertension diagnosis, treated for hypertension; diabetes, type 1 and 2.*

of psychiatric disorder treated with either medication or counseling, and included for example: depression, anxiety disorders, burnout, bipolar disorder, psychotic disorders, and challenging behavior. Respiratory disorders included for example: pneumonia, asthma, sleep apnoea, and problems clearing airways of phlegm. Epilepsy was defined as having recurring seizures or taking antiepileptic medication. Diabetes included both type 1 and type 2. Pressure ulcers were defined as a pressure ulcer, grade II, or worse, according to international guidelines (20).

Statistics

Descriptive statistics were used to document participant characteristics and the prevalence of health conditions. Age was classified in three categories: 37–44, 45–52, 53–60 years. The associations between the presence of each health condition and the age categories, the GMFCS or CFCS level were analyzed with the Mantel-Haenzsel i.e., linear-by-linear association test for trends. The associations between each health condition and sex, CP subtype, intellectual disability, or another health condition were analyzed with the Pearson Chi-square, or the Fisher's exact test when cases were few. The significance level was set at a two-tailed $p < 0.05$. All analyses were conducted using IBM SPSS Statistics version 25.

RESULTS

The current study comprised 153 adults with all CP subtypes and all levels of physical and intellectual disability (**Table 1**). The most common health problem domains were pain 65%, GI disorders 61%, psychiatric disorders 39%, and respiratory disorders 30%. The specific health conditions most commonly reported were pain 65%, upper GI disorders 33%, dysphagia 29%, epilepsy 29%, and depression 27% (**Tables 2A**,**B**).

Among the 100 participants reporting pain, 58% reported moderate pain, 47% daily pain, and 75% a pain duration of over 3 months, while only 30% reported taking pain medication (**Table 3**). Pain was significantly associated with CP subtype, and was less often reported from participants with a more impaired communication (a less functional CFCS level) or with intellectual disability (**Table 2**). There was no association between pain and GMFCS level in the total group. However, subgroup analysis showed that among participants without intellectual disability pain was more common in participants with a less functional GMFCS level ($p = 0.022$). Among participants with intellectual disability there was no association between pain and GMFCS level.

The GI disorders most commonly reported were upper GI disorders, dysphagia, and constipation (**Table 2**). Dysphagia was associated with pneumonia ($p = 0.041$) and problems with phlegm ($p = 0.006$). Five participants had a gastrostomy and all five had an intellectual disability and were classified as GMFCS and CFCS levels IV or V.

The most common psychiatric disorder was depression, and the most common respiratory disorders were pneumonia and problems with phlegm (**Table 2**). Twelve participants were treated with inhalations for airway symptoms such as asthma or phlegm. Chronic obstructive pulmonary disease (COPD) or chronic bronchitis was not reported by any participant nor in any medical records.

TABLE 3 | Pain characteristics ($n = 100$).

Intensity		
Mild	17	(17)
Moderate	58	(58)
Severe	25	(25)
Frequency		
Monthly	13	(13)
Weekly	23	(23)
Daily	47	(47)
Unknown	17	(17)
Duration		
<3 months	8	(8)
>3 months	75	(75)
Unknown	17	(17)
Pain medication		
Yes	30	(30)

Values are n (%).

While 18% were treated for hypertension, 41% had a blood pressure of ≥140/90 mmHg measured at the visit (**Table 2**). The median BMI was 25.9 kg/m^2 and the median waist circumference 94 cm. Underweight was significantly related to male sex, a less functional GMFCS and CFCS level, and intellectual disability (**Table 4**). All six participants who were underweight had both intellectual disability and dysphagia but only two had a gastrostomy.

The presence of health conditions varied with the nature and severity of impairments. For example, participants with dyskinetic CP were the most affected by both upper GI disorders, dysphagia, and respiratory disorders, and a less functional GMCS level was significantly associated with a higher prevalence of GI disorders, respiratory disorders, and pressure ulcers. Intellectual disability was significantly associated with several health conditions, but also with a lower prevalence of pain and hypertension (**Table 2**).

There were no significant associations between age or sex and CP subtypes, impairments, or health conditions, except for an association between sex and high blood pressure measured at the visit (Table 5 in **Supplementary Material**).

The CFCS level was very closely related to the presence of intellectual disability ($p < 0.001$), with 94% of participants without intellectual disability classified as CFCS level 1.

DISCUSSION

The most common health conditions in this population-based study of adults with CP of all CP subtypes and levels of physical and intellectual impairment, were pain, upper GI disorders, dysphagia, epilepsy, and depression. Additionally, the prevalence of several common health conditions were shown to

TABLE 4 | Waist and body mass index (BMI) in adults with CP, by age, sex, CP subtype, and impairments ($n = 152$).

	Waist		BMI		Underweight			Obesity		
All	94		25.9		6	(4)		32	(21)	
Age		$p = 0.606$[a]		$p = 0.942$[a]			$p = 0.452$[c]			$p = 0.809$[c]
37–44 years	92		26.2		2	(4)		12	(24)	
45–52 years	92		25.9		0	(0)		9	(18)	
53–60 years	94		25.9		4	(8)		11	(22)	
Sex		$p = 0.248$[a]		$p = 0.413$[a]			$p = 0.036$*[b]			$p = 1.000$[b]
Female	92		26.5		0	(0)		14	(21)	
Male	95		25.6		6	(7)		18	(21)	
CP subtype		$p = 0.019$*[a]		$p = 0.003$*[a]			$p = 0.250$[b]			$p = 0.084$[b]
Unilateral	95		27.0		1	(2)		16	(25)	
Bilateral	95		26.4		2	(4)		14	(26)	
Dyskinetic	88		23.6		3	(10)		2	(7)	
Ataxic	85		24.5		0	(0)		0	(0)	
GMFCS level		$p = 0.585$[a]		$p = 0.297$[a]			$p = 0.001$*[c]			$p = 1.000$[c]
I	94		26.3		0	(0)		13	(22)	
II	94		26.1		1	(3)		7	(22)	
III	93		26.2		0	(0)		3	(17)	
IV	93		25.5		1	(4)		5	(20)	
V	81		20.8		4	(24)		4	(24)	
CFCS level		$p = 0.056$[a]		$p = 0.050$*[a]			$p < 0.001$*[c]			$p = 0.090$[c]
I	95		26.4		0	(0)		28	(26)	
II	90		24.9		1	(6)		1	(6)	
III	89		22.7		0	(0)		1	(11)	
IV	81		20.1		3	(30)		1	(10)	
V	77		20.5		2	(25)		1	(13)	
ID		$p = 0.073$[a]		$p = 0.330$[a]			$p < 0.001$*[b]			$p = 0.642$[b]
IQ < 70	85		22.9		6	(18)		6	(18)	
IQ > 70	94.0		26		0	(0)		26	(22)	

*Values for Wast and BMI are median, values for underweight and obesity are n (%), *Significant, $p < 0.05$. p-values are [a]Median test, [b]Fisher's exact test, [c]Mantel-Haenzsel Linear-by-linear Association. Missing data for waist (n = 2). CP, cerebral palsy; GMFCS, gross motor function classification system; CFCS, communication function classification system; ID, intellectual disability; IQ, intelligence quotient; Waist, waist circumference in cm; BMI, body mass index, underweight, BMI < 18.5 kg/m^2; Obesity, BMI ≥ 30 kg/m^2.*

be significantly related to the CP subtype, the GMFCS level, the CFCS level, or the presence of intellectual disability.

The high prevalence of pain in our study was in accordance with a recent systematic review of pain in adults with CP (15). In our study pain was less frequently reported by participants with intellectual disability or a more impaired communication, in spite of the adaptations made to enable all participants to answer for themselves. A possible explanation for this could be that some individuals with intellectual disability might not be able to understand or express that the discomfort they feel is pain. In addition, some might express pain non-verbally in ways that their carers don't always recognize and others may be so accustomed to a chronic pain that they don't express it at all. Many adults in our study reported pain but took no medication. This was maybe not so surprising, as chronic pain is often better managed with other strategies than pain medication. Many also reported avoiding activities in daily life that they knew would cause pain. According to earlier studies, adults with CP don't always access health care providers for help with managing pain, and a majority of those who receive treatments still have pain (21, 22). The pain in CP can have a great variety of origins, including musculoskeletal, neurogenic, or internal organs, and assessment can be challenging (21, 23). Thus, there is a risk that adults with CP are missing out on suitable interventions for alleviating pain and there is also the possibility that some adults with CP have pain with an origin that could have been prevented, treated, or cured instead of coped with.

A majority of our participants reported GI disorders. Though dysphagia, gastroesophageal reflux disease, and chronic constipation are frequent problems in the clinic, and the mechanisms by which CP causes GI disorders has been well-described in children with CP (24), there is a paucity of research on adults with CP, both on how these mechanisms affect adults and on how they best can be treated (25, 26).

The proportion of participants who reported that they had been treated for psychiatric disorders such as depression and anxiety, at some point in their lives, was higher than in previous studies of adults with CP (1, 4). This is what could be expected, since our study covered a longer time period and included treatments other than medication. Interestingly, in our study the

prevalence of depression and anxiety were not related to any of the other impairments studied.

The prevalence of epilepsy was high compared to previous studies (14). There are several possible explanations for this. Firstly, the prevalence of epilepsy is closely related to the prevalence of intellectual disability in the study sample. Secondly, in our study both resolved and current epilepsy, from birth to middle age, was included. We have previously shown that epilepsy in CP indeed can be resolved (17), but nevertheless it remains one of the most common and consequential health conditions in CP.

One-third of our participants reported respiratory disorders, but only 6% reported having asthma and no participants reported COPD. Some cases of pneumonia were classified as aspiration pneumonia in the medical records, but in many cases the cause of the pneumonia could not be ascertained. Respiratory disorders is a complex issue in adults with CP, with spasticity and weakness, gastroesophageal reflux disease and dysphagia causing chronic aspiration, chronic airway inflammation, poor airway clearance, and impaired lung function, all of which then predispose for respiratory infections and respiratory failure (12, 27). However, in health care registers, the respiratory disorder most often found in adults with CP is asthma (1, 3). It seems possible that the diagnosis of asthma is used as a sort of proxy, for lack of better diagnostic codes, but it might also be a sign of health care professionals lacking insight into the complexity of respiratory disorders in adults with CP. According to our results, respiratory disorders such as pneumonia and problems with phlegm, were more common in participants with dysphagia than in those without, and more common in participants with a dyskinetic CP subtype, a less functional GMFCS level, or intellectual disability. This finding provides a link between the studies showing shorter survival in individuals with any of these impairments, and the studies showing respiratory disorders to be the leading cause of death in adults with CP. However, there is currently little or no evidence for the interventions used for prevention and management of respiratory disorders in individuals with CP, making this an important area for future research (28).

High blood pressure measured at the visit was twice as common (41%) compared to the number of participants who had a diagnosis of hypertension and were using antihypertensive medication (18%). In comparison, a recent systematic review of hypertension in CP reported a 28.9% prevalence of hypertension and 0–18% using antihypertensive medication (29). They found no difference related to GMFCS levels, but the association with intellectual disability seems not to have been analyzed. Surprisingly, our results show a markedly lower prevalence of hypertension among participants with intellectual disability. This finding is contrary to recent studies of hypertension in adults without CP, stating a prevalence of 31.1% in all adults (30), and 36.7% in adults with intellectual disability (31) and at this stage we have found no explanation for it. The high prevalence of high blood pressure measured at the visit might partly be due to the "white coat effect," since the visit was a potentially stressful situation for the participant (19). Of course, there could also be hitherto undetected cases of hypertension. Since a single visit with a high blood pressure is not sufficient for a diagnosis of hypertension, all participants with high blood pressure at the visit were recommended to contact a general practitioner (GP) for a proper assessment.

The median BMI and the prevalence of obesity were in line with a recent systematic review (14), whereas the median waist circumference was higher. In adults with CP, where the motor impairment might cause lower muscle mass and bone density, waist circumference might be a better indicator of excessive body fat and cardiovascular risk (13). The prevalence of obesity was not related to age, sex, or any of the impairments. In contrast, underweight was related to male sex, a less functional GMFCS and CFCS level and to intellectual disability. Similar associations were observed for pressure ulcers, underscoring the medical vulnerability of the most severely impaired adults with CP.

According to our results, intellectual disability was associated with an increased prevalence of a variety of health conditions, most notably epilepsy, GI disorders, pneumonia, and pressure ulcers. To our knowledge this has not been studied in adults with CP before. Even though the individuals who are still alive are likely to have been the healthiest, these findings provide important information regarding the factors behind the increased risk of early mortality in adults in this population. To some extent, these health conditions and causes of death might be preventable. Adults with intellectual disability constitute a high risk population, many of whom have difficulties identifying symptoms or are dependent on others for seeking medical attention, and who therefore should be offered regular health checks (32, 33). Our results confirm the importance of providing regular follow-up and preventive care for adults with CP and intellectual disability.

The associations between CFCS levels and health conditions were affected by the close relationship between CFCS levels and intellectual disability, and the individuals with intellectual disability were too few for meaningful subgroup analyses. Nonetheless, it is likely that examining a larger population of individuals with intellectual disability would reveal associations between health conditions and communication function. Not only in accessing primary care, but also during hospital care, individuals with communication impairments can have difficulties gaining the attention of the medical staff and communicating their symptoms, and for this reason have an increased risk of complications and death (11, 34, 35).

The finding that the prevalence of several health conditions were related to the CP subtype and the severity of impairments indicates that CP might be a factor in the development of these health conditions. If CP is involved in the development of a health condition, it seems reasonable that it might also affect the effectiveness of treatments. For example, there are other mechanisms leading to recurring respiratory infections in CP than in the general population, and treatments need to be chosen with this in mind (27). Hence, both preventive health care and standard treatments used for the general population might need to be adapted to suit the specific health risks, increased morbidity, and early mortality of adults with CP.

Further research is needed to clarify how symptoms, disease mechanisms, and treatments for specific health conditions might differ between adults with CP and the general population.

Limitations

A major strength of this study is the use of a combination of a population-based CP-register for the identification of adults with CP, and a follow-up visit during which current impairments were assessed and self-reported health conditions were recorded. At the same time, the interview and assessment demanded considerable time and effort from the participants and their carers, maybe leading to a low response rate.

The medical records from hospitals and habilitation units were reviewed. However, many health conditions, such as pain, phlegm in the airways, dyspepsia, or constipation, had been treated mainly in primary care. Even though these health conditions were often mentioned in the medical history in hospital or habilitation records, they were seldom the reason for the visit and were therefore not worked-up or coded for. If the participants did not remember them during our interview, such health conditions could be underreported in our results. In particular, adults with intellectual disability living in group home facilities and being cared for by GPs might be less likely to be referred to hospital care and less likely to report all experienced health conditions. In addition, health conditions might be underreported because of the difficulties adults with CP experience in accessing care, and of diagnostic overshadowing, where new symptoms are attributed to CP instead of a comorbid condition.

The health conditions presented in this study were self-reported or as mentioned in medical records. The prevalence of each health condition needs to be interpreted with this in mind. Future work is required to further investigate and objectively verify their prevalence. It seems likely, however, that the associations described between CP subtypes, impairments and health conditions would be relevant to objectively verified, as well as subjectively described health conditions.

Some childhood data on the non-responders were available from the register. There were no differences regarding sex, age, or GMFCS level, but the prevalence of intellectual disability and epilepsy was higher in non-responders (Table 6 in **Supplementary Material**). Since participants with ID had a higher prevalence of many health conditions, the true prevalence of these health conditions in the population of adults with CP is likely to be somewhat higher than in our results. Even so, this should not affect the associations between the CP subtypes, impairments, and health conditions.

Conclusion

Adults with CP have health conditions stemming from several different organ systems. Hence, follow-up and preventive care for adults with CP needs to include not only the impairments, but an assessment of general health as well. Knowledge of how the prevalence of specific health conditions is related to CP subtype and impairment severity can help individualize preventive care and also inspire future research into disease mechanisms and treatments.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of privacy and ethical restrictions. The anonymized data that support the findings of this study are available on request from the corresponding author. Requests to access the datasets should be directed to ulrica.jonsson@neuro.gu.se.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Swedish Ethical Review Authority. The participants or their legal guardians provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

UJ and KH conceptualized and designed the study and analyzed and interpreted the data. UJ, KH, and ME were involved in the data collection. UJ drafted the manuscript. All authors critically revised the manuscript and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.732939/full#supplementary-material

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Quality of Life in Young Adults With Cerebral Palsy: A Longitudinal Analysis of the SPARCLE Study

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Introduction: While most people with cerebral palsy (CP) will have a life expectancy similar to that of the general population, international research has primarily focused on childhood and adolescence; and knowledge about the quality of life (QoL) of young adults with CP, its trajectories, and associated factors remains scarce.

Methods: This longitudinal study included young adults with CP living in five European regions and who had previously participated in the SPARCLE cohort as children and/or adolescents. Their QoL in the psychological well-being and social relationships domains was estimated using age-appropriate validated instruments (KIDSCREEN-52 in childhood/adolescence and WHOQOL-Bref in young adulthood). We used generalized linear mixed-effect models with random intercept to estimate long-term trajectories of QoL in both domains and to investigate whether severity of impairment, pain, and seizure influenced these trajectories. We sought to identify potentially different trajectories of QoL from childhood to adulthood using a shape-based clustering method.

Results: In total, 164 young adults with CP aged 22–27 years participated in the study. Psychological well-being linearly decreased by 0.78 points (scale 0–100) per year (95% confidence interval (CI) −0.99 to −0.56) from childhood to young adulthood, whereas QoL in the social relationships domain increased (β coefficient 1.24, 95% CI 0.92–1.55). Severity of impairment was associated with reduced QoL in all life periods of the study (childhood, adolescence, and young adulthood): motor impairment with social relationships, and more nuancedly intellectual disability with psychological well-being and social relationships. At all periods, frequent pain significantly reduced psychological well-being, and seizures were associated with lower QoL in the social relationships domain. In both domains, we identified a group of individuals with CP who presented a reverse trajectory compared with the general QoL trajectory.

Conclusion: Identification of QoL trajectories and their associated factors yields improved knowledge about the experience of individuals with CP until young adulthood. Further studies are needed to better understand the determinants that have the greatest influence on the different shapes of long-term trajectories of QoL.

Keywords: cerebral palsy, quality of life, trajectories, impairments, pain, adults

INTRODUCTION

It is now recognized that most people with cerebral palsy (CP) enjoy a life expectancy similar to that of the general population (1). This opens new perspectives for understanding of the impact of childhood disability on young adults. Quality of life (QoL) has been considered a key concept in disability research for the past two decades (2). However, its conceptual definition and its measurement in people with disabilities or chronic conditions are complex and still debated in the literature (3). In short, while health-related QoL (HRQoL) refers to those aspects of life that are directly influenced by disability, health problems, or treatments (4, 5), QoL is viewed as a broader concept that is not limited to functioning but encompasses subjective well-being and life satisfaction (6) in line with the approach proposed by the World Health Organization (WHO). Thus, QoL is a multidimensional construct defined as "the individual's perception of his or her position in life in the context of the culture and value system in which he or she lives, and in relation to his or her goals, expectations, norms, and concerns" (7).

Two points deserve particular attention when exploring trajectories of QoL from childhood to adulthood in people with childhood-onset disabilities. First, QoL explores subjective well-being across a range of domains that vary in relevance over time, necessitating the use of age-appropriate instruments. Second, because QoL measurement is weighted by the respondent's internal norms and values, having functional limitations does not systematically mean poor QoL for a given individual (6, 8). Previous studies have nonetheless shown that people with disabilities or chronic conditions report lower QoL scores as a group than the general population. However, the difference varies in magnitude depending on the context, suggesting that these differences may be more related to personal and environmental factors (personal resources, mental health, social support, and socioeconomic status) than to disability (9).

There has been little research on QoL in young adults with CP and even less on change in QoL from childhood. From studies carried out in children and adolescents, we know that pain is a factor strongly associated with a reduced QoL and that severity of impairment and associated conditions also negatively influence QoL (10–15). Deterioration in mobility, high rates of pain, and mental health problems have been observed in young adults with CP (16–20) and justify study of the impact of functional deterioration on QoL in a changing context for these persons who have new expectations and concerns (such as living independently or having romantic and intimate relationships). In addition, from a clinical perspective, it would be interesting to better understand the impact of disability on change in QoL across the life span and to identify what early factors, if any, can limit the deterioration of QoL. To the best of our knowledge, only one Dutch study (21) has explored QoL trajectories from childhood to transition to adulthood in individuals with CP, but it had several limitations. One of these was that it did not include young adults with intellectual disabilities. Overall, it is a major limitation of the existing literature that individuals with the most severe phenotypes are often excluded, notably because of their inability to self-report their QoL. Many authors have raised concerns about proxy-patient reporting, such as its lack of reliability and accuracy, particularly when exploring social or emotional domains (22–24). This leads to a poor representation of this population in studies.

The SPARCLE study aims to document the impact of personal and environmental factors on QoL, with the explicit goal of allowing all individuals with CP to contribute regardless of their severity profile. In this analysis, using longitudinal data from the European SPARCLE cohort, we sought to identify how the QoL of individuals with CP evolves from childhood to young adulthood and whether the severity of impairment and frequency of pain and seizures affect their QoL. We also aimed to determine whether different shapes of QoL trajectories exist in order to better understand the impact of impairment and comorbidities on QoL.

METHODS

Study Design and Population

The SPARCLE cohort is a multicenter European observational population-based study designed to investigate the role of a comprehensive set of environmental factors and the contribution of health care to social participation and QoL in individuals with CP. The eligible population consisted of individuals born between 1991 and 1997, with a diagnosis of CP according to the Surveillance of Cerebral Palsy in Europe network (SCPE) definition (25). This cohort followed up individuals with CP in three targeted life periods, namely, childhood, adolescence, and young adulthood. The study design has previously been described in detail elsewhere (26).

Initially, the SPARCLE cohort randomly sampled children with CP (aged 8–12 years in 2004–2005, SPARCLE1) from population-based registers in eight European regions with an overrepresentation of the most severe cases and from several independent sources in an additional region. These individuals were followed up when they were adolescents (aged 13–17 years in 2009–2010, SPARCLE2), while an additional sample was recruited in order to maintain statistical power for the third wave of follow-up in young adulthood. The third wave included participants with CP (aged 22–27 years in 2018–2020, SPARCLE3) and was implemented in five of the nine European regions initially involved, namely, southwest and southeast France (departments of Haute-Garonne and Isère), northwest Germany, western Sweden (Göteborg region), and central Italy (Viterbo area).

In the above regions, 387 children were enrolled during the first wave. Among them, 278 (72%) agreed to participate in SPARCLE2, and a supplementary sample of 29 adolescents was recruited. At that stage, all participants gave their permission for further contact. Of the 416 individuals with CP who had previously taken part in at least one of the first two waves of the

Abbreviations: BFMF, Bimanual Fine Motor Function; CI, confidence interval; CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; HRQoL, health-related quality of life; IQ, intelligence quotient; MS, mean score; OR, odds ratio; QoL, quality of life; SCPE, Surveillance of Cerebral Palsy in Europe network; SPARCLE, Study of PARticipation of children with Cerebral palsy Living in Europe; WHO, World Health Organization.

SPARCLE cohort, 14 were excluded because their date of birth did not fit the eligibility criteria. Thus, 402 individuals with CP who had previously participated at least once in the SPARCLE cohort were eligible for SPARCLE3 (**Figure 1**).

Dropout

The SPARCLE cohort has been prone to non-response ($n = 226$) due to non-traceability, refusal to participate, or death. To identify factors potentially associated with dropout, we tested separately the following variables collected at inclusion using unconditional logistic regressions adjusted for gender and region: severity of gross motor function impairment [measured with the Gross Motor Function Classification System (GMFCS) (27)], cognitive functioning [estimation of the intelligence quotient (IQ)], parental characteristics [parental educational qualification and parenting stress index (28)], and family structure (combining parental marital status and lifestyle). In addition, we searched for potential interactions with region. We observed a significant increase in dropout rate among individuals with at least one parent who did not complete secondary education (37.6% in individuals who dropped out of the study and 25.0% in participants, odds ratio (OR) 4.0, 95% confidence interval (CI) 1.9–8.4 (**Supplementary Material 1**).

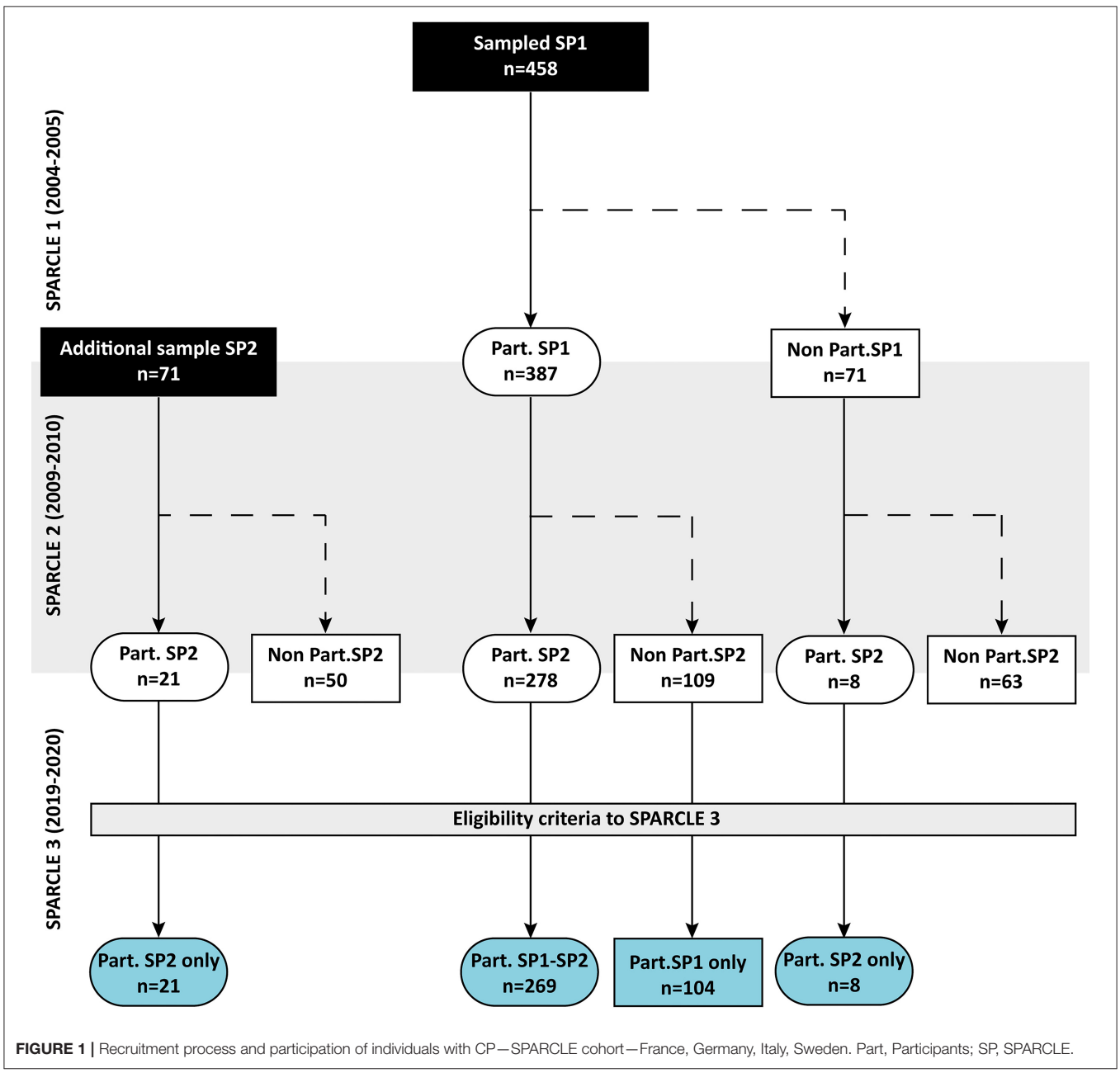

FIGURE 1 | Recruitment process and participation of individuals with CP—SPARCLE cohort—France, Germany, Italy, Sweden. Part, Participants; SP, SPARCLE.

Data Collection

In all waves of the SPARCLE follow-up, trained research associates conducted standardized home interviews under identical conditions in each region of the study. Whenever possible, the questionnaire was self-completed, with the interviewer's assistance if necessary. In cases where self-report was not possible, even with help, the interview was conducted with an individual (parent, personal assistant, and partner) who knew the person with CP very well (i.e., they were significantly involved in their daily life).

As in previous waves, the questionnaire used in SPARCLE3 was administered with a logical flow and in a fixed order and elicited information on sociodemographics, physical impairment, comorbidities associated with CP, personal medical history, QoL, social participation, and environment (26). With regard to QoL, as context and expectations evolve along the life span, measurements were carried out using validated age-appropriate instruments. For childhood and adolescence, QoL was measured using the KIDSCREEN-52 (29), a generic instrument measuring 10 dimensions of health-related QoL, while young adults with CP completed the WHOQOL-Bref questionnaire (30) with 24 items measuring their QoL in four areas. Both instruments cover three comparable domains of QoL, namely, physical well-being, psychological well-being, and social relationships. As one item used to measure physical well-being with the KIDSCREEN instrument was adapted for persons with CP in the version used in children and adolescents (14), this paper focused on the psychological well-being and social relationships domains. In both domains, the two instruments have a comparable number of items and response modalities; and a raw QoL score of 0–100 is obtained, with a higher score indicating a higher QoL (**Supplementary Material 2**).

In all waves of the SPARCLE cohort, we collected information on participants' walking ability (GMFCS), fine motor skills [Bimanual Fine Motor Function (BFMF)] (31), frequency of pain in the previous week, and seizures in the year predating the interview. At inclusion, intellectual ability was assessed either with formal IQ testing or using an algorithm based on a set of questions to child's parents (32) and thereafter categorized as dichotomous variable ($<70/\geq 70$), while the subtype of CP was available from the registers.

Statistical Analyses

Of the SPARCLE3 participants ($n = 176$), 12 individuals who were out of the targeted age range at the time of interview (<22 or >27 years old) were excluded *a posteriori* from analysis.

Each of the two QoL domains was analyzed separately. We first described the distribution of QoL reported in childhood, adolescence, and young adulthood. To estimate the mean variation of raw QoL scores by age from childhood to young adulthood, we used a generalized linear mixed-effect model with random intercept (SAS 9.4, SAS Institute Inc., Cary, NC, USA) adjusted for parental education level at inclusion in order to limit non-response effects. All models were also adjusted for sex and region. In order to identify factors potentially associated with QoL variation from childhood to young adulthood, we added separately to the previous model the following variables: pain frequency in the previous week, seizures in the previous year, GMFCS, BFMF (all measured in each wave of follow-up), and IQ and CP subtypes (measured at inclusion). We also tested for interaction with age. A multivariate model that controlled for significant variables and interaction with age ($p < 0.20$) was performed. A descending step-by-step method was applied in order to reduce this model. The criterion for statistical significance was $p < 0.05$. To evaluate the impact of type of reporting on our results, we performed sensitivity analyses by excluding young adults with CP who were unable to self-respond to the questionnaire.

Then, in order to identify potential different trajectories of QoL variation from childhood to adulthood, we used a shape-based clustering method (kmlShape, R package v0.9.5, Genolini, 2016) that uses Fréchet means and Fréchet distances. This method uses a set of several parametric and non-parametric criteria [such as Calinski–Harabasz, Ray–Turi, Davies–Bouldin, Bayesian information criterion (BIC), and Akaike information criterion (AIC)] to determine the correct number of clusters (33). Individuals with CP who participated in all waves of the SPARCLE cohort were selected. Due to the small number of individuals in each identified cluster, we performed only descriptive analysis to determine whether profiles of individuals with CP identified in these clusters of QoL trajectories may be defined by impairment characteristics in childhood, adolescence, and young adulthood. We therefore considered pain frequency in the previous week, seizures in the previous year, GMFCS, BFMF, IQ (childhood only), and CP subtype (childhood only).

RESULTS

Our longitudinal sample included 164 young adults with CP (40.8% of eligible subjects) of whom more than two-thirds self-reported (with or without assistance) to the SPARCLE 3 questionnaire ($n = 111$, 67.7%). A total of 130 subjects participated in all the waves of the SPARCLE cohort with a similar self-report rate ($n = 89$, 68.5%).

Sociodemographic and Impairment Characteristics

Young adults assessed in our SPARCLE3 longitudinal sample had a mean age of 24.3 years [standard deviation (SD) $\pm$ 1.6 years] at the time of interview, with a male-to-female ratio of 1.2. A large majority (77.4%) lived in urban or semi-urban areas (population $\geq$3,000 inhabitants), less than a third (29.3%) lived independently (alone, with a partner, or in cohabitation), and less than half (44.5%) were employed or in education when interviewed. Individuals who participated in all waves of the SPARCLE cohort had similar sociodemographic characteristics (**Table 1**).

The CP subtypes were spastic 75.6%, dyskinetic 16.5%, and ataxic 7.3%. At inclusion, 32.3% of participants had severe gross motor function limitations (GMFCS IV–V), 24.4% had

TABLE 1 | Sociodemographic characteristics of young adults with CP: SPARCLE cohort—France, Germany, Italy, and Sweden.

	All participants ($n = 164$)		Participants in all waves ($n = 130$)	
	N	%	*n*	%
Region				
Southeast France	37	22.6	20	15.4
Southwest France	29	17.7	22	16.9
Northwest Germany	49	29.9	42	32.3
Central Italy	20	12.2	17	13.1
Western Sweden	29	17.7	29	22.3
Sex				
Male	90	54.9	72	55.4
Female	74	45.1	58	44.6
Age (years)				
22	31	18.9	24	18.5
23	21	12.8	11	8.5
24	37	22.6	34	26.1
25	37	22.6	33	25.4
26	20	12.2	15	11.5
27	18	10.9	13	10.0
Means (SD)	24.3	(1.6)	24.3	(1.5)
Parental education level				
Did not complete secondary education	40	24.4	30	23.1
Secondary education	99	60.4	79	60.8
Tertiary education	25	15.2	21	16.1
Size of unit of residence (inhabitants)				
<3,000	36	22.0	31	23.8
3,000–200,000	63	38.4	49	37.7
>200,000	64	39.0	49	37.7
Missing	1	0.6	1	0.8
Lifestyle				
Living with partner	12	7.3	11	8.5
Living alone	31	18.9	23	17.7
Living in cohabitation	5	3.1	5	3.9
Living with parents	90	54.9	73	56.1
In care facilities	23	14.0	16	12.3
Other	3	1.8	2	1.5
Current activity				
Paid work	48	29.3	38	29.2
Non-paid work	4	2.4	2	1.5
In education	21	12.8	18	13.9
Unemployed	17	10.4	14	10.8
Permanently sick or disabled	45	27.4	32	24.6
Other	29	17.7	26	20.0

CP, cerebral palsy; SD, standard deviation.

severe BFMF impairment (BFMF IV–V), 51.8% had intellectual impairment (IQ < 70), and 18.3% had seizures in the previous year. Level of impairment and associated conditions remained stable over time. More than two episodes of pain in the week prior to inclusion were reported by 32.3% of participants. No between-region heterogeneity was found for any of these variables (**Table 2**).

Quality of Life

Table 3 and **Figure 2** present the distribution of QoL reported in childhood (T1), adolescence (T2), and young adulthood (T3) for the psychological well-being and social relationships domains. Median scores were >60 for each domain in young adulthood, with a wider variation for social relationships. From childhood to young adulthood, psychological well-being showed a significant linear decrease by an average of 0.78 points per year (95% CI −0.99 to −0.56), whereas QoL in the social relationships domain showed a significant linear increase by an average of 1.24 points per year (95% CI 0.92 to 1.55; models adjusted for region, sex, and parental level of education). Similar variations were found in the group of individuals who participated in all waves (**Table 3**).

The β coefficients in **Table 4** show average variations in QoL by impairment severity, seizure problems, and pain. Whatever their age, individuals with the more severe phenotypes of CP reported, on average, a lower QoL for psychological well-being and, more importantly, for social relationships compared with those less severely impaired. The severity of motor impairment significantly affected QoL in social relationships but had no significant effect on psychological well-being. On the contrary, IQ and seizures had a significant impact in both domains. In the final multivariate models, individuals with the most severe BFMF limitation (groups II–III and IV–V) reported significantly impaired QoL as compared with those without limitation (BFMF I) in the social relationships domain of 5.85 points (95% CI −11.08 to −0.63) and 8.49 points (95% CI −15.03 to −1.96), respectively. Similarly, seizures were significantly associated with lower QoL in the social relationships domain (β −10.60, 95% CI −16.61 to −4.48). Individuals with an IQ <70 had a lower QoL in psychological well-being (β −4.33, 95% CI −8.06 to −0.60) and in social relationships (β −9.44, 95% CI −14.74 to −4.14). Frequent pain was associated with a lower QoL only in psychological well-being (β −6.27, 95% CI −9.71 to −2.83). The associated factors identified in the multivariate models explained around 16 and 18% (R^2) of the variation of QoL in the psychological well-being and social relationships domains, respectively.

The clustering method revealed various shapes of QoL trajectories in both domains. For psychological well-being (**Figure 3A**), two groups of individuals showed a parallel trajectory, with a slight decrease of QoL during adolescence before stabilization in young adulthood. However, one group started with a high QoL in childhood (Group 1, $n = 67$ (54.5%), T1 QoL mean score (MS) = 87.1, T3-MS = 68.5), while the other had a moderate QoL in childhood (Group 2, $n = 22$ (17.9%), T1-MS = 68.6, T3-MS = 45.5). A third group, which comprised about one-quarter of the sample ($n = 34$, 27.6%), had a different profile, with low QoL during childhood, an increase during adolescence, and stabilization in young adulthood at a level close to that of Group 1 (T1-MS = 52.6; T3-MS = 64.0). Individuals who had moderate and low psychological well-being in childhood seemed to have more frequent seizures (22.7 and 20.6% in Groups 2 and 3, respectively) and pain (45.5 and 44.1%

TABLE 2 | Impairment characteristics of young adults with CP: SPARCLE cohort—France, Germany, Italy, and Sweden.

	All participants								Participants in all waves					
	Inclusion* (*n* = 164)		Childhood (*n* = 147)		Adolescence (*n* = 147)		Adulthood (*n* = 164)		Childhood (*n* = 130)		Adolescence (*n* = 130)		Adulthood (*n* = 130)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
GMFCS														
I–II	81	49.4	71	48.3	75	51.0	82	50.0	64	49.2	65	50.0	67	51.5
III	30	18.3	29	19.7	20	13.6	20	12.2	23	17.7	19	14.6	16	12.3
IV–V	53	32.3	47	32.0	52	35.4	62	37.8	43	33.1	46	35.4	47	36.2
Bimanual Fine Motor Function														
I. Without restriction//limitation	49	29.9	40	27.2	47	32.0	50	30.5	38	29.2	38	29.2	41	31.5
II–III. Moderate restrictions	75	45.7	70	47.6	70	47.6	68	41.5	60	56.2	65	50.0	53	40.8
IV–V. Severe restrictions	40	24.4	37	25.2	30	20.4	46	28.0	32	24.6	27	20.8	36	27.7
Intellectual impairment*														
≥70	77	47.5	-	-	-	-	-	-	66	51.2	-	-	-	-
<70	85	52.5	-	-	-	-	-	-	63	48.8	-	-	-	-
Missing	2		-	-	-	-	-	-	1		-	-	-	-
Seizures in the previous year														
No seizures (with or without medication)	134	81.7	119	80.9	117	79.6	135	82.3	106	81.5	102	78.5	110	84.6
Seizures	30	18.3	28	19.1	30	20.4	29	17.7	24	18.5	28	21.5	20	15.4
Frequency of pain in previous week														
None	67	41.4	60	41.4	45	31.0	46	28.2	53	41.1	38	29.5	36	27.9
Once or twice	42	25.9	38	26.2	33	22.8	35	21.5	31	24.0	29	22.5	27	20.9
Frequent	53	32.7	47	32.4	68	46.9	82	50.3	45	34.9	62	48.0	66	51.2
Missing	2		2		1		1		1		1		1	
Cerebral palsy subtype*														
Unilateral spastic	51	31.3	-	-	-	-	-	-	41	31.5	-	-	-	-
Bilateral spastic	73	44.8	-	-	-	-	-	-	59	45.4	-	-	-	-
Dyskinetic	27	16.6	-	-	-	-	-	-	23	17.7	-	-	-	-
Ataxic	12	7.4	-	-	-	-	-	-	7	5.4	-	-	-	-
Missing	1		-	-	-	-	-	-	0		-	-	-	-

CP, cerebral palsy; GMFCS, Gross Motor Function Classification System.

**Data provided at inclusion in the SPARCLE cohort in childhood (n = 147) or in adolescence (n = 17).*

TABLE 3 | Distribution and variation of QoL of individuals with CP from childhood to young adulthood: SPARCLE cohort—France, Germany, Italy, and Sweden.

	All participants ($n = 164$)		Participants in all waves ($n = 130$)	
	Psychological well-being	**Social relationships**	**Psychological well-being**	**Social relationships**
Childhood				
n	142	140	123	119
Mean (SD)	73.9 (18.1)	50.2 (26.7)	74.2 (18.6)	51.3 (26.2)
[Min–max]	[20.0–100.0]	[0.0–100.0]	[20.0–100.0]	[0.0–100.0]
Adolescence				
n	144	143	123	119
Mean (SD)	71.1 (20.7)	53.5 (27.5)	73.5 (19.2)	56.7 (26.7)
[Min–max]	[0.0–100.0]	[0.0–100.0]	[16.7–100.0]	[0.0–100.0]
Young adulthood				
n	155	160	123	119
Mean (SD)	61.7 (13.2)	66.7 (20.8)	63.1 (12.5)	68.3 (19.5)
[Min–max]	[25.0–87.5]	[0.0–100.0]	[25.0–87.5]	[8.3–100.0]
Change in QoL scores*				
β	−0.78	1.24	−0.81	1.12
[95% CI]	[−0.99 to −0.56]†	[0.92 to 1.55]†	[−1.04 to −0.58]†	[0.79 to 1.46]†

QoL, quality of life; CP, cerebral palsy.

**β coefficients and 95% CI estimated by generalized linear mixed-effect model with random intercept adjusted for region, sex, and parental education level. β coefficients show the average difference in quality of life by 1 year of age. †95% CI excluding zero.*

in Groups 2 and 3, respectively) in childhood than those in Group 1 with high initial QoL (10.4% had seizures and 23.9% had frequent pain). Individuals in Group 3 had a similar distribution of seizures and pain in adolescence as in childhood, whereas those in Group 2 reported more frequent seizures and pain in adolescence than in childhood. In Group 2 and Group 3, we observed a marked increase in the proportion of young adults who reported frequent pain, while seizures seemed to be less frequent than in adolescence (**Table 5**). Three clusters of trajectories were also identified for the social relationships domain (**Figure 3B**). The first two clusters showed an increase in QoL during adolescence that continued in a slight degree during young adulthood for Group 1 ($n = 65$, 54.6%) and became stable for Group 2 ($n = 38$, 32.8%). But these two groups had an entirely different profile in childhood, with moderate QoL in Group 1 (T1-MS = 63.8) and a very low QoL in Group 2 (T1-MS = 23.6). A third group (Group 3, $n = 16$, 13.5%) had a moderate QoL in childhood (T1-MS 66.1) that markedly decreased until early young adulthood (T3-MS = 46.9). Young adults in Group 2 had more severe phenotypes (higher proportions of GMFCS IV–V, BFMF III–V, IQ < 70, and seizures) than those in Group 1. No differences were observed between Groups 1 and 3 for impairments in adolescence, while the proportion of individuals with frequent pain markedly increased in Group 3 and the proportion of individuals who experienced seizures decreased in Group 2 between adolescence and young adulthood (**Table 5**).

In our sensitivity analyses, long-term trajectories did not change after excluding individuals with proxy responses. The associations between frequency of pain and psychological well-being and between seizures and social relationships were still observed. Conversely, there was no longer an association between BFMF and social relationships, whereas intellectual disability was no longer associated with lower QoL in either domain.

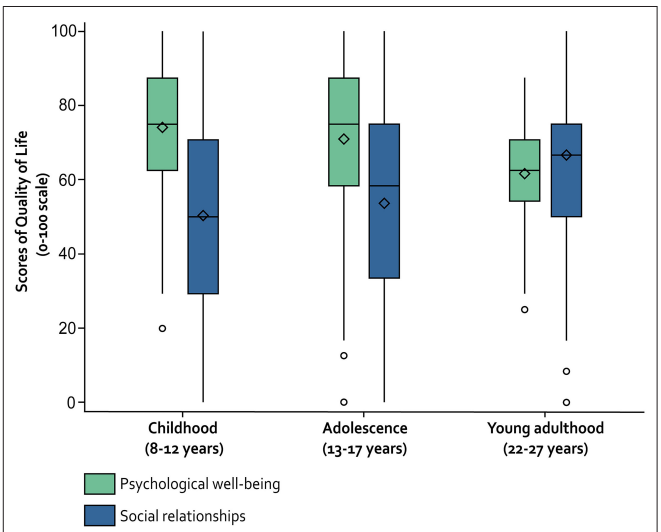

FIGURE 2 | Distribution of QoL scores of individuals with CP from childhood to young adulthood—SPARCLE cohort—France, Germany, Italy, Sweden.

DISCUSSION

In this longitudinal analysis of the SPARCLE cohort, we observed that QoL in individuals with CP linearly decreased

TABLE 4 | Average variations (by 1 year of age) in QoL by impairment severity, pain, and seizure problems in individuals with CP: SPARCLE cohort—France, Germany, Italy, and Sweden.

	Psychological well-being		Social relationships	
	β^a	95% CI[b]	β^a	95% CI[b]
Models considering each impairment separately*				
GMFCS				
I–II	0.00	Ref.	0.00	Ref.
III	−2.50	[−7.52 to 2.52]	−3.74	[−10.89 to 3.42]
IV–V	−2.06	[−6.14 to 2.03]	−7.72	[−13.50 to −1.93]†
BFMF				
I	0.00	Ref.	0.00	Ref.
II–III	−0.65	[−4.39 to 3.09]	−7.99	[−13.34 to −2.65]†
IV–V	−4.28	[−8.94 to 0.39]	−12.42	[−18.94 to −5.89]†
IQ				
≥70	0.00	Ref.	0.00	Ref.
<70	−3.99	[−7.85 to −0.13]†	−13.50	[−18.70 to −8.30]†
Seizure in the previous year				
No (with or without medication)	0.00	Ref.	0.00	Ref.
Seizures	−5.22	[−9.47 to −0.98]†	−14.16	[−20.11 to −8.21]†
Frequency of pain in the previous week				
None	0.00	Ref.	0.00	Ref.
Once or twice	−1.44	[−5.25 to 2.37]	0.59	[−5.01 to 6.18]
Frequent	−6.08	[−9.52 to −2.63]†	−4.19	[−9.28 to 0.91]
Multivariate model*				
BFMF				
I			0.00	Ref.
II–III			−5.85	[−11.08 to −0.63]†
IV–V			−8.49	[−15.03 to −1.96]†
IQ				
≥70	0.00	Ref.	0.00	Ref.
<70	−4.33	[−8.06 to −0.60]†	−9.44	[−14.74 to −4.14]†
Seizure in the previous year				
No (with or without medication)			0.00	Ref.
Seizures			−10.60	[−16.71 to −4.48]†
Frequency of pain in the previous week				
None	0.00	Ref.		
Once or twice	−1.28	[−5.09 to 2.53]		
Frequent	−6.27	[−9.71 to −2.83]†		
R^2 (%)	15.85		17.95	

BFMF, Bimanual Fine Motor Function; GMFCS, Gross Motor Function Classification System; IQ, intelligence quotient; QoL, quality of life; CP, cerebral palsy.

**All generalized linear mixed-effect model with random intercept models were adjusted for region, sex, and parental education level.*

[a] β coefficients show the average difference in quality of life between the relevant category and the reference category (Ref.). β coefficients <0 indicate a lower quality of life in the relevant category compared with the reference category.

[b] CIs were calculated by bootstrapping.

† 95% CI excluding zero.

from childhood to young adulthood in the domain of psychological well-being, whereas it linearly increased in social relationships. Severity of impairment was associated with reduced QoL in all life phases studied (childhood, adolescence, and young adulthood): motor impairment with social relationships, and intellectual impairment with psychological well-being and social relationships. At all time periods, frequent pain reduced psychological well-being, and seizures were associated with poorer QoL in the social relationships domain. Using clustering methods, we identified a group of young adults with CP who presented a reverse pattern to the overall trajectory of QoL in both domains.

To our knowledge, our study is the first to investigate long-term trajectories of QoL in young people with CP from childhood to early adulthood using individual longitudinal data. A Dutch study by Tal et al. also investigated long-term trajectories of QoL dimensions related to psychological and social functioning but

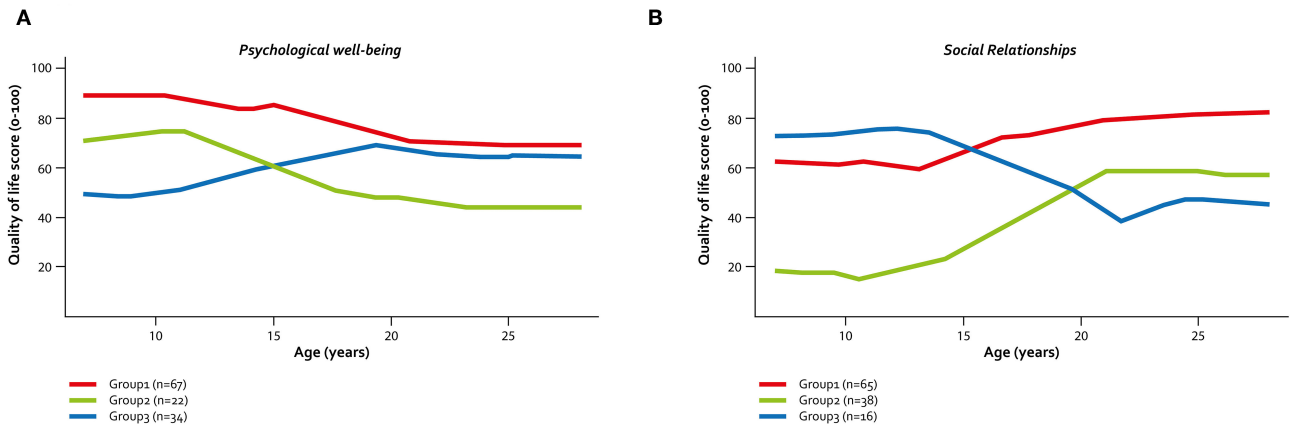

FIGURE 3 | Identified QoL trajectories in individuals with CP. **(A)** QoL trajectories in psychological well-being. **(B)** QoL trajectories in social relationships—SPARCLE cohort—France, Germany, Italy, Sweden.

reconstituted a longitudinal sequence with four neighboring 4-year follow-up cohorts: toddlers ($n = 97$), children ($n = 116$), adolescents ($n = 108$), and young adults ($n = 103$) (21). Unlike our findings, QoL in the domains of psychological and social functioning did not change significantly over time. Apart from study design, a series of differences between the two studies may explain the divergent results. Whereas, Tal et al. considered aspects of life directly influenced by disability, health problems, or treatments (4, 5), we used a broader definition of subjective QoL that encompassed the concept of holistic well-being (6). Although QoL and HRQoL reflect the individual's subjective perception of their position in life (30), these outcomes are substantially different (34, 35). In addition, the sample used by Tan et al., consisting of individuals with CP recruited from rehabilitation centers, had less severe impairment than those in our study and did not include young adults with intellectual disabilities. However, our results relating to long-term trajectories of QoL were unchanged when we excluded from analysis young adults with intellectual disabilities or those with proxy reports (94% with intellectual disability, 60% with GMFCS IV–V). Interestingly, we demonstrated that change in QoL with age was not one-directional. Our clustering analysis showed that 26.2 and 12.3% of the study population displayed a reverse trajectory of QoL in the psychological well-being and social relationships domains, respectively, as compared with their peers. Inclusion in these groups did not appear to be related to a specific profile of disability severity. The proportion of proxy reports did not significantly differ between these particular groups and the other two groups. Nevertheless, because of the small size of the groups, we were not able to investigate whether these reverse QoL trajectories were determined by specific factors. In young adults with CP, the association between severity of motor impairment and QoL appears to depend on the domain considered. Three cross-sectional studies investigated the association between GMFCS levels and psychological well-being (17, 36, 37) and reported conflicting results. Although they all used the concept of HRQoL, two studies showed no significant difference in perceived mental health across the range of GMFCS levels (36, 37), in agreement with our findings, whereas one study (17) showed that young adults with the most severe gross motor function impairments (GMFCS III–V) were more likely to have better perceived mental health than those less severely impaired (GMFCS I–II). On the other hand, our findings suggesting that severe motor impairment may affect the subjective perception of social relationships during childhood, adolescence, and young adulthood are not consistent with the findings of Tan et al. (21). While analysis of the SPARCLE data collected in childhood and adolescence identified GMFCS as a factor associated with QoL in the social relationships domain (14), it is interesting to note that fine motor function appears to have a more determining role for social interaction in young adults with CP. However, this association disappeared when individuals who proxy-reported their QoL were excluded (sensitivity analyses). The interpretation of these latter results is difficult. First, they may point to a specific social condition of individuals with the most severe profiles. Second, we cannot exclude that our findings may be supported by under- or overestimation of QoL in the social relationships domain due to proxy responses. Individuals reporting on behalf of another person often have a substantially different perspective on the QoL domain under consideration (23). To our knowledge, identification of intellectual impairment and seizures as factors associated with lower QoL in the social relationships domain from childhood to young adulthood has never previously been reported in the literature. Interestingly, these associated factors have previously been identified as determinants of non-inclusion at school (38), whereas severe intellectual impairment and seizures have also been reported as factors associated with unemployment (39–42). Because a recent qualitative study has highlighted the relationship between social participation and

TABLE 5 | Distribution of impairment severity, pain, and seizure problems from childhood to young adulthood by identified QoL trajectories in individuals with CP: SPARCLE cohort—France, Germany, Italy, and Sweden.

	Psychological well-being						Social relationships					
	Group 1 (*n* = 67)		Group 2 (*n* = 22)		Group 3 (*n* = 34)		Group 1 (*n* = 65)		Group 2 (*n* = 38)		Group 3 (*n* = 16)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Childhood												
GMFCS												
I–II	32	47.8	14	63.6	15	44.1	37	56.9	15	39.5	8	50.0
III	12	17.9	3	13.6	7	20.6	12	18.5	7	18.4	2	12.5
IV–V	23	34.3	5	22.7	12	35.3	16	24.6	16	42.1	6	37.5
BFMF												
I	20	29.8	9	40.9	9	26.5	27	41.5	6	15.8	4	25.0
II–III	32	47.8	10	45.5	16	47.0	28	43.1	20	52.6	9	56.2
IV–V	15	22.4	3	13.6	9	26.5	10	15.4	12	31.6	3	18.8
IQ*												
≥70	35	52.2	10	45.4	20	58.8	44	67.7	12	31.6	8	50.0
<70	32	47.8	12	54.6	14	41.2	21	31.3	26	68.4	8	50.0
Seizure in the previous year												
No (with or without medication)	60	89.6	17	77.3	27	79.4	57	87.7	27	71.0	16	100.0
Seizures	7	10.4	5	22.7	7	20.6	8	12.3	11	29.0	0	0.0
Frequency of pain in the previous week												
None	35	53.0	7	31.8	10	29.4	24	37.5	21	55.3	7	43.8
Once or twice	15	22.7	5	22.7	9	26.5	16	25.0	7	18.4	6	37.5
Frequent	16	24.3	10	45.5	15	44.1	24	37.5	10	26.3	3	18.7
Missing	1		0		0		1		0		0	
CP subtype*												
Unilateral spastic	15	22.4	10	45.4	13	38.2	24	36.9	8	21.1	5	31.3
Bilateral spastic	34	50.7	8	36.4	15	44.1	31	47.7	15	39.5	9	56.2
Dyskinetic	13	19.4	2	9.1	6	17.7	7	10.8	11	28.9	2	12.5
Ataxic	5	7.5	2	9.1	0	0.0	3	4.6	4	10.5	0	0.0
Adolescence												
GMFCS												
I–II	31	46.3	14	63.6	18	52.9	37	56.9	17	44.7	8	50.0
III	12	17.9	1	4.6	4	11.8	11	16.9	4	10.5	2	12.5
IV–V	24	35.8	7	31.8	12	35.3	17	26.2	17	44.7	6	37.5
BFMF												
I	20	29.9	7	31.8	11	32.4	26	40	6	15.8	5	31.2
II–III	36	53.7	13	59.1	13	38.2	32	49.2	20	52.6	8	50.0
IV–V	11	16.4	2	9.1	10	29.4	7	10.8	12	31.6	3	18.8
Seizures in the previous year												
No (with or without medication)	60	89.5	14	63.6	26	76.5	57	87.7	25	65.8	14	87.5
Seizures	7	10.5	8	36.4	8	23.5	8	12.3	13	34.2	2	12.5
Frequency of pain in the previous week												
None	23	34.3	3	13.6	11	32.3	21	32.3	11	28.9	5	31.2
Once or twice	17	25.4	6	27.3	6	17.7	11	16.9	11	28.9	5	31.2
Frequent	27	40.3	13	59.1	17	50.0	33	50.8	16	42.2	6	37.5
Young adulthood												
GMFCS												
I–II	35	52.2	12	54.5	17	50.0	40	61.5	17	44.7	7	43.8
III	10	14.9	2	9.1	3	8.8	8	12.3	4	10.6	3	18.7
IV–V	22	32.9	8	36.4	14	41.2	17	26.2	17	44.7	6	37.5

(Continued)

TABLE 5 | Continued

	Psychological well-being						Social relationships					
	Group 1 (*n* = 67)		Group 2 (*n* = 22)		Group 3 (*n* = 34)		Group 1 (*n* = 65)		Group 2 (*n* = 38)		Group 3 (*n* = 16)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
BFMF												
I	21	31.3	7	31.8	13	38.2	29	44.6	7	18.4	4	25.0
II–III	28	41.8	10	45.5	11	32.4	26	40.0	16	42.1	8	50.0
IV–V	18	26.9	5	22.7	10	29.4	10	15.4	15	39.5	4	25.0
Seizures in the previous year												
No (with or without medication)	62	92.5	16	72.7	29	85.3	63	96.9	26	68.4	14	87.5
Seizures	5	7.5	6	27.3	5	14.7	2	3.1	12	31.6	2	12.5
Frequency of pain in the previous week												
None	27	40.3	2	9.1	5	14.7	16	24.6	15	39.5	2	12.5
Once or twice	16	23.9	5	22.7	5	14.7	17	26.2	5	13.1	2	12.5
Frequent	24	35.8	15	68.2	24	70.6	32	49.2	18	47.4	12	75.0

BFMF, Bimanual Fine Motor Function; GMFCS, Gross Motor Function Classification System; IQ, intelligence quotient; CP, cerebral palsy.
**Data only provided in childhood.*

QoL (43), it is possible that the factors associated with lower QoL in the social relationships domain identified in this study indirectly reflect limited access to education or employment or, more generally, restrictions on social participation. Given that pain has been shown to be strongly associated with reduced psychological QoL in childhood and adolescence (12–14), it was not surprising to observe that this association continued in young adulthood. This finding confirms the importance of addressing pain across the life span in people with CP, especially as the prevalence of frequent pain is high regardless of age (44–49). In addition, fatigue frequently co-occurring with pain (48, 50) should be considered in further analyses of the role of pain. Our models for QoL in the psychological well-being and social relationships domains explained 16 and 18%, respectively, of the variance in outcome, which may seem low. However, this is not surprising because from childhood to early adulthood, people with CP face numerous and complex barriers that can impact QoL, and these barriers are not limited to the severity of impairment and the presence and frequency of pain (51–53). The SPARCLE cohort is, to the best of our knowledge, the largest prospective study of people with CP from childhood to young adulthood. Our sample was selected from European population-based registries or various sources in northwest Germany, thus limiting selection bias. We purposely overrepresented the most severe forms of CP to investigate this less common group in depth. However, our choice calls into question the external validity of our findings, notably for QoL trajectories. Moreover, we cannot exclude that dropouts during follow-up led to the exclusion of the most severe cases. All analyses were adjusted for the predictors of non-response identified in this study to limit the impact of dropout. Despite these potential differential errors, it is interesting to note that the participants in the SPARCLE cohort who contributed to the third wave had a similar distribution of impairment and seizures when they were children as the individuals born between 1990 and 2006 and recorded by the SCPE (54).

No instrument has been developed to adequately measure QoL over such a wide age range. Therefore, we used two different instruments based on the same concept and the WHO definition (7). As mentioned earlier, these two instruments presented the advantage of having a comparable number of items and response modalities, and of providing QoL scores on a 0–100 scale. Nevertheless, we cannot be sure that this choice is valid for bridging the age gap between adolescence and young adulthood. First, it is likely that the two instruments have different Rasch scaling. Therefore, it would have been better to use transformed Rasch scores that take into account discriminant ability of items rather than raw scores as we did. However, we were limited by the lack of data on the psychometric properties and population norms of the WHOQOL-Bref in our specific population of European young adults, whereas Rasch scores exist for the KIDSCREEN-52 and were constructed to meet the population norms of European children and adolescents (mean = 50, SD = 10) (29). We considered additional analyses to explore this point, but none seemed satisfactory. Among them, use of the KIDSCREEN index, a short form of the KIDSCREEN-52, which was collected in all waves of this study, was considered; but unfortunately, this instrument only measures overall QoL and not domain-specific QoL. The exact opposite is true for the WHOQOL-Bref. This limited our ability to use the KIDSCREEN index as a validation tool in our study. Finally, we performed the analyses by pooling self-reports and proxy reports to describe QoL across the whole range of severity of our population, considering that regardless of the respondent, the report was the best available estimate of QoL. We cannot rule out a potential for under- or overestimation of QoL when using proxy reports (23). But the majority of our findings did not change when proxy

reports were excluded from our sensitivity analyses, reducing the impact of this limitation. Only the association between BFMF and QoL in the social relationships domain was no longer significant, which may nuance our findings in this particular domain. Furthermore, given that the majority of individuals with intellectual disability (IQ < 70) was in the proxy-reporting group ($n = 50/85$, 58.9%) while almost all of those with an IQ ≥ 70 were able to answer the questionnaire themselves ($n = 75/77$, 97.4%), the significant impact of intellectual disability on QoL trajectories observed in the total sample was no longer significant when the analyses were restricted to self-reports.

CONCLUSION

Identification of QoL trajectories and their associated factors improves our knowledge of the experience of individuals with CP up till young adulthood. Further studies are needed to better understand which of the disability, personal, and contextual factors have the most influence on the differently shaped long-term trajectories of QoL.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: dataset is accessible after submission of a scientific project and approval of the project by the investigators of each participating country. Requests to access these datasets should be directed to Catherine Arnaud, catherine.arnaud@univ-tlse3.fr.

ETHICS STATEMENT

The relevant Ethics and Regulatory authorizations were sought in each country and the study fully approved by the below: France: The data were collected and stored in accordance with the reference methodology MR003 [Declaration No. 2205849 at the Commission for Data Protection and Liberties (CNIL)] each patient having been informed individually of the research under Article L1122-1 of the Public Health Code. Germany: Ethikkommission der Universität zu Lübeck [AZ 18-172]. Italy: Comitato Etico Lazio 1c/o A.O. San Camillo Forlanini [2143/CE Lazio 1]. Sweden: Regional Ethical Review Board in Göteborg. All young people with CP or their legal representatives gave written informed consent to participate, or non-opposition where appropriate.

AUTHOR CONTRIBUTIONS

NVEB and CA conceived and designed the analysis. NV performed the analysis under the supervision of VE and drafted the manuscript. CA, JF, SS-S, UT, KH, and MM conceived and designed the cohort and contributed to the longitudinal data. CA, CD, SS-S, UT, KH, and MM designed the third wave of follow-up, which was managed by CD. All authors contributed to the article, provided critical feedback, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.733978/full#supplementary-material

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Health Concerns of Adolescents and Adults With Spina Bifida

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Due to advancements in medical care, people with spina bifida (SB) are surviving well into adulthood, resulting in a growing number of patients transitioning to an adult sector unequipped to care for people with chronic rehabilitative and medical needs. The Transitional and Lifelong Care (TLC) program is a multidisciplinary clinical service that compensates for this gap, providing comprehensive, coordinated care to adolescents, and adults with SB. As a relatively new clinical service, objective data about the patients using the service and their needs is scant. This study sought to identify the most common health concerns among TLC patients with SB at initial clinical consultation. A retrospective chart review of 94 patient charts was performed. Following data extraction, descriptive analyses were completed. The mean age of the sample was 29.04 ± 13.8 years. One hundred individual concerns and 18 concern categories were identified. On average, patients or care providers identified nine health concerns across various spheres of care, with care coordination being the most prevalent concern identified (86%). Patients also commonly had concerns regarding neurogenic bladder (70%), medications (66%), assistive devices (48%), and neurogenic bowel (42%). The numerous and wide-ranging health concerns identified support the need for individualised, coordinated care and a "medical home" for all adolescents and adults with SB during and following the transition to adult care. Health care providers caring for this population should continue to address well-documented health concerns and also consider raising discussion around topics such as sexual health, mental health, and bone health. Further research is required to understand how best to address the complex medical issues faced by adults with SB to maximise health and quality of life and improve access to healthcare.

Keywords: spina bifida (SB), health concerns, healthcare transition, adolescents, adults, multidisciplinary health care, care coordination, medical home

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INTRODUCTION

Spina bifida (SB) is one of the most common permanently disabling conditions in humans (1). It is a non-progressive defect that results from incomplete closure of the neural tube during the first few weeks of embryonic development (1, 2). The most common form of SB is myelomeningocele, in which meninges and neural elements protrude through the spinal defect, necessitating neonatal surgical repair (3, 4). The clinical spectrum of SB ranges from mild to severe neurological impairment, with severity determined by several factors, including the size and location of the spinal cord malformation, the degree of spinal cord or nerve involvement in the defect, and

whether the opening in the spine is covered (3, 4). The clinical consequences of SB are largely related to the degree of nervous system abnormalities resulting from the neural tube defect (4). Brain abnormalities, such as hydrocephalus and Chiari type II malformation, may occur and can be associated with learning disabilities, executive dysfunction, strabismus, precocious puberty, and/or epilepsy (4). The spinal cord malformation itself leads to a spectrum of sensory and motor impairments below the lesion level (typically located in the thoracic, lumbar, or sacral spine) and often to the development of neurogenic bowel and bladder dysfunction (4). The bony vertebral anomalies may lead directly to musculoskeletal consequences, including scoliosis and kyphosis (4, 5). Managing SB involves surgical closure of the defect, commonly initiated shortly after birth (though recent advances have resulted in more frequent consideration of pre-natal foetal surgery to repair the defect ((6))), and medical intervention throughout the lifespan (1). This may include continuous specialty care from urology, neurosurgery, orthopaedics, and physical medicine and rehabilitation, as well as access to therapy services from psychology and assistive technology services (4, 7).

Although life expectancy for people with SB has dramatically increased in the last several decades, the population is at increased risk for excess morbidity and early mortality in adulthood (1, 5, 8, 9). Adults with SB experience complex, multi-system disorders from childhood and adolescence throughout their lifespan (5, 8), co-morbid conditions and medical complexities that stem directly from their SB, as well as complications that may be indirectly related to SB, such as issues with infertility, poor mental health, obesity, and skin breakdown (5, 8). Moreover, adults with SB are at risk for health concerns and chronic health conditions common in the general population, such as hypertension, diabetes, and cancer (5). The consequences of SB may also impact cognition, such that specific learning disabilities or cognitive challenges that persist from childhood may impact independence and educational, social, and employment opportunities in adulthood (5, 8). As such, a similar level of health care service and comprehensive support must exist throughout adulthood as in childhood and adolescence (8). However, this is often not the case, and unsurprisingly, many adults with SB begin to experience a deterioration in their health soon after their discharge from paediatric health care services (8, 10, 11).

In Canada and internationally, youth with SB typically receive specialised, multidisciplinary health care services, often in well-structured paediatric rehabilitation centres (1, 12, 13). In these programs, children and adolescents with SB receive assessment, diagnosis, and management for their condition from a team of diverse health care practitioners, most often including orthopaedics, urology, neurosurgery, nursing, social work, as well as occupational, speech, and physical therapy (1, 4, 13). The approach to care is family-centred, comprehensive, and holistic, considering the physical, emotional, social, and behavioural aspects of development (14). However, transfer to adult care is inevitable and typically occurs between 18 and 21 years of age once adolescents become ineligible for paediatric services (12, 15). Unfortunately, many people with SB struggle to find similarly equipped adult health care programs that can effectively address their complex needs after discharge from their children's treatment centre (16).

A large body of scientific literature documents the many barriers inherent in the adult health care system—in Canada and internationally—that prevent successful transition and pose challenges to ongoing care (15, 17, 18). Although the usual adult model of care may be appropriate for the general population, transition to adult care can be particularly difficult for those with complex disabilities who face a lack of multidisciplinary care; fragmentation of services (separate appointments with different specialists across multiple settings must be booked and coordinated); scarce resources; poor coordination and communication between the adult and paediatric health care sectors and within the adult health care sector; lack of preparation or information for transition; and a paucity of health care professionals that are knowledgeable, properly trained, or interested in caring for adults with SB (15, 18). These barriers can pose further challenges for those people with SB facing more significant cognitive or psychosocial challenges, or those who are heavily reliant on caregivers (16). Difficulties in transition may also be exacerbated by significant cultural differences between paediatric and adult care services (12, 19, 20). Paediatric care is developmentally focused, multidisciplinary, and family-centred, where adult care tends to place a greater focus on independence, maturity, and single discipline visits (12, 19–21). Therefore, it is perhaps unsurprising that many adolescents and adults with SB and their families associate the transition experience with negative feelings (22). Several studies have also identified negative consequences of transitioning to adult care, including difficulty accessing health care services (8), failure to seek medical attention or access age-appropriate services (15), challenges accessing funding or insurance (8), higher use of emergency and inpatient health care (5, 8, 23), and a decline in health status over time (11).

As a first step in improving health care services for adults with SB, more must be known about the population and their health care needs. The Institute for Health Improvement's (IHI) Triple Aim Framework suggests that to achieve appropriate reform of the health care system, there is a need to: (1) improve the experience of care: (2) improve the health of populations; and (3) reduce per capita costs of health care, where the accomplishment of the aims requires a focus on a defined population and an organisation or an "integrator" that can coordinate health care services (24). Therefore, the purpose of the present study was to identify the most common health care concerns affecting patients with SB at the time of presentation to a transitional and lifelong care clinic. It was hypothesised that patients would present to the clinic with multiple health concerns spanning multiple clinical areas, and that the most frequently identified patient concerns would relate to common conditions specific to SB, such as neurogenic bowel and bladder, as well as common secondary consequences of SB, such as osteoporosis and pressure ulcers.

Abbreviations: SB, Spina Bifida; TLC, Transitional and Lifelong Care.

TABLE 1 | TLC services offered in initial consultation and follow-up visits.

Initial consultation	Follow-up visits
Transitional ("overlap") clinics at Thames Valley Children's Centre for adolescents nearing transition Access to interdisciplinary services, including (but not limited to) physiotherapy, occupational therapy, speech and language therapy assessment and treatment, and dietitian consultation and support	Outpatient clinic visits at Parkwood Institute for adult ("post-transition") patients System navigation Telephone/telehealth support for patients and community partners (e.g., Family Physicians, home-care providers) Access to interdisciplinary services, including (but not limited to) physiotherapy, occupational therapy, speech, and language therapy assessment and treatment, and dietitian consultation and support

TABLE 2 | Patient factors and concerns extracted.

Data elements extracted
Age (in years, at the time of initial consult)
Date of birth
Sex
Individual reporting concerns (communication status)
Self, other, unknown, or not reported
Type of SB
Myelomeningocele, meningocele, occulta, other (normal exam), or not reported
Neurological level
Thoracic, high lumbar, low lumbar, sacral, unknown, or not reported
Ambulatory status (according to the Hoffer Classification of Ambulation for patients with spina bifida or other diagnoses ((49)))
Community ambulator, household ambulator, or non-ambulator
Surgical history
Epilepsy history
Current medications and active non-medical treatment
Physical exam results
Hip flexion contracture, knee flexion contracture, plantar flexion contracture, or scoliosis
Presenting issues or concerns at initial consult

MATERIALS AND METHODS

Study Purpose

The objectives of this study were to identify the clinical health care concerns among patients with SB presenting to the Transitional and Lifelong Care (TLC) program, located in London, Ontario, at the Parkwood Institute site of St. Joseph's Health Care.

Study Design

This study used an observational design involving a retrospective medical chart review of initial TLC patient consultation encounters between 2014 (time of the program's inception) and December 2017. All patients who presented to the clinic during this time with a diagnosis of SB were included in the study. There were no restrictions on age (or other patient characteristics) as the TLC clinic is a lifelong care program where a significant proportion of people in adult care have unmet health needs. Ethics approval was initiated through the Lawson Health Research Institute and approved by the Health Sciences Research Ethics Board at Western University.

The TLC program was developed in line with best-practise recommendations around transition to adult care (25) and addresses the diverse needs of adolescents and adults with chronic childhood-onset disabilities, including SB. It functions both as a transition service and an ongoing clinical program (otherwise known as a "medical home") that provides scheduled and as-needed support for patients with SB throughout their lifespan, with access to knowledgeable clinicians and coordination of services in one comprehensive care setting. The program houses a multidisciplinary team of health care practitioners, including a physiatrist, nurse practitioner, social worker, physiotherapist, occupational therapist, speech-language pathologist, registered dietitian, and rehabilitation assistant. In line with paediatric services offered to children with complex health care needs, this diverse team provides a holistic approach to health care, considering physical and psychosocial well-being. See **Table 1** for specific program services.

A physician referral is required to be admitted to the TLC program. Since the inception of the TLC program, patients can be admitted through one of two "pathways": (1) transition from paediatric care or (2) direct referral from primary care physician after a period of receiving non-specialised care. Patients admitted to the TLC program following a structured transition from paediatric care may transition at any age (up to 21 years) depending on their readiness to transition and where the team feels the patients' needs are best met. Patients admitted to the TLC program from a community primary care physician are often older and have experienced a period where non-specialised/coordinated care was provided only by their primary care physician. After referral, in either pathway, prospective patients are scheduled for an appointment with the physiatrist and/or nurse practitioner, who may refer the patients to other team members for discipline-specific assessment and treatment as appropriate.

Data Collection

Particular data elements that were extracted from patient medical charts are listed in **Table 2**. All data extraction was conducted electronically using a data extraction tool created in the REDCap research database platform. In this study, neurological level was defined as the lowest level at which sensory or motor function was preserved in a patient, where function was fully intact above that level. As SB lesions are typically not discrete, with some blurring of normal and abnormal function in the zone of the anatomical spinal cord defect (6), neurological levels were broadly grouped as thoracic, upper lumbar, lower lumbar, and sacral. In the event that patients had asymmetrical neurological presentations

TABLE 3 | Demographic characteristics.

Patient characteristic	N(94)	
	n	%
Sex		
Male	28	29.8
Female	66	70.2
Communication		
Self	7	7.4
Other	22	23.4
SDM	*21*	*95.5*
Other	*1*	*4.5*
Not reported	65	69.1
SB type		
Myelomeningocele	72	76.6
Occulta	7	7.4
Other	13	13.8
Not reported	2	2.1
Neurological level		
Thoracic	25	26.6
High lumbar (L1-L3)	19	20.2
Low lumbar (L4-L5)	35	37.2
Sacral	10	10.6
Normal exam	5	5.3
Ambulatory status		
Community ambulator	40	42.6
Household ambulator	7	7.4
Non-ambulator	47	50
Independent with transfers	*31*	*66*
Assistance with transfers	*2*	*4.3*
Dependent with transfers	*14*	*29.8*
Surgical history		
Neurosurgery	70	74.5
Bowel or bladder	19	20.2
Orthopaedic	53	56.4
Epilepsy history		
Yes	14	14.9
No	77	81.9
Unclear	2	2.1
Unknown	1	1.1
Medications		
Antiepileptic	7	7.4
Psychotropic	11	11.7
Tone	4	4.3
Pain	10	10.6
Bowel/GI	22	23.4
Bladder	33	35.1
Other	31	32.9
Physical exam results		
Hip flexion contracture	25	26.6
Knee flexion contracture	34	36.2
Plantar flexion contracture	0	0
Scoliosis	50	53.2

The "Other" subcategory within "SB Type" represented those with lipomyelomeningocele, dermal sinus tract, occulta, or an unknown SB subtype.
The "Normal Exam" subcategory within "Neurological Level" represented patients who had an atypical neurological presentation.
The "Other Non-orthopaedic" subcategory within "Surgical History" represented other surgical procedures that were not explicitly collected on the data extraction instrument.
"Other" medications included calcium, vitamin D, iron, melatonin, Trazodone, Zopiclone, and Scopolamine.

on the right and left side, the patient was classified as the higher (i.e., worse) of the two neurological levels. Presenting concerns included any health care or socioeconomic matter that the patient or caregiver felt required the attention of the physician or of another TLC team member, or any issue that the physician felt needed attention at the time of presentation to the TLC program. Comorbid conditions that were controlled or stable and not leading to any active concerns (i.e., were not raised as pressing concerns by the patient/caregiver and/or the physician at the initial clinical consult) were not identified as presenting concerns for this study. Presenting concerns (found within the dictated chart notes of the initial clinical consult, in the concluding treatment plan/list of final recommendations) were summarised and extracted in a list format alongside the collection of other data elements using the REDCap data extraction tool. Patients were included in the study if they presented to the TLC clinic between 2014 and 2017 and had a diagnosis of SB.

Data Analysis

All presenting concerns (for each patient) were extracted from the REDCap database. From the raw data, each unique health concern was named. With the information extracted from patient medical charts, each patient was then coded as either having or not having each named/identified health concern. Individual health concerns were then grouped into broader "concern categories" to help report the most common concerns across the cohort. Patients were coded as having no concerns, at least one concern, or two or more concerns within each concern category. Descriptive statistics were used to summarise the characteristics of the sample using frequencies, percentages, mean, standard deviation, median, range, minimum, and maximum as appropriate. Concern categories and the individual health concerns within each category were reported as frequencies and percentages. To determine the most common concerns, only the proportion of patients with at least one concern was considered. Total number of concerns were reported as mean, median, standard deviation, and range.

RESULTS

Patient Characteristics and Total Concerns

A total of 94 patients with SB were seen in the TLC program between 2014 and 2017 (**Table 3**). The mean age of the patients was 29.04 years (*SD* = 13.8), where the range was 13–77. Age was not normally distributed, the median was 26 years, the mode was 19 years, and few patients were over the age of 60, establishing that the majority of the patients were within younger age cohorts. The median number of concerns reported at initial consultation was 9.0 (*M* = 9.2, *SD* = 3.9), and ranging from a single concern to a maximum of 22 concerns.

Top Concerns

One hundred individual patient concerns and 18 concern categories were identified (**Supplementary Material**). Thirteen health concern categories affected at least 25% of the patient population (**Figure 1**).

The most common health concern was care coordination (defined as any referral or consideration of another service or specialty within or outside the TLC program), with 86% of patients requiring coordination relating to one or more health issue(s). Unpacking this further, the greatest number of patients required physiotherapy services (35%), most often to address physical activity concerns, and often to address pain, weight loss, wheelchair, and gait concerns. The medical team also referred 15% of patients to recreational therapy, 14% to dietetics, 14% to social work, and 14% to occupational therapy.

Secondly, patients commonly had at least one concern regarding neurogenic bladder (70%), and/or neurogenic bowel (42%). Bladder or kidney concerns included monitoring bladder/renal function (with urinalysis, blood pressure monitoring, renal and bladder ultrasound and/or urodynamics); bladder management (including catheterization, incontinence treatment, hygiene, bladder irrigation, and consideration of need for surgical intervention); bladder education; and concerns about upper or lower urinary tract infections. Health concerns related to neurogenic bowel included constipation, establishing bowel routines, addressing incontinence or changes in bowel patterns, and hygiene.

More than half of the patients (66%) had medication concerns. Medication concerns included requiring or considering new prescriptions; restarting medications; needing to switch or stop medications or alter their dosage; needing to refill existing medications; and concerns with medication compliance. Patient medication concerns were most often related to the management of pain, seizures, bladder or bowel routines, spasticity, hypertension, and ADHD. Several initial clinical encounters also included discussions about supplementation, including vitamin D and calcium for bone health, and magnesium, fibre, or probiotics for bowel management.

Concerns about assistive devices were reported by 45% of patients and mostly involved needs related to orthoses (25%) and wheelchair or seating (19%). Concerns about existing devices, device assessments, and new device options or prescriptions were often discussed.

Social concerns were prevalent (39%) in this population. The most common social concerns related to finances or funding (15%) and social participation (15%). Social participation concerns included an interest in community involvement, opportunities to socialise, leisure activities, support groups, and social programming. Other less common social concerns were associated with school or education (4%) and future care or living arrangements (4%).

In addition, 39% of patients had pain concerns, most commonly back pain (19%), lower extremity pain (14%), and required pain management (14%). Concerns regarding diet were also prevalent, specifically related to food/nutrition (21%) or weight management (13%). A total of 34% of patients had a physical activity or fitness concern. In this area, patients were prescribed specific exercise or physiotherapy programs, stretching, strengthening, and range of motion exercises, and/or had specific concerns about physical activity, exercise, fitness, or sports participation. Furthermore, 34% of patients had concerns about neurologic function, most involving spasticity (12%) and changes possibly related to symptomatic tethered cord syndrome (7%).

Skin health concerns were reported by 31% of the sample and included issues around skin breakdown/redness, the need for plastic surgery, and preventative strategies to maintain skin health. Sexual/reproductive health and family planning concerns were reported by 30% of patients, with family planning being the most common (20%), representing concerns centred around birth control, folate/folic acid supplementation, and SB prevention. Finally, 29% of patients experienced orthopaedic concerns, and 24% had other (miscellaneous) concerns, occurring at too low a frequency to be grouped into concern categories. Some concerns that were less prevalent, but notable, were mental health and functional mobility concerns.

DISCUSSION

Top Concerns

In line with the literature (5, 8, 26), patients with SB continue to face multiple conditions associated with SB, affecting multiple organ systems, and creating secondary complications during and after the transition to adult health care. On average, patients had a total of 9 health care concerns and as many as 22 at their initial consultation, with considerable variation in concerns across patients. The results of this study provide evidence that many health concerns persist from childhood and that new health concerns may arise over the life course, necessitating individualised, lifelong care in a medical home, in addition to the support provided during the health care transition from paediatric to adult care.

Care coordination was the most common concern reported by patients with SB, with almost all patients (86%) reporting at least one need in this area. This finding highlights the importance of a service like the TLC program since it can provide access to and coordinate the provision of multidisciplinary care (both within and beyond the program's walls), thus removing the burden of coordinating care from individuals and their families. It also underscores the need for continued access to multiple health

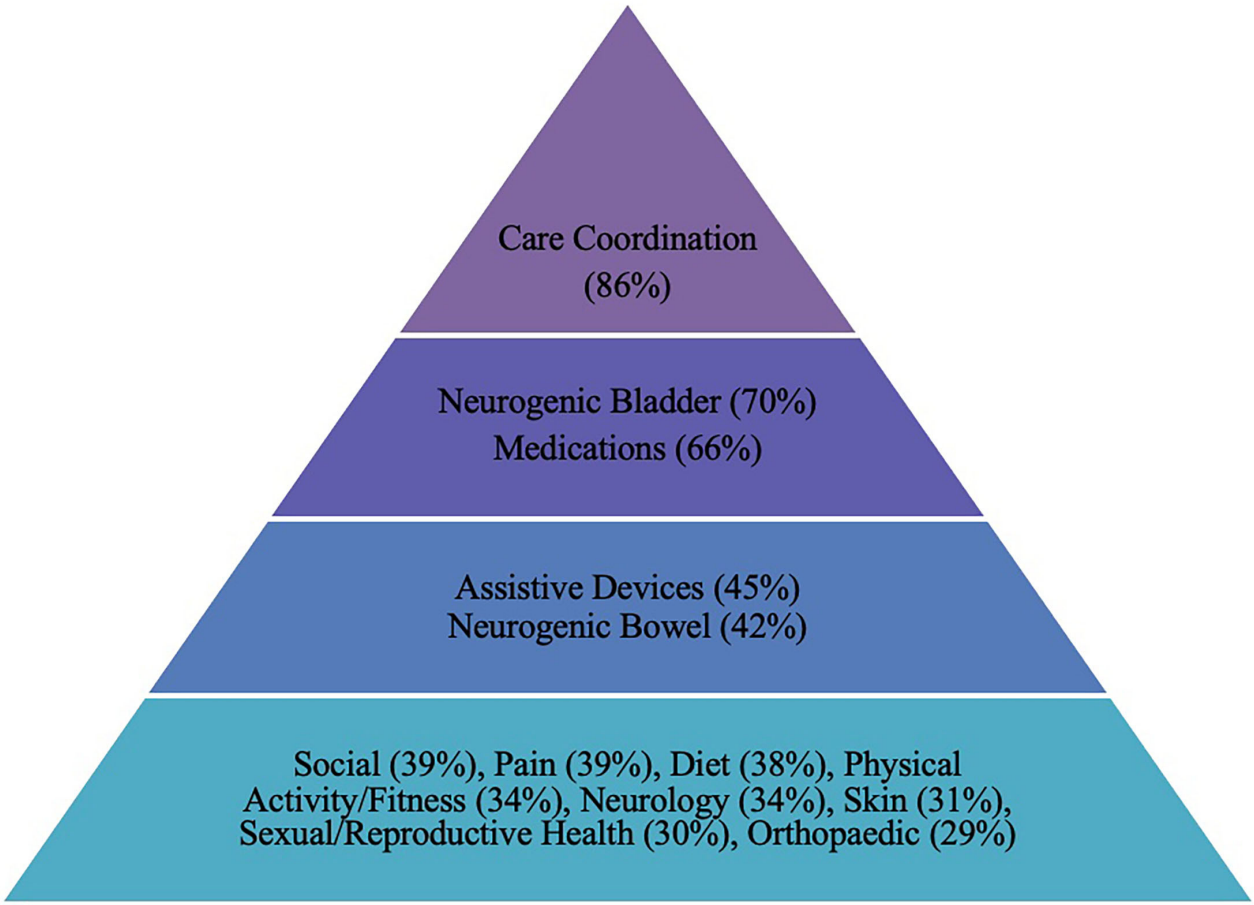

FIGURE 1 | Most common concerns (in order).

care professionals, including allied health, in the management of SB throughout adulthood. Just at the initial clinical encounter, patients were referred to several health care professions, such as physiotherapy, recreation therapy, dietetics, occupational therapy, and social work. In particular, half of the patients had two or more concerns or needs related to accessing and coordinating care among multiple health care services/providers. Many referrals were specifically to services available within the TLC program, where there are knowledgeable clinicians interested in caring for people with complex health care needs. Elsewhere, difficulty with navigating the health care system and accessing competent health care providers who have an interest in SB is common (15). Care coordination and multidisciplinary health services are rarely available for adults with SB (15). Young et al. found that adolescents with SB were more likely to receive health care services from a greater variety of health professionals than adults with SB (27), even though adults with SB continue to identify a wide variety of needs spanning various health care specialties. Many studies have also noted a decline in contact with health and social services after discharge from paediatric care (8, 11, 15). These findings further point (at least partially) to the importance of care coordination and an adult-centred medical home in facilitating access to the appropriate health care professionals in adulthood. The volume of care coordination concerns suggests that the TLC program fills a major gap in the health care system by providing coordinated, multidisciplinary care in a single setting, and serving as a "hub" of knowledge for where and how to access services for patients who are geographically distant.

Previous studies have found that bowel concerns, including faecal incontinence, and bladder concerns, such as incomplete bladder emptying, urinary tract infections, and urinary incontinence, are significant issues for adults with SB (5, 26, 28). The present study further identified a specific need for bladder and kidney monitoring, which is particularly important as renal failure secondary to neurogenic bladder dysfunction continues to be a frequent and sudden cause of death in people with SB (5, 9). As such, bowel and bladder monitoring and management are necessary (1, 4), both at initial consultation and routine follow-up. Additionally, two-thirds of patients had concerns regarding medications, and similar to the findings of Lidal et al. (26), only 10% of participants were not taking any medications at the

time of initial consultation. This finding suggests that a medical home plays a significant role in recommending, prescribing, and managing pharmacological treatment and medication regimens for this population (25), which is necessary due to the potential for complications to arise without comprehensive and well-managed treatment strategies (29).

Half of the patients in this sample were non-ambulatory, with only 11% having a sacral neurological level of impairment, pointing at a large proportion of patients with significant limitations in motor function (4). Therefore, it comes as no surprise that concerns relating to assistive devices were prevalent. Assistive devices (such as orthoses, wheelchairs, and gait aids) are commonly used to improve mobility in adults with SB, where preservation of mobility is an important determinant of functioning and quality of life (29). However, many adult practitioners have limited medical training and experience with chronic childhood-onset disabilities (15). The medical home model (in this case, the TLC) mitigates the challenges patients with SB have in accessing services that address their specific assistive device needs within the typical adult care system by providing access to practitioners familiar with the unique and specialised orthotic and device needs of this population. Transition programming must continue to address concerns with existing patient devices and prescribe or advocate for appropriate devices that support mobility, functioning, and participation (29). Physiatrists should also aim to appropriately preserve the physical function and mobility of both ambulatory and non-ambulatory patients through specific rehabilitative programming (29).

Several prominent but less commonly cited concerns identified by this study also warrant clinical consideration, including social concerns, pain, diet, and physical activity. Social well-being is necessary for overall health (30). Many people with SB experience brain abnormalities that present cognitive and physical challenges that can affect independence, education, employment, and/or other social outcomes (4, 31). Research suggests that such consequences may be mitigated or well-managed in a multidisciplinary care setting (31), such as the TLC program. The prevalence of social concerns found in this study suggests that patients experienced challenges in accessing social services, including social work and recreational therapy before the inception of the TLC clinic.

In a recent study conducted by Lidal et al. (26) a cohort of older adults (mean age 58) with SB reported that their most notable health concern was pain. In the current study, while pain was not the most common concern, it affected 40% of patients, with most reporting pain in the lower extremities or the back, in line with the findings in Lidal et al. (26). The younger average age in this study may explain why pain was reported less as, in the literature, pain is more common among older adults with SB (32). A significant portion of patients in the current study also had two or more pain concerns, suggesting that pain in one area may coincide with pain in another body region. The findings from this study further support the literature that adults with SB are likely to experience pain and have a higher prevalence of pain than the general population (33). For this reason, and because pain can affect quality of life and point to underlying treatable conditions (4), specific attention to pain in health care interactions is warranted (4, 26, 34).

Diet is also an important concern to consider in the clinical encounter as a high proportion of older adults with SB are overweight or obese and have hypertension (8, 26). The likelihood of being overweight or obese in adults with SB also increases with age (35) and has been linked to a decline in mobility or ambulatory functioning (26, 35). Another commonly discussed concern at the initial clinical encounter was physical activity/fitness (34%). Physical activity or exercise is particularly important in youth and adults with SB due to their increased risk of obesity, pain, hypertension, and decline in mobility later in life (26). A narrative review of the literature found that adults with SB are more likely to be inactive, have decreased aerobic capacity, lower daily physical activity, and higher levels of obesity compared to other groups of people (36). Bloeman et al. (37) found that children and adolescents who use a manual wheelchair are more sedentary and less physically active than their peers with typical development, increasing the risk for secondary health conditions (37). Exercise training in people with SB can improve elements of fitness (38); therefore, it may be beneficial to consider physical activity as a preventative strategy or to encourage general physical activity for all patients with SB to promote optimal health and well-being. Diet counselling combined with physical activity and fitness programming should be considered essential programming for adults with SB to ensure optimal health and to aid in the prevention of secondary conditions (38, 39). There may be opportunities to run group programming related to dietary and physical activity needs across multiple populations as a cost-effective method of addressing these patient concerns in the current adult healthcare model.

Sexual/reproductive health and family planning (although only a concern for 30% of the population) is also an important area to note considering the younger mean age of this population, the potential for sexual dysfunction in males (4), and the larger number of female SB patients within the TLC clinic who are likely to have unique concerns regarding their reproductive health (puberty, sexuality, pregnancy, childbirth, and menopause) (40). A recent study by Akre et al. (41) also reported that adolescents and young adults with SB report concerns, challenges, and questions regarding their sexuality, fertility, and romantic relationships (41). They reported difficulty in finding answers to their questions and expressed a desire for information directly from their physicians (41). Adult health care providers within the general adult health care system often lack the knowledge and experience to effectively care for people with SB and can be uncomfortable or ambivalent when discussing specific health care topics (15). Meanwhile, health care providers within the TLC program are knowledgeable and interested in caring for the specific needs of this population. The smaller percentage of concerns in this area in this study may reflect that sexual and reproductive health concerns discussed more heavily in follow-up visits once patients feel more comfortable and have established a relationship with the TLC program team. Even so, an opportunity exists to direct more attention to empower and educate youth and adults about their sexual health to further

healthy physical and psychosocial development and successful transition to adult care (41).

Two concerns that fell below the threshold set for determining the most "common" concerns (25%) but are worth noting due to the clinical implications include bone health and mental health. The lack of bone health concerns among this cohort may actually reflect suboptimal screening in the initial clinical appointment and point to the "silent" threat of poor bone health, whereby only fractures or significant complications may bring attention to any bone-related issues. On the other hand, since a significant portion of patients were taking vitamin D at the time of consultation, it is also plausible that osteoporosis or fracture risk was considered well-managed among patients transitioning into the program during this period and therefore not identified as a concern. Osteoporosis and bone health are common issues among people with SB and more common in adults with SB than in the general population (5, 42). People with a higher level of neurological impairment and youth are especially at an increased risk of fractures (potentially due to inexperience navigating the physical environment and changes in bone mineral density during adolescence) (43, 44). As such, transition and ongoing adult health care programming must consider bone health in treating and rehabilitating patients with SB and specifically consider risk factors for fractures and low bone mineral density in future clinical encounters (42, 44, 45).

Similarly, mental health concerns were less frequently reported among this group compared to other concerns. Only 15% of the cohort had a specific concern relating to affective disorders, and only a small number of other mental health issues were discussed in the initial consultation. However, mental health problems are frequent and undertreated among people with SB (5, 46). Like sexual and reproductive health concerns, due to the stigma associated with mental illness, patients may prefer to develop a more robust therapeutic relationship before disclosing mental health concerns, where analysis of concerns beyond the initial consultation may have resulted in identifying a higher number of mental health concerns. In a recent study by Dicianno et al. (47), over 25% of adult participants (including younger and older adults) had depressive symptoms, which was comparable to rates in younger people with SB. The authors also estimated that the rate of participants with a history of depression could have been as high as 46% (47). Furthermore, The Mental Health Guidelines for the Care of People with Spina Bifida (46) summarise that due to the social, cognitive, physical, and neuropsychological challenges surrounding SB, people with SB are at risk for symptoms of depression, anxiety, and lower quality of life than the general population (46). Although healthcare providers within the TLC program can screen, provide interventions, and refer patients to the appropriate mental health professionals following the initial patient consultation, specific, concrete strategies should be integrated into all initial clinic visits and follow-up appointments to meet the guidelines proposed by Kritikos et al. (46).

Considerations

SB is a unique population, and only recently has research begun to explore the specific transition and lifelong care needs of this population. SB can cause complex constellations of clinical features and may present a transition challenge for healthcare providers (16). Adolescents and adults must manage the transfer of multiple areas of care to multiple new health care and social support providers, all while learning to self-manage their condition and comorbidities, advocate for themselves, and coordinate these diverse health care services (16). This transition proves to be even more complex for those who have reduced cognitive functioning and are heavily reliant on caregivers (16). While SB presents unique challenges and clinical manifestations, people with chronic childhood-onset disabilities share a common need for planned and coordinated transition from paediatric to adult health care and ongoing rehabilitative and medical care and social supports throughout adulthood (15, 48).

Interestingly, in evaluating health and health care utilisation among adults with SB from a multidisciplinary adult clinic in the United States, Liptak et al. (8) found that many participants struggled with accessing health care due to inadequate medical resources or for other unspecified reasons. Although programs such as the TLC program may be helpful, it is possible that barriers to accessing care still exist, which may continue to adversely affect health outcomes in adults with SB (37). While program development is still in its infancy, research on optimal processes and outcomes of transition programming is critical to understand what is needed in transition programs to achieve optimal health through adolescence and adulthood for those with childhood-onset disabilities.

As this was a retrospective study evaluating patient needs at the initial clinical encounter with the TLC program, this study only reflects patient concerns at the initial point of contact, during the transition or re-initiation of care with the TLC clinic. Future research will need to determine whether these patient needs have been addressed and if patients are satisfied with the services provided by the TLC program. Additionally, since this study could not address the third aim of the IHI Triple Aim Framework (reduce per capita costs of health care) (24), future research should include economic evaluations of transition programs and medical homes for patients with SB. Future research should also consider mixed-methods or qualitative study designs to fully capture patient and family needs, experiences, and voices.

LIMITATIONS

The major limitation of this study was its retrospective nature. Due to the study design, specific data elements not consistently reported within patient medical charts resulted in difficulties with the standardisation of data collection and extraction of certain data elements. This challenge inevitably led to high percentages of unreported variables of interest, including hip status, that ultimately had to be excluded from this initial study. The concerns identified in this study were derived from clinical consultation notes, which are subject to bias based on how the healthcare provider asked patients and their caregivers about their concerns, and how their concerns were recorded. There

could be variability in reporting between providers, including medical residents. Of particular note, there was no method to distinguish between concerns reported by the patient or caregiver and concerns raised by the healthcare provider. Furthermore, the TLC program primarily involves screening by a generalist (physiatrist/nurse practitioner) and referral to other specialists as needed. This program structure is partially responsible for the highest concern category (care coordination) and may have led to some specific concerns not being well-screened for (i.e., mental health concerns, surgical needs, etc.). The wide range in total number of concerns at initial consultation may be partially attributed to the amount of time spent in the clinic visit or the physician's persistence in discussing patient concerns.

This study also has an inherent selection bias in including only TLC patients. Those with less pressing concerns may never have been referred for comprehensive management, thus introducing the possibility of over-estimating the health care needs of this population. Lastly, as age was not normally distributed in this sample, the concerns identified in this study may be more applicable to younger adults (18–21 years of age) and may not reflect the top concerns of adults with SB more generally.

CONCLUSION

This study identified many common health concerns in adolescents and adults with SB initiating care in the TLC program. In particular, it established the significance of the usefulness of a medical home in care coordination, medication management, and facilitating assistive device use. It also identified common SB-related health conditions of concern, most notably, neurogenic bladder/bowel. Furthermore, at the initial clinical consultation, patients frequently presented with multiple health concerns. As such, there is a need for continuous and individualised care for people with SB throughout their lifespan, in line with expert recommendations (48). Health care providers within the TLC clinic, and other transition programs and medical homes, must continue to address well-documented concerns, including bladder and bowel, mobility, social, and pain concerns. Consideration must also be given to less frequently discussed topics (identified in the literature as significant in this population), such as sexual health, mental health, and bone health. This research is the first critical step in improving the experience of care and the health of adults with SB through comprehensive and coordinated services. The findings of this study also help to inform priority setting for future development of other transition efforts to improve the standard of care for this population more globally.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Western University, the Office of Human Research Ethics. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CC and LB conceptualised, designed, and initiated the study. JS collected the data, performed the analysis, and drafted the manuscript. CC and LB supported data analysis and provided critical feedback to the manuscript. JS, CC, and LB edited the manuscript. All authors contributed to the article and approved the submitted version.

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Examining the Relationship Between Community Integration and Mental Health Characteristics of Individuals With Childhood Acquired Neurological Disability

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Nguyen C, Leung A, Lauzon A, Bayley MT, Langer LL, Luong D and Munce SEP (2021) Examining the Relationship Between Community Integration and Mental Health Characteristics of Individuals With Childhood Acquired Neurological Disability. Front. Pediatr. 9:767206. doi: 10.3389/fped.2021.767206

Background: Many individuals with cerebral palsy (CP) or acquired brain injury (ABI) are at higher risk of lowered psychosocial functioning, poor mental health outcomes and decreased opportunities for community integration (CI) as they transition to adulthood. It is imperative to understand the characteristics of those at highest risk of dysfunction so that targeted interventions can be developed to reduce the impact.

Methods: This quantitative, cross-sectional study examines current patients of the Living Independently Fully Engaged [(LIFEspan) Service], a tertiary outpatient hospital-based clinic. The Patient Health Questionnaire-4 (PHQ-4) and the Community Integration Questionnaire (CIQ) were administered to participants. Personal health information was also collected from participants' health charts, and participant interviews. Associations of sex and condition with the outcomes of screening for further assessment of depression, screening for further assessment of anxiety, and CI were calculated using *t*-tests and Chi-square tests.

Results: 285 participants completed standardized screening tools for depression and anxiety (PHQ-4) and 283 completed the Community Integration Questionnaire (CIQ). Mean age was 23.4 (4.2) years; 59% were diagnosed with CP, 41% diagnosed with ABI, and 56% were male. A moderate proportion of the sample screened positive for further assessment of anxiety (28%) and depression (16%), and the overall mean score on the CIQ for the sample was 15.8 (SD 5.1). Participants that screened positive for further assessment of depression and anxiety on the PHQ-4 had lower scores on the Social Integration subscale of the CIQ ($p = 0.04$ and $p = 0.036$, respectively). Females were found to have significantly higher community integration than males ($p = 0.0011$) and those diagnosed with ABI were found to have significantly higher community integration than those with CP ($p = 0.009$), respectively. A weak negative association was found between age for the total sample and overall PHQ-4 score ($p = 0.0417$). Presence

of an intellectual or learning disability/challenge was associated with a lower CIQ score ($p = 0.0026$).

Conclusions: This current study, highlights the need for further research to explore the unique needs and barriers faced by this population. This study may inform assessments and interventions to support the mental health and community integration of this population.

Keywords: cerebral palsy, acquired brain injury, depression, anxiety, community integration, transitional care services, Patient Health Questionnaire-4, Community Integration Questionnaire

INTRODUCTION

With advances in medical care, ninety percent of children with childhood-onset disability will now survive into adulthood (1). However, more than half report receiving inadequate support and services during adolescence and the transition to adult healthcare (1). Adolescents with childhood-onset disability transitioning from the pediatric to the adult healthcare system are particularly vulnerable as their medical and mental health services may become scarcer due to the fact that many adult programs target recent, not childhood-onset conditions (2, 3). Other barriers these individuals may face include a lack of specialist clinicians, their own financial limitations, or a lack of institutional support (e.g., age-cut off policies or insurance policies) (3). Without appropriate services, health concerns may remain undetected, putting adolescents at increased risk of developing preventable secondary physical and mental health complications and comorbidities (4). The transition process is further complicated as young adults with disabilities may be at risk for additional psychosocial difficulties associated with the adolescent stage including poor social functioning, anxiety disorders, depression, suicidal ideation, and suicide attempts (5–10).

Among the most common childhood-onset disabilities are cerebral palsy (CP) and acquired brain injury (ABI) (11). CP is the leading cause of physical disability in childhood affecting 2–2.5 per 1,000 live births (2). It includes a group of permanent conditions that affect the development of movement and posture (11). It is caused by non-progressive disturbances that have occurred in the developing fetal or infant brain (11). Impairments may include physical impairments such as hemiparesis, diplegia or quadriplegia, speech disorders, sensory deficits, intellectual disabilities and seizures (11). Childhood-onset ABI is an injury to the brain that is not due to hereditary or degenerative causes, and may have a traumatic or non-traumatic cause that may also negatively impact individual development and function (12).

Many individuals with CP or ABI experience long-term physical, cognitive, emotional, and behavioral problems that are substantial barriers to achieving formal post-secondary education, economic independence, and social inclusion needed for a successful transition to adulthood (12). For individuals with these childhood-onset conditions, their transition into adulthood is not only marked by changes to musculoskeletal disabilities, but also changes in psychological and social development (13). The combined effects of the disability with the physical, emotional, and social changes that accompany typical transitions into adolescence create an added burden to individuals with these conditions. Without addressing these unique needs, individuals may be at higher risk of lowered psychosocial functioning, such as poor mental health outcomes and decreased opportunities for community engagement and participation (14, 15).

Until recently, the mental health characteristics among young adults (i.e., 18 years and older) with childhood onset disabilities, including CP and childhood onset ABI, have not been well-characterized. Thus, the objectives of the current study are to describe the mental health characteristics i.e., anxiety, depression, as well as community integration (CI) of adults with CP and childhood-onset ABI, including: examining whether there are sex differences in the levels of CI and proportions of positive screens for further assessment of depression and anxiety among adults with CP and childhood-onset ABI; examining whether there are condition-specific differences (CP vs. ABI) in the levels of positive screens for further assessment of depression, positive screens for further assessment of anxiety, and CI among adults with CP and ABI; examining whether there is association between CI and scores on measures screening for further assessment of depression and anxiety; and examining other variables such as severity of condition, age, and cognitive ability and their relation to CI and scores on measures screening for further assessment of depression and anxiety. A better understanding of these associations could help to inform the development of targeted mental health interventions and programs for this population.

METHODS

Study Design

This is a cross-sectional study of individuals that are current patients of a transitional care service called the Living Independently Fully Engaged (LIFEspan) Service. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines for reporting observational studies were followed (16).

Setting

The LIFEspan Service aims to target the unique psychosocial challenges faced by adolescents with CP and ABI and represents a partnership service between Toronto Rehabilitation Institute at the University Health Network (TRI-UHN) and Holland Bloorview Kids Rehabilitation Hospital in Toronto, Ontario,

Canada. The LIFEspan Service is a multi-disciplinary service delivery model for individuals with childhood-onset neurological disabilities, including CP and ABI. The LIFEspan Service aims to bridge the gap for these individuals as they transition from pediatric to adult rehabilitation systems. It aims to deliver continuous coordinated care to support physical, emotional, as well as functional development of this population. In particular, this service offers programs and services that target prevention and management of mental health and psychosocial development. Specific programs include physical activity engagement, social and communication skill building, and self-management skills, with an overarching goal of promoting independent skill building and self-advocacy skills to increase community engagement.

Participants and Recruitment

Eligible participants included individuals who (1) were >17 years of age; (2) registered with LIFEspan Service; (3) had a diagnosis of CP or childhood-onset ABI; and (4) were able to comprehend and communicate in English or have an interpreter or use augmentative and alternative communication. Individuals who had severe intellectual disability or could not answer the questionnaires were excluded from the study.

Participants were recruited in person by a team member working at the LIFEspan Service who was not part of the participants' immediate circle of care to minimize conflicts of interest. A convenience sample was used, as participants were recruited while they were at TRI-UHN (i.e., for clinic visits). All participants were recruited between September 2017 and August 2019.

Data Collection and Database Items

Demographic variables included the participants' sex, age, and diagnosis of CP or ABI.

Other variables collected included the participants' use of assistive devices, education level, co-morbid medical conditions, intellectual/learning disabilities or learning challenges, medications, and severity of condition. The Gross Motor Function Classification System (GMFCS) was collected to describe the severity of CP patients, but due to the heterogeneity of the cause of brain injuries, no specific information was collected for severity of ABI patients.

Standardized measures for screening depression and anxiety and CI were used for this study. The assessments were the Patient Health Questionnaire-4 (PHQ-4) and the Community Integration Questionnaire (CIQ). They were completed by the participant while waiting for the clinic appointment and reviewed by the LIFEspan Nurse Practitioner (AL) during the participant's scheduled clinic appointment.

Data Items and Measures

PHQ-4

The PHQ-4 (17) is a brief and valid screening tool for further assessment of depression and anxiety. It has a 4-item inventory (2 for anxiety and 2 for depression) that is rated on a 4 point Likert-type scale. It provides separate scores for anxiety and depression. Each item is scored as 0- not at all, 1- several days, 2- more than half the days, and 3- nearly every day. The PHQ-4 has been correlated with mental health ($r = 0.80$), social functioning ($r = 0.52$), general health perceptions ($r = 0.48$), role functioning ($r = 0.37$), bodily pain ($r = 0.36$), and physical functioning ($r = 0.36$). Anxiety is defined as a score higher than or equal to 3 on the Anxiety subscale of the PHQ-4 (questions 1 and 2), and depression is defined as a score of higher or equal to 3 on the Depression subscale (questions 3 and 4). Scores are rated as normal (0–2), mild (3–5), moderate (6–8), and severe (9–12) and indicate the level of psychological distress.

CIQ

The CIQ (18) is a 15-item inventory developed to measure levels of community integration. It has typically been used among adults following diagnosed traumatic brain injuries. Community integration is defined as "integration into a home-like setting, integration into a social network, and integration into productive activities such as employment, school or volunteer work." The CIQ has demonstrated good test-retest reliability and internal consistency. The assessment score ranges from 0 to 29, where the total score is calculated using a summation of the scores from individual questions. A higher score indicates greater integration, whereas a lower score reflects less integration. The CIQ can be divided into three subscales which specifically measure at Home Integration (items 1–5), Social Integration (items 6–11), and Productivity (summation of item 12 and the Productivity variable). While the CIQ has increasingly been used in studies with non-brain injury populations, including CP, there measure has not actually been validated for use in CP populations.

Data Analysis

Descriptive statistics of the participants' characteristics, socio-demographic factors, and assessment scores were calculated. Participants' scores on the PHQ-4 and the CIQ were compared by sex and condition (i.e., CP or ABI). *T*-tests, Chi-square, Fisher's exact, or ANOVA tests were used to determine group differences (i.e., sex, condition, severity of condition, and presence of intellectual/learning disability/challenge) in the levels and proportions of anxiety and depression, as well as group differences in overall CIQ score. A Spearman ranked correlation was performed between depression and anxiety composite scores on the PHQ-4 and the CIQ. Statistics were calculated using SPSS version 25. Alpha was set to 0.05.

Research Ethics

This study was approved by the Research Ethics Board at University Health Network, ID# 16-5875. All patients provided written informed consent to have the data from the PHQ-4 and CIQ entered into the database.

RESULTS

Demographic and Clinical Characteristics

There were 285 participants that were recruited for the study over the course of almost 24 months (the LIFEspan Service sees ∼250 eligible participants per year). The average age was 23.4 (4.2 SD) years and 56% of the sample was male. The majority

of the sample was single (96%) and lived with family members (92%). There was a diverse range of education levels within the sample, including participants who were currently attending or had finished secondary school as well as participants who were currently completing or had finished a postgraduate degree. Additionally, employment status varied within the sample, including participants who had full-time or part-time work, were students, had a volunteer position, or were on disability income.

Fifty nine percent of the sample had a diagnosis of CP. There was a wide range of mobility needs within the population, with all participants reporting that they used some type of assistive devices such as a brace or a power wheelchair. More than half (60%) reported having some form of concurrent intellectual/learning disability or learning challenges. The demographic and clinical characteristics of the sample population are described in **Table 1**.

Community Integration and Depression and Anxiety

The overall mean score on the CIQ was 15.8 (SD 5.1). Based on the PHQ-4, 28% of this population screened positive for further assessment of anxiety, and 16% screened positive for further assessment of depression. There was a weak negative Spearman correlation between the CIQ score and depression screening composite score on the PHQ-4 (rho $= -0.13$, $p = 0.032$). Participants that screened positive for further assessment of depression on the PHQ-4 had lower scores on the Social Integration ($p = 0.04$) and Productivity subscales ($p = 0.0012$) of the CIQ. Social Integration was also lower for participants that screened positive for further assessment of anxiety on the PHQ-4 than those that did not ($p = 0.036$) (see **Table 2** for CI differences by mental health status).

Differences by Sex in Community Integration, Depression, and Anxiety

Female participants were significantly more integrated in their community compared to male participants, as demonstrated by higher total CIQ scores ($p = 0.0011$) and higher scores on the Home ($p = 0.002$) and Social Integration subscales ($p = 0.015$). There were no sex differences in the proportions of positive screens for further assessment of depression or positive screens for further assessment of anxiety. Sex differences in CI scores and proportions of positive screens for further assessment of depression and anxiety have been reported in **Tables 3.1**, **3.2**.

Differences by Condition in Community Integration, Depression, and Anxiety

Participants with ABI reported significantly higher scores (i.e., greater integration) on their total CIQ scores compared to participants with CP ($p = 0.009$), and significantly higher scores on the Social Integration ($p = 0.007$) and Productivity ($p = 0.02$) subscales of the CIQ. No condition-specific differences were found for the total PHQ-4 score or in the proportions of positive and negative screening for further assessment of depression or anxiety. Differences by condition in CI scores and proportions of positive and negative screening for further

TABLE 1 | Demographic and clinical characteristics of patients of the LIFEspan service.

Characteristic	*N* = 285 *n* (%)
Age	
Mean (SD)	23.4 (4.2)
Median	23
Interquartile range	20–26
Sex	
Male	160 (56)
Female	125(44)
Relationship status	
Married/common-law	11 (4)
Single	274 (96)
Education	
Currently in or finished high school	106 (37)
Currently attending college or university	79 (28)
Finished college or university	79 (28)
Currently in/finished postgraduate degree	3 (1)
Unknown	5 (2)
Employment	
Working FT	44 (16)
Working PT	48 (17)
Student	104 (37)
Volunteering	17 (6)
Unemployed	11 (4)
On disability	56 (20)
Use of assistive devices/mobility aids	
Brace	62 (22)
Cane	23 (8)
Walker	38 (13)
Scooter	7 (2)
Wheelchair	29 (10)
Power wheelchair	57 (20)
Diagnosis	
Cerebral palsy (CP)	167 (59)
Acquired brain injury (ABI)	118 (41)
PHQ-4 screen	
Anxiety (positive screen)	79 (28)
Depression (positive screen)	47 (16)
Intellectual disability, learning disability or learning challenges	
Yes	168 (60)
No	113 (40)
Falls	
Yes	76 (27)
No	207 (73)
Living situation	
Family/spouse	262 (92)
Alone	10 (4)
University/college residence	9 (3)
With roommates	4 (1)
Pain	
Yes	126 (45)
No	157 (55)

TABLE 2 | Community integration differences by mental health status.

		Mean	Standard deviation	*p*-value
Depression—positive screen for further assessment				
CIQ score	Yes	14.6	5.9	0.075
	No	16.0	5.0	
Home integration	Yes	3.3	2.3	0.74
	No	3.4	2.3	
Social integration	Yes	6.7	2.3	0.04*
	No	7.4	2.0	
Productivity	Yes	3.9	2.2	0.012*
	No	4.7	1.9	
Anxiety—positive screen for further assessment				
CIQ score	Yes	15.6	5.4	0.67
	No	15.9	5.1	
Home integration	Yes	3.4	2.4	0.91
	No	3.4	2.2	
Social integration	Yes	6.9	2.2	0.036*
	No	7.5	2.0	
Productivity	Yes	4.5	2.1	0.74
	No	4.6	1.9	

**represents statistical significance.*

TABLE 3.1 | Sex differences in the CIQ and PHQ-4.

	n	Mean	Standard deviation	*p*-value (2-tailed)
CIQ total score	283	15.8	5.1	
Male	158	14.9	5.2	0.0011*
Female	125	17.9	4.9	
CIQ home integration	283	3.4	2.3	
Male	158	2.9	2.3	0.0002*
Female	125	3.9	2.2	
CIQ social integration	283	7.3	2.1	
Male	158	7.1	2.2	0.015*
Female	125	7.7	2.0	
Productivity	283	4.6	1.9	
Male	158	4.5	1.9	0.52
Female	125	4.7	2.0	
Total PHQ-4 score	285	2.9	3.0	
Male	160	2.7	3.1	0.14
Female	125	3.2	2.8	

*Equal variances assumed. *indicates statistical significance.*

assessment of depression and anxiety symptoms have been reported in **Tables 4.1**, **4.2**.

Age and Community Integration, Depression, and Anxiety

No association was found between age and CIQ score. A Spearman ranked correlation test found a weak negative association between age for the total sample and overall PHQ-4 score ($\rho = -012$, $p = 0.0417$), however, no associations were found when analyzing by condition.

GMFCS and Community Integration, Depression, and Anxiety

The highest proportion of CP participants were classified in Level 1 (33%) or Level 4 (34%) of the GMFCS. When collapsing the GMFCS into three categories of mild (Level 1), moderate (Level 2 and Level 3), and severe (Level 4 and Level 5), the highest proportion of participants were found in the severe category (42%). The complete breakdown is reported in **Table 5**. An ANOVA found no relationship between GMFCS level and CIQ score, and Chi-square tests found no relationship between GMFCS levels and the proportions of positive and negative screening for further assessment of depression or anxiety.

Cognitive Challenges and Community Integration, Depression, and Anxiety

Those with an intellectual or learning disability/challenge had a lower mean score on the CIQ (15, SD 5.28) than those without (17, SD 4.76). A *T*-test found the difference in means to be significant ($p = 0.0026$). Chi-square tests found no relationship between presence of intellectual or learning disability/challenge and the proportions of positive and negative screening for further assessment of depression or anxiety.

TABLE 3.2 | Sex differences in screening for further assessment of depression and anxiety.

	Positive screen depression *n* (%)	Negative screen depression *n* (%)	χ^2, *p*-value
Male	136 (86)	24 (14)	
Female	102 (82)	23 (18)	$\chi^2(1) = 0.39$, $p = 0.53$
	Positive screen anxiety *n* (%)	**Negative screen anxiety *n* (%)**	**χ^2, *p*-value**
Male	123 (77)	37 (23)	
Female	83 (66)	42 (34)	$\chi^2(1) = 1.41$, $p = 0.23$

DISCUSSION

This present study is one of the first to describe the relationship between mental health (anxiety symptoms, depression symptoms) and CI amongst adults with CP and childhood-onset ABI. An additional strength included examining sex and condition-specific differences in depression, anxiety, and CI among adults with CP and childhood-onset ABI. The results demonstrated that participants that screened positive for further assessment of depression on the PHQ-4 had lower scores on the Social Integration and Productivity subscales of the CIQ. Those that screened positive for further assessment of anxiety on the PHQ-4 also had lower scores on the Social Integration

TABLE 4.1 | Condition-specific differences in the CIQ and PHQ-4.

	n	Mean	Standard deviation	*p*-value (2-tailed)
CIQ total score	283	15.9	5.1	
CP	165	15.1	5.2	0.009**
ABI	118	16.7	5.0	
CIQ home integration	283	3.4	2.3	
CP	165	3.2	2.2	0.059
ABI	118	3.7	2.4	
CIQ social integration	283	7.3	2.1	
CP	165	7.0	2.0	0.007**
ABI	118	7.7	2.2	
CIQ productivity	283	4.6	1.9	
CP	165	4.4	2.0	0.02*
ABI	118	4.9	1.7	
Total PHQ-4 score	285	2.9	3.0	
CP	167	2.9	3.2	0.99
ABI	118	2.9	2.7	

** and **indicates statistical significance.*

TABLE 4.2 | Condition-specific differences in screening for further assessment of depression and anxiety.

	Positive screen depression *n* (%)	Negative screen depression *n* (%)	χ^2, *p*-value
CP	138 (83)	29 (17)	
ABI	100 (85)	18 (15)	$\chi^2(1) = 0.088$, $p = 0.77$
	Positive screen anxiety *n* (%)	**Negative screen anxiety *n* (%)**	**χ^2, *p*-value**
CP	118 (71)	49 (29)	
ABI	88 (75)	30 (25)	$\chi^2(2) = 0.24$, $p = 0.63$

subscale of the CIQ. Females were found to be more integrated in the community when compared to their male counterparts, and individuals with ABI had higher CI scores (i.e., were more integrated) than those with CP. Those with an intellectual or learning disability/challenge had lower CIQ scores. Our findings did not demonstrate any significant differences with respect to sex and presence of depression or anxiety symptoms, condition and presence of depression or anxiety symptoms, severity of condition and presence of depression or anxiety symptoms, or presence of intellectual or learning disability/challenge and presence of depression or anxiety symptoms.

Levels of Depression and Anxiety in LIFEspan Participants

Our study found that 17% of the sample with CP had a PHQ-4 score consistent with a positive screen for further assessment of depression; this finding is fairly consistent with some existing

TABLE 5 | GMFCS breakdown in CP participants.

Characteristic	*N* = 164 *n* (%)
Levels of GMFCS	
Level 1	54 (33)
Level 2	19 (12)
Level 3	22 (13)
Level 4	56 (34)
Level 5	13 (8)
Collapsed levels of GMFCS	
Mild (Level 1)	54 (33)
Moderate (Level 2 & 3)	41 (25)
Severe (Level 4 & 5)	69 (42)

evidence that indicates that 20–25% (19, 20) of adults with CP have clinically significant levels of depressive symptoms, as assessed by the Child Behavior Checklist (19) and the Epidemiological Studies Depression Scale (20).

A recent study in 501 adults with CP from a US clinic demonstrated that 39% of patients met the criteria for a diagnosis of anxiety disorder (21). This proportion is higher than the 28% of patients in our study with a PHQ-4 score who screened positive for further assessment of anxiety; however, similar to our study, a greater proportion of the study's sample also demonstrated a higher proportion of individuals with CP with anxiety vs. depression symptoms. Furthermore, results from a retrospective longitudinal cohort study demonstrated that individuals with CP had an increased risk of being diagnosed as having depression or anxiety, compared with a matched control group of adults without CP (22). The authors indicated that these results could have been observed because adults with CP experience many physiological, psychological, social, and health-related risk factors that have been shown to be associated with depression and anxiety in the general population such as multimorbidity, increased pain, functional limitations, non-communicable diseases, difficulties with social relationships, and worse sleep (22). Furthermore, and as described previously, poor transitions between pediatric and adult healthcare systems may leave young adults with childhood-onset conditions even more vulnerable to poorer health outcomes and at risk for both physical and mental health complications (3, 13). Lastly, and not surprisingly, the demonstrated proportions of young adults with symptoms consistent with a positive screen for further assessment of depression (16%) and anxiety (28%) in our overall sample were much higher than those reported in the general Canadian population over the age of 15, where 4.7 and 2.5% have self-reported symptoms related to a major depressive episode and generalized anxiety disorder, respectively (23, 24). In fact, it is argued that the proportions demonstrated in our study may have potentially been higher without the programs and supports associated with the LIFEspan Service, which target prevention and management of mental health and psychosocial development. Furthermore, our finding that there was weak negative association between age and PHQ-4 score may indicate the possibility that younger patients with ABI and CP experience

more anxiety and depression during the initial transition process, which tapers off with time spent in the LIFEspan service.

The findings that sex was not associated with depression or anxiety among adults with CP and childhood-onset ABI is in contrast to previous research findings in the general population where sex has been shown to play a role in the prevalence of depression and anxiety. For depression, females after puberty experience major depression at roughly twice the rate of males (25). Similarly, for anxiety, the lifetime prevalence of generalized anxiety disorder is found to be 6.6% in women, compared to 3.6% in men (8, 25). This sex difference is found to emerge in mid-adolescence and is associated with hormonal changes during this time period (23). Studies conducted with children with spastic bilateral CP and autism have noted that there were no differences in the prevalence of depression and anxiety found between males and females (20, 26). Further investigations are warranted to confirm whether sex differences exist. Identifying/confirming these differences could inform the development of future interventions to better target and effectively prevent and manage mental health challenges in these populations.

While we did not find any association between condition, or severity of condition and presence or levels of depression and anxiety distress, previous research on depression in individuals with CP has shown that depression or depressive symptoms have been shown to be related to the severity of the condition (2). It may be that the services that LIFEspan patients receive mitigate this relationship; nonetheless this relationship warrants examination in future research.

Levels of Community Integration in LIFEspan Participants

The current study demonstrated sex differences with respect to levels of CI, with females demonstrating higher levels of integration than males. Previous literature has demonstrated that there are sex differences in the symptoms experienced by adults post-brain injury (27). For example, sex differences in executive functioning post-brain injury have been found, with females performing better than males (28). Higher executive dysfunction in males post-ABI may interfere with their ability to self-regulate and adapt to changes in their environment which may also contribute to their lower scores on the CIQ. Similar sex differences in CI have been previously found in CP. For children with CP, previous literature has found that adolescent girls with CP experience higher levels of participation and enjoyment in social, informal activities compared to adolescent boys with CP (29). Thus, the need to tailor interventions and treatments based on sex differences and experiences should be a consideration for clinicians when working with individuals with childhood-onset conditions.

Cognitive levels may be another important factor to consider for improving community integration. Participants in our study with intellectual or learning challenges/disabilities demonstrated lower CI that those without. This is consistent with research in other populations, such as multiple sclerosis, where higher levels of cognitive impairment were associated with lower scores on the CIQ (30). Interventions will need to be designed with this mind in order to be optimally effective.

Our study also found that individuals with ABI were more integrated within their community compared to individuals with CP, and previous literature is largely consistent with these findings. For example, adolescents and young adults with childhood-onset physical disabilities have reported many barriers to participating in their community (31). Some of these barriers have included lacking feelings of fulfillment and enjoyment, experiencing fatigue and lack of energy, and having complications and fears associated with the condition (31). Individuals with CP, specifically, have reported being poorly integrated in paid employment and sport activities (32). Relatedly, the leisure activities that adults with CP participate in tend to be non-intensive, more passive, home-based, and lack variety (33, 34). Lastly, and as previously noted, social factors including difficulties with social relationships have been shown to be associated with depression and anxiety in the general population; thus, the observed associations between depression and anxiety symptoms and social integration in the current study are not surprising.

Limitations

We acknowledge some limitations. The generalizability of these results to other youth with CP and ABI are limited due to the selection bias of the sample. All participants of this study were patients in the LIFEspan Service, which offers clinical support and interventions to holistically target the myriad of challenges present in this population. As a result of the resources these individuals have access to, the findings may not be representative of youth with CP and ABI in the general population. Instead, the current sample likely represents a healthier and more engaged group of individuals with CP and ABI.

Another limitation is that this current study did not address the severity of condition of all participants. Lack of information on this variable limits our ability to understand its role and influence on functional outcomes, such as mental health and community integration.

Furthermore, components of the standardized measures chosen may not have been applicable or relevant to our sample population. Most notably, while the CIQ was developed for use in the brain injury population, the psychometric properties for the CP population are not known. Although anecdotally and intuitively, the CIQ items make sense as including important aspects of participation in non-brain injury populations, further validation is needed. Also importantly regarding the CIQ, participants provided feedback indicating that some questions in the CIQ were difficult to interpret. For example, the question, "Do you have a best friend with whom you confide?" was difficult to answer for some participants if they had a group of close friends. This finding alone may represent some of the inherent limitations of psychosocial measures currently used in these populations. In addition, the PHQ-4 was intended as a brief screening tool for depression and anxiety and may not be the most appropriate for this study as it is not a standardized diagnostic tool (18).

Future Directions

Future research should focus on conducting a longitudinal study starting with a younger population of individuals with CP

and childhood-onset ABI using the same objectives. Through tracking and monitoring changes over time, we could identify what can best support these populations as they develop, as well as monitor the effectiveness of the LIFEspan Service. This would provide further insight into psychosocial functioning at different stages of development, as well as the transition of care between pediatric and adult healthcare systems.

Future research should also examine how comorbidities commonly experienced by individuals with CP and ABI impact mental health outcomes. This would be a particularly worthy investigation, as some comorbidities commonly experienced by individuals with ABI and/or CP have been found to have significant impacts on mental health outcomes. For example, it has previously been reported that 20–30% of patients with epilepsy experience symptoms of depression (35); individuals with CP have been found to have a higher frequency of epilepsy compared to matched controls (22). Thus, individuals with co-occurring CP and epilepsy might be at higher risk for depression. A better understanding of factors influencing mental health outcomes will help better develop and target interventions for these populations.

As identified in our study limitations, more research is needed to further explore the impact of severity of conditions on mental health characteristics. Previous literature has suggested that higher severity levels may be associated with more negative function and quality of life for individuals with chronic childhood-onset conditions (2). It would be worthwhile to examine this relationship to identify how to better target and support each specific condition.

Lastly, it would be beneficial to expand the study to include a comparison group of youth with CP and ABI that may not have had access to similar coordinated care services. This would help to elucidate the effects of transitional services such as the LIFEspan Service.

Conclusions

Our current study, along with previous literature, highlights the need for further research to explore the unique needs and barriers faced by these populations. In addition, our findings may help to inform future assessments, treatment, and interventions to support the mental health and community engagement of individuals with CP and ABI.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University Health Network Research Ethics Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CN and ALe: led the creation of this manuscript. SM: research project and manuscript creation. All authors contributed to the review and feedback of the manuscript.

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Postural Asymmetries and Assistive Devices Used by Adults With Cerebral Palsy in Lying, Sitting, and Standing

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Purpose: To describe the use of assistive devices and postural asymmetries in lying, sitting and standing positions in adults with cerebral palsy, and to analyze postural asymmetries and any associations with their ability to maintain or change position and time in these positions.

Methods: A cross-sectional study based on data from the Swedish Cerebral Palsy follow-up program of 1,547 adults aged 16–76 years, at Gross Motor Function Classification System (GMFCS) levels I ($n = 330$), II ($n = 323$), III ($n = 235$), IV ($n = 298$), and V ($n = 361$). Assistive devices such as wheelchairs, seating systems, adjustable beds, standing equipment and time in each position were reported. The Posture and Postural Ability Scale was used to identify asymmetries and rate the ability to maintain or change position. Binary logistic regression models were used to estimate odds ratios (OR) for postural asymmetries in supine, sitting and standing.

Results: Assistive devices were used by 63% in sitting (range 5–100% GMFCS levels I–V), 42% in lying (4–92% levels I-V), and 32% in standing (2–70% levels II–V). Wheelchairs were used as seating systems by 57%. Most adults had postural asymmetries in supine (75%; range 35–100% levels I–V), sitting (81%; 50–99% levels I–V) and standing (88%; 65–100% levels I–V). Men were more likely than women to have postural asymmetries, and the likelihood of postural asymmetries increased with age, GMFCS levels and inability to change position. Inability to maintain position increased the probability of postural asymmetries in all positions from OR 2.6 in standing to OR 8.2 in lying and OR 13.1 in sitting.

Conclusions: Almost twice as many adults used assistive devices in sitting than in lying or standing. Two thirds of the adults who used standing devices used it for <1 h per day, indicating that they might spend the remaining 23 out of 24 h per day either sitting or lying. Asymmetric postures were frequent across all ages and were highly associated with inability to change or maintain position.

Keywords: adults (MeSH), asymmetries, assistive devices, cerebral palsy, posture (MeSH), sitting position, standing position, supine position

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INTRODUCTION

Reduced postural ability is often a key problem in adults with cerebral palsy. Assistive devices can be used to accommodate a lack of stability and make it possible to maintain lying, sitting or standing positions (1, 2). Assistive devices for standing are used by 31% of children with cerebral palsy and for sitting by 42% (3) but little is known about the use of assistive devices to maintain position in adults with cerebral palsy.

Postural asymmetries are frequent and associated with a limited range of joint motion and an inability to change position (4, 5). Asymmetric postures sustained for long periods of time are associated with deformities, contractures and pain, which most commonly affect the spine and the lower extremities (5–8). Inability to move and having a sustained posture increases the likelihood for contractures, making each posture relative to the time spent in that position clinically important throughout a 24-h cycle (4, 5, 9). Supported standing programs for adults with neurological conditions have been suggested to improve range of motion and activity when used regularly at least 30 min, 5 times a week (10).

In 1994, Sweden introduced a follow-up program and registry for children with cerebral palsy called CPUP (11). In 2009, the program expanded and offered regular examinations also to adults with cerebral palsy. However, most adults currently enrolled have not previously been followed as children (4). The registry includes information on neurologic subtype, gross motor function, posture and postural ability, assistive devices used in sitting, standing and lying and time spent in these positions.

The purposes of this study were to describe the use of assistive devices and postural asymmetries in sitting, lying and standing positions in adults with cerebral palsy at all levels of motor function, and to analyze postural asymmetries and any association with their ability to maintain or change position and time in these positions.

METHODS

Design and Inclusion

A cross-sectional study was performed based on data of all adults with cerebral palsy in Sweden, born between 1941 and 2002 who were examined within the follow-up program and reported into the registry between January 2016 and December 2018. Data from the last examination was used and no individual was excluded due to missing data. Inclusion criteria for cerebral palsy in this program were based on the Surveillance of Cerebral Palsy in Europe network with neurological symptoms of either spastic, ataxic, or dyskinetic cerebral palsy (12). Adults at all levels of the expanded and revised version of the Gross Motor Function Classification System level (GMFCS) I–V were included (13). GMFCS levels were classified by the local physical therapists at the examinations. Variables extracted from the follow-up program were type of assistive devices and time spent in sitting, standing and lying positions, postural asymmetries, ability to maintain and change position, and demographic variables such as sex, age and GMFCS level.

Assistive Device and Time in Each Position

Assistive devices to maintain a body position were reported as "Yes or No" for lying and standing. Positioning equipment used for lying was reported as either adjustable bed or positioning cushions/rolls. Standing devices were specified as individually molded bilateral hip-knee-ankle-foot orthosis (HKAFO), standing frame/tilt board, or standing wheelchair. Equipment for mobility or transfers e.g., crutches, walkers or hoists were not included. For sitting, the options were either regular chair or assistive devices categorized as follows: custom molded seating systems; tilt-in-space wheelchairs (usually a recline manual or power wheelchair with high back rest); wheelchairs without tilt-in-space (usually a regular or active wheelchair); or adaptive seating (any modular seating system or adaptive seating prescribed as an assistive device to sit). A new variable was created based on all reported devices for sitting, with any assistive device to sit coded as "Yes" and a regular chair coded as "No." Time spent standing was only reported for adults using standing devices into < 1, 1–2, 3–4, or >4 h, while time sitting and lying were reported for all individuals as <8, 8–12, or >12 h daily. Questions were asked by the therapists at the examinations and answered by the adult and/or proxy when needed.

Postural Asymmetries and Ability to Change Position

Postural asymmetries and the ability to maintain and change position were assessed using the Posture and Postural Ability Scale (PPAS) (14). It shows high interrater reliability and validity when used with adults with cerebral palsy (14). The ability to maintain or change position was rated on a 7-point ordinal scale ranging from level 1 (unplaceable in an aligned position) to level 7 (able to move into and out of position independently). In this study, we refer to level 1 and 2 as "Cannot maintain position," level 3 and 4 as "Maintains position," level 5 and 6 as "Moves within position" and level 7 as "Changes position." Postural asymmetries were rated in supine, sitting and standing positions, separately for the frontal (anterior-posterior) and the sagittal (medio-lateral) views. Symmetry of head, trunk, pelvis, leg, arm and foot position, and even weight distribution were scored as "1 point," with a total score of 6 points for each position. Asymmetry or uneven weight distribution scored "0 points," resulting in a total score ranging from 0 to 6 points. We refer to postural asymmetries as being "Severe" when the whole body is affected (0–1 point), as "Moderate" when 3 to 4 body segments are asymmetric (2–3 points), or as being "Mild" when 1 to 2 segments are asymmetric (4–5 points).

Age and Sex

Age was grouped into six categories: 16–19, 20–24, 25–29, 30–39, 40–49, and 50–76 years, with a narrower age span in the younger age groups, when young adults transition from school and living with parents to higher education, employment and independent living (15). Sex was based on the legal gender, female or male.

Ethical Approval

Ethical approval was granted by the Regional Ethical Review Board Lund, LU 443-99.

Statistical Analyses

Spearman's rank correlation coefficients were used to estimate correlation coefficients among ordinal variables. Chi-square and Chi-square for trend were used to analyze differences between subgroups and increasing or decreasing trends in ordinal data (e.g., GMFCS levels). Binary logistic regression models were used to estimate odds ratios (OR) with 95% confidence intervals (CIs) for associations between postural asymmetries in lying, sitting or standing positions with their ability to maintain or change position in these positions, sex, age and GMFCS level. For the regression analyses, the primary outcome postural asymmetries was dichotomized into two groups, with 0 to 3 points graded as "Moderate and Severe asymmetry" and 4 to 6 points as "Mild or No asymmetry." Interactions between adjusted variables were explored. The significance level was set to 0.05. The statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corporation, Armonk, NY).

RESULTS

In total, 1,547 adults with cerebral palsy were included, 854 men and 693 women, median age 25 (range 16–76 years). Most adults were classified as having bilateral spastic cerebral palsy (55.6%) and severe motor impairment, GMFCS V (23.3%) (**Table 1**).

Assistive Devices and Time in Each Position

Assistive devices were used by 63% of all adults in sitting, by 42% in lying, and by 32% in standing. The use of assistive devices was similar for males and females but differed between age groups. The proportion of adults using assistive devices in lying and sitting was incrementally higher from 35 to 55% of the 20–24-year olds up to 52 and 78% of the 40–49-year olds (**Figure 1**). The use of standing devices ranged from 31 to 37% in the 16–49-year olds but dropped to 17% in the 50–76-year olds (**Figure 1**).

The use of assistive device increased with GMFCS level in sitting ($r_s = -0.78$) and lying ($r_s = -0.67$) ($p < 0.001$), from only 4–5% in those classified at GMFCS I, up to 92–100% of the adults at GMFCS V (**Table 2**). Positioning rolls or pillows were used by 31% of the adults and equally as many used adjustable beds (32%), with the vast majority being used by adults at GMFCS V. Wheelchairs were used as seating systems by 57%, by far the most common assistive device. Most individuals at GMFCS III and IV used regular wheelchairs, whereas the majority of those at GMFCS V used wheelchairs with tilt-in-space and almost half used a custom molded seating system. Standing devices were used by 32% of the adults and of those, 22% used either a standing frame or tilt-table, 12% used individually molded rigid bilateral HKAFO as their primary standing support, while 7% of adults used standing wheelchairs. The use of standing devices increased from 2% in adults at GMFCS II up to 70% of those at GMFCS V ($r_s = -0.62$, $p < 0.001$) (**Table 2**).

Two thirds of the adults (67%) spent 8–12 h per day in bed, while 22% spent <8 h and 11% spent more than 12 h per day lying. Half of the adults (50%) spent 8–12 h per day sitting, while 27% sat <8 h and 22% sat more than 12 h per day. Almost two thirds (67%) used their standing support <1 h per day, while 28% were standing for 1–2 h daily and only 4% used it for more than 2 h daily. A slightly higher proportion of adults at GMFCS V (35%) spent at least 1 h standing daily compared with those classified at GMFCS III (28%) and IV (30%).

TABLE 1 | Description of all 1,547 participants with cerebral palsy.

		N	%
Sex	Male	854	55.2%
	Female	693	44.8%
Age (years)	16–19	304	19.7%
	20–24	450	29.1%
	25–29	288	18.6%
	30–39	251	16.2%
	40–49	142	9.2%
	50-76	112	7.2%
CP subtype	Spastic unilateral	335	22.0%
	Spastic bilateral	846	55.6%
	Ataxic	61	4.0%
	Dyskinetic	192	12.6%
	Mixed type	88	5.8%
	Missing	25	
GMFCS	GMFCS I	330	21.3%
	GMFCS II	323	20.9%
	GMFCS III	235	15.2%
	GMFCS IV	298	19.3%
	GMFCS V	361	23.3%

GMFCS, Gross Motor Function Classification System.

Postural Asymmetries and Ability to Change Position

Postural asymmetries were frequent in all positions and increased with GMFCS levels. In total, 75% of the adults had postural asymmetries in the frontal and/or sagittal view in lying, ranging from 35% of those at GFMCS I through 65% at level II, up to 95–100% of the adults at GMFCS levels IV and V. In sitting, 81% had postural asymmetries, ranging from 50% at GMFCS I up to 88% of the adults at level III and 98–99% at level IV and V, respectively. Almost nine out of 10 (88%) had postural asymmetries in standing, from 65% at GMFCS I and 90% at level II, to almost all adults at level III, IV and V (98–100%). A substantially higher proportion of the adults at GMFCS IV and V had severe asymmetries in all three positions compared to adults at GMFCS I and II (**Figure 2**).

As expected, postural ability decreased with lower levels of motor function and correlated significantly ($p < 0.001$) with the GMFCS in lying ($r_s = -0.82$), sitting ($r_s = -0.87$) and standing ($r_s = -0.86$). All adults at GMFCS level I and II were able to change their position independently. Median values and 25 and 75th percentiles for postural asymmetry and postural ability are presented in **Table 3**. Individuals classified at GMFCS III showed the most variability between different positions, with most able to

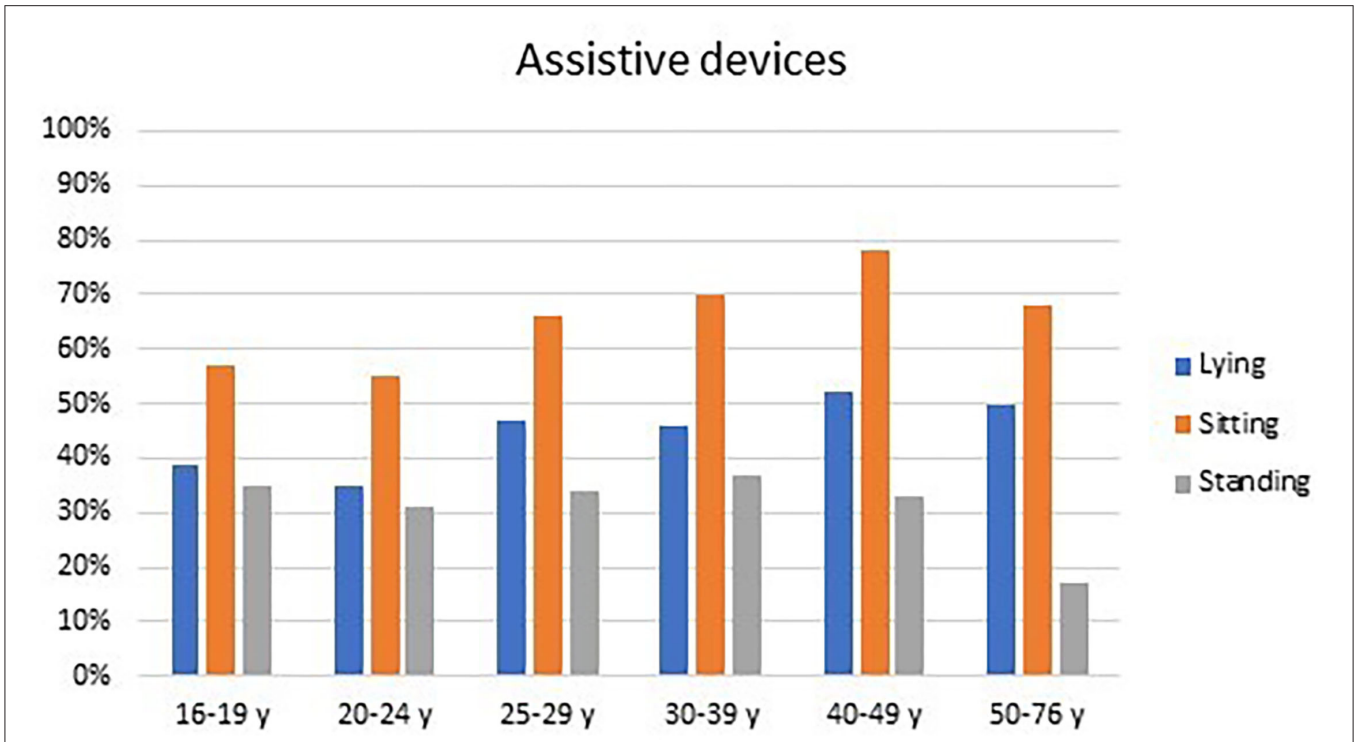

FIGURE 1 | Assistive devices used in lying, sitting, and standing by adults at different age groups.

TABLE 2 | Assistive devices used in lying, sitting and standing by adults at GMFCS I to V.

	GMFCS I (*n* = 330)		GMFCS II (*n* = 323)		GMCFS III (*n* = 235)		GMFCS IV (*n* = 298)		GMFCS V (*n* = 361)		Total (*n* = 1,547)	
	N	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**
Assistive devices in lying	15	4%	47	15%	79	34%	183	61%	332	92%	656	42%
Cushions, positioning rolls	11	3%	26	8%	43	18%	105	35%	290	80%	475	31%
Adjustable bed	4	1%	22	7%	47	20%	143	48%	282	78%	498	32%
Assistive devices in sitting	16	5%	99	31%	200	85%	298	100%	360	100%	973	63%
Moulded seating	0	0%	0	0%	6	3%	45	15%	170	47%	221	14%
Tilt in space wheelchair	0	0%	7	2%	30	13%	130	44%	277	77%	444	29%
Wheelchair no tilt	0	0%	48	15%	157	67%	190	64%	43	12%	438	28%
Adaptive seating	16	5%	70	22%	101	43%	88	30%	50	14%	322	21%
Assistive devices in standing	0	0%	7	2%	59	25%	181	61%	254	70%	501	32%
Standing frame/tilt board	0	0%	6	2%	44	19%	109	37%	181	50%	340	22%
HKAFO	0	0%	0	0%	10	4%	45	15%	135	37%	190	12%
Standing wheelchair	0	0%	3	1%	21	9%	58	20%	23	6%	105	7%

GMFCS, Gross Motor Function Classification System; HKAFO, an individually molded rigid bilateral hip-knee-ankle-foot orthosis.

change position in lying but unable to maintain position without support in standing (**Table 3**).

Of the adults with severe asymmetries in lying, 95% of those at GMFCS V used lying support, while 76% of those at GMFCS IV and only 20% of those at GMFCS III did the same. Also, quite a high proportion of adults without asymmetries used lying support: 75% of those at level V and 40% at level IV. All individuals at GMFCS IV and V with severe asymmetries in sitting used seating support. In standing, all adults with severe asymmetries used standing support except those at GMFCS V, where only half (51%) used standing support.

Men were more likely than women to have postural asymmetries in supine (OR 1.77, 95% CI 1.34–2.35) and sitting (OR 1.37, 95% CI 1.05–1.79), and the likelihood of postural asymmetries increased with age, GMFCS levels and

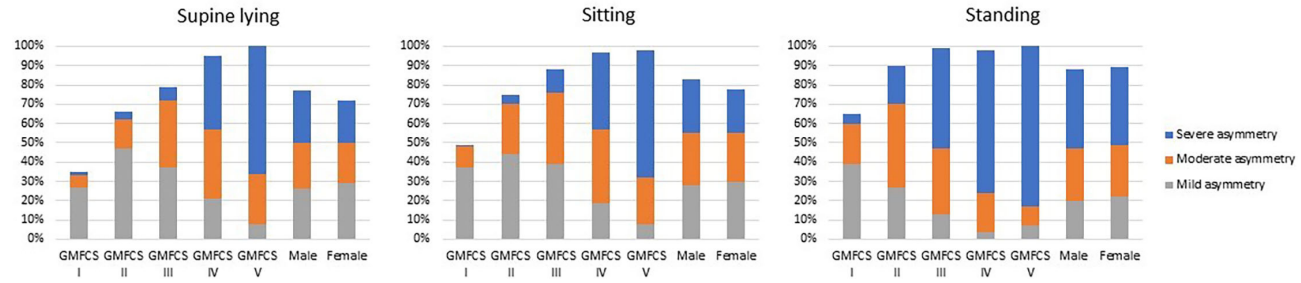

FIGURE 2 | Postural asymmetries in supine lying, sitting, and standing positions of adults by GMFCS levels and sex.

TABLE 3 | Median values with 25 and 75th percentiles for the Posture and Postural Ability Scale scores for posture and postural ability in supine, sitting and standing positions of adults at GMFCS I to V.

		GMFCS I		GMFCS II		GMFCS III		GMFCS IV		GMFCS V	
		Median	**Percentile**	**Median**	**Percentile**	**Median**	**Percentile**	**Median**	**Percentile**	**Median**	**Percentile**
Posture	Supine, frontal	6	(5–6)	5	(4–6)	5	(3–6)	2	(1–4)	1	(0–2)
	Supine, sagittal	6	(6–6)	6	(5–6)	5	(3–6)	3	(1–4)	2	(1–3)
	Sitting, frontal	6	(5–6)	5	(4–6)	4	(3–6)	2	(1–4)	1	(0–3)
	Sitting, sagittal	6	(5–6)	5	(4–6)	4	(3–5)	3	(2–4)	2	(0–3)
	Standing, frontal	5	(4–6)	4	(2–5)	2	(1–4)	1	(0–2)	0	(0–1)
	Standing. sagittal	6	(5–6)	4	(2–5)	2	(1–3)	1	(0–2)	0	(0–1)
Postural ability*	Supine lying	7	(7–7)	7	(7–7)	7	(7–7)	5	(4–7)	3	(3–4)
	Sitting	7	(7–7)	7	(7–7)	7	(6–7)	4	(2–5)	2	(2–2)
	Standing	7	(7–7)	7	(7–7)	6	(2–7)	2	(2–2)	2	(1–2)

GMFCS, Gross Motor Function Classification System.

**Level 7, Able to move into and out of position; Level 6, Able to move out of position; Level 5, Able to transfer weight laterally and regain posture; Level 4, Able to initiate flexion/extension of trunk; Level 3, Able to maintain position when placed but cannot move; Level 2, Placeable in an aligned posture but needs support, Level 1, Unplaceable in an aligned posture (see section Postural Asymmetries and Ability to Change Position for more details).*

inability to change position (**Table 4**). Inability to maintain position increased the likelihood of an asymmetric posture in both supine (OR 8.18, 95% CI 2.92–22.95), sitting (OR 13.1, 95% CI 6.26–27.41) and standing positions (OR 2.62, 95% CI 1.38–4.97) even when adjusted for age, sex, and GMFCS level (**Table 4**).

DISCUSSION

This study describes the use of assistive devices in lying, sitting and standing positions in adults with cerebral palsy at all GMFCS levels, postural asymmetries and associations with their ability to maintain or change position and time in these positions.

Assistive Device and Time in Each Position

The use of assistive devices in standing (32%) was similar to previous findings reported for children (31%) (3), while the use of assistive devices in sitting was substantially higher in adults (63%) compared with children (42%) (3). The use of wheelchairs as seating systems (57%) in adults can also be associated with an increased use of wheelchairs for mobility with age, as previously reported for children and adolescents with cerebral palsy (16, 17). Transfers between different assistive devices may also be more challenging and time-consuming in adults than in younger children and may lead to the use of wheelchairs as a seating solution and not only as mobility equipment in adults. In addition, lying support was used by 42% of adults. We found no comparable data of lying support for children.

The use of assistive devices was similar for men and women. If we look more closely at the adults at GMFCS IV and V, everyone used assistive devices to sit, and a vast majority also used lying support (61–92%), which indicates that a majority of adults with cerebral palsy have postural support most of the day and night. Proper use of adjustable beds and positioning equipment such as rolls and pillows should provide comfortable non-harmful postures in lying, increase the weight-bearing area to improve sleep and minimize pain and pressure. A significant improvement in sitting posture and postural control has previously been found in people with cerebral palsy using seating support, such as orthotics, seat inserts, external supports and modular seating systems (18–20). We found that all adults at GMFCS level IV and V who had an asymmetric sitting posture used an assistive device in sitting, which is encouraging. Almost half of those at GMFCS V used custom molded seating

TABLE 4 | Odds ratios (OR) with 95% confidence intervals (CI) and R square (R^2) estimated for moderate to severe postural asymmetries in lying, sitting and standing positions.

Postural asymmetries	Supine lying (R^2 = 0.52)				Sitting (R^2= 0.47)				Standing (R^2 = 0.37)			
	OR	95% CI		*P*-value	OR	95% CI		*P*-value	OR	95% CI		*P*-value
Female	*Ref*				*Ref*							
Male	1.77	1.34	2.35	<0.001	1.37	1.05	1.79	0.021	1.21	0.93	1.59	0.162
Age	1	0.99	1.01	0.743	1.01	1.00	1.03	0.014	1.01	1.00	1.03	0.043
GMFCS I	*Ref*				*Ref*				*Ref*			
GMFCS II	2.44	1.44	4.11	0.001	3.50	2.15	5.73	<0.001	3.21	2.25	4.58	<0.001
GMFCS III	5.64	3.34	9.51	<0.001	4.92	2.89	8.37	<0.001	5.45	3.35	8.88	<0.001
GMFCS IV	15.50	8.68	27.69	<0.001	9.13	4.69	17.77	<0.001	9.06	4.29	19.14	<0.001
GMFCS V	27.36	13.45	55.64	<0.001	5.47	2.33	12.80	<0.001	14.93	6.27	35.50	<0.001
Changes position	*Ref*				*Ref*				*Ref*			
Moves within position	1.73	1.08	2.77	0.023	1.53	0.91	2.57	0.106	1.23	0.49	3.08	0.667
Maintains position	3.36	1.97	5.74	<0.001	3.26	1.81	5.86	<0.001	1.35	0.59	3.12	0.481
Cannot maintain position	8.18	2.92	22.95	<0.001	13.10	6.26	27.41	<0.001	2.62	1.38	4.97	0.003

Binary logistic regression models with all variables adjusted for all other variables in the model.
GMFCS, Gross Motor Function Classification System.

systems and two thirds used tilt-in-space wheelchairs. These are provided for free and the total annual fee for visits to therapists, general practitioners, assistive technology centers, primary health care or hospitals for adults in Sweden is limited to 113 euros.

We found that three in four adults spent at least 8 h of the 24 h in a day lying (76%) and 8 h or more in sitting (74%). Almost two thirds (67%) of the adults who used standing support used it <1 h per day, which is similar to the 64% previously reported for children in the UK (21). This finding is concerning, as it implies that adults who use standing devices spend 23 out of the 24 h per day either sitting or lying. In addition, most of the adults using standing support (GMFCS IV and V) were unable to change their position independently while lying or sitting. The time spent in each position is more important for those who cannot change position independently, as they are more likely to remain in the same position over long periods (5). The opportunity for a change in position was reported as an indication of a need for standing devices in children by almost 80% of the parents and clinicians in the UK (21).

Postural Asymmetries and Ability to Change Position

Postural asymmetries were more frequent and involved more body segments in a standing position than in sitting or lying. This contrasts with previous findings in young adults with cerebral palsy where those at GMFCS level V were reported to have fewer asymmetries in standing compared with sitting and lying (4). This may be partly explained by the difference in sample size (102 vs. 1,547) and age span (19–23 vs. 16–76 years). Alternatively, it might indicate that the asymmetries seen in young adults might be more reducible when provided with appropriate support, while the asymmetries in older adults might be more associated with non-correctable fixed deformities. A recent study of children with cerebral palsy shows an increasing trend, with more asymmetries in older children and adolescents than in younger children (7). However, the asymmetries were already seen in children before the age of 3 years (7). This is a major concern, as asymmetric posture in early life is associated with the development of fixed deformities such as windswept hips and scoliosis (22). Also, contractures have a tendency to develop over time in individuals with cerebral palsy (23) and they increase the risk of fixed deformities (24).

Despite challenges with asymmetric standing postures, the use of assistive devices in a standing position was almost the same in adults as previously reported for children. Our results indicate that a reduced ability to change and maintain a position increases the likelihood of an asymmetric posture. As noted above, asymmetric postures in sitting and lying are associated with scoliosis and windswept deformity in both children and adults with cerebral palsy (5, 8, 25), which might be explained by the longer time spent in these two positions. Several adults without asymmetries used adjustable beds and positioning equipment in lying. Hopefully this is a sign of proactive rather than reactive treatment strategies.

Maintaining or changing a standing position is normally more challenging, compared with sitting and supine positions. This observation is in line with our findings where the median scores and 25 and 75th percentiles for postural ability in standing were lower for adults at GMFCS levels III to V compared with those in supine and in sitting. There was also a clear trend for lower postural ability for adults at GMFCS III, IV and V. Not being able to maintain or change position can lead to the development of contractures and deformities (5). Individuals with cerebral palsy at GMFCS levels IV and V, accounting for a total of 43% of our cohort, were unable to maintain or change position independently and thereby are at a high risk of developing

contractures and deformities. We found postural asymmetries across all GMFCS levels, but they were more frequent in adults at GMFCS IV and V. Surprisingly, men were more likely than women to have postural asymmetries in both supine and sitting positions, but their use of assistive devices to stay in these positions were similar. Moreover, inability to maintain or change position was identified as an independent risk factor and significantly increased the likelihood for asymmetric postures in all three basic body positions even when adjusted for age, sex and GMFCS levels.

Limitations

The cross-sectional design cannot establish any causal relationships but only identify associations between variables. Even though we had access to a relatively large cohort, including adults classified at all functional levels and with a wide age span, it does not represent the total population of adults with cerebral palsy. The age distribution of our cohort is skewed, with a preponderance of younger adults under 30 years of age. There is a slightly higher proportion of adults with spastic bilateral cerebral palsy and less with spastic unilateral cerebral palsy than reported by others (26–28). There is also a higher proportion of adults with more severe motor impairment classified at GMFCS V and less at GMFCS I compared with the distribution of GMFCS levels reported for children (27). We cannot say if this is a selection bias or an indication of the decline in gross motor function seen in adults with CP. In Sweden, assistive devices such as lying support and sitting and standing support, are usually provided as a loan by regional Assistive Technology Centers. Therefore, the results of this study are likely to reflect the use of assistive devices without regard to the socioeconomic situation of the individuals. Even though this study represents un unselected population of adults with CP reported into the registry regardless of their age, sex, motor function, communication and cognitive abilities or neurological impairment, the findings may not be representative for other countries with different healthcare systems. All data is retrieved from a National Registry and as such, covers the whole country. Even though all data is reported into the database according to established guidelines and manuals, there might be some errors due to classification or reporting errors. Time spent in different positions was self-reported and/or reported by proxy. This could potentially affect the results as the agreement between these two has not been evaluated. Even so, the use of GMFCS and PPAS has previously shown a high reliability and validity for adults with cerebral palsy (14, 29).

CONCLUSIONS

In this study we found that two out of three adults with cerebral palsy used assistive devices in sitting, which was almost twice as many as those who used assistive devices in lying and standing. Most adults used their wheelchairs as seating systems. Two thirds of the adults who used standing devices used it for <1 h per day, indicating that they might spend the remaining 23 out of 24 h per day either sitting or lying. Standing is normally more challenging and postural asymmetries were more frequent and involved more body segments in standing than in sitting or lying. An unexpected finding was that men were more likely than women to have postural asymmetries. We found postural asymmetries across all GMFCS levels, but they were more frequent in adults at GMFCS IV and V and they were highly associated with inability to change or maintain position. Therefore, it should be a priority to facilitate more frequent changes in position for those who cannot change position on their own. However, it is encouraging that several adults without asymmetries used adjustable beds and positioning equipment in lying. Hopefully this is a sign of proactive rather than reactive treatment strategies and efforts to prevent the development of postural asymmetries.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data analyzed in this study were obtained from the Cerebral Palsy Follow-Up Program (CPUP) registry, the following licenses/restrictions apply: requests to access the datasets are subject to ethical approval and must first be granted by KVB Region Skåne. Requests to access the datasets should be directed to https://vardgivare.skane.se/kompetens-utveckling/forskning-inom-region-skane/utlamnande-av-patientdata-samradkvb/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Ethical Review Board Lund. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

ER-B and AA designed the study, analyzed the data, drafted the manuscript, and approved the final draft. Both authors contributed to the article and approved the submitted version.

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Body Fat Distribution and Associated Risk of Cardiovascular Disease in Adults With Cerebral Palsy

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Objective: Fat distribution has increasingly been acknowledged as a more significant health parameter than general obesity, in terms of the risk of cardiovascular disease (CVD). We aimed to investigate the regional fat distribution pattern and general body fat characteristics of adults with cerebral palsy (CP), and we explored the risk of CVD in this population.

Methods: People aged ≥20 years who were diagnosed with CP were recruited between February 2014 and November 2014. The subjects underwent a structured interview, laboratory studies, and physical examination. The amount and distribution of fat were determined directly by dual-energy X-ray absorptiometry. Laboratory analysis was performed to measure total cholesterol and triglyceride, high-density lipoprotein (HDL), low-density lipoprotein, and fasting plasma glucose levels. The Framingham risk score (FRS) was used to present the 10-year risk for having CVD, and predictors such as sex, age, total cholesterol, HDL, systolic blood pressure, treatment for hypertension, and smoking status were used to calculate the FRS.

Results: Ninety-nine adults (58 men, mean age 41.77 ± 8.95 years) with CP were included. The participants consisted of all five levels of the Gross Motor Function Classification System. The mean body mass index (BMI) was 22.52 ± 4.58 kg/m². According to BMI criteria, 54.9% were overweight and 27.3% were obese. The fat mass index criteria revealed 10.1% excess fat and 7.6% obesity. In univariable regression analysis, age, the timing of physical function deterioration, and android fat percentage were associated with the FRS ($p < 0.001$, $p < 0.001$, and $p = 0.007$, respectively). In multiple regression analysis, the FRS was associated with age and android fat percentage, based on the following formula:

$$\text{"FRS} = -18.549 + 0.410 * \text{Age} + 0.577 * \text{Android percent fat (\%)}\ (R^2 = 0.528)''$$
$$(p < 0.001).$$

Conclusions: Body fat distribution in the android area is significantly associated with future CVD risk in adults with CP.

Keywords: cerebral palsy, cardiovascular risk, framingham risk score, fat distribution, android fat distribution, adults

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INTRODUCTION

When people with cerebral palsy (CP) mature into adulthood, they frequently face various secondary conditions. Among the major challenges of this population, lack of physical activity, decreased physical fitness, and a sedentary lifestyle are often reported in adulthood (1, 2). There is a medical concern that these factors may increase the risk of cardiovascular disease (CVD) in the CP population (1–4). Several previous studies have shown that CVD-related mortality is higher in people with CP than in the general population (1, 3, 5).

Physical inactivity in people with CP may increase the risk of obesity. At the same time, they have an increased risk of dysphagia and other gastrointestinal problems, which may lead to nutritional deficiency (6, 7), while spasticity can lead to increased energy consumption (8–10). The reported prevalence of actual obesity in the adult CP population has varied across studies (2, 4).

Recently, fat distribution has been proposed to be more closely associated with CVD risk than with the general measures of obesity, such as total fat mass or body fat percentage (11, 12). Android fat distribution, which refers to the central distribution of body fat, is an important risk factor for future cardiovascular events, independent of overall fat volume (13). More specifically, adults with CP are exposed to secondary musculoskeletal changes, including loss of muscle mass, muscle shortening, joint contractures, and deformity (14). Deficits in lean mass, with replacement by fat tissue, have been reported in several studies on people with CP (15–17). It has been reported that children with CP present with greater intermuscular adiposity than the neurologically intact group (18). Adults with CP also show larger visceral and subcutaneous adiposity (4). Furthermore, the prevalence of sarcopenia in adults with CP is higher than that in the general population (19). Fat distribution may be particularly important in this population because of possible differences in body composition. Therefore, it is assumed that the regional fat distribution, as well as general body fat characteristics, may show a profile in people with CP that differs from that in the general population.

Therefore, we sought to identify the prevalence of obesity and the characteristics of body fat distribution in an adult population with CP, and we assessed their cardiovascular risks and the relationship thereof with body fat distribution in this population.

MATERIALS AND METHODS

Participants

Participants were recruited from the community, with the cooperation of nationwide organizations for persons with disabilities, and four hospitals in Gyeonggi and Seoul in South Korea. A total of 243 adults with CP were included in this study. Participants were excluded if they were not able to understand or answer the questionnaire despite receiving assistance from an interviewer, if they failed to complete dual-energy X-ray absorptiometry (DXA), or if they withdrew before data collection. Data were collected between February 1, 2014, and November 31, 2014.

All study procedures were approved by the institutional review boards of the participating institutions, operating in compliance with the Guidelines for Good Clinical Practice. Written informed consent was obtained from all participants. After obtaining consent from the participants, questionnaire surveys on basic information, assessments, and measurements were conducted.

Structured Interview and Physical Examination

A structured interview and physical examination were conducted by a physiatrist or a trained research nurse in order to complete the questionnaire regarding demographics and physical function. The questionnaire included questions on sex, age, current smoking status, and drinking habits. Current smoking was defined as any cigarette smoking within the previous month. Never cigarette smokers and ex-cigarette smokers were classified as non-smokers. Likewise, drinkers were classified as those with any alcohol consumption in the past previous month.

Waist circumference and resting blood pressure were also measured. Waist circumference was measured in subjects in a standing position, at normal expiration. It was measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, using a stretch-resistant tape (20), once for each participant. Systolic blood pressure (SBP; mmHg) was determined as the average of two measurements taken 1 min apart, with the subjects in the supine position, after subjects had rested quietly in a chair for at least 5 min. Treatment for hypertension was also recorded.

The types of CP and the areas affected were investigated. They were determined by a single physiatrist (SHJ) with more than 15 years of clinical experience in CP. The types of CP were classified as spastic, dystonic, dyskinetic, ataxic, or mixed (21). Affected areas were determined as quadriplegia, diplegia, hemiplegia, and monoplegia of the upper and lower extremities (22).

For gross motor function, we used the Gross Motor Function Classification System (GMFCS). This is a five-level scale, where level I represents the least disability and level V the most, based on typical performance rather than the maximal capacity (23, 24). People with GMFCS level I walk without limitations, whereas people with level V are transported in a manual wheelchair. It is widely used to describe abilities and limitations in gross motor function, including sitting and walking, in children and adolescents, aged up to 18 years, with CP (25). The subject's current and best previous GMFCS levels were determined by a physiatrist after a structured interview and clinical examination.

The age at deterioration of physical function was also examined. GMFCS levels in 10-year intervals were determined, and the age span of physical deterioration was defined as the period when there was a regression of GMFCS level. The participants were also categorized according to the GMFCS level: ambulatory (GMFCS levels I, II, and III) and non-ambulatory groups (GMFCS levels IV and V). History of fall and number of falls in the past year were recorded by interviewing the patients.

The Short Physical Performance Battery (SPPB) was assessed by a trained physiotherapist. It is a group of measures that

combines the results of gait speed, chair stand, and balance tests (26). It is an important indicator of functional mobility and independence (26).

Criteria for General Obesity

Basic body anthropometry was performed to measure height and body weight. Cutoffs for body mass index (BMI, kg/m^2) were as follows: overweight (BMI of 25.0–29.9), and class 1, 2, and 3 obesity (BMI of 30–34.9, 35.0–39.9, and ≥40.0, respectively) (27). Fat mass index (FMI, kg/m^2) was calculated as fat mass divided by the square of height. Cutoffs for FMI were as follows: fat deficit (<5%), normal (5%−9%), excess fat (>9%−13%), class I obesity (>13%−17%), and class II–III obesity (>17%) (28).

Measurement of Body Fat Composition

For body composition assessment, DXA (GE Lunar Prodigy, Bedford, MA, United States) was used. DXA provides a precise evaluation of body composition at a relatively low cost (29). DXA differentiates bone mineral, lean, and fat soft tissues by measuring two different energy levels emitted from each type of tissue. The regions of interest (ROIs) were defined and calculated using the software provided by the manufacturer for local fat composition assessment. The android ROI was defined from the pelvis cut (lower boundary) to above the pelvis cut, by 20% of the distance. The gynoid area was from the lower boundary of the umbilicus ROI (upper boundary) to a line equal to two times the height of the android fat distribution ROI (lower boundary) (**Figure 1**).

Laboratory Studies

A venous blood sample was obtained for laboratory analysis. The participants fasted for at least 8 hr before their blood was drawn. Blood composition analysis included total cholesterol and triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and fasting plasma glucose (FPG) levels.

Calculation of the Framingham Risk Score

The FRS has been widely used for the risk assessment of CVD (30, 31). The FRS was used to represent a participant's 10-year risk of coronary heart disease. The FRS was calculated using a web-based calculator (http://cvdrisk.nhlbi.nih.gov). This tool was designed for adults aged 20 years and older. The FRS estimates the 10-year coronary heart disease risk based on predictors, such as sex, age, total cholesterol, HDL, SBP, treatment for hypertension, and smoking status (32).

Statistical Analysis

Means ± SD and 95% confidence intervals (CIs) were calculated for continuous variables. The clinical characteristics were compared between groups using an independent *t*-test for continuous variables and Student's *t*-test or Fisher's exact test for categorical variables. Adjustment of alpha level was not made for multiple comparisons in this study, as the authors assumed that it may lead to fewer errors in interpretation (33).

Associations between the FRS and other factors were examined using univariable and multiple regression analyses. To determine the factors independently associated with the FRS, variables with $p < 0.05$ on univariable regression analysis were used for multiple regression analysis.

All *p*-values were calculated from two-tailed tests of statistical significance, with significance declared at the 5% level. All statistical analyses were conducted using the SPSS version 20.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Characteristics of the Participants

Ninety-nine adults with CP were enrolled; however, 79 adults were included in the analysis in this study. DXA could not be performed in 20 adults. In 17 adults, precise measurement was not possible because of deformities and abnormal postures. Two adults had dystonic-type CP and one adult had athetoid-type CP and could not remain still during the measurement. The mean age of the study population (45 men and 34 women) was 42.2 ± 8.5 (95% CI, 40.3–44.2) years. The participant's characteristics, physical functions, and laboratory results are shown in **Table 1**.

Body Composition

There was no significant difference between sexes in waist circumference, BMI, BMI criteria, total body fat mass and fat percentage, and gynoid fat mass (**Table 2**). However, women had significantly higher gynoid fat mass, a higher percentage of gynoid and android body fat relative to the total body fat, and a lower android/gynoid fat ratio ($p = 0.001$, $p = 0.003$, $p < 0.001$, respectively). The FMI was significantly higher in women than in men ($p = 0.006$). According to the FMI criteria, more men had a fat deficit than women ($p = 0.002$) (**Table 2**).

There was no significant difference between the ambulatory and non-ambulatory groups in waist circumference, BMI, and body fat composition. However, there was a higher proportion of underweight individuals, by BMI criteria, in the non-ambulatory group ($p = 0.006$) and a higher proportion of individuals with normal FMI in the ambulatory group ($p = 0.036$).

The 10-year risk of developing coronary heart disease was higher in men than in women ($p < 0.001$). The FRS and 10-year risk of developing coronary heart disease did not differ between the ambulatory and non-ambulatory groups.

Framingham Risk Score and Related Factors

Univariable regression analysis showed that FRS was positively associated with increasing age ($p < 0.001$; **Table 3**). The FRS also increased as the percentage of android fat increased ($p = 0.007$). In women, the android/gynoid fat ratio was positively associated with FRS ($p = 0.047$).

Multiple regression analysis of the FRS was performed with the factors (age and android fat percentage) that were significantly associated with FRS in univariable regression analysis. Multiple regression analysis showed that the FRS was associated with age and android fat percentage based on the formula below ($p < 0.001$). R^2 shows the percentage of variance

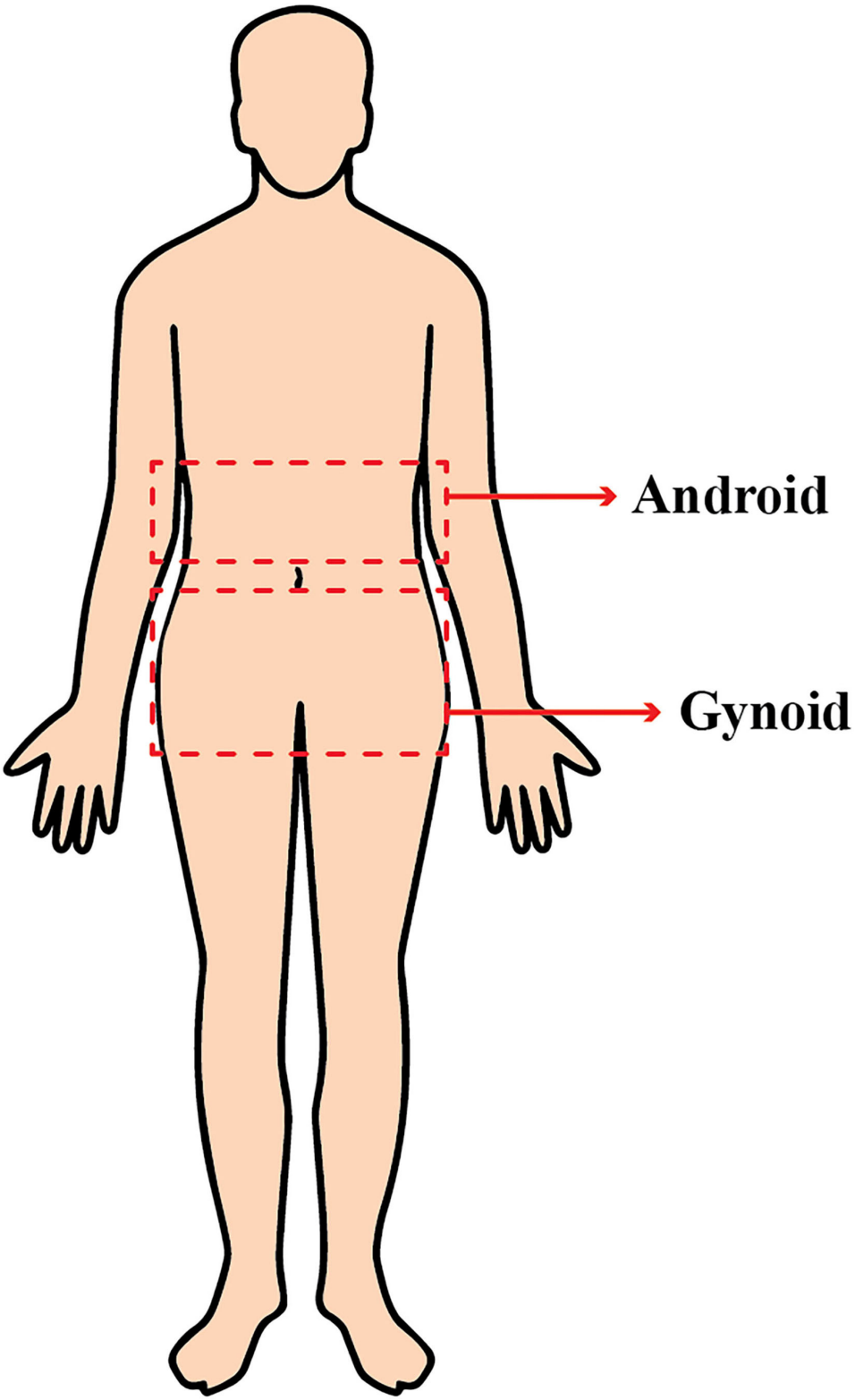

FIGURE 1 | Android and gynoid body fat distribution.

TABLE 1 | Participant's characteristics, physical function, and laboratory results.

	Total (*N* = 79)	Men (*N* = 45)	Women (*N* = 34)
Age (year)	42.2 ± 8.5 (40.3–44.2)	42.7 ± 9.9 (39.8–45.7)	41.6 ± 6.4 (39.3–43.8)
Smoking (*N* = 77)			
Current smoker	15 (19%)	14 (31%)	1 (3%)
Alcohol (*N* = 74)			
Drinker	43 (54%)	26 (61%)	17 (55%)
Types of CP			
Spastic	27 (34%)	16 (36%)	11 (32%)
Dystonic	13 (17%)	9 (20%)	4 (12%)
Dyskinetic	7 (9%)	3 (6%)	4 (12%)
Ataxic	1 (1%)	1 (2%)	0
Mixed	31 (39%)	16 (36%)	15 (44%)
Affected area (*N* = 76)*		**(*N* = 42)**	**(*N* = 34)**
Quadriplegic	46 (60%)	23 (52%)	23 (72%)
Diplegic–both LE	12 (16%)	10 (23%)	2 (6%)
Diplegic–both UE	6 (8%)	2 (5%)	4 (13%)
Hemiplegic	8 (10%)	7 (16%)	1 (3%)
Monoplegic	4 (5%)	2 (4%)	2 (6%)
Current GMFCS level			
I	10 (13%)	4 (9%)	6 (18%)
II	21 (26%)	9 (20%)	12 (35%)
III	4 (5%)	4 (9%)	0
IV	41 (52%)	28 (62%)	13 (38%)
V	3 (4%)	0	3 (9%)
Best previous GMFCS level	**(*N* = 73)***	**(*N* = 42)**	**(*N* = 31)**
I	14 (19%)	8 (19%)	6 (19%)
II	30 (41%)	12 (29%)	18 (58%)
III	5 (7%)	5 (12%)	0
IV	22 (30%)	17 (40%)	5 (16%)
V	2 (3%)	0	2 (7%)
Age at physical function deterioration	**(*N* = 61)***	**(*N* = 32)**	**(*N* = 29)**
<10 (year)	7 (12%)	2 (6%)	5 (17%)
10–20 (year)	6 (10%)	3 (9%)	3 (10%)
20–30 (year)	16 (26%)	8 (25%)	8 (28%)
30–40 (year)	19 (31%)	11 (35%)	8 (28%)
40–50 (year)	10 (16%)	5 (16%)	5 (17%)
50< (year)	3 (5%)	3 (9%)	0
SPPB (*N* = 60)	4.9 ± 4.7 (3.6–6.1)	4.0 ± 4.6 (2.4–5.6)	5.9 ± 4.7 (4.0–7.8)
Number of falls in the past year	1.5 ± 0.6 (1.3–1.6)	1.5 ± 0.6 (1.3–1.6)	1.4 ± 0.7 (1.2–1.7)
Glucose (mg/dL)	103.5 ± 21.3 (98.7–108.3)	104.9 ± 25.9 (97.1–112.7)	101.6 ± 13.3 (97.0–106.2)
Albumin (g/dL)	4.3 ± 0.2 (4.2–4.3)	4.4 ± 0.2 (4.3–4.4)	4.2 ± 0.2 (4.1–4.3)
Triglycerides (mg/dL)	136.6 ± 85.9 (117.4–155.9)	152.1 ± 90.5 (124.9–179.3)	116.1 ± 76.0 (89.6–142.7)
Total cholesterol (mg/dL)	175.4 ± 33.6 (167.9–182.9)	177.2 ± 35.0 (166.7–187.7)	173.1 ± 32.1 (161.9–184.3)
HDL (mg/dL)	48.4 ± 12.0 (45.7–51.1)	46.0 ± 9.3 (43.3–48.8)	51.5 ± 14.4 (46.5–56.6)
LDL (mg/dL)	99.1 ± 30.2 (92.3–105.8)	100.6 ± 28.4 (92.1–109.2)	97.0 ± 32.7 (85.6–108.4)

CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; SPPB, Short Physical Performance Battery; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
**Missing data for each column are shown by the total number of participants.*
Data are shown as mean ± SD (95% confidence intervals).

in the outcome explained by all variables in the model.

$$FRS = -18.549 + 0.410 * Age + 0.577 * Android\ percent\ fat\ (\%)\ (R^2 = 0.528)$$

DISCUSSION

This study shows that age and android fat percentage are independently associated with CVD risk in adults with CP. On the other hand, factors such as BMI, GMFCS level, and functional abilities were not found to be related to CVD risk in adults with CP. Notably, the CVD risk was significantly associated with the android fat proportion rather than the measures of overall adiposity, such as BMI and total body fat, in adults with CP.

Age and disproportionate distribution of body fat were the major predictors of CVD risk in this study. It is widely accepted that the risk of CVD increases with age (34–36). The American Heart Association (AHA) reports that the incidence of CVD is ca. 40% from 40 to 59 years, ca. 75% from 60 to 79 years, and ca. 86% in those older than 80 years (37). Recently, disproportionate fat distribution has been suggested as an important factor predicting CVD risk (38, 39). Although the underlying mechanism of the associations between regional adiposity and CVD risk is not yet clear, regional body fat distribution around the abdominal area is known to be related to metabolic syndromes, such as dyslipidemia, hypertension, and type 2 diabetes mellitus (40) even in normal-weight people, children, and older individuals (11, 41, 42). It has been reported that android body fat is strongly associated with circulating levels of CRP and fibrinogen, thus increasing the risk of subclinical inflammation, leading to endothelial dysfunction (41).

In this study, body fat distribution was different between sexes, while BMI and total body fat did not differ. Women showed a markedly higher 10-year risk of CVD than men. These results are in line with those of the general population. Fat distribution differs between sexes in non-abled populations (43, 44). CVD is markedly more common in men in the general population (45). The reasons for the sex differences have not yet been fully elucidated (46). However, it has been suggested that android fat distribution may contribute to metabolic disturbances that affect CVD risk (47, 48). One of the suggested reasons for regional

TABLE 2 | Body anthropometry, body composition, Framingham risk score, and 10-year cardiovascular disease risk analysis by sex and ambulatory function.

	Total (*N* = 79)	Men (*N* = 45)	Women (*N* = 34)	*p*-value	Ambulatory group (*N* = 35)	Non-ambulatory group (*N* = 44)	*p*-value
Waist circumference (cm)	79.1 ± 18.8 (74.7–83.4)	77.3 ± 22.7 (70.3–84.4)	81.4 ± 12.0 (77.1–85.7)	0.363	82.8 ± 12.3 (78.3–87.4)	76.4 ± 22.1 (69.6–83.2)	0.145
Body weight (kg)	58.0 ± 12.8 (55.2–60.9)	61.2 ± 14.5 (56.9–65.6)	53.7 ± 8.5 (50.8–56.7)	0.009	59.2 ± 10.00 (55.8–62.6)	57.1 ± 14.6 (52.6–61.5)	0.467
Body mass index (kg/m²)	22.8 ± 4.6 (21.8–23.9)	23.0 ± 5.2 (21.4–24.5)	22.7 ± 3.6 (21.4–23.9)	0.774	23.2 ± 3.3 (22.0–24.3)	22.5 ± 5.4 (20.9–24.2)	0.523
Underweight (< 18.5 kg/m²)	12(15%)	9(20%)	3(9%)	0.171	1(3%)	11(25%)	**0.006**
Normal (18.5–24.99 kg/m²)	45(57%)	22(49%)	23(67%)	0.095	24(69%)	21(47%)	0.063
Overweight (25–29.99 kg/m²)	16(20%)	10(22%)	6(18%)	0.616	8(23%)	8(18%)	0.608
Class I Obesity (30–34.99 kg/m²)	4(5%)	2(4.5%)	2(6%)	1	2(5%)	2(5%)	1
Class II Obesity (35–39.99 kg/m²)	2(3%)	2(4.5%)	0	0.503	0	2(5%)	0.5
Class III Obesity (≥ 40 kg/m²)	0	0	0	–	0	0	–
Total body fat mass (kg)	16.6 ± 8.9 (14.6–18.6)	15.0 ± 9.5 (12.1–17.9)	18.7 ± 7.8 (16.0–21.4)	0.071	18.0 ± 7.6 (15.4–20.6)	15.5 ± 9.9 (12.5–18.5)	0.211
Android fat mass (g)	1575.2 ± 973.2 (1357.2–1793.2)	1562.4 ± 1073.3 (12.4–18.8)	1592.1 ± 837.9 (1299.8–1884.5)	0.894	1690.2 ± 776.3 (1423.6–1956.9)	1483.7 ± 1105.5 (1147.6–1819.8)	0.352
Gynoid fat mass (g)	2979.5 ± 1430.5 (2659.1–3299.9)	2544.9 ± 1394.1 (2126.0–2963.7)	3554.7 ± 1283.2 (3107.0–4002.4)	**0.001**	3268.7 ± 1294.7 (2824.0–3713.5)	2749.4 ± 1504.7 (2292.0–3206.9)	0.109
Percent body fat (%)	27.6 ± 11.6 (25.0–30.2)	23.0 ± 10.3 (19.9–26.1)	33.6 ± 10.4 (30.0–37.3)	0.071	29.8 ± 9.6 (26.5–33.1)	25.9 ± 12.7 (21.9–29.8)	0.137
Android body fat (% of total)	9.4 ± 1.8 (9.0–9.8)	10.3 ± 1.5 (9.9–10.8)	8.3 ± 1.4 (7.8–8.8)	**<0.001**	9.5 ± 2.0 (8.8–10.2)	9.4 ± 1.6 (8.9–9.9)	0.798
Gynoid body fat (% of total)	18.7 ± 3.0 (18.0–19.3)	17.8 ± 2.7 (17.0–18.6)	19.8 ± 3.0 (18.7–20.8)	**0.003**	18.4 ± 2.7 (17.5–19.3)	18.9 ± 3.2 (17.9–19.8)	0.503
Android/gynoid ratio	0.5 ± 0.2 (0.5–0.6)	0.6 ± 0.2 (0.5–0.6)	0.4 ± 0.1 (0.4–0.5)	**<0.001**	0.5 ± 0.2 (0.5–0.6)	0.5 ± 0.2 (0.5–0.6)	0.683
Fat mass index (kg/m²)	6.6 ± 3.7 (5.8–7.4)	5.6 ± 3.6 (4.6–6.7)	7.9 ± 3.4 (6.7–9.1)	**0.006**	7.1 ± 3.1 (6.1–8.2)	6.2 ± 4.1 (5.0–7.4)	0.258
Fat deficit (<5)	27 (34%)	22 (49%)	5 (14%)	**0.002**	8 (23%)	19 (43%)	0.058
Normal (5–9)	37 (47%)	16 (35%)	21 (62%)	0.021	21 (60%)	16 (37%)	**0.036**
Excess fat (> 9 to 13)	8 (10%)	4 (9%)	4 (12%)	0.72	4 (11%)	4 (9%)	1
Class I Obesity (> 13 to 17)	6 (8%)	3 (7%)	3 (9%)	1	1 (3%)	5 (11%)	0.219
Class II–III Obesity (> 17)	1 (1%)	0	1 (3%)	0.43	1 (3%)	0	0.433
Framingham risk score	4.32 ± 5.22 (3.14–5.50)	5.20 ± 5.23 (3.63–6.77)	3.09 ± 5.02 (1.28–4.90)	0.081	4.00 ± 4.98 (2.34–5.66)	4.69 ± 5.81 (3.10–6.27)	0.84
†**10-year risk of developing CVD**	2.36 ± 4.01 (1.45–3.27)	3.88 ± 4.68 (2.48–5.29)	0.22 ± 0.49 (0.04–0.40)	**<0.001**	1.65 ± 2.85 (0.69–2.59)	3.09 ± 4.52 (1.86–4.33)	0.199

CVD, Cardiovascular disease.

†*Two patients were not included in the analysis as smoking history was not recorded.*

Data are shown as the mean ± SD or percentage. The 95% confidence intervals (CI) around the mean are also shown.

Independent t-test was performed independently of sexes and ambulatory function.

fat differences is sex hormones (49). Female sex hormones are known to cause the accumulation of body fat in the lower body regions, which is essential for reproductive function (50, 51). This may account for one of the reasons for the difference in CVD risk between the sexes (36).

Overweight and obesity rates based on general obesity measures were 22% in the study population. According to the Organization for Economic Co-operation and Development (OECD) reports released in 2012, the average overweight and obesity rate in South Korea was 35.1%. We found that Korean adults with CP in this study were not obese compared to the general Korean population. It has been debated whether adults with CP are more obese than the general population. Most studies have reported that adults with CP are more likely to be obese due to a lack of physical activity and a sedentary lifestyle (2, 5, 52–54). As we focused on individuals who were able to participate in the survey, those with intellectual disabilities were not included, and this may account for the different results, as

TABLE 3 | Univariable regression analyses for the Framingham risk score.

Domain	Variable	Total			Men			Women		
		β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Anthropometry	Age	0.429	−13.897	**<0.001**	0.348	−9.688	**<0.001**	0.693	−26.047	**<0.001**
	Body weight	−0.038	6.526	0.423	−0.092	10.813	0.093	0.033	1.36	0.783
	Waist circumference	−0.007	4.706	0.845	−0.001	5.368	0.977	0.036	−0.315	0.676
Physical function	GMFCS level	0.096	3.911	0.849	0.155	4.698	0.841	−0.284	3.679	0.676
	SPPB total score†	−0.077	4.418	0.614	−0.027	5.471	0.897	0.062	1.808	0.784
	Number of falls in the past year	−0.92	5.581	0.352	−0.715	6.293	0.607	−1.353	4.846	0.325
	Age at physical deterioration‡	1.122	0.58	0.027	1.336	0.82	0.065	0.555	1.274	0.442
Body fat amount and distribution parameters	Body mass index	−0.107	6.751	0.426	−0.234	10.565	0.122	0.296	−3.519	0.301
	Total fat mass	0	5.941	0.144	0	7.103	0.126	2.709	2.595	0.823
	Android fat mass	−0.01	5.145	0.397	−0.001	6.985	0.121	0.001	1.591	0.385
	Gynoid fat mass	−0.01	6.565	0.08	−0.001	7.232	0.161	0	3.458	0.896
	Android fat percent	0.897	−4.19	**0.007**	0.298	2.123	0.573	1.674	−10.835	**0.006**
	Gynoid fat percent	−0.269	9.334	0.184	0.057	4.177	0.848	−0.43	11.567	0.149
	Android/ gynoid fat ratio	6.563	0.829	0.066	0.158	5.106	0.975	12.803	−2.552	**0.047**
	Percent body fat	−0.067	6.217	0.201	−0.074	7.01	0.349	0.027	2.182	0.756
	Fat mass index	−0.222	5.773	0.181	−0.323	7.022	0.143	0.135	2.047	0.627

GMFCS, Gross Motor Function Classification System; SPPB, Short Physical Performance.
†*SPPB was not performed in 20 patients.*
‡*There were 12 missing data.*
Data are shown as mean ± SD.
β refers to the regression coefficient, and SE refers to the standard error of estimate.

obesity rate in adults with CP is known to be closely related to intellectual disability (54). Previous studies did not exclude those with intellectual disabilities (2, 5, 52–54). Studies by van der Slot et al. showed that the obesity rate is slightly lower in adults with CP than in the general population (2). In the study by Van der Slot, the included subjects were relatively young, with ages ranging from to 25 to 45 years, and those with severe intellectual disabilities were excluded. In addition, since most of the previous studies investigating obesity among patients with CP have been conducted in Western countries, the results of our study on the Korean population could be different due to cultural differences or eating behaviors. Likewise, in a study on the growth profile assessment of adults with tethered cord syndrome in Korea, these subjects had lower height, weight, and BMI than controls of the same age (55), which differ from the previous results of higher rate of obesity among spinal bifida patients in Western countries (56, 57). It is conceivable that since the participants in this study had relatively diverse CP types and function levels, the risk of undernutrition due to dysphagia or feeding problems also existed.

On the other hand, the FRS scores in this population group were higher than those in the general Korean population. Park et al. (58) showed that according to the 2012 Korea National Health and Nutrition Examination Survey, the FRS in the general population was 2.85, while that of our study population was 4.4, which was higher than that of the general population. These results were in line with previous reports that the CVD risk is higher in adults with CP (1, 3, 5). It should be noted that the overall obesity rate was lower in adults with CP than in the general population. This further indicates that general obesity may not be very predictive of CVD risk in adults with CP.

The discrepancy between BMI and FRS may underestimate the risk of metabolic disease in adults with CP who have normal or low BMI. The reason for the discordance may be explained by the body fat distribution, because age and android fat percentage were the factors that were associated with FRS, while factors such as BMI, GMFCS, or functional abilities were not found to be related to FRS.

Due to altered body morphology and changes in lifestyle over a long period, the measures of overall adiposity, such as BMI, would not be appropriate for adults with CP. In adults with CP, higher excess adiposity can be detected despite a normal BMI when compared to neurologically intact adults. Therefore, it is important to evaluate fat distribution rather than general adiposity measures in this population. Peterson et al. assessed intermuscular adipose tissue and trunk adiposity using abdominal computed tomography (CT) (4). CT can distinguish between visceral adipose tissue and subcutaneous adipose tissue, while DXA can assess body compartment compositions, such as the android and gynoid areas. There are several limitations to the use of CT scans for body composition assessment. There could be a potential concern for over- or underestimation of fat tissue, as only the selected levels of fat area were measured. In addition, CT has greater radiation hazards than

DXA (59). With DXA, bone density or skeletal muscle mass can also be measured, as osteoporosis and sarcopenia are other conditions that should be considered in adults with CP (5).

In our study, it is notable that the ambulatory group had a higher proportion of individuals with a normal FMI. Moreover, both the fat-deficit and obese groups (according to FMI) were higher in the non-ambulatory group. On the other hand, the CVD risk by FRS was not significantly different between the non-ambulatory and ambulatory groups. The non-ambulatory group may be at risk of potential undernutrition caused by dysphagia and gastrointestinal problems, resulting in a fat deficit (6, 7). On the other hand, decreased levels of physical activity may lead to excess fat deposits. The ambulatory group may have led a lifestyle similar to the general population and were likely to be more "fit" than the non-ambulatory group. However, there was no significant difference in CVD risk according to the ambulatory status in this study. Heyn et al. showed that those with GMFCS level III had an increased CVD risk when compared to those with GMFCS levels I and II. The average age of the study group in Heyn et al. study was 24 ± 5 years. In contrast, the average age was relatively older in our study (42.2 ± 8.5 years). The age of the study group may have affected the general activity level, even if they had the same GMFCS level. In addition, the relatively small number of participants may have been insufficient to show a statistically significant difference.

This study had some limitations. First, this was a cross-sectional study. Therefore, we were unable to determine a cause-and-effect relationship. Second, a head-to-head comparison with the general population was not performed. Instead, we were only able to compare our data with the general population data from the OECD reports. Since the cohort represents a sample that is relatively small for determining prevalence in the CP population, a future study with a larger sample size would address this limitation. Third, other information, such as socioeconomic status or nutritional status, was not analyzed in this study. With these considerations, further detailed studies on body fat distribution and CVD risk in adults with CP could be performed.

In conclusion, android body fat distribution and age are the two significant factors associated with 10-year CVD risk in adults with CP. Body fat distribution is more closely related to CVD risk than measures of general obesity in adults with CP.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board at Seoul National University Boramae Medical Center. All subjects provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SJ and HS: drafted the manuscript. SJ: conceived the study and critically revised the manuscript for important intellectual content. All authors have read and approved the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Social Outcomes of School Leavers With Cerebral Palsy Living in Victoria

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Objective: In Australia, the National Disability Strategy provides a framework to guide actions and investment to achieve equity in social inclusion and economic participation for people with disability. We investigated the social outcomes of school leavers with cerebral palsy (CP) in Victoria, Australia and explored the determinants of desirable outcomes.

Methods: We used the Victorian CP Register to invite all adults with CP aged 18–25 years ($n = 649$). On-line and/or paper-based surveys explored participation in education, employment, community activities, living situation, relationships and life satisfaction. Functional and health status data were collected. Social outcomes were summarized descriptively and compared between individuals with CP and non-disabled peers aged 18–25 years from the Household Income and Labor Dynamics in Australia dataset. Within the CP cohort we explored whether physical and mental health and level of functioning were associated with social outcomes. In addition, a descriptive comparison was undertaken between the social outcomes of the current CP cohort with that of a previously reported 2007 cohort.

Results: Ninety participants (57% male; mean age 22.4 years (SD: 2.2) in 2020; 61.1% self-reported) provided data for analyses; response rate 16.9%. CP characteristics were similar between respondents and non-respondents. In comparison to similar aged peers, 79.8% had completed secondary school (compared to 83.2%); 32.6% (compared to 75.8%) were in paid work; 87.5% (compared to 48.2%) were living in their parental home; and 3.4% (compared to 31.6%) were married or partnered. Individuals with CP and higher levels of functional capacity and better physical health were more likely to undertake post-secondary education. Higher levels of functional capacity and physical health, as well as lower mental health status were associated with being employed.

Conclusions: While foundational education completion rates were similar to non-disabled peers, significant gaps in social outcomes remain, including residence in the parental home and single status. While addressing these issues is challenging, substantial efforts are needed to reduce these disparities—work that needs to be done in collaboration with people with CP and their families.

Keywords: economic participation, social outcomes, life satisfaction, survey method research, cerebral palsy, young adult

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INTRODUCTION

Adults with cerebral palsy (CP) experience social and economic inequalities and challenges (1–3), related to impairments associated with CP (4), societal barriers such as discrimination, and a lack of accommodations they require to cater for their needs (5, 6). There is evidence that participation in life situations becomes more challenging as children with CP transition to adulthood. As their social roles change, they expect and desire to participate in common adult activities such as employment, further education, independent living and intimate relationships (7).

CP is a lifelong condition that occurs as a result of damage to the developing brain in utero or in the first 2 years of life (8). While the primary disorder is of movement and posture, people with CP experience a range of co-morbidities (e.g., intellectual impairment, epilepsy, hearing or vision impairment, musculoskeletal contractures and deformities) and functional impacts (8). For example, almost half require assistance to mobilize, two-thirds require help to handle objects, one-fifth require assistance to communicate, one quarter have behavioral concerns and three-quarters experience chronic pain (9). While prognostic data is most commonly found in studies of children, more recent research that has focused on adults, confirms the epidemiology of ongoing functional impacts of CP into adulthood (10). Given that in Australia over 75% of the estimated 35,500 individuals who have CP are adults (11), evidence of outcomes for Australian adults with CP is needed.

The 2010–2020 National Disability Strategy provided a policy framework to guide investment and activity to improve performance of mainstream services for people with disability, increase the visibility of disability issues and improve inclusion of those with disability (12). The second 10-year National Disability Strategy will be released late 2021. In 2013, within the life of the 2010–2020 Strategy, a National Disability Insurance Scheme (NDIS) was legislated for implementation, representing a major policy shift and re-direction of disability funding (13). The intent of the NDIS was to give choice and control to individuals with severe and permanent disability *via* funding packages which they could use to purchase supports and services (14). The NDIS funding is explicitly to support individuals to meet their goals for participation in the usual activities of life (13) (see also, www.ndis.gov.au). In 2018, ∼5% of NDIS recipients were those with CP, however, they required the second highest annualized support package in dollar value (11), emphasizing that an understanding of participation gaps and supports required, is needed.

In 2007, we investigated the social situation of 335 young adults with CP aged 20–30 years (2). Our results showed that compared to their non-disabled peers, many of those with CP had not completed secondary education (50 vs. 20%), were unemployed (64 vs. 20%), and had an annual income of <$20,000 Australian dollars (80 vs. 39%). These findings have been substantiated in more recent international research. For example, a series of studies from The Netherlands (7), found that difficulties in participation in domestic life and interpersonal relationships for individuals with CP increased from the age of 16 years. In related work, van Wely et al. (15) demonstrated that family and daily supports, along with personal coping styles and prior participation patterns predicted participation in adulthood in domestic life and interpersonal relationships. Schmidt et al. (16) also found that individuals with CP appeared to lag behind their age-matched non-disabled peers in the development of autonomy in life domains, including finances, intimate relationships and housing. Those with lower gross motor function were at risk of not achieving full autonomy. This body of work from The Netherlands provides important evidence but is limited by its exclusion of individuals with CP with intellectual impairments. In Sweden, Jacobson et al. (17) also described the social participation of young adults with CP aged 20–22 years, including those with intellectual impairment. Jacobson et al. (17) found young adults with CP were likely to be living in the parental home, be unemployed and dependent on family for financial and basic support for daily activities. Comparisons with age-matched peers were not provided in that study, but the relationships between communication, intellectual and manual abilities and participation outcomes was highlighted (i.e., higher levels of activity limitation were associated with decreased participation).

Research that involves adults with CP has been growing rapidly over the past two decades. A recent overview of systematic reviews of research about adults with CP identified 19 reviews and mapped their content and focus to the domains of the International Classification of Functioning, Disability and Health (ICF) (18). One finding of the overview was that the predominant focus of research has been at the ICF level of body functions, with 12 of the 19 included reviews mapped to this aspect (19). While an overview of systematic reviews does not identify all pertinent research, nevertheless it does highlight the need to shift the focus in research with adults with CP beyond mobility and gait, to broader social outcomes. The need for a change in focus is supported by Lindsay's (20) qualitative synthesis—a systematic review of lived experiences of children and youth with CP. Lindsay found that young people's accounts of their experience of CP focused on social inclusion and aspects of the environment (i.e., family, peers, services, supports) and when aspects of body functions were discussed, they were more likely to be pain, fatigue and mental health, rather than mobility, assistive devices and activities of daily living.

Ensuring optimal outcomes for young people with CP is crucial so that they can participate fully in home and community life. We have little knowledge of how Australian young adults with CP are progressing at the current time and what could be put in place to improve their social and economic participation. When young people are at school, they often receive considerable support and are linked with a range of services. When they leave school, there are significant changes in their care and management (21). Some attend higher education facilities, others seek open or supported employment, whilst others may participate in community activities or in day centre programs. With the advent of the NDIS and the National Disability Strategy in Australia, it is crucial that information is generated so that gaps in service provision can be addressed and that the needs of the individuals themselves, and their families,

can play a central role in guiding allocation of resources into the future.

The purpose of this study, therefore, was to investigate the social outcomes of young adults with CP (aged 18–25 years) in Victoria, Australia and determine the factors that may result in desirable outcomes. While this cohort was not fully comparable [included age range of the previous study was 20–30 years, mean = 24.7 years (SD 2.8)] to the 2007 cohort (2), we also aimed to explore whether social outcomes had changed since the study 13 years ago. The specific research questions were:

1. What are the social outcomes of Victorian young adults with CP in terms of further education, employment, living situation and community participation?
   a. How do educational, employment, living arrangements, marital status and financial outcomes compare to young adults without CP?
   b. Are the social outcomes of the current cohort comparable to that of the 2007 cohort of young adults with CP living in Victoria, Australia?
2. What are the determinants of social outcomes for young adults with CP aged 18–25 years in terms of individual (e.g., functional or health status) and environmental (e.g., socio-economic status, educational background) factors?
3. How satisfied are young adults with CP, or those responsible for their care, with their outcomes?

METHODS

Design

This descriptive study used survey methods and secondary analyses of matched datasets to address the research aims. Our multi-disciplinary research team also engaged with stakeholders (young adults with CP and parents) as a consultation group during inception of the study.

Ethical Considerations

Ethical approval for the study was received from the Australian Catholic University Human Ethics Committee (ACU HREC 2018–43H). Participants provided written informed consent to participate in the study, with substitute decision makers (e.g., parent, primary carer) providing consent on the behalf of participants who did not have the capacity to consent. As we aimed to recruit participants with a diverse range of impairments, options for survey completion were provided as follows: (i) choices made by myself and filled out by myself; (ii) choices made by myself and filled out by another person; or (iii) choices made on my behalf and filled out by another person.

Participants and Recruitment

Participants were eligible to participate in the study if they were aged 18–25 years, had a diagnosis of CP of any type or severity, no longer attended secondary school and currently lived in Victoria, Australia. Participants were also included *via* a proxy respondent (parent, or responsible other identified by the individual) if they were unable to complete the survey on their own. Efforts were made to engage and include individuals across all five Gross Motor Function Classification System (GMFCS) (22) levels and those with difficulties relating to communication and/or intellectual function to achieve diversity of participants' experience.

Participants were recruited for the study *via* letters of invitation through the Victorian Cerebral Palsy Register (VCPR; $n = 649$ eligible), advertising in newsletters of the Cerebral Palsy Support Network and snowball invitations between participants and social media posts. Follow up letters were sent to those with current addresses on the VCPR as reminders.

Data Collection

The survey questions were developed following a literature review to explore participation of school leavers with CP. The review, plus consultations with a reference group of adults with CP, was used to identify the important life situations to include as well as potential factors to consider when designing the survey. The result was a survey that sought information about (i) the following life situations—further education, employment, friendships and intimate relationships, living situation, health care provision, community participation; (ii) individual factors influencing participation—CP functional status, mental and physical health status, personal factors (gender, education attainment); (iii) environmental factors influencing participation (parental roles and education, school setting, transport availability, provision of health services); and (iv) life satisfaction. We then sought valid and reliable outcomes to measure the identified variables (see **Table 1**) to which items about participation in education, employment, living situation and community life were added, to create a compilation of measures as an online or paper-based survey. The survey comprised 89 items and took ∼30 mins to complete.

Demographic data were also collected, including gender, date of birth, Indigenous status, parents' education, employment and place of birth, and languages spoken at home. The resultant survey was reviewed and piloted to ensure clarity of understanding with a small number of individuals known to the researchers, and modifications were made as necessary. While the survey was intended to be delivered in an online environment, for respondents who could not, or preferred not to access the online version, a paper-based version of the survey was also available. The online survey was supported and distributed using the web-based application Research Electronic Data Capture (REDCap) (31, 32). Data collection occurred during the latter part of 2019 and ceased in March 2020, just prior to the impacts of COVID-19 in Australia.

For the purposes of assessing the likely representativeness of the final sample, de-identified data of eligible non-participants were obtained from the VCPR. To compare outcomes of the CP sample with the general population, data were extracted from the Household, Income and Labor Dynamics in Australia (HILDA) 2019 Survey after filtering for the age range of interest (18–25 years) (33, 34). HILDA is a nationally representative survey of Australian households with individual data collected on all household residents over 15 years of age.

TABLE 1 | Validated measures included in the compiled survey.

Variable	Measure/s	Validity/reliability	Scores/interpretation
Cerebral palsy descriptors of functional levels			
Gross motor function	GMFCS E & R (22)	Inter-rater reliability therapists/parents Kappa = 0.716 (CI 0.596 to 0.836)	Ordinal—5 levels; I to V with V = no independent mobility
Manual ability	MACS (23)	Rater reliability parents/therapist ICC 0.96 (0.89–0.98)	Ordinal—5 levels; I to V with V = severely limited manual ability
Communication function	CFCS (24)	Test–retest reliability 0.82.	Ordinal; 5 levels; I to V with V = seldom effective sending or receiving
Eating and drinking ability	EDACS (25)	Rater reliability parent/ professional $\kappa = 0.82$	Ordinal—5 levels; I to V with V = unable to eat and drink safely
Mental and physical health			
Global health	PROMIS Scale V1.25 Global health (26)	Good internal consistency for two scales ($\alpha = 0.82$–0.88)	Scale—High scores better health; Score Mean = 50, SD 10 Item scores: 1–5
Mental health	K10 measure of anxiety and depression (27)	Good internal consistency: $\alpha = 0.93$	Scale—High scores worse mental health: <20: likely well 20–24 mild 25–29: moderate 30+: severe disorder
Measures of variables that may influence participation in life situations			
Psychosocial job quality	Scales from HILDA survey (28) Job demands and complexity Job security Job control	Factor structure and validity confirmed Internal consistency range: $\alpha = 0.60$ to 0.82	Ordinal—High scores = higher job adversity (worse); Range: 0 to 6
Availability of supports	RAND social support scales: Emotional/informational Tangible Affectionate Positive social interactions (29)	Factor structure and validity confirmed Internal consistency of scales range: $\alpha = 0.91$ to 0.96	Scale—High scores = more available support; Range: 0–100
Life satisfaction			
Wellbeing/satisfaction	Personal Wellbeing Index (30) 8 items: Life as whole Standard of living Health Life achievements Relationships Feeling of safety Part of community Spirituality	Factor structure, validity and reliability established; Test-retest reliability: ICC = 0.84	High scores = high satisfaction Range: 0–10 scales Australian normative range (scale converted 0–100): 73.4–76.4

GMFCS, Gross Motor Function Classification System; MACS, Manual Ability Classification System; CFCS, Communication Function Classification System; EDACS, Eating and Drinking Ability Classification System; HILDA, Household Income and Labor Dynamics in Australia; α, alpha coefficient; ICC, intra-class correlation coefficient.

Data Processing and Analysis

All survey responses were either collected directly using REDCap or entered from paper-based questionnaires. All data cleaning and analyses were undertaken using R software version 4.02 (35). Individuals were included in the CP sample if they had returned their survey and provided information for at least one item beyond the demographic characteristics. A comparison of the respondents to invited non-respondents was undertaken using de-identified VCPR data. This comparison was to assess similarity of key CP characteristics between the groups, and to quantify how generalisable the findings would be to the CP population.

Responses to closed-ended questions were summarized using descriptive statistics and described under domains of interest. In the presence of incomplete survey responses, analysis was conducted on observations with complete information only, and frequency of missing data summarized in tabulated results. For the first research question, social outcomes for young adults with CP were reported and compared to a same-aged cohort without CP (via the HILDA dataset restricted to ages 18–25 years). Comparison between the cohorts was made using two approaches. First, responses to common questions within both datasets were summarized and compared descriptively. Second, when appropriate to aid discussion, logistic regression was used

to investigate the impact of CP on dichotomised social outcomes of interest, whilst adjusting for potential confounding effects of gender and age. A separate logistic regression model was fitted for each social outcome, with the estimated odds ratio used to quantify the strength of association between exposure (CP vs. no CP) and outcome (e.g., employed vs. unemployed). Odds ratios are reported with their 95% confidence intervals (CI) and probability values to aid in interpretation of the effect size, variability in the observed data, and strength of the evidence, not to make a dichotomized decision of significant/not significant (36, 37). A descriptive comparison was further used to compare the social outcomes of the current CP cohort with that of the 2007 cohort.

For the second research question, responses to questions around potential determinants (individual and environmental factors) of social outcomes were summarized using descriptive statistics within the cohort with CP. To describe the functional impact of CP characteristics on an individual, function was categorized into three levels: high (those classified at Level I or II on GMFCS, MACS, CFCS and with no intellectual impairment or learning disability only), low (those classified at Level IV or V on GMFCS, MACS, CFCS, and severe or moderate intellectual disability) or medium (individuals not in either high or low category). The distribution of functional level was then described (using proportions) to identify the probability of the social outcomes given functional status. Where relevant, and enough responses were obtained, univariate logistic regression was further used to estimate the impact of these factors separately on dichotomized social outcomes for the CP cohort. As before, a separate logistic regression model was fitted for each factor and social outcome of interest. For the third research question, survey responses pertaining to life satisfaction were summarized and described for the young adults with CP.

RESULTS

Response Rates and CP Group Characteristics

In total, 110 surveys were returned (16.9% response rate); one duplicate was removed, and 90 surveys had complete information in relevant fields and were included in the analyses. Of these, 61.1% were completed by self-report ($n = 55$), defined as individuals making decisions themselves (regardless of who completed the survey), and 38.9% by proxy ($n = 35$), of which most ($n = 32$) were completed by a parent and $n = 3$ by a carer or other responsible person.

In total, 43.3% ($n = 39$) of individuals were female, and 56.7% male ($n = 51$). The mean age of participants at time of survey completion was 22.4 years (SD 2.2 years, range 18.6 to 25.8 years). Participants included those classified at each level of the GMFCS (22), Manual Ability Classification System [MACS; (23)], Communication Function Classification System [CFCS; (24)], and the Eating and Drinking Ability Classification System [EDACS; (25)] functional classification systems, indicating the sample represented the diversity of CP characteristics (see **Table 2**). Participants with no intellectual disability made up 45.6% ($n = 41$) of the total, while the proportion of those with moderate or severe intellectual disability was 37.8% ($n = 34$). Comparison of the CP cohort with VCPR non-respondents suggested the distribution of functional abilities was comparable between the two groups, with the age of non-participants being slightly younger (see **Table 3**). The results pertaining to each research question are reported sequentially within each social outcome domain of interest.

Social Outcomes

After restricting to the age range of interest (18 to 25 years), the HILDA cohort included information on 2,375 individuals. In comparison to the CP cohort, there was a smaller proportion of males in the HILDA group (49.1% HILDA compared to 56.7% CP cohort), with the mean age being similar between the cohorts [21.7years (SD: 2.3) HILDA; 22.4years (SD: 2.2) CP cohort]. Key demographic information and social outcomes for both cohorts are presented in **Table 4**, with specific outcomes discussed in further detail below.

Educational Achievement

Just over half of the young adults with CP had received their education through mainstream schools (53.4%, 47/88), with 46.6% (41/88) attending a special school. Within the CP cohort, 79.8% of young adults (71/89) reported completing high school (year 12 or equivalent); a higher proportion than the 50% reported in the previous study (2). Despite the high rate of high-school completion, over half of the young adults with CP had not attempted any additional qualifications after school (59.0%, 49/83). Approximately a third of young adults with CP reported they were currently completing formal tertiary study at the time of survey (30.3%, 27/89).

In comparison to the general population, the proportion of young adults obtaining qualifications after high school was similar between cohorts (41.0% in the CP group compared to 38.9% in the general population), with a similar proportion obtaining a University qualification (15.4 and 19.3%, respectively). Within the CP group, the odds of completing post-secondary education increased with better physical health scores (OR = 1.10, 95% CI: 1.04 to 1.17, $p < 0.01$). Mental health [PROMIS OR = 1.03, 95% CI: 0.99 to 1.08, $p = 0.19$; K10 OR = 1.05, 95%CI: 0.99 to 0.11, $p = 0.11$)] and pain (OR = 0.98, 95%CI: 0.82 to 1.18, $p = 0.85$) had little impact on the odds of completing post-secondary education within the CP group. Individuals with higher functional capacity (i.e., classified at Levels I or II on the functional classification systems and/or no intellectual disability) were more likely to obtain a post-secondary qualification (65.5%, 19/29) compared to those with categorized as medium (33.3%, 15/45) or low (0%, 0/9) capacity. Two thirds of individuals reported that their health affected their participation in education (68.9%, 62/90).

Impacts on education are summarized in **Table 5**. The following environmental factors were reported to somewhat or greatly affect participation in education: lack of access to transport (35.8%), lack of available education close by (30.7%) and lack of family help or assistance (21.5%). In addition, respondents reported that a lack of confidence (48.7%), along

TABLE 2 | Characteristics of the CP cohort by survey reporting status.

	Missing[a] *n* (%)	Total CP cohort	Self-report group	Proxy-report group
n		90	55	35
Topographical distribution—*n* (%)	0 (0)			
Both sides of body		52 (57.8)	28 (50.9)	24 (68.6)
Only on one side of body		29 (32.2)	20 (36.4)	9 (25.7)
Other		9 (10.0)	7 (12.7)	2 (5.7)
Mobility: GMFCS—*n* (%)	0 (0)			
Level I		25 (27.8)	24 (43.6)	1 (2.9)
Level II		27 (30.0)	19 (34.5)	8 (22.9)
Level III		11 (12.2)	4 (7.3)	7 (20.0)
Level IV		10 (11.1)	3 (5.5)	7 (20.0)
Level V		17 (18.9)	5 (9.1)	12 (34.3)
Manual ability: MACS—*n* (%)	0 (0)			
Level I		18 (20.0)	17 (30.9)	1 (2.9)
Level II		34 (37.8)	25 (45.5)	9 (25.7)
Level III		14 (15.6)	8 (14.5)	6 (17.1)
Level IV		9 (10.0)	3 (5.5)	6 (17.1)
Level V		15 (16.7)	2 (3.6)	13 (37.1)
Communication function: CFCS—*n* (%)	0 (0)			
Level I		42 (46.7)	39 (70.9)	3 (8.6)
Level II		17 (18.9)	9 (16.4)	8 (22.9)
Level III		5 (5.6)	2 (3.6)	3 (8.6)
Level IV		15 (16.7)	3 (5.5)	12 (34.3)
Level V		11 (12.2)	2 (3.6)	9 (25.7)
Eating and drinking: EDACS—*n* (%)	0 (0)			
Level I		42 (46.7)	37 (67.3)	5 (14.3)
Level II		24 (26.7)	13 (23.6)	11 (31.4)
Level III		9 (10.0)	4 (7.3)	5 (14.3)
Level IV		8 (8.9)	1 (1.8)	7 (20.0)
Level V		7 (7.8)	0 (0.0)	7 (20.0)
Intellectual ability—*n* (%)	0 (0)			
None (normal or better intelligence)		41 (45.6)	37 (67.3)	4 (11.4)
Learning disability		9 (10.0)	8 (14.5)	1 (2.9)
Mild		6 (6.7)	5 (9.1)	1 (2.9)
Moderate		20 (22.2)	4 (7.3)	16 (45.7)
Severe		14 (15.6)	1 (1.8)	13 (37.1)
Vision difficulty—*n* (%)	4 (4.4)			
No		62 (72.1)	44 (81.5)	18 (51.4)
Yes—some difficulty		16 (18.6)	9 (16.7)	4 (11.4)
Yes—a lot of difficulty		5 (5.8)	1 (1.9)	7 (20.0)
Cannot do at all		3 (3.5)	0 (0.0)	3 (8.6)
Hearing difficulty—*n* (%)	1 (1.1)			
No		78 (87.6)	49 (90.7)	29 (82.9)
Yes—some difficulty		9 (10.1)	4 (7.4)	5 (14.3)
Yes—a lot of difficulty		2 (2.2)	1 (1.9)	1 (2.9)
Cannot do at all		0 (0.0)	0 (0.0)	0 (0.0)
Additional health condition: Yes—*n* (%)	1 (1.1)	35 (39.8)	15 (42.9)	15 (42.9)
PROMIS Physical Health: mean (SD)	5 (5.6)	45.0 (8.5)	47.0 (8.7)	41.8 (7.2)
PROMIS Mental Health: mean (SD)	5 (5.6)	43.1 (9.9)	44.1 (11.3)	41.2 (7.0)
K10 Mental health—*n* (%)	7 (7.8)			
Likely to be well (score <20)		45 (54.2)	22 (41.5)	23 (76.7)
Mild disorder (scores 20–24)		9 (10.8)	7 (13.2)	2 (6.7)

(Continued)

TABLE 2 | Continued

	Missing[a] *n* (%)	Total CP cohort	Self-report group	Proxy-report group
Moderate disorder (scores 25–29)		12 (14.5)	9 (17.0)	3 (10.0)
Severe disorder (scores 30+)		17 (20.5)	15 (28.3)	2 (6.7)
PROMIS Fatigue—*n* (%)	4 (4.4)			
None		10 (11.6)	6 (11.3)	4 (12.1)
Mild		28 (32.6)	19 (35.8)	9 (27.3)
Moderate		37 (43.0)	21 (39.6)	16 (48.5)
Severe		7 (8.1)	6 (11.3)	1 (3.0)
Very severe		4 (4.7)	1 (1.9)	3 (9.1)
PROMIS Pain rating (range 0–10)—mean (SD)	3 (3.3)	2.5 (2.4)	2.7 (2.6)	2.2 (2.1)
Self-care support needs—*n* (%)	1 (1.1)			
Always/sometimes need help and/or supervision		47 (52.8)	15 (27.8)	32 (91.4)
Have difficulty but don't need help and/or supervision		7 (7.9)	6 (11.1)	1 (2.9)
Don't have difficulty but use aids/equipment		5 (5.6)	4 (7.4)	1 (2.9)
Have no difficulty		30 (33.7)	29 (53.7)	1 (2.9)
Domestic care support needs—*n* (%)	1 (1.1)			
Always/sometimes need help and/or supervision		58 (65.2)	23 (42.6)	35 (100)
Have difficulty but don't need help and/or supervision		6 (6.7)	6 (11.1)	0 (0.0)
Don't have difficulty but use aids/equipment		2 (2.2)	2 (3.7)	0 (0.0)
Have no difficulty		23 (25.8)	23 (42.6)	0 (0.0)
General management support need—*n* (%)	2 (2.2)			
Always/sometimes need help and/or supervision		55 (62.5)	20 (37.7)	34 (97.1)
Have difficulty but don't need help and/or supervision		9 (10.2)	8 (15.1)	1 (2.9)
Don't have difficulty but use aids/equipment		3 (3.4)	3 (5.7)	0 (0.0)
Have no difficulty		22 (25.0)	22 (41.5)	0 (0.0)

[a]*In the presence of missing data, presented percentages are relative to records with complete responses for characteristic of interest.*

with not having required background experience or education were impediments (62.7%).

Employment Status

The rate of employment was much lower for participants with CP than young adults in the general population (32.6% compared to 75.8%), with a substantially higher rate of individuals with CP not being in the labor force (i.e., not working or looking for work: 49.4% compared to 16.0%). After adjusting for age and sex, the odds of employment were substantially lower for individuals with CP compared to those without CP (adjusted OR: 0.14, 95% CI:0.09 to 0.22, $p<0.01$). For those working, reported job quality in the CP cohort was consistent with that reported in the general population with relatively low levels of adversity (Psychosocial Job Quality (28): job demand and complexity mean = 2.5 SD 1.3; job security mean = 3.6 SD 1.5; and job control mean = 2.7 SD 2.0 (see **Table 4**). The majority of employed young adults with CP reported working 20 hours or less in the last week across all jobs (57.7%, 15/26), with 46.4% of employed individuals expressing they wanted to work more hours (13/28).

In comparison to the prior study, there has been little change in the proportion of young adults with CP being employed (36.3%, compared with general population of 80.0%) or not being in the labor force (53.5%, compared with general population of 14.6%) (2).

Within the CP cohort, the odds of being employed increased with better physical health scores (OR = 1.06, CI: 1.01 to 1.13, $p = 0.04$). However, poorer mental health using the K10 measure was also associated with being employed (i.e., increased odds of being employed with higher K10 scores; OR = 1.06, CI: 1.00 to 1.12, $p = 0.05$); although the PROMIS mental health score indicated little association with employment status. In addition, reported pain had little impact on the odds of employment (OR = 0.99, 95% CI: 0.82 to 1.19, $p = 0.91$). Individuals with higher functional capacity (i.e., classified at Levels I or II on the functional classification systems and/or no intellectual disability) were more likely to be employed (55.9%, 19/29), compared to those categorized as medium (22.2%, 10/45) or low (0%, 0/10) capacity. Respondents commonly reported their long-term health affected their participation in work (72.7%, 64/88).

Other impacts on participation in employment included experiencing unfair treatment or discrimination during job-seeking, lack of transport, lack of available work close by and a lack of family support (see **Table 5**). Individual factors reported to somewhat or greatly impact employment included lack of confidence (50.7%) and not having appropriate qualifications or experience (71.0%).

Financial Status

Young adults with CP reported having a lower personal income than individuals in the general population, with 62.8% (32/51)

TABLE 3 | Comparison of the CP cohort with VCPR non-respondents.

	Missing[a] *n* (%)	Non-respondents [b]	Missing[a] *n* (%)	Respondents
n		562		87
Sex: Male—*n* (%)	0 (0.0)	337 (60.0)	0 (0.0)	46 (52.9)
Age, years—mean (SD)		20.7 (2.1)		21.2 (1.9)
Motor topography—*n* (%)	3 (0.5)		0 (0.0)	
Hemiplegia/monoplegia		214 (38.3)		27 (31.0)
Diplegia/triplegia		171 (30.6)		26 (29.9)
Quadriplegia		174 (31.1)		34 (39.1)
Mobility: GMFCS—*n* (%)	10 (1.8)		1 (1.1)	
Level I		193 (35.0)		25 (29.1)
Level II		168 (30.4)		26 (30.2)
Level III		57 (10.3)		11 (12.8)
Level IV		67 (12.1)		13 (15.1)
Level V		67 (12.1)		11 (12.8)
Speech—*n* (%)	30 (5.3)		1 (1.1)	
No impairment		211 (39.7)		34 (39.5)
Some impairment		192 (36.1)		29 (33.7)
Non-verbal		129 (24.2)		23 (26.7)
Intellect—*n* (%)	28 (5.0)		2 (2.2)	
Probably no impairment		268 (50.2)		44 (51.8)
Probable impairment		266 (49.8)		41 (48.2)
Vision—*n* (%)	33 (5.9)			2 (2.2)
Not blind		507 (95.8)		81 (95.3)
Blind		22 (4.2)		4 (4.7)
Hearing—*n* (%)	29 (5.2)		1 (1.1)	
Not deaf bilaterally		470 (88.2)		77 (89.5)
Deaf bilaterally		63 (11.8)		9 (10.5)

[a]*In the presence of missing data, presented percentages are relative to records with complete responses for characteristic of interest.* [b]*Presented characteristics were obtained from the VCPR, with small discrepancies between those reported within the surveys for the respondents.*

reporting an annual income of $20,000 Australian dollars or less (before taxation), compared to 47.1% of those without CP. After adjusting for age and sex, there was a strong impact of CP on earning potential, with the odds of earning over $20,000 being lower for individuals with CP compared to those without CP (adjusted OR: 0.38, 95% CI: 0.20 to 0.69, $p<0.01$). At the time of survey, ∼70.6% (60/85) of individuals with CP were receiving money from the NDIS. Many respondents were receiving the Disability Support Pension (68.8%, 55/80), with a smaller proportion receiving the New Start or unemployment benefit (6.2%, 4/65) or other government benefits (22.8%, 13/57).

Partnered or Married

Very few young adults with CP were married or partnered at the time of survey (3.4%, 3/88); a proportion substantially lower than adults in the general population (31.6%), and lower than the prior study of young adults with CP (7.5%, compared to 47.9% in the general population at that time (2). In addition, none of the individuals with CP currently surveyed reported having any children ($n = 88$).

Living Arrangements

At the time of survey, a small proportion of young adults with CP reported living away from the parental home (12.5%, 11/88) compared to 51.8% of young adults in the general population. In comparison to the prior study, proportions living away from the parental home were lower for both the CP group (20.9%) and the general population (77.9%) (2).

Within the CP cohort, there was little association between the reported physical and mental health (PROMIS physical health OR = 1.01, 95% CI: 0.94 to 1.09, $p = 0.77$; PROMIS mental health OR = 1.00, 95% CI: 0.94 to 1.07, $p = 0.99$) and living away from the parental home. The PROMIS mental health result was consistent with the K10 measure of mental health. In addition, reported pain had little impact on the odds of living away from home (OR = 1.05, 95%CI: 0.80 to 1.35, $p = 0.69$). Those with a higher functional capacity (i.e., classified at Levels I or II on the functional classification systems and/or no intellectual disability) were more likely to be living away from home (18.2%, 6/33) compared to those categorized as medium (8.9%, 4/44) or low (10%, 1/10) functional capacity. When asked about having choice over their living situation, just over one third expressed they had complete choice over where they lived (35.3%) or who they lived with (34.5%; see **Table 5**).

Community Participation

In comparison to their similar aged peers, a higher proportion of young adults with CP were an active member of a club or association (41.4% compared to 30.0%), with a similar distribution of event attendance frequency between the two groups (see **Table 4**). Within the CP group, participation in community service tended to be low (22.7%, 20/88), with a very low rate of participation in religious services (77.0%, 67/87 never attend). Between half and two-thirds of respondents reported having complete choice over how they spend their time (62.8%), who they spend time with (58.8% complete) and how they spend their money (54.1%).

In relation to factors that may influence participation in community, on average, young adults with CP reported high levels of emotional/informational support, tangible support, affectionate support, and presence of positive social interactions (mean scores range: 74.3 to 92.1), however there was high variability in responses within the group (see **Table 5**).

Life Satisfaction

Young adults had a lower mean life satisfaction score [Personal Well-being Index (30)] than similar aged peers without disability [mean = 66.3 (SD 23.3), compared with mean = 80.3 (SD 13.6) see **Table 4**]. Within the CP cohort, individuals reported high satisfaction with their standard of living (mean = 81.3, SD 19.8) and safety (mean = 80.3, SD 24.5). However, they reported lower satisfaction in their health (mean = 69.2, SD = 22.9), achieving in life (mean = 62.0, SD 27.9), being part of a community (mean = 66.4 (SD 26.2) and personal relationships (mean = 63.2, SD = 28.2).

TABLE 4 | Comparison of demographic characteristics and social outcomes for CP and HILDA cohorts.

	Missing[a] *n* (%)	CP cohort	Missing[a] *n* (%)	HILDA cohort
n		90		2375
Demographic characteristics	0 (0.0)		0 (0.0)	
Sex: Male—*n* (%)		51 (56.7)		1165 (49.1)
Age, years—mean (SD)		22.4 (2.2)		21.7 (2.3)
Highest qual. after school—*n* (%)	7 (8.4)		0 (0.0)	
University degree		16 (19.3)		365 (15.4)
Associate degree of diploma		4 (4.8)		126 (5.3)
Certificate III or IV		2 (2.4)		434 (18.3)
Other certificate		12 (14.5)		0 (0.0)
Did not complete further education		49 (59.0)		1450 (61.1)
Employment Status—*n* (%)	1 (1.1)		0 (0.0)	
Employed		29 (32.6)		1799 (75.8)
Unemployed		16 (18.0)		196 (8.3)
Not in labor force		44 (49.4)		380 (16.0)
Employment: Psychosocial job quality[b]				
Scores (0 = strongly disagree, 6 = Strongly agree)—mean (SD)				
Job demands and complexity	1 (3.4)	2.5 (1.3)	282 (15.7)	2.8 (1.1)
Job security	3 (10.3)	3.8 (1.6)	278 (15.5)	3.8 (0.9)
Job control	0 (0.0)	2.7 (2.0)	287 (16.0)	2.7 (1.5)
Annual income before tax—*n* (%)	39 (43.3)		0 (0.0)	
< 20,000 AUD		32 (62.8)		1118 (47.1)
≥ 20,000 AUD		19 (37.3)		1257 (52.9)
Marital status—*n* (%)	2 (2.2)		0 (0.0)	
Married or partnered		3 (3.4)		750 (31.6)
Married		1 (1.1)		125 (5.3)
Defacto		2 (2.3)		625 (26.3)
Single		85 (96.6)		1625 (68.4)
Single, never married		85 (96.6)		1619 (68.2)
Separated		0 (0.0)		5 (0.2)
Divorced		0 (0.0)		1 (0.04)
Live away from parental home: Yes—*n* (%)	2 (2.2)	11 (12.5)	0 (0.0)	1230 (51.8)
Active member of club/association: Yes—*n* (%)	3 (3.3)	36 (41.4)	338 (14.2)	611 (30.0)
Frequency of event attendance—*n* (%)	3 (3.3)		314 (13.2)	
Never		7 (8.0)		192 (9.3)
Rarely		18 (20.7)		613 (29.7)
Occasionally		28 (32.2)		483 (23.4)
Sometimes		15 (17.2)		431 (20.9)
Often		17 (19.5)		254 (12.3)
Very often		2 (2.3)		88 (4.3)
Life satisfaction overall—mean (SD)	2 (2.2)	66.3 (23.3)	0 (0.0)	80.3 (13.6)

[a]In the presence of missing data, presented summary statistics are calculated for complete responses only. [b]Data only includes those who were employed (CP n = 29; HILDA n = 1,799); HILDA, Household Income and Labor Dynamics in Australia; qual, qualification.

DISCUSSION

Overview of Findings

The findings of this survey suggest that the social outcomes of young adults with CP remain significantly different than the general Australian population of the same age (18–25 years), with lower proportions obtaining higher education qualifications, gaining employment, being partnered, living away from the parental home and having reasonable finances. The only area in which there was evidence of greater participation in young adults with CP compared to the general population, was in community clubs and associations. Some explanatory variables were related to functional impairment, that is, having higher levels of functional capacity was associated with better outcomes. There is, however, also some evidence that physical health, mental health and presence of pain play a role in relation to

TABLE 5 | Self-reported factors influencing participation.

	Missing[a] *n* (%)	Study CP cohort (*N* = 90)
Impacts on education		
Lack of access to transport to get to and from school—*n* (%)	9 (10.0)	
Does not affect what I do		52 (64.2)
Somewhat affects what I can do		17 (21.0)
Greatly affects what I can do		12 (14.8)
Lack of availability of schooling/education close to where I live—*n* (%)	12 (13.3)	
Does not affect what I do		54 (69.2)
Somewhat affects what I can do		14 (17.9)
Greatly affects what I can do		10 (12.8)
Lack of family help or assistance—*n* (%)	11 (12.2)	
Does not affect what I do		62 (78.5)
Somewhat affects what I can do		12 (15.2)
Greatly affects what I can do		5 (6.3)
Lack of confidence—*n* (%)	12 (13.3)	
Does not affect what I do		40 (51.3)
Somewhat affects what I can do		27 (34.6)
Greatly affects what I can do		11 (14.1)
Not having the qualifications, experience or skills—*n* (%)	15 (16.7)	
Does not affect what I do		28 (37.3)
Somewhat affects what I can do		21 (28.0)
Greatly affects what I can do		26 (34.7)
Long-term health affect participation in education: Yes—*n* (%)	0 (0.0)	62 (68.9)
Impacts on employment		
Lack of access to transport to get to and from work—*n* (%)	19 (21.1)	
Does not affect the work I can do		41 (57.7)
Somewhat affects the work I can do		17 (23.9)
Greatly affects the work I can do		13 (18.3)
Lack of availability close to home—*n* (%)	19 (21.1)	
Does not affect what I do		30 (42.3)
Somewhat affects what I can do		19 (26.8)
Greatly affects what I can do		22 (31.0)
Lack of family help or assistance—*n* (%)	19 (21.1)	
Does not affect what I do		53 (74.6)
Somewhat affects what I can do		13 (18.3)
Greatly affects what I can do		5 (7.0)
Lack of confidence—*n* (%)	19 (21.1)	
Does not affect what I do		35 (49.3)
Somewhat affects what I can do		28 (39.4)
Greatly affects what I can do		8 (11.3)
Not having the qualification, experience or skills—*n* (%)	21 (23.3)	
Does not affect what I do		20 (29.0)
Somewhat affects what I can do		18 (26.1)
Greatly affects what I can do		31 (44.9)
Long-term health affecting employment participation: Yes—*n* (%)	2 (2.2)	64 (72.7)
Experiences in employment		
Experienced unfair treatment or discrimination—*n* (%)		
Looking for a job: Yes	22 (24.4)	16 (26.5)
Applying for a job: Yes	23 (25.6)	12 (17.9)
During a job interview: Yes	23 (25.6)	10 (14.9)
Choice in living arrangements		
How spend their time—*n* (%)	4 (4.4)	
No choice at all		6 (7.0)
Some choice		26 (30.2)
Complete choice		54 (62.8)
How spend their money—*n* (%)	5 (5.6)	
No choice at all		9 (10.6)
Some choice		30 (35.3)
Complete choice		46 (54.1)
Where they live—*n* (%)	5 (5.6)	
No choice at all		27 (31.8)
Some choice		28 (32.9)
Complete choice		30 (35.3)
Who they live with—*n* (%)	6 (6.7)	
No choice at all		34 (40.5)
Some choice		21 (25.0)
Complete choice		29 (34.5)
Who they spend time with—*n* (%)	5 (5.6)	
No choice at all		12 (14.1)
Some choice		23 (27.1)
Complete choice		50 (58.8)
Community and social support		
Social support (RAND, standardized)—mean (SD)		
Emotional/informational support	9 (10.0)	75.9 (25.7)
Tangible support	4 (4.4)	92.1 (14.3)
Affectionate support	4 (4.4)	87.2 (19.5)
Social interaction	9 (10.0)	74.3 (23.7)
Overall support	15 (16.7)	80.5 (17.4)

[a] *In the presence of missing data, presented summary statistics are calculated for complete responses only.*

participation. Although we did not have enough data for a robust evaluation of the influence of environmental factors on social outcomes, this group of young adults with CP reported impacts on their participation from known factors (38, 39), for example availability of transport and social supports.

One key and positive finding was that the proportion of young adults with CP completing foundational education has improved since the 2007 survey undertaken: from 50 to ∼80%. This may relate to shifts in educational policy that has increasingly required inclusion of students with disability (40). Following completion of Year 12, however, the proportion undertaking further education was similar to the proportion in

the prior study (2), and given the slightly older aged cohort in the 2007 study (mean age 24 years), this suggests that ongoing educational attainment may also be improving, however without an equivalent aged cohort it is difficult to tell. While impairments may limit capacity for further education for some young people, the respondents in the current study reported several other factors that acted to constrain their educational participation: lack of transport, availability of programs, social supports, confidence and prior experience or qualifications. Most of these factors are modifiable. In addition, the discrepancy between the 45.6% of participants who reported no intellectual disability or learning difficulty, and the 68.9% who reported health impacts on educational participation, requires further investigation regarding the additional health care supports that may be needed.

Employment outcomes for young adults with CP remain poor and do not appear to have changed in the past 13 years. This is consistent with evidence from broader disability research in Australia (41). Although those with higher functional capacity were more likely to obtain employment, some young adults in the work force (employed or looking for work) reported a range of difficulties associated with obtaining work (unfair treatment or discrimination), and a lack of resources and environmental supports affecting what they can do. Positively, when working, these young adults mostly reported psychosocial job quality in relation to job demands, security and control at very similar levels to their similar aged peers. Once again, health status was commonly identified by this group (73%) as impacting on their participation in employment. The suggestion that those who are working have higher levels of pain and mental health concerns, raises questions as to whether these are particularly resilient individuals, or if there is an impact on health from working. The finding that poorer mental health is associated with increased employment among people with CP is, however, hard to explain particularly as other literature shows that employment rates are low in groups with mental health conditions (42). Previous Australian research has shown that people with disability are more likely to have poor quality jobs than their non-disabled peers which has impacts on their mental health (43). However, our sample reported relatively good job quality. Further research exploring this outcome is needed. In addition, not having the appropriate experience or qualification for employment choices was identified as a potential barrier. Consistent with their reports of impacts on their participation in both education and employment, these young adults' satisfaction with "achieving in life" was also lower than data obtained in 2019 from a representative sample of 2000 Australians [mean = 62.0 compared with mean = 73.5; (44)]. These findings reinforce the importance of optimizing participation in education of young people with disability, both during mandated school years and beyond. Educational attainment at the level of the individual's capacity is a crucial resource for living, a finding highlighted in a recent studying examining what adults with CP identify as enablers of their success in adulthood (45).

Most young adults with CP are living in the parental home, compared to their similar-aged peers. Changes over time (i.e., a higher proportion still living with parents) may be explained by the slightly younger age cohort than in the prior study (2); we expect that more young adults will move out of home as they get older. In addition, the age at which young adults leave the parental home in Australia has increased in recent years, from 2001 when 37% of women, and 47% of men aged 18–29 years were living with a parent, up to 54 and 57% respectively, in 2017. Thus, the gap between those with and without CP is closing, because of changes in the general population, driven by economic (e.g., cost of housing, employment concerns for young adults) and social (e.g., increasing involvement in post-school education) factors (46). Most of the young people with CP in this study expressed that they had no, or only some, choice over where they lived or who they lived with—a finding that is at least partly explained by their continuing to live in the parental home. They also had high levels of satisfaction with their standard of living (mean = 81.3 CP cohort), similar to that of other Australians in 2019 (mean = 78.1) (44). Only a very small proportion were partnered or married. Difficulties in establishing social and sexual relationships have been reported previously (47, 48).

Community participation was the one domain in which young people with CP had higher proportions of participation—in clubs and community organizations—than those without CP. Dependent on the type of club, this may or may not provide opportunity to develop friendships and more intimate relationships. In addition, these young adults with CP indicated they were most likely to have "some" or "complete" choice over who they spent time with, how they spent their money and their time. Their reported personal wellbeing varied, however, depending on the aspect considered, with lower levels of satisfaction being expressed, in comparison to other Australians, in personal relationships (mean = 63.2, compared with 79.4), being part of a community (mean = 66.4, compared with 71.2), overall satisfaction (mean = 66.6, compared with 77.6), and health (mean 69.2 compared with 74.5).

Contribution to Literature/Knowledge

The age of adolescence has recently been proposed to extend well beyond 18 years, suggesting that the time required to achieve the tasks of that developmental period is also extended (49). Findings of this study for those without CP are consistent with that assumption, with high proportions of young adults continuing to live with parents, still undertaking education, and having limited financial resources. Young adults with neurodevelopmental disabilities have been reported to take even longer than their non-disabled peers to achieve developmental outcomes (50), with an implicit (and sometimes explicit) assumption that the reason for that sits solely within the individual—that is, it is impairment related. While some young adults with CP have severe or even profound intellectual and physical impairments, many do not: and social outcomes for all people occur as a result of the transactional exchanges that occur over time between people and context (51).

The environment matters. CP is a complex heterogeneous condition: many individuals with CP will require ongoing supports: indeed, in this study, only 25–30% had no difficulty and did not require aids or equipment to support their independence

in self-care, domestic activities or general management. Given that participation is strongly influenced by the person-environment fit (52), the ongoing large discrepancies in participation outcomes between young adults with CP and their peers suggests more needs to be done to build supportive environments and to work toward meeting our obligations in relation to the United Nations Convention on the Rights of Persons with Disability (53).

The substantial increase in the proportion of young people with CP completing foundational education is very positive and provides an important opportunity for young people to be set on a strong path following school leaving. However, attendance at school, while positive, is not enough: the extent to which young people are engaged in learning and provided with the scaffolded experiences that support their incremental skill development is critical. The young adults with CP in this study reported that lack of confidence was a factor in both their educational and employment participation and that they were not as satisfied with their achievements in life as other Australians. Adults with CP have described needing pathways for developing competence, acceptance and support in school life and skills for making friends (45): these early formative experiences, along with an expectation that they will take part in society from parents, teachers and themselves, (45) provide a foundation for adulthood successes, when the needed contextual supports are also in place.

Despite around 70% of participants reporting having individualized NDIS funding, tangible supports, like accessible transport, availability of suitable education or work and social supports, were commonly reported to be a barrier. Prior research reports varied experiences of the NDIS, with some individuals greatly valuing the additional opportunities afforded for autonomy and participation, and others experiencing great difficulty with accessing and using the scheme in ways that meet their preferences (14). There are high hopes for the NDIS to close the participation gap and social outcomes for people with disability but also concerns about implementation, cost and sustainability (54). Currently we need a stronger body of evidence-based approaches and a more sophisticated evaluation of outcomes than is currently available to inform decisions about what works for whom, and when.

Employment outcomes for many young people with neurodevelopmental disabilities have remained poor over a long period, despite evidence being available about what is needed for improvement. Sheppard et al. (41) describe six key principles to supporting the transition from school to employment for those with disability: (1) the expectation that young people can work; (2) collaboration across sectors; (3) participation in meaningful work during the school years; (4) skills development (of all those involved in school transitions); (5) family involvement; and (6) early transition planning.

The relatively high prevalence of mental health concerns in this group, along with presence of pain and fatigue for more than 50% of individuals suggest greater attention is needed to ensure good quality healthcare in early adulthood. In this sample, nearly 40% had yet to transfer from paediatric to adult health care services. The gap in consistent quality healthcare for adults with CP has been recognized, with significant attention in recent years to transition planning (55). Best practice principles for effective healthcare transition are similar to those for transitioning to employment: (1) collaboration across health systems; (2) capacity building in people and communities starting early; (3) supported navigation (that involves family) through the process; (4) accessible information and resources; and (5) education for young people, parents and healthcare professionals (56).

Participation in meaningful life situations is a fundamental right of all people. Young adults with CP may experience a range of impairments of body functions and structures, but if provided with appropriate supports, participation is possible in many aspects of life. There is good evidence that participation outcomes are influenced by interventions delivered in real-world contexts that are tailored to address the individual-context fit to provide the necessary supports to ensure that learning and engagement are effective (57, 58).

Limitations

This descriptive study used survey methods and did not achieve a strong response rate [110 returned surveys of 649 VCPR known eligible participants (16.9%)]. Of these only 90 were usable. Along with item-level missing data, this meant that some questions had incomplete information and limited the possible analyses and interpretations. Use of population-based comparative data provided evidence that the sample was broadly representative of the population of those with CP living in Victoria. The potential for response bias is acknowledged, however, the direction of any bias is unknown. A larger cohort of participants would have allowed a more detailed analysis of the factors influencing participation in key aspects of life, and potentially allowed subgroup analyses for some outcomes (e.g., determinants of employment). Our categorisation of functional capacity into three levels may be critiqued, however, it did provide a mechanism for considering a constellation of functional capacities given that individuals with CP may experience varied severity of impairment across functional domains. A more detailed questioning of NDIS supports would have been valuable, given just over 70% of participants were receiving some funding. In addition, the standard questions included in this survey about being partnered or married and presence of social and emotional supports, did not capture information about friendships and intimate relationships—areas in which young people with CP and their parents have previously expressed dissatisfaction (7, 45). This survey sought to replicate data that is commonly sought when measuring "outcomes in adulthood" implicitly labeling participation success as having further education and training, being employed, partnered and living out of the parental home. These are inherent cultural biases that can be perpetuated through research, unless the work is grounded in consumer perspectives.

Implications for Practice, Policy, Research

There is an ongoing need for attention to be given to supporting young people with CP to achieve meaningful participation. Using evidence already available to us (58), stronger pathways

to employment (41) and community (38) participation can be built.

The advantage of survey methods is the capacity to reach—potentially—large numbers of participants who are geographically dispersed. Future surveys are likely to be more helpful, however, if there is greater involvement of young adults with CP, their parents and other support people in their development to ensure that their lived experiences assists in designing surveys in which; (1) the most important (or a broader range of) life situations are asked about; (2) significant individual and environmental influences on outcomes are captured; and (3) methods of engaging with individuals are broader (e.g., delivered as an interview) to ensure that those who are able to provide their own, rather than a proxy response, can do so. In addition, surveys that are followed up by more in-depth interviews with those who can provide rich information about specific life situations will provide more nuanced knowledge to inform policy and practice.

CONCLUSION

Findings of this study indicate substantial increase in the proportion of young people with CP completing school since the prior study in 2007, but less evidence of improved participation outcomes in employment or living situation. This is over a decade in which substantial disability policy reform has occurred in Australia; but there is still much work to be done. Closing the gap between those with and without CP will require addressing multiple issues at the individual level including reducing pain, improving mental health and building confidence and self-esteem. Environmental and contextual changes are an imperative to achieve the vision of an inclusive society where people with disability have the same opportunity as others to live productive and meaningful lives.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because we did not seek participant consent for re-use of the data. Requests to access the datasets should be directed to christine.imms@unimelb.edu.au.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Australian Catholic University Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CI, DR, and AK conceived and designed the study and obtained the grant funding. CI led the development of the survey, supervised the data collection phase, and drafted the manuscript. DS undertook data cleaning and analyses. All authors contributed to the interpretation of findings, reviewed and contributed to the preparation of the manuscript, and approved the final version.

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The Use and Outcomes of Motor Rehabilitation Services Among People With Cerebral Palsy Change Across the Lifespan

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Background and Aims: The provision of coordinated and multidisciplinary rehabilitation programs that adapt to the individual with cerebral palsy (CP) evolving rehabilitation needs throughout the different phases of life is highly challenging for healthcare systems. The aim of this study was to report the changes in motor rehabilitation (MR) environmental factors, service use and patient outcomes between children and adults with cerebral palsy and to identify if changes took place earlier or later than the standard division between pediatric and adult healthcare systems at 18 years.

Methods: We used data from the French ESPaCe survey to select a set of indicators for MR environmental factors, service use and patient outcomes, highlighted by patients and families in previous studies. We then compared the distribution of the indicator data between children and adults, as well as between four transition age groups: children under 12, adolescents up to 17 years, young adults, and adults over 25 years of age. We estimated odds ratios adjusted for motor involvement, associated impairments and informant type.

Results: A total of 997 respondents over 2 years of age were included in this study (484 children and 513 adults). Finding an available physiotherapist was very difficult for almost half of the children, and a greater proportion of adolescents and adults. Physiotherapy was provided in a private outpatient practice for twice as many adults over 25 years as children and adolescents. The weekly amount of physical therapy decreased as outpatient practice increased. Multidisciplinary rehabilitation decreased sharply from adolescence and was halved at adulthood. Satisfaction with the MR program decreased from childhood into adolescence and adulthood. Perceived impact of physiotherapy on people with CP and their main carers were less positive in adolescents.

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Conclusions: Healthcare policies should focus on accessibility issues at all ages, consider adolescents as a specific population, consider a wide transition phase (12–25 yo) and maintain a multidisciplinary approach at adulthood. There is a strong need for national rehabilitation strategies for individuals with CP.

Keywords: disability, cerebral palsy, rehabilitation, healthcare service, transition to adult care, adult neurology

INTRODUCTION

Coordinated and multidisciplinary rehabilitation is essential to fully address the health problems encountered by individuals with cerebral palsy (CP) over their lifetime. Despite the fact CP is a lifelong condition, most research on rehabilitation for people with CP has been conducted in children (1). Although the cerebral lesions that interfere with the brain development are non-progressive, deteriorations occur early in all dimensions of the International Classification of Functioning with aging. In particular, mobility becomes increasingly limited, pain increases and cardio-vascular diseases and cognitive disorders develop earlier than expected (2–12). These changes in health status over the course of a person's life generate different medical and rehabilitation needs, which have recently become the object of a growing research interest in adults with CP. However, the provision of coordinated and multidisciplinary rehabilitation programs that adapt to each individual's evolving rehabilitation needs throughout the different phases of life is highly challenging for healthcare systems.

Pediatric and adult healthcare services are quite distinct and the transition to adult services is rarely smooth; people with CP often report experiencing a void when they leave the pediatric system (13–15). Although clinical guidelines for the childhood-adulthood transition have been established in different countries over the past 10 years (16, 17), young adults with CP continue to report that the transition between life phases is problematic (18). In France, the healthcare system provides 100% coverage of all healthcare expenditures under a national solidarity scheme ("Assurance Maladie – Sécurité Sociale") to thirty chronic conditions, including CP, whereas other conditions receive 65–80% coverage. This extended financial coverage does not seem to avoid difficulties for people with CP in the transition phase. For instance, a regional study of 502 individuals with CP found that the use of medication increased with age, however the provision of physical types of health care (rehabilitation, physical medicine and rehabilitation follow-up, and provision of equipment) decreased, independently of ambulatory status. The drop in service provision occurred mainly after the transition to adult services (19). Individuals with CP frequently report that the transition between healthcare systems is a "brutal" experience. Furthermore, the transition to adult services occurs at a fixed age, which does not necessarily correspond to the individual's needs. It is highly likely that the period of transition actually starts during adolescence ($\geq$12 yo) and ends in the late twenties (20). Indicators need to be determined so that transition between rehabilitation services can be tailored appropriately. To ensure the relevance of such evidence-based adaptations, public views must be taken into account to prioritize actions, establish the importance of specific outcomes and generate patient preference-informed guidelines (21).

The ESPaCe survey was a national survey designed to report the unmet needs and expectations about motor rehabilitation (MR) of children, adolescents and adults with CP and their families in France (22, 23). The questionnaire was co-designed by service users and professionals to evaluate chosen key indicators of the health care user's experience such as self-reported environmental factors (access to rehabilitation, MR coordination, rehabilitation settings etc.), rehabilitation service use (amount of physiotherapy, multidisciplinary teams etc.) and patient outcomes and experiences (satisfaction, impact on activities of daily living etc.). Evaluating the changes throughout the lifespan of such modifiable, self-reported factors would guide the national development of rehabilitation services that consider the different phases of an individual's life.

We hypothesized that MR environmental factors, service use and patient outcomes and experiences reported as indicators by people with CP would change between childhood and adulthood, and that some changes would occur during adolescence (12–17 yo) and others would occur in young adults (18–25 yo) or later in life, depending on the indicators.

The aim of this study was to report the changes in motor rehabilitation (MR) environmental factors, service use and patient outcomes between children and adults with CP and to identify if changes took place earlier or later than the standard division between pediatric and adult healthcare systems at 18 years.

METHODS

Participants

The Enquête Satisfaction Paralysie Cérébrale (ESPaCe: cerebral palsy satisfaction survey) was a cross-sectional study coordinated by a CP research foundation (Fondation Paralysie Cérébrale, France) in collaboration with patient and professional organizations (22). People were included if they reported living in France with a motor impairment consistent with the definition of CP (24). They were excluded if the descriptive information provided in the survey regarding their motor impairment was insufficiently detailed or not consistent with the definition of CP (e.g., progressive disorders). The present study included respondents who were at least 2 years of age and both those who were undergoing MR and those who were not.

The study fulfilled the French legal data protection requirements at the time of the data collection. The ESPaCe survey was registered in ClinicalTrials.gov with the identifier NCT04509544.

Study Variables

The ESPaCe questionnaire was developed by a multidisciplinary group that included individuals with CP and representatives from patient and family organizations, professional and scientific societies. The questions covered the topics identified in a preliminary qualitative study that involved in-depth interviews with individuals with CP and their families.

Outcomes

For this study, we selected a set of questionnaire items prioritized by ESPaCe participants as indicators of MR environment, service use and patient outcomes.

MR Environmental Factors

Participants were asked about the availability of physiotherapists, the access to a physiotherapist trained in CP rehabilitation, the care setting in which they attended MR (private outpatient clinic vs. healthcare organization), the presence of an identified healthcare professional coordinating their MR and of regular communication between professionals.

Rehabilitation Service Use

Participants reported their current participation in MR, the weekly amount of physical therapy (PT) received ($\geq$90 min per week), MR multidisciplinarity (two or more therapies) and whether the goal setting process was shared.

Rehabilitation Service Patient Outcomes

Satisfaction with rehabilitation services was evaluated using the CSQ-8 questionnaire (25), satisfaction with pain management during PT sessions, perceived outcome of MR (impact of MR on activities of daily living and quality of life for people with CP and for their main carer).

Some outcome responses were dichotomous (service provider, MR multidisciplinarity, attending school or work) but most were scales 0–5 (availability of physiotherapists, access to a physiotherapist with specific training, communication between professionals, satisfaction with pain management, shared physiotherapy goal setting) or −5 to 5 (impact of MR on people with CP and their main carer).

Main Determinant

Participant age was the main study determinant. Age was dichotomized at 18 years to mirror the split between pediatric and adult healthcare systems. To further explore the transition age, the variable was categorized in four levels: children (2–11 years), adolescents (12–17 years), young adults (18–24 years) and over 25 years old.

Population Factors

Participants reported their gender, CP subtype, Gross Motor Function Classification System (GMFCS) and Manual Ability Classification System (MACS) levels, associated impairments (severe visual, hearing, intellectual impairment, and epilepsy), mother education, frequency of episodes of pain, participation in school or professional activities.

The questionnaire was released in both web and paper format. Participation was open from June 2016 to June 2017. The study was promoted nationally through advocacy groups, scientific and professional societies and social media, and locally by patient associations and healthcare professionals. The questionnaire instructions stated that it should be preferably self-reported by the individual with CP or proxy-reported by the main carer, and that professionals involved in MR should not be asked to help complete the questionnaire.

Statistical Analysis

The distribution of population factors and outcome variables were described across the 2 and 4 age groups. For clarity of presentation of the univariate results, outcome variables measured on scales were dichotomized. Proportions were compared across age groups using a Cochran-Armitage trend test, Chi-square test or Kruskal-Wallis test. The adjusted age effects were estimated for the 2 and 4 age category variables. The dependent variables were analyzed as ordinal with proportional odds logistic regression models after checking the proportional odds assumption, or with binary logistic models. Multivariable age effect estimates were adjusted on gender, CP subtype (unilateral or bilateral spastic CP vs. dyskinetic/ataxic CP), GMFCS, visual or hearing impairments (severe), intellectual impairment (severe, moderate, mild/no), epilepsy, and informant type. Odds ratios and 95% confidence intervals (95% CI) are presented for the 2 and 4 age category variables. In addition, if no differences between the 4 age categories were identified, a reduced age variable was fitted in the model and estimates reported if the predictive ability of the model improved and new age category differences showed a p-value < 0.1. The complete record analysis was implemented under the assumption that data missingness was not related to both the main predictor (age) and the outcomes. Sensitivity analyses were performed to assess the impact in the results of rehabilitation non-users and of the choice of adjustment variables – e.g., socioeconomic indicator. The analysis for this paper was generated using SAS/STAT software version 9.4/14.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study Population

Out of 1,010 eligible participants in the ESPaCe survey, 997 over the age of 2 years were included in the present study: 341 (34%) were children (2–11 yo), 143 (15%) were adolescents (12–17 yo), 111 (11%) were adults aged between 18 and 25 yo and 398 (40%) were older than 25 yo; 54% were male.

The CP subtypes reported were unilateral spastic (32%), bilateral spastic (54%), dyskinetic (11%) and ataxic (4%). Thirty-three percent of respondents had a Gross Motor Function Classification System (GMFCS) level of I-II, 19% had level III, and 47% had levels IV-V. Fifty-one percent reported at least one severe associated impairment (intellectual, visual, auditory or epilepsy). **Table 1** shows the differences in individual

TABLE 1 | Age distribution of population factors as reported in ESPaCe, the French National Survey on Motor Rehabilitation Services.

Population factors			**Age distribution (Transition age groups)**					
		Missing data	**02–11 y**	**12–17 y**	**18–24 y**	**25–74 y**	**Total**	
		***N* = 997**	***N* = 341**	***N* = 143**	***N* = 111**	***N* = 398**	***N* = 997**	***p*-value**
	Response categories	**%**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	**%**	
Non-modifiable factors								
Gender		1%						0.003
	Male		201 (59)	84 (59)	48 (44)	195 (50)	528 (54)	
CP Subtype		10%						<0.0001
	Unilateral spastic CP		136 (43)	42 (33)	21 (21)	90 (26)	289 (32)	
	Bilateral spastic CP		139 (44)	70 (54)	66 (65)	208 (59)	483 (54)	
	Dyskinetic CP		34 (11)	11 (9)	10 (10)	41 (12)	96 (11)	
	Ataxic CP		9 (3)	6 (5)	4 (4)	14 (4)	33 (4)	
Gross motor function classification system		5%						<0.0001
	Level I		67 (21)	19 (14)	11 (10)	19 (5)	289 (12)	
	Level II		93 (29)	29 (21)	25 (23)	56 (15)	203 (21)	
	Level III		40 (12)	29 (21)	15 (14)	93 (25)	177 (19)	
	Level IV		56 (17)	26 (19)	27 (25)	110 (29)	219 (23)	
	Level V		69 (21)	33 (24)	29 (27)	99 (26)	230 (24)	
Manual ability classification system		7%						0.3
	Level I		36 (11)	14 (10)	7 (7)	55 (15)	112 (12)	
	Level II		121 (38)	40 (29)	47 (44)	126 (34)	334 (36)	
	Level III		83 (26)	28 (21)	23 (22)	75 (20)	209 (22)	
	Level IV		40 (12)	29 (21)	14 (13)	57 (16)	140 (15)	
	Level V		41 (13)	25 (18)	15 (14)	54 (15)	135 (15)	
Associated impairments								
	Severe visual imp.	7%	40 (14)	18 (13)	18 (18)	51 (14)	127 (14)	0.4
	Severe hearing imp.	7%	6 (2)	8 (6)	5 (5)	11 (3)	30 (3)	0.5
	Severe intellectual imp.	14%	40 (14)	26 (20)	22 (22)	68 (20)	156 (18)	0.5
	Epilepsy	9%	88 (28)	41 (32)	36 (37)	120 (34)	285 (32)	0.073
Mother education		24%						<0.0001
	Higher education		226 (80)	84 (77)	57 (64)	118 (44)	485 (65)	
Modifiable factors								
Pain, frequency (0–5)		21%						<0.0001
	0 - No episodes		88 (31)	24 (24)	19 (22)	49 (16)	180 (23)	
	4–5 - High frequency		26 (9)	19 (19)	24 (28)	109 (35)	178 (23)	
Schooling or professional activities		3%						<0.0001
	Involved		298 (90)	106 (77)	46 (42)	100 (26)	550 (57)	
Informant								
Questionnaire respondent		2%						<0.0001
	Family members		335 (100)	111 (80)	69 (63)	175 (45)	690 (71)	
	Individuals with CP		0%	28 (28)	41 (37)	212 (55)	281 (29)	

characteristics by age group. The proportion of participants with at least one severe impairment was lower in children (44%) than in adolescents or adults (54%), $p < 0.004$. The proportion of mothers with higher education decreased in successive age groups, from 80% in children to 44% in adults, $p < 0.001$. Frequent episodes of pain were reported by 9% of children and 35% of adults over 25 yo, $p < 0.001$. Participation in school or employment decreased in successive age groups, from 90% in children to 26% after 25 years, $p < 0.001$.

Seventy-one percent of questionnaires were answered by a family member. Twenty percent of the 12–17 yo, 37% of the 18–24 yo and 55% of the ≥25 yo completed the questionnaire themselves. Participants included in the study lived in twelve of the thirteen regions of France. No responses were received from

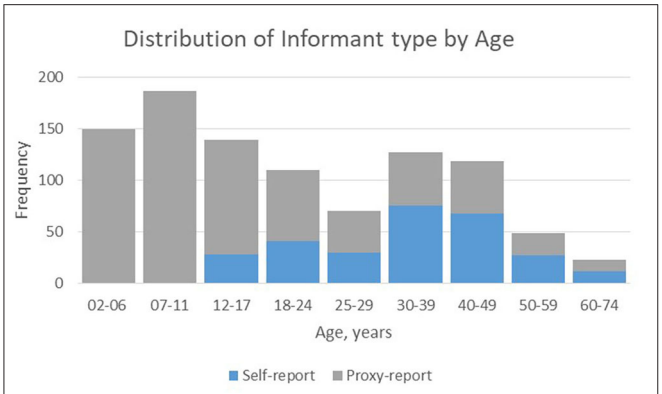


FIGURE 1 | Informant type: self-reported vs. proxy-reported by age.

the least populated region; participation from the most populated region (21%) was proportional to its relative population at the national level (19%) (**Figure 1**).

Data missingness on population factors was lower than 10% except for intellectual impairment (14%) and mother's education (24%), see **Table 1**. Missing data on outcomes was mostly in the range of 20–25%, see **Table 2**.

Motor Rehabilitation Environmental Factors

Finding an available physiotherapist was reported as very difficult for 47% of children, and even more for adolescents and adults, 58%, odds ratio 2.3 (1.6–3.4). Finding a physiotherapist trained in CP rehabilitation was reported as very difficult for 61% of children and adolescents and 66% of adults, odds ratio 2.0 (2.3–3.0). Physiotherapy was provided in a private outpatient practice more frequently in young adults than adolescents, 27 vs. 41%, odds ratio 2.7 (1.2–6.0), and even more in adults over 25 years, 57%, odds ratio 2.1 (1.1–4.1). The presence of an MR coordinator was less frequently reported for adults than for children and adolescents, 46 vs. 59%, odds ratio 0.59 (0.38–0.93). Regular communication between health professionals was less frequently reported in adults, 52 vs. 77%, odds ratio 0.38 (0.27–0.56). **Table 2** shows the age effects on multivariable analysis: **Table 2A**, shows the adult vs. pediatric age effect; **Table 2B** shows the transition age effects. **Figure 2** summarizes the age distribution of the service indicators according the health system split, the transition age categories and according to the age effect.

Motor Rehabilitation Service Use

Almost all respondents participated in rehabilitation sessions, although slightly fewer adults participated than children and adolescents, 99 vs. 92%, odds ratio 0.21 (0.10–0.45). Physiotherapy sessions, specifically, were attended by 95% of children and adolescents and 87% of adults. Multidisciplinary care decreased sharply from adolescence, 82% in children vs. 64% in adolescents, odds ratio 0.32 (0.19–0.54) and again in adults (41%) vs. adolescents, odds ratio 0.44 (0.27–0.72). Half of children and adolescents reported receiving at least 90 min of PT weekly; the frequency decreased to 42% for young adults (18–25 yo), odds ratio 0.51 (0.27–0.96), and it further decreased to 32% after 25 yo, odds ratio 0.47 (0.25–0.89).

Motor Rehabilitation Service User Satisfaction and Impact of MR Services

Satisfaction with the current MR program decreased at adolescence, from 58% above the median CSQ-8 score in childhood to 39% in adolescence and adulthood, odds ratio 0.38 (0.25–0.57). Pain management during physiotherapy sessions was reported as strongly satisfying less frequently after 12 yo, 80 vs. 66%, odds ratio 0.52 (0.32–0.85). Goal setting was reported as strongly shared by 56% of children, adolescents and young adults and 52% of adults over 25 yo, odds ratio 0.57 (0.39–0.83). The impact of MR on daily life was reported as positive less frequently in adolescents (31%) than in children, 54%, odds ratio 2.7 (1.6–4.4), or adults, 50%, odds ratio 2.3 (1.4–3.7). The impact of MR on carers was reported as positive less frequently in adolescents and young adults (22%) compared to children, 34%, odds ratio 0.6 (0.38–0.96), and adults over 25 yo, 27%, odds ratio 1.6 (1–2.5).

DISCUSSION

This study explored the effect of age on a set of MR environmental factors, service use variables and patient outcomes, all of which were reported by people with CP or their main carer. Changes across the lifespan were reported, as hypothesized, for all indicators with, generally, less positive results in adults than children. A more detailed analysis using 4 age categories (2–11, 12–17, 18–24, >25) revealed a wide window of transition between childhood and adulthood that often does not correspond to the pediatric-adult healthcare organization divide. The findings of the study lead to implementing specific actions in motor rehabilitation services in adults, and also in the transition window starting at 12 and up to 24 years of age.

An important result of this study was for accessibility to rehabilitation services: finding an available physiotherapist was reported as highly difficult by almost half of children and an even greater proportion of adolescents and adults. Finding a physiotherapist trained in CP rehabilitation was even more difficult, and this difficulty was increased for adults. The accessibility issues we identified cannot be related to the direct financial cost of MR sessions, as care is fully covered for both children and adults with CP by the healthcare system in France. Instead, accessibility could rather be related to healthcare availability and organization. There was a marked switch in the setting in which rehabilitation was provided. Children and adolescents mainly attended MR in a healthcare organization setting while adults, particularly over 25 yo, mostly had rehabilitation sessions in private outpatient practices. Coincidently, a decrease in the presence of an MR coordinator and in the perceived communication between healthcare professionals was reported at adulthood. Moreover, a distinct lack of multidisciplinary management was observed in adults (41%) and adolescents (61%) compared to children (82%), in contrast with the recent call by the WHO for a stronger multidisciplinary

TABLE 2A | Age effect on motor rehabilitation service factors adjusted on GMFCS, CP subtype, severe visual, hearing and intelligence impairments, epilepsy, gender and informant type with binomial/ordinal logistic regression models.

Motor rehabilitation service: environmental factors, service use and outcomes			**Adult vs. pediatric age effect**			
			A			
	Missing data *N* = 997	**Response variable**		**Odds ratio estimate**		***p*-value**
			Reference category	**Point estimate**	**(95% CI)**	
Motor rehabilitation environmental factors						
Difficulty finding a PT available	24%	Ordinal (0–5)	18–74 vs. 02–17 y	1.8	1.2 2.7	0.003
Difficulty finding a CP trained PT	26%	Ordinal (0–5)	18–74 vs. 02–17 y	2.0	1.3 3.0	0.0006
Service provider*	18%	Binary	18–74 vs. 02–17 y	4.8	2.9 8.1	<0.0001
A professional coordinates MR activities	23%	Binary (yes/no)	18–74 vs. 02–17 y	0.59	0.38 0.93	0.022
Regular communication between HC professionals	18%	Ordinal (0–5)	18–74 vs. 02–17 y	0.38	0.27 0.56	<0.0001
Motor rehabilitation service use						
Currently involved in a motor rehabilitation activity	0%	Binary (yes/no)	18–74 vs. 02–17 y	0.21	0.096 0.45	<0.0001
PT mean weekly min. amount	21%	Binary (<90/90≤)	18–74 vs. 02–17 y	0.30	0.19 0.47	<0.0001
Multidisciplinarity	0%	Binary (2≤/1)	18–74 vs. 02–17 y	0.25	0.16 0.37	<0.0001
Motor rehabilitation service outcomes						
Satisfaction, CSQ-8 score	25%	Ordinal (quartiles)	18–74 vs. 02–17 y	0.47	0.32 0.71	0.0003
Satisfaction with pain management during PT[&]	30%	Ordinal (0–5)	18–74 vs. 02–17 y	0.59	0.36 0.95	0.031
Shared PT Goal setting	24%	Ordinal (0–5)	18–74 vs. 02–17 y	0.66	0.45 0.97	0.035
Impact of PT on people with CP ADL[#]	23%	Binary (1 to 5/−5 to 0)	18–74 vs. 02–17 y	1.3	0.89 1.9	0.18
Impact of PT on carers of people with CP ADL[#]	30%	Binary (1 to 5/−5 to 0)	18–74 vs. 02–17 y	0.89	0.59 1.3	0.58

Age: 2 categories, 18–74 vs. 02–18 y.

GMFCS, Gross Motor Function Classification System; PT, Physiotherapy; CP, Cerebral Palsy; HC, Healthcare; CSQ-8, The Client Satisfaction Questionnaire; Clinic, Private Outpatient Clinic (in the original French version of the questionnaire, "Libéral") vs. outpatient or inpatient HC organization; [&]0–5 scale; [#]ADL, Activites of daily living.*

rehabilitation workforce and promotion of the role of allied health professionals in a coordinated strategy aiming at better health outcomes (26). These changes that occurred around 18 years of age suggest that the pediatric healthcare system has well-identified and promoted rehabilitation pathways while the adult system may be less adapted to the needs of people with CP. A failure to provide a seamless transition has been well-described in adulthood (13–15) but has also been described much earlier in the transition from pre-school to school-based services (27), highlighting the need to consider a broader window of transition.

MR service use, especially PT, was reported by almost all participants, even if the rate was slightly lower in adults. This result was expected since, in France, PT is traditionally prescribed, and now recommended (28), as a first-line therapy; it is also consistent with a previous study of adults with CP in a region of France (29). The detailed analysis showed that the amount of weekly physiotherapy provided was lower in young adults than in children and adolescents, and decreased further after the age of 25 years. This finding is in line with data from many countries with different healthcare systems: US (30), Canada (31), UK (32), Australia (33) Singapore (34), as well as in low- and middle-income countries (35). The decrease in rehabilitation service use could be either related to the differences in healthcare provision offered in the French system after 18 years of age, or to a change in specific needs of individuals with CP.

User satisfaction is considered as a key indicator of healthcare service quality (36). Satisfaction with MR was found to be lower in adolescents and adults. Satisfaction with pain management during PT sessions was also lower in adolescents and adults. Lower levels of satisfaction indicate a larger gap between expectations and experiences: in the present study this gap is between perceived rehabilitation needs and care provision. Overall, the results showed a concomitant decrease in satisfaction, amount of rehabilitation, access to rehabilitation services and environmental factors with age. A previous study of satisfaction with MR in CP revealed independent determinants of patient satisfaction (23): higher special needs (pain, impairment severity), lower rehabilitation quality indicators (rehabilitation access, pain management, a lack of shared PT goals and a lack of care coordination), as well as being an adolescent predicted lower levels of satisfaction. Special needs during adolescence were also identified in the current study as the impact of MR on activities of daily living was reported to be less favorable in adolescents and young adults compared to children and adults.

The concurrent decrease in well-organized rehabilitation and patient satisfaction with age reflects an inadequacy between the changing needs of individuals with CP and the healthcare system. This inadequacy occurs roughly in parallel with a marked decrease in the social participation indicator. School attendance was reported below reference population levels for children

TABLE 2B | Age effect on motor rehabilitation service factors adjusted on GMFCS, CP subtype, severe visual, hearing and intelligence impairments, epilepsy, gender and informant type with binomial/ordinal logistic regression models.

Motor rehabilitation service: environmental factors, service use and outcomes			Transition age effect					
			B					
	Missing data $N = 997$	Response variable		Odds ratio estimate			*p*-value	
			Reference category	Point estimate	(95%CI)		Category	Overall
Motor rehabilitation environmental factors								
Difficulty finding a PT available	24%	Ordinal (0–5)	12–17 vs. 02–11 y	2.0	1.2	3.3	0.004	0.0004
			18–24 vs. 12–17 y	1.5	0.82	2.7	0.19	
			25–74 vs. 18–24 y	0.75	0.44	1.3	0.29	
			12–74 vs. 02–11 y	2.3	1.5	3.4	<0.0001	
Difficulty finding a CP trained PT	26%	Ordinal (0–5)	12–17 vs. 02–11 y	1.4	0.84	2.2	0.20	0.003
			18–24 vs. 12–17 y	1.4	0.76	2.6	0.27	
			25–74 vs. 18–24 y	1.3	0.74	2.2	0.37	
Service provider*	18%	Binary	12–17 vs. 02–11 y	1.1	0.58	2.1	0.78	<0.0001
			18–24 vs. 12–17 y	2.7	1.2	6.0	0.013	
			25–74 vs. 18–24 y	2.1	1.1	4.1	0.034	
A professional coordinates MR activities	23%	Binary (Yes/No)	12–17 vs. 02–11 y	0.82	0.47	1.4	0.48	0.021
			18–24 vs. 12–17 y	0.71	0.35	1.4	0.34	
			25–74 vs. 18–24 y	0.91	0.49	1.7	0.76	
Regular communication between HC professionals	18%	Ordinal (0–5)	12–17 vs. 02–11 y	0.79	0.49	1.3	0.3	<0.0001
			18–24 vs. 12–17 y	0.48	0.27	0.85	0.013	
			25–74 vs. 18–24 y	0.90	0.55	1.5	0.7	
Motor rehabilitation service use								
Currently involved in a motor rehabilitation activity	0%	Binary (yes/no)	12–17 vs. 02–11 y	1.2	0.35	3.9	0.81	<0.0001
			18–24 vs. 12–17 y	0.16	0.05	0.54	0.003	
			25–74 vs. 18–24 y	1.3	0.59	2.8	0.52	
PT mean weekly min. amount	21%	Binary (<90/90≤)	12–17 vs. 02–11 y	0.81	0.47	1.4	0.45	<0.0001
			18–24 vs. 12–17 y	0.57	0.28	1.2	0.12	
			25–74 vs. 18–24 y	0.47	0.25	0.89	0.020	
			18–24 vs. 02–17 y	0.51	0.27	0.96	0.037	<0.0001
			25–74 vs. 18–24 y	0.47	0.25	0.90	0.022	
Multidisciplinarity	0%	Binary (2≤/1)	12–17 vs. 02–11 y	0.31	0.18	0.53	<0.0001	<0.0001
			18–24 vs. 12–17 y	0.59	0.32	1.1	0.099	
			25–74 vs. 18–24 y	0.67	0.39	1.2	0.15	
			12–17 vs. 02–11 y	0.32	0.19	0.54	<0.0001	<0.0001
			18–74 vs. 12–17 y	0.44	0.27	0.72	0.0009	
Motor rehabilitation service outcomes								
Satisfaction, CSQ-8 score	25%	Ordinal (quartiles)	12–17 vs. 02–11 y	0.45	0.28	0.73	0.001	<0.0001
			18–24 vs. 12–17 y	0.71	0.37	1.3	0.29	
			25–74 vs. 18–24 y	1.4	0.74	2.7	0.92	
			12–74 vs. 02–11 y	0.38	0.25	0.57	<0.0001	
Satisfaction with pain management during PT&	30%	Ordinal (0–5)	12–17 vs. 02–11 y	0.59	0.32	1.1	0.088	0.050
			18–24 vs. 12–17 y	0.93	0.43	2.0	0.86	
			25–74 vs. 18–24 y	0.83	0.44	1.6	0.55	
			12–74 vs. 02–11 y	0.52	0.32	0.85	0.009	
Shared PT goal setting&	24%	Ordinal (0–5)	12–17 vs. 02–11 y	0.92	0.58	1.5	0.72	0.036
			18–24 vs. 12–17 y	1.0	0.56	1.9	0.90	
			25–74 vs. 18–24 y	0.57	0.33	0.99	0.047	
			25–74 vs. 2–24 y	0.57	0.39	0.83	0.004	

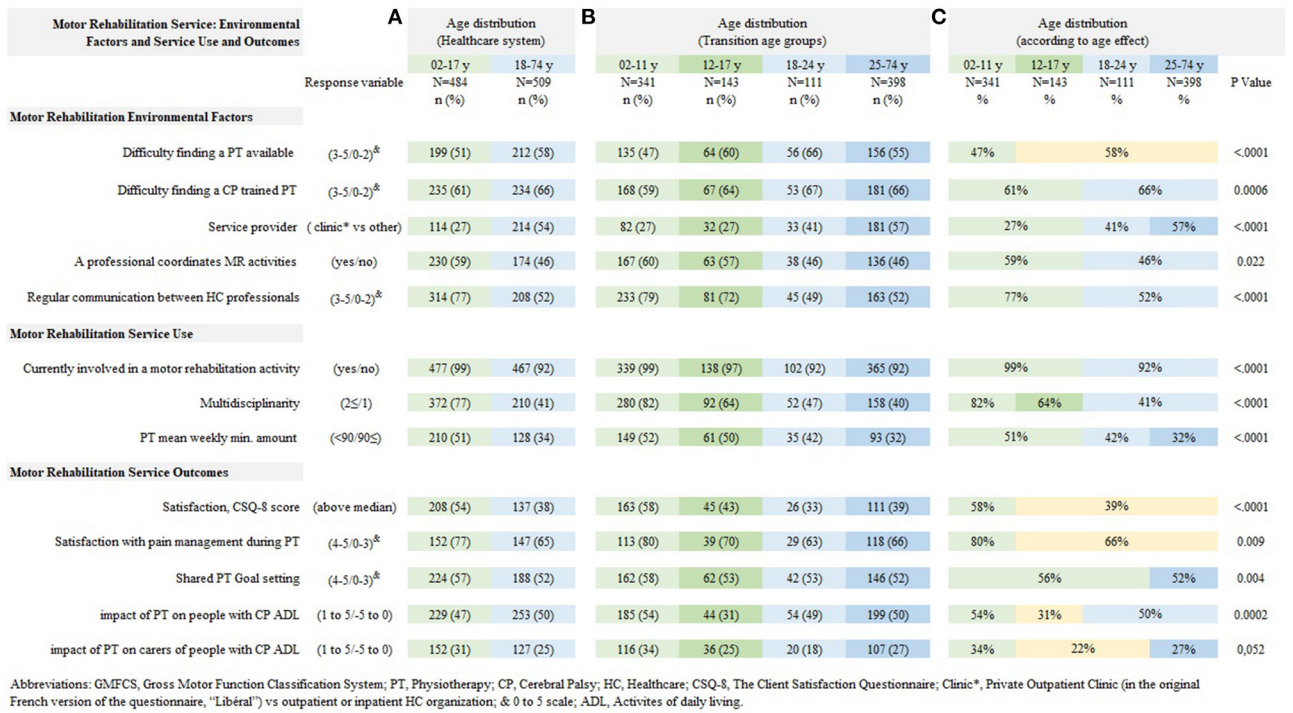
(Continued)

TABLE 2B | Continued

Motor rehabilitation service: environmental factors, service use and outcomes	Missing data N = 997	Response variable	Transition age effect B					
				Odds ratio estimate			*p*-value	
			Reference category	Point estimate	(95%CI)		Category	Overall
Motor rehabilitation service outcomes								
Impact of PT on people with CP ADL[#]	23%	Binary (1 to 5/−5 to 0)	12–17 vs. 02–11 y	0.38	0.23	0.61	<0.0001	0.0008
			18–24 vs. 12–17 y	2.3	1.3	4.3	0.007	
			25–74 vs. 18–24 y	0.97	0.57	1.6	0.91	
			02–11 vs. 12–17 y	2.7	1.6	4.4	<0.0001	0.0002
			18–74 vs. 12–17 y	2.3	1.4	3.7	0.0008	
Impact of PT on carers of people with CP ADL[#]	30%	Binary (1 to 5/−5 to 0)	12–17 vs. 02–11 y	0.70	0.42	1.2	0.18	0.071
			18–24 vs. 12–17 y	0.65	0.31	1.3	0.23	
			25–74 vs. 18–24 y	2.0	1.1	3.8	0.029	
			12–24 vs. 02–11 y	0.60	0.38	0.96	0.032	0.052
			25–74 vs. 12–24 y	1.6	1	2.5	0.0499	

Age: 4 transition categories.

GMFCS, Gross Motor Function Classification System; PT, Physiotherapy; CP, Cerebral Palsy; HC, Healthcare; CSQ-8, The Client Satisfaction Questionnaire; Clinic, Private Outpatient Clinic (in the original French version of the questionnaire, "Libéral") vs. outpatient or inpatient HC organization; &0–5 scale; #ADL, Activites of daily living.*



Motor Rehabilitation Service: Environmental Factors and Service Use and Outcomes	Response variable	A Age distribution (Healthcare system) 02-17 y N=484 n (%)	A 18-74 y N=509 n (%)	B Age distribution (Transition age groups) 02-11 y N=341 n (%)	B 12-17 y N=143 n (%)	B 18-24 y N=111 n (%)	B 25-74 y N=398 n (%)	C Age distribution (according to age effect) 02-11 y N=341 %	C 12-17 y N=143 %	C 18-24 y N=111 %	C 25-74 y N=398 %	P Value
Motor Rehabilitation Environmental Factors												
Difficulty finding a PT available	(3-5/0-2)&	199 (51)	212 (58)	135 (47)	64 (60)	56 (66)	156 (55)	47%		58%		<.0001
Difficulty finding a CP trained PT	(3-5/0-2)&	235 (61)	234 (66)	168 (59)	67 (64)	53 (67)	181 (66)	61%		66%		0.0006
Service provider	(clinic* vs other)	114 (27)	214 (54)	82 (27)	32 (27)	33 (41)	181 (57)	27%		41%	57%	<.0001
A professional coordinates MR activities	(yes/no)	230 (59)	174 (46)	167 (60)	63 (57)	38 (46)	136 (46)	59%		46%		0.022
Regular communication between HC professionals	(3-5/0-2)&	314 (77)	208 (52)	233 (79)	81 (72)	45 (49)	163 (52)	77%		52%		<.0001
Motor Rehabilitation Service Use												
Currently involved in a motor rehabilitation activity	(yes/no)	477 (99)	467 (92)	339 (99)	138 (97)	102 (92)	365 (92)	99%		92%		<.0001
Multidisciplinarity	(2≤/1)	372 (77)	210 (41)	280 (82)	92 (64)	52 (47)	158 (40)	82%	64%	41%		<.0001
PT mean weekly min. amount	(<90/90≤)	210 (51)	128 (34)	149 (52)	61 (50)	35 (42)	93 (32)	51%		42%	32%	<.0001
Motor Rehabilitation Service Outcomes												
Satisfaction, CSQ-8 score	(above median)	208 (54)	137 (38)	163 (58)	45 (43)	26 (33)	111 (39)	58%		39%		<.0001
Satisfaction with pain management during PT	(4-5/0-3)&	152 (77)	147 (65)	113 (80)	39 (70)	29 (63)	118 (66)	80%		66%		0.009
Shared PT Goal setting	(4-5/0-3)&	224 (57)	188 (52)	162 (58)	62 (53)	42 (53)	146 (52)		56%		52%	0.004
impact of PT on people with CP ADL	(1 to 5/-5 to 0)	229 (47)	253 (50)	185 (54)	44 (31)	54 (49)	199 (50)	54%	31%	50%		0.0002
impact of PT on carers of people with CP ADL	(1 to 5/-5 to 0)	152 (31)	127 (25)	116 (34)	36 (25)	20 (18)	107 (27)	34%	22%		27%	0,052

Abbreviations: GMFCS, Gross Motor Function Classification System; PT, Physiotherapy; CP, Cerebral Palsy; HC, Healthcare; CSQ-8, The Client Satisfaction Questionnaire; Clinic*, Private Outpatient Clinic (in the original French version of the questionnaire, "Libéral") vs outpatient or inpatient HC organization; & 0 to 5 scale; ADL, Activites of daily living.

FIGURE 2 | Age distribution of Motor Rehabilitation Service Factors. Age categories according to **(A)** healthcare system (adult and pediatric), **(B)** transition age groups, and **(C)** according to adjusted age effect on multivariable analysis.

(90%) and adolescents (77%) in the ESPaCe survey. This has also been well-described in Sweden with a lower rate than typically developing peers (37). Furthermore, the rate of ESPaCe respondents in employment was especially low (18%). "Late adulting" in several social and participation domains has been described in the Netherlands (20), and low levels of employment

of people with CP have been reported in several countries (38, 39). These difficulties have been found even in high functioning young adults with CP who have no intellectual disability (40) and in other dimensions of participation like "having a cohabiting partner" or "having a biological descendance" (41). This parallel evolution between systems throughout the wide transition period from childhood to adulthood requires policy makers to develop national strategies that are adapted to the changing needs of individuals with CP in all domains.

Limits

The study sample represented an estimated 1% of the total population of people with CP living in France. The distribution of CP subtypes was similar to reports in population-based registers, but the proportion with higher levels of gross motor impairment was increased (42, 43). People attending rehabilitation activities were likely overrepresented. Although the sample selection could not guarantee representativeness, the aims of the study were addressed. The age effect estimates were adjusted for gender, CP subtype, GMFCS, single associated impairments (visual, hearing, intelligence and epilepsy), and informant type which is a strong strategy appropriate to the population characteristics. We explored data missingness patterns and concluded that the complete record analysis approach would be appropriate under the assumption that data missingness would not be related to both the main determinant (age) and the study outcomes. We performed sensitivity analyses to assess the effect of rehabilitation non-users at the time of the survey and concluded that a likely underrepresentation of non-users would not bias our results. We also assessed through sensitivity analyses the impact of not including socioeconomic status in the multivariable models due to high data missingness. We concluded that although socioeconomic status may determine rehabilitation access, the estimates of the association between age and outcomes were not impacted by not adjusting for mother's education level. We cannot rule that other participant selection issues, misclassified or unmeasured factors, may have biased the age effect estimates. The questionnaire items selected as indicators did not go through a rigorous validation process but convergent results between indicators were found. These indicators were selected and prioritized by people with CP and advocacy groups and are convergent with the scientific literature, supporting their relevance. More granularity in the age analysis might have provided further information, but the selected transition age groups allowed to analyze the impact of current healthcare features and the study objectives to be addressed.

CONCLUSION

This study, which focused on changes in rehabilitation system indicators and patient outcomes with age, brings a new, lifespan vision of how the French healthcare system is perceived and used by people with CP. The results provide grounds for proposing actions at the individual and at the system level: (1) Considering a larger window of transition starting from early adolescence and ending in the late twenties, (2) Developing MR programs that specifically address the needs of adolescents (3) Maintaining a multidisciplinary approach in adulthood (4) Providing access to MR professionals trained in CP at all ages and (5) Promoting pain management and shared goal setting during the MR at all ages but especially in adulthood. Finally, the appropriate management of the needs of people with CP, as reported in this and other studies, is highly challenging for national healthcare systems. This study provides yet further evidence of the need for comprehensive national strategies for the management of individuals with CP that jointly address healthcare, rehabilitation, educational, employment and social support systems.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because consent was not obtained to publish the anonymised data. Requests to access the datasets should be directed to Javier De la Cruz, javier.delacruz@salud.madrid.org.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

ESPaCe COMMITTEE

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AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Associations of Circulating Insulin-Growth Factor-1 With Cognitive Functions and Quality of Life Domains in Ambulatory Young Adults With Cerebral Palsy: A Pilot Study

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Ng TKS, Heyn PC, Tagawa A, Coughlan C and Carollo JJ (2022) Associations of Circulating Insulin-Growth Factor-1 With Cognitive Functions and Quality of Life Domains in Ambulatory Young Adults With Cerebral Palsy: A Pilot Study. Front. Neurol. 13:748015. doi: 10.3389/fneur.2022.748015

Objective: Adults with cerebral palsy (CP) often have impaired cognitive functions. CP also has deteriorations in multiple quality-of-life (QoL) domains. The bio-psycho-social health psychology model posits that biological factor interacts with social and psychological functions. However, the biological determinant of psycho-social and functional outcomes in CP has been scarcely examined. Circulating Insulin-like growth factor-1 (IGF-1) is associated with cognitive deficits in older adults, we thus aimed to examine the associations of circulating IGF-1 with: (1) objectively measured cognitive functions, (2) self-reported cognitive functions, and (3) QoL measures in adults diagnosed with CP.

Methods: Seventy-two adults with CP and varying degrees of cognitive functions were recruited from an accredited clinical motion analysis laboratory at a regional Children's Hospital. Circulating IGF-1 was measured using post-fasting serum. The Wechsler Adult Intelligence Scale (WAIS) tests were administered to assess multiple cognitive functions, whereas the Patient-Reported Outcomes Measurement Information System (PROMIS) was used to measure multiple domains of self-reported health, including cognitive complaints and eight QoL domains.

Results: Sixty-eight participants had complete data [mean age = 25 (SD = 5.3), female = 52.8%]. Controlling for covariates, circulating IGF-1 was associated with multiple cognitive domains, including positively with declarative memory and executive function and inversely with visual-spatial and motor skills, and processing speed, while no association with subjective memory complaint was detected. Circulating IGF-1 was also inversely associated with four QoL domains, including depressive symptoms, executive function, physical function, and social roles and activities.

Conclusions: In CP, circulating IGF-1 might be a useful biological determinant of objective cognitive functions and several quality-of-life domains commonly impaired in CP.

Keywords: cognition, cerebral palsy, insulin-like growth factor 1 (IGF-1), quality-of-life, patient-reported outcomes measurement information system (PROMIS), biomarkers, aging, aging model

HIGHLIGHTS

- Circulating IGF-1 is involved in cognitive decline in normal aging and dementia. Patients with cerebral palsy frequently have co-morbid cognitive decline and thus have increased risk for developing dementia. They also have impairments in functional and quality-of-life (QoL) domains. However, whether there are associations between circulating IGF-1 and multiple neurocognitive assessments and QoL functional measures in CP is unknown.
- We showed pilot findings on circulating IGF-1 associated with multiple objective neurocognitive measures and self-reported quality-of-life outcome measures in ambulatory adults with CP.
- If validated in longitudinal causal analysis, circulating IGF-1 could potentially provide an objective and minimally invasive biomarker measure for healthcare workers, aiding risk prediction and the determination of the optimal time to introduce interventions and treatments.

INTRODUCTION

Cerebral palsy (CP) is a lifelong condition that presents challenges at every stage of development. Evidence suggests that adults with CP are at a higher risk of developing chronic secondary health conditions associated with aging, such as diabetes, hypertension, heart diseases, and metabolic syndrome, and at a much earlier age than typically-developing adults (1–5). These chronic diseases are also risk factors for dementia and have been shown to be associated with mobility impairment, due to fatigue, walking inefficiency, frailty, and muscle and joint pain (6). Adults with CP rely on physical therapy services and novel rehabilitation research, not only to improve their day-to-day physical challenges, but also to avoid developing chronic and comorbid conditions. The health services and rehabilitation need of adults with CP are similar to the older adult population, however their health is exacerbated by CP, a pediatric onset disability, throughout their life span. Due to advancements in healthcare and specifically rehabilitation, patients with CP have longer life expectancy and often survive to old age. Despite improved longevity, compared to typically developing adults, adults with CP have impaired quality of life (QoL). The biopsychosocial model of health psychology postulates that biological factors interact and are bidirectionally influenced by social and psychological constructs, affecting physical and mental health, and dictates how people can lead healthier lives (7, 8). Thus, identifying key biological determinants, i.e., biomarkers, associated with the early deteriorations in cognitive, and functional outcomes could inform the optimal timing of implementing rehabilitation interventions for adults with CP.

One important but underdiagnosed clinical condition in adults with CP is cognitive impairment (2, 9–11). Our previous study showed that a great proportion, i.e., 75%, of our adult patients with CP screened positive for cognitive impairment defined as mild cognitive impairment (MCI) (2). We thus postulated an "accelerated aging phenomenon" for adults aging with CP, with inflammation and alterations in several vital signs posing as shared risk factors for mild cognitive impairment (MCI) and serving as plausible physiological determinants of this phenomenon (2). In our previous study, we also highlighted the need to examine insulin-growth factor 1 (IGF-1) as a potential biomarker for cognitive impairment and functions in CP (2). IGF-1 increases cell proliferation in hippocampal cells (12, 13) and its expression is also increased in the affected brain hemisphere after an ischemic injury (14, 15). Indeed, compared to matched-controls, circulating IGF-1 concentrations have been shown to be reduced in CP. A previous case-control study of fifty children and adolescents with CP were directly compared to 50 healthy age-, sex-, and pubertal stage-matched children and adolescents, showing that 62% of the participants with CP had reduced IGF-l and IGFBP-3 concentrations (16). Another study similarly showed that children with CP and retarded growth had lower circulating IGF-1 compared to healthy children controls (17). A third study showed that in 31% of patients with CP, plasma IGF-1 and IGFBP3 were under the normal values for their corresponding ages (18). Lastly and similarly, another age-matched-case-control study showed reduced serum IGF-1 in CP (19).

IGF-1 is a growth and neurotrophic hormone, that plays essential roles in body growth, tissue remodeling, neuronal plasticity, and skeletal and musculature functions (20). The receptors for IGF-1 are widely expressed in the nervous system, and IGF-1 can be regulated at the expression level and cross the blood-brain barrier (20). Despite complex roles in brain functions, IGF-1 appear to have a central role in information processing, learning and memory across the lifespan (21). Specifically, mounting evidence in the older adult suggests that reductions in circulating IGF-1 signaling are involved in cognitive decline during the normal aging process (22) and could serve as a biomarker of cognitive aging (23). Decreased concentrations of circulating IGF-1 have also been associated with, and precede, cognitive impairment in neurodegenerative conditions, such as Alzheimer's disease (AD) (22–24). Thus, low concentrations of circulating IGF-1 could serve as a risk factor for the development of AD and other types of dementia (20, 22, 24).

Although we previously showed evidence supporting cognitive impairment in individuals with CP that is comparable to those observed in the older adult population with MCI (2), biological determinants of cognitive decline in adults with CP are still in scarcity (2, 25). Despite a previous study examining the roles of circulating IGF-1 in bone mineral density in young adults with CP (19, 26), no studies have associated circulating IGF-1 with cognition in adults with CP. Whether circulating IGF-1 is a biological determinant of cognitive aging in adults with CP is thus unknown. As circulating IGF-1 is a prominent biomarker for cognitive decline across multiple domains in aging, MCI, and AD (27, 28), and based on our previous findings that unveiled several commonalities between CP and MCI (2), we postulated that circulating IGF-1 could be a biological determinant and hence be associated with cognitive functions in CP.

Compared to typically-developing adults, adults with CP have worse QoL outcomes, including executive function, ambulation, and mental health (29, 30). However, whether there is a specific biological determinant which are tightly coupled with psycho-social and functional outcomes in CP has been scarcely examined. Specifically, circulating IGF-1 is a growth hormone primarily produced in the hepatocytes of the liver and, in smaller amounts, by other tissues. Due to its sensitivity to the psycho-social environment, its level can potentially reflect QoL outcomes, which encompass multiple functional and psychosocial domains. Given that circulating IGF-1 is a pleotropic biomarker associated with multiple functional and psychosocial outcomes in older populations, we postulated that circulating IGF-1 could be significantly associated with these functions in adults with CP as well.

To address these issues, iIn this study, we analyzed data from our cohort study, entitled "Cerebral Palsy Adult Transition Study (CPAT)," to evaluate circulating IGF-1 as a potential biological determinant, i.e., biomarker, for young adults with CP. The CPAT parent study's goal is to understand how young adults with CP age in general, and specifically the secondary health conditions and loss of ambulation that accompanies aging in this population (1, 2, 31–34). Specifically, in this study, capitalizing a plethora of bio-psycho-social measures, focusing on the within-population instead of between-population variability, we aimed to holistically investigate if circulating IGF-1 could be a potential biomarker associated with multiple cognitive and quality of life domains that are impaired in ambulatory young adults with CP. We thus formulated three *a priori*-set aims. The primary aim of this study is to evaluate the associations between circulating IGF-1 and multiple objective cognitive domains in CP, as assessed by the Wechsler Memory Scale-Fourth Edition (WMS-IV) and the Wechsler Adult Intelligence Scale-fourth edition (WAIS- IV) tests. Second, we focused on the Applied Cognition—General Concerns domain from the PROMIS scale as a construct for subjective cognitive concerns, and investigate its associations with circulating IGF-1. Third, we examined if circulating IGF-1 is associated with multiple quality-of-life outcomes, by employing the Patient-Reported Outcomes Measurement Information System (PROMIS) scale, which has been validated in many clinical populations, including CP (35–37). Lastly, we explored if circulating IGF-1 is significantly associated with three related biomarkers, i.e., IL-6, insulin, and IGFBP-3.

MATERIALS AND METHODS

Study Setting and Design

This report represents data collected from the parent study, the "Cerebral Palsy Adult Transition Study" (CPAT), that had the goal of understanding how ambulatory adults with CP age. The CPAT study has been previously described (1, 2, 31). The CPAT study was performed at a regional children's hospital that has been serving the health needs of individuals with CP for over 20 years. All protocol procedures were performed under rigorous and standard clinical laboratory quality assurance. The study was approved by the University of Colorado Institutional Review Board and all participants signed informed consent prior to participation.

Role of the Funding Source

The funders played no role in the design, conduct, or reporting of this study.

Study Cohort and Participants

A total of 129 participants from a patient registry were identified as potential participants and underwent a short telephone screening survey to determine if they were (1) interested and able to participate in the study and (2) able to walk across a 35-foot (10.6 m) walkway, with or without assistive devices, at least three times. A total of 72 ambulatory participants were enrolled and completed the parent project (CPAT) (1, 2, 31).

For this sub-analysis, we included the data from the participants who were able to complete the cognitive and blood laboratory tests (**Figure 1**). All study procedures were conducted by qualified clinical and research staff utilizing an accredited, on campus, clinical laboratory who followed the institutions systematic and research training procedures.

Assessment Tools

Blood Laboratory Work and Biomarker Examinations

Each participant also performed a blood draw to assess blood biomarkers. Participants fasted for 8–12 h before their blood was drawn and blood collections were scheduled in the morning to minimize diurnal variations. Blood draw *via* venipuncture was performed by a certified phlebotomist from an accredited clinical laboratory. The samples were kept at room temperature for a maximum of 3 h before being processed in the laboratory. The serum samples were then stored at −80°C until further analyses. After sample collections from all the participants were completed, all samples were assayed on the same day and on the same plates in the laboratory to avoid batch effects. Biomarker concentrations were examined in serum samples, using commercially available enzyme-linked immunosorbent assay (ELISA) kits. Four biomarkers were measured, namely IGF-1(Immunodiagnostics Systems, East Boldon, United Kingdom, USA), insulin (Immunodiagnostics Systems, East Boldon, United Kingdom), IGFBP-3 (Immunodiagnostics Systems, East Boldon, United Kingdom), and IL-6 (Meso Scale Diagnostics

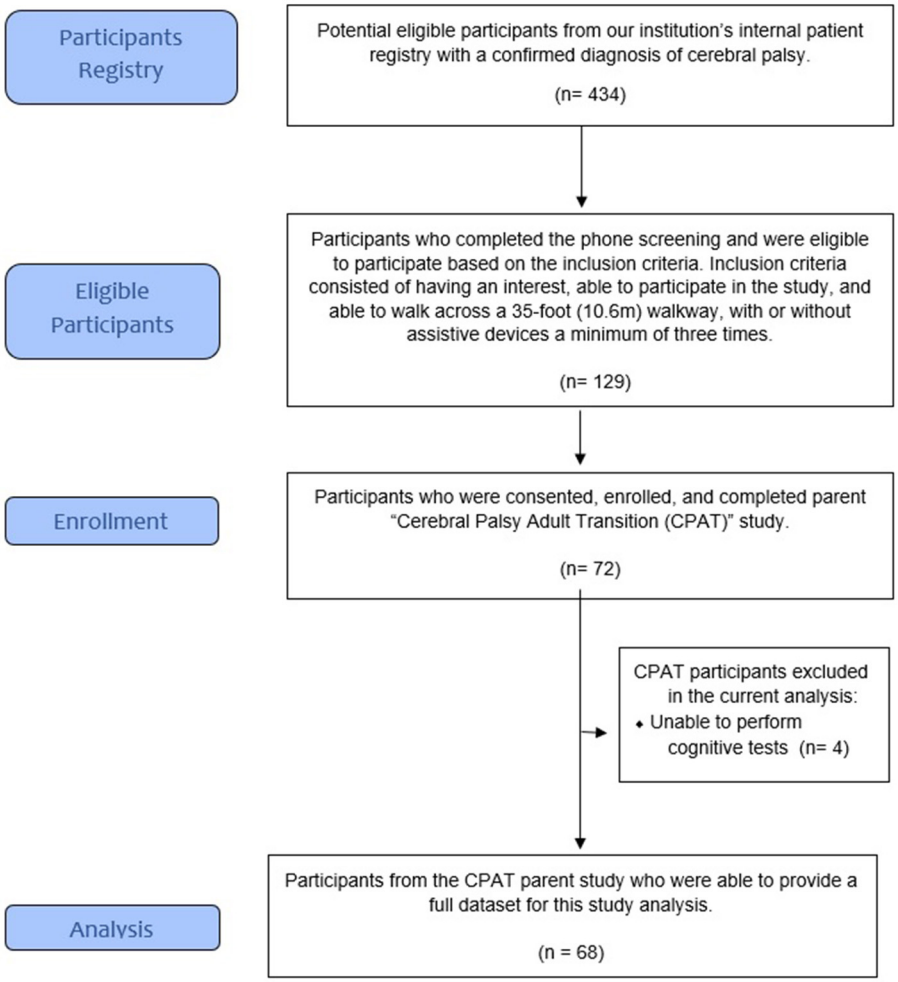

FIGURE 1 | Study participant flow diagram.

Maryland, USA). All the experiments were performed as per the instructions of respective manufacturers of the kits in singlets on IDS-iSYS automated instrument. The intra- and inter-assay coefficients of variations (CVs), in sequence, for the biomarkers are 2 and 9.5% for IGF-1, 1.6 and 2.8% for insulin, 3.4 and 4% for IGFBP-3, and 6 and 6.2% for IL-6.

Cognitive Function Assessments

To assess the detailed cognitive functions and different cognitive domains, sub-tests from the Wechsler Memory Scale IV (WMS-IV), and the Wechsler Adult Intelligence Scale IV (WAIS-IV) (39) were administered to all participants. The WMS-IV assesses a person's memory (38), while the WAIS-IV assesses cognitive ability (39). The WMS-IV assessed a person's memory, specifically a person's performance in five Index Scores: Auditory Memory, Visual Memory, Visual Working Memory, Immediate Memory, and Delayed Memory. The WAIS-IV is used as a general test the intelligence to assess overall cognitive ability for adults.

Table 2 reports all the subtests that were administered. The Short Test of Mental Status (STMS) is a screening tool for global cognitive status and was also administered during the study (40). For all three cognitive assessment tools, three researchers were trained in administering the tests and all tests were administered in the same clinical sites. The higher the scores, the better the participants' cognitive functions.

PROMIS-57 Scale Assessments

Patient-Reported Outcomes Measurement Information System (PROMIS)-57 was used to assess global patient-reported health-related quality of life domains, encompassing physical, mental, and social wellbeing (41). The PROMIS-57 is made up of 57 items, which assesses nine domains related to quality-of-life, including cognitive concerns, anxiety, depression, fatigue, sleep quality, participation in social roles and activities, pain interference, executive functions, and physical functions. All surveys were reviewed in person with the research team for clarity and, if necessary, were corroborated by caregivers (42, 43).

TABLE 1 | Demographics, clinical characteristics, and biomarker data of study participants.

Demographics characteristics	CP current study ($N = 68$)	Excluded cohort participants with no neuropsychological test scores ($N = 4$)	*P*-values
	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	
Age (in years)	24.94 ± 5.35	25.38 ± 4.99	0.873
Sex			
Female	38 (55.9)	0 (0)	0.045*
Male	30 (44.1)	4 (100)	
Ethnicity			
Caucasian	51 (75)	4 (100)	0.566
Other ethnicities	17 (25)	0 (0)	
Years of Formal Education	13.54 ± 2.29	12.50 ± 1.00	0.370
Employment status			
Had active roles, either employed full time or part time, student or volunteer	44 (64.7)	1 (25)	0.290
No active roles nor employed	24 (35.3)	3 (75)	
Biomarkers			
Raw IGF-1; ng/mL	210.85 (72.78)	255 (68.24)	0.241
Log-transformed IGF-1	2.30 ± 0.16	2.39 ± 0.13	0.243
Raw insulin; uIU/mL	10.02 (5.79)	9.85 (5.23)	0.954
Log-transformed insulin	0.93 ± 0.26	0.93 ± 0.28	0.973
Raw IGFBP-3; ng/mL	4377.01 (929.57)	4925.50 (572.22)	0.249
Log-transformed IGFBP-3	3.63 ± 0.10	3.69 ± 0.05	0.222
Raw IL-6; pg/mL	0.53 (0.36)	0.31 (0.23)	0.223
Log-transformed IL-6	−0.38 ± 0.32	−0.61 ± 0.35	0.155
CP Diagnosis/Subtypes, *N* (%)			
Hemiplegic	26 (38.2)	1 (25)	1
Non-hemiplegic	42 (61.8)	3 (75)	
STMS#			
Screened as having normal cognition	18 (26.5)	0 (0)	0.612
Screened as having MCI	50 (73.5)	2 (100)	
GMFCS, *N* (%)			
I	28 (41.2)	0 (0)	0.168
II	25 (36.8)	4 (100)	
III	13 (19.1)	0 (0)	
IV	2 (2.9)	0 (0)	
V	0 (0)	0 (0)	

*STMS, Short test of mental status; GMFCS, Gross motor function classification system; #, the total n for STMS was only 70, due to two of the participants not having complete data for this measure; *$p < 0.05$.*

For four domains, i.e., cognitive concerns, participation in social roles and activities, executive functions, and physical functions, the higher the scores, the better the participants' quality of life domains. For the other five domains, i.e., anxiety, depression, fatigue, sleep quality, and pain interference, where the higher the scores, the worse the participants' quality of life domains.

Statistical Analyses

Based on a power calculation with 80% power at 5% significance with a 2-tailed test, a sample size of 65 could detect an effect size of 0.35 for a significant correlation. Hence, the targeted total sample size needed to be 65 or more. All continuous measures were expressed as mean ± standard deviation (SD) and categorical variables in percentages. The differences in baseline variables were examined using Student's *t*-test, chi-square or Fisher's exact tests as the data necessitated. The raw values of the biomarker measurements did not fulfill the normality assumption; therefore, they were log-transformed for subsequent analyses and were successfully normalized, based on dot plots, skewness, and kurtosis. All the analyses were performed according to the three *a priori*-set aims. In investigating aim 1, we performed linear regression analyses using the IGF-1 level as the independent variable, associating with the objective neurocognitive measures. To investigate aims 2 and 3, we used the IGF-1 as the independent variable and associated it with the different domains of the PROMIS-57 scale, which were

TABLE 2 | Associations between IGF-1 concentrations with objective cognitive measures.

Objective cognitive measures	Models	IGF-1 concentrations		
		β (95% CI)	*P*-values	R^2
Total logical memory I—immediate recall raw score	Bivariate	12.821 (−1.692 to 27.333)	0.082	0.045
	Adjusted	19.329 (2.837 to 35.822)	**0.022***	0.141
Total visual paired associates I—immediate recall raw score (A + B + C + D)	Bivariate	21.542 (−1.147 to 44.231)	0.062	0.052
	Adjusted	20.5 (−6.373 to 47.373)	0.132	0.074
Total logical memory II—delayed recall raw score	Bivariate	18.027 (2.494 to 33.561)	**0.024***	0.075
	Adjusted	26.483 (8.885 to 44.082)	**0.004***	0.173
Total logical memory II—recognition raw score	Bivariate	3.659 (−2.623 to 9.941)	0.249	0.021
	Adjusted	4.62 (−2.41 to 11.65)	0.194	0.148
Total number of animals in 60 s	Bivariate	5.82 (−3.392 to 15.033)	0.212	0.024
	Adjusted	3.185 (−7.419 to 13.79)	0.55	0.101
Total block design raw score	Bivariate	−21.55 (−44.052 to 0.951)	0.060	0.054
	Adjusted	−31.428 (−56.325 to −6.53)	**0.014***	0.196
Total digit span raw score (forward + backward + sequencing)	Bivariate	1.732 (−9.626 to 13.09)	0.762	0.001
	Adjusted	−2.025 (−14.452 to 10.403)	0.746	0.169
Total symbol search raw score	Bivariate	−6.908 (−23.501 to 9.685)	0.409	0.011
	Adjusted	−17.586 (−35.715 to 0.543)	**0.057**	0.181

*IGF-1, insulin growth factor-1; 95% CI, 95% confidence interval. Bold text & * indicate trending and significant p-values, respectively. Bivariate, bivariate association between IGF-1 and cognitive domains. Adjusted, controlled for age, sex, ethnicity (Caucasian vs. Other ethnicities), years of education and employment status (active roles, either employed full time/part time, student, volunteer).*

the dependent variables. Lastly, to examine the exploratory aim, we associate IGF-1 as the independent variable with three related biomarkers, i.e., IL-6, insulin, and IGFBP-3. To control for potential confounding effects from other variables, regression analyses with and without controlling for covariates were performed; The covariates controlled for included age, sex, ethnicity, the years of education, and employment status. All the analyses were performed using the Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 24.0 (IBM Corp., Armonk, N.Y., USA). We followed other pilot studies of exploratory nature, which have adopted the practice of not correcting for multiple testing (27, 28). Hence, a two-tailed *p*-values of 0.05 and below were considered statistically significant.

RESULTS

Demographics

A total of 68 participants had complete data for this study. Compared to the participants excluded from this present study, no significant differences were detected in all variables, except sex ($p = 0.045$). **Table 1** summarizes the baseline characteristics of the sample. Their ages ranged from 19 to 49 years (mean = 25 years, SD = 5.35) and most participants were Caucasian ($n = 51$, 75%). Overall, the sample's sex distribution was well-balanced. The sample ambulatory characterization, measured by the Gross Motor Function Classification System I-V (GMFCS) showed that $n = 28$, 41.2% of the participants were able to walk independently (GMFCS I), $n = 25$, 36.8% were able to walk independently but with some assistance (GMFCS II), and $n = 15$, 22% were dependent of assistance and or a device to be able to ambulate (GMFCS III/IV).

Addressing Aim 1: Associations of Circulating IGF-1 With Objective Cognitive Measures

As shown in **Table 2**, at the bivariate level, circulating IGF-1 was only significantly associated with Total Logical Memory II—Delayed Recall Raw Score (β = 18.027, 95% CI = 2.494–33.561, $p = 0.024$). Upon controlling for covariates, circulating IGF-1 was significantly associated with multiple objectively measured and age-sensitive neurocognitive measures. They included the Total Logical Memory I—Immediate Recall Raw Score (β = 19.329, 95% CI = 2.837–35.822, $p = 0.022$), Total Logical Memory II—Delayed Recall Raw Score (β = 26.483, 95% CI = 8.885–44.082, $p = 0.004$), and Total Block Design Raw Score (β = −31.428, 95% CI = −56.325–−6.53, $p = 0.014$). Total Symbol Search Raw Score also had a trending association with circulating IGF-1 (β = −17.586, 95% CI = −35.715–0.543, $p = 0.057$).

Notably, while the associations between circulating IGF-1 and Total Logical Memory I—Immediate Recall Raw Score/Total Logical Memory II—Delayed Recall Raw Score are positive, the associations between circulating IGF-1 and Total Block Design Raw Score and Total Symbol Search Raw Score were inverse. The other cognitive tests were not significantly associated with circulating IGF-1.

Addressing Aim 2: No Associations Between Circulating IGF-1 and Subjective Cognitive Concerns

As shown in **Table 3**, no significant association of circulating IGF-1 with the PROMIS Applied Cognition domain, which indicated self-reported cognitive concerns, were observed at both the bivariate ($\beta = 2.413$, 95% CI $= -8.689$–13.514, $p = 0.666$) and multivariate concentrations ($\beta = 3.591$, 95% CI $= -9.086$–16.268, $p = 0.573$).

Addressing Aim 3: Associations of Circulating IGF-1 With Other Subjective Self-Reported PROMIS-57 Domains

As shown in **Table 3**, circulating IGF-1 was not significantly associated with other non-cognitive domains of PROMIS scale at the bivariate level. Upon controlling for covariates, circulating IGF-1 became significantly associated with several other non-cognitive domains of PROMIS scale, namely the PROMIS-57 Physical Function ($\beta = -15.234$, 95% CI $= -29.168$–-1.3, $p = 0.033$) and Social Roles & Activities sub-scales ($\beta = -14.397$, 95% CI $= -28.424$–-0.369, $p = 0.044$). Circulating IGF-1 also has trending associations with executive functions and depressive symptoms ($\beta = -20.683$, 95% CI $= 41.538$–0.172, $p = 0.052$) and ($\beta = 10.642$, 95% CI $= -0.363$–21.647, $p = 0.058$), respectively.

No significant nor trending association(s) were detected with the other PROMIS-57 domains, including anxiety, fatigue, sleep disturbance, and pain interference.

Exploratory Analysis: Associations Between Circulating IGF-1 and Related Biomarkers

As shown in **Table 4**, circulating IGF-1 was associated significantly with IGFBP-3 (bivariate: $\beta = 0.376$, 95% CI $= 0.271$–0.481, $p < 0.001$& adjusted: $\beta = 0.388$, 95% CI $= 0.269$–0.507, $p < 0.001$) and IL-6 (bivariate: $\beta = -0.457$, 95% CI $= -0.922$–0.008, $p = -0.054$ & adjusted: $\beta = -0.56$, 95% CI $= -1.087$–-0.033, $p = 0.038$). No significant association was detected between circulating IGF-1 and insulin. No significant associations were detected between these related biomarkers with the psycho-social measures, i.e., neurocognitive assessments and PROMIS domains (data not shown).

DISCUSSION

Employing the bio-psycho-social health psychology model, this is a pilot study holistically investigating IGF-1 as a biological determinant of a plethora of cognitive and QoL domains in adults with CP. Given multiple significant associations upon adjusting for pertinent covariates, IGF-1 might be a biological determinant/ biomarker of multiple objectively measured cognitive functions and subjective quality-of-life outcomes in adults with CP. These findings highlighted the pleiotropic roles of IGF-1 in aging adults with CP, particularly from the perspective of aging. On the other hand, the lack of association of IGF-1 with subjective cognitive complaint illuminated the discrepancy between objectively and subjectively measured cognitive functions, thus stressing the need to assess cognition in an objective manner in this specific population. By further showing that IGF-1 was significantly associated with and hence potentially a biological determinant of several domains of quality-of-life measures, the findings showed the pleiotropic roles of IGF-1 in young adults with CP, providing pilot data for future validation studies.

These findings illuminated the biological underpinnings of cognitive functions and suggest the utility of IGF-1 as a potential biomarker for multiple cognitive functions in young adults with CP. In particular, several of these cognitive domains include attention, memory, executive function, information processing speed, visual perception, and visuospatial skill. These functional cognitive outcomes have important implications for learning and memory, as well as daily functions, such as managing finances (44).

Considering these findings in the context of the extant literature, most studies examining the associations between IGF-1 and cognitive function in other populations have focused on global cognition (22, 27, 45). Supportive of our findings, for example, a clinical trial on children with CP has previously shown that recombinant growth hormone replacement increased IGF-1 concentrations and led to improved multiple functioning, including cognitive functions, especially psychomotor and executive functions, personal and psychosocial skills (46). Hence, IGF-1 concentrations may imply endogenous growth hormone concentrations or the liver responsiveness to growth hormone. Supporting our accelerated aging phenomenon hypothesis (2). Another study showed that IGF-1 deficient mice exhibited worsened microhemorrhages, suggesting that the pro-vascular and protective effects of circulating IGF-1 in the preservation of brain health and maintenance of cognitive function (47).

For these less-commonly-investigated specific cognitive domains, contradictory findings persist. One plausibility would be due to sensitivity issues of the neurocognitive measures used or, the biomarkers assessed in previous studies, or a combination of the two (48). For instance, a previous study showed that *lower* IGF-1 level was associated with *better* cognitive function across multiple domains (49). On the other hand, Dik et al. demonstrated that *reduced* IGF-1 predicted *declining* processing speed (48). Intriguingly, in our study, we observed a differential in the directions of effects depending on the subtype of objective cognitive measures utilized and thus the different cognitive domains. The attention and memory domains were unequivocally positively associated with IGF-1, whilst information processing speed and visual perception, and visuospatial skill were negatively associated with IGF-1 concentrations. Previous studies have shown that lower IGF-1 concentrations were associated with hippocampal atrophy (49), areas vital for learning and memory. We showed a similar trend of association, in that higher IGF-1 concentrations were associated with better learning and memory. For executive functions, a randomized controlled trial (RCT) showed that by increasing the IGF-1 concentrations in older adults, executive functioning, and to a smaller extent verbal memory, were significantly improved (50). In contrast, we showed that higher

TABLE 3 | Associations between IGF-1 concentrations with patient self-reported measures – PROMIS-57 scale domains.

PROMIS-57 scale domains	Models	IGF-1 concentrations		
		β (95% CI)	*P*-values	R^2
Applied cognition—cognitive concerns	Bivariate	2.413 (−8.689 to 13.514)	0.666	0.003
	Adjusted	3.591 (−9.086 to 16.268)	0.573	0.092
Anxiety	Bivariate	0.889 (−10.118 to 11.896)	0.873	0
	Adjusted	3.464 (−9.21 to 16.138)	0.587	0.073
Depression	Bivariate	5.873 (−3.601 to 15.347)	0.220	0.021
	Adjusted	10.642 (−0.363 to 21.647)	**0.058**	0.076
Fatigue	Bivariate	0.45 (−10.316 to 11.216)	0.934	0
	Adjusted	1.116 (−11.327 to 13.558)	0.858	0.065
Sleep disturbance	Bivariate	−2.367 (−12.097 to 7.362)	0.629	0.003
	Adjusted	−0.093 (−11.442 to 11.255)	0.987	0.052
Social roles and activities	Bivariate	−8.664 (−20.961 to 3.632)	0.164	0.028
	Adjusted	−14.397 (−28.424 to −0.369)	**0.044***	0.116
Pain interference	Bivariate	−4.511 (−15.395 to 6.373)	0.411	0.010
	Adjusted	−2.629 (−15.45 to 10.191)	0.683	0.040
Executive functions	Bivariate	−9.021 (−29.228 to 11.185)	0.376	0.011
	Adjusted	−20.683 (−41.538 to 0.172)	**0.052**	0.263
Physical functions	Bivariate	−4.59 (−17.856 to 8.676)	0.492	0.007
	Adjusted	−15.234 (−29.168 to −1.3)	**0.033***	0.234

*IGF-1, insulin growth factor-1; 95% CI, 95% confidence interval. Bold text & * indicate trending and significant p-values, respectively. Bivariate, bivariate association between IGF-1 and PROMIS-57 Scale Domains. Adjusted, controlled for age, sex, ethnicity (Caucasian vs. Other ethnicities), years of education, and employment status (active roles, either employed full time/part time, student, volunteer).*

TABLE 4 | Associations between IGF-1 concentrations and other biomarkers.

Other biomarkers	Models	IGF-1 concentrations		
		β (95% CI)	*P*-values	R^2
Insulin	Bivariate	0.301 (−0.074 to 0.676)	0.114	0.035
	Adjusted	0.257 (−0.172 to 0.686)	0.237	0.117
IGFBP-3	Bivariate	0.376 (0.271 to 0.481)	**<0.001*****	0.422
	Adjusted	0.388 (0.269 to 0.507)	**<0.001*****	0.483
IL-6	Bivariate	−0.457 (−0.922 to 0.008)	**0.054**	0.052
	Adjusted	−0.56 (−1.087 to −0.033)	**0.038***	0.146

*IGF-1, insulin growth factor-1; 95% CI, 95% confidence interval. Bold text & * indicate trending and significant p-values, respectively, *** indicates $p < 0.001$. Bivariate, bivariate association between IGF-1 and other relevant biomarkers. Adjusted: controlled for age, sex, ethnicity (Caucasian vs. Other ethnicities), years of education, and employment status (active roles, either employed full time/part time, student, volunteer).*

IGF-1 concentrations were associated with worse executive functions, for both objectively measured functions and those measured on a self-reported scale. One plausible reason could be that in our cohort of young adults with CP, many presented with cognitive functions comparable to MCI (2). Thus, we speculate that a physiological compensatory mechanism might be occurring, increasing IGF-concentrations above those observed in non-MCI individuals, in an attempt to buffer the neurobiological processes compromised by aging and dementia pathologies (21, 50–52). Indeed, such a compensatory mechanism of IGF-1 has been shown in upregulating the clearance mechanism of amyloid beta in the brains of older adults (53). In adults with CP, we postulate that this phenomenon could be differential, based on the hierarchy of cognitive functions, in that the compensatory mechanisms of IGF-1 kicks in at the lower hierarchy of cognition (learning and memory), and thus the positive associations. However, at the higher hierarchy of cognition (executive functions), the compensatory mechanism could have overshot and hence resulting in inverse associations with executive functions. Another interpretation could be the presence of a "threshold effect" (48), such that when IGF-1 is below a certain concentration that it is significantly associated with decline in processing speed.

Another plausible interpretation is the developmental effects of IGF-1 in cellular stress resistance and late-life mortality. A previous mice study demonstrated that a reduced IGF-1

level in the early lifespan is associated with increased lifespan, suggesting that there might be detrimental effects of high IGF-1 concentrations in the early lifespan, possibly through reduced intracerebral hemorrhage (54). In animals with significantly reduced IGF-1 concentrations caused by genetically-determined deficiencies, the incidence of other diseases, such as cancer and kidney disease, were also significantly lower. In all, while this study provided pilot and suggestive data, the contradictory roles of IGF-1 in various cognitive functions in young adults with CP warrant further investigations.

We have recently published findings similarly using the bio-psycho-social health psychology model, advocating the triaging of findings using biomarkers in older adults (55, 56). A second major finding of this study is that by demonstrating the utility of IGF-1 as an objectively-measured biological determinant, we triaged the self-reported outcomes and observed a discrepancy between objectively measured cognitive functions and self-reported cognitive complaints. These findings highlighted that cognitive decline, as measured by objective neurocognitive tests in CP, has biological underpinnings in IGF-1 in a similar manner to that observed in older adults experiencing aging, MCI and AD. On the other hand, subjective cognitive complaints, which are self-reported and subjective in nature, did not seem to a good measure for assessing cognitive health in this population, based on the lack of association with IGF-1. In contrast, subjective cognitive complaints reported by cognitively healthy older adults, have shown significant associations between the complaint scores and multiple brain degeneration markers (57–59). This discrepancy could lie in the ability of the patient to accurately appraise their own cognitive abilities, since our population had a high percentage of individuals with characteristics of MCI (75%), who could have dismissed minor cognitive issues as forgetfulness. Indeed, studies conducted with older adults with CI/MCI showed that they tend to overestimate their cognitive abilities (60). Similarly, this overestimation in young adults with CP may have attenuated the association with IGF-1. Taken together, these findings advocate that, rather than relying on quick assessment through self-reported cognitive complaints, there is likely a need for more detailed and objective assessments, either using neurocognitive tests or IGF-1, as the more accurate measures for assessing cognitive functions in young adults with CP.

The third major finding of this study is that IGF-1 was associated with four self-reported quality-of-life (QoL) domains as measured by the PROMIS scale, encompassing depressive symptoms, executive function, physical functions, and social roles and activities. Instead of divergent directions of associations as seen with objective neurocognitive measures, IGF-1 had consistent negative associations with QoL measures, in that higher IGF-1 concentrations were consistently associated with worse QoL measures. This is congruent with our postulation that IGF-1 elicits a compensatory mechanism, with higher IGF-1 concentrations compensating for deteriorating higher-level functions, such as the QoL functions. Despite presenting with contradictory findings in children with CP (46, 61), no previous studies have associated biomarker with comprehensive QoL measures in young adults with CP. Hence, this finding has potential implication in that detecting elevations in IGF-1 could be an objective measure for various declining self-reported functioning in aging adults with CP, ranging from several cognitive domains, depressive symptoms, physical functions, and social roles and activities. Importantly, these findings show that these self-reported functions are not merely subjective and fleeting feelings, and they also have a biological basis in IGF-1 concentrations, similar to how psychological wellbeing is significantly associated with IL-6 concentrations (56, 62) and metabolomics markers associated with health-related QoL measure (63). Taken together, these findings are thus supportive of the bio-psycho-social model. Hence, these findings could have profound implications in non-pharmacological interventions, especially when subjective outcome measures are the main outcome measures, with scarcity in examining objective biomarker measures. Hence, future interventional studies which focus on these self-reported and more subjective measures may be validated by concurrently measuring IGF-1.

Lastly, we showed IGF-1 was significantly associated with IGFBP-3 and IL-6. Our findings concur with those of previous studies conducted with older adults, which showed longitudinal changes in IGF-1 and IGFBP-3 were strongly and positively correlated (23). Here, for the first time, we showed the presence and the magnitudes of associations between these biomarkers in CP (45).

IGF-1 and IGFBP-3 are biomarkers of the growth hormone system, specifically insulin signaling, while IL-6 is a powerful indicator of low-grade systemic inflammation (64, 65). Our findings suggest that a network of insulin signaling dysfunction, and low-grade inflammation, potentially with alterations in IGF-1 as the precipitating event, similar to IGF-1's pleiotropic roles in other clinical conditions, partially contribute, directly or indirectly, to the objective cognitive impairments and other subjective QoL functions in young adults with CP (66, 67). With these preliminary data established and pending future validation studies, longitudinal monitoring of this panel of biomarkers could be useful in tracking subtle preclinical declines, before young adults with CP present with overt clinical symptoms, allowing for early interventions (45).

LIMITATIONS AND STRENGTHS

We acknowledge a few limitations, such as the study's relatively modest sample size. However, to our knowledge, our cohort is the largest adult cohort with CP to date, and we extensively characterized measurements from a holistic perspective, including clinical, QoL, and biomarker measurements, representing a wide range of both objectively and subjectively measured functions in CP, which are typically not available in a single dataset. Since this is an exploratory study, we did not correct for multiple testing and, hence we cannot eliminate the possibility of having false positive findings. However, this is the first study to provide strong suggestive evidence for alterations in IGF-1 having pleiotropic roles in multiple facets of functions impaired in CP. It is worth noting that this study was of a cross-sectional design, and thus no causal

relationships could be inferred from the associations, warranting longitudinal examinations.

Despite these limitations, this is the first study in the field to *a priori* examine associations of IGF-1 with multiple objective and subjective measures in adults with CP, made possible by the extensive characterizations of multimodal measures based on a holistic bio-psycho-social approach and framework. Furthermore, our regression models also controlled for several covariates, minimizing residual confounding effects. As CP is a life-long condition, but most CP studies focus solely on children with CP, this study thus addresses the scarcity of data and gaps in evidence on how patients with CP age and the risk factors associated with the aging process, which predispose them to geriatric syndromes. Upon longitudinal causal validation, these findings thus have potential clinical implications in risk prediction and interventions in this severely understudied population.

CONCLUSIONS

Previous studies have shown that aging adults with CP suffer from secondary geriatric chronic diseases, which we termed the "accelerated aging phenomenon" (2). However, the biological determinant of this phenomenon, specifically cognitive impairment, has not been elucidated. This study filled the gaps by identifying an important biological determinant, and by extension related biological pathways, involved in multiple facets of impairments in aging adults with CP. This first insights into the underlying biological determinant of cognitive impairment and QoL functional outcomes in CP point to the potential implications of targeting a single molecule, IGF-1, as a tailored prevention and treatment strategy to maintain cognitive and physical functioning in adults with CP, along with the possibility of preventing premature secondary health conditions and cumulative impairments. Furthermore, the discrepancy observed between objectively measured cognitive functions and self-reported cognitive complaints highlights the need for detailed objective measures in this specific patient population. These findings provide the impetus for further investigations in larger studies with longitudinal design, to fully comprehend and assess the potential implications of measuring IGF-1 as a biomarker of pathology and the implications of focusing on altering IGF-1 concentrations to prevent the onset of secondary pathologies, particularly cognitive decline, observed in aging adults with CP. Lastly, gait abnormalities could manifest at early stages of Alzheimer's disease and are associated with cognitive decline, and can be used as an early biomarker to identify patients at risk of progressing to late-stage dementia. Hence, relationships between IGF-1 and cognitive tests with gait abnormalities may represent a future direction in CP research (68). These findings would have potentially important implications for cognitive impairment prevention and early intervention.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: data could be made available on reasonable request. Requests to access these datasets should be directed to AT; Alex.Tagawa@childrenscolorado.org.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Colorado Institutional Review Board and all participants signed informed consent prior to participation. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TN: conceptualization (present study), data analyses, data interpretation, and writing of the first draft (all sections). JC and PH: conceptualization (parent cohort). AT: data curation. TN, AT, JC, CC, and PH: methodology and critical inputs and revisions. TN, AT, and PH: project administration. TN and PH: supervision. AT and PH: intro & methods. All authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.748015/full#supplementary-material

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