DEMENTIA, FRAILTY AND AGING

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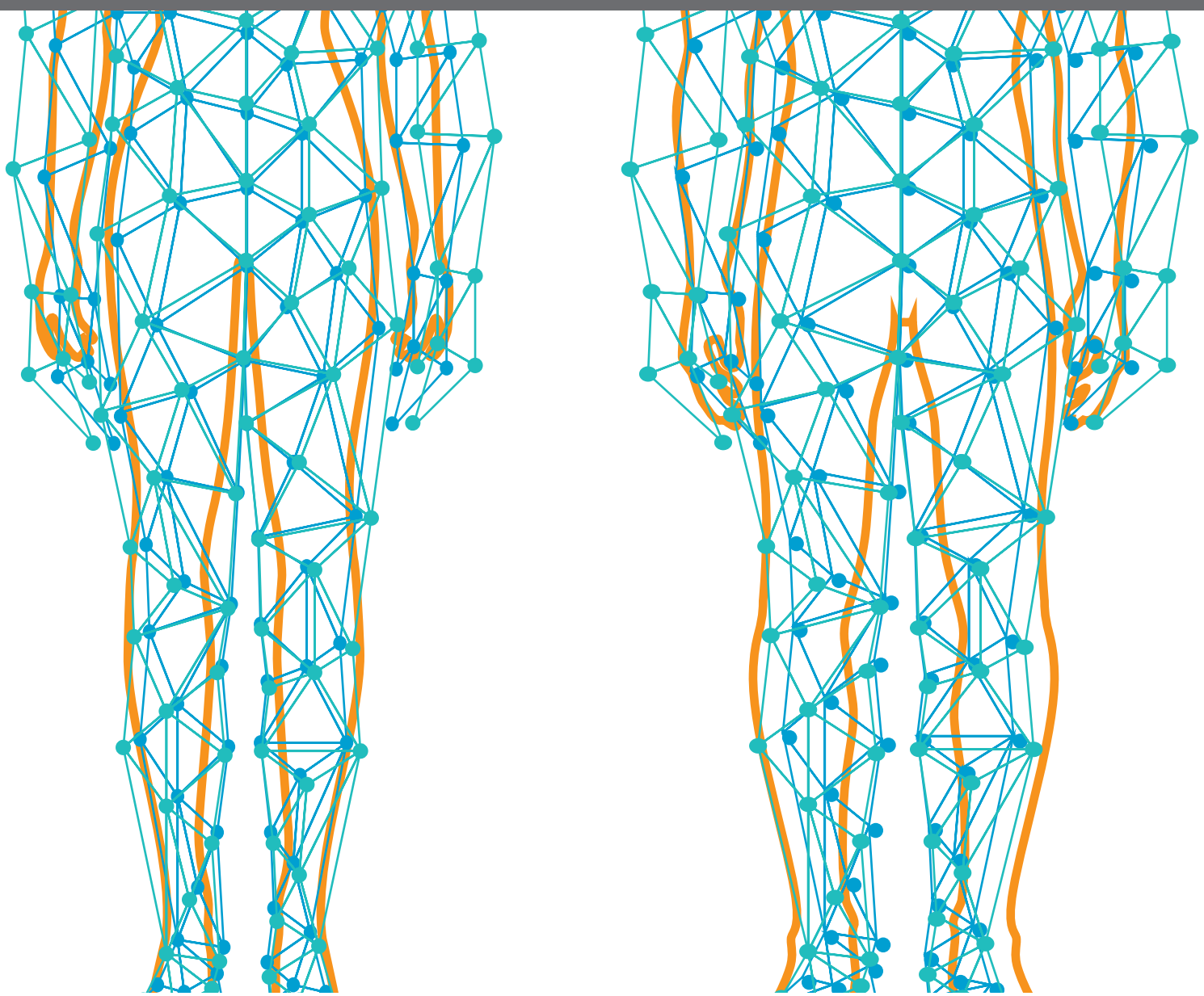

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DEMENTIA, FRAILTY AND AGING

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The number of older subjects is rapidly increasingly worldwide. As a consequence, the nature of clinical conditions is also changing. Traditional medicine and models of care have been based on the evaluation and treatment of single and usually acute conditions occurring in relatively young individuals. Today, the usual clinical manifestation of diseases is characterized by multiple and often chronic conditions affecting older people.
In this scenario, frailty and dementia have been triggering special interest both in research and clinical settings due to their high prevalence, impact on the individual's quality of life, and consequences for public health worldwide. These conditions aptly reflect the complexity of age-related pathological conditions, finding as causal factor a myriad of heterogeneous, interacting, and often still unclear pathophysiological processes. Indeed, their study is strongly affected by the difficulty to differentiate the effects of a normal aging process from eventual pathological deviations of the underlying systems. Their occurrence and trajectories over time are strongly affected by a wide array of factors and determinants that can be hardly attributed to the deficit/involvement of single biological systems and/or health domains. Moreover, environment and social factors also play a key role in the determination of phenotypes. The present Research Topic is aimed at widening our understanding of the frailty and dementia phenomena occurring with aging, in order to improve the clinical and public health approaches to these burdening conditions.

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NOVEL APPROACHES

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EDITORIAL
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Editorial: Dementia, Frailty and Aging

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Keywords: dementia, frailty, aging, population aging, big data

Editorial on the Research Topic

Dementia, Frailty and Aging

Population aging is both a worldwide success story and a worldwide health conundrum, with the increasing age of populations around the world leading to unprecedented challenges (1). According to the United Nations report on World Population Prospects (2017), there is an estimated 962 million people aged 60 years and above who comprise 13% of the global population (2). The beginning of the twenty-first century has seen health systems worldwide struggling to deliver quality healthcare amidst challenges posed by aging populations (3). Traditional medicine and models of care have been premised on the evaluation and treatment of standalone and usually acute diseases occurring in relatively younger individuals. This contrasts with the current reality of multiple, interacting, and often chronic conditions affecting older persons. It is thus necessary to disentangle the pathophysiological mechanisms, clinical manifestations, and inter-relationships of age-related conditions in order to personalize clinical interventions and realign health systems to better address the unmet needs of frail older persons (4, 5).

Against this backdrop, frailty and dementia have emerged as priority areas in both research and clinical settings due to their high prevalence, impact on the individual's quality of life, and public health impact (6–8). These conditions aptly reflect the complexity of age-related pathological conditions, causally underpinned by a myriad of heterogeneous, interacting, and often unclear pathophysiological processes. Indeed, a hallmark of both conditions is the inherent difficulty in differentiating the effects of the normal aging process from the eventual pathophysiological deviations of the underlying disease (9, 10). Their occurrence and trajectories over time are strongly affected by a wide array of factors and determinants that are not confined to single biological systems and/or health domains (10). Moreover, environment and social factors also substantially influence the definition of different phenotypes. This raises the clarion call for a broader, integrated, and holistic approach that is able to more adequately capture the biological, clinical, and psychosocial complexities of frailty and dementia, thus paving the way for improvement in the consequent outcomes (11–13).

The present Research Topic represents a timely addition to the burgeoning body of evidence which aims to provide fresh perspectives in our understanding of the frailty and dementia phenomena occurring with aging. An area of particular interest is the emerging construct of cognitive frailty (CF), which is designed to operatively capture the co-existence of frailty and cognitive impairment in the absence of dementia (14). Using a modified version of the IANA/IAGG criteria (15), Ma et al. reported a 2.7% prevalence of CF in a Chinese older population. Older persons, women, and people living in rural areas were found to be at higher risk of CF. Corroborating the recommendations of the Lancet Commission report (7), depression and hearing impairment were independently associated with CF in elderly individuals with physical frailty. The study by Nyunt et al. explored the physical frailty phenotype in mild cognitive impairment (MCI). When compared with participants with "normal high cognition," there was a higher prevalence of frailty and pre-frailty attributable to low lean mass, slow gait speed, or balance and gait impairment. In their 5-year observational study of 91 subjects with amnestic MCI,

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Trebbastoni et al. also noted that frailty was associated with increased risk of conversion to Alzheimer's dementia, even in those with high baseline level of cognitive performance.

Four papers in this Research Topic shed further insights to illuminate the knowledge gap in our understanding of the interface between cognitive and physical domains. In their study of 269 elderly individuals with subjective memory complaints, Hooper et al. did not find any significant cross-sectional associations between fatigue and Aβ load. However, sensitivity analysis revealed a weak association with increased Aβ in the hippocampus in subjects with MCI, thereby providing indirect support for the construct of CF at the early stages of Alzheimer's disease. Chhetri et al. proposed the motoric cognitive risk (MCR) syndrome, characterized by the simultaneous presence of gait disturbances and memory complaints in older adults, as a means to examine the close interactions between cognitive and physical domains and identify individuals at risk of dementia and other age-related adverse outcomes. By summarizing the existing evidence from both human and animal models, Bellelli et al. highlighted the multiple common pathophysiologic mechanisms and pathways of delirium and frailty, to lay out the case for delirium as the cognitive harbinger of a state of frailty in the context of an acute clinical event. This opens the door for further studies to examine the contribution of physical frailty to adverse outcomes in delirium, and conversely, the deleterious impact of delirium on physical frailty (16). Using the examples of frailty and MCI, the review by Canevelli et al. challenged the widely-held assumptions of these entities as unequivocally prodromal stages of a future disease state by providing a timely reminder of our incomplete understanding of the transitions of clinical at-risk conditions and their potential for clinical improvement and spontaneous reversion.

Dementia is a devastating and debilitating illness that has far-reaching public health, social and economic ramifications. Therefore, the Research Topic submissions also covered pertinent areas in dementia such as caregiving and diagnosis. To keep pace with the projected exponential rise in dementia, it is imperative that we tap upon the "invisible workforce" of family caregivers and understand the factors that predispose to caregiver burden (17). Li et al. confirmed the existence of the unique "worry about performance" (WaP) burden in the multidimensionality of caregiver burden beyond role and personal strain. Unlike other factors, WaP was significantly reported even in early cognitive impairment, suggesting its potential as a possible target for interventions aimed at improving self-efficacy among caregivers in the milder stages of burden (18). In their study examining the rapidly expanding group of caregivers of dementia in oldest-old (CDOO), Win et al. reported these were mainly older adult children who experienced significant role and personal strain rather than WaP while caring for their oldest-old family members with more impaired cognitive and physical function. To address the challenges of under-detection of dementia in the primary care setting, Teixeira et al. described a potentially scalable multi-stage strategy for community detection that involved initial screening by health professionals to identify at-risk individuals for more comprehensive evaluation. With the recent release of the NIA-AA Research Framework directed toward a biological definition of Alzheimer's disease (19), the real-world study of geriatrics outpatients by Dolci et al. highlighted the discrepancy between clinical diagnosis of Alzheimer's disease with cerebrospinal fluid and neuroimaging biomarkers, thereby reiterating the caution against premature and inappropriate usage of biomarker-based research frameworks in general medical practice.

Novel approaches are also suggested in this Research Topic. Reviving a 100-year old idea about a possible role played by gut microbiota in modulating brain morphology and function across the life-course (20), Calvani et al. proposed the fascinating concept of the "second brain aging" which links age-related changes in the gut mircrobiota to neurodegeneration and related conditions (including depression, Alzheimer's disease, and Parkinson's disease). This raises the tantalizing prospect of developing interventions that target the gut microbiota as part of a comprehensive strategy in dementia prevention and treatment. Yatawara et al. explicated the cognitive-anatomical basis of getting lost behavior in patients with mild Alzheimer's disease. They reported that the top-down modulation deficit is localized to the medial temporal lobe and did not follow the typical mechanism in healthy aging, highlighting the need to target both working memory and visuospatial deficits simultaneously. Lastly, the thoughtful review by Lenca et al. explored the potential of harnessing big data approaches to improve current preventive and predictive models in dementia care and research (e.g., enabling earlier diagnosis, optimizing resource allocation, and delivering individualized treatments tailored to patients). The authors highlighted technical, scientific, ethical, and regulatory challenges and proposed the need for multi-level integrative approaches to chart the route ahead for research, ethics, and policy.

As guest editors for this research topic on frailty, dementia, and aging, we are delighted to commend to you the collection of 14 articles as an important contribution to "evidence-balanced medicine" in the real world of frail older persons (21).

AUTHOR CONTRIBUTIONS

W-SL, MarC, and MatC conceived the manuscript. W-SL drafted the paper. MatC critically appraised and edited the manuscript. All authors read and approved the final version of the paper.

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ORIGINAL RESEARCH
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Cognitive Frailty in China: Results from China Comprehensive Geriatric Assessment Study

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Objective: Cognitive frailty (CF) refers to the co-occurrence of physical frailty (PF) and cognitive impairment in persons without dementia. We aimed to explore the prevalence and associated factors of CF in China.

Method: Data were obtained from the China Comprehensive Geriatric Assessment Study. A total of 5,708 community-dwelling older adults without dementia were included. CF was assessed using the Mini–Mental State Examination for the evaluation of cognitive status and the Comprehensive Geriatric Assessment-Frailty Index for the evaluation of PF. Participants with both cognitive impairment and PF were classified as having CF. Sociodemographic and clinical history was also collected. Logistic analysis was used to explore the association between the associated factors and CF.

Results: The overall crude prevalence of CF was 3.3% [95% confidence interval (CI) = 3.0–4.0], and the standard prevalence of CF was 2.7% (95% CI = 2.0–3.0). The prevalence of CF was significantly higher in women than men and higher in residents of rural areas than urban areas. Moreover, the prevalence of CF was found to increase with age. Multiple factor analysis showed that depression (OR = 2.462, 95% CI = 1.066–5.687) and hearing impairment (OR = 2.713, 95% CI = 1.114–6.608) were independent associated factors of CF in elderly individuals with PF.

Conclusion: Our results provide the first empirical evidence of CF in China. We have identified several associated factors with CF which should be considered while assessing older adults. More studies in Chinese population with CF are demanded to confirm with our findings.

Keywords: cognitive frailty, elderly, comprehensive geriatric assessment, epidemiology, frailty index

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INTRODUCTION

Frailty in older adults is characterized by a nonspecific state of vulnerability, specifically, reduced multisystem physiological reserve, decreased resistance to stressors, and increased risk for adverse health outcomes (1–3). The relationship between physical frailty (PF) and cognitive impairment has been recognized for decades and thought to be connected by their similar pathophysiological

Abbreviations: CF, cognitive frailty; PF, physical frailty; CGA, Comprehensive Geriatric Assessment; FI, frailty index; MMSE, Mini-Mental State Examination.

mechanisms (4). There is a frequent coexistence of frailty and cognitive impairment, which also had cumulative effect mortality (5, 6). Hence, demanding the need of a novel entity to discriminate associated risk factors of both PF and cognitive impairment, as well as to provide better prevention and therapy strategies for those frail patients who are prone to cognitive disorders (7). Accordingly, the International Academy on Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) proposed a new construct "cognitive frailty" (CF) (8), to define a condition characterized by the simultaneous presence of PF and cognitive impairment in the absence of dementia, which might be marked as a promising target for the prevention of age-related disorders (9). In this new concept, PF precedes the onset of cognitive impairment (8, 9), thus, intervention programs targeted to improve frailty may prevent late-life cognitive disorders. Several studies have investigated the concept of CF, and reported the prevalence of CF to be ranging between 10.7 and 40% in clinical settings and 0.9–12.0% in community-based population (7). A recent study claimed that CF is a precursor of neurodegenerative processes and could be potentially reversed (10). Furthermore, other research reported that CF was a useful predictor of mortality and dementia, even after adjusting for vascular risk factors and depressive symptoms (11).

Accordingly, this new concept poses challenges as well as opportunities for geriatricians. Nonetheless, the validity and utilization of CF in the Chinese population which represents the largest and fastest growing aging population in the world remains unclear. Hence, we aimed to explore the prevalence and associated factors of CF in the Chinese population.

MATERIALS AND METHODS

Participants

Data were obtained from the China Comprehensive Geriatric Assessment Study (CCGAS) (2011–2012) which used a two-step statistical sampling techniques including cluster, stratification, and random selection (12). In the first step, seven cities representing the six main regions of China were selected: Beijing, Xi'an, Harbin, Chengdu, Chongqing, Changsha, and Shanghai. Then, participants from the above seven cities were selected regarding urban–rural areas, age, and gender in the second step. Further details regarding the CCGAS have been reported (12). Finally, 9,694 elderly participants were enrolled including 6,867 elderly adults living in community and 2,827 inpatients. Of the 6,867 community-dwelling older adults, 5,708 of those without a self-history of diagnosed dementia and with Comprehensive Geriatric Assessment-Frailty Index (CGA-FI) and Mini-Mental State Examination (MMSE) data were included. This study was reviewed and approved by the ethics committee of Xuanwu Hospital of Capital Medical University. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

The Construct of CF

Cognitive frailty was operationalized using CGA-FI for the evaluation of PF and MMSE for the evaluation of cognitive status. Participants were stratified by educational level to determine thresholds for global cognition. The thresholds for those who were illiterate, or attended at most primary school, middle school, or university were ≤17, ≤20, ≤22, and ≤24, respectively (13). Participants who scored below the threshold value for their education group were recorded as cognitive impairment. As we previously published (14), CGA-FI was measured by 68 parameters, but in the current study the "cognition" variable of FI was excluded, thus 67 parameters from the following five variables remains: demographic characteristics, physical health, physical function, living behavior and social function, and mental health. Further detail on CGA-FI is in Table S1 in Supplementary Material. The FI score was defined as the cumulative sum of the total score of each index divided by 67. PF was defined as FI $\geq$ 0.25 (15, 16). Participants positive for both instruments were classified as having CF. Dementia was defined by a reported disease history diagnosed by a doctor. All of the participants were free of dementia.

Sociodemographics

Using face-to-face interviews, we examined the sociodemographic variables, medical conditions, and physical function based on the standard CGA instrument (12). Area of residence was classified into urban and rural. Northern cities included Beijing, Xi'an, and Harbin, and southern cities included Chengdu, Chongqing, Changsha, and Shanghai. Participants were divided into the following five age groups: 60–64, 65–69, 70–74, 75–79, and ≥80 years. Education status was recorded as illiterate or literate. Participants were also stratified by monthly income: USD < 180 and USD ≥ 180. Marital status was listed as married or widowed.

Medical Conditions

Participants were considered to have a medical condition if they had a self-reported history of chronic disease diagnosed by a doctor. Clinical syndromes and geriatric syndromes were also recorded. Functional ability was assessed on the basis of activities of daily living (ADL) and instrumental activities of daily living (IADL) (17). Participants with one or more impaired ADL or IADL were defined as having a disability. The Geriatric Depression Scale was used to assess depression (18), with a total score ranging 0–30. A score of ≥11 typically indicates clinical depression. Comorbidity was defined as having ≥2 chronic diseases. A walking speed below the height-adjustment threshold value in 20 m walking test was considered a slow pace. Regular exercise was defined as exercising for ≥3 h/week over the past 12 months. We also screened for a history of spontaneous fractures that occurred over the past 2 years and falls that occurred twice or more often in the past year.

Statistical Analysis

EpiData was used to establish the database, input, and automatically verify the data. Statistical analyses were performed by SPSS version 11.5 (Inc., Chicago, IL, USA). Count data were expressed as percentages, with standardized rates (weighted values) calculated using the national standard population composition ratio as at the Sixth National Census (2010). The bootstrap confidence interval for the prevalence was estimated based on 1,000 bootstrap samples and was bias-corrected. Chi-square tests were performed to compare percentages. Forward stepwise logistic

regression was done to explore the association between the various factors as independent variables and CF as the dependent variable. Adjustments were made for sociodemographic variables and age-related factors. All statistical tests were two-sided and statistical significance was set at a P-value < 0.05.

RESULTS

Figure 1 presents the prevalence of CF in older adults. Of the 5,708 older adults, 187 individuals demonstrated CF, accordingly, the overall crude prevalence and standard prevalence of CF were 3.3% [95% confidence interval (CI) = 3.0–4.0%] and 2.7% (95% CI = 2.0–3.0%), respectively. The prevalence of CF was significantly higher in women and those living in rural areas. Moreover, the prevalence of CF increased with age, with the highest values recorded for participants aged ≥80 years (9.8%) and the lowest values observed among those aged 60–64 years (1.1%, **Figure 1**).

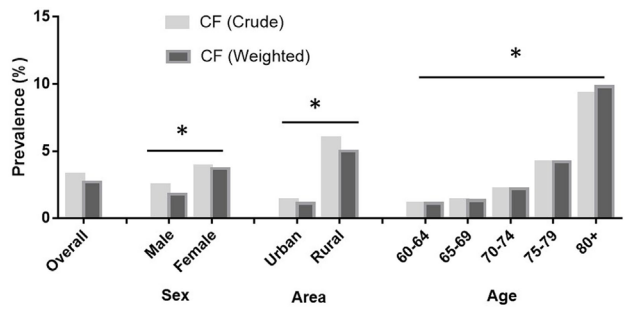

FIGURE 1 | Prevalence of cognitive frailty (CF) in older adults by gender, area, and age. The prevalence of CF among adults aged 60+ in China by China Comprehensive Geriatric Assessment Study, 2011–2012. Data were weighted by the national standard population composition ratio based on the Sixth National Census (2010). The total sample population in the analysis was 5,708.

The effect of sociopsychological factors and physical function on CF are shown in **Table 1**. The prevalence of CF was higher among participants who were illiterate, had a low income, or widowed, and it was also found to be relatively higher among participants who had depression (**Table 1**). We observed a higher prevalence of CF among participants with comorbidities, disabilities, slow walking speed, vision impairment, and hearing impairment. Those who had less exercise and a low body mass index demonstrated a higher prevalence of CF. Participants who reported spontaneous fractures or falls showed a higher prevalence of CF (**Table 1**).

The results of logistic regression models are shown in **Table 2**. In the context of the robust elderly individuals, comorbidity, depression, less exercise, hearing impairment, disability, and falls were independent factors influencing CF. Furthermore, when referred to the elderly individuals with PF, depression and hearing impairment were independently associated with CF.

DISCUSSION

Our results showed that the standard prevalence of CF was 2.7%, and increased with age in the Chinese older population. Women and participants living in rural areas were found to be at higher risk for CF. Currently, owing to different definitions of CF, the prevalence varies from 0.9 to 40% across countries (7, 19–21). In the Singapore Longitudinal Ageing Studies, the estimated prevalence of PF coexisting with cognitive impairment was 1.8%; moreover, the prevalence of pre-frailty and frailty coexisting with cognitive impairment was 10.7% and was associated with more severe functional disability, hospitalization, poor quality of life, and mortality (19). In an Italian study, the prevalence of CF was 4.4% among older adults, and those with CF showed more severe

TABLE 1 | Effect of sociopsychology factors and physical function on cognitive frailty (CF).

	Total	NC, *n* (%)	CF, *n* (%)	Weighted (%)	χ^2	*P*
Sociopsychology factors						
Education						
Illiterate	1,040	941 (90.5)	99 (9.5)	9.1	156.423	<0.001
Not illiterate	4,668	4,580 (98.1)	88 (1.9)	1.6		
Monthly income (US$)						
<180	2,633	2,502 (95.0)	131 (5.0)	4.2	56.035	<0.001
≥180	2,922	2,879 (98.5)	43 (1.5)	1.2		
Marital status						
Married	4,398	4,286 (97.5)	112 (2.5)	2.1	31.065	<0.001
Widowed	1,306	1,232 (94.3)	74 (5.7)	5.3		
Smoking	1,628	1,573 (96.6)	55 (3.4)	2.4	0.075	0.784
Depression	691	587 (84.9)	104 (15.1)	13.3	343.966	<0.001
Physical function						
Comorbidity	3,249	3,089 (95.1)	160 (4.9)	4.4	64.678	<0.001
Disability	414	292 (70.5)	122 (29.5)	29.1	966.413	<0.001
Slow walking speed	647	616 (95.2)	31 (4.8)	4.2	38.596	<0.001
Vision impairment	383	338 (88.3)	45 (11.7)	10.6	93.019	<0.001
Hearing impairment	272	231 (84.9)	41 (15.1)	15.1	125.446	<0.001
Less exercise	1,210	1,093 (90.3)	117 (9.7)	8	198.067	<0.001
Fall	252	218 (86.5)	34 (13.5)	12.9	86.831	<0.001
Fracture	190	179 (94.2)	11 (5.8)	5.2	3.918	0.048
Low body mass index	317	296 (93.4)	21 (6.6)	5.9	11.876	0.001

TABLE 2 | Forward stepwise logistic regression for associated factors with CF.

	Model 1			Model 2		
	OR	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Age (≥75 years)	4.237	1.955–9.183	<0.001	4.918	1.845–13.107	0.001
Area (rural)	5.670	2.454–13.099	<0.001	22.196	8.258–59.659	<0.001
Comorbidity	11.761	4.041–34.231	<0.001	/	/	/
Depression	11.371	5.302–24.387	<0.001	2.462	1.066–5.687	0.035
Less exercise	3.213	1.529–6.754	0.002	/	/	/
Hearing impairment	3.519	1.410–8.779	0.007	2.713	1.114–6.608	0.028
Disability	13.418	5.317–33.865	<0.001	/	/	/
Fall	6.653	2.651–16.697	<0.001	/	/	/

Model 1: Logistic regression for risk factors associated with CF in the robust and CF population. The variables not in the equation were gender, smoking, marital status, education, income, walking speed, vision impairment, low body mass index, and fracture. Adjusted for sociodemographic variables and age-related factors.
Model 2: Logistic regression for risk factors associated with CF in the population with physical frailty. The variables not in the equation were gender, smoking, marital status, education, income, walking speed, vision impairment, comorbidity, exercise, disability, fall, low body mass index, and fracture. Adjusted for sociodemographic variables and age-related factors.
OR, odds ratio; CI, confidence interval; CF, cognitive frailty.

disability than those without frailty (22). Similarly, the findings of our study also showed that older participants with comorbidity, disability, and fall were independently associated with CF.

Past studies have shown PF to be associated with cognitive decline in older adults (23, 24). Compared to the individuals with only cognitive impairment (i.e., without PF), those with CF showed poorer scores on executive and attention tests (25). Furthermore, baseline frailty was found to be strongly associated with subsequent changes in cognition assessed by MMSE (26, 27) and higher risk for non-AD dementia (28). In addition, studies have shown frailty state transitions to be associated with cognitive deterioration in participants with mild to moderate Alzheimer disease (29). Another study reported that PF was a stronger indicator of cognition than age (30).

Hearing impairment is one of the principal causes of chronic disability in older adults (31), and our study showed that old individuals with hearing impairment were independently associated with CF either in robust or frail population. A previous study suggested that hearing impairment to be a prognostic marker of frailty in older age and could identify older persons with adverse health outcomes (31–33). Recently, CF was considered to embody two different manifestations: slow gait and low cognition, which may share a common underlying mechanism (34). Furthermore, Verghese et al. validated a new Motoric Cognitive Risk syndrome, which was defined as the presence of cognitive complaints and slow gait, and found it was associated higher risk of developing dementia (35). Our study also showed that participants with slow gait speed demonstrated a higher prevalence of CF; however, gait speed was not an independent factor per the logistic regression analysis. Nevertheless, other studies found that gait speed was associated with severity of cognitive impairment, after adjusting for age, gender, and age-related factors (36).

We used the CGA-FI to assess for PF in this study, while majority of the other studies used the Fried criteria (11, 19, 21, 22, 25, 34, 37, 38). However, it is noteworthy that in fact, the construct of CF itself is rather controversial, and the past studies on CF implemented non-uniform operational criteria both for assessing PF and cognitive impairment (7). Moreover, the operational definition of PF still remains unresolved (8), which might partially explain the non-uniformity. Although the consensus paper of IANA/IAGG definition of CF has been described by Fried criteria for PF (8), an obvious question emerges: can frailty be defined by FI in the construct of CF? It has not yet fully explored in the literature. Fried criteria and FI are the two most commonly used measurements in the world, and they share common characteristics and complementarity when applied to the Chinese older population (39); moreover, the preliminary results of our study further demonstrated the feasibility of this method in a Chinese population. A previous study reported that using a multi-dimensional FI, both baseline status and within-person changes in frailty were predictive of cognitive trajectories (40); furthermore, this tool was shown to be effective in identifying individuals at high risk for cognitive decline (41). Thus, FI may be a promising instrument for determining the vulnerability of dementia and was also recommended to be used for assessing CF (42). CGA can be used to identify the medical, psychosocial, and functional capabilities of older adults (43), in addition, CGA-FI can predict both cognitive changes and mortality (27); therefore, CGA-FI has applications in frailty measurements in elderly individuals with cognitive impairment.

This is the first study to report the prevalence of CF and the associated factors in China; furthermore, our results show that the CGA-FI is a feasible tool for defining CF. CGA is regularly used as an assessment tool for old individuals. In older adults, most health deficits are known to be associated with late-life cognitive impairment (5). Our study provides a quick and simple method to identify CF in any individual with CGA data; furthermore, this approach allows for rapid diagnosis of CF, such that prevention of and intervention for dementia and disability can be established at an early stage (44). However, these results must be interpreted in light of several limitations. First, we chose only seven cities in China; although our methodology was strong, the small number of cities and participants included may have biased our results. Second, this is a cross-sectional study, further longitudinal studies that incorporate frailty and cognition and randomized controlled trials are needed to provide more information on the cause-and-effect relationship of frailty and cognition, risk factors of CF and the transition to

dementia. Third, this is a study designed for screening tools, so dementia was defined by a reported disease history diagnosed by a doctor, and a lack of some important examinations specific for dementia such as neuroimaging tests and other neuropsychiatric scales, in this perspective, some patients with potential dementia might be included in this population. Besides, the relationship between PF and cognitive impairment was not explored in the study. The existing cognitive decline in this study is uncertain to be driven by the physical domain makes the criteria arbitrary to be defined as CF, which indicates that there is a disparity in our operational construct and the construct recommended by IANA/IAGG consensus. However, it is worthwhile to note that both the clinical diagnosis of dementia and the identification of non-neurodegenerative cognitive impairment require a comprehensive neuropsychological battery which is hard to apply in busy daily clinical practice. Fourth, only one kind of frailty measurements was used in this study, so further research on the comparison between FI model and Fried model needs to be conducted to confirm with our findings. Additionally, biomedical variables were not included in this study. Last, in spite of the fact that CGA is most evidence-based for detection and severity grade of frailty, it is bounded by the resource-intensive and time-consuming process, thus further simple and more efficient instruments are expected to be developed for daily clinical work (45).

In conclusion, while preliminary, this work contributes to expanding the knowledge that CF may be a promising new concept for the assessment of vulnerability in patients with cognitive impairment, as well as identifying individuals at high risk for negative outcomes. Our study identified that depression and hearing impairment were independent associated factors of CF in elderly individuals with frailty in China, showing the possibility of controlling further cognitive deterioration in a population with PF. Our results shed new light on the identification and related factors for CF and suggest that many health deficits are associated with CF. Therefore, in order to narrow the gap between the hopefully promising concept and the limited evidence from current studies, especially in the situation that CF was still considered to be far away from clinical and research scenario (7), the reliability and predictive validity of the operational definition of CF should be clarified in future studies, as well as the underlying biological characteristics. Prospective studies will be needed to address the early intervention strategies to integrate physical and cognitive function.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the ethics committee of Xuanwu Hospital of Capital Medical University. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

PC and ZT contributed to the design of the work. LM drafted the manuscript and wrote it together with PC, ZT, and YZ. LZ and YL contributed to the analysis and interpretation of data. All the authors contributed to writing the paper and revising it critically and gave final approval of this version.

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SUPPLEMENTARY MATERIAL

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Characterisation of Physical Frailty and Associated Physical and Functional Impairments in Mild Cognitive Impairment

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Objective: To characterize the physical frailty phenotype and its associated physical and functional impairments in mild cognitive impairment (MCI).

Method: Participants with MCI (N = 119), normal low cognition (NLC, N = 138), and normal high cognition (NHC, N = 1,681) in the Singapore Longitudinal Ageing Studies (SLAS-2) were compared on the prevalence of physical frailty, low lean body mass, weakness, slow gait, exhaustion and low physical activity, and POMA balance and gait impairment and fall risk.

Results: There were significantly higher prevalence of frailty in MCI (18.5%), than in NLC (8.0%) and NHC (3.9%), and pre-frailty in MCI (54.6%), NLC (52.9%) than in NHC (48.0%). Age, sex, and ethnicity-adjusted OR (95% CI) of association with MCI (versus NHC) for frailty were 4.65 (2.40–9.04) and for pre-frailty, 1.67 (1.07–2.61). Similar significantly elevated prevalence and adjusted ORs of association with MCI were observed for frailty-associated physical and functional impairments. Further adjustment for education, marital status, living status, comorbidities, and GDS significantly reduced the OR estimates. However, the OR estimates remained elevated for frailty: 3.86 (1.83–8.17), low body mass: 1.70 (1.08–2.67), slow gait: 1.84 (1.17–2.89), impaired gait: 4.17 (1.98–8.81), and elevated fall risk 3.42 (1.22–9.53).

Conclusion: Two-thirds of MCI were physically frail or pre-frail, most uniquely due to low lean muscle mass, slow gait speed, or balance and gait impairment. The close associations of frailty and physical and functional impairment with MCI have important implications for improving diagnostic acuity of MCI and targetting interventions among cognitively frail individuals to prevent dementia and disability.

Keywords: mild cognitive impairment, frailty, physical function, gait, strength

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INTRODUCTION

Late life cognitive impairment and physical impairment are principal causes of disability, falls, hospitalisation, institutionalisation, and death among the elderly. In elderly persons, chronic disability rather than multi-morbidity is the strongest negative prognostic factor for functionality and survival (1), and in the oldest old, known predictors such as smoking and obesity lose their importance,

whereas high disability level, poor physical, and cognitive performance, predict mortality (2). Based on accumulating evidence, it is increasingly appreciated that cognitive and physical impairment in late life are inter-related through shared pathophysiological mechanisms and could probably be manifestations of a single complex phenotype (3).

Mild cognitive impairment (MCI) and the physical frailty phenotype are early cognitive and physical syndromes preceding the development of dementia and disability among older people. MCI is a transitional state of cognition between normal ageing and dementia that may progress to dementia, remain stable, or reverse to normal cognition over a defined period of time. MCI is defined by subjective or objective evidence of cognitive decline greater than expected for the individual's age and education level but that does not interfere notably with activities of daily life (4). Studies show that older individuals with MCI compared to their counterparts without cognitive impairment performed more poorly not just on tests of neurocognitive performance tasks, but also on tests of complex motor and psychomotor domains tasks (5–7), and exhibited greater gait impairment especially on tests that include motor-cognitive dual tasks (8–12). These motor functional deficiencies in MCI are also present in physical frailty, a syndrome that may also reverse to the robust state or progress to functional disability (13). The physical phenotype of frailty is represented by low levels of lean body mass, muscle strength, gait performance, physical activity (PA), and energy.

Studies suggest that gait and other physical manifestations of the frailty syndrome are associated with cognitive decline and dementia. For example, the presence of weight loss or being underweight is well known to precede the onset of Alzheimer's disease (14), lower grip strength, and extremity motor performance were associated with cognitive decline and decreased risk of MCI, and MCI conversion to AD (7, 15), frailty was associated with incident AD and cognitive decline (14, 15), and low levels of PA was associated with cognitive decline (16).

Some authors have argued that motor functional changes should be considered clinical features of MCI, and complex psychomotor tests such as gait speed may be as useful as cognitive tests in the identification of MCI particularly among elderly patients with less education (17). Converging lines of research and consensus also advocate defining MCI more precisely in terms of cognitive-physical constructs of "cognitive frailty" (the simultaneous presence of both physical frailty and MCI) (18), or the analogous motoric cognitive risk (MCR) syndrome (presence of cognitive complaints and slow gait) (19). Few studies have described the prevalence of frailty and its physical and functional impairments in MCI. The associations of specific physical and functional impairments of frailty with MCI are also unclear.

In this population-based study of community dwelling, older persons in the second Singapore Longitudinal Ageing Study (SLAS-2), we compared the prevalence of the physical frailty syndrome, low lean muscle mass, low muscle strength, slow gait speed, exhaustion, low PA, impaired balance, impaired gait, and elevated fall risk between individuals with MCI and non-MCI individuals with normal (high and low) cognitive functioning. We also examined the effects of psycho-social and health-related factors on these associations. We hypothesise that the prevalence of the physical frailty syndrome and its physical and functional impairments are higher in MCI compared to their cognitively normal counterparts, and this association is independent of psycho-social and health-related factors.

MATERIALS AND METHODS

Participants

This study was conducted as part of the Singapore Longitudinal Ageing Studies (SLAS), an ongoing prospective cohort observational study of community-dwelling older adults, aged 55 and above. A first wave (SLAS-1) cohort was recruited between 2003 and 2004 from the South-East region of Singapore. A second wave (SLAS-2) cohort was recruited between 2009 and 2011 in the South West and South-Central regions of Singapore. Participants were identified by door-to-door census, which had demographic characteristics similar to the rest of the population. Residents who were severely physically or mentally ill and incapacitated to give informed consent or participate were excluded. The study was approved by the National University of Singapore Institutional Review Board, and all participants signed written informed consent. Detailed descriptions of the methodology in the SLAS cohorts have been previously described (20).

In this study, we used baseline data from the participants of SLAS-2. A total of 3,270 older adults were enrolled at baseline with an estimated response rate of 78%. Trained research nurses and psychologists conducted questionnaire interviews, testing, and assessment to collect an extensive range of sociodemographic and health-related data. These included questionnaire and physical testing of frailty status, and multi-phasic cognitive screening, assessment and diagnosis of neurocognitive disorders. The participants included 2,844 Chinese, 259 Malay, 148 Indian, and 15 other ethnicities. After excluding participants who did not participate in neurocognitive tests, and those with dementia, there were 2,052 participants who were identified as MCI or normal cognition. Among them, 114 did not have complete frailty data. The final study sample thus comprised 1,938 subjects for analysis.

Identification of MCI and Normal Cognition

The participants' cognitive status was determined using a two-stage screening and diagnostic assessment process. In the first stage, global cognitive assessments were performed using the MMSE (21), and the Montreal Cognitive Assessment (MoCA) (22), which has been previously validated for use in the multi-ethnic population of Singapore in English, Malay, and Chinese languages (23, 24). Participants who were screened positive by scoring 26 or below on either the MMSE or MoCA underwent the Clinical Dementia Rating (CDR) assessment conducted by trained research nurses, and a comprehensive battery of neurocognitive testing conducted by psychology-trained research assistants, prior to consensus diagnosis of MCI (and dementia) or normal cognition by a panel of geriatricians and psychiatrists, who reviewed all relevant interview, testing, and assessment data.

The neurocognitive assessment included tests of memory [Rey Auditory Verbal Learning Test (25) and Story Memory (26)]; attention [longest span of the digit span subtest, forwards and backwards, from WAIS-III (27)]; visuospatial ability [Brief Visuospatial Memory Test-Revised (28) and Clock Reading Test (29)]; language [Boston Naming Test (30)]; executive functioning [Colour Trails Test 1 and 2 (31)]; and the Block Design subtest from the WAIS-III (27).

At a screening interview, a total of 1,681 participants who scored 27 and above on the MMSE and MOCA were denoted as normal (high) cognition (NHC) (32). There were a total of 138 participants who were screened positive on the MMSE or MOCA but were not assessed ($N = 60$) or provided incomplete or unreliable responses ($N = 23$) on the neurocognitive testing or the CDR, or did not meet the criteria for diagnosis of MCI or dementia ($N = 55$). These participants who were not successfully adjudicated as cases of MCI (or dementia) were assigned the status of normal low cognition (NLC). In 119 participants, MCI was defined according to criteria recommended by the MCI Working Group of the European Consortium on Alzheimer's disease (33):

1. Personal or informant report of cognitive decline relative to previous abilities during the past year.
2. Objective deficit in one or more cognitive domains; defined as a score that was 1.5 SD below age and education adjusted norms (34).
3. CDR of 0.5 or Sum of Boxes score less than 3 (35).
4. Functional independence on basic activities of daily living (Barthel Index).
5. No dementia.

Frailty and Physical Function Measures

Physical frailty was assessed by scores (1 = present, 0 = absent) for five components (shrinking, weakness, slowness, exhaustion, and low PA) proposed by Fried et al. (36) and used in the Cardiovascular Health Study (CHS), with the following operational modifications:

(i) Shrinking was defined by unintentional weight loss of 4 kg or more in the past 6 months, or a body mass index of less than 18.5 kg/m^2, or calf circumference of 31 cm or less.
(ii) Weakness was assessed using knee extension strength measured using dominant knee extension, using the average value from three trials in kilograms, standardised on gender and BMI strata.
(iii) Slowness was assessed by the 6-m fast gait speed test using the average of two measurements, and the lowest quintile values stratified for gender and height to classify participants as slow, based on data in a previous large population-based study (17).
(iv) Exhaustion was measured as a combined score of three questions from the SF-12 quality of life scale, "Did you have lots of energy?" "Did you feel tired?" (reverse-scored) and, "Did you feel worn out?" (reverse-scored) (37). A score of <10 was used to denote exhaustion.
(v) Low PA was determined by the total amount of time spent on performing moderate and vigorous activities per week based on questions in the LASA PA questionnaire (38) that fell below the gender-specific lowest quintile determined in the forerunner SLAS-1 study.

As per the CHS criteria, participants were categorised by their total scores as robust (score = 0), pre-frail (score = 1–2), and frail (score = 3–5).

Falls risk was assessed using the Tinetti performance-oriented mobility assessment (POMA) (39). Balance was assessed using standard scoring criteria (0, 1, or 2) to grade sitting balance, standing balance immediately after arising, turning around, and other manoeuvres (total score 0–16). Gait performance (gait initiation, step length and height, symmetry, continuity, path deviation, trunk sway, and walking stance) by having the subject stand with examiner, walks down hallway or across the room, first at "usual" pace, then back at "rapid, but safe" pace (using usual walking aids), total score (0–12). Falls risk was assessed by total balance and gait scores of <19 = high fall risk, 19–24 = medium fall risk, and 25–28 = low fall risk.

Covariates measured included (i) sociodemographic data including age, gender, and education, living status (live alone), (ii) medical comorbidity (determined from self-reports of a known diagnosis and/or treatment of 14 specific conditions (hypertension, diabetes, high cholesterol, stroke, heart attack, atrial fibrillation, heart failure, cataracts, kidney failure, asthma, chronic obstructive pulmonary disease, arthritis, hip fracture), and/or other chronic conditions in the past year, and the total number of medical illnesses), (iii) lifestyle including current smoking and daily alcohol drinking, (iv) depressive symptoms [assessed by the Geriatric Depression Scale (GDS) (40)], (v) disability status assessed by dependency on basic activity of daily living (BADL) (41) and instrumental activities of daily living (42).

Statistical Analyses

The prevalence of frailty and pre-frailty, low lean body mass, weakness, slow gait, exhaustion, low PA, impaired balance, impaired gait, and elevated fall risk were compared between MCI, NLC, and NHC using chi-squared tests of significance, and odds ratio and 95% confidence intervals (95% CI) of association estimated from logistic regression, adjusted for age, sex, and ethnicity. Further adjustment for education, marital status, living status, comorbidities, GDS, and IADL ability were performed to assess the effects of common psycho-social and health-related factors in mediating these associations.

RESULTS

The study participants comprised 119 (6.3%) MCI, 138 (7.2%) NLC (MMSE and MOCA scores <27), and 1,681 (85.5%) NHC (MMSE and MOCA scores ≥27) (**Table 1**). Among MCI participants, 18.5% were frail, compared to 8.0% among NLC and 3.9% among NHC. The prevalence of pre-frailty was similarly higher in MCI (54.6%) and in NLC (52.9%) than in NHC (48.0%) (**Table 2**). Age, sex, and ethnicity-adjusted OR (95% CI) of association with MCI (versus NHC) for frailty was 4.65 (2.40–9.04) and for pre-frailty was 1.67 (1.07–2.61). In addition, significantly

TABLE 1 | Demographic and personal characteristics among mild cognitive impairment (MCI), normal high cognition (NHC), normal low cognition (NLC) groups.

Variables (*N* = 1,938)	NHC[a]		NLC[b]		MCI		*P*-value*
Sample *N*		1,681		138		119	
Age; 55–64	38.8	(653)	23.2	(32)	31.9	(38)	<0.001
65–74	53.4	(897)	55.8	(77)	46.2	(55)	
≥75	7.8	(131)	21.0	(29)	21.9	(26)	
Male gender	37.8	(636)	33.3	(46)	36.1	(43)	0.55
Chinese ethnicity	91.1	(1,530)	90.6	(125)	80.7	(96)	0.001
Single, divorced, widow	27.4	(460)	57.2	(59)	49.6	(60)	<0.001
Education: none	8.1	(136)	38.4	(53)	43.7	(52)	<0.001
Primary	41.4	(694)	44.9	(62)	44.5	(53)	
Living status: alone	13.7	(229)	27.5	(38)	19.7	(23)	<0.001
Alcohol: yes	3.4	(57)	2.9	(4)	2.5	(3)	0.85
Smoking: non smoker	80.9	(1,360)	71.7	(99)	75.6	(90)	0.07
Ex-smoker	10.4	(175)	16.7	(23)	14.3	(17)	
Current smoker	8.7	(146)	11.6	(16)	10.1	(12)	
APOE-e4 allele	17.5	(264)	24.8	(29)	15.0	(18)	
MMSE	28.97	±1.14	25.85	±2.98	24.59	±3.50	<0.001
MoCA	27.7	±1.26	21.37	±3.74	19.57	±4.64	<0.001
GDS	0.51	±1.04	1.20	±2.15	1.10	±1.89	<0.001
Noof comorbidities	2.16	±1.41	2.61	±1.47	3.1	±1.71	<0.001
IADL disability	5.9	(98)	11.0	(15)	25.2	(30)	<0.001

[a]*NHC have MMSE and MOCA scores ≥27.*

[b]*NLC have MMSE and/or MOCA <27, but have no MCI diagnosis.*

Figures are % (N) and mean ± SD.

P-values of significance are derived from Chi square test for categorical variables and ANOVA for continuous variables.

higher prevalence of low lean body mass, weakness, slow gait, exhaustion, low PA, impaired balance, impaired gait, and elevated falls risk were observed in the MCI group than in the NLC and NHC groups (**Table 2**). The age, sex, and ethnicity-adjusted ORs of association with MCI ranged between 1.71 and 6.99 for these factors (**Table 3**).

To determine the effects of psycho-social and health-related factors influencing the observed association, further adjustment for education, marital status, living status, comorbidities, GDS, and IADL ability were performed and found to significantly reduce the OR of association (**Table 3**). However, the OR (95% CI) of association with MCI (versus NHC) remained significantly elevated for frailty: 3.86 (1.83–8.17); low body mass: 1.70 (1.08–2.67); slow gait: 1.84 (1.17–2.89); impaired gait: 4.17 (1.98–8.81); and elevated falls risk: 3.42 (1.22–9.53).

DISCUSSION

This study supports the strong and intimate relationship between cognitive and physical impairment, which are present in both MCI and physical frailty. The relationship may be explained by common underlying pathophysiological factors, which include pathways involved in the development of cardiovascular and cerebrovascular diseases, insulin-mediated metabolic disturbances, protein-calorie undernutrition, sex steroids, growth hormones, vitamin D, chronic inflammation, and oxidative stress (3).

In this study, almost two-thirds of community dwelling older adults with MCI manifested the physical syndrome of frailty or pre-frailty, including low lean muscle mass, low muscle strength,

TABLE 2 | Physical frailty characteristics among mild cognitive impairment (MCI), normal high cognition (NHC), normal low cognition (NLC) groups.

Variables (*N* = 1,938)	NHC		NLC		MCI		*P**
Sample *N*		1,681		138		119	
Frailty status (global)							
Robust	48.1	(809)	39.1	(54)	26.9	(32)	<0.001
Pre-frail	48.0	(807)	52.9	(73)	54.6	(65)	
Frail	3.9	(65)	8.0	(11)	18.5	(22)	
Frailty status (domains)							
Shrinking	18.5	(310)	28.3	(39)	33.6	(40)	<0.001
Slowness	15.0	(252)	21.7	(30)	37.8	(45)	<0.001
Weakness	11.3	(190)	16.7	(23)	24.4	(29)	<0.001
Exhaustion	14.3	(241)	12.3	(17)	23.5	(28)	0.017
Low physical activity (PA)	13.1	(220)	16.7	(23)	23.5	(28)	0.004
Impaired balance (POMA ≤14)	2.9	(48)	6.5	(9)	10.4	(12)	<0.001
Impaired gait (POMA ≤10)	2.3	(38)	6.5	(9)	14.3	(17)	<0.001
Medium-high fall risk (POMA ≤24)	1.1	(19)	3.6	(5)	8.7	(10)	<0.001
Physical function measures							
Frailty scores	0.74	±0.86	0.98	±0.99	1.43	±1.19	<0.001
Calf circumference	34.41	±3.72	33.67	±4.03	34.02	±5.83	0.07
BMI, kg/m^2	59.89	±10.81	57.16	±10.47	59.45	±12.44	0.018
Gait speed, s	4.66	±1.49	5.25	±1.81	6.14	±2.77	<0.001
Knee extension, kg	16.40	±6.22	14.14	±6.23	12.93	±4.51	<0.001
Energy score	12.06	±2.19	11.94	±2.10	11.54	±2.34	0.041
PA level	11.53	±1.91	10.97	±1.48	10.85	±1.41	<0.001
POMA Balance score	15.86	±0.61	15.77	±0.19	15.68	±0.86	0.004
POMA Gait score	11.87	±0.74	11.70	±0.98	11.41	±1.42	<0.001
POMA total score	27.73	±1.13	27.47	±1.50	27.10	±1.88	<0.001

Figures are % (N) and mean ± SD.

P-values of significance are derived from Chi square test for categorical variables and ANOVA for continuous variables.

TABLE 3 | Odds ratio of association of physical frailty status and components with cognitive status [mild cognitive impairment (MCI), normal low cognition (NLC), normal high cognition (NHC)].

		Unadjusted			Adjusted: age, sex, ethnicities			Adjusted: age, gender, ethnicity, education, APOE-e4, marital status, living status, comorbidities, GDS, IADL		
		OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Frailty versus robust	NHC	1			1			1		
	NLC	2.54	1.26–5.08	0.009	1.47	0.70–3.08	0.31	1.28	0.50–3.26	0.602
	MCI	8.56	4.70–15.57	<0.001	4.65	2.40–9.04	<0.001	3.49	1.47–8.31	0.005
Pre-frail versus robust	NHC	1			1			1		
	NLC	1.36	0.94–1.95	0.103	1.67	0.80–1.70	0.42	1.02	0.67–1.56	0.929
	MCI	2.04	1.32–3.14	0.001	1.67	1.07–2.61	0.02	1.37	0.85–2.23	0.197
Low body mass	NHC	1			1			1		
(Calf circumference ≤31)	NLC	1.74	1.18–2.57	0.005	1.37	0.91–2.06	0.13	1.28	0.81–2.04	0.294
	MCI	2.24	1.50–3.34	<0.001	1.74	1.14–2.64	0.01	1.58	0.96–2.59	0.071
Low muscle strength	NHC	1			1			1		
	NLC	1.57	1.0–2.52	0.06	1.21	0.74–1.96	0.45	1.10	0.63–1.92	0.747
	MCI	2.53	1.62–3.95	<0.001	1.79	1.12–2.86	0.02	1.65	0.95–2.87	0.075
Slow gait speed	NHC	1			1			1		
	NLC	1.58	1.03–2.41	0.04	1.19	0.76–1.85	0.45	0.89	0.53–1.49	0.667
	MCI	3.45	2.33–5.11	<0.001	2.36	1.56–3.58	<0.001	1.68	1.02–2.79	0.042
Impaired gait (POMA) (POMA ≤10)	NHC	1			1			1		
	NLC	2.35	1.13–4.90	0.02	2.78	1.28–6.02	0.01	1.97	0.78–4.95	0.148
	MCI	3.93	2.03–7.63	<0.001	5.53	2.87–10.65	<0.001	3.71	1.62–8.46	0.002
Impaired balance POMA (POA ≤16)	NHC	1			1			1		
	NLC	3.00	1.42–6.34	0.004	1.84	0.86–3.96	0.12	1.36	0.55–3.35	0.507
	MCI	7.17	3.91–13.14	<0.001	2.75	1.35–5.59	0.01	1.90	0.79–4.53	0.149
Medium-high fall risk (POMA ≤ 24)	NHC	1			1			1		
	NLC	3.25	1.20–8.84	0.02	3.17	1.13–8.91	0.03	1.55	0.40–6.03	0.528
	MCI	8.24	3.74–18.16	<0.001	6.99	2.96–16.51	<0.001	3.02	0.95–9.53	0.060
Exhaustion	NHC	1			1			1		
	NLC	0.84	0.50–1.42	0.52	0.81	0.47–1.38	0.43	0.51	0.26–0.98	0.042
	MCI	1.84	1.18–2.87	0.007	1.73	1.09–2.75	0.02	1.21	0.69–2.12	0.499
Low PA	NHC	1			1			1		
	NLC	1.33	0.83–2.12	0.24	1.14	0.70–1.84	0.60	1.03	0.60–1.77	0.921
	MCI	2.04	1.31–3.19	0.002	1.71	1.07–2.73	0.02	1.29	0.74–2.23	0.371

Adjusted for age, sex, ethnicity, education, APOE-e4, marital status, living status, comorbidities, GDS, and IADL ability.

slow gait speed, exhaustion and low PA, as well as balance and gait impairment, which pose elevated risk of falls, in greater proportions compared to their cognitively normal counterparts. Psycho-social and health-related factors did not wholly account for the association, such that frailty, low lean body mass, slow gait speed, gait impairment, and impaired gait and balance measure of elevated falls risk remained independently associated with MCI. The OR estimates suggest a very strong association and appears to be specific for phenotypic measures of low lean body mass, slow gait speed, and gait and balance impairment, but not exhaustion or low PA.

Prior studies have shown that older persons with MCI exhibited greater gait variability especially during dual-tasking walking than cognitively normal controls (8, 9). Walking is a complex activity that involves executive functioning, spatial orientation, navigation, and memory, among other cognitive functions (43). The use of simple measures of gait speed or POMA balance and gait scores may thus complement cognitive tests in the identification of MCI among elderly patients especially those with less education (44). At least one other study have shown that the combination of cognitive complaints and slow gait (MCR syndrome) successfully predict increased risk of cognitive decline and dementia (19). However, it remains unclear which components or combinations of physical frailty and cognitive impairment are most optimal in identifying cognitively frail older persons.

In the years, since the conceptual definition of MCI was first proposed, numerous studies have shown that non-cognitive manifestations such as depressive and neuropsychiatric symptoms (45–47), sensory impairment such as in hearing (48), or smell (49), and subtle IADL impairments involving complex functions (50, 51) are over-represented in MCI significantly more than non-MCI controls, and were able to enhance the ability of MCI to predict future risks of dementia. This is also true of physical functional impairment that co-occurs in MCI. Cases

of MCI with concomitant physical frailty may be considered to fulfil the criteria for cognitive frailty (18). Taken together, these findings suggest that the understanding of MCI beyond the conceptual confines of cognitive impairment may help to improve diagnostic acuity and present meaningful targets for interventions among cognitively frail individuals to prevent dementia and disability.

In this regard, the cognitive frailty concept has potential clinical and research advantages in better stratifying the risk profiles of older people for developing dementia and functional disability. Recent studies have shown that the cognitive frailty construct more accurately predict greater risks of cognitive decline and dementia than MCI alone (15, 44, 52, 53). However, it has not been determined whether it is also in fact a more stable construct than MCI, in being less liable to revert to cognitive normal. Another point to note is the prevalence of the cognitive frailty construct. In this study, the prevalence is very low (1.1%) if cases were defined by 22 frail MCI subjects (out of 1,938 participants), but is higher (4.5%) if cases were defined by 65 pre-frail plus 22 frail MCI subjects. It is possible that in this study, the overly restrictive criteria used to define both the cognitive and physical components of this construct may contribute to under-estimating its prevalence, as further discussed below.

The diagnosis of MCI in this study was based on clinical panel consensus review of relevant data according to internationally recommended criteria and is a strength of this study. However, the restrictive criteria for diagnosis of MCI may exclude subjects akin to cases labelled in some studies as "cognitive impairment-no dementia" (CIND). Doubtful cases of MCI were consigned into the category of NLC, a heterogeneous group of subjects, which also included those with below normal global performance on the MMSE or MOCA but who failed to provide supportive cognitive domain or CDR data to merit a MCI diagnosis or otherwise. On close scrutiny, this NLC group appeared to include significantly more participants who were living alone and with higher GDS depression scores, a possible explanation for their failed clinical assessment. The results for NLC showed a pattern of relationship with frailty and its associated physical and functional impairments that was intermediate between cognitive (high) normal and MCI, but with no significantly strong associations with physical functional impairments.

The results for frailty components of exhaustion (fatigue) and low PA were negative. However, this may reflect the limitations of our operationalised measurement of these phenotypic features, and further studies using more sensitive and discriminating instruments are required to ascertain the replicability of these findings. Because of the small numbers, we did not further distinguish MCI participants into amnestic or non-amnestic subtypes. Further studies should investigate the ability of combined cognitive, physical, and functional markers of MCI in predicting future risks of developing dementia.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Human Biomedical Research Act, Singapore Ministry of Health; with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the National University of Singapore IRB.

ROLE OF THE SPONSORS

The sponsors had no role in the conduct of the study or preparation of this manuscript.

AUTHOR CONTRIBUTIONS

TN formulated the hypothesis, designed the study, reviewed the data, and revised the manuscript. WL, TL, PY, and KY reviewed clinical data and adjudicated on MCI diagnosis. GQ performed the data preparation. MN analysed the data. CYS reviewed the literature, drafted and revised the manuscript; all authors participated in the study design and data collection, reviewed the results and manuscript, and approved the manuscript submission.

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The Impact of Frailty on the Risk of Conversion from Mild Cognitive Impairment to Alzheimer's Disease: Evidences from a 5-Year Observational Study

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The frailty construct has increasingly been adopted in the field of cognitive disorders. The aim of the present study was to measure frailty in a cohort of individuals with mild cognitive impairment (MCI) and to explore whether frailty measures may consent to predict the risk of conversion to dementia. We retrospectively reviewed the clinical charts of outpatients with amnesic MCI (aMCI) consecutively recruited at our Department, and followed-up for 5 years. Individual frailty status was measured by means of a frailty index (FI) consisting of 39 deficits (including signs, symptoms, diagnoses, and disabilities). Univariate analyses were used to compare the socio-demographic and clinical characteristics between subjects converting or not converting to probable Alzheimer's disease (AD) dementia over the follow-up. Risk for conversion to AD dementia was assessed using Cox regression models. Ninety-one subjects with aMCI (mean age 72.7, SD 7.1 years; women 49.5%) were consecutively recruited over a period of 12 months. Low levels of frailty were documented in the sample (mean FI score 10.0, SD 5.3). A statistically significant correlation between age and FI was observed. Overall, 58 participants converted to AD dementia over time. The Cox regression analysis showed that age (HR: 1.04, 95% CI: 1.00–1.08), male sex (HR: 0.52, 95% CI: 0.30–0.91), Mini–Mental State Examination score (HR: 0.85, 95% CI: 0.77–0.94), and FI (HR: 1.11, 95% CI: 1.05–1.18) were all significantly associated with the probability of MCI conversion. Individual's frailty status may increase the risk of conversion from a condition of MCI to overt AD dementia. The adoption of constructs comprehensively reflecting the biological decline of the aging subject may add useful estimates and information in the clinical approach to cognitive disorders.

Keywords: mild cognitive impairment, Alzheimer's disease, dementia, frailty, aging

INTRODUCTION

Frailty has been conceptualized as "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death" (1). This construct has increasingly been adopted in order to capture the biological decline of the aging individual

and his/her risk profile for negative health-related outcomes (2). Moreover, it is growingly acquiring public health relevance as it may support the realignment of models of care to the changing needs of our aging populations (3).

In these last years, the relationship between frailty and cognition has triggered special interest. The contribution of cognitive skills and capacities to the individual's vulnerability and resiliency has more consistently been considered and recognized (4). Cross-sectional analyses have repeatedly shown that frail individuals have lower cognitive performance compared with non-frail persons (5, 6). Accordingly, several longitudinal studies have documented a higher risk of incident cognitive impairment and dementia among frail subjects (5). More recently, frailty indexes (FIs) have been found to predict poorer outcomes (i.e., mortality, institutionalization, faster cognitive worsening) in populations of patients already exhibiting overt dementing conditions (7, 8). However, to our knowledge, no study has yet explored the impact of the individual frailty status on the clinical trajectories over time of subjects with milder cognitive deficits.

The aim of the present study was to measure frailty in a cohort of individuals with mild cognitive impairment (MCI) and to explore whether frailty measures may consent to predict the risk of conversion to dementia.

MATERIALS AND METHODS

Setting and Participants

The present study was conducted at the Department of Neurology and Psychiatry of the "Sapienza" University of Rome (Italy). We retrospectively reviewed the clinical charts of outpatients with amnesic MCI (aMCI) consecutively recruited at our Department between April 2011 and April 2012 and followed up with clinical and neuropsychological evaluations (at least twice a year) for 5 years.

Amnesic MCI was defined according to the International Working Group criteria (9). To be included, subjects should have: (1) a self-reported cognitive concern confirmed by the caregiver; (2) the evidence of a lower performance in the memory domain or in the memory and other cognitive domains; (3) the complete preservation of independence in functional abilities; and (4) at least two clinical and neuropsychological assessments per year over an observation period of 5 years. Probable Alzheimer's disease (AD) dementia was diagnosed according to the National Institute on Aging-Alzheimer's Association criteria (10). A comprehensive neuropsychological assessment was performed in order to define aMCI and dementia and to evaluate cognitive changes over time. The test battery included the following standardized tests: Rey Auditory Verbal Learning Test (11, 12), Babcock Story Recall Test (13), Corsi Block-Tapping Test (13, 14), Digit Span Test (14), Visual Search Matrix Test (13), Boston Naming Test (11, 15), Verbal Semantic Fluency Test (11, 13), Verbal Phonemic Fluency Tests (11), Clock Drawing Test (16), Frontal Assessment Battery (17), Mini–Mental State Examination (MMSE) (18), and Clinical Dementia Rating Scale (19).

The cohort was divided in two groups of subjects based on the outcome of cognitive disturbances at the end of the observation period: (1) "MCI converters": exhibiting a clinical progression toward a probable AD dementia and (2) "MCI non-converters": whose cognitive and functional abilities either remained stable or improved during the follow-up.

Patients and caregivers (or legal guardians when necessary) provided written informed consent for allowing the utilization of the collected data for research purposes (as required by the local Ethics Committee). Data used in the present analyses were retrieved from medical charts where information was recorded as part of the standard clinical routine. In particular, comorbidities were defined on the basis of: (a) self-reports concerning previous diagnoses and/or laboratory findings and/or (b) available medical documents and/or (c) available medical prescriptions.

Socio-Demographic and Clinical Variables

Socio-demographic (i.e., age, sex, and education) and clinical (i.e., comorbidities, physical and neurological examination, concomitant therapies, duration of cognitive symptoms) data were abstracted by the clinical charts of participants. Measures of global cognitive performance, assessed through the MMSE were also collected.

Frailty Assessment

Frailty was measured by means of a FI, generated following a standard procedure (20) by computing 39 age-related, multidimensional deficits (including signs, symptoms, diagnoses, and disabilities) retrospectively resumed by the clinical charts (**Table 1**). Each item included in the FI was coded so that a value of 0 indicated the absence of the deficit and a value of 1 its presence. The FI was calculated as the ratio between the number of deficits presented by the individual and the number of considered deficits (i.e., 39) multiplied per 100 (in order to better show its statistical properties). Thus, the FI potentially ranged between 0 (no deficit) and 100 (all deficits).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Science for Mac (version 21, IBM Corporation, New York, NY, USA). Univariate analyses were conducted to compare the baseline data between "MCI converters" and "MCI non-converters." Cox regression models were performed to measure the associations between the variables identified as significant or at borderline level of statistic significance in the univariate analyses and time to develop AD dementia, controlling for sex and age of participants. Hazard ratios with relative 95% confidence intervals were estimated. Sensitivity analyses stratified for MMSE scores were also conducted. Spearman's correlations were used to assess the strength and direction of the relationship between age and FI. Statistic level of significance was set at $p < 0.05$.

RESULTS

One hundred thirty-two subjects were consecutively diagnosed with aMCI between April 2011 and April 2012 at our Department. The retrospective analysis showed that 109 of them were followed-up for the next 5 years. Nevertheless, only 91 subjects (women 49.5%) received two or more clinical and neuropsychological evaluations per year and were, thus, finally considered for the

TABLE 1 | Items included in the computation of the 39-item frailty index.

1.	Hypertension
2.	Dyslipidemia
3.	Diabetes
4.	History of TIA
5.	History of stroke
6.	Ischemic heart disease
7.	Arrhythmia
8.	Chronic heart failure
9.	Gastric disorder
10.	Intestinal disorder
11.	Thyroid disease
12.	Cancer
13.	Arthritis
14.	Osteoporosis
15.	COPD
16.	Renal failure
17.	Cirrhosis
18.	Hematologic disease
19.	Peripheral artery disease
20.	Hearing impairment
21.	Vision impairment
22.	Parkinsonism
23.	Focal neurological signs
24.	Peripheral neuropathy
25.	Vascular encephalopathy (neuroimaging)
26.	Obesity (BMI ≥ 30)
27.	Underweight (BMI < 18.5)
28.	Depression
29.	Anxiety
30.	Sleep disorders
31.	Irritability
32.	Language disturbances
33.	Spatiotemporal disorientation
34.	Dizziness
35.	Falls
36.	Balance disorder
37.	Involuntary weight loss (≥4.5 kg in the last 6 months)
38.	Urinary incontinence
39.	Mobility disability (inability to walk 400 m)

BMI, body max index; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack.

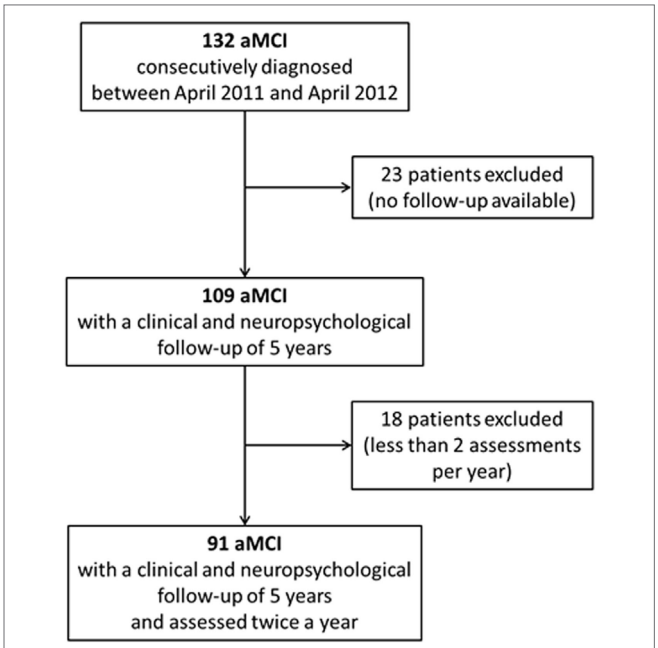

FIGURE 1 | Flow chart of the study. One hundred thirty-two amnesic MCI (aMCI) patients were initially enrolled. Forty-one participants were retrospectively excluded (23 resulted were lost to follow-up; 18 did not undergo two or more clinical and neuropsychological assessments per year). Data from 91 aMCI subjects were finally considered for the present analyses.

TABLE 2 | Baseline sociodemographic and clinical characteristics of the sample according to MCI outcomes.

	Mild cognitive impairment (MCI) converters (n = 58)	MCI non-converters (n = 33)	p-Value
Age (years)	74.4 ± 4.9	69.7 ± 9.2	<0.01
Sex (women)	56.9	36.4	0.08
Education time (years)	7.3 ± 3.6	8.5 ± 3.4	0.13
MCI subtype			0.71
Single-domain aMCI	41.4	45.5	
Multiple-domain aMCI	58.6	54.5	
Hypertension	50.0	39.4	0.33
Dyslipidemia	34.5	33.3	0.91
Diabetes	12.1	0.0	0.04
Ischemic heart disease	13.8	9.1	0.51
Stroke	0.0	3.0	0.18
TIA	3.4	3.0	0.91
Chronic renal failure	0.0	3.0	0.18
COPD	0.0	3.0	0.18
Depression	41.4	42.4	0.92
Anxiety	24.1	18.2	0.51
Duration of cognitive disturbances (months)	25.8 ± 13.0	21.6 ± 11.6	0.12
MMSE	24.7 ± 3.0	26.7 ± 1.9	≤0.001
Frailty index	11.6 ± 5.3	7.3 ± 4.1	≤0.001

Data are expressed as % or mean ± SD.
aMCI, amnesic mild cognitive impairment; COPD, chronic obstructive pulmonary disease; MMSE, Mini–Mental State Examination; TIA, transient ischemic attack.

present analyses (**Figure 1**; **Table 2**). Participants had a mean age of 72.7 (SD 7.1) years and a mean educational level of 7.7 (SD 3.6) years. MMSE values at the baseline (mean 25.4, SD 2.8) indicated a globally preserved cognitive functioning. Low levels of frailty were documented in the sample (mean FI score 10.0, SD 5.3). Accordingly, none of the subjects resulted as frail [i.e., FI score ≥ 25.0 (8)]. A statistically significant correlation between age and FI was observed (Spearman's $r = 0.31$; $p < 0.01$) (**Figure 2A**).

Over a follow-up of 5 years, 58 subjects converted from MCI to probable AD dementia, whereas 33 did not exhibit a clinical worsening. At the basal evaluation, "MCI converters" were older, more severely cognitive impaired, and exhibited a higher prevalence of diabetes compared to "MCI non-converters" (**Table 2**). Moreover, subjects converting to dementia had significantly higher mean scores at the FI (11.6, SD 5.3 vs. 7.3, SD 4.1; $p < 0.001$), indicating greater levels of frailty (**Table 2** and **Figure 2B**).

The Cox regression model, adjusted for age and sex, showed that increasing age, male sex, lower MMSE scores, and higher FI scores were all significantly associated with an increased probability of MCI conversion (**Table 3**). The positive association between FI and the risk of conversion was also confirmed when restricting the analyses to only those subjects exhibiting normal MMSE scores

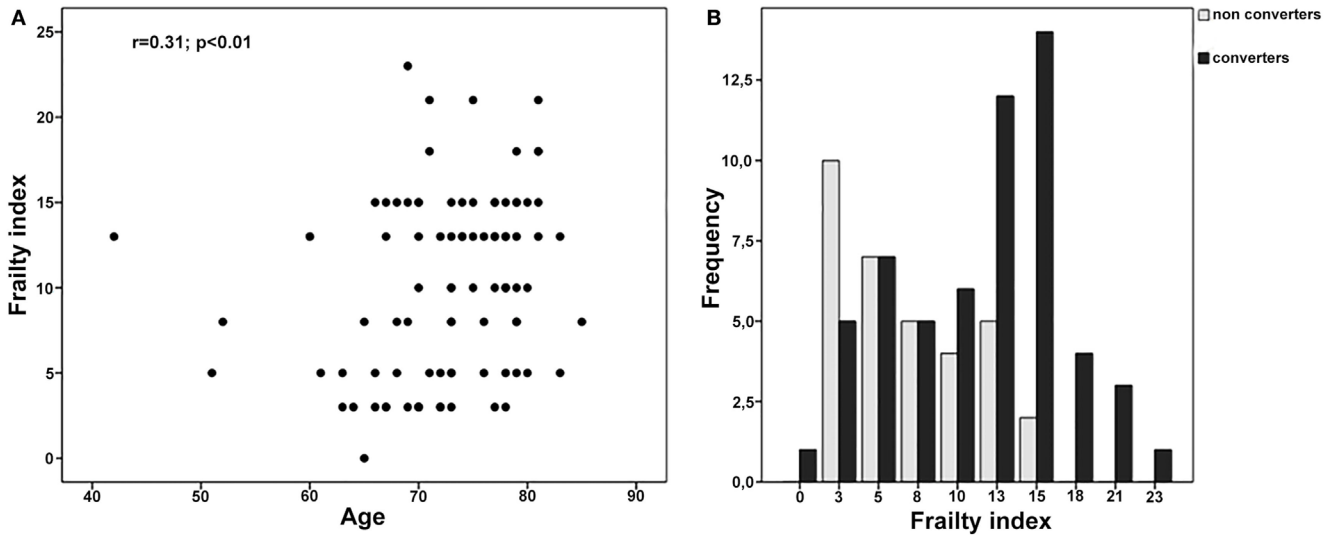

FIGURE 2 | **(A)** Correlation between age and frailty index (FI) in the overall sample. **(B)** FI values among MCI converters and MCI non-converters.

TABLE 3 | Cox regression analysis of factors predicting MCI conversion to AD dementia.

	HR	95% CI	*p*-Value
Sex (M)	0.52	0.30–0.91	0.02
Age	1.04	1.00–1.08	0.05
MMSE	0.85	0.77–0.94	<0.01
Frailty index	1.11	1.05–1.18	<0.001

p-Values were obtained from Wald χ^2 tests, degrees of freedom = 1.
CI, confidence interval; HR, hazard ratio; MMSE, Mini–Mental State Examination.

(i.e., ≥24) (HR: 1.20; 95% CI: 1.05–1.19; $p < 0.001$) or the highest level of cognitive performance (i.e., MMSE ≥ 27, upper quartile of the distribution) (HR: 1.20; 95% CI: 1.05–1.19; $p < 0.001$).

DISCUSSION

To our knowledge, this is the first study exploring the impact of the individual's frailty status and biological decline on the risk of conversion from MCI to dementia. Overall, frailty levels, measured through a FI, resulted to be strongly associated with the risk of cognitive and functional worsening. In fact, subjects with higher FI scores exhibited a significantly increased risk of developing future AD dementia.

Nowadays, special attention is being focused on the possibility of identifying the clinical factors and laboratory findings consenting to early/timely detect those subjects at increased risk of dementia. In this scenario, MCI has increasingly been considered as the optimal phase to explore the clinical and pathophysiological modifications anticipating the onset of overt dementing syndromes (21). To date, most of studies on the conversion of MCI have been concentrated on the contribution of crude socio-demographic (e.g., sex, age, and educational level) and clinical (e.g., comorbidities, neuropsychiatric symptoms) variables, mostly exploring the predictive value of findings and measures individually referring to a specific individual's health domain (e.g., neuropsychological functions, functional abilities, neuroimaging abnormalities, genetic traits) (22). Nevertheless, existing models of prediction of MCI progression have been shown to have several limitations, including poor discrimination and low positive predictive values (22). Accordingly, the adoption of novel approaches, more properly accounting for the clinical and biological heterogeneity of older people at risk for cognitive decline, has repeatedly been solicited (23).

In this context, the introduction of constructs more broadly reflecting the individual's frailty status and his/her biological aging may open promising scenarios in the field. This approach may facilitate to multidimensionally capture the pathophysiological complexity of cognitive disorders and neurodegenerative conditions. Moreover, it may consent to more holistically consider the overall health status of the aging individual experiencing the onset of cognitive disturbances, thus not neglecting the multiple and variegate aspects (from sleep disorders to depression, from nutritional deficiencies to polypharmacy) potentially contributing to their occurrence and influencing their phenotypic expression (24). As a proof, in our study, beside the well-established impact of age and baseline cognitive functioning (i.e., MMSE scores), the accumulation of clinical/biological deficits (captured by the FI) significantly influenced the risk of AD dementia. Specifically, FI scores influenced the overall risk of MCI conversion more than age, a well-established risk factor for cognitive decline and dementia. It is noteworthy that the discriminative capacity of the FI was observed despite the cohort being composed exclusively by robust subjects, and was confirmed also among those participants exhibiting the best levels of cognitive performance. These findings are in line with that obtained in cohorts of patients already exhibiting dementing conditions, with frailty measures predicting cognitive outcomes and trajectories (8).

More in particular, our results confirm that the FI may provide useful information when approaching individuals with cognitive

disturbances. This model is also easy-to-adopt, being potentially applicable (even retrospectively) from existing datasets and available clinical information. Its use will be even more simplified by the increasing use of electronic medical records (25). In parallel, it can be directly implemented in the clinical practice without requiring changes in the routine/standard approach, not requiring the adoption of specific tests, tools, and *ad hoc* questionnaires, potentially resulting in costly and time-consuming procedures (24).

The present study has some limitations worth to be mentioned. In particular, the small sample size does not consent to draw firm conclusions on the topic. The study population was composed by highly selected MCI subjects attending a university memory clinic, thus with potentially issues in terms of external validity. Moreover, we only focused on the conversion of aMCI to AD dementia, thus not considering the outcomes of different MCI subtypes and the progression toward different dementing conditions.

In conclusions, frailty may significantly increase the individual risk of conversion from a condition of MCI to overt AD dementia. The adoption of constructs comprehensively reflecting the biological decline of the aging subject may add useful estimates and information to those provided by monodimensional variables and traditional cognitive evaluations. In this context, models of frailty (such as the FI) may be easily and promisingly introduced in the neurological practice with the aim of improving both clinical and research standards.

ETHICS STATEMENT

All the data used in the analyses were exclusively retrieved from medical charts where information was recorded as part of the standard clinical routine. The patients and their caregivers (or legal guardians when necessary) provided written informed consent for allowing the utilization of the collected data for research purposes in accordance with the Declaration of Helsinki. The local Ethics Committee, "Comitato Etico Sapienza," approved the protocol.

AUTHOR CONTRIBUTIONS

AT and MC conceived and designed the work, performed the literature search, and wrote the manuscript. LI, LP, and LR collected the neuropsychological data. FD, AC, and VC collected the clinical data. GB and CL participated to the critical appraisal of the available evidence on the topic.

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Cross-sectional Associations of Fatigue with Cerebral β-Amyloid in Older Adults at Risk of Dementia

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Fatigue is a common symptom in the elderly and has also been associated with impaired cognition in older adults. Hence, we sought to explore the cross-sectional relationship between fatigue and cerebral β-amyloid (Aβ) in 269 elderly individuals reporting subjective memory complaints from the Multidomain Alzheimer Preventive Trial. Standard uptake value ratios (SUVRs) were generated by [^{18}F] florbetapir positron emission tomography (PET) using the cerebellum as a reference. Cortical-to-cerebellar SUVRs (cortical-SUVRs) were obtained using the mean signal from the frontal cortex, temporal cortex, parietal cortex, precuneus, anterior cingulate, and posterior cingulate. Other brain regions independently assessed were the anterior cingulate, anterior putamen, caudate, hippocampus, medial orbitofrontal cortex, occipital cortex, parietal cortex, pons, posterior cingulate, posterior putamen, precuneus, semioval center, and temporal cortex. Fatigue was defined according to two questions retrieved from the Center for Epidemiological Studies-Depression scale. Chronic fatigue was defined as meeting fatigue criteria at two consecutive clinical visits 6 months apart between study baseline and 1 year (visits were performed at baseline, 6 months and 1 year then annually). Cross-sectional associations between fatigue variables and cerebral Aβ were explored using fully adjusted multiple linear regression models. We found no statistically significant cross-sectional associations between fatigue assessed at the clinical visit closest to PET and Aβ in any brain region. Similarly, chronic fatigue was not significantly associated with Aβ load. Sensitivity analysis in subjects with a Clinical Dementia Rating of 0.5 showed that fatigue reported at the clinical visit closest to PET was, however, weakly associated with increased Aβ in the hippocampus (B-coefficient: 0.07, 95% CI: 0.01, 0.12, $p = 0.016$). These preliminary results suggest that fatigue might be associated with Aβ in brain regions associated with Alzheimer's disease in subjects in the early stages of disease.

Keywords: fatigue, β-amyloid, Alzheimer's disease, frailty, cognition

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INTRODUCTION

Fatigue is the sense of persistent general tiredness and exerts a significant negative impact on health status (1). It is a common symptom in older adults and has been suggested to serve as a clinically relevant biomarker for pathological aging (2). Fatigue is specifically associated with physical frailty (2, 3) and cognitive frailty, where physical frailty presents with cognitive impairments (4, 5).

Research into fatigue and Alzheimer's disease (AD), the most common form of dementia in the elderly (6), is limited. However, fatigue has been cross-sectionally associated with brain atrophy and compromised cognition in cognitively normal older adults (7) and longitudinally with increased risk of cognitive decline in older adults without dementia (8). Fatigue has also been more frequently reported in patients with dementia at 3-year follow-up (9) and fatigue is a symptom of depression, a condition that often co-presents with dementia (10, 11).

In accordance with the amyloid cascade hypothesis of AD, β-amyloid (Aβ) is thought to be the main driver of AD pathology culminating in neurofibrillary tangle formation, which in turn precipitates neuronal loss and cognitive impairments (12, 13). It has been suggested that fatigue might occur as a result of depleted physiological reserves (14), and fatigue has been associated with increased oxidative stress (15). Moreover, frailty is associated with pro-inflammatory changes (16–18), but due to the biological complexity of the frailty phenotype specific associations with its fatigue component are difficult to distinguish. It seems plausible, therefore, that fatigue might lead to alterations in homeostasis leading to secondary increases in Aβ deposition especially considering that oxidative stress and inflammation fuel amyloidogenesis (19, 20). Furthermore, polypharmacy and conditions prevalent in the elderly such as anemia and sleep apnea are associated with fatigue (21–25). Sleep apnea has been associated with increased cerebral Aβ (26) and iron deficiency leads to alterations in the expression of genes involved in amyloidogenesis (27). Moreover, polypharmacy is a risk factor for cognitive impairment (28), which potentially might manifest through Aβ-dependent mechanisms. Hence, in this study, we sought to explore the cross-sectional associations between fatigue and cerebral Aβ in older adults reporting subjective memory complaints. We hypothesized that fatigue would be associated with increased cerebral Aβ load.

MATERIALS AND METHODS

The Multidomain Alzheimer Preventive Trial (MAPT): Standard Protocol Approvals, Registrations, and Ethics

Data were obtained from a [^{18}F] florbetapir positron emission tomography (PET) study carried out as part of the Multidomain Alzheimer Preventive Trial (MAPT), which was a large phase III, multicentre, randomized, placebo-controlled trial (29) (registration: NCT00672685). The trial had a four-arm design comprising a placebo group and three treatment groups; omega 3 polyunsaturated fatty acid (n-3 PUFA) supplementation, multidomain intervention (involving nutritional and exercise counseling and cognitive training), and n-3 PUFA supplementation plus multidomain intervention. The trial was designed to assess the efficacy of the interventions in slowing cognitive decline in older adults at risk of dementia (n = 1,680) (29). In the main analysis of MAPT, no significant effects of any of the interventions were found on the composite cognitive score compared to placebo after adjustment for multiple testing (30). Both the MAPT and [^{18}F] florbetapir PET study were approved by the ethics committee in Toulouse (CPP SOOM II) and written consent was obtained from all participants.

Participants

A total of 271 subjects participated in the MAPT-[^{18}F] florbetapir ancillary study. At inclusion, participants were community-dwelling, men and women without dementia, aged ≥70, and who met at least one of the following criteria: spontaneous memory complaints, limitation in executing ≥1 Instrumental Activity of Daily Living or slow gait speed (<0.8 meters/sec). Two participants were excluded because they developed dementia at the clinical assessment closest to PET [Clinical Dementia Rating (CDR) ≥ 1]. Thus, a total of 269 subjects were included in the analyses described here. The participants of the main MAPT study not assessed for cerebral Aβ load were similar to the participants in the PET sub-study in terms of age at baseline (main MAPT study: 75.9 ± 4.5 years, PET sub-study: 75.2 ± 4.2 years), sex (main MAPT study: 65.6% female, PET sub-study: 60.2% female) and cognition at baseline measured as mini mental state examination test score (main MAPT study: 28.0 ± 1.6, PET sub-study: 28.3 ± 1.5).

[^{18}F] Florbetapir PET

PET-scans were performed once during MAPT in volunteers using [^{18}F] florbetapir as previously described (29, 31). All data acquisitions were begun 50 min after injection of a mean of 4 MBq/kg weight of [^{18}F]-Florbetapir. Radiochemical purity of [^{18}F]-Florbetapir was always superior to 99.5%. Standard uptake value ratios (SUVRs) were generated from semi-automated quantitative analysis using the cerebellum as a reference. Cortical-to-cerebellar SUVRs (cortical-SUVRs) were obtained using the mean signal from the following cortical regions: frontal, temporal, parietal, precuneus, anterior cingulate, and posterior cingulate as previously described (32). Other brain regions independently assessed were the: anterior cingulate, anterior putamen, caudate, hippocampus, medial orbitofrontal cortex, occipital cortex, parietal cortex, pons, posterior cingulate, posterior putamen, precuneus, semioval center, and temporal cortex. A quality control based on semi-quantification process was also performed. The median and interquartile range (IQR) for the time interval between baseline and PET-scan assessment was 487.5 days (IQR: 349–728) and 3.7% (10 out of 269) of subjects received a PET-scan at study baseline.

Fatigue

Fatigue was defined according to the following two questions retrieved from the Center for Epidemiological Studies-Depression scale: (a) I felt that everything I did was an effort, (b) I could not get going. The question is asked "How often in the last week did you feel this way?" and subjects score their responses: 0 = rarely or none of the time (<1 day), 1 = some or a little of the time (1–2 days), 2 = a moderate amount of the time (3–4 days), 3 = most of the time. Subjects answering 2 or 3 to either of these questions were designated as fatigued otherwise subjects were classed as non-fatigued. Subjects were classed as having chronic fatigue if answering 2 or 3 to either of the questions at two consecutive visits between study baseline and 1 year (visits were performed at

baseline, 6 months, and 1 year after which they were performed annually) otherwise subjects were deemed non-chronically fatigued. The adopted definition of fatigue is commonly used to define the "exhaustion" criterion in the field of frailty (3).

Confounding Variables

On the basis of data availability and the literature on dementia (33), we selected the following confounders: age at PET-scan assessment, gender, educational level, cognitive status assessed at the clinical visit closest to PET-scan (CDR: scores 0 or 0.5), MAPT group allocation (four groups: placebo, multidomain intervention, n-3 PUFA supplementation and multidomain intervention + n-3 PUFA supplementation), depressive symptoms assessed closed to PET-scan (Geriatric Depression Scale: scores 0–30) and Apolipoprotein E ε4 (ApoE ε4) genotype (carriers of at least one ε4 allele versus non-carriers).

Statistical Analysis

Descriptive statistics are presented as median (IQR) or absolute values/percentages as appropriate. After completing analysis of the primary hypotheses in MAPT (30), we performed *post hoc* analyses using multiple linear regression models to explore the cross-sectional relationships between fatigue and cerebral Aβ load (measured as SUVR). Clinical and demographic characteristics were compared between the participants deemed as non-fatigued or fatigued (with fatigue assessed at the clinical exam closest to PET-scan) using chi squared tests for categorical variables and Wilcoxon rank sum tests for continuous variables. We ran multiple linear regression analysis to explore the cross-sectional relationship between fatigue at the clinical exam closest to PET-scan and cortical-SUVR and region specific SUVR (13 regions described above) adjusting for all confounders. Sensitivity analysis was performed in subjects with a CDR score of 0.5 as this sub-group represents those more likely to develop AD (34). We also ran multiple linear regression analysis to explore the cross-sectional relationship between chronic fatigue and cortical-SUVR and regional SUVR (13 regions) adjusting for all confounders. There was no correction for multiple comparisons due to the exploratory nature of this study: $p < 0.05$ was considered statistically significant. All analyses were performed using Stata version 14 (Stata Corp., College Station, TX, USA).

RESULTS

Sample Characteristics

Clinical and demographic characteristics of the study participants are shown in **Table 1**. The median age of the participants was approximately 75 years and around 60% of the subjects were female and approximately half of the subjects had a CDR score of 0.5. Participants exhibited a high educational level and approximately 30% of the subjects were ApoE ε4 carriers. There were no statistically significant differences between subjects classed as non-fatigued or fatigued (with fatigue assessed at the clinical exam closest to PET-scan). A total of 42 participants out of 269 (15.6%) were classified as fatigued and of these 42.9% (18 out of 42) were Aβ positive using a threshold of mean cortical-SUVR ≥ 1.17 (31, 35). A total of 26 participants out of 269 (9.7%) were classified as having chronic fatigue and of these 38.5% (10 out of 26) were Aβ positive.

TABLE 1 | Participant characteristics.

Variables	Non-fatigued subjects ($n = 227$)	Fatigued subjects ($n = 42$)	*p*-Value
Age, years	75 (72–79)	76 (73–79)	0.434
Sex, women (%)	134 (59.0%)	28 (66.7%)	0.353
Education (%)			0.190
No diploma or primary school certificate	54 (24.1%)	14 (34.1%)	
Secondary education no high-school diploma	72 (32.1%)	7 (17.1%)	
High-school diploma	31 (13.8%)	8 (19.5%)	
Higher diploma	67 (29.9%)	12 (29.3%)	
Group allocation (%)			0.550
Multidomain intervention	57 (28.6%)	11 (26.2%)	
n-3 PUFA supplementation	48 (21.1%)	12 (28.6%)	
Multidomain intervention and n-3 PUFA supplementation	65 (28.6%)	8 (19.0%)	
Placebo	57 (25.1%)	11 (26.2%)	
% of CDR 0.5 (%)	108 (47.6%)	23 (54.7%)	0.392
ApoE ε4 carriers (%)[a]	53 (26.8%)	12 (32.4%)	0.480
Cortical-SUVR	1.1 (1.0–1.3)	1.1 (1.1–1.3)	0.927

Age and CDR score closest to PET-scan are presented. Data are expressed as median (interquartile range) or as absolute values/percentages. Clinical and demographic characteristics were compared between the participants deemed as non-fatigued or fatigued (with fatigue assessed at the clinical exam closest to PET-scan) using chi squared tests for categorical variables and Wilcoxon rank sum tests for continuous variables.

ApoE, apolipoprotein E; CDR, clinical dementia rating; n-3 PUFA, omega 3 polyunsaturated fatty acid; SUVR, standard uptake ratio values.

[a]*ApoE ε4 status available for n = 235.*

Exploration of the Relationship between Fatigue and Cerebral Aβ

There were no statistically significant cross-sectional associations of fatigue at the clinical exam closest to PET-scan with cortical or region specific Aβ load after adjustment for all confounders (**Table 2**). Sensitivity analysis performed in subjects with a CDR score of 0.5, however, showed a weak positive association between fatigue reported at the clinical exam closest to PET-scan and Aβ load in the hippocampus (**Table 3**). Chronic fatigue was not significantly associated with cortical Aβ or Aβ found in any other brain region after adjustment for all confounders (**Table 4**).

DISCUSSION

In this study, we did not find any significant cross-sectional associations between fatigue (assessed closest to PET-scan examination or chronic) and cortical or region specific Aβ load in our total study population. However, sensitivity analysis in subjects with a CDR of 0.5 showed that fatigue reported closest to PET-scan was associated with increased Aβ load specifically in the hippocampus.

Why fatigue might be specifically associated with hippocampal Aβ pathology in subjects at increased risk of AD (CDR = 0.5) requires further research attention. However, there is evidence that fatigue, modeled in rats through the induction of sleep

TABLE 2 | Multiple linear regressions examining the cross-sectional associations between fatigue at the clinical exam closest to PET-scan and cerebral β-amyloid load.

β-amyloid load	Unadjusted model (n = 269)			Adjusted model (n = 231)		
	B-coeff.	95% CI	p-Value	B-coeff.	95% CI	p-Value
Cortical-SUVR	−0.01	−0.06, 0.05	0.800	−0.04	−0.10, 0.02	0.184
SUVR by brain region;						
Anterior cingulate	−0.01	−0.08, 0.06	0.832	−0.06	−0.14, 0.02	0.140
Anterior putamen	−0.02	−0.12, 0.08	0.683	−0.05	−0.17, 0.06	0.367
Caudate	0.05	−0.06, 0.16	0.344	0.04	−0.09, 0.17	0.532
Hippocampus	0.02	−0.02, 0.06	0.263	0.04	−0.00, 0.08	0.071
Medial orbitofrontal cortex	−0.00	−0.05, 0.04	0.939	−0.02	−0.07, 0.03	0.494
Occipital cortex	−0.02	−0.08, 0.04	0.553	−0.06	−0.13, 0.01	0.073
Parietal cortex	−0.03	−0.09, 0.03	0.339	−0.06	−0.13, 0.01	0.080
Pons	−0.01	−0.05, 0.04	0.702	−0.00	−0.06, 0.05	0.896
Posterior cingulate	0.00	−0.06, 0.06	0.975	−0.03	−0.10, 0.04	0.362
Posterior putamen	−0.01	−0.09, 0.07	0.727	−0.02	−0.11, 0.07	0.667
Precuneus	−0.00	−0.08, 0.08	0.964	−0.05	−0.13, 0.03	0.245
Semioval center	0.02	−0.03, 0.08	0.424	0.02	−0.04, 0.09	0.507
Temporal cortex	−0.00	−0.06, 0.05	0.891	−0.03	−0.09, 0.02	0.253

The adjusted model contained fewer subjects due to missing data on confounders.
B-coeff, B-coefficient; CI, confidence intervals; p, probability; SUVR, standard uptake ratio values.

TABLE 3 | Multiple linear regressions examining the cross-sectional associations between fatigue at the clinical exam closest to PET-scan and cerebral β-amyloid load in subjects with a CDR score of 0.5.

β-amyloid load	Unadjusted model (n = 131)			Adjusted model (n = 113)		
	B-coeff.	95% CI	p-Value	B-coeff.	95% CI	p-Value
Cortical-SUVR	−0.01	−0.09, 0.07	0.829	−0.03	−0.12, 0.05	0.438
SUVR by brain region;						
Anterior cingulate	0.01	−0.10, 0.11	0.922	−0.03	−0.15, 0.09	0.597
Anterior putamen	−0.01	−0.15, 0.13	0.869	−0.05	−0.21, 0.12	0.585
Caudate	0.08	−0.07, 0.24	0.276	0.11	−0.06, 0.29	0.204
Hippocampus	0.04	−0.01, 0.09	0.106	0.07	0.01, 0.12	0.016
Medial orbitofrontal cortex	0.00	−0.06, 0.06	0.974	0.00	−0.06, 0.06	0.973
Occipital cortex	−0.01	−0.10, 0.08	0.750	−0.05	−0.15, 0.04	0.265
Parietal cortex	−0.05	−0.14, 0.03	0.241	−0.08	−0.16, 0.01	0.085
Pons	0.01	−0.06, 0.07	0.802	0.01	−0.06, 0.08	0.762
Posterior cingulate	−0.01	−0.09, 0.08	0.824	−0.04	−0.13, 0.05	0.426
Posterior putamen	−0.01	−0.11, 0.09	0.810	−0.02	−0.14, 0.09	0.693
Precuneus	−0.00	−0.12, 0.11	0.958	−0.04	−0.17, 0.08	0.496
Semioval center	0.04	−0.03, 0.12	0.249	0.06	−0.02, 0.15	0.147
Temporal cortex	0.00	−0.07, 0.08	0.904	−0.02	−0.10, 0.06	0.688

The adjusted model contained fewer subjects due to missing data on confounders.
B-coeff, B-coefficient; CI, confidence intervals; p, probability; SUVR, standard uptake ratio values.

deprivation, reduces hippocampal as well as cortical dendritic spines (36) and inhibits long-term potentiation and hippocampal dependent learning tasks (37). Thus, it might be that fatigue also modulates cell signaling cascades to promote amyloidogenesis specifically in the hippocampus. In line with this, in mouse models of AD, acute sleep deprivation is associated with increased levels of interstitial brain levels of Aβ, whereas chronic sleep deprivation has been associated with increased Aβ plaques (38). Increased brain Aβ load has also been cross-sectionally associated with poor sleep (39) and longer sleep latency (time taken to fall asleep) (40) in human subjects. Oxidative stress is associated with fatigue (15) and pro-inflammatory mediators such as interleukin 6 and C-reactive protein have been associated with frailty (which includes fatigue in the phenotype) (16, 18); therefore such signalling intermediates might promote fatigue-induced amyloidogenesis at the molecular level (19, 20). Interestingly, fatigue has also been associated with compromised cognition in older adults without dementia (7, 8). With this in mind, fatigue might modulate cognition *via* Aβ-dependent mechanisms in human subjects with early AD. More research is needed to verify the links between fatigue and Aβ deposition, particularly to rule out the possibility that increased Aβ in the brain might precipitate fatigue. A better understanding of the biological basis of fatigue would facilitate such studies.

The strengths of the current study are the large sample size with PET [^{18}F] florbetapir imaging data and the simultaneous

TABLE 4 | Multiple linear regressions examining the cross-sectional associations between chronic fatigue and cerebral β-amyloid load.

β-amyloid load	Unadjusted model (n = 269)			Adjusted model (n = 231)		
	B-coeff.	95% CI	p-Value	B-coeff.	95% CI	p-Value
Cortical-SUVR	−0.01	−0.08, 0.06	0.854	−0.03	−0.10, 0.05	0.452
SUVR by brain region;						
Anterior cingulate	−0.01	−0.10, 0.07	0.760	−0.05	−0.14, 0.04	0.293
Anterior putamen	0.02	−0.10, 0.15	0.736	0.01	−0.13, 0.14	0.922
Caudate	0.02	−0.11, 0.16	0.714	0.02	−0.13, 0.17	0.798
Hippocampus	−0.01	−0.06, 0.03	0.518	−0.01	−0.06, 0.04	0.677
Medial orbitofrontal cortex	−0.01	−0.07, 0.04	0.687	−0.02	−0.08, 0.04	0.433
Occipital cortex	−0.01	−0.09, 0.06	0.756	−0.04	−0.12, 0.04	0.286
Parietal cortex	0.00	−0.07, 0.08	0.994	−0.00	−0.08, 0.07	0.903
Pons	−0.02	−0.08, 0.03	0.425	−0.02	−0.08, 0.04	0.464
Posterior cingulate	−0.01	−0.09, 0.06	0.716	−0.04	−0.12, 0.04	0.384
Posterior putamen	−0.00	−0.10, 0.10	0.967	0.01	−0.10, 0.12	0.920
Precuneus	0.01	−0.09, 0.10	0.857	−0.02	−0.12, 0.08	0.639
Semioval center	−0.00	−0.07, 0.07	0.943	−0.01	−0.09, 0.07	0.847
Temporal cortex	−0.01	−0.07, 0.06	0.773	−0.03	−0.10, 0.04	0.379

The adjusted model contained fewer subjects due to missing data on confounders.
B-coeff, B-coefficient; CI, confidence intervals; p, probability; SUVR, standard uptake ratio values.

availability of successive fatigue measurements over time enabling the creation of a chronic fatigue variable. Nevertheless, there are some limitations. The main limitation of this study is that it is a secondary analysis of the MAPT imaging sub-study; thus, the study was not specifically powered to address our hypothesis on the association of fatigue with increased cerebral Aβ load. The cross-sectional nature (due to lack of longitudinal imaging data) precluded the examination of the relationship between fatigue and Aβ temporally. Furthermore, it should be noted that PET-scans were performed throughout the three year period of MAPT, so the study was not of a true cross-sectional nature. Moreover, although used by others (2, 41) as a measure of fatigue, the self-reported fatigue variable used here was derived from a questionnaire designed to measure depression and as such may not robustly capture the physiological component of fatigue but rather focus on the psychological element. There was also no data available on other diseases that might contribute to fatigue such as anemia, sleep apnea, or cancer.

In conclusion, we have shown here that fatigue might be associated with increased Aβ in the hippocampus specifically in subjects with an augmented risk of AD. Further research is required to confirm our preliminary findings. A longitudinal study examining the temporal association between fatigue and Aβ would provide more evidence as to whether fatigue might modulate cerebral Aβ levels.

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ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Toulouse ethics commitee (CPP SOOM II) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

CH was responsible for data analysis and writing the manuscript. PB supervised the data analysis and was involved in the critical appraisal of the manuscript. NC was involved in data analysis and critical appraisal of the manuscript. PP and AS performed the [^{18}F] florbetapir PET. SA, MC, and BV were involved in study design and critical appraisal of the manuscript.

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Motoric Cognitive Risk Syndrome: Predictor of Dementia and Age-Related Negative Outcomes

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Cognitive disorders represent a leading cause of disability in the aging population, of which dementia has the highest global burden. Early signs of dementia such as slow gait and memory complaints are known to present well before the overt manifestation of the disease. Motoric cognitive risk (MCR) syndrome characterized by the simultaneous presence of gait disturbances and memory complaints in older subjects has been proposed to study the close interactions between the physical and cognitive domains as well as a possible approach to identify individuals at increased risk of dementia. In addition, studies have shown MCR as a predictor of other negative outcomes in older adults, including disability, falls and death. However, the concept of MCR is still in its early stage and approach to the syndrome is still not well established. This review aims to put together the various aspects of MCR syndrome including its pathophysiology, diagnosis, epidemiology, and relationship with other geriatric conditions.

Keywords: dementia, motoric cognitive risk, gait, cognition, subjective memory complaint, geriatric disorders

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INTRODUCTION

Older adults are known to have decreased functional capacity (e.g., sensory, cognitive, physical), which makes them vulnerable to adverse events such as disability, dependency, falls, or even death (1–5). Poor mobility of lower limbs with aging is one of the most commonly presented form of physical limitation in older individuals (6). Several studies have shown gait speed to predict major health-related events in older adults (6–8). Similarly, decline in memory is another common form of cognitive limitation associated with increase in age, which might potentially progress to dementia (9, 10). Furthermore, evidences from past studies have shown coexistence of cognitive decline and gait abnormality (that might be of musculoskeletal or neuro-sensory-motor etiology) to be a common condition in older adults (3, 11, 12). Besides, these functional limitations are known to be the major causes of disability and dependency in older adults (7, 11, 13, 14).

Growing body of evidence suggests that simultaneous presence of cognitive complaints with reduced gait speed may indicate early signs of dementia (presenting decades before actual presentation of cognitive impairment) (15–20). Unfortunately, very little is known about how the actual interaction between the cognitive and physical domain (such as which domain triggers the other, or time-point of initiation) occurs with the phenomenon of aging. Intuitively, an entity that captures both physical and cognitive functional status of an aging individual could reflect a more implicit functional status of the individual. Moreover, such entity would aid researchers to better understand the interaction between cognition and physical domains in aging individuals who are at high-risk of dementia and other geriatric disorders.

In this review, we discuss on a novel concept described as motoric cognitive risk (MCR) syndrome that captures the state of concomitant presence of gait disturbances and cognitive decline in older adults (20). Studies have shown MCR to be an effective tool in predicting various geriatric conditions such as dementia (19), falls (21), disability (22), and mortality (1).

GAIT AND COGNITION IN OLDER ADULTS

Gait: Walking is a very common activity of daily living, which at a glance appears to be an entirely unsophisticated automated motor task. However, maintaining of normal gait is a much complex process requiring intact multisystem (nervous, sensory, musculoskeletal, cardiorespiratory) function and coordination (3, 16, 17). With increase in age, the parameters of gait (velocity, stride length, swing time) are affected as a result of disturbances in either of the musculoskeletal functions, locomotor function, balance, postural reflexes, sensory function and sensorimotor integration, and cardiorespiratory functions (23), resulting abnormal gait.

At present, gait speed or gait velocity has increasingly been implemented in clinical settings to evaluate functional status in older subjects and even to predict adverse events (1, 18, 21, 22, 24). In addition, slow gait speed is thought to be a sensitive marker of cognitive decline with aging (18, 25–28). However, the methods and cut-off values for assessment of gait in older subjects is known to vary widely. Moreover, every cut-point might be arbitrary because the relationship between gait speed and risk of negative outcomes follows a linear trend. Nevertheless, gait speed less than 0.8 m/s over a 4-m track is one of the most commonly used cut-points to assess gait speed in older subjects (29). The cut-point has been suggested to predict adverse events in older adults by the International Academy on Nutrition and Aging task force (29) and recommended for further clinical investigation by the European consensus on sarcopenia (30). On the other hand, the concept of "dis-mobility" describes a much slower gait speed of less than 0.6 m/s to be a relevant cut-point suitable for improving clinical care, research, and regulatory approval of treatments to improve mobility in older adults (31). Gait abnormalities have been identified from early neurological studies and subclassified as unsteady, ataxic, frontal, parkinsonian, neuropathic, hemiparetic, or spastic (23, 32) depending upon the nature of the disturbances that should be properly identified by physicians while assessing older adults.

Cognition: Cognition relates to the functioning processes of the brain, which tends to change with age (33). Cognitive functions such as attention, intelligence, memory, processing speed, and executive function are known to decline with increase in age with varying degree between individuals (34), which could affect the overall functioning of an individual including gait. This alteration in cognition with aging has been associated primarily with decline in brain gray and white matter volume (35), brain hippocampus volume (36), and deposition of protein beta-amyloid in brain [a primary marker of Alzheimer's disease (AD)] (37). Factors such as cardiovascular diseases (and associated risk factors), genetics, low level of education and depression have been identified as major contributing factors for cognitive decline (38), which could simultaneously influence the overall physical functioning. Assessment scales such as clinical dementia rating (CDR) (39), Mini-Mental State Examination (40), and other forms of dementia screening questionnaire have been widely used to assess overall cognitive status of older adults.

Link between Gait and Cognition

As discussed before, gait is a sequel of multifactorial and multisystem coordination, but primarily the result of neuromuscular interaction capacity of an individual. Anatomically speaking, brain frontal subcortical circuits predominantly mediate gait (41). Executive function (3, 42) and attention (42–44) have been suggested to be the primary cognitive processes associated. However, the frontal lobe itself is vulnerable to age-related changes (42), which could alter gait speed and cognition in older adults. In addition, declination or improvement in executive function and attention over time was found to effect gait progression (speed) in older adults (17, 27, 42). Increased brain subcortical white matter hyper-intensities (leukoaraiosis) (45) and decrease in cerebellar gray matter volume (46) and hippocampal volumes (47) were found to be associated with reduced gait speed. This overlap between the brain areas controlling gait and cognition explains the relationship between slow gait and dementia pathologies. Furthermore, a dual-task methodology termed as "walking while talking" was developed for making the gait speed assessment more challenging and included the evaluation of cognition (48–50). The participant's change in motor performance during dual-task was observed suggesting requirement of additional cognitive resources to maintain multisystem coordination, which might be difficult to achieve for older individuals with cognitive limitation, leading to detrimental effects such as falls. Besides, a recent meta-analysis has shown evidences of brain structure to be associated with muscle structure and function (51), showing the consequential association between these domains, which could alter gait function.

Factors Associated

Physical limitations and cognitive decline have been suggested to present bidirectional relationship (3, 17, 52). These conditions most likely share the common risk factors and pathways such as chronic inflammation, hormonal pathways, lifestyle factors, and even genetic pathway (11, 53–57).

Low-grade chronic inflammation or "inflamm-aging" might be the primary biological pathway shared by gait and cognition in older individuals (58–62). Atherosclerosis, a chronic inflammatory condition in older adults is known to promote cardiovascular dysfunction that could increase functional loss (both cognitive and physical) in aged individuals (61, 63, 64). Furthermore, chronic inflammation is found to directly impact the central nervous system (e.g., neurofibrillary tangles, amyloid plaques) of older adults (65–67) and promote cardiovascular risk factors (59, 61, 68, 69). Increased serum C-reactive protein, interleukin-6, and plasma tumor necrosis factor-α are the inflammatory markers associated with decrease in total brain volume (58, 65, 70, 71) that could affect cognition and gait simultaneously.

Cardiovascular risk factors (e.g., hypertension, diabetes, hyperlipidemia) are known to enhance incidences of cerebral

ischemia affecting the periventricular white matter (64, 72, 73). As explained before, brain white matter plays an important role in the control of gait and cognitive processing and responsible for executive function (45, 64, 73). Similarly, other conditions such as neurodegeneration (e.g., in Parkinson's disease) in older adults is well known to impact both cognition and motoric functions (74).

Needless to elaborate, nutritional factor is a key component to influence physical function in humans. Besides, abundant studies have shown that the deficiency of nutritional factors may affect both cognition and physical functions in older adults (53, 54, 75, 76). Similarly, physical exercise is another factor that is well known to influence both cognition and physical limitations in older adults (77–80). Functional decline in older adults is also known to be influenced by hormonal alteration (such as downregulation of insulin-like growth factor) with aging (81) and genetic factors such as apolipoprotein-E4 (APOE-4 genotype) (55, 56).

MCR SYNDROME

Motoric cognitive risk syndrome is defined as a condition characterized by slowness of gait in the presence of subjective cognitive complaint in older adults without any form of dementia or mobility disability (1, 18–22). The theory that slowness of gait coexisting with cognitive decline might be an early sign of dementia, which has been used in this novel entity, potentially resembling a pre-dementia syndrome (18, 19, 22) (**Figure 1**).

The following four criteria have been proposed to be met for the diagnosis of MCR (although the use of scales was not uniform in prior studies—**Table 1**) (1, 18–22): (1) presence of subjective cognitive complaints, assessed using standardized questionnaire (e.g., CDR, GDS, or AD screening questionnaire), (2) presence of slow gait: defined as velocity one SD or more below age- and sex-appropriate mean values, (3) preserved mobility, and (4) absence of dementia.

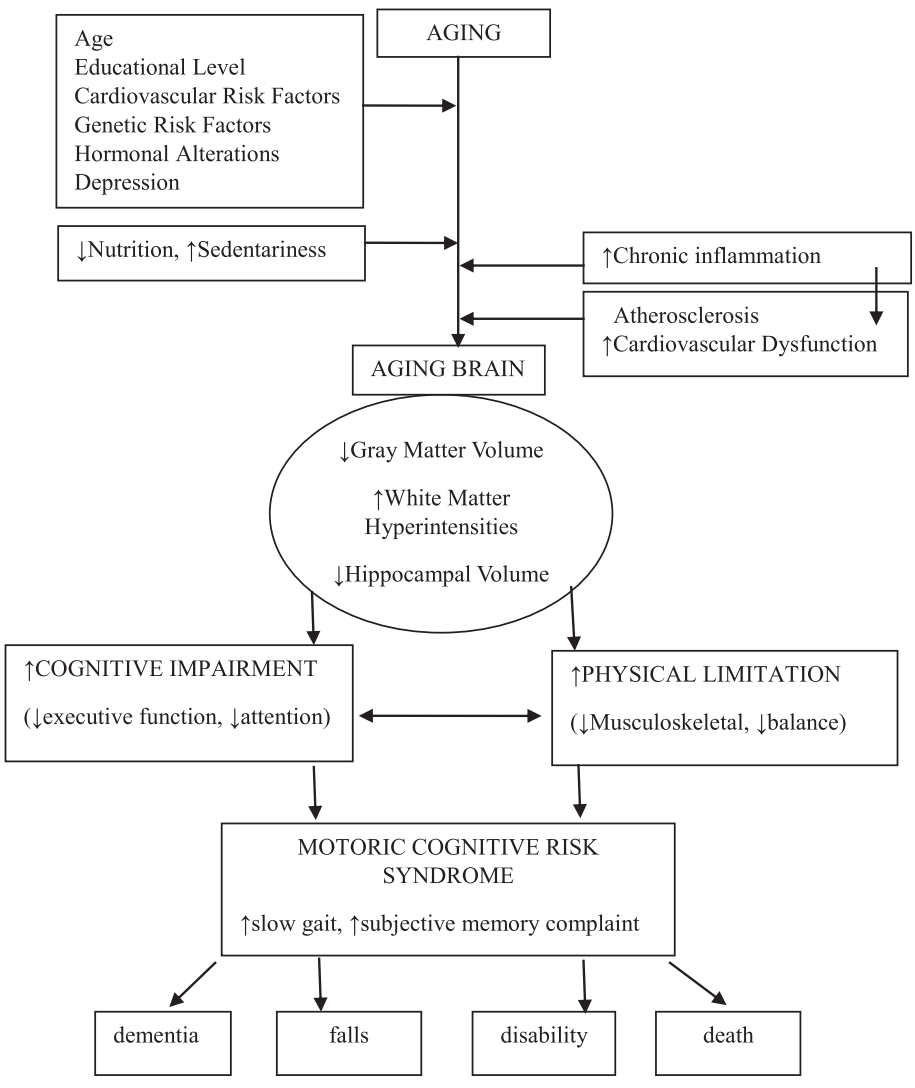

FIGURE 1 | Diagrammatic presentation of motoric cognitive risk syndrome.

TABLE 1 | Frequent methods implemented to diagnose motoric cognitive risk syndrome.

Study	Setting	*N*	Age	Assessment of diagnostic criteria			
				Cognitive complaints	Slow gait	Preserved mobility	Absence of dementia
Verghese et al. (19)	CS	997	≥70 years	CERAD questionnaire	Instrumented walkway (GAITRite)	Preserved ADL assessed by a scale developed for assessing function in community-residing older adults (82) + clinician's interviews	DSM-IV
Verghese et al. (83)	MC	26,802	≥60 years	Self-report cognitive questionnaire, GDS*, GDS and AD8, IADL	Instrumented walkway (GAITRite)/ timed walk (over 4, 6, 8, 9, 10 feet)	Exclusion of mobility disability (inability to ambulate with or without assistive devices)	Clinical diagnosis/DSM-IV and III R
Verghese et al. (84)	MC	3,128	≥60 years	Self-report	Instrumented walkway (GAITRite)/ timed walk	Exclusion of mobility disability (inability to ambulate with or without assistive devices)	BIMC, MMSE
Allali et al. (85)	CS	314	≥65 years	CDR/GDS*/AD8	Instrumented walkway (GAITRite)	Preserved ADL (82)	Clinical and neuropsychological information
Doi et al. (86)	CS	9,683	≥65 years	GDS*	Timed walk (over 6.4 m)	Independent in basic ADL	MMSE

Slow gait = one SD or more below age- and sex-appropriate mean values established in the same cohort.

CS, community setting; MC, multiple cohorts; N, number of subjects; CERAD, Consortium to Establish a Registry for Alzheimer's Disease questionnaire; GDS, Geriatric Depression Scale; GDS, "Do you feel you have more problems with memory than most?" A positive response ("yes") on the question was used to define subjective memory complaints; DSM-IIIR/IV R), Diagnostic and Statistical Manual of Mental Disorders (revised third or fourth edition criteria); AD8, cognitive screening instrument; CDR, clinical dementia rating; ADL, activities of daily living; IADL, instrumental activities of daily living; BIMC, blessed information-memory-concentration; MMSE, Mini-mental State Examination.*

Motoric cognitive risk was found to have a prevalence ranging from 2 to 18% (83, 84, 86, 87). A multi-country (17 countries worldwide) study showed an overall pooled prevalence of almost 10% (83). These studies have shown MCR to have a higher prevalence and incidence in older age irrespective of gender. Based on the current availability of data, cross country comparison lowest prevalence of 2% was found in the United Kingdom and Australian cohort, and higher prevalence of 15% in Indian cohort and the highest prevalence of 16–18% was found in French population (83, 84, 86, 87).

Factors such as stroke, diabetes, obesity, depression, and sedentariness have been found to be associated with high risk of MCR in older adults (85, 86). Additional studies in much diverse sociodemographic settings are required for confirming the global burden of the condition and accordingly identify the associated risk factors.

MCR Syndrome As a Predictor Of Dementia

Relevant links between cognition and gait have been established earlier. Older adults with cognitive impairment are known to have slower pace (26). Verghese and colleagues in the early 2000 implicated that presence of neurological gait in older adults could predict the risk of dementia (18). However, predictive capacity of MCR with regards to subtypes of dementia was found to be different according to study cohort. In the Einstein Aging Study, MCR was found to be highly prevalent with age and was a strong predictor of vascular dementia (VaD) (19). Older subjects with MCR were found to be at more than 3-folds risk [hazard ratio (HR) = 3.27] of future dementia (except AD) and particularly over 12-folds risk (HR = 12.81) of VaD. However, slow gait was the only gait parameter used which might have decreased the predictive validity of MCR.

In another multi-country study, MCR predicted dementia in multiple cohorts as well as pooled sample, with risks ranging from 1.79- to 2.10-folds (83). Interestingly, MCR was found to be associated with increased risk of AD in two cohorts of the study with 2.21- and 1.97-folds risk, while very few cases of VaD dementia were present in the cohort. However, the cohorts were limited to only 17 countries; therefore, the predictive strength cannot represent for all at-risk subjects [as the primary criteria of MCR cognitive complaint and slow gait can vary demographically (88)], and not to forget the major risk factors that have varied demographic distribution. Additionally, information on APOE-4 genotype [that is known to impact progression of dementia (55)] was not included on this multi-country study, which could have further strengthened the validity of MCR dementia predictive capacity.

Interestingly, a retrospective study in Japanese older population has further elaborated the relation between MCR and dementia (89). The authors have reported the rate of conversion to dementia was 119.8/1,000 persons per year in MCR population, while the non-MCR group was 102.5/1,000 persons per year (OR = 1.38). Slow gait and low scores in executive function tests were found to be predictive of higher rate of conversion to dementia.

Falls

A very high frequency of falls (32–42% per year) in older people over 70 years has been estimated (90), which could result in many detrimental effects including disability or death (91, 92).

As discussed earlier, maintaining a normal well-balanced gait requires an efficient integration of motoric, cognitive, and psychological function (3, 5, 16, 17) and the inability to maintain a normal gait could result in falls. Impairment in cognitive domains such as executive function, attention, processing speed, and memory is known to increase the risks of falls. However, age-related loss in white matter integrity is thought to be one of the key mechanisms affecting the cognitive domain responsible (57, 93). Thus, from our explanations earlier, we could expect MCR to be a sensitive predictor of falls in older adults.

A study by Callisaya and colleagues with a combined five large cohorts across three countries found subjects with MCR to be at 44% at high risk of falls in pooled analysis (21). The study showed that slow gait [risk ratio (RR) = 1.30] and memory complaints (RR = 1.25) were also individually associated with increased risk of falls. Whereas, exclusion of MCR case in the study showed a slight decreased association of slow gait (RR = 1.25) and memory complaints (RR = 1.17) with falls. Even after adjustments for previous falls, MCR was significantly associated with falls (RR = 1.29) and multiple falls (RR = 1.37) in pooled analysis. No doubt, the results from the study show MCR to be an effective risk screening tool for falls, as the associations observed were relatively stronger. However, due to different criteria/procedures used for diagnosis of MCR and falls, heterogeneity was present in the pooled analysis.

Disability

Very few studies discussing the associations of MCR and disability are available. However, it can be expected that older individuals with coexisting memory decline and physical limitation are likely to be disabled (or lose independency) if not provided with proper medical attention at an early phase. A very recent study involving 4,235 Japanese older adults (mean age of 72 years) has suggested MCR to be able to predict risk for disability (HR = 1.69) (22). The diagnostic criterion for disability was here regarded as certification by long-term care insurance. Nevertheless, the study has provided some perspectives for future studies, which could implement a more clinical diagnostic method for disability. The findings from this study have verified that individuals with slow gait and cognitive impairment are at high risk of disability, and more studies are demanded to confirm the findings.

Death

As discussed earlier, maintaining intact gait is a complex process requiring multisystem/multifunction coordination, therefore could represent a person's holistic level of healthiness. Studies have shown gait speed to be a very strong predictor of survival (8) and cognitive impairment is also known to predict mortality (94). MCR involves both cognition and gait, has a high prevalence (83, 84, 86, 87), is known to predict falls (21), dementia (18, 19, 22), and therefore could be a more sensitive predictor of death.

A study by Ayers and Verghese (1) including 11,867 participants from three different cohorts found MCR at baseline was associated with increased overall mortality (HR = 1.69) and increased risk of death even after adjustments for gait and memory test scores (HR = 1.19). The results from the study showed MCR to be a predictor of 2 years mortality, but MCR death predictive capacity in dementia subjects was found to be insignificant. However, it should be noted that the included cohorts of the study were from Europe and United states; therefore, results from the study cannot be interpreted as the global mortality predictive capacity of MCR. Moreover, the study population were community dwelling older adults, who tend to be in better shape compared to the institutionalized. As the study was a population-based study cases of diagnosed dementia could have been underreported, which could have underestimated the prediction of mortality in diagnosed dementia subjects.

THE PARADOX OF MCR SYNDROME

An existing paradox of the MCR is whether to consider it as a condition to treat or a mere matter for research purposes? As discussed above, MCR was found to predict wide spectrum of abnormalities in older adults (1, 19, 21, 22) and has a high prevalence ranging up to 18% (83, 84, 86, 87). For these reasons, attention on further approach of this novel syndrome is necessary. Although past studies have stressed on the versatility of diagnosing MCR (20), the clinical approach of the syndrome is vague. In the clinical scenario, we could only attempt to investigate the underlying pathologies of the condition and treat them in traditional manner (that requires various medical tests, despite of considering MCR easy to diagnose), which might require more resources and perhaps even create additional confusion in clinicians. On the other hand, if we consider it as screening tool to identify the at-risk population for the abnormalities it can predict, various effective tools for the purpose already exist (with prior extensive studies involving different sociodemographic population settings). In this context, MCR might be more suitable as a research entity to exclusively investigate the interactions between the physical and cognitive domains (which is not well understood yet) in older population with high risk of conditions that can be predicted by it. Furthermore, these understandings could enable us to design preventive strategies to ameliorate many geriatric conditions including dementia.

CONCLUSION

In summary, with population aging, the burden of cognitive disorders such as dementia is still escalating. Frequent coexistence of physical limitation and cognitive decline occur in aging individuals, leading to many detrimental effects. MCR includes the evaluation of potential precursors of physical limitation (i.e., gait speed) and cognitive decline (i.e., subjective memory complaints) in order to predict multiple age-related conditions including dementia. Future perspective of MCR might be as a research tool to particularly investigate the relationship between physical and cognitive domain in older adults, further elucidate our understanding of the interaction between these two domains. Results from such studies could facilitate in designing more effective preventive intervention strategies against dementia and other age-related negative outcomes.

AUTHOR CONTRIBUTIONS

JC: manuscript preparation and drafting; all authors: conception and design, critical revision, and approvement for final version.

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REVIEW
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Is Delirium the Cognitive Harbinger of Frailty in Older Adults? A Review about the Existing Evidence

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Frailty is a clinical syndrome defined by the age-related depletion of the individual's homeostatic reserves, determining an increased susceptibility to stressors and disproportionate exposure to negative health changes. The physiological systems that are involved in the determination of frailty are mutually interrelated, so that when decline starts in a given system, implications may also regard the other systems. Indeed, it has been shown that the number of abnormal systems is more predictive of frailty than those of the abnormalities in any particular system. Delirium is a transient neurocognitive disorder, characterized by an acute onset and fluctuating course, inattention, cognitive dysfunction, and behavioral abnormalities, that complicates one out of five hospital admissions. Delirium is independently associated with the same negative outcomes of frailty and, like frailty, its pathogenesis is usually multifactorial, depending on complex inter-relationships between predisposing and precipitating factors. By definition, a somatic cause should be identified, or at least suspected, to diagnose delirium. Delirium and frailty potentially share multiple pathophysiologic mechanisms and pathways, meaning that they could be thought of as the two sides to the same coin. This review aims at summarizing the existing evidence, referring both to human and animal models, to postulate that delirium may represent the cognitive harbinger of a state of frailty in older persons experiencing an acute clinical event.

Keywords: frailty, delirium, older adults, review of literature pathophysiology, geriatric syndromes

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INTRODUCTION

Although frailty and delirium are intuitively associated, a clear taxonomy of their biological and clinical relationship has not provided yet in geriatric medicine.

For many years, age has been considered as one of the most powerful predictors of mortality and adverse outcomes in older people. However, growing empirical evidence and several scientific publications have clearly shown that "chronological age" is not able *per se* to capture with sufficient accuracy the extreme heterogeneity of the health status in older persons (1, 2). In order to promote a measure more focused on the individual's functions and biology, the concept of frailty has

received special attention over the past years. In fact, frailty has been indicated as a condition which may accurately capture the homeostatic reserves of the organism and, as such, improve the assessment of the risk profile. In other words, frailty might represent the new criterion for defining the individual as (biologically) old and replace the obsolete age concept (2). Interestingly, this change of paradigm might also support a more person-tailored approach in the design of clinical interventions.

According to a commonly accepted definition, frailty is defined as a medical syndrome characterized by a decrease of functional reserve capacities, diminished strength, and endurance. The consequence of this increased vulnerability is that a frail person is more prone than a non-frail to develop negative health-related outcomes, including decline in functional and motor performance, prolonged length of hospital stay, institutionalization, rehospitalization, and mortality (2–4). Frailty might thus be considered as the complex biological background on which multiple protective and disruptive factors interact in the determination of the clinical manifestations and negative outcomes (2, 4). From a pathophysiological perspective, it is well accepted that the physiological systems which are involved in the determination of frailty, including brain, endocrine system, immune system, and skeletal muscle, are mutually interrelated, so that when decline starts in a given system, implications may also regard the others. To support this, it has shown that the number of abnormal systems is more predictive of frailty than are the abnormalities in any particular system (4). Recently, to explore the mechanistic relationship between aging, frailty, and mortality, Rutenberg et al. developed a computational model in which possible health attributes are represented by the nodes of a complex network, with the connection showing a scale-free distribution (1). Each node can be either damaged (i.e., a deficit) or undamaged. The most connected nodes are the mortality nodes; the next most connected nodes are frailty nodes that broadly correspond to clinically or biologically significant health characteristics. According to this model, individuals die when mortality nodes are highly damaged. Nodes are damaged randomly reflecting environmental influences, intrinsic features, and their interactions (5). Through interactions, the rate of damage of an individual node increases as more of its connected neighbors are damaged. This model can explain why frail individuals are at higher risk of vulnerability and mortality than robust ones, and facilitates the initial understanding of the factors influencing the health trajectories of older individuals (1).

Delirium is a transient neurocognitive disorder, characterized by an acute onset and fluctuating course, inattention, cognitive dysfunction, and behavioral abnormalities, which develops in association with another underlying medical condition (6). Sometimes, though not invariably, delirium presents with behavioral disturbances, including sleep-wake cycle disruption, psychotic symptoms, and agitation (7). It has been shown that delirium complicates about one out of five hospital admissions (8, 9), representing a clear burden for the patient as well as for public health. Like frailty, delirium is independently associated with a number of negative outcomes, including increased length of hospital stay, elevated healthcare costs, accelerated cognitive impairment, delayed or limited recovery of functional decline, increased risk of institutionalization, and mortality (10–14). In addition, delirium may cause patient and caregiver's emotional distress (15, 16). Although a single factor can cause it (e.g., infections), its pathogenesis is usually multifactorial (10), depending on complex inter-relationships between predisposing and precipitating factors acting on the substratum of biological vulnerability (i.e., frailty). According to this view, delirium can thus be regarded as a clinical consequence of frailty in older persons experiencing stressful events. It is also important to mention that frailty and delirium are expected to rise in their prevalence in the next years, largely due to global aging of the populations worldwide.

In this review, we will summarize the existing evidence on the relationship between the two conditions (i.e., frailty and delirium), referring both to human and animal models.

COMMONALITIES AND DIFFERENCES BETWEEN FRAILTY AND DELIRIUM

Frailty and delirium share several commonalities but also have specific differences (**Table 1**). Both should be considered as multifactorial health conditions, characterized by multiple risk factors and causation which are not necessarily specific to a given organ system failure. This notion is indirectly confirmed by a growing body of evidence, from cardiology (17, 18) to infectious disease medicine (19, 20), from oncology (21, 22) to anesthesiology (23, 24), that these two conditions have a crucial role in clinical and research areas. Both frailty and delirium share many commonalities. In particular, they are both predictive of several negative health-related outcomes, most of which might be prevented by applying adapted and personalized interventions. A common biological substratum between the two conditions can also be suggested, possibly involving inflammation, endocrine and vascular systems, and oxidative stress (25). However, since both frailty and delirium find their biological roots in the aging process, it might be hypothesized that the same mechanisms responsible for the aging of the individual may become the causes of the conditions of interest when abnormally enhanced/stimulated by negative (endogenous or exogenous) stressors.

At the same time, frailty and delirium also differ in many aspects. Frailty is the long-term result of a decline in the homeostatic individual's capacity across multiple physiological systems and it is usually considered as the endpoint of the progressive activity of corrosion exerted by chronic diseases during the normal aging process. On the contrary, delirium is an acute condition that occurs in response to a stressor (generally a medical problem) that may have a relatively rapid resolution, though sometimes it can persist weeks or even months. Delirium can be thought as an acute brain failure, reflecting the interaction between a predisposing factor (i.e., brain vulnerability) and one or more precipitating factor (i.e., the noxious insults), in which the brain is not able to compensate. Frailty may thus represent the ideal pabulum for the development of delirium, and delirium, on its side, may represent the clinical manifestation of underlying frailty in a patient suffering from an acute decompensation.

The relationship between frailty and delirium is even more complicated than above depicted. From a clinical perspective,

TABLE 1 | Commonalities and differences between delirium and frailty.

Criteria	Delirium	Frailty
Definition	Neuropsychiatric syndrome characterized by acute and fluctuating deterioration in cognition, which develops in association with underlying medical conditions	Long-term clinical condition characterized by decrease of functional reserves, increasing vulnerability towards endogenous/exogenous stressors
Features	Inattention, thought disorders, impaired arousal, and behavioral abnormalities	Reduced homeostatic reserves due to age-related accumulation of deficits. Major physical features are characterized by malnutrition, abnormal energy expenditure, mobility impairment, and weakness
Prevalence	Delirium occurs in one in five hospitalized patients. Although less frequently, it can also occur in patients at home. Its prevalence is expected to rise in next years, due to the progressive ageing of population	About 10% of older community-dwellers have frailty, rising to between a quarter and a half of those aged over 85 years. The prevalence of frailty is expected to rise in next years, due to the progressive aging of the population
Time course	Acute onset (hours or days) with fluctuation in severity and duration; most cases are transient, resolving after a few days, but some persist for weeks or months	Chronic; in most cases, it is a progressive and irreversible disorder if adequate interventions are not applied
Pathophysiology	Inflamm-aging and immune-senescence are prerequisite for its onset. Hypothesized pathophysiologic mechanisms include inflammation, oxidative stress, neuroendocrine dysfunction, and circadian dysregulation	Inflamm-aging, immune-senescence, and endocrine dysfunction represent the cornerstones for the frailty biology
Impact on cognitive domain	Delirium is a strong predictor of new-onset dementia and acceleration of existing cognitive decline	Frailty, even when considered as a mere physical condition, is capable of substantially affect cognitive function. A bidirectional relationship between frailty and cognitive impairment has been demonstrated
Impact on functional domain	Delirium may affect mobility, especially in patients with increased pre-delirium vulnerability. It can also affect long-term functional performances	After exposure to endogenous/exogenous stressors, frailty may negatively affect the capacity to recover and regain or maintain functional independence

frailty cannot be considered exclusively a pure disorder of function, though the criteria that are currently used for its definition may suggest. Indeed, there is empirical evidence that isolating physical from cognitive performance is really challenging in several cases. Some researchers have even proposed the terms of "cognitive frailty" and "reversible cognitive frailty" to describe heterogeneous cognitive conditions characterized by the simultaneous presence of both physical frailty and cognitive impairment (26). It is noteworthy that these concepts nest the idea of a reversible condition, the characteristic of dynamic mechanisms linking the physical and cognitive domains. The demonstration that cognitive impairment might reverse over time has been provided by a recent systematic review, showing that mild cognitive impairment (MCI) can return to normality with 8% reversion rate in clinical-based studies and 25% rate in population-based studies. The frequency of reversion from MCI to normality further increases to 26% when considering only studies of better quality (27).

Similar to what occurs for frailty, even delirium cannot be regarded only as an isolated mental disorder but there is evidence that it affects motor function as well. A study by Bellelli et al. compared four groups of 15 patients [with delirium alone, with dementia alone, with delirium superimposed on dementia (DSD), and with neither delirium nor dementia], finding that the mechanisms leading to the onset of delirium can also worsen motor performance (11). Other studies indirectly support such hypothesis, showing that delirium can complicate the functional recovery after adverse clinical events (13, 28). The reasons underlying this phenomenon are under study. It is possible that delirium causes motor fluctuations due to the disrupture of key central neurotransmitters (for example, related to attentive and executive functions) leading to an inability in planning and sustaining movement (11). According to Rockwood, it can also be hypothesized that the mobility impairment accompanying delirium is a reflection of the whole-system failure. Indeed, when complex systems collapse, their failure follows a cascade where highest order functions decline first. As such, the mobility impairment occurring in the course of delirium may represent a sign of a complex system close to failure. The more critical the individual's health status is before the delirium onset, the higher will then be the likelihood that delirium will lead to mobility impairment (29).

Under a broad viewpoint, frailty reflects the life-long accumulation of deficits, thus defining the more or less state of vulnerability of the individual. Such (more or less overt) accentuated susceptibility to stressors represents the biological background where delirium might find its onset. In an optimal scenario, frailty should be detected in order to take adequate preventive countermeasures for avoiding the onset of its negative outcomes (including delirium). Nevertheless, delirium might become the condition making clinically evident for the first time a previously unknown/overlooked substratum of frailty.

REVIEW OF STUDIES ON FRAILTY AND DELIRIUM IN HUMANS

To date, only few studies have specifically focused on the relationship between frailty and delirium in older people, and even less have assessed if frailty is a predictor of delirium. In a prospective observational study in 133 elective cardiac surgery patients, frailty was assessed using three different methods, i.e., a Modified Fried Criteria (MFC), the Short Physical Performance Battery (SPPB), and a 35-itemFrailty Index (FI).

The primary exposure variable was postoperative delirium, assessed using the Confusion Assessment Method (CAM) (30). A proportion of patients ranging from 35.3 to 66.2% were frail, according to the method used to define it, and 18% had postoperative delirium. After adjusting for covariates, the presence of frailty resulted in a threefold to eightfold increase in risk of postoperative delirium, independent of the severity of the cardiac disease. In another study (31), carried out in 89 patients who underwent trans-catheter aortic valve implantation (TAVI), frailty was assessed by clinical judgment and as a summary score from baseline components, including the score assigned for Mini–Mental State Examination; Basic Activities of Daily Living; Instrumental Activities of Daily Living; Mini Nutritional Assessment, and impaired mobility. Delirium was assessed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Again, frailty predicted delirium onset and conferred additional value in the prediction of mortality after TAVI but only when frailty was assessed by subjective clinical judgment. On the contrary, such association was not found when frailty was assessed using the summary score. A third small study of older non-cardiac surgical patients evaluated whether a preoperative frailty score was an independent predictor of postoperative delirium. One-third of patients were frail and 25% developed postoperative delirium. In the multivariable logistic regression, frailty score (odds ratio = 1.84; 95% confidence interval = 1.07–3.1; $P = 0.028$) was independently associated with the development of postoperative delirium. More recently, in a prospective cohort of older patients admitted to a specialized delirium unit, Chew et al. assessed frailty with a 20-item index derived using items from a comprehensive geriatric assessment and delirium using the CAM (32). The authors also measured the residual subsyndromal delirium (RSSD) before discharge from the unit by using the Delirium Rating Scale-Revised-98 severity score. The functional status was measured the modified Barthel Index on admission and 12 months post-delirium. In a logistic regression model, independent predictors of RSSD were as follows: frailty (OR 4.1, 95% CI 2.1–8.2, $P < 0.001$), the severity of delirium symptoms on admission (OR 1.2, 95% CI 1.1–1.2), and a pre-existing dementia (OR 4.2, 95% CI 2.0–8.6) (32). Interestingly, RSSD significantly mediated the effect of baseline frailty status on functional recovery at 12 months (32).

Other studies have assessed whether the coexistence of frailty and delirium is associated with an increased risk of death (33), or if delirium was associated with higher levels of frailty, in both studies finding that it was the case (34). However, other studies did not find a significant relationship between these two conditions (35–37).

Differences in the methods used to assess frailty and delirium as well as the selected populations and the length of follow-up can explain the heterogeneity in the study results. Taken together, the data from these studies suggest that further research is urgently needed to understand the complex relationship between frailty and delirium.

A further point is whether delirium may predispose itself to frailty. Indeed, several studies have demonstrated that delirium may be a risk factor for not only for dementia or a worsening of a preexisting dementia (14, 38), but also for subsequent functional impairment (12, 13, 39). Patients with persistent delirium are also less likely to regain activity of daily living function in comparison with non-delirious patients (40, 41). Moreover, when delirium is superimposed on dementia (which may represent itself a marker of pre-existing frailty), the risk to die in the middle short term is overall increased (42). It can be therefore hypothesized that the persistent or residual effects of delirium may delay or even hamper cognitive and functional recovery, ultimately resulting in new or increasing frailty and long-term disability and institutionalization (25). Future studies should better clarify this point.

COMMON BIOMARKERS AND PATHOPHYSIOLOGICAL MECHANISMS OF FRAILTY AND DELIRIUM

A premise is required before describing the pathophysiological mechanisms proposed for both frailty and delirium. With aging, a number of changes occur in several interrelated physiological systems, one of the most important being the immune system. The changes in the immune system that occurs with aging are termed "immunosenescence" and may be defined as an age-associated decline in immune function that includes increased susceptibility to infections, reduced vaccination responses, and increased risk of chronic inflammatory diseases. Immunosenescence occurs in parallel with inflamm-aging, i.e., the increased presence of a low-grade chronic systemic inflammatory state typical of older age (43, 44). Inflamm-aging is characterized by increased levels of proinflammatory cytokines [e.g., interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α), C-reactive protein (CRP)] and reduced concentrations of anti-inflammatory cytokines (e.g., IL-10, IL-1RA) (43). A variety of tissues (e.g., adipose tissue, muscle), organs (e.g., brain, liver), systems (e.g., immune system), and ecosystems (e.g., gut microbiota) of the body may contribute in a different manner to the onset and progression of inflamm-aging (45). Immunosenescence and inflamm-aging are particularly relevant for the pathophysiology of both delirium and frailty.

The exact pathophysiological mechanisms of delirium are not completely understood. A recent review by Maldonado suggests that at least five mechanisms are involved in delirium pathophysiology, including neuronal aging, neuroinflammation, oxidative stress, neuroendocrine dysregulation, and circadian dysregulation (46). In this review, we will focus exclusively on the three mechanisms which are thought to be more relevant for a common understanding of both delirium and frailty pathophysiology.

The neuroinflammatory hypothesis of delirium proposes that an acute peripheral inflammatory trigger (either infective, surgical, or traumatic) can provoke the activation of brain parenchymal cells, leading to an overexpression of proinflammatory cytokines and inflammatory mediators in the brain parenchyma, neuronal, and synaptic dysfunction and subsequent cognitive and behavioral symptoms of delirium (47). Importantly, brain is able to constantly monitor the presence of peripheral inflammation and how, upon exposure to specific stimuli, individuals may react to illness with a "sickness behavior," i.e., a constellation of non-specific physiologic and behavioral signs and symptoms, including

fever, malaise, fatigue, anorexia, lethargy, social withdrawal, and depressed mood (48, 49). According to the neuroinflammatory hypothesis, delirium may thus represent the CNS manifestation of a systemic disease, with an overproduction of cytokines that provoke a chain reaction in the neuronal cells of the brain (47). The immune signals and cytokines may enter the brain through two pathways (i.e., the neural pathway and the humoral pathway) where they determine the release of other proinflammatory cytokines by macrophage-like cells expressing toll-like receptors. In the neural pathway, the cytokines may activate primary afferent nerves, such as the vagus, and enter the brain through saturable transport system. In the humoral pathway, cytokines enter the brain at the level of the choroid plexus and the circumventricular organs. When enter the brain, cytokines may activate microglial cells. Microglial cells are the resident macrophages of the CNS and represent the 5–10% of all CNS cells. In the healthy brain, these are in a quiescent state, but, when they detect injured CNS cells or invading pathogens, they are able to adopt a specific phenotype with an amoeboid morphology. Phenotype modifications lead to further secretion of proinflammatory cytokines, and the expression of different cell surface receptors. With immunesenescence, microglial cells are characterized by an exaggerated proinflammatory response, acquiring a phenotype of primed less ramification, and reducing their chemotactic, phagocytic, and regulatory functions. A primed microglial phenotype is present also in chronic neurodegenerative processes where microglia cells lost their supportive role in neuroplasticity, thus favoring cognitive decline and synaptic dysfunction (50–53). Several studies, in patients of surgical and medical hospital wards, have shown that delirium is associated with significantly higher circulating levels of these inflammatory markers in comparison with non-delirium (54, 55). Importantly, cytokines can disrupt the neurotransmitter system balance, leading to reduced acetylcholine release (56) and decreased cholinesterase activity (57) and can activate the microglial cells, provoking an inflammatory response which can interfere with the connection and transmission functions of synapses (58, 59).

The oxidative stress hypothesis proposes that a number of physiologic and pathological events, such as tissue damage, hypoxia, illness, and infections, may lead to increased oxygen consumption, decreased oxygen availability, and reduced cerebral oxidative metabolism, which in turn may provoke cerebral dysfunction and associated cognitive and behavioral symptoms of delirium (47). Abnormal oxidative stress has been found in patients undergoing cardiopulmonary bypass surgery and in intensive care unit patients (60, 61). In one of these studies, Seaman has also shown that poor oxygenation is associated with cerebral dysfunction. Among a cohort of 101 patients, the authors assessed three measures of oxygenation (hemoglobin, hematocrit, pulse oximetry) and two measures of oxidative stress (sepsis, pneumonia), finding that indicators of oxidative dysfunction were more common in those who developed more frequently delirium, and this was not linked to illness severity (60). Pericytes may also be a potential target of interest in this framework. The pericytes are specific cells located at the abluminal side of the brain and muscular capillaries, which have the potential to express the inducible nitric oxide synthase (iNOS) and generate reactive oxygen and nitrogen species (RONS) (62). These studies suggest that pericytes, under specific circumstances such as an increased inflammatory status, may not only increase the production of iNOS and RONS but also by behaving as immune cells they are able to enhance the inflammatory response (63). Taken together, these data suggest that an increased oxidative stress at vascular level and in the brain parenchyma may predispose and underlie delirium development, with potential interaction between inflammation and oxidative stress.

The neuroendocrine hypothesis proposes that delirium reflects a reaction to acute stress. It is commonly accepted that stress can activate the hypothalamic–pituitary–adrenal axis: stressors activate the paraventricular nucleus of the hypothalamus resulting in the release of corticotrophin-releasing hormone, which acts on the pituitary gland, releasing adrenocorticotrophic hormone, which promotes glucorticoid release from the adrenal gland (47). Under normal circumstances, glucorticoids act to help the body in coping with the demands imposed by stress exposure, but there is evidence demonstrating that glucorticoids secreted during stress can have deleterious effects in the brain, inducing delirium and cognitive dysfunction (64, 65). Current evidence also suggests that the highly catabolic glucorticoids induce a general metabolic vulnerability in brain neurons and thus compromise their ability to survive various toxic insults (66), indirectly suggesting that the effect of increased glucorticoid secretion may be not always reversible.

The pathophysiology of frailty is complex too. With aging, the muscle undergoes several changes in its structure and composition, which are in part related to both immunosenescence and inflamm-aging. For example, proteomic studies in senescent mice have reported an increase of iron load and changes in redox homeostasis, associated with a severe loss of muscle function and loss of satellite cell recruitment (67). Importantly, these changes appear to occur in parallel with biochemical, morphological, and functional changes including a decrease of myelinated and unmyelinated fibers, ballooning, splitting, and enfolding of myelinated fibers (68) and decreased axonal neurofilaments (69). Other studies have confirmed that metabolic and structural changes are common between muscle and nerve, suggesting that both tissues may share a common signaling associated with muscle and nerve decline (67, 70). Furthermore, a release of metabolites, amino acids, and a dysregulation of myokine signaling seem to be related to "inflamm-aging" (44) with increased cytokine release.

The imbalance in the cytokine network may influence frailty either directly by promoting protein degradation or indirectly by affecting important metabolic pathways (71). A recent meta-analysis including 32 cross-sectional studies and 23,910 older subjects has shown that frailty and pre-frailty (i.e., a condition which is thought to be intermediate between the normal and the frailty status) are associated with significantly higher than normal serum inflammatory parameters, including CRP, IL-6, white blood cell, and fibrinogen levels (72). In other studies, frailty was associated also with lower serum levels of IL-12 and IL-23, two interleukins that are able to modulate the production of other interleukins (i.e., IL-17 and IL-22) in lymphocytes as well as the rapid recruitment of neutrophils in stressful conditions (73). Importantly, these changes in inflammatory patterns are

consistent in frail individuals across various geographical regions and are associated with a decreased muscle strength, resistance to physical exercise and walking distance as determined by the 6-min walking test (74).

Cytokines dysregulation is also related to the lack of response to some hormones and anabolic factors (75), which typically underlie frailty development (75). These hormones include the dehydroepiandrosterone sulfate (DHEA-S), testosterone, cortisol, and insulin-like growth factor-1 (IGF-1). The DHEA, in particular, plays an important role in the maintenance of muscle mass (76) and both increased cortisol serum levels and an increased cortisol: DHEA-S ratios in the serum are associated with a decline in individual's functional performance (77). Interestingly, the cortisol serum levels are elevated in frail individuals as compared with non-frail individuals, and are associated with both an increased muscle breakdown rate (78) and loss of bone density (79). The same role seems to be exerted by IGF-1 that is related to the maintenance of muscle mass structure and muscle strength by the way to inhibit apoptosis and to lower the oxidative stress in muscle (80).

In addition to the above-depicted mechanisms, it has recently been shown that body composition might play a dual role as source of inflammatory stimulus (through endocrine secretion of pro-inflammatory adipokines) (81) and target of the negative effects (i.e., induction of catabolic, apoptosis, autophagic muscular pathways) (82). This is of particular importance since sarcopenia (i.e., a loss of muscle mass and strength and/or reduced physical performance) is a key component of frailty, if not its central biological substrate (83). In this context, IL-6 was identified as being produced by immune cells as well as by muscle and adipose tissue, as also suggested by the fact that its expression acutely increases during muscle contraction. In addition, IL-6 induces insulin resistance which suppresses activity of various intrinsic and extrinsic modulators of muscle synthesis (84). Another pro-sarcopenic effect of inflammation is related to the generation of cortisol within tissues. Cortisol is profoundly catabolic and can be synthesized from inactive cortisone by the actions of the enzyme 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1). The activity of the (11β-HSD1) increases with age and is induced by cytokines, including TNF-α and IL-6. Interestingly, IL-6 has been indicated as a cytokine for gerontologists due to its contribution in the pathogenesis in multiple age-related conditions (83).

REVIEW OF STUDIES ON FRAILTY AND DELIRIUM IN ANIMALS

Preclinical animal models may be of particular importance for the study of both frailty and delirium, given the absence of neuropathological studies in humans on these two conditions (**Figure 1**).

Animal models for delirium are substantially based on the neuroinflammatory hypothesis of delirium. A recent review by Hoogland et al. discuss the studies with animal experiments related to the effects of systemic inflammation on the microglial and inflammatory response in the brain (85). The authors identified 51 studies of which the majority was performed in mice ($n = 30$) or in rats ($n = 19$). Despite heterogeneity in the outcomes measures and in the methods used to assess microglial activation, these studies clearly showed that peripheral inflammatory stimuli can cause microglial activation. The authors also observed distinct differences in microglial activation between systemic stimulation with (supranatural doses) LPS and live or heat-killed bacteria (85). Another systematic review included not

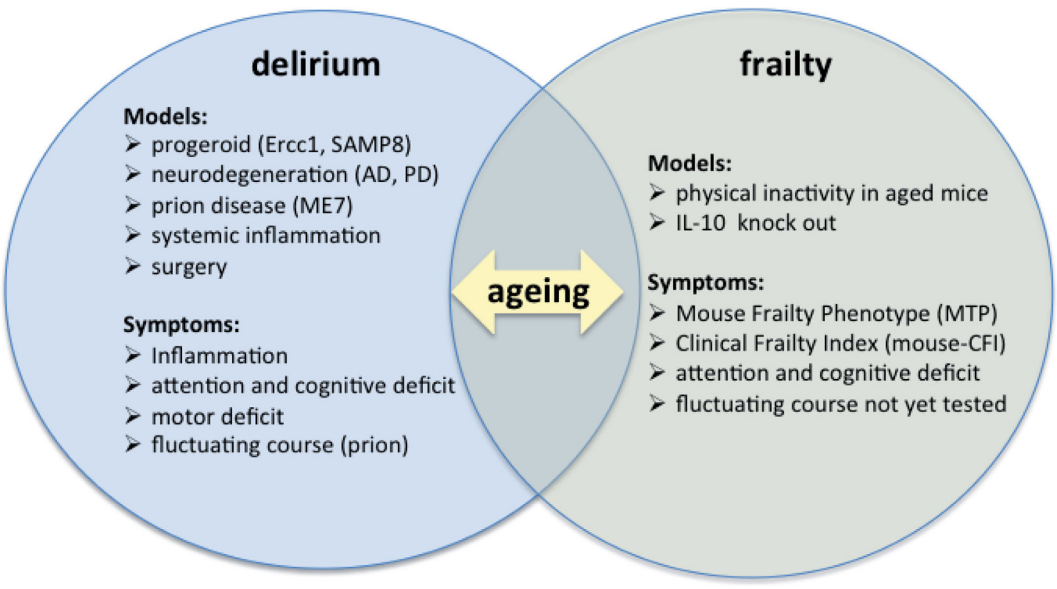

FIGURE 1 | Preclinical models of frailty and delirium. Current studies on preclinical models of delirium and frailty must be put in the context of aging, as shown by the intersection of the two diagrams.

only studies with inflammatory challenge but also studies based on the effect of surgery (86). The effect of acute administration of bacterial endotoxin was reported in 29 comparative studies on normal animals (24 LPS and 5 *Escherichia coli* bacterial), 3 studies on progeroid model (Ercc1 mutant mouse deficient in DNA repair and the SAMP8 mouse, characterized by overproduction of amyloid precursor protein and oxidative damage), and 14 studies on disease models related with delirium (ME7 prion disease mice, Tg2576, 3_Tg, and APPswe Tg Alzheimer's mice, Parkinson disease, basal forebrain cholinergic lesions) (87–89). Furthermore, the effects of different surgery procedures, such as clamping of the upper mesenteric artery, hepatectomy, laparotomy, splenectomy, and appendectomy, reported in 13 comparative studies were also included (10 in mice; 3 in rats) (90). It was found that, in a comparison of adult with young animals, acute peripheral challenges in old animals induce a highest inflammatory response. In particular, studies found that ageing was associated with (a) higher circulating (IL6, TNF-α, and IL10) and brain (IL1b, IL6, TNF-α) cytokines levels or transcripts, (b) increased activated microglia cells and astrocytes, and (c) sickness behavior and reduced cognitive skills with reduced performance at different tests including those evaluating to anxiety, attention or cognition, or activity (fear conditioning, water maze, novel object recognition, attentional set-shifting, social exploratory, general activity, or locomotor test). Considering the effect of surgery, the majority of studies reported an increase of brain proinflammatory cytokines (IL-1b, TNF-a, IL-6). Activation of microglia or astrocytes, increase of neuronal apoptosis, and loss of neuronal dendritic spine were also reported in some studies, confirming a tight link between primed microglial cells and neuronal plasticity (91). It should also be considered that neurodegeneration (or the presence of progeroid genetic defects) may anticipate the exaggerated inflammatory response that it is associated with a more rapid cognitive decline and disease progression. Administration of low doses of LPS (100 μg/kg) in ME7 animals, for example, induced transient working memory deficits with increased and prolonged transcription of inflammatory mediators in the brain. Results of these studies indicate that preexisting synaptic loss and microglial priming are predisposing factors for acute cognitive impairments provoked by systemic inflammation. In the same animal model, the peripheral administration of a single proinflammatory cytokine, like TNF-α in pre-symptomatic phase, is able to produce an exaggerated sickness behavior response but not neuronal death, synaptic loss, or hyperphosphorylation of tau. In a recent study, a fluctuating course of cognitive dysfunction was also reported in ME7 mice injected with 0.1 mg/kg LPS. LPS precipitated severe and fluctuating cognitive deficits in 16-week ME7 with a lower incidence or no deficits in 12-week ME7 and controls, respectively. Fluctuating impairments were associated with progressive thalamic synaptic loss and axonal pathology (14, 92).

Another relevant finding for delirium was obtained in a mouse model of lesioned basal forebrain cholinergic system, based on the administration of ribosomal toxin saporin linked to the p75 neurotrophin receptor. In this model, cognitive deficits induced by systemic LPS are restored by donepezil. However, in this model no signs of increased brain inflammation were detected, suggesting that factor other than primed microglial cells may be involved in the development of cognitive dysfunction and that neuronal vulnerability may represent predisposing factor to peripheral inflammation associated cognitive impairment (87).

Various tools for the assessment of frailty have been developed in mice, based on the assessment tools used in humans (93). Parks et al. proposed a preclinical frailty Index scale based on the assessment of deficits in activity skills, body composition, metabolic status, and vascular system (94). Whitehead and colleagues developed a mouse Clinical Frailty Index (mouse-CFI) assessment tool based on a 31 different impairments and deficits (95) and Liu et al. developed the Mouse Frailty Phenotype (MTP) scale, including grip strength, speed in walking, physical activity, and endurance (96). These tools have demonstrated to be consistent in frailty assessment in that (a) their scores increase in severity with aging in both male and female; (b) the increase in score severity which is observed with aging is similar to that observed in humans; and (c) the age-associated changes in myocytes are more prominent in animals with elevated frailty scores than in others. In a recent study (97), the mouse-MTP scale and the mouse-CFI were compared in a group of mice aged 23–24 months. Using the first tool, none of the mice was classified as frail. On the contrary, the second tool classified 16.6% of mice as frail. As indicated by the authors, similar difference in estimating the true incidence of frailty can be found when the frailty phenotype model and the frailty index tools are compared in humans: indeed, 6–16% of older adults (70–85 years old) are defined as frail with the phenotype-model tool and 22–32% with the FI (65 years and older) (98, 99). Despite the different sensitivity between the tools, however, both are able to detect frailty at preclinical level (93). Based on the known association between physical activity and frailty, Gomez-Cabrera et al. proposed physical inactivity as a mouse model of frailty (100). They adapted to animals the frailty phenotype developed for human and defined a score (the Valentia score for frailty evaluation) to be used in mice. Scores were calculated on the basis of five different components, such as weight loss (change in body weight), weakness (grip strength), poor endurance and slowness (incremental treadmill test), and low activity level (motor coordination), and were expressed with frailty scores similar to these defined for human being. Sedentary and wheel runner animals were compared in longitudinal study until the age of 28 months. Results of the study indicate that sedentary animals become frail as they get older whereas lifelong spontaneous exercise signicantly retards the onset of frailty.

Another animal model for frailty is the IL-10 (tm/tm) mouse developed by Walston (101). The lack of the anti-inflammatory cytokine interleukin-10 (IL-10) makes this animal more susceptible to the activation of inflammatory pathway activation. With aging, this mouse shows higher than normal levels of circulating IL-6, reduced muscular strength, impaired skeletal muscle ATP kinetics and cardio-vascular functions, and increased expression of gene associated with the regulation mitochondrial function and apoptosis (102).

CONCLUSION AND FUTURE DIRECTIONS

There is initial evidence that frailty and delirium might share common pathophysiological links and are strictly interrelated

from a clinical perspective. Altered inflammatory status is clearly involved in the pathophysiology of both frailty and delirium. Muscle and adipocytes may be a source of inflammatory stimulus (through endocrine secretion of pro-inflammatory adipokines) and also a target of the negative effects (i.e., induction of catabolic, apoptosis, autophagic muscular pathways) (81, 82). The inflammatory markers produced at the muscle and adipocytes level, on one side, may enter the brain through neural and/or humoral pathways, priming microglia and other neuronal cells of the brain that react with overexpression of cytokines. The primed microglia are able, under these conditions, to promote neuronal dysfunction leading to cognitive and behavioral symptoms of delirium (85).

Another pathophysiological link may be at vascular level. Pericytes are spatially isolated contractile cells on capillaries and venules throughout the body, which are designated to control cerebral blood flow physiologically, and to limit blood flow after ischemia. In skeletal muscle, pericytes are located at the interstitium, where they can express typical markers associated with capillaries. Pericytes have also adipogenic and myogenic properties, contributing to muscle fat generation and lipotoxicity. It could be hypothesized that an exaggerated activation of these cells leads to increased inflammatory response and nitrosative stress in the muscle, thus contributing to sarcopenia, a key feature of frailty. At the brain level, pericytes may contribute to enhance the inflammatory response under specific circumstances, which may represent both a predisposing and a precipitating factor for delirium occurrence in frail subjects. Pericyte alterations may also be responsible for increased permeability of the blood brain barrier microvascular endothelium, which in turn may lead to an overexpression of inflammatory markers in the brain and overactivation of microglial cells (103). Indeed, it has been demonstrated an upregulation of proteins in the cerebrospinal fluid of delirious patients within clusters related to inflammation, protease inhibitors, chromogranins/secretogranins and apolipoproteins, triggered by infections, metabolic problems and adverse drug reactions (104). Increased oxidative stress and neuroendocrine abnormalities may also occur at both levels (i.e., at the body and brain levels), igniting a chain of reactions that include overexpression of cytokines and other inflammatory markers.

The review also suggests that the complex relationship between frailty and delirium should be thought as a dynamic and continuous cross-talk between the body and the brain. Future studies should therefore try to identify biomarkers specific for body cells and brain in frail individuals with delirium. An excellent example of the cross-talk between muscle and brain should be represented by the Brain-derived neurotrophic factor (BDNF). BDNF is strongly expressed in the brain (105), where it regulates neuronal development, synaptic plasticity, and influence memory (106) but it is also expressed in skeletal muscle, where it contributes to fat oxidation and modulates myogenesis inducing satellite cell activation and skeletal muscle regeneration (107, 108).

From a clinical perspective, frailty may be considered a risk factor for delirium, although full evidence is still lacking, and delirious individuals may be regarded by default as frail individuals. Moreover, delirium may be viewed, in some cases (e.g., when it persists for long time) as a precipitating factor for worsening frailty. Specific attention will therefore be paid by clinicians both on frailty assessment, since it may allow to anticipate delirium occurrence and to the systematic screening of delirium since it may help identifying individuals at risk of subsequent worsen of frailty.

With regard to animal models, future research is needed to identify a panel of biomarkers that should be relevant both in humans with delirium and in mouse models of frailty, specifically challenged with triggers causing delirium, in order to explore new pathophysiological pathways.

AUTHOR CONTRIBUTIONS

All authors drafted and reviewed the manuscript.

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Spontaneous Reversion of Clinical Conditions Measuring the Risk Profile of the Individual: From Frailty to Mild Cognitive Impairment

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The number of people living with disabilities worldwide is rapidly growing due to a longer life expectancy and the subsequent increasing burden of chronic diseases. The need of developing and implementing effective strategies aimed at delaying or preventing disability has been repeatedly underlined and is currently the main focus of several health-care policies. In this scenario, a special attention is addressed to the identification of specific clinical conditions measuring the risk profile of the individual of developing an overt disability and other negative outcomes. These risk profiles can indeed become promising targets for developing and implementing preventive interventions. When the disabling cascade is fully established, in fact, the reversing/attenuating the process becomes more challenging. However, the exact nature of these relatively new constructs is not yet sufficiently clear, and several related issues remain poorly explored. In particular, these entities tend to be considered as unequivocally prodromal stages of a future disease, neglecting and underestimating their fluctuations/transitions over time and their potential to clinically improve/revert. This unbalanced judgment did probably contribute to an ambiguous and biased use of these conditions. Considering them as an early stage of an unavoidable future disease, in fact, determined a tendency to start a targeted intervention as if in presence of the disease itself, with the subsequent risk of over-diagnosis and over-treatment. In the present article, we discuss the dynamics underlying the reversion from a clinical at-risk condition to normality and its implications, specifically focusing on the examples of frailty and mild cognitive impairment.

Keywords: disability, frailty, mild cognitive impairment, reversion, trajectories, prevention, public health

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INTRODUCTION

Populations are rapidly aging worldwide as result of a longer life expectancy (1). Such progressive increase in longevity is the sign of major scientific and societal accomplishments (2). However, the longer life expectancy is associated with an increased prevalence of chronic diseases and disabling conditions (3). The number of people living with some form of disability is, in fact, globally growing (4). In this scenario, the identification and implementation of effective strategies aimed at delaying or preventing disability is the main focus of many health-care policies (1, 5).

The early identification and targeting of specific clinical profiles that could potentially serve as targets for preventive actions against disabilities and other negative outcomes has, reasonably and not surprisingly, focused the interest of both research and public health. In fact, once any disabling condition is fully established, the possibilities of functional improvement result drastically reduced.

Several clinical conditions measuring the risk profile of the individual have recently been proposed in different fields of research. Some of these are also gradually acquiring some relevance in the clinical setting (6–9). However, a number of aspects related to these constructs still do not focus enough attention, thus risking to remain poorly explored, to cause misunderstandings, and to be the target of disputable interventions. In particular, these entities are frequently considered as prodromal stages, within a unidirectional pathway toward subsequent disabilities. This approach mistakenly overlooks the possible fluctuations/transitions of the risk profile over time, and do not adequately consider the potential for spontaneous clinical improvement/remission. Such "inverse" trajectories, though commonly observed in routine clinical practice, are often underestimated, thus leading to unbalanced and biased consideration of these conditions.

In the present review, we present and discuss available evidence on the spontaneous reversion to normality from two of the most frequently studied and adopted at-risk conditions, namely frailty and mild cognitive impairment (MCI). Although they have been differently conceived and refer to different functions/domains of the individual, both these constructs have been developed in order to capture and measure the risk of developing poor health-related outcomes. This parallelism allows to address some of the issues potentially arising from such "anticipatory" approach to disabling conditions (i.e., disability and dementia in these cases).

Reversion of MCI

Mild cognitive impairment is defined as an objective impairment of cognitive abilities that does not affect the subject's functional independence (9). It is often considered as an intermediate stage in the progression from normal cognitive functioning to dementia (10). To date, the scientific and clinical interest on this construct has mostly been due to its being a condition increasing the risk of developing overt dementia. Subjects with MCI, in fact, show an annual rate of progression to dementia ranging from 5 to 15%, depending on the setting and the considered operational definitions (11). Within this framework, MCI may be considered as a promising clinical condition to identify early signs of a possible progression to dementia and thus design *ad hoc* preventive interventions.

However, MCI does not necessarily convert to dementia, but can potentially follow other trajectories over time (12) (**Figure 1**). The majority of subjects with MCI does not experience a worsening of cognition over time, but tends to remain clinically stable. Population-based studies have actually shown that "stability" might be the most common pattern after a diagnosis of MCI, occurring in 37–67% of the overall cases (12). The limited length of follow-up adopted by available studies on the topic, however, does not allow to draw conclusions on the actual length of this plateau. Anyway, an adequate description of MCI should not omit considering the absence of a conversion to cognitive decline. Moreover, an increasing number of longitudinal data show that a relevant proportion of subjects with MCI may even revert to normal cognition. Two systematic reviews and meta-analyses have recently been carried out to estimate the rate of "reversion" from MCI to normality (13, 14). A first review considered 25 longitudinal studies (published from 1999–2015) enrolling subjects with MCI with a follow-up equal or longer than 2 years (13). An overall 18% (95%CI 14–22%) reversion rate from MCI to normal cognition was observed. In particular, estimates significantly varied according to study setting, with an 8% (95%CI 4–11%) reversion rate in clinical-based studies, and a 25% (95%CI 19–30%) rate in population-based ones. When considering only studies meeting higher quality standards (reported in **Table 1**), the frequency of reversion further increased to 26%. Consistently,

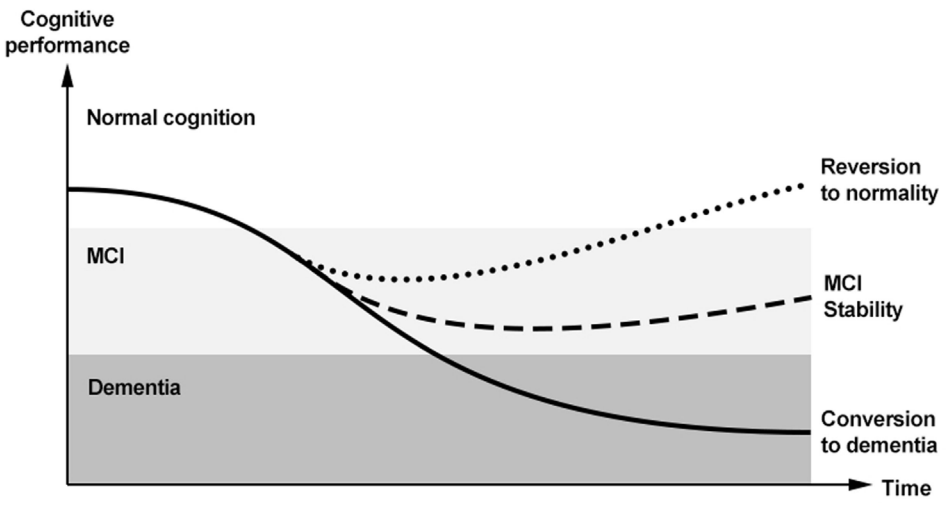

FIGURE 1 | Trajectories of cognitive functioning and potential outcomes of mild cognitive impairment (MCI) in the so-called "dementia continuum."

TABLE 1 | Characteristics of available observational studies meeting high quality standards addressing the spontaneous reversion of mild cognitive impairment (MCI).

Reference	Setting	*n*	Sex (%F)	Mean age	Follow-up (years)	MCI definition	Reversion (%)
Grande et al. (15)	C	374	60.2	75.1 ± 6.9	2.7 ± 2.1	IWG	5.6
Roberts et al. (16)	P	534	44.6	na	5.1	IWG	37.6
Sachdev et al. (17)	P	320	51.1	11.5 ± 0.8[a]	1.9 ± 0.1	IWG	20.6
Manly et al. (18)	P	564	68.0	76.5 ± 1.3[a]	5	Mayo Clinic	30.1
Pérès et al. (19)	P	285	57.2	na	2	Mayo Clinic	21.4
Larrieu et al. (20)	P	58	na	na	2	Mayo Clinic	41.4

Modified from Ref. (13).

C, clinical-based study; P, population-based study; na, not available; IWG, International Working Group criteria for MCI; Mayo, Mayo Clinic criteria for MCI.

[a]*Weighted mean values.*

In the present table, we report the six studies of "better quality," defined using the Quality in Prognostic Studies tool (21), included in a previous meta-analysis on the topic (13).

high rates of reversion (31% in the community setting and 14% in the clinical setting) were also documented by a second systematic review, which did not apply restrictions based on the length of follow-up, and only included studies adopting the Mayo Clinic criteria to define amnestic MCI (14).

Despite such high rates of reversion, research on the identification of potential factors associated with a favorable trajectory of MCI is still lacking. Evidence from the few available studies indicates that genetic traits (i.e., absence of APOE ε4 alleles), sociodemographic factors (i.e., younger age and higher educational level), clinical features (i.e., greater degree of non-neurological comorbidities), functional independence (i.e., better scores on functional tests), the subtype of MCI (i.e., single-domain non-amnesic), the global cognitive performance (i.e., higher scores at the cognitive tests), and neuroimaging findings (i.e., larger hippocampal volumes) may positively influence the probability of reversion (12, 15, 17, 22).

Another aspect in this field that has not yet been adequately explored is the cognitive stability of subjects reverting from MCI to a normal cognitive function. In the Pittsburgh Cardiovascular Health Study-Cognition Study, a relevant heterogeneity was observed in the clinical course of "reverters." Some of the participants remained stable within the normal cognition range, but other reconverted to MCI or even progressed to dementia (23). Consistently, another study found that subjects with MCI who reverted to normal cognition were still at an increased risk of developing dementia later in time when compared to cognitively normal subjects (16).

An additional point that needs to be further investigated is whether the adoption of biomarkers reflecting *in vivo* the occurrence of neuropathological modifications may improve the differentiation of the heterogeneous MCI trajectories. Some specific biomarkers might possibly support a better discrimination of MCI cases and help identifying those with a higher probability of progressing to dementia or reverting to normal cognition. Research, however, has been primarily focused on identifying biomarkers associated with a negative outcome (i.e., progression to dementia), largely ignoring those potentially predicting a reversion to normality. It is very likely that these latter cannot be exhaustively found in pathophysiological mechanisms responsible for the onset of the disease, but they may worth the opening of a novel axe of research. In fact, there are reports of clinical reversion to normality among subjects with MCI clearly exhibiting the traditional neuropathological abnormalities (i.e., amyloid deposition) suggestive of an underlying neurodegeneration (24).

Reversion of Frailty

Frailty is defined as "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death" (5). It is also considered as a marker of biological aging and increasingly indicated as a condition of public health interest (25).

To date, frailty has frequently been approached as a pre-disability state (26) and as a condition increasing the risk of adverse health-related outcomes (e.g., falls, functional loss, hospitalization, institutionalization, death) in the elderly (6). Similarly to MCI, much of the interest toward this construct has been due to its ability to predict subsequent negative events. Several studies, however, have proven the dynamic nature of frailty, with frail individuals either worsening or improving over time and showing multiple and bidirectional health "transitions" (6). Again, the potential of frailty for spontaneous clinical remission has, to date, been rarely investigated.

The group of observational studies that have, so far, addressed the spontaneous reversion of frailty are described in **Table 2** (27–33). Only articles published on PubMed, from inception to July 2017, or retrieved from the bibliographies of pertaining studies were considered for the present purposes. Available evidence mostly comes from population-based studies enrolling representative samples of community-dwelling older people, with sample sizes ranging from 122 (29) to 15,776 (31) participants, and time spans of observation varying from 1 (29) to 6.4 years (32). One study specifically investigated the transitions of frailty among subjects with cognitive disorders (29). All the studies defined frailty using modified versions of the phenotype proposed by Fried and colleagues (34), which differentiates the specific conditions of robustness, pre-frailty, and frailty. Relevant rates of spontaneous reversion were observed across the available studies, with 13.8 (33) to 44.6% (30) of frail participants reverting to pre-frailty or robustness. One study estimated the possibility of reversion over time using data from three follow-up visits (33). It documented a time-dependent reduction in the probability of favorable transitions. In the overwhelming majority of cases, the most common positive trajectory was toward a pre-frail status rather than to robustness.

TABLE 2 | Characteristics of available observational studies addressing the spontaneous reversion of frailty.

Reference	Setting	*n*	Sex (%F)	Mean age	Follow-up (years)	Frailty prevalence (%)	Frailty definition	Reversion (%)
Trevisan et al. (27)	P	3,099	59.7	74.4 ± 7.3	4.4	7.6	mFP	28.2
Jamsen et al. (28)	P	1,705	0.0	76 (median)	2	Na	mFP	Overall transitions to prefailty/ robustness: 17.4
		1,366	0.0	78 (median)	2–5	Na		
Chong et al. (29)	C	122	59.4	75.4 ± 7.2	1.0	41.0	mFP	32.0
Lee et al. (30)	P	3,427	43.7	74.0 ± 1.6[a]	2.0	7.9	mFP	44.6
Borrat-Besson et al. (31)	P	15,776	na	na	4.0	6.1	mFP	38.9
Espinoza et al. (32)	P	597	55.1	69.6 ± 3.4	6.4	9.3	mFP	28.8
Gill et al. (33)	P	754	64.6	78.4 ± 5.3	1.5	25.7	mFP	23.0
		679	65.1	79.7 ± 5.2	1.5–3	31.8		17.9
		626	66.3	81.0 ± 5.1	3–4.5	36.7		13.8

C, clinical-based study; P, population-based study; mFP, modified Frailty Phenotype; na, not available.
[a]*Weighted mean values.*

Research on the factors associated to or predicting a spontaneous reversion from frailty are still inconclusive. Results from available studies on possible sex differences are conflicting. Some studies, in fact, reported higher reversion rates among women (27, 30), other studies failed to show any significant association between gender and reversion rates, and one study reported that men were more likely to improve (31). Other determinants that were studied as possible predictors of reversion from frailty are younger age (only in women), higher educational levels, living alone, low-to-moderate alcohol consumption, being overweight, and practicing regular physical activity (27, 30, 31). One study found no association between the overall number of medications and burden of anticholinergic drugs, and the progression/regression from frailty over time (28). As for MCI, no consistent data are available describing the long-term trajectories of frail subjects having experienced a spontaneous clinical improvement.

DISCUSSION

Considering available evidence, reversion should be seen as a quite common outcome of clinical conditions measuring the risk profile of the individual such as MCI and frailty. Knowing that these at-risk profiles have the potential to spontaneously regress, a more balanced and cautious attitude should be adopted when approaching these entities both in clinical and in research settings.

Widening the knowledge on the phenomenon of reversion, within the preventive management of disabling conditions, may have important practical implications. The possibility of identifying those subjects that are more likely to show a positive outcome, in fact, may allow to better allocate health-care resources in the heterogeneous population of aging individuals (35). Moreover, it may prevent possible negative consequences arising from the (mis)diagnosis of a potentially disabling conditions (e.g., discrimination, stigmatization, over-medicalization) (13). Finally, it may improve the design of clinical trials and the interpretation of their results. For example, excluding subjects whose cognitive function or frailty levels are unlikely to decline over time may increase the effect size of potentially effective interventions. As of today, this point seems of crucial interest, considering that nearly 180 RCTs are currently recruiting subjects with frailty and/or MCI worldwide (source: www.clinicaltrials.gov; search updated in August 2017).

Several hypotheses may be proposed to explain the observed remission of the considered at-risk conditions (13). First, it may simply be due to the wrong classification of subjects participating in the studies, with either normal individuals misdiagnosed as frail/MCI at enrollment, or with frail/MCI subjects misclassified as normal at the end of the observation period. According to this hypothesis, the spontaneous remission of the considered conditions might be explained by the weakness of the adopted definitions and diagnostic tools adopted. At the same time, the intrinsic tendency of these entities—that define a risk and not a nosological condition—to fluctuate over time and exhibit unstable courses cannot be ignored. This aspect is strongly related to the multiple factors (e.g., nutritional deficits, affective disorders, cerebrovascular events, sleep disorders, social issues) that can be at the basis of their clinical manifestations. Thus, among the large number of individuals at risk (due to frailty or MCI), there will undoubtedly be a subgroup with the features leading to unavoidable further decline, but there will also be a group, labeled as having a "positive" risk profile, who will not necessarily follow a negative trajectory, and is simply categorized as at risk due to a temporary/reversible condition and/or to a mistake in the evaluation process. The correct definition of these aspects is extremely relevant in terms of public health. The current trend is to extend the boundaries of clinical interventions to at-risk conditions, without adequately considering the possibility of spontaneous reversion, and this is unsustainable in terms of a health economics, because it exponentially increases the number of "individuals to treat."

Overall, these considerations underline the limits arising from attempting to approach age-related disabling conditions using the traditional medical approach based on a stand-alone disease model. The prevention of clinical conditions cannot meet the same standards and follow the methodologies applied in the treatment of diseases. Defining new conditions to treat does not mean carrying out effective preventive actions. The prevention of age-related conditions requires the adoption of a more naturalistic approach to older subjects, thus should be

focused on identifying the trajectories of their functions rather than on a punctual assessment of (arbitrary and categorical) entities. The complexity of health conditions in older age and of age-related disorders might be better approached by adopting measures reflecting the trajectories of personal capacities and abilities, and identifying the interaction between the intrinsic characteristics of each subject and his/her environment (1). This model may better support the personalization of care and the implementation of person-tailored interventions. Special attention should also be devoted to those events or variables that may constitute "switching factors" along the individual's trajectories, thus positively or negatively modifying the direction of functional and clinical changes over time.

In conclusion, considering their unstable and potentially bidirectional course, MCI, frailty and other similar risk profiles associated with disabling conditions should not be framed into nosological conditions nor considered as prodromal phases of an unavoidable subsequent disease. They should be more adequately approached as the heterogeneous at-risk conditions they were originally designed to be. Such more balanced perspective will allow to reduce the risk of over-diagnosis and over-treatment, and to improve the clinical and research standards in this field. Moreover, the progressive adoption of longitudinal constructs that are more precise at reflecting the complex functioning of aging people and at overcoming the weaknesses of traditional categorical frameworks should be promoted.

AUTHOR CONTRIBUTIONS

MCa and MCe designed the study and wrote the manuscript. FR, CV, and EL participated in the review of the literature. GB and NV contributed to the discussion of the available evidence on the topic. All the authors were involved in drafting the manuscript.

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Worry About Caregiving Performance: A Confirmatory Factor Analysis

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Recent studies on the Zarit Burden Interview (ZBI) support the existence of a unique factor, worry about caregiving performance (WaP), beyond role and personal strain. Our current study aims to confirm the existence of WaP within the multidimensionality of ZBI and to determine if predictors of WaP differ from the role and personal strain. We performed confirmatory factor analysis (CFA) on 466 caregiver-patient dyads to compare between one-factor (total score), two-factor (role/personal strain), three-factor (role/personal strain and WaP), and four-factor models (role strain split into two factors). We conducted linear regression analyses to explore the relationships between different ZBI factors with socio-demographic and disease characteristics, and investigated the stage-dependent differences between WaP with role and personal strain by dyadic relationship. The four-factor structure that incorporated WaP and split role strain into two factors yielded the best fit. Linear regression analyses reveal that different variables significantly predict WaP (adult child caregiver and Neuropsychiatric Inventory Questionnaire (NPI-Q) severity) from role/personal strain (adult child caregiver, instrumental activities of daily living, and NPI-Q distress). Unlike other factors, WaP was significantly endorsed in early cognitive impairment. Among spouses, WaP remained low across Clinical Dementia Rating (CDR) stages until a sharp rise in CDR 3; adult child and sibling caregivers experience a gradual rise throughout the stages. Our results affirm the existence of WaP as a unique factor. Future research should explore the potential of WaP as a possible intervention target to improve self-efficacy in the milder stages of burden.

Keywords: Zarit Burden Interview, caregivers, dementia, dimensions, factor analysis

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INTRODUCTION

Dementia is a disease that is frequently associated with significant caregiving burden. One of the most widely used instruments to quantify caregiving burden is the Zarit Burden Interview (ZBI) (1). The ZBI has been validated in different populations and has been shown to be invariant across different educational levels and gender (2). The degree of caregiving burden has traditionally been assessed using pre-defined cutoffs on the ZBI total score, essentially constituting a unidimensional approach (3, 4). Subsequent studies have since pointed toward caregiving burden as a multidimensional

construct. The seminal study by Whitlatch and colleagues was the first to outline the dual-factor structure of role and personal strain as distinct constructs measured by the ZBI (5). Role strain refers to how the caregiving role is in conflict with other roles that the caregiver has to manage while personal strain refers to how the caregiving experience is personally stressful. Subsequent studies have built upon the general structure of role and personal strain and partially replicated the factor structure (6–10). This partial replication across diverse populations with cultural and societal differences (11) raises the possibility of a latent dimension beyond the general structure of role and personal strain.

Of note, a factor has consistently emerged in recent studies, known variously as: "self-criticism" (9, 10, 12), "guilt"(13–15), "feelings of inadequacy" (16, 17), and "worry about performance" (7, 8). This factor highlights a distinct dimension of burden describing caregiver concerns about doing more (item 20) and doing a better job (item 21), either in isolation or in combination with other items (3). It represents a conceptual continuum of a negative aspect of caregiving arising from self-appraisal of caregiving performance (18), ranging from milder degrees of "inadequacy" and "worry" to "self-criticism" and "guilt" on the severe end. The low correlation with other factors and total ZBI score, consistency of items 20 and 21 co-occurring in same factor, and its conceptual consistency across the continuum of self-appraisal of caregiving performance corroborate the existence of this unique construct within the ZBI.

This provided the basis for our earlier proposal that there are three key dimensions that underpin ZBI-defined burden, namely role strain, personal strain, and the unique factor comprising items 20 and 21, which we termed worry about caregiving performance (WaP) (3). Using exploratory factor analysis in a multiethnic Chinese predominant Asian context, we demonstrated the presence of the unique factor WaP above and beyond role and personal strain (8). In addition, our factor solutions outlined two possible components of "role strain" comprising "role strain (demands)" and "role strain (control)." These findings are consistent with the broader literature that reports the multidimensionality of ZBI beyond the dual-factor structure, which was originally proposed by Whitlatch and colleagues (5). The number of ZBI factors reported in these studies ranged from three to five, suggesting that additional factors beyond the three core components may represent variants of either role or personal strain. In support of this, a recent study in an Asian Chinese population similarly reported an optimal four-factor structure comprising two factors of role strain (captivity and loss of control), and one factor each of personal strain and self-criticism (items 20 and 21) (9).

The relationship between WaP with various socio-demographic and diseases characteristics is hitherto not well understood. Unlike role strain and personal strain, stressors of functional impairment and neuropsychiatric symptoms do not predict WaP (3, 8, 13). Previous studies reported younger age of caregiver as a major predictor of WaP and a significant elevation of scores in the mild stage (3, 8, 13). This suggests that the inverse relationship of age with WaP is indicative of higher levels of WaP burden among adult children relative to spousal and other caregivers (19). The influence of relationship with care recipient on the variation of WaP across the severity spectrum of cognitive impairment remains to be elucidated (8). Earlier studies also focused on the impact of severity of neuropsychiatric symptoms rather than the resultant distress from these symptoms (3, 13).

This provided the impetus for our current follow-up study in a separate cohort of predominantly Chinese multiethnic Asian population attending a memory clinic. Our primary objective was to determine if WaP is a unique factor that exists within the ZBI, and whether splitting role strain into two factors contributes to a better model fit as opposed to keeping it intact as one factor. The secondary objective was to explore the relationships of the various factors of ZBI in relation to socio-demographic variables and disease characteristics, and how relationship with care recipient (adult children, spouse and sibling) can influence the factor scores across the severity spectrum of cognitive impairment.

MATERIALS AND METHODS

Study Design and Participants

This is a cross-sectional study of 466 caregiver-patient dyads of community-dwelling older adults with cognitive complaints presenting for the first time to the Memory Clinic, Tan Tock Seng Hospital, Singapore, from January 2010 to December 2011. The study was approved by the institutional review board of the National Healthcare Group.

We included caregiver-patient dyads who fulfilled the following criteria: (1) patients who were aged 55 years and above with a Clinical Dementia Rating (CDR) (20) global score of >0 and a diagnosis of mild cognitive impairment (MCI) or dementia; (2) community-dwelling patients who were not residing in an assisted living facility or nursing home; (3) primary caregiver of the patient, defined as the family member above 21 years of age who was most involved in the provision of day-to-day care and who was familiar with the patient's medical and social condition. We excluded the following categories of caregivers: (1) non-family members (e.g., domestic helper, friend); (2) inability to converse fluently in English or Mandarin; (3) refusal to fill out the ZBI. Among 784 caregiver-patient dyads presenting for the first time to the memory clinic over the 2-year period, 466 caregiver-patient dyads were recruited based on the inclusion and exclusion criteria.

Assessment

Details of the evaluative approach at the memory clinic have been previously described (21). All MCI and dementia subjects in this study underwent detailed semi-structured clinical evaluation, as well as relevant laboratory investigations and neuroimaging to exclude potentially reversible causes of cognitive impairment. Standardized neuropsychological assessment was performed on all MCI subjects. A consensus meeting was conducted to determine the diagnosis, etiology, and staging of cognitive impairment based on inputs from the multi-disciplinary team comprising physicians, nurse clinicians, and psychologists.

The severity of cognitive impairment was staged using the CDR (20). A CDR of 0 indicates no cognitive impairment; 0.5 indicates either MCI or very mild dementia; and 1, 2, and 3 indicate mild, moderate, and severe dementia, respectively. Convergent validity

of the CDR to discriminate milder stages of dementia has been demonstrated locally (22). Our operational definition of the MCI subgroup in accordance with the International Working Group criteria has been previously described (21). Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (23). The dementia etiologic subgroups of Alzheimer's disease (AD), vascular dementia (VD) and mixed dementia were made using standardized criteria such as National Institute of Neurological and Communicative Disorders & Stroke—Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (24) and National Institute of Neurological Disorders and Stroke—Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) (25).

Measurements and Instruments

We collected socio-demographic characteristics of the patients and caregivers such as age, gender, ethnicity, level of education, family relationship (spouse, adult children, sibling, or others), and living situation (with or apart from patient). Cognition was assessed using the Chinese Mini Mental Status Examination (CMMSE), which has been validated locally (26). This version has modifications made to the original instrument to ensure its relevance locally. This modified instrument has a total score of 28 with lower scores indicating lower cognitive abilities.

Functional assessment consisted of the Modified Barthel Index (MBI) (27) and the Lawton scale (28). The MBI measures the degree of independence in 10 self-care tasks. It is scored 0 to 100 with a higher score indicating greater independence in basic activities of daily living (BADL). The Lawton scale measures the degree of independence in more complex instrumental activities of daily living (IADL) such as housekeeping, shopping, handling finances, and meal preparation. Patients were scored 0 to 23 with higher scores indicating greater independence.

Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q) (29). The two components of the NPI-Q, severity and distress, were scored 0 to 3 and 0 to 5, respectively. Severity is an indication of seriousness and distress is an indication of the stress experienced by the caregiver for a symptom or area of concern. Both the severity and distress scores were used as they reflect different perspectives in relation to caregiving burden from the patient and caregiver, respectively.

Caregiver burden was measured using the Zarit Caregiver Burden (ZBI), which is a self-administered 22-item instrument for caregivers (1). The questions are scored on a 5-point Likert scale ranging from 0 to 4 corresponding to "never," "rarely," "sometimes," "quite frequently," and "nearly always." Individual items are summated to yield a maximum possible score of 88, with higher scores indicating greater burden. For caregivers who were unable to comprehend the English version, a validated Chinese version was used instead (30). The validation of the Chinese version included back-translation procedures which ensured that both versions are being interpreted similarly. This mitigates concerns of the threats to internal validity in the use of both languages.

Statistical Analysis

We made comparisons of model fits between five different factor models of ZBI derived from literature and previous work, such as (1) unidimensional model (all items); (2) two-factor model comprising role strain (items 1, 4, 5, 8, 9, 14, 16, 17, 18, 19, 20, and 21) and personal strain (items 2, 3, 6, 11, 12, and 13) (5); (3) three-factor model adapted from Cheah and colleagues (8), comprising a single role strain factor (items 1, 2, 3, 4, 7, 8, 11, 12, 14, 13, 15, 16, 17, and 18), a personal strain factor (items 5, 6, 9, 10, 19, and 22) and WaP (items 20, 21); (4) four-factor model following the original four factors of Cheah and colleagues (8), namely role strain due to demands of care (items 1, 2, 3, 4, 7, 8, 11, 12, and 14), role strain secondary to loss of control over the situation (items 13, 15, 16, 17, and 18), personal strain and worry about performance and (5) four-factor model by Cheng and colleagues (9) comprising captivity (items 11, 12, 13 and 14), loss of control (items 16, 17 and 19), personal strain (items 1, 2, 3, 4, 6, 7, 8, 9 and 10), and self-criticism (items 20 and 21).

We included item 22 ("Overall, how burdened do you feel in caring for your relative?") in the analysis. Several prior studies opted not to include this item (9, 12, 15, 17, 31, 32) while others did (6–8, 13, 33, 34). The studies that included item 22 cited its global nature and high correlation with other factors of the ZBI as a reason to exclude it from analysis. While item 22 theoretically represents an overall perception of burden by the caregivers, caregivers may interpret it differently and align their answer closer to one of the latent factors. This is evident from its loading on the personal strain factor in our prior study (8). To be conceptually aligned with these prior results, we elected to retain item 22 in the analyses.

We conducted confirmatory factor analysis (CFA) to determine if the presence of WaP (models 3–5) improves the model fit compared with total ZBI score (model 1) and role/personal strain (model 2). CFA was also used to assess if splitting role strain into two factors (models 4 and 5) is superior to retaining it as one factor (model 3). Robust weighted least squares were used as the estimator for the CFA as the ZBI is an ordinal scale. We used different indices to compare the fit of the four models: χ^2, root mean square error of approximation (RMSEA), standardized root mean square residual (SRMR), non-normed fit index (NNFI), and comparative fit index (CFI). We used the criteria proposed by Hu and Bentler (35) to determine a good fit, namely RMSEA (<0.06), SRMR (<0.08), NNFI (>0.95), and CFI (>0.95). In addition, we compared all the models against the one-factor model using χ^2 difference tests as the one-factor model is nested within all models with more than one factor.

From the best fitting model, factor scores for each factor were computed for use in the subsequent analyses. We computed correlations between the factors to determine how they relate to each other. We also performed multiple linear regression analyses to explore the relationships between ZBI total and factor scores with the candidate predictor variables MBI, Lawton IADL, NPI-Q severity, NPI-Q distress, and CMMSE. These variables were chosen based on previous work (3) with three modifications. First, we included both scales of the NPI-Q to better understand the differential impact of symptom severity versus resultant distress on caregiver burden. Second, we included the CDR stage of the

patient to determine if disease severity had any bearing on the level of burden on the caregivers. Third, we substituted caregiver age with "relationship with patient" due to strong collinearity between these two variables, assessed using generalized variance inflation factors and correlation matrices. We chose to include "relationship with patient" in the final model as we wanted to ascertain whether our previous finding of a relationship between younger age and caregiving burden could be explained by different dyadic relationship with the care recipient (3). To further clarify this relationship, we investigated the profile of each factor score across CDR score ranges, stratified by dyadic relationship. CDR was used as it is a uniform gauge of the severity of dementia in general (36).

All analyses were conducted using R 3.1.2 and Mplus 7. Descriptive statistics were used to describe our sample. Mean and standard deviation values were computed for continuous variables, and frequencies were computed for categorical variables. For inferential statistics, the *p*-value threshold considered significant was set at 0.05. Missing data and some socio-demographic variables were present in the ZBI. For the ZBI, we imputed the seven cases with one missing data point per case with the median of each question. The median was used to retain the ordinal nature and interpretability of the scale used in the ZBI. For socio-demographic variables, the 63 cases with missing data were not significantly different in all measures reported in the study ($p > 0.05$) and hence were excluded from regression analyses.

RESULTS

Characteristics of Caregivers and Patients

Four-hundred sixty-six caregiver-patients dyads were included in the study (**Table 1**). Caregivers had a mean age of 53.8 years (SD = 13.5) and were predominantly Chinese female with an average of 11 years of formal education (SD = 4.5). Most of the caregivers were adult children (61.4%) followed by spouses (26.6%). The patients had a mean age of 76.4 years (SD = 7.4), were predominantly female Chinese with an average of 4.9 years of formal education (SD = 4.7). Compared with adult children caregivers, sibling caregivers tended to be older [age, mean (SD): 47.43 (8.70) vs. 64.63 (9.07)] and mainly females (65.73 vs. 87.50%). Most of the patients were diagnosed with AD (53.2%) followed by other forms of dementia (i.e., not VD or mixed dementia) (21.1%). The majority (44.2%) had mild dementia (CDR 1.0), followed by moderate dementia (CDR 2.0) (27.3%). The mean total ZBI score was 24.9 (SD = 17.4), and the mean factor z-scores were −0.003 (SD = 0.978), −0.008 (SD = 0.976), 0.002 (SD = 0.957), and 0.024 (SD = 0.859) for personal strain, role strain (control), role strain (demands), and WaP, respectively.

TABLE 1 | Sample characteristics (*n* = 466).

Patient characteristics	
Age in years	76.4 (7.4)
Female gender, *n* (%)	275 (59.0)
Education level in years	4.9 (4.7)
Ethnic Group, *n* (%)	
Chinese	417 (89.5)
Malay	14 (3.0)
Indian	29 (6.2)
Others	6 (1.3)
Disease characteristics	
Global CDR score, *n* (%)	
CDR 0.5 (MCI)	58 (12.4)
CDR 0.5 (very mild dementia)	60 (12.9)
CDR 1.0 (mild dementia)	206 (44.2)
CDR 2.0 (moderate dementia)	127 (27.3)
CDR 3.0 (severe dementia)	15 (3.2)
Dementia types, *n* (%)[a]	
AD	217 (53.2)
VD	79 (19.4)
Mixed AD/VD	26 (6.4)
Others	86 (21.1)
CMMSE (range 0–28)	16.6 (6.1)
BADL (range 0–100)	92.9 (36.4)
IADL (range 0–23)	12.2 (5.9)
NPI-Q	
Severity (range 0–36)	5.6 (5.0)
Distress (range 0–60)	5.9 (7.3)
Caregiver characteristics	
Age in years	53.8 (13.5)
Female gender, *n* (%)	287 (61.6)
Education level in years	11 (4.5)
Relationship with patient, *n* (%)	
Spouse	124 (26.6)
Adult children	286 (61.4)
Sibling	8 (1.7)
Others	48 (10.3)
Living with patient, *n* (%)	351 (75.3)
ZBI score (range 0–88)	24.9 (17.4)

[a]*n = 408, excluding MCI cases.*

Mean (SD) unless otherwise stated.

AD, Alzheimer's dementia; BADL, Basic Activities of Daily Living; CDR, Clinical Dementia Rating; CMMSE, Chinese Mini Mental Status Examination; IADL, Instrumental Activities of Daily Living; MCI, mild cognitive impairment; NPI-Q, Neuropsychiatric Inventory Questionnaire; VD, Vascular dementia; ZBI, Zarit Burden Interview.

CFA of ZBI

The χ^2 difference tests were all significant, suggesting that models with more than one factor fit the data better than the one-factor model. **Table 2** shows the fit indices used to determine the best fit among the four factor models. RMSEA, NNFI, and CFI do not fit the criteria for a good fit for all five models. For SRMR, all the models fit the criteria for a good fit with the exception of the one-factor model. In making the comparison to determine if the presence of WaP improved model fit, we noted that NNFI for factor models without WaP was lower than models with WaP. This is of particular significance as NNFI penalizes models for greater complexity and the factor models with WaP are more complex than the factor models without WaP.

We also compared the three- and four-factor models from our previous work to determine if splitting role strain into two factors is better than keeping it as one. The fit indices unanimously indicate that the four-factor models were superior in fit to the three-factor model although the differences were quite small. In view of the better explanatory power of the four-factor model, we opted to use the four-factor model for further analyses. **Table 3** shows the standardized factor loadings and standard errors of the four-factor model.

TABLE 2 | CFA fit indices.

	df	χ^2		RMSEA	SRMR	NNFI	CFI
1 factor (Zarit and Zarit, 1982) (37)	209	1849.888	***	0.130	0.080	0.863	0.876
2 factor (Whitlatch et al., 1991) (5)	134	1543.840	***	0.150	0.087	0.844	0.864
3 factor (Cheah et al., 2012) (8)	206	1018.985	***	0.092	0.065	0.931	0.939
4 factor (Cheah et al., 2012) (8)	203	969.183	***	0.090	0.063	0.934	0.942
4 factor (Cheng et al., 2014) (9)	129	689.290	***	0.097	0.061	0.938	0.948

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

CFA, confirmatory factor analysis; CFI, Comparative Fit Index; df, degrees of freedom; NNFI, Non-normed Fit Index; RMSEA, Root Mean Square Error of Approximation; SRMR, Standardized Root Mean Square Residual.

TABLE 3 | Standardized factor loadings and standard errors for the four-factor Zarit Burden Interview model (8).

Items	Role strain (control)	Role strain (demands)	Personal strain	Worry about caregiving performance	SE
I01	0.587				0.032
I02	0.822				0.017
I03	0.834				0.016
I04	0.640				0.033
I07	0.611				0.030
I08	0.718				0.026
I11	0.846				0.017
I12	0.859				0.016
I14	0.656				0.029
I13		0.779			0.028
I15		0.660			0.031
I16		0.835			0.021
I17		0.881			0.018
I18		0.796			0.023
I05			0.709		0.027
I06			0.733		0.026
I09			0.826		0.017
I10			0.811		0.021
I19			0.716		0.026
I22			0.852		0.016
I20				0.957	0.028
I21				0.807	0.029

Correlations

Correlation analysis was performed using the four factors as reported by Cheah and colleagues (8) (**Table 4**). WaP correlated only moderately with the other three factors ($r = 0.572$–0.588, $p < 0.001$) and total ZBI ($r = 0.624$, $p < 0.001$), unlike the high correlation seen among the other factor scores ($r = 0.956$–0.991, $p < 0.001$).

Predictors of Different Factors of ZBI

Linear regressions conducted on ZBI total and factor scores were all significant ($p < 0.05$), with the WaP model having a much lower adjusted R^2 (0.091) compared to the other models (0.251–0.283) (**Table 5**). Significant predictors for total ZBI, role strain (demands), role strain (confidence), and personal strain are relationship (adult child), IADL and NPI-Q distress, compared with relationship (adult child) and NPI-Q severity for WaP. Notably, IADL and NPI-Q distress were significantly associated with all factors of the ZBI except for WaP; the reverse was true for NPI-Q severity. BADL, CMMSE, caregiver gender, co-residence, and severity of dementia (relative to MCI as reference group) did not predict total ZBI or factor scores.

Relationship Across Disease Severity by Different Dyadic Relationships

WaP exhibits a unique trajectory across the CDR stages by different dyadic relationships when compared with the other three factors (**Figure 1**). A limitation of the plot is the lack of data points for MCI and CDR 3 for the "sibling as caregiver" plot. In all three dyadic relationships, WaP had the highest score in MCI and CDR 0.5 dementia. Among adult child and sibling caregivers, WaP showed only a modest increase moving across the CDR stages, in contrast to the much steeper increase with increasing dementia severity for the other three factors. Among spousal caregivers, WaP remains relatively stable from MCI to CDR 2, unlike the general trend of increase for the other factors; all four factors exhibit a corresponding steep rise moving from CDR 2 to 3 stages.

DISCUSSION

Our study adds to the growing body of evidence that supports the existence of WaP as a distinct dimension of caregiving burden, and thus corroborates our earlier proposal that the three key dimensions of role strain, personal strain, and WaP underpin the multidimensionality of ZBI-defined burden. It also supports splitting role strain into two factors given the superior model fit. In addition, the regression analysis furthered our understanding of the predictors of WaP by highlighting the differential impact of NPI-Q distress relative to NPI-severity, and affirming the influence of dyadic relationship in previously reported observations of an inverse age relationship with WaP. To our knowledge, this is also the first study to demonstrate how WaP trends differently across the CDR stages for different dyadic relationships compared to the other three factors.

Comparisons of the models within a CFA framework provided the first piece of evidence that WaP is a distinct dimension of caregiving burden. While the majority of fit indices suggest that the data did not have a good fit with the various competing models, there is a consistent trend of superior fit indices in all models that incorporated WaP. Second, the weaker correlation of WaP with total ZBI score and the other factors supports that WaP measures a distinct domain when compared to role and personal strain. Third, in regression analysis, the WaP model has a much lower R^2 and yielded predictors that differ from the more "conventional" predictors of role and personal strain. Fourth, WaP exhibits a

TABLE 4 | Correlation matrix between factors and total ZBI score and Cronbach's α.

	Role strain (demands)	Role strain (control)	Personal strain	Worry about performance	ZBI total
Role strain (demands)		***	***	***	***
Role strain (control)	0.966		***	***	***
Personal strain	0.990	0.991		***	***
Worry about performance	0.572	0.588	0.587		***
ZBI total	0.956	0.960	0.966	0.624	

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
ZBI, Zarit Burden Interview.

distinct trajectory across the different stages of cognitive impairment for different dyadic relationships. Taken together, the above evidence strongly supports the construct validity of WaP as a distinct dimension within ZBI-defined burden.

The CFA also provides evidence that splitting role strain into two factors contributes to a better model fit as opposed to keeping it intact as one factor. While the improvement in fit indices may be slight, earlier studies suggest that the items assigned to the two factors of role strain are qualitatively different (8, 9). One role strain factor assesses the demands of care imposed on the caregiver while the other role strain factor assesses the amount of confidence and control over situations imposed by the caregiving role (8). Thus, both factors relate to distinct aspects of the role of a caregiver, differentiating them from personal strain and WaP factors.

In our regression analyses, we also explicated the discordance in earlier studies regarding the influence of behavioral and psychological symptoms of dementia (BPSD) on WaP (8, 9). Specifically, we found that NPI-Q distress was a significant predictor for both role and personal strain, while NPI-Q severity was a significant predictor for WaP. This difference suggests that different mechanisms possibly drive the different factors of caregiving burden. For role and personal strain, the appraisal of how each neuropsychiatric symptom is distressing possibly relates more to the amount of effort the caregiver has to put in to properly assume the role and manage their own psychological well-being (38). In contrast, for WaP, the caregiver may associate the severity of neuropsychiatric symptoms as a reflection of how well one is performing as a caregiver, thus resulting in burden arising from worry about one's caregiving performance (3, 18). These results suggest the importance of managing both the severity and distress from BPSD to address different aspects of caregiving burden.

While the difference in general burden levels between the adult child and spouse is well documented (39), this study is the first to investigate the stage-dependent differences between WaP and other factor scores by dyadic relationship. Our results affirm the findings of earlier studies that unlike the other factors, WaP is significantly endorsed even in the milder stages of cognitive impairment (3, 8). Investigation of the interaction between dyadic relationship and stage of cognitive impairment further reveals that WaP increased only slightly in CDR 2–3 among adult children/sibling caregivers, unlike spousal caregivers where WaP remained relatively stable until the steep rise in CDR 3. This suggests a differential pattern of self-appraisal of caregiving performance between the two groups. Among adult children caregivers, WaP may represent in the milder stages of cognitive impairment worry and anxiety about caregiving performance in relation to the strong sense of obligation on assuming the caregiving role, which can progress to more complicated feelings associated with caregiving such as self-criticism and inadequacy if left unaddressed (3, 17). In contrast, among spousal caregivers, the sharp rise of WaP in CDR 3 may herald the onset of guilt in conjunction with overall caregiver stress arising from decompensated coping mechanisms due to increased care demands from functional needs or behavioral disturbances (3, 13). This corresponds to earlier findings that WaP interacts with personal strain to increase total ZBI in higher burden states (3).

Our results raise the intriguing question about the possible relationship between WaP with mastery and self-efficacy beliefs among caregivers. Self-efficacy refers to an individual's assessment of his or her ability to perform specific activities and achieve a desired outcome (40). Whereas the related concept of mastery refers to a global assessment (41), self-efficacy pertains to beliefs about one's competence to successfully perform discrete or specific tasks. Self-efficacy beliefs influence the initiation and maintenance of effort in demanding situations, and may vary across specific activities of caregiving such as performing ADLs, handling problem behaviors, and use of community support services (42). Self-efficacy has been found to predict caregiver burden and depressive symptoms (43, 44); it also mediates the influence of social support on caregiver well-being, as well as the response to skill-building psychoeducational intervention programs (45, 46). An understanding of the natural history of WaP and how it interacts with self-efficacy may provide useful insights about potential interventional strategies. For instance, caregivers with milder degrees of WaP burden and low self-efficacy may benefit from specific intervention programs to equip them with the necessary coping skills, thereby increasing the sense of self-efficacy and mastery and averting the slippery slope to more negative appraisals of one's caregiving performance that may result in guilt, overall caregiver stress, and ultimately burnout (47). Future studies should explore whether WaP, akin to the more established factors of role and personal strain, can be amenable to intervention if detected early (48, 49). This is especially salient in light of the findings that WaP, unlike the other dimensions, occurs early in MCI and CDR 0.5 dementia (8), and in the trajectory of multidimensional ZBI burden (14).

Taken together, our results corroborate WaP as a unique factor that is distinct from role or personal strain. We

TABLE 5 | Regression of factors and ZBI total score on caregiver and care recipient characteristics.

	Total ZBI			Role strain (demands)			Role strain (control)			Personal strain			Worry about performance		
Regression	***b***	**β**	***p*-Value**	***b***	**β**	***p*-Value**	***b***	**β**	***p*-Value**	***b***	**β**	***p*-Value**	***b***	**β**	***p*-Value**
Relationship with care recipient (reference: spouse)															
Adult child	0.207	0.126	0.023 *	0.245	0.123	0.029 *	0.316	0.161	0.005 **	0.284	0.142	0.012 *	0.329	0.184	0.003 **
Sibling	0.509	0.092	0.048 *	0.506	0.075	0.112	0.693	0.104	0.029 *	0.631	0.093	0.049 *	−0.062	−0.010	0.845
Others	0.085	0.016	0.726	0.086	0.014	0.772	0.032	0.005	0.915	0.053	0.008	0.860	0.172	0.030	0.562
Caregiver gender (reference: female)															
Male	−0.007	−0.004	0.918	−0.032	−0.016	0.716	0.002	0.001	0.986	−0.014	−0.007	0.874	−0.081	−0.045	0.359
Living with care recipient (reference: no)															
Yes	0.022	0.012	0.796	0.039	0.017	0.714	0.025	0.011	0.812	0.025	0.011	0.813	−0.151	−0.071	0.158
Caregiver education	−0.010	−0.061	0.244	−0.008	−0.039	0.457	−0.016	−0.080	0.134	−0.012	−0.060	0.258	−0.002	−0.011	0.853
BADL (0–100)	−0.001	−0.026	0.581	−0.001	−0.023	0.638	0.000	−0.013	0.792	0.000	−0.013	0.794	0.001	0.057	0.288
IADL (0–23)	−0.017	−0.129	0.031 *	−0.028	−0.175	0.004 **	−0.025	−0.156	0.011 *	−0.025	−0.159	0.009 **	0.003	0.021	0.756
NPI-Q severity (0–36)	0.011	0.071	0.407	0.007	0.040	0.647	0.014	0.077	0.375	0.010	0.055	0.522	0.032	0.189	0.049 *
NPI-Q distress (0–60)	0.035	0.336	0.000 ***	0.042	0.323	0.000 ***	0.037	0.289	0.001 ***	0.041	0.321	0.000 ***	0.001	0.009	0.924
CMMSE (0–28)	0.004	0.030	0.635	0.006	0.037	0.565	0.005	0.034	0.606	0.006	0.037	0.567	−0.002	−0.011	0.875
CDR [Reference: CDR 0.5 (MCI)]															
CDR 0.5 (very mild dementia)	−0.081	−0.035	0.550	−0.121	−0.043	0.469	−0.076	−0.027	0.650	−0.099	−0.035	0.557	0.240	0.095	0.151
CDR 1.0 (mild dementia)	0.060	0.039	0.610	0.059	0.031	0.686	0.081	0.044	0.576	0.069	0.037	0.637	0.160	0.094	0.272
CDR 2.0 (moderate dementia)	0.198	0.114	0.205	0.198	0.094	0.304	0.172	0.083	0.370	0.185	0.088	0.340	0.326	0.173	0.090
CDR 3.0 (severe dementia)	0.438	0.092	0.114	0.541	0.094	0.114	0.418	0.074	0.220	0.514	0.089	0.136	0.441	0.085	0.196
Adjusted R^2	0.285		0.000 ***	0.262		0.000 ***	0.248		0.000 ***	0.260		000 ***	0.091		0.000 ***

*$^*p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

BADL, basic activities of daily living; IADL, Instrumental Activities of Daily Living; MCI, mild cognitive impairment; NPI-Q, Neuropsychiatric Inventory Questionnaire.

conceptualize WaP as part of a broader concept of self-appraisal of caregiving performance that encompasses both positive and negative valences (3, 18). Rather than a yes/no dichotomous phenomenon, WaP is likely to represent a continuum that ranges from more positive aspects of conscientious and wanting to do better, through intermediate degrees of inadequacy and self-criticism, to guilt and shame at the negative end of the extreme. However, given that it only has two items, it is inherently an unreliable factor and a decision needs to be made to either remove it from the ZBI or to expand it (9, 50). Taking into account the insights that WaP can confer, especially when viewed in relation to stage of disease, nature of the dyadic relationship, interaction with role strain and possibly self-efficacy in influencing overall burden, we argue that the information provided by WaP in enhancing our understanding of the caregiving burden phenomena would be too rich to ignore (3, 13, 50). In support of this, a recent study of the 12-item ZBI in Hong Kong Chinese dementia caregiver found Bédard's two-factor model of personal strain and role strain to be inadequate, and that the best fit was obtained with a three-factor model that also included "self-criticism" comprising items 20 and 21 (10). Acknowledging the need for brevity in a clinical instrument, our approach may be the first to expand the number of items to better delineate the WaP construct before employing item-reduction strategies to only retain items that show good psychometric properties.

Some limitations are worth noting. While the cross-sectional design is adequate in validating the four-factor model in a fresh sample, novel findings such as the difference across CDR stages for different dyadic relationships need to be interpreted with caution and preferably replicated in longitudinal studies. The lack of comprehensive data across the spectrum of cognitive impairment in the sibling group also limits interpretability. In addition, the small R^2 for the regression models suggests that there are other unaccounted-for factors that affect the variance of total ZBI and its dimensions in the models. For instance, information on socioeconomic factors such as financial status, whether one or more caregivers were involved and the degree of social support from other family caregivers, as well as variability in and access to healthcare services and community support, are potentially important factors that can mediate burden. Also, our study population of "middle-old" patients in a predominantly Chinese multiethnic population in an Asian country may limit the generalizability of our findings to the "oldest-old" (51) and other sociocultural context; nonetheless, the coherence with other studies across different cultures that demonstrated WaP to be a distinct factor supports that WaP is possibly a phenomenon that is applicable across different cultures. Finally, to retain the representativeness of our sample relative to the naturalistic multiethnic setting of Singapore, we elected to retain the Malay and Indian participants in our study. Similarly, to avoid selecting a skewed population of more highly educated English-speaking caregivers, we employed both English and Chinese versions of the ZBI so that the subset of non-English-speaking caregivers would not be excluded. We were mindful to utilize a rigorously validated version of the ZBI (30) and believe that this would also improve the external validity of our results in other multiethnic societies.

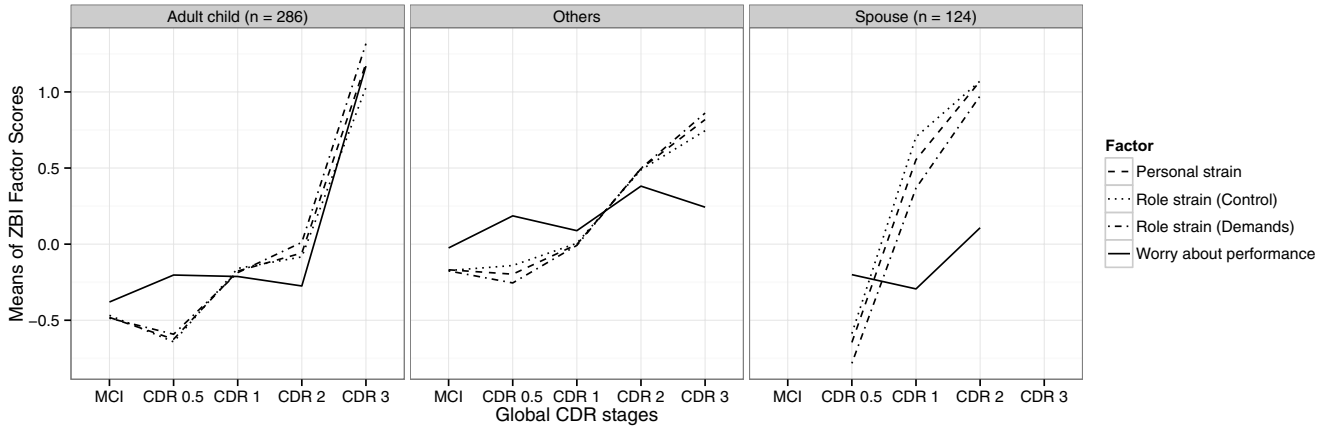

FIGURE 1 | Zarit Burden Interview (ZBI) total and factor scores by disease severity of different dyadic relationships.

In conclusion, our study supports the findings of earlier studies that WaP is a distinct dimension of caregiving burden in addition to role and personal strain in the multidimensional of ZBI-defined burden. The four-factor structure that splits role strain into two factors yielded the best fit. WaP is predicted by NPI-severity and adult child relationship, but not NPI-distress or physical function. Understanding how WaP trends across the CDR stages for different dyadic relationships can fuel future research to explore the potential of WaP as a possible intervention target in the milder stages of burden if detected early. Moving forward, we therefore recommend an expansion of items in WaP and that future studies examine burden as a multidimensional construct beyond the total score to incorporate role strain, personal strain, and WaP. More research is also needed to understand the impact on caregiver burden of subjective presenting complaint and objective primary domain of cognitive involvement, and whether this can help to delineate subsets of WaP.

ETHICS STATEMENT

As this study involved the retrospective review of medical records of patients attending the Memory clinic as part of a registered database, waiver of informed consent was approved by the Institutional Review Board of the National Healthcare Group.

AUTHOR CONTRIBUTIONS

RL was responsible for data analysis and writing the manuscript. WL supervised the data analysis and was involved in the critical appraisal of the manuscript. MC, PC, BT and NA were involved in study design and critical appraisal of the manuscript.

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Burden among Family Caregivers of Dementia in the Oldest-Old: An Exploratory Study

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Background: With >85 years, the fastest growing age segment in developed countries, dementia in the oldest-old is projected to increase exponentially. Being older, caregivers of dementia in oldest-old (CDOO) may experience unique challenges compared with younger-age groups. Thus, we aim to explore demographic characteristics and burden pattern among CDOO.

Methods: We studied 458 family caregiver-patient dyads attending an outpatient memory clinic. We classified patients into three age-groups: <75, 75–84, and ≥85 years. We measured caregiver burden using the Zarit Burden Interview (ZBI) 4-factor structure described by Cheah et al. (1). We compared care recipient characteristics, caregiver demographics, and ZBI total/factors scores between the three age-groups, and performed 2-way analysis of variance (ANOVA) to ascertain the effect of age-group by disease severity interaction.

Results: Oldest-old care recipients were more impaired in cognitive function and instrumental ADL; there was no difference in behavior and basic ADL. Compared with the other two age-groups, CDOO were older (mean age: 50.4 vs 55.5 vs 56.8 years, $P < 0.01$), and overwhelmingly adult children (85.9%) as opposed to spouses (5.3%). CDOO also had higher ZBI total score, role strain, and personal strain (all $P < 0.05$). However, there was no difference in worry about performance scores. 2-way ANOVA did not reveal significant age-group by disease severity interaction for ZBI total and factor scores, although distinctive differences were seen between role/personal strain with worry about performance in mild cognitive impairment and very mild dementia.

Conclusion: Our study highlighted that CDOO were mainly older adult children who experienced significant role and personal strain independent of disease severity while caring for their family member with more impaired cognitive and physical function. These results pave the way for targeted interventions to address the unique burden faced by this rapidly growing group of caregivers.

Keywords: dementia, oldest-old, caregiver burden, Zarit Burden Interview, dimensions

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INTRODUCTION

Globally, the oldest-old population, variously defined as 80 or 85 years and older, has emerged as the fastest growing age segment, especially in developed countries. The oldest-old population is projected to increase 151 percent between 2005 and 2030, far outstripping the 21 percent increase for those under age 65 and 104 percent increase for those aged 54 years and above (2). In line with this worldwide trend, the prevalence of the oldest-old population in Singapore has grown exponentially from 4,500 in 1980 to over 27,800 in 2009 (3).

The prevalence of age-associated diseases such as dementia is expected to mirror this worrying global demographic trend of population aging, such that growth of dementia in the oldest-old (DOO) is expected to exhibit a corresponding exponential rise that far outstrips other age groups. Recent studies support this assertion that the oldest-old represents the fastest growing population with dementia. The WiSE study (4) conducted in Singapore in 2013 showed that the prevalence of dementia was 10% in the elderly population above 60 years of age and the likelihood of dementia for those 85 years and above were 18.4 times higher compared to those aged 60–74 years. A systematic review and metaanalysis on the global prevalence of dementia reported that 18.7% of those between 85 and 89 years and 35.4% of those above 90 years of age in the South East Asian regions were estimated to be affected by dementia (5).

This increase in DOO coincides with a dramatic decline in the potential support ratio, namely persons aged 20–64 per person aged 65 or older. Population projections for Singapore predict that the potential support ratio will drop from 5.7 in 2015 to around 2.1 by 2030, with similar declines expected in most countries worldwide (6). Because the growth in health-care professionals trained in dementia care is unlikely to keep pace with this burgeoning demand, it is anticipated that the responsibility of caring for persons with DOO will increasingly fall upon informal family caregivers such as spouses, children, grandchildren, siblings, or other relatives. As family is expected to be the primary source of care going forward, especially in Asian populations, understanding the potential challenges faced by family caregivers of dementia in oldest-old (CDOO) is, therefore, of great salience and importance.

Caregivers of dementia in oldest-old are expected to be older in age and are likely burdened with more concerns such as health issues, family commitments, or financial constraint compared to their younger counterparts. Furthermore, persons with DOO are likely to require higher care needs, such that the caregiving role can have deleterious impact on one's physical and psychological well-being. Despite this, the majority of research in caregivers in dementia focuses on the younger old, and there is limited literature that specifically pertains to CDOO and the caregiving burden that they may experience relative to the younger-old age group. For instance, the study by Liu et al. among Chinese adult children taking care of their oldest-old parents was limited to care recipients who were relatively cognitively well and did not require much assistance in their activities of daily living (7). More recently, Liu et al. reported that Chinese adult children experience strain from worry about performance when providing care for their oldest-old parents (8). These results suggest that CDOO may face unique challenges in their caregiving role, particularly in Asian populations that are often heavily influenced by notions of filial piety and obligatory care (9, 10).

In light of this, it is imperative that the study of caregiver strain in DOO is approached from a multidimensional perspective as opposed to solely assessing the total burden score, constituting what is effectively a unidimensional approach. Caregivers with an identical score may express difference aspects of burden (11); while one may be affected by physical demands of care recipients, other may be worried about his caregiving performance (9). Recent studies suggest that the different dimensions of caregiver burden as measured by the Zarit Burden Interview (ZBI) among Chinese informal caregivers for dementia exhibit different trajectories across the severity of dementia (12). Thus, using the validated 4-facture structure proposed by Cheah et al. (1), we aim to describe care recipient and caregiver characteristics, as well as caregiver burden, in DOO compared to young-old (below 75 years old) and middle-old (75–84 years old) individuals with dementia. Our secondary objective is to compare the burden pattern across the spectrum of disease severity among the three age-groups.

MATERIALS AND METHODS

Study Design and Participants

This is a cross sectional study involving 458 caregiver-patient dyads of community dwelling older adults who were referred to the Memory Clinic, Tan Tock Seng Hospital, Singapore from January 2010 to December 2011. The Memory Clinic is a tertiary referral clinic within the Department of Geriatric Medicine that receives referrals from polyclinics, family physicians, other restructured hospitals, and other departments within Tan Tock Seng Hospital. Patients are referred for assessment of cognitive and memory difficulties as well as behavioral issues without significant functional limitations. The annual attendance at the Memory clinic in 2010 and 2011 were 500 and 943 new cases, respectively.

Our inclusion criteria were: (1) patients aged 55 years and older with a Clinical Dementia Rating (CDR) global score of >0 and with a diagnosis of mild cognitive impairment (MCI) or dementia (13); (2) presence of a primary caregiver, defined as the family member who was most involved in the provision of daily care and familiar with the patient's social and medical status; (3) completion of the 22-item ZBI questionnaire. We excluded caregivers who were non-family members (for example, domestic helpers or friends), unable to understand the Chinese or English language, or unable to complete the ZBI questionnaire. The study was approved by the Institutional Review Board of the National Healthcare Group. As this study involved the retrospective review of medical records of patients attending the Memory clinic as part of a registered database (TTSH/2008-0027), waiver of informed consent was approved by the Institutional Review Board of the National Healthcare Group.

Assessment

All participants underwent standardized assessment by a geriatrician and nurse clinician, blood investigations, neuroimaging

and whenever relevant, psychometric assessment. A consensus meeting was conducted to determine the diagnosis, etiology, and staging of cognitive impairment based upon multi-disciplinary inputs from the physician, nurse clinicians, and psychologist. Dementia was diagnosed based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria, and etiology classified using published international criteria for dementia, as previously described (11). MCI was diagnosed using the revised Petersen criteria (14). The severity of cognitive impairment was rated using the locally validated clinical dementia rating scale (CDR) (15). CDR 0 indicates no cognitive impairment; CDR 0.5 designates either MCI or very mild dementia; and CDRs 1, 2, and 3 indicate mild, moderate, and severe dementia, respectively (16).

Measurements and Instruments

We collected baseline demographic data of care recipients and their caregivers, including age, gender, ethnicity, and educational level. We also collected information on caregiver characteristics such as relationship and co-residence with care recipients.

We assessed cognitive performance using the locally validated Chinese Mini-Mental State Examination (total score of 28) (17). Functional status was assessed using the modified Barthel Index (score 0–100) (18) and Lawton instrumental activities of daily living (IADL) (score 0–23) (19). Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q); severity (20) and carer distress scores (21) were computed separately. These assessments form part of the routine clinical evaluation for all patients attending the Memory Clinic and are routinely gathered and documented in the files.

Caregiver burden was assessed using the 22-item ZBI questionnaire, which was administered either in English or Chinese. Each item was scored on a 5-point Likert scale, ranging from 0 = "never" to 4 = "nearly always," yielding a total score ranging from 0 to 88. We used the 4-factor structure reported by Cheah et al., which accounted for 62.2% of the variance with good internal consistency (1): (1) factor 1: role strain from demands of care and social impact on caregiver (40.6% of variance); (2) factor 2: role strain from lack of confidence or control over the situation (9.7% of variance); (3) factor 3: personal strain due to psychological impact on caregiver (6.4% of variance); and (4) factor 4: worry about caregiving performance (5.6% of variance).

Statistical Analysis

We performed descriptive and analytical statistics using SPSS (version 21.0; SPSS Inc., Chicago, IL, USA). All tests were 2-sided and the level of significance set at 0.05. We categorized caregiver-patient dyads into three groups based upon the age of the care recipient: young-old (aged below 75 years), middle-old (aged between 75 and 84 years), and oldest-old (aged 85 years and above). We compared the characteristics of care recipients and caregivers between the three age groups, as well as ZBI total and factor scores stratified by relationship with care recipient. We conducted X^2 test for categorical variables and one-way analysis of variance (ANOVA) with *post hoc* comparison corrected for the Turkey HSD test was used for continuous variables. We further performed two-way ANOVA to ascertain the effect of age group by disease severity interaction on caregiver burden (ZBI total and individual factor scores).

RESULTS

Characteristics of Caregiver-Patient Dyads

Our final sample of 458 caregiver-patient dyads was predominantly of Chinese ethnicity (**Table 1**). The mean age of care recipients was 76.5 years (SD 7.4 years) with 59% of female gender. Alzheimer's dementia was the major etiology (46.7%), followed by other dementias (i.e., not vascular dementia nor mixed dementia) (18.6%), vascular dementia (17%), and mixed dementia (6.1%). About half of the recipients were rated CDR 1 (44.3%) followed

TABLE 1 | Characteristics of caregiver and care recipient dyads.

	Care recipients	Caregivers
	***n* = 458**	***n* = 458**
Demographics		
Age	76.5 ± 7.4	53.8 ± 13.5
Female gender, *n* (%)	270 (59)	287 (62.7)
Ethnicity, *n* (%)		
Chinese	409 (89.3)	
Malay	29 (6.3)	
Indian	14 (3.1)	
Others	6 (1.3)	
Years of formal education	4.8 ± 4.6	11 ± 4.5
Relationship with care recipients, *n* (%)		
Spouse		139 (30.3)
Adult children		295 (64.5)
Others		20 (4.4)
Living with care recipient, *n* (%)		351 (76.6)
Disease characteristics		
Dementia type, *n* (%)		
Alzheimer's dementia	214 (46.7)	
Vascular dementia	78 (17)	
Mixed dementia	28 (6.1)	
Others	85 (18.6)	
Global CDR score, *n* (%)		
CDR 0.5 (mild cognitive impairment)	55 (12)	
CDR 0.5 (very mild dementia)	58 (12.7)	
CDR 1 (mild dementia)	203 (44.3)	
CDR 2 (moderate dementia)	127 (27.7)	
CDR 3 (severe dementia)	15 (3.3)	
CMMSE (range 0–28)	16.6 ± 6	
BADL (range 0–100)	92.8 ± 36.7	
IADL (range 0–23)	12.1 ± 5.9	
Behavioral symptoms		
NPI-Q severity (range 0–36)	5.6 ± 5	
NPI-Q distress (range 0–60)		5.8 ± 7.2
Caregiver burden—ZBI scores		
Total ZBI (range 0–88)	25.0 ± 17.4	
Factor 1 (range 0–36)	12.1 ± 8	
Factor 2 (range 0–20)	3.7 ± 4.3	
Factor 3 (range 0–24)	6.2 ± 5.3	
Factor 4 (range 0–8)	3.1 ± 2.4	

Mean (SD) unless otherwise stated.

BADL, Barthel index of Basic Activities of Daily Living; CDR, clinical dementia rating; CMMSE, Chinese Mini Mental Status Examination; IADL, Instrumental Activities of Daily Living; NPI-Q, Neuropsychiatric Inventory Questionnaire; ZBI, Zarit Burden Interview.

by CDR 2 (27.7%), CDR 0.5 dementia (12.7%), and MCI (12%) and CDR 3 (3.3%).

The mean age of caregivers was 53.6 years (SD 13.5 years) and majority were daughters (42.4%), followed by spouses (30.3%) and sons (22.1%). The majority of caregivers (76.6%) resided with the care recipient. The NPI-Q severity and distress mean scores were 5.6 (SD 5), and 5.8 (SD 7.2), respectively. The mean ZBI scores are: total ZBI, 25 (SD 17.4); factor 1, 12.1 (SD 8); factor 2, 3.7 (SD 4.3); factor 3, 6.2 (SD 5.3); and factor 4, 3.1 (SD 2.4), respectively.

Care Recipient Characteristics

There was no difference in gender or ethnicity across the age groups (**Table 2**). Compared with the other two age-groups, care recipients with DOO are older ($P < 0.01$), more likely to be female ($P < 0.05$), and have lower educational level ($P < 0.01$). Alzheimer's disease was the predominant etiologic diagnosis for all three groups. Care recipients in the young-old groups was more likely to present at earlier stages such as MCI (18.1%) or CDR 0.5–1 dementia (60%); in contrast, close to half (47.4%) of DOO patients presented with CDR 2–3 moderate-to-severe dementia. DOO patients also scored lower on the CMMSE ($P = 0.003$) and were more impaired in IADL ($P < 0.01$) although less impaired in BADL. Though the NPI-Q severity score was similar across the three age groups, NPI-Q carer distress score was higher in the DOO group.

TABLE 2 | Comparison of care recipient and disease characteristics.

	Young-old	Middle-old	Oldest-old	*P*-value
	<75 years	75–84 years	≥85 years	
	n = 155	*n* = 246	*n* = 57	
Age of care recipients	68.5 ± 5	78.9 ± 2.7[a]	88 ± 2.7[b,c]	<0.01
Female gender, *n* (%)	90 (58.1)	136 (55.3)	44 (77.2)	0.01
Ethnicity, *n* (%)				
Chinese	137 (88.4)	221 (89.8)	51 (89.5)	0.56
Malay	13 (8.4)	15 (6.1)	1 (1.8)	
Indian	4 (2.6)	5 (2)	5 (8.8)	
Others	1 (0.6)	5 (2)	0 (0)	
Years of formal education	5.8 ± 4.7	4.6 ± 4.7[a]	3.4 ± 4.6[b]	<0.01
Primary diagnosis, *n* (%)				0.626
Alzheimer's dementia	66 (51.6)	121 (53.8)	27 (51.9)	
Vascular dementia	23 (18)	42 (18.7)	13 (25)	
Mixed dementia	13 (10.2)	13 (5.8)	2 (3.8)	
Others	26 (20.3)	49 (21.8)	10 (19.2)	
Global CDR score	2.7 ± 1.1	3.1 ± 0.9[a]	3.3 ± 1.0[b]	<0.001
Clinical staging, *n* (%)				0.004
Mild cognitive impairment	28 (18.1)	22 (8.9)	5 (8.8)	
Very mild dementia	25 (16.1)	27 (11)	6 (10.5)	
Mild dementia	68 (43.9)	116 (47.2)	19 (33.3)	
Moderate dementia	29 (18.7)	75 (30.5)	23 (40.4)	
Severe dementia	5 (3.2)	6 (2.4)	4 (7)	
CDR sum of boxes	5.4 ± 3.9	6.4 ± 3.8[a]	8.03 ± 4.7[b,c]	<0.01
Cognitive status				
CMMSE (0–28)	17.8 ± 6.3	16.1 ± 5.7[a]	15 ± 6.4[b]	0.003
Functional status				
BADL (0–100)	93.6 ± 13.6	91.2 ± 16.3	97.7 ± 96.3	0.461
IADL (0–23)	13.9 ± 5.8	11.7 ± 5.6[a]	8.7 ± 5.4[b,c]	<0.001
Behavioral symptoms				
NPI-Q severity score (0–36)	5.6 ± 5.1	5.5 ± 4.9	5.6 ± 5.3	0.943
NPI-Q carer distress score (0–60)	5.7 ± 7	5.6 ± 3	6.7 ± 8.7	0.78

Values are reported as mean ± SD or frequency (%) unless otherwise stated.
Post hoc comparison with Turkey HSD test (P < 0.05).
[a]Young-old vs middle-old.
[b]Young-old vs oldest-old.
[c]Middle-old vs oldest-old.
BADL, Barthel index of Basic Activities of Daily Living; CDR, Clinical Dementia Rating; CMMSE, Chinese Mini Mental Status Examination; IADL, Instrumental Activities of Daily Living; NPI-Q, Neuropsychiatric Inventory Questionnaire.

Caregiver Characteristics and Burden

Compared with the younger-old age groups, CDOO were older in age ($P < 0.01$), and were mainly adult children (daughters followed by the sons) or others, compared with spouses and daughters in the younger-old age groups (**Tables 3** and **4**). When caregiver age was stratified by relationship, adult–child CDOO were older compared with the other two age groups. Spousal CDOO also tended to be older compared with the young-old age group (72.0 vs 64.6 years), although the converse was true for non-spousal non-children CDOO (58.0 vs 47.6 years).

In addition, CDOO expressed higher caregiver stress with higher total ZBI, role strain/demands, role strain/control, and personal strain (all *P*-value $P < 0.05$). In contrast, there was no difference in worry about performance across the three groups. When stratified by relationship, spousal CDOO endorsed higher ZBI total score and all factor scores with the exception of worry about performance; however, these results were not statistically significant, possibly due to small numbers ($N = 3$) in the spousal CDOO group. For adult–child CDOO, there is also a trend for

TABLE 3 | Comparison of caregiver characteristics.

	Young-old	Middle-old	Oldest-old	*P*-value
	<75 years	75–84 years	≥85 years	
	N = 155	*n* = 246	*n* = 57	
Age, overall group	50.4 ± 14.3	55.2 ± 13.4[a]	56.8 ± 10[b]	<0.01
Spouse	64.6 ± 7.1	72.9 ± 8.1[a]	72.0 ± 9.6	<0.01
Daughters	40.0 ± 7.5	48.9 ± 5.5[a]	56.5 ± 7.1[b,c]	<0.01
Sons	39.4 ± 8	48.3 ± 6.5[a]	57.5 ± 6.2[b,c]	<0.01
Others	58.0 ± 0	46.6 ± 21.4	47.6 ± 20	0.783
Female gender, *n* (%)	96 (64.4)	152 (67.9)	39 (69.6)	0.707
Relationship with care recipient, *n* (%)				<0.01
Spouse	65 (42.8)	71 (29)	3 (5.3)	
Daughters	55 (36.2)	105 (42.9)	34 (59.6)	
Sons	30 (19.7)	56 (22.9)	15 (26.3)	
Others	2 (1.3)	13 (5.3)	5 (8.8)	
Living with care recipient, *n* (%)	129 (86)	181 (79.7)	41 (73.2)	0.087
Years of formal education	11.1 ± 4.8	10.8 ± 4.5	11.2 ± 4.2	0.889

Values are reported as mean ± SD or frequency (%) unless otherwise stated.
Post hoc comparison with Turkey HSD test (P < 0.05).
[a]Young-old vs middle-old.
[b]Young-old vs oldest-old.
[c]Middle-old vs oldest-old.

TABLE 4 | Comparison of Zarit Burden Interview (ZBI) total and factor scores across the three age groups stratified by relationship.

All subjects	**Young-old**	**Middle-old**	**Oldest-old**	***P*-value**
	<75 years	**75–84 years**	**≥85 years**	
	***n* = 155**	***n* = 246**	***N* = 57**	
Total ZBI (range 0–88)	22.9 ± 16.8	25.1 ± 17.1	30.5 ± 19.2[a]	0.017
Factor 1 (0–36)	11 ± 7.9	12.2 ± 7.9	14.3 ± 8.3[a]	0.025
Factor 2 (0–20)	3.2 ± 3.9	3.7 ± 4.2	5.2 ± 5.1[a,b]	0.008
Factor 3 (0–24)	5.7 ± 5.1	6.1 ± 5.2	7.9 ± 5.8[a,b]	0.018
Factor 4 (0–8)	3 ± 2.5	3.2 ± 2.3	3.1 ± 2.4	0.876
Spouses	*N* = 65	*n* = 71	*n* = 3	
Total ZBI (range 0–88)	20.8 ± 16.3	19.7 ± 18.2	35 ± 20.3	0.324
Factor 1 (0–36)	10.6 ± 8	10.2 ± 8.3	17.3 ± 8.5	0.328
Factor 2 (0–20)	2.4 ± 3	2.8 ± 4.1	5.6 ± 6	0.319
Factor 3 (0–24)	5.1 ± 5	4.5 ± 5.3	9.3 ± 5.7	0.268
Factor 4 (0–8)	2.6 ± 2.9	2.2 ± 2.5	2.6 ± 2.3	0.576
Daughters	*N* = 55	*n* = 105	*n* = 34	
Total ZBI (range 0–88)	24.5 ± 16	27.9 ± 16.3	30.1 ± 19	0.277
Factor 1 (0–36)	11.8 ± 7.9	13.3 ± 7.5	14.3 ± 8.3	0.276
Factor 2 (0–20)	3.3 ± 3.5	4.1 ± 4.2	5.3 ± 5.1	0.092
Factor 3 (0–24)	5.9 ± 5.1	6.8 ± 5.1	7.5 ± 5.9	0.356
Factor 4 (0–8)	3.6 ± 2.3	3.7 ± 2.2	3.1 ± 2.3	0.379
Sons	*N* = 30	*n* = 56	*n* = 15	
Total ZBI (range 0–88)	24.7 ± 17.4	27.01 ± 16.1	31.8 ± 21	0.429
Factor 1 (0–36)	10.6 ± 7.2	12.8 ± 7.7	14.5 ± 9	0.252
Factor 2 (0–20)	4.4 ± 5	4 ± 4.2	5.5 ± 5.8	0.557
Factor 3 (0–24)	6.4 ± 4.9	6.6 ± 4.8	9.1 ± 6.1	0.204
Factor 4 (0–8)	3.3 ± 2.0	3.7 ± 2.0	2.8 ± 2.5	0.339

Post hoc comparison with Turkey HSD test (P < 0.05).
[a]*Young-old vs oldest-old.*
[b]*Middle-old vs oldest-old.*

higher total, role strain, and person strain scores, albeit not statistically significant. In contrast, worry about performance was lowest in CDOO compared with the other two age groups. Adult-son CDOO also showed higher factor three scores (psychological impact from caregiving) than adult-daughter CDOO though this difference was not statistically significant by independent sample *t*-test.

Effect of Disease Severity on Caregiver Burden

Two-way ANOVA revealed that there was no statistically significant interaction between age group and disease severity for ZBI total and factor scores. Examination of the graphical plots yielded interesting insights about how the trend of burden scores across disease severity for DOO differs from the younger-old age groups. For instance, ZBI total score was highly endorsed among CDOO in MCI and very mild dementia and progressively increased with disease severity to merge with the curves for the other age groups (**Figure 1A**). A comparable trend was noted for factors 1–3. In contrast, for factor 4, a reverse pattern was noted with CDOO endorsing the lowest score in the MCI stage (**Figure 1B**). Factor 4 scores subsequently increased with dementia severity to merge with the curves for the other two groups.

DISCUSSION

To our knowledge, this is the first study to shed light on the unique challenges faced by caregivers of the oldest-old care recipients with dementia, who tend to present at more severe stages of dementia and are more cognitively and functionally impaired. An earlier Chinese study of oldest-old caregivers was limited to care recipients who were cognitively well and required less assistance in basic and IADL (7, 8). An added strength of our study is the use of a multidimensional approach to illuminate the pattern of caregiver burden by relationship and across the severity of cognitive impairment. Our results reveal that CDOO are older and typically an older adult–child or a younger non-spousal/non-child family member. Compared with their counterparts looking after the middle-old and young-old age groups, CDOO experience higher caregiver burden in the domains of role strain and personal strain but not worry about performance, even in the earliest stages of MCI and very mild dementia.

Our study affirmed the fact that relative to caregivers looking after the younger-old with dementia, CDOO experienced greater overall burden, increased demands, and lack of control over situation leading to role strain, and the psychological impact of personal strain. Notably, CDOO endorsed higher stress from behavioral symptoms even with comparable severity of behavioral symptoms, alluding to how the strain of caregiving may have affected their appraisal of the stress arising from behavioral symptoms. As individuals with dementia survive into the oldest-old age group, the fewer the number of spouses who remain as the primary caregiver and the more likely that older adult children take over this role. In a predominantly Chinese Asian society such as ours, adult–child CDOO may be thrusted into the caregiving role as there are social expectations to care for elderly family members, and filial piety is a core value in Chinese culture. Being generally older and approaching the age of retirement, adult–child CDOO may struggle even more if they have not yet made adequate arrangements for their jobs, their families, and post retirement financial security, or have concomitant health issues. Pearlin et al. reported that two types of role conflicts may appear in adult–child caregivers: one is the conflict between the caregiver role and the roles in their nuclear family, such as spouse and parent; the other one is the conflict between the caregiver role and their roles in the workplace, such as employer or employee (22). Zhan also reported that caregivers who assisted with mostly instrumental care reported greater levels of emotional and relational frustration (23). It is, therefore, not surprising that adult–child CDOO who are often unprepared for their transition into the caregiving role with increased demands of providing assistance in instrumental ADL and physical care and coping with dementia behaviors, experience the resultant emotional and relational strain arising from the caregiving role.

Our study also highlighted the differences in burden pattern among spousal and adult–child CDOO. Both groups endorsed endorsed higher ZBI total score and factor 1–3, although the scores are higher in spousal than adult–child CDOO. This observed trend might be due to factors such as closer relationship of spouses with care recipients (24), co-residence with

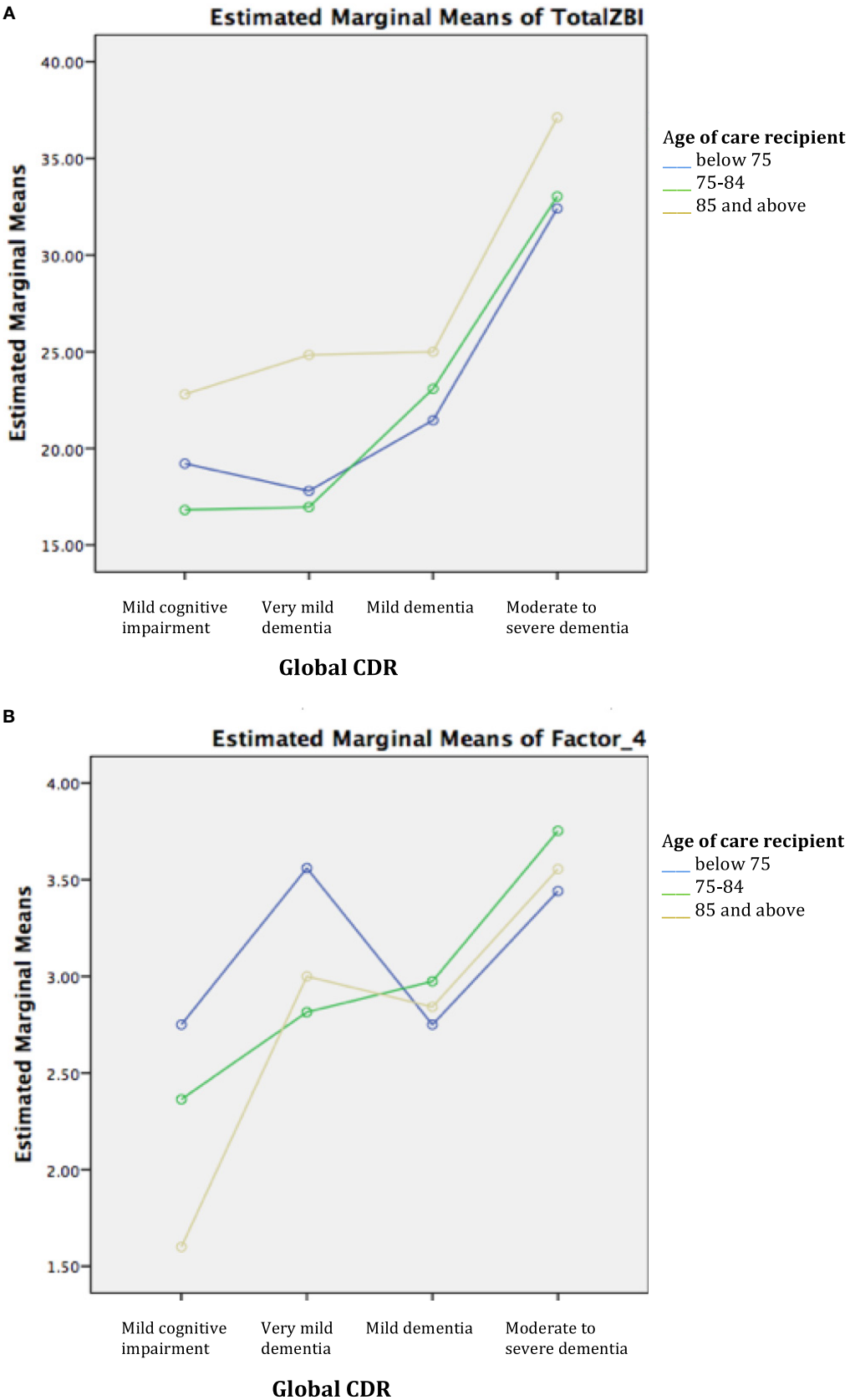

FIGURE 1 | **(A)** Trend of total Zarit Burden Interview (ZBI) across disease severity by age group. **(B)** Trend of factor 4 across disease severity by age group.

care recipients, and concomitant health and physical ailments, leading to a greater degree of perceived stress when providing long-term care (25). Comparing between the children relationships, adult-son CDOO endorsed higher factor 3 score compared to their daughter counterparts. This may be attributable to the psychological impact arising from risk of role overload from conflicting responsibilities. Because sons are generally more esteemed than daughters in more traditional Chinese families, adult-son CDOO may be expected to play a leading role in care provision for their aged parents, and this in turn can create psychological strain if they feel sandwiched between this caregiving role on top of their work and family commitments (11, 26).

In addition, our study identified that the higher overall burden among CDOO is accounted for by role and personal strain. Contrary to the findings of Liu et al. (8) that the adult–child caregiver experience significant burden from worry about performance, the adult–child CDOO (both daughters and sons) in our study paradoxically experience lower worry about performance compared with the younger-old age groups. Worry about performance is self-appraisal of their caregiving performance, which encompasses both positive and negative valences (27). On the positive end, caregivers may have positive perceptive of their capability to take good care of their family member with dementia. Conversely, worry about performance may signify negative feelings of inadequacy and self-criticism leading to guilt and shame (9). It is, therefore, important to consider the difference in context between the two studies when interpreting the seemingly discrepant findings. Liu et al. (8) examined elders who were cognitively well and required less assistance in basic and IADL, hence their adult–child caregivers would naturally "worry" how they can take better care of their parents to maintain the overall good health. In contrast, our study involved oldest-old care recipients who present at more advanced stages of dementia with increased physical and emotional care needs. Having to juggle multiple competing stressors such as personal health, family commitments, and financial issues on top of their caregiving role, adult–child CDOO not surprisingly experience role and personal strain while having a lower predilection for worry about performance stress. Our results, therefore, corroborate the findings of Lim et al. that in the context of dementia, younger age is the most important predictor of worry about performance stress even amongst adult–child caregivers (9).

Indeed, caring of frail elderly individuals with dementia can be challenging causing both physical and mental health problems in caregivers, yet, the responsibilities of caring for DOO will still fall upon the informal caregivers. So, it is vital to provide caregiver support interventions to reduce the burden faced by CDOO. Support at the individual level can be beneficial in reducing physical and psychological burden of caregiving. Interventions such as creating network for caregiver support, respite care arrangement, counseling on coping abilities and financial support can reduce caregiving burden and improve caregiving abilities in this vulnerable group of DOO patient–caregiver dyads.

Several limitations are worth highlighting. First, because this is a cross sectional study, reverse causality cannot be excluded. Further longitudinal studies will be required to affirm the findings. Second, our study sample of oldest-old care recipients is relatively small; hence the results of our exploratory study need to be further verified in larger study populations. Third, our study population of patients with milder severity of dementia of predominantly Chinese Asian ethnicity may limit the generalizability of our findings to other socio-cultural context. Fourth, we excluded friends or employed caregivers who may experience different patterns of burden compared to family caregivers. Future studies should examine the impact on psychological well-being by examining outcomes such as depression, anxiety, and quality of life. Finally, we did not collect data on certain variables that can influence the severity of caregiver stress and burden pattern, such as the duration of caregiving and the number of caregivers who are involved in the care.

In summary, our study demonstrated the unique burden faced by the caregivers of the oldest-old with dementia, who were mainly older adult children experiencing significant role and personal strain but not worry about performance from looking after their family members with more impaired cognition and physical function. Although this unique pattern of caregiver burden is generally independent of disease severity, overall burden, role strain, and personal strain are already high in the early stages of cognitive impairment, and increases further as the disease progresses. The results of our exploratory study provide insight, which paves the way to address the unique burden faced by this vulnerable group of caregivers through individualized interventions that target coping resources and stressors to increase caregiving mastery, which acts as a buffer against the deleterious impact of role and personal strain from the caregiving role (28).

ETHICS STATEMENT

The study was approved by the Institutional Review Board of the National Healthcare Group. As this study involved the retrospective review of medical records of patients attending the Memory clinic as part of a registered database (TTSH/2008-0027), waiver of informed consent was approved by the Institutional Review Board of the National Healthcare Group.

AUTHOR CONTRIBUTIONS

KW conducted the study, carried out the statistical analysis, and wrote the manuscript. MC, NA, and MC supported the development of study design and methodology, and reviewed the manuscript. WL designed the study and supported the writing of the manuscript.

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Screening of Dementia in Portuguese Primary Care: Methodology, Assessment Tools, and Main Results

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The objectives of this article are as follows: (1) to describe the assessment protocol used to outline people with probable dementia in Primary Health Care; (2) to show the methodological design and procedure to obtain a representative sample of patients with probable dementia; and (3) to report the main characteristics of the sample collected in the context of the study "Characteristics and needs of people with probable dementia." The study protocol was based on the "Community Assessment of Risk and Treatment Strategies (CARTS) Program" and is composed by a set of instruments that allow the assessment of older adults with probable dementia in several areas (health, psychological, functionality, and other). Descriptive analysis was used to characterize the final sample ($n = 436$). The study protocol as well as the methodological procedure to obtain the referral of research participants and data collection on the condition of people with probable dementia in Primary Health Care proved to be a valuable tool to obtain a sample of patients distributed by the full range of probable dementia in a large geographical area. Results may allocate the design of care pathways for old people with cognitive disorders to prevent, delay impairment, and/or optimize quality of life of patients.

Keywords: caregivers, cognitive decline, dementia, old people, primary care

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INTRODUCTION

The Portuguese Census 2011 (1) showed that in Portugal 19.1% of the total population ($n = 2{,}010{,}064$) was aged 65 or plus. According some projections, this population will increase, with the group age 80 + reaching the 15% in 2060 (2).

Presently little information is known in Portugal about the needs of the old people with probable dementia and their informal caregivers. Nunes et al. (3) estimated that the prevalence of cognitive impairment and dementia in Portuguese people living in the north of the country were 16.8 and 2.1% in rural areas, and 12 and 2.7% in urban areas, respectively; the majority of the reported cases were related with cerebrovascular diseases and vascular risk factors (48%). A more recent study (4) revealed that the prevalence of dementia/Alzheimer's disease was 5.91% in the Portuguese population with 60 or more years old. Considering the international context, the prevalence of dementia estimated by the World Health Organization (WHO) in South Europe increases with age, varying between 0.026% for individuals aged 65–69 years and 0.324% for those aged 85+ years (5). In addition, it will be expected an increase in the number of people with dementia, doubling by 2030 and tripling by 2050. These numbers have a high impact in the quality of life of the people and in the economy of the families and communities, representing one of the highest challenges/priorities of public health offices/professionals.

Early detection of probable dementia is very important, and it appears to be under diagnosed by general practitioners (GPs). Nevertheless, GPs are well positioned to notice the possible cognitive decline of their patients and can be a major potential source for increasing the rate of case detection [e.g., Ref. (6, 7)]. In a Finnish population based study, Lopponen et al. (8) found less than 50% of the patients with dementia with a diagnosis documented in primary care; the existence of diagnosis increased in more advanced stages of dementia.

High levels of poverty need to be considered in the topic of dementia (9–11) and must be addressed together with cultural aspects in the Portuguese context, namely, the low educational levels. This cross-sectional study has a main objective to draw a physical and mental health profile of the old people with dementia living in the north of Portugal and to understand their risk situation to further planning adequate responses and services for this specific population.

The main objectives of this article are as follows: (1) to describe the assessment protocol used to outline people with probable dementia in Primary Health Care; (2) to show the methodological design and procedure to obtain a representative sample of patients with probable dementia; and (3) to report the main characteristics of the sample collected in the context of the study "Characteristics and needs of people with probable dementia."

MATERIALS AND METHODS

Participants

The population of this study was defined as Portuguese people with 65 years and over, living in the community in the geographical area covered by the Portuguese North Regional Health Authority (ARS North) with mental health concerns. The geographical area is composed by 86 municipalities, which are organized in 24 Associations of Health Centres (ACES). The inclusion criteria were as follows: (a) outpatient of a health-care units integrated in an ACES covered by the ARS North and (b) age 65 or + years old. The exclusion criteria were as follows: (a) patient not using a primary health-care unit covered by the ARS North; (b) age less than 65 years old; (c) living in nursing home, hospital or psychiatric institution; and (d) absence of memory concerns [patients classified in stage 1 of the Global Deterioration Scale (GDS) (12, 13)].

Sample

Based on the distribution of Portuguese population with 65+ years old (1) and on the prevalence of dementia in the Western Europe predicted by the WHO (5), an estimate of Portuguese population with dementia by age groups is presented in **Table 1**. The sample size, calculated for each age group, was considered as 1% of the estimated population with dementia. 572 participants with probable dementia compose the final sample. **Table 1** the sample size calculation (total and by age group) according the prevalence of dementia.

Measures

The study protocol was based on the "Community Assessment of Risk and Treatment Strategies (CARTS) Program" developed in the University College Cork, Ireland (14). The study protocol includes instruments divided in three main parts: Part A: assessment of the patient with probable dementia; Part B: assessment of the patient with probable dementia by the health professional (GP or nurse); Part C: evaluation of the informal caregiver of the patient with probable dementia (if available). **Table 2** resumes the domains evaluated and the instruments used in each part of the study protocol.

Mini-Mental State Examination (15, 16) is widely used for cognitive decline screening and is composed by 19 questions divided in 6 domains. The final score vary between 0 and 30. *GDS* (12, 13) is used to classify individuals with cognitive decline according to a scale of seven points: 1. Without cognitive decline; 2. Very mild cognitive decline; 3. Mild cognitive decline; 4. Moderate cognitive decline; 5. Moderately severe cognitive decline; 6. Severe cognitive decline; and 7. Very severe cognitive decline. *AB Clinician Depression Screen* (17) is a brief version of the Geriatric Depression Scale and is composed by five dichotomist questions (yes/no). The final score vary between 0 and 5, and individuals with a score equal or higher to 3 present high probability of depression. *Timed "Up and Go"* (18) is a simple test used to assess a person's mobility, using the time that a person takes to rise from a chair, walk 3 m, turn around, walk back to the chair, and sit down. *Malnutrition Universal Screening Tool* (19, 20) is a five-step screening tool to identify adults at risk of malnutrition or obese. The final score vary between 0 and 6, considering three categories: 0. Low risk; 1. Moderate risk; and ≥2. High risk. *Short-Form Mini Nutritional Assessment* (21, 22) is a valid nutrition screening and assessment tool that can identify patients who are malnourished or at risk of malnutrition and consist in six questions. The score vary between 0 and 14 and a score equal or higher to 11 is indicator of possible malnutrition. *Bedside Swallow Assessment* allows the evaluation of swallowing after sitting the people in a right posture and asking the person to drink 30 ml of water. Three criteria were recorded and the final score of the test corresponds to the number of observed criteria: 1. No criteria; 2. Presence of 1 criterion; 3. Presence of 2 or more criteria. *Handgrip strength* is evaluated using a dynamometer considering four attempts, two in each hand. The final score correspond to the mean of the highest values. *Exhaustion* is evaluation considering a dichotomy

TABLE 1 | Sample size calculation (total and by age group) according the prevalence of dementia.

	65–69 years	70–74 years	75–79 years	80–84 years	85+ years	Total
Population	180,352	150,687	136,275	97,113	72,399	636,826
Prevalence of dementia	0.026	0.043	0.074	0.129	0.324	–
Estimated population with dementia	4,689	6,480	10,084	12,528	23,457	57,238
Final sample (1%)	47	65	101	125	235	572

TABLE 2 | Study protocol: domains and instruments used in each part.

Part A		
A1. Sociodemographic questionnaire	Sex Age Education level Profession Marital status Household Residence context Type of residence	Infrastructures accessibilities Formal care Informal care Use of health services Medication Health subsystem Health expenditures
A2. Cognition	Mini-Mental State Examination (15, 16) Global Deterioration Scale (12, 13)	
A3. Depression	AB Clinician Depression Screen (ABCDS) (17)	
A4. Biobehavioral aspects	Timed "Up and Go" (18) Malnutrition Universal Screening Tool (19, 20) Short-Form Mini-Nutritional Assessment (21, 22) Bedside Swallow Assessment Handgrip strength Exhaustion Physical activity Tobacco and alcohol consumption Whispered Voice Test (23) Snellen Test (24)	
Part B		
B1. Physical health	Older Americans Resources and Services (25, 26)	
B2. Adverse events	The Community Assessment of Risk Tool (14)	
Part C		
C1. Caregiver burden	Caregiver Burden Score (27)	
C2. Depression	ABCDS (17)	
C3. Mental health	Neuropsychiatric Inventory Questionnaire (28, 29)	

question (yes/no) "In the last month, do you feel that you had very little energy to do the things you wanted to do?" *Physical activity* frequency evaluated using a four-point question: 1. >1/week; 2. 1/week; 3. 1–3/month; and 4. Almost never or never. *Alcohol and tobacco* consumption evaluated considering a set of questions about quantity, duration, and type. *Whispered Voice Test* (23) evaluate the audition and *Snellen Test* (24) the vision The physical health dimension of the *Older Americans Resources and Services* (25, 26) comprises a checklist of 16 diagnoses. *The Community Assessment of Risk Tool-CART* (14) evaluates the perceived risk of three adverse events: institutionalization, hospitalization and death. *Caregiver Burden Score* (27) assess the caregiver burden and score vary between 0 and 30. Score equal or higher to 15 is indicator of burden. *Neuropsychiatric Inventory Questionnaire* (28, 29) is a brief version of the Neuropsychiatric Inventory and allows the evaluation of psychopathology in dementia and its repercussion on the caregiver's overload. For each symptom, it evaluates the presence (yes/no), severity (1. Low; 2. Moderate; and 3. Severe) and caregiver distress (0. Not at all; 1. Minimally; 2. Mildly; 3. Moderately; 4. Severely; and 5. Very severely or extremely).

Ethical Procedure

The study was submitted to the ethical committee of the ARS North—procedure number 6/2014 and approved at 7 January 2014. All the participants signed the informed consent form that was developed according the Declaration of Helsinki.

Data Collection

The data collection started in 2014 January and ended in 2016 April. **Figure 1** shows the data collection's flowchart.

The first step consisted in the contact with the 24 ACES to obtain the authorization to do the study. All ACES had accepted to participate.

The second step consisted in contacting at least two health-care units of each ACES with health professionals presenting interest in participating in the study. The health professional had as main responsibility filling in the screening instrument regarding the identification of people at risk of adverse health outcomes, namely, mental health concerns. The instrument used was the Risk Instrument for Screening in the Community (30), which is a new risk instrument for screening of old people. Based on the information about the patient, the health professional classified the patient in three different domains (mental health, ADLs, and physical/medical health) in a perceived risk scale (from 1. Minimum risk to 5. Extreme risk) for the following three adverse events: hospitalization, institutionalization, and death. All health professional involved in this step received training to use this instrument by the investigators and the sessions took place in the health-care unit facilities. In this screnning, 55 health-care units were enrolled, with the participation of 285 health professionals who filled 7,298 valid screenings.

In the third step, and based on this screening and considering only patients with mental health concerns ($n = 2{,}734$), the sample was calculated using the stratified probability sampling method, considering sex, age groups, and ACES as strata. The technique used to extract patients for the sample was the lottery technique. Each patient with mental health concerns received a random number. The patients who received the higher numbers were invited to participate in the study, until all planned quotas were completed.

The health-care office contacted the selected patients, explaining the purpose of the study; if the patients agreed to participate they were further referred to the research team. In a second moment, the interviewers contacted the patients to schedule the interviews according to their availability. A limit of four contacts was fixed until a patient was withdrawn. In these situations, if available, another patient with similar conditions of the previous one was selected, according the sampling method described earlier.

The majority of the interviews were done in the health-care units (79.6%), in an appropriate local where confidentiality was guaranteed. If it was impossible to do the interview in the health-care unit, the interviews were completed at patients' home (19.9%). The main reason for the interviews to take place at home was the incapacity of the patient due to being bedridden or presenting low mobility. In the first moment of the interview, the patient was informed about the conditions of participation in the study, with the opportunity to clarify doubts. In order to formalize the interest of the patient in participating in the study, a personal Informative Consent was signed. If the patient did not have cognitive capacity, the signature of the consent was required to his/her legal representative.

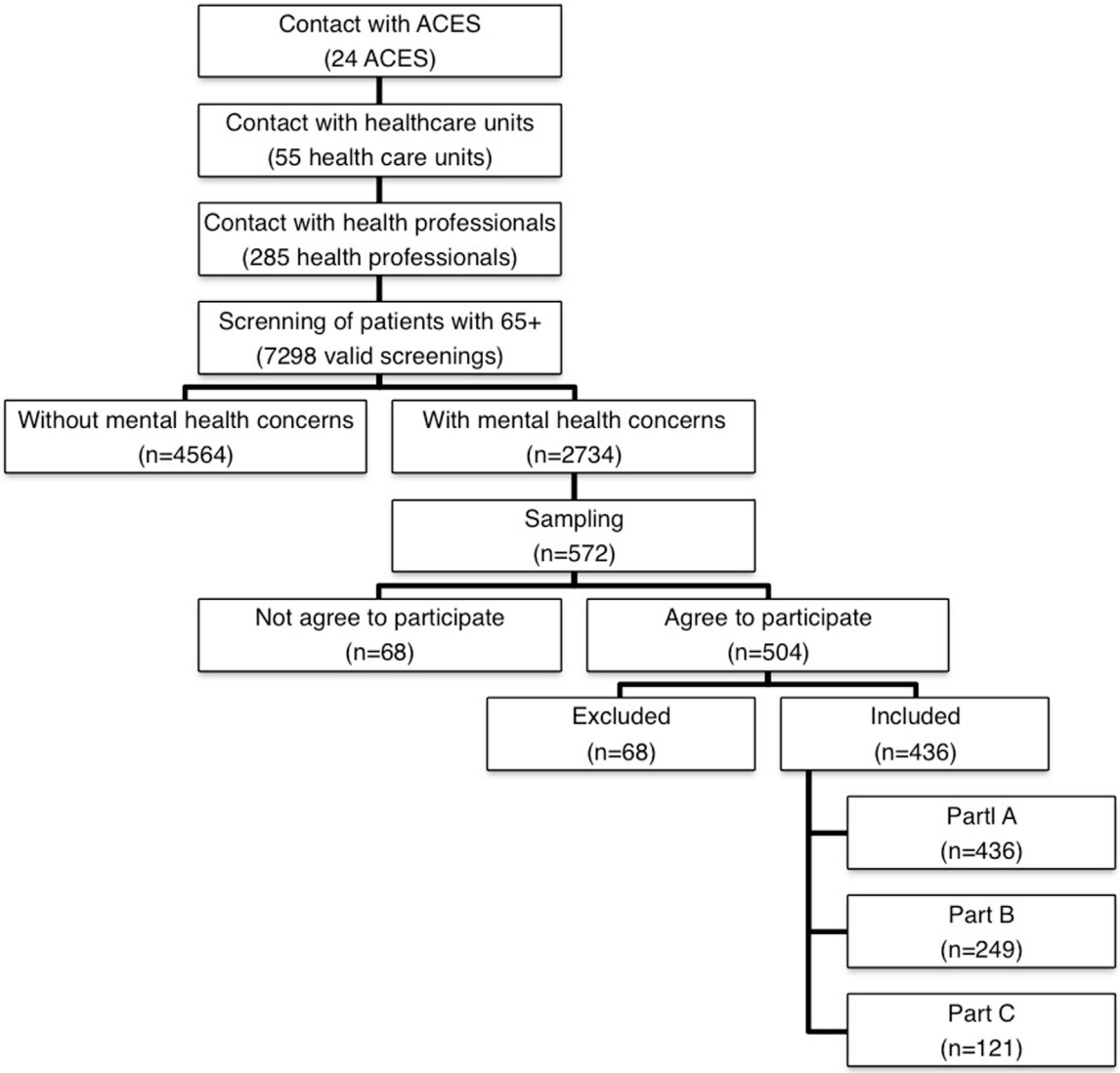

FIGURE 1 | Data collection's flowchart.

The study protocol took on average 45 min to complete. If the informal caregiver was present, the interviewer asked him/her to fill the Part C. After the interview, the health professional (GP or nurse) complete the Part B.

Regular meetings occur between the interviewers and the coordinator of the study with the purpose of supervising and monitoring of the data collection. The planning of data collection, the discussion of cases and the analysis of problems related with the scoring of the scales included in the study protocol were the main aspects discussed in the meetings.

The final sample comprised 436 patients with probable dementia. The ratio of execution was 76.2%. The observed differences between the expected and collected samples are associated with some constrains related with the data collection, namely, difficulties/mistakes in the referral of cases and the high number of refuses to participate in the study (**Figure 1**).

Statistical Analysis

Given the presence of non-response related with the data collection, some groups were over- or underrepresented. A weighting adjustment procedure was implemented considering the projections of the population distributed by sex and age groups for 2012 (2). Descriptive analysis of the final weighted sample was performed to obtain a sociodemographic description of this population.

RESULTS

The sociodemographic characteristics of the sample ($N = 436$) are presented in **Table 3**. The sample included mostly women (58.7%). The mean age was 75.2 years old (SD = 7.2 years old). The education level with higher representation was primary level (1–4 years), and a relevant percentage of the sample was illiterate (21.0%). Sixty-one percent were married/living with partner, 93.3% had children and

TABLE 3 | Sociodemographic characteristics of the sample.

Sociodemographic characteristics	*N*	%
Sex	436	
Male		41.3
Female		58.7
Age	436	
Years, mean (SD)		75.2 (7.2)
Education level	434	
Illiterate		21.0
1–4 years		69.7
5–6 years		4.5
7–9 years		2.1
10–12 years		1.9
>12 years		0.8
Marital status	435	
Single		5.9
Married/lived with partner		60.9
Separated/divorced		4.5
Widowed		28.7
Children	316	
No		6.7
Yes		93.3
n, mean (SD)		3.4 (2.3)
Grandchildren	242	
No		16.2
Yes		83.8
n, mean (SD)		3.9 (3.6)
Living arrangement	432	
Alone		15.7
Partner		62.9
Children		33.6
Other relative		21.2
Other		1.1
Context	416	
Rural		47.9
Urban		52.1

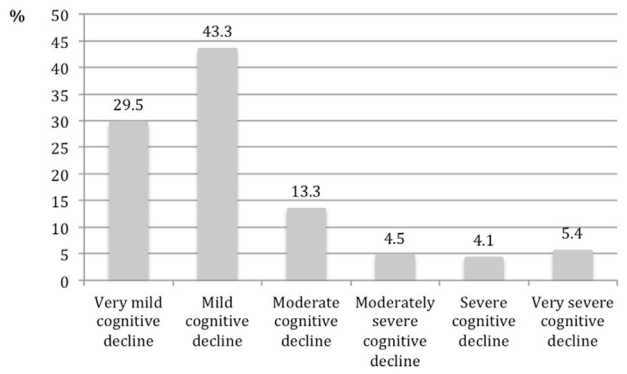

FIGURE 2 | Distribution of the sample according to the stage of the GDS scale.

83.8% had grandchildren. The majority of the patients lived with a spouse or partner, with an expressive percentage living alone (15.7%). The distribution of people by urban/rural contexts was balanced (52.1% in urban areas and 47.9% in rural areas).

The distribution of the sample according to the stage of the GDS scale is presented in **Figure 2**. Forty-three percent of the sample was classified with mild cognitive decline, followed by 29.5% classified as very mild cognitive decline, and 13.3% as moderate cognitive decline. The most severe stages included 14% of the sample, with the stage "very severe cognitive decline" reaching 5.4%. In the group of people evaluated by the GP ($N = 249$), 39% had a formal diagnosis of dementia.

CONCLUSION

The research design covering a large geographical area and the high participation of GPs in pre-screening patients from where the random sample was extracted are the main strengths of this study. The participation rate of GPs in the second phase of patients' assessment is the major limitation. The complex methodological process to obtain data on probable dementia patients in primary care, described earlier reflects the difficulty to tackle dementia in Primary Health-Care Services. Nevertheless, this procedure may configure a pathway of care that ultimately saves time and financial resources to GPs, preventing the comprehensive assessment of older patients that are not at risk of developing dementia.

The study protocol proved to be a valuable tool for a comprehensive assessment to identify patients and characterize their health needs and staging the cognitive decline. Based on GDS, the distribution of patients by different levels of probable dementia corroborate the findings of Lopponen et al. (8) and Prince et al. (31) for developed countries.

The enrollment of the primary health-care team and of the primary caregivers in the research facilitates the access to relevant data and mobilizes attention of professionals and family to an under diagnosis and under treated disease that leaves patients and carers helplessness.

It is barely feasible or adequate to assess every old adult for cognitive decline and we know that dementia seems to be reducing its prevalence at least in UK (32). Selecting people with mental health concern before sampling appears to be a good methodological approach to arrive to a clear distribution of patients across different stages of probable dementia. This will contribute to design effective pathways of care for people with cognitive decline. Mobilizing and training GPs and other primary care professionals will foster referral of patients to customized bundles of care, leading to a global and effective plan for dementia.

ETHICS STATEMENT

The study was submitted to the ethical committee of the ARS North—procedure number 6/2014 and approved at 7 January 2014. All the participants signed the informed consent form that was developed according the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

LT and CP conceived the research project design, wrote the manuscript, and conducted the data analysis. PS and AL contributed in the project conception and reviewed the manuscript. SA, MA, and MD were enrolled in the data collection and revised the manuscript.

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Alzheimer's Disease Diagnosis: Discrepancy between Clinical, Neuroimaging, and Cerebrospinal Fluid Biomarkers Criteria in an Italian Cohort of Geriatric Outpatients: A Retrospective Cross-sectional Study

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Background: The role of cerebrospinal fluid (CSF) biomarkers, and neuroimaging in the diagnostic process of Alzheimer's disease (AD) is not clear, in particular in the older patients.

Objective: The aim of this study was to compare the clinical diagnosis of AD with CSF biomarkers and with cerebrovascular damage at neuroimaging in a cohort of geriatric patients.

Methods: Retrospective analysis of medical records of ≥65-year-old patients with cognitive impairment referred to an Italian geriatric outpatient clinic, for whom the CSF concentration of amyloid-β (Aβ), total Tau (Tau), and phosphorylated Tau (p-Tau) was available. Clinical diagnosis (no dementia, possible and probable AD) was based on the following two sets of criteria: (1) the *Diagnostic Statistical Manual of Mental Disorders* (*DSM*-IV) plus the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and (2) the National Institute on Aging-Alzheimer's Association (NIA-AA). The Fazekas visual scale was applied when a magnetic resonance imaging scan was available.

Results: We included 94 patients, mean age 77.7 years, mean Mini Mental State Examination score 23.9. The concordance (kappa coefficient) between the two sets of clinical criteria was 70%. The mean CSF concentration (pg/ml) (±SD) of biomarkers was as follows: Aβ 687 (±318), Tau 492 (±515), and p-Tau 63 (±56). There was a trend for lower Aβ and higher Tau levels from the no dementia to the probable AD group. The

percentage of *abnormal liquor* according to the local cutoffs was still 15 and 21% in patients without AD based on the *DSM*-IV plus NINCDS-ADRDA or the NIA-AA criteria, respectively. The exclusion of patient in whom normotensive hydrocephalus was suspected did not change these findings. A total of 80% of patients had the neuroimaging report describing chronic cerebrovascular damage, while the Fazekas scale was positive in 45% of patients overall, in 1/2 of no dementia or possible AD patients, and in about 1/3 of probable AD patients, with no difference across ages.

Conclusion: We confirmed the expected discrepancy between different approaches to the diagnosis of AD in a geriatric cohort of patients with cognitive impairment. Further research is needed to understand how to interpret this discrepancy and provide clinicians with practical guidelines.

Keywords: Alzheimer, aging, clinical criteria, biomarkers, neuropsychological tests, cerebrovascular disease

INTRODUCTION

For decades, Alzheimer's disease (AD) has been diagnosed only based on clinical criteria (1). With the increasing knowledge of the pathogenic processes underlying this and other dementias, several biomarkers have been proposed to support the diagnosis, also at early stages (2–4). Biomarkers are defined as any objective measurement of an *in vivo* pathological process (5). Cerebrospinal fluid (CSF) proteins [amyloid-β (Aβ) protein, total Tau (Tau), and phosphorylated Tau (p-Tau)] and functional and anatomical neuroimaging findings represent the most studied biomarkers of AD.

The role of these biomarkers in the diagnosis of AD in clinical practice has not been completely clarified yet, as both the American (1) and International Working Group Guidelines (6) underline. Understanding their role in the diagnostic workflow might be particularly challenging in an older population (>85 years) presenting with cognitive impairment. There is evidence suggesting that, as age increases, the prevalence of pathological patterns that have been associated with the disease, increases also in subjects without cognitive impairment (7, 8). Also, the association between the presence of neuritic plaques in autoptic specimens and dementia is less strong in older people (9, 10). Changes in neuroimaging may be less salient in the older ages, in which atrophy often coexists with cerebrovascular damage. Furthermore, chronic cerebrovascular disease is such a frequent neuroimaging finding that its contribution to the cognitive deficit remains difficult to define, especially when not properly quantified (11). Finally, in the oldest patients, the burden of comorbidities often makes the scenario more complex (6). All these reasons increase the chance of conflicting findings between biomarkers and clinical symptoms. The whole picture is further complicated by the fact that the existing sets of diagnostic criteria for AD proposed by different scientific societies assign a different place to some clinical symptoms and signs. In fact, the diagnostic criteria have changed over time, integrating the new knowledge upon the disease mechanisms and biomarkers and reflecting different disease definitions (1, 6, 12). However, the newer criteria have not replaced the older ones, which are still being used in clinical research, and in particular in studies evaluating therapies for AD (13). The dimension of the problem can be substantial and represents a barrier to a straightforward diagnostic process in routine practice, especially in those clinical settings providing care to less selected older patients such as geriatrics.

With such a background, the objective of our study was to represent the level of discrepancy between different diagnostic approaches, describing a population of older patients with cognitive impairment referred to an Italian geriatric outpatient clinic. In particular, we compared the diagnosis based on clinical criteria with the CSF biomarkers and with cerebrovascular damage finding at neuroimaging.

MATERIALS AND METHODS

Study Design and Population

This is a retrospective cross-sectional study of medical records of 65-year-old or older patients, referred to the Alzheimer Evaluation Unit (UVA) of the Division of Geriatrics of the IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan between June 2009 and October 2014. Ethical approval was not required for this study in accordance with the institutional guidelines.

We included in the study all those patients with a cognitive impairment who underwent at physician's discretion a lumbar puncture during the diagnostic workup and for whom the concentration of Aβ, Tau, and p-Tau in the CSF was available. There was no exclusion criterion. In particular, as per our practice, patients undergo a lumbar puncture with liquor collection and examination: (i) in the context of differential diagnosis of dementia, when the treating physician deems it as necessary to help confirm or rule out a clinical suspicion of AD, and (ii) in the context of diagnosis and therapy (i.e., *ex juvantibus*) of normotensive hydrocephalus.

All patients undergo the lumbar puncture only if a specific written informed consent was provided by the patient or by her/his next of kin.

Retrospectively, but in a blind fashion with respect to the actual diagnosis made by the treating physician, we characterized

the patients according to different diagnostic approaches. We first classified the patients using two different sets of clinical diagnostic criteria for AD (not taking into account the laboratory findings) and then compared the clinical diagnoses with the results of CSF biomarkers. Second, we described the prevalence of signs of vascular damage at neuroimaging according to different approaches, i.e., standard descriptive reports versus visual quantitative scales, and its correlation with the clinical and the liquor-based classifications. Within this framework, we also evaluated the contribution of neuropsychological (NPS) tests in making the diagnosis of AD. In fact, it is known that many patients with cognitive impairment have poor awareness or understanding of their cognitive impairment (14). Thus, an objective cognitive assessment lies at the core of an appropriate diagnostic workup for cognitive decline. Moreover, NPS tests can help define early or prodromal states like a mild cognitive impairment (MCI), in which biomarkers might be already positive (6, 15, 16). Finally, all the patients for whom a brain magnetic resonance imaging scan was available were included in the sub-study on neuroimaging.

To have an objective comparison across different diagnostic tools, we included all patients with a CSF record, regardless of the final diagnosis made by the treating physician. Patients with a clinical suspicion of normotensive hydrocephalus were included in the main analyses as expected negative cases (i.e., cases in which CSF biomarkers were expected to be negative). They were then excluded as a sensitivity analysis.

Data Collection

Patient medical records temporarily close but preceding the time of the lumbar puncture were evaluated for the purpose of our study. The study investigators were guarantor for protecting the confidential data from any inappropriate use beyond the purpose of this study.

Clinical Diagnostic Criteria and NPS Assessment

Two investigators (GD and AG) screened the patient charts independently and retrospectively reanalyzed medical records of patients included in the study, being blinded to the diagnosis that was made by the treating geriatrician. Clinical diagnosis of dementia and of AD was based on the criteria of the *Diagnostic Statistical Manual of Mental Disorders* (*DSM*-IV) (17) and of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) 1984 (18), respectively (Appendix in Supplementary Material). Patients were also classified according to the criteria for dementia and AD of the National Institute on Aging-Alzheimer's Association (NIA-AA) 2011 (1) (Appendix in Supplementary Material). Based on each of the two sets of clinical criteria, patients were classified into no dementia, possible AD, and probable AD. The results of the following clinical investigations were taken into account for the classification of each patient upon those criteria, when available: the multidimensional geriatric assessment, blood tests, NPS tests, and neuroimaging. In particular, we relied on the results of the NPS assessment, when available, in case of inconsistency between the NPS report and the record of the geriatric visit for what concerned the presence of memory deficits and the level of impact on function. In order to preserve the comparative analyses of our sub-study, when we applied the clinical diagnostic criteria, we used the neuroimaging reports only to rule out the presence of a clear alternative diagnosis (i.e., normotensive hydrocephalus, multi-infarct disease, and tumor). The descriptive finding of "leukoaraiosis" or "chronic cerebrovascular disease" was not considered sufficient for meeting the criterion of an alternative (i.e., vascular) etiology of dementia.

We looked for the NPS assessment that preceded or coincided with the date of the lumbar puncture. In patients with multiple assessments, we used the outcome of the assessment that was temporarily closer to the date of the lumbar puncture. We used the outcome of NPS tests performed after the lumbur puncture only if temporarily very close (no more than 1 month later). The battery of NPS tests was administered by an expert neuropsychologist. Global cognitive functioning was assessed by means of the Mini Mental State Examination (MMSE) (19) and general intellectual functioning was investigated by using Raven's colored progressive matrices (20). For temporal orientation, the first item of the MMSE was considered. Anterograde long-term memory was rated with the prose recall test (21) and the delayed recall of the Rey–Osterreith complex figure test (17). Verbal short-term memory was assessed by means of the forward digit span test (18). The digit cancelation test (21) was administered to examine visual attention. Executive prefrontal functions were evaluated using the backward digit span test (17), the trail-making test (22), and the phonological fluency test (23). Spatial skills were divided into spatial orientation, assessed by the second item of the MMSE, and spatial abilities, explored by means of the copy of geometrical figure test (20) and the copy of the Rey–Osterreith complex figure test (17). Language was examined using the picture-naming test (24). All tests, excepted for the orientation one, have been validated and standardized in a sample of healthy Italian subjects. Most of the normative data are referred to the study from Spinnler and Tognoni (21). According to the outcome of the NPS assessment, patients were classified into: normal cognition, MCI, or diffuse/severe cognitive impairment. Patients classified as MCI were divided into the following four subtypes: only memory domain affected, single-domain MCI with a deficit other than on memory domain, multiple domain MCI with memory domain affected, and multiple domain MCI with deficits other than on memory domain.

CSF Biomarkers

The lumbar puncture was performed according to procedural standards. The dosage of Aβ protein, Tau, and p-Tau in the liquor was performed on site. The cerebrospinal fluid sample was centrifuged at 4°C and stored at −30°C until analysis. Aβ42 protein, Tau and p-Tau 181 were determined by ELISA kits (Innogenetics). The local laboratory cutoff points for normal protein concentrations are as follows: Aβ42 > 600 pg/ml, Tau < 500 pg/ml, and p-Tau < 61 pg/ml.

Neuroimaging

Available brain MRI images were examined independently and retrospectively by three operators blinded to the patient clinical

history. The Fazekas visual scale (25) was applied on at least one long TR sequence, Flair or T2. Given the smallest number of missing data, for the purpose of the analysis, only axial plane images were considered. The Fazekas scores range from 0 (normal) to 3 (extensive, diffuse, and confluent lesions of the subcortical white matter). For the purpose of our analyses, we dichotomized the Fazekas scores into negative (0 or 1) and positive (≥2). We chose this cutoff in order to be more specific in this population at high prevalence of chronic cerebrovascular damage.

We decided not to include the assessment of atrophy according to the qualitative versus quantitative approach in our comparative analyses, because only a very small subgroup of patients had suitable MRI images to apply atrophy quantitative scales. Functional neuroimaging (positron emission tomography) was available only for few patients.

Statistical Analysis

Descriptive statistics (mean, SD, median and range in case of numerical variables, and frequency in case of categorical variables) were used to present the classification of patients according to the clinical criteria (*DSM*-IV plus NINCDS-ADRDA versus NIA-AA), the CSF biomarkers, and the neuroimaging biomarkers of cerebrovascular disease. First, the two different clinical criteria were compared and the concordance was measured by Cohen's kappa calculation (to take into account the effect of chance). Distributions of biomarkers were compared with the clinical diagnoses according to the NIA-AA criteria, using cross tabulations and Pearson χ^2 or Kruskal–Wallis test, in the whole cohort and by age groups. As sensitivity analyses, the comparison was repeated (i) excluding patients that underwent the lumber puncture in the context of a suspicion of normotensive hydrocephalus and (ii) taking into account the NPS diagnosis. Inter-rater reproducibility for the MRI visual scales was also calculated as Kappa.

RESULTS

The clinical records of 94 patients were examined. **Table 1** shows the baseline characteristics of the study cohort. In most of the cases (68%), the lumbar puncture was performed in the context of a differential diagnosis for AD. In 11 of these 64 patients, alternative dementia etiologies were considered: Lewi Body Dementia in four patients; Fronto-Temporal Dementia in six patients (in one of these patients normotensive hydrocephalus etiology was also under consideration); and subclinical hypothyroidism in one patient. In 30 patients, normotensive hydrocephalus was the main diagnostic hypothesis and the main reason for the lumbar puncture.

Table 2 summaries the availability of data for the comparison of the different diagnostic tools.

Classifications According to Clinical Diagnostic Criteria and CSF Biomarkers

A total of 55 (58%), 13 (14%), and 26 (28%) patients were classified as being affected by no dementia, possible AD, and probable AD, respectively, according to the *DSM*-IV plus NINCDS-ADRDA criteria; 39 (41%), 27 (29%), and 28 (30%), respectively, according to the NIA-AA. As pre-specified, criterion on the presence of memory deficits was fulfilled using the objective outcome of the NPS assessment. In fact, 64% of those patients who had no objective memory deficit at the NPS tests had expressed a memory complaint during the clinical visit.

Table 3 compares patient classification according to the *DSM*-IV plus NINCDS-ADRDA with the NIA-AA clinical

TABLE 1 | Baseline characteristics.

Characteristics	Distribution
Mean age (SD), years	77.7 (5.2)
Female, *n* (%)	58 (61.7)
Mean MMSE (SD)	23.9 (4.1)
Mean basic ADL score (SD)	4.7 (1.6)[a]
Mean instrumental ADL score (SD)	4.3 (2.5)[a,b]
History of hypertension, *n* (%)	58 (61.7)
History of diabetes mellitus, *n* (%)	18 (19.1)
History of dyslipidemia, *n* (%)	40 (42.5)
Smoker, *n* (%)	
Yes	53 (53.4)
No	10 (10.6)
Ex	31 (33.0)
History of coronary artery disease, *n* (%)	9 (9.6)
History of stroke or TIA, *n* (%)	8 (8.5)
History of peripheral artery disease, *n* (%)	4 (4.2)
Carotid atherosclerosis, *n* (%)	43 (45.7)[c]

n, number; MMSE, Mini Mental State Examination; ADL, activity of daily living; TIA, transient ischemic attack.

[a]*Information missing for one patient.*

[b]*In 35 patients (30 men), The maximum number of applicable items was less than 8.*

[c]*Stenosis of at least 20% at the US scan.*

TABLE 2 | Availability of data on the different diagnostic approaches in the study cohort.

Diagnostic approach	Number of patients with data (% of the total cohort)
Clinical criteria	94 (100)
CSF biomarkers	94 (100)
NPS assessment	71 (75)
Neuroimaging—standard report	76 (81)
Neuroimaging—Fazekas scale	40 (42)

CSF, cerebral spinal Cerebrospinal fluid; NPS, neuropsychological.

TABLE 3 | Comparison of *Diagnostic Statistical Manual of Mental Disorders* (*DSM*-IV) plus National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for the diagnosis of Alzheimer's disease (AD).

Clinical diagnostic criteria		NIA-AA criteria			
		No dementia, *n* (%)	**Possible AD, *n* (%)**	**Probable AD, *n* (%)**	**Total, *n* (%)**
***DSM*-IV plus NINCDS-ADRDA criteria**	**No dementia, *n* (%)**	39 (71)	16 (29)	0 (0)	55 (58)
	Possible AD, *n* (%)	0 (0)	11 (85)	2 (15)	13 (14)
	Probable AD, *n* (%)	0 (0)	0 (0)	26 (100)	26 (28)
	Total, *n* (%)	39 (41)	27 (29)	28 (30)	94 (100)

criteria. Every patient who was classified as demented according to the *DSM*-IV criteria was also classified as demented according to the NIA-AA criteria; whereas 29% classified as demented according to the NIA-AA criteria were not demented according to *DSM*-IV criteria. The crude concordance between the two sets of criteria for the diagnosis of dementia was 83%, with a kappa coefficient of 67%. The crude concordance for the specific diagnosis (no dementia, possible and probable AD) between the two criteria was 81% with a kappa of 70%.

The mean (SD) value of Aβ, Tau, and p-Tau in the study population was 687 pg/ml (318), 492 pg/ml (515), and 63 pg/ml (56), respectively. According to the local laboratory cutoffs, Aβ and Tau values were on average normal whereas mean p-Tau values were abnormal (high).

There was a statistically significant difference in the CSF concentration of Aβ and Tau but not of p-Tau, across the three diagnoses made according to both NINCDS-ADRDA and NIA-AA criteria (**Figure 1**). In particular, there was a trend for lower Aβ values and higher Tau levels going from the no dementia group to probable AD group, more evident in the case of the NINCDS-ADRDA diagnoses.

When the biomarkers levels were dichotomized based on local lab cutoffs into *positive* (i.e., abnormal) or *negative* (i.e., normal), the frequency of biomarkers positivity differed across the diagnoses in a statistically significant way only for Aβ, with both *DSM*-IV plus NINCDS-ADRDA and NIA-AA classification (4). Every biomarker tended to be more frequently positive in the case of patients with a diagnosis of probable AD compared to patients with a diagnosis of possible AD or no dementia (**Table 4**). Compared to patients with no dementia, patients with possible AD tended to present with positive biomarkers more frequently when *DSM*-IV plus NINCDS-ADRDA criteria were used but less frequently when NIA-AA criteria were used (**Table 4**).

Then, the CSF biomarkers were considered as a whole and the patient classified as having *positive liquor* only when the level of all the three proteins was abnormal (i.e., reduced Aβ, elevated Tau, and p-Tau). In this case, only 18 patients (19%) had *positive liquor*. Patients with *positive liquor* were on average younger than those with *negative liquor* [mean age 74.7 (SD ±3.7) versus 77.2 (SD ±2.7), p for Kruskal–Wallis test = 0.002].

Table 5 shows the distribution of the *liquor* biomarker according to the different diagnoses and to different age groups. The trend for *positive liquor* was the same in the whole population and in the two age groups, with a higher prevalence of *positive liquor* in probable AD than in possible AD and no dementia, in both clinical classifications. The prevalence was again higher in those with no dementia than in those with possible dementia in the case of NIA-AA criteria. In any age group and in any clinical diagnosis group, a *negative liquor* was more prevalent than *positive liquor* (**Table 5**).

When we considered age cutoffs progressively lower than 80, the percentage of patients with *positive liquor* became higher than the percentage of patients with *negative liquor* only among patients with a diagnosis of probable AD (any set of criteria) younger than 76 years (66% positive versus 33% negative).

Thirty of the 94 patients underwent a lumbar puncture in the context of a clinical suspicion of normotensive hydrocephalus. When re-classified in a blinded fashion according to the two sets of clinical criteria, these patients were all classified as with no dementia according to the *DSM*-IV criteria. According to the NIA-AA criteria, 19 (63%) patients were not demented and 11 (27%) patients had a possible AD. **Table 6** shows the comparison between the clinical (NIA-AA criteria) and the liquor diagnoses when patients with normotensive hydrocephalus were excluded. The trend did not change compared with the main analysis.

NPS Assessment

The outcome of the NPS assessment was available for 71 patients. Only one patient had a normal test performance; 44 patients were diagnosed as affected by diffuse cognitive impairment; and 26 patients were diagnosed as affected by MCI. Age was no significantly different between patients with diffuse cognitive impairment (mean 76.4 years, SD ±3.8) and patients with MCI (mean 76.4 years SD ±5.5). Twenty-six of the 27 patients classified as with no dementia according to the NIA-AA criteria (96.3%) were diagnosed as affected by MCI, most of them (88%) with deficits in multiple cognitive domains. In particular, the definition into MCI subtypes was available for 25 patients: three (12%) patients were classified as single MCI with only memory domain affected; 15 (60%) patients were classified as multiple domain MCI with memory domain affected; and seven (26%) patients were classified as multiple domain MCI with deficits other than on memory domain. No patient was classified as single-domain MCI with a deficit other than on memory domain.

Tables 7 and **8** show the frequency of liquor positivity according to the NPS outcome and MCI phenotypes, respectively. There was no statistically significant difference in the frequency of positivity across NPS definitions. In particular, the biomarker liquor tended to be more frequently positive in patients with MCI than in patient with diffuse cognitive impairment.

Cerebrovascular Burden at Neuroimaging

MRI images were available for 40 patients. Thirty-two of these 40 (80%) patients had a diagnosis of cerebrovascular damage according to the qualitative report made by the radiologist. Mean Fazekas score was 1.55 ± 1. According to the Fazekas score 18 of the 40 (45%) patients were *positive*. **Table 9** shows the mean Fazekas scores and positivity according to the clinical diagnostic criteria. According to both clinical classifications, Fazekas was positive in about half of the patients with no dementia or possible AD, while it was positive in about one-third of the patients with probable AD. When only patients with a diagnosis of probable AD according to the NIA-AA criteria were considered, the proportion of patients with a positive Fazekas in progressively younger subgroups remained the same or increased compared with the whole population or with the oldest ones (**Table 10**). The results were the same for patients with probable AD according to *DSM*-IV plus NINCDS-ADRDA criteria.

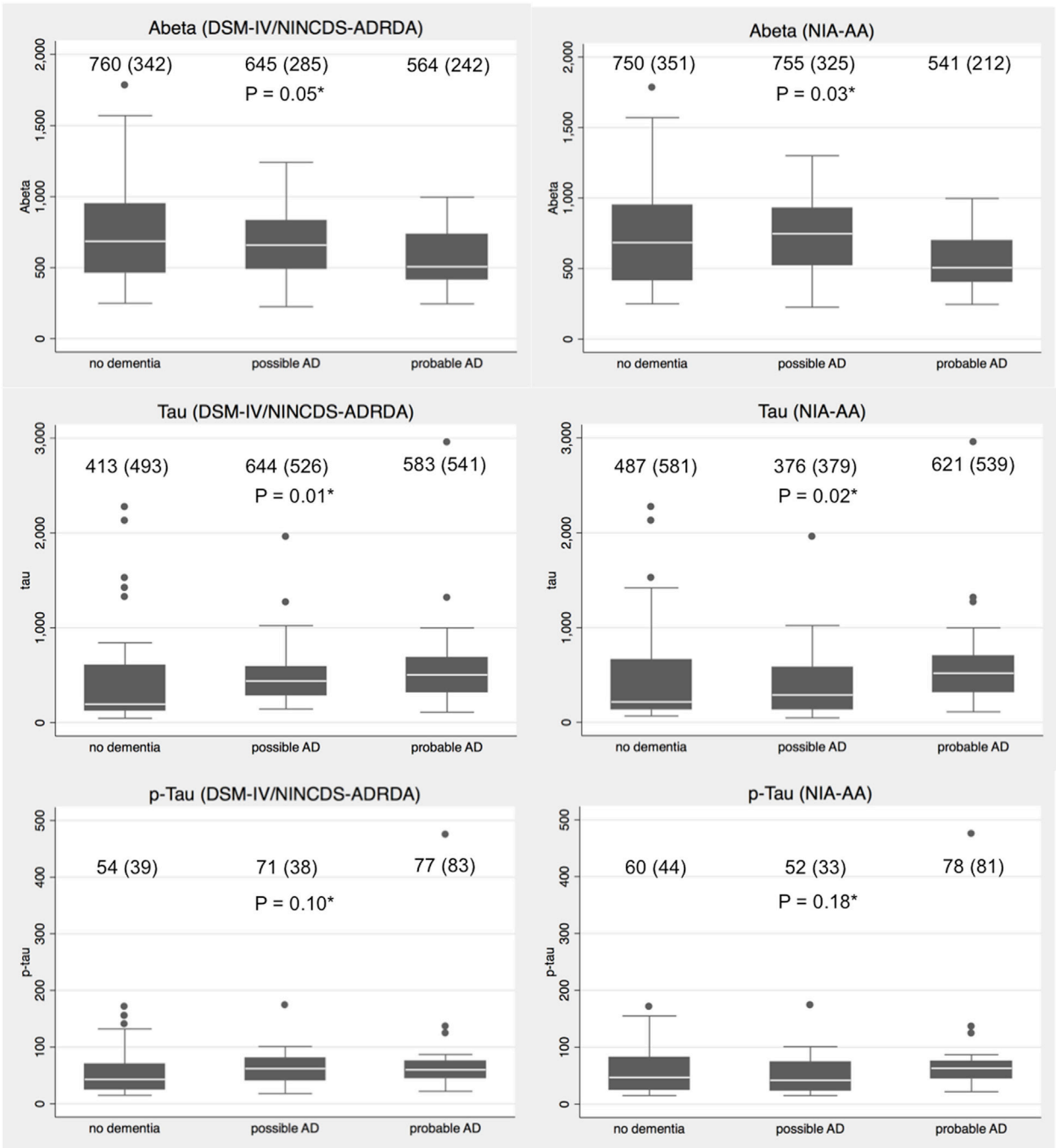

FIGURE 1 | Distributions of amyloid-β (Aβ), total Tau (Tau), and phosphorylated Tau (p-Tau) values in no dementia, possible Alzheimer's disease (AD) and probable AD patients according to *Diagnostic Statistical Manual of Mental Disorders* (*DSM*-IV) plus National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and National Institute on Aging-Alzheimer's Association (NIA-AA) criteria. Legend: mean (SD) concentration is provided for each diagnostic category. *Kruskal–Wallis test for difference in the protein distribution across diagnostic groups.

When in the same patients with a clinical diagnosis of probable AD (according to NIA-AA or NINCDS-ADRDA criteria) the Fazekas results were cross-tabulated with the CSF results (**Table 11**), there was no statistically significant difference in frequency distribution.

DISCUSSION

Our retrospective analysis of a cohort of patients with a cognitive deficit referring to a geriatric outpatient clinic (mean age 78 years), confirmed a non-negligible discrepancy between the

TABLE 4 | Relationship between CSF biomarkers and clinical diagnosis.

	Diagnostic Statistical Manual of Mental Disorders-IV plus National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria			National Institute on Aging- Alzheimer's Association criteria		
	Amyloid-β (Aβ)	Total tau (Tau)	Phosphorylated tau (p-Tau)	Aβ	Tau	p-Tau
	Positive, *n* (%)	Positive, *n* (%)	Positive, *n* (%)	Positive, *n* (%)	Positive, *n* (%)	Positive, *n* (%)
No dementia	20 (36)	17 (31)	19 (35)	16 (41)	12 (31)	15 (39)
Possible AD	5 (38)	5 (38)	7 (54)	8 (30)	8 (30)	9 (33)
Probable AD	18 (69)	13 (50)	13 (50)	19 (68)	15 (54)	15 (54)
Pearson χ^2, *p*	0.012	0.251	0.261	0.013	0.102	0.277

TABLE 5 | Distribution of the biomarker *liquor* according to the *Diagnostic Statistical Manual of Mental Disorders* (*DSM*-IV) plus National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADDRDA) and National Institute on Aging-Alzheimer's Association (NIA-AA) diagnosis and age groups.

Age (years)	*DSM*-IV plus NINCDS-ADRDA criteria			NIA-AA criteria		
	Diagnosis	Positive liquor, *n* (%)	Pearson χ^2, *p*	Diagnosis	Positive liquor, *n* (%)	Pearson χ^2, *p*
Any	No dementia	8 (15)	0.208	No dementia	8 (21)	0.027
	Possible AD	2 (15)		Possible AD	2 (4)	
	Probable AD	8 (31)		Probable AD	8 (32)	
≥80	No dementia	2 (7)	0.324	No dementia	2 (11)	0.321
	Possible AD	0 (0)		Possible AD	0 (0)	
	Probable AD	1 (20)		Probable AD	1 (20)	
<80	No dementia	6 (24)	0.494	No dementia	6 (27)	0.168
	Possible AD	2 (16)		Possible AD	1 (7)	
	Probable AD	7 (33)		Probable AD	8 (35)	

TABLE 6 | Distribution of the biomarker *liquor* according to National Institute on Aging-Alzheimer's Association (NIA-AA) diagnosis in patients without a clinical suspicion of normotensive hydrocephalus.

Diagnosis NIA-AA criteria	Positive liquor, *n* (%)	Pearson χ^2, *p*
No dementia	7 (35)	0.102
Possible AD	1 (4)	
Probable AD	9 (32)	
Any	17 (27)	

TABLE 7 | Positivity of the biomarker according to different neuropsychological (NPS) diagnosis.

	Positive liquor among all patients with NPS assessment (71), *n* (%)	Positive liquor among those patients with NPS assessment with no normotensive hydrocephalus suspect (62), *n* (%)
Cognitive normal	1 (100)	–
Mild cognitive impairment	7 (27)	7 (35)
Diffuse cognitive impairment	10 (23)	10 (24)
Total	18 (25)	17 (27)

TABLE 8 | Positivity of the biomarker *liquor* according to different mild cognitive impairment (MCI) phenotypes and age groups.

Age (years)	Neuropsychological phenotype	Negative liquor, *n* (%)	Positive liquor, *n* (%)
≥80	Amnestic MCI	0	0
	Multiple domain MCI+	3 (60)	2 (40)
	Multiple domain MCI–	5 (100)	0 (0)
<80	Amnestic MCI	2 (67)	1 (33)
	Multiple domain MCI+	7 (70)	3 (30)
	Multiple domain MCI–	1 (50)	1 (50)

+, with amnestic component; –, without amnestic component.

diagnosis of AD when based on clinical criteria, CSF biomarkers, or neuroimaging.

First, we confirmed a substantial discordance between the two sets of clinical diagnostic criteria, i.e., *DSM*-IV plus NINCDS-ADRDA (1984) versus NIA-AA (2011) criteria, with an agreement of only 70% when adjusted for the effect of chance. The discordance likely reflects the evolution in the definition of dementia and AD and was someway expected. However, we wanted to quantify this discrepancy in a cohort of patients with a higher probability of a complex phenotype, since 1984 criteria have been used to define patient eligibility for approval studies of many current drugs available for AD and are still being used in research (13, 26–29). According to our data, most (16 out of 27, 59%) of the "possible AD" patients according to the newer criteria would have been classified as "no dementia" by the older approach (**Table 3**) and would have been not eligible for those studies. The results of those studies are therefore not necessarily applicable to this subset of patients defined as "possible AD" according to a more comprehensive understanding of the disease.

TABLE 9 | Cerebrovascular damage at neuroimaging according to the Fazekas scale and clinical diagnosis of dementia.

Diagnosis	*Diagnostic Statistical Manual of Mental Disorders*-IV plus National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria			National Institute on Aging-Alzheimer's Association criteria		
	Fazekas, mean (SD)	Positive Fazekas,[a] *n* (%)	*p* (Pearson χ^2 test)	Fazekas, mean (SD)	Positive Fazekas,[a] *n* (%)	*p* (Pearson χ^2 test)
No dementia	1.1 (1.1)	12 (52)	0.453	1.6 (1.1)	10 (53)	0.451
Possible AD	1.2 (0.9)	2 (50)		1.6 (1.1)	4 (50)	
Probable AD	1.4 (1.0)	4 (31)		1.3 (1.0)	4 (31)	

[a]*Score ≥2.*

TABLE 10 | Distribution of the positive Fazekas score in different age subgroups in people with a clinical diagnosis of probable AD (National Institute on Aging-Alzheimer's Association criteria).

Age (years)	Positive Fazekas, *n* (%)
≥80	1 (33)
<80	3 (30)
<75	2 (40)
<72	1 (100)

TABLE 11 | Correlation of the biomarker *liquor* and cerebrovascular burden at neuroimaging according to Fazekas scores, in subjects with a clinical diagnosis of probable AD (National Institute on Aging-Alzheimer's Association criteria) in different age subgroups.

	Negative Fazekas, *n* (%)	Positive Fazekas, *n* (%)	*p*
Total			
Negative liquor	6 (67)	3 (33)	0.764
Positive liquor	3 (75)	1 (25)	
<80 years			
Negative liquor	4 (67)	2 (37)	0.778
Positive liquor	3 (75)	1 (25)	
≥80 years			
Negative liquor	2 (67)	1 (33)	–
Positive liquor	0 (0)	0 (0)	
≤75 years			
Negative liquor	1 (50)	1 (50)	0.709
Positive liquor	2 (67)	1 (33)	
>75 years			
Negative liquor	5 (71)	2 (29)	0.537
Positive liquor	1 (100)	0 (0)	

One of the main differences between the two criteria is that the older ones, but not the newer, include the presence of amnesic deficits as a necessary criterion for AD diagnosis. Interestingly, in our cohort, the majority of patients (64%), who had no objective memory deficiency at the NPS tests, had in fact complained about forgetfulness during the clinical visit. This datum has been already described in the literature (30). This confirmed the role of the NPS assessment, which in practice might be sometimes forgone in the assessment of the oldest old patients. An extended NPS battery helped us to better define not only the phenotype but also the severity of the cognitive disorder (6, 31, 32), which, in some cases, allowed us to suppose a higher functional impairment, or a higher contribution of the cognitive deficits to the functional impairment, among other possible health and social contributors, compared to what the interview with the patients or their caregivers had suggested.

The distribution of the CSF biomarkers levels in our population was quite sparse, even in patients with a clinically probable AD. In particular, patients with positive liquor biomarkers still represented a minority among those that would have been classified as probable AD based on clinical criteria only; they represented the majority only in a younger (i.e., <76 years) subset of patients. In 2012, Mattsson et al. investigated the effect of age on the diagnostic performance of CSF biomarkers in a large multi-center study population and they found that although the diagnostic accuracy for AD decreased with age, the predictive values for a combination of biomarkers remained essentially stable. In comparison with our population, their cross-sectional cohort of patients with AD had a lower median age (71 versus 77.7), an higher percentage of male subjects (57 versus 38.3%) and a lower MMSE median score (22 versus 23.9) (33). In that study the clinical diagnosis of AD was based on *DSM*-IV plus NINCDS-ADRDA criteria. In our study too, there was a non-statistically significant trend for an increased liquor positivity going from "no dementia" to "possible" and then "probable AD," only when the *DSM*-IV plus NINCDS-ADRDA were used. This suggests a higher concordance between the CSF biomarkers so far known and the classical AD variant, rather than with the more comprehensive AD definition. In contrast, when we looked at the relationship between the CSF protein distribution and the NPS outcome, we did not find the expected association between a classical amnesic MCI phenotype and positive biomarkers.

Our findings confirm that quantitative methods based on neuroimaging (i.e., the Fazekas scale) can help refine the classification of patients upon the degree of cerebrovascular damage compared to descriptive radiological reports (34). Yet, the clinical relevance of neuroimaging remains uncertain among relatively older patients. Indeed, we less frequently found a positive Fazekas in patients with probable AD, compared with patient with possible or no AD, suggesting that the vascular damage is not a typical pathogenic mechanism of the disease. However, there was still a substantial percentage (31%) of positive Fazekas among patients with probable AD. Furthermore, we found that a positive Fazekas tended to be only slightly more frequent among probable AD with *negative liquor* than among those with a *positive liquor*, regardless of age. This finally

suggests that the two pathogenic pathways, i.e., the vascular and the degenerative, can definitely coexist and not necessarily only in patients who would easily meet the definition of vascular/mixed dementia (such as patients with a history of stroke).

The retrospective nature and the small sample size are the main limitations of our study, which could be only descriptive and explorative in nature. Then, although less selected in terms of age and clinical complexity than in randomized controlled trials, our cohort still represented a selected population. Indeed, including only patients who underwent a lumbar puncture might have led to the exclusion of the oldest and most complex patients for whom the lumbar puncture is more frequently thought not to have a favorable risk-benefit profile. Finally, we had to deal with missing and incomplete information, given the retrospective nature of our study and the use of data from routine practice. The time lag between the date in which the patient underwent the lumbar puncture and the time in which some other study variables were collected could represent a limitation to the actual concurrency of the cross-sectional comparison. However, this is consistent with the routine practice.

CONCLUSION

To conclude, we showed a significant degree of discordance between clinical criteria, NPS assessment, liquor biomarkers, and neuroimaging when used to characterize cognitive disorders in geriatric outpatients. Given the methodological limitations of our study, prospective larger multi-center studies, including inception cohorts of unselected patients that undergo a clinical, laboratory, and neuroradiological assessment, and with a clinical follow-up, would be theoretically necessary to better understand the role of biomarkers in the diagnostic workup of geriatric patients with cognitive disorders. However, practical and ethical issues might hinder the conduction of such a type of study, while the current demographic trend will lead quickly to a further increase of the prevalence of this patient population. Hence, researchers and clinicians in the field should make the efforts to combine their experience and expertise to reach a consensus on the best diagnostic practice in this population.

ETHICS STATEMENT

The study was a retrospective analyis of data routinely collected for clinical purpose, retrieved from patient medical charts. No approval from an ethics committee was sought. Given the nature of the study, the patients did not provide a specific consent. They had provided an informed consent to the clinical procedures performed as outpatients at the geriatric clinic, as per good clinical practice. The analyses were performed, and the results reported with full respect of anonymity and confidentiality. The data retrieved for the purpose of this study were not used for any other purpose.

AUTHOR CONTRIBUTIONS

GD and MM are the lead investigators and headed study design, data collection, and article writing. MM is also the senior mentor of the study and oversaw the study design. VS, AG, AA, and GF are coinvestigators and participated in study design, data collection, and article review. SD helped with statistical analysis and participated in article review. PR, CA, SI, and BA contributed to the study design, facilitated access to medical records, and participated in article review. DM is the medical director of the Geriatric Unit of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan. ES is the responsible of the Alzheimer Evaluation Unit of the Neurodegenerative disease Unit of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan. DM and ES are the guarantors for study compliance to ethical principles and participated in article review. All the authors reviewed and accepted the final version of the article.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/article/10.3389/fmed.2017.00203/full#supplementary-material.

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Of Microbes and Minds: A Narrative Review on the Second Brain Aging

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In recent years, an extensive body of literature focused on the gut–brain axis and the possible role played by the gut microbiota in modulating brain morphology and function from birth to old age. Gut microbiota has been proposed as a relevant player during the early phases of neurodevelopment, with possible long-standing effects in later life. The reduction in gut microbiota diversity has also become one of the hallmarks of aging, and disturbances in its composition are associated with several (age-related) neurological conditions, including depression, Alzheimer's disease, and Parkinson's disease. Several pathways have been evoked for gut microbiota–brain communication, including neural connections (vagus nerve), circulating mediators derived by host-bacteria cometabolism, as well as the influence exerted by gut microbiota on host gut function, metabolism, and immune system. Although the most provoking data emerged from animal studies and despite the huge debate around the possible epiphenomenal nature of those findings, the gut microbiota–brain axis still remains a fascinating target to be exploited to attenuate some of the most burdensome consequences of aging.

Keywords: gut microbiota, neurological disorders, inflamm-aging, gut–brain crosstalk, gut metabolism, brain development, Alzheimer, Parkinson

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GUT MICROBIOTA AND CENTRAL NERVOUS SYSTEM (CNS) IN HEALTH AND DISEASE: I "GUT" A FEELING

Over the past decades, few aspects of human physiology have attracted the interest of researchers all over the world as the interaction between gut microbiota and human host (1). According to the current literature, the human holobiont (or superorganism) contains at least the same number of microorganisms (bacteria, archaea, fungi, and viruses) as its own cells (2). More than a billion years of mammalian–microbial coevolution have shaped a life-long interdependency (3). Growing evidence suggests that gut microbiota may be "at the intersection of everything," being implicated in virtually all physiological or pathological situations (1). Gut microbiota has been implicated in the maturation and modulation of the host immune response (4), interactions (positive and negative) with pathogens (5), regulation of bone density (6), vitamin biosynthesis (7), intestinal 5–10% of daily host energy requirements derives from gut microbiota metabolic activities (8).

Not surprisingly, gut microbiota composition and activities have been associated with a plethora of conditions, ranging from obesity to cardiovascular disease, chronic inflammatory diseases, and cancer (9–11).

Recently, a great emphasis has been placed on the role of intestinal microbiota in regulating the gut–brain axis (12–15). Gut microbiota and brain may influence one another through several pathways (**Figure 1**). Gut microbes–brain bidirectional communication is mediated by the vagus nerve that conveys information from the gastrointestinal tract to the CNS and back from CNS to

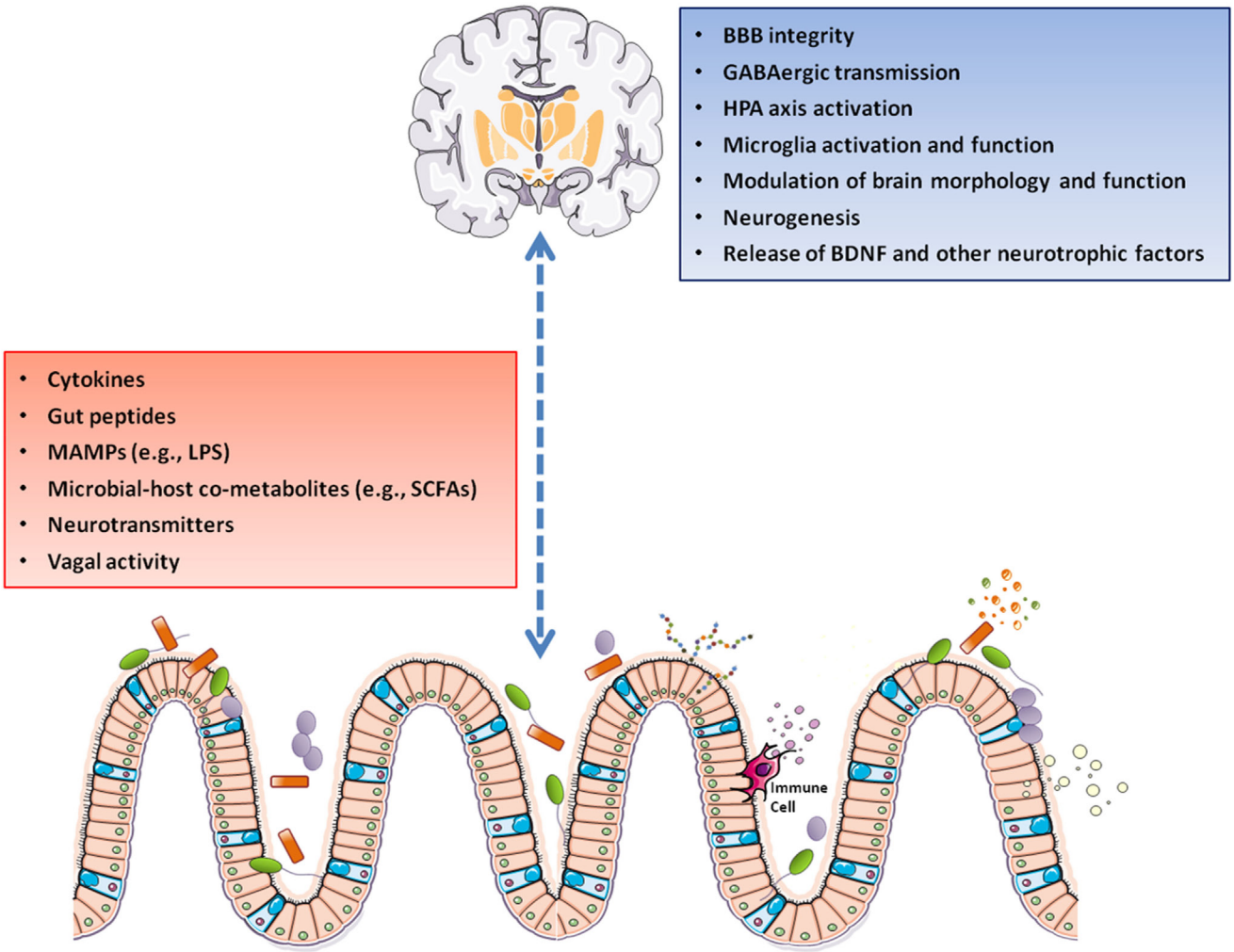

FIGURE 1 | A gut–brain axis supports the interactions between gut microbiota and the CNS through direct and indirect pathways involving vagal nerve activation, cytokine production, and release of neuropeptide/neurotransmitters and SCFAs. These mediators can pass the BBB and control the maturation and activation of brain immune cells (microglia). Following its activation, microglia modulates immune surveillance, synaptic pruning, and clearance of debris. On the other side, the HPA axis can suppress microglia activation, as well as influence cytokine release and trafficking of monocytes from the periphery to the brain. Abbreviations: BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid; HPA axis, hypothalamic–pituitary–adrenal axis; LPS, lipopolysaccharide; MAMPs, microbe-associated molecular patterns; SCFAs, short-chain fatty acids; CNS, central nervous system.

the intestine to modulate intestinal motility, release of neurotransmitters and intestinal immune tone (16, 17). The sympathetic branch of the autonomic nervous system is also involved in intestinal homeostasis and gut immune regulation (18). Gut microbiota may also synthesize (or modulate the synthesis of) a number of neurotransmitters, including dopamine (DA), serotonin (5-HT), noradrenaline (NA), and gamma-aminobutyric acid (19–22). The hypothalamic–pituitary–adrenal axis (HPA axis) is another bidirectional route of communication through which host and gut microbes may interact to orchestrate the core response to both physical and psychological stress challenges (23–25). Bacterial metabolic activities may influence host metabolism and lead to the production of metabolites with neuroactive properties, including short-chain fatty acids (SCFAs) and dietary amino acid catabolites (26, 27). Finally, bacterial mediators in the forms of microbe-associated molecular patterns may drive neuroinflammation (28).

Through all these pathways, gut microbiota exerts a widespread influence on key neurological and behavioral processes and may be involved in critical phases of neurodevelopment and neurodegenerative disorders (12–14, 29). In this scenario, microbial activities on gut–brain axis seem to be especially relevant at the two extremities of human life course (13, 15). Early-life gut microbiota may play a role in shaping neuronal networks influencing cognitive, emotional, and social domains (13). Aging is associated with a reduction in microbial complexity, while alterations in intestinal microbiota composition, structure, and function have been retrieved in older individuals with Alzheimer's disease (AD) and Parkinson's disease (PD) (30, 31).

In this narrative review, recent evidence on life-long gut microbiota–brain axis is summarized, with a particular focus on aging and age-related neurodegenerative diseases. All accessible relevant studies written in English were included.

GUT MICROBIOTA AND NEURODEVELOPMENT: EARLY ORIGINS OF LATE NEUROLOGICAL DISEASES?

The notion of "developmental origins of health and disease" poses that prenatal and perinatal life stages are critical periods in which environmental stimuli exert direct and indirect effects on the fetus that might be reflected in later health and disease conditions (32). In this context, early host–microbiota interactions seem to be among the most relevant factors in "programming" adult phenotypes (33). It has been postulated that a succession of microbiota components occurs through major steps at birth (depending on the timing and mode of delivery), then during breastfeeding and first interactions with the environment, and finally during and after weaning. Maternal–host factors (genetic background of mother–infant dyad) and perinatal exposure to antibiotics are among the most relevant factors in shaping the newborn's microbiota (33, 34). Interaction with colonizing microbiota may prime immune and metabolic functions and have a long-lasting influence on the risk of developing several conditions in later life, including gastrointestinal, allergic, autoimmune, and metabolic diseases (34).

Neurodevelopment is one of the most complex and fascinating aspects of human physiology that may be affected by early contact with gut microbiota (12–14, 35). Human brain development starts during the third gestational week and lasts through adolescence and into early adulthood in humans under the control of both genetic and environmental factors (36). The development of cognitive, emotional, and social brain circuits occur in parallel under the fine modulation by several molecular regulatory networks (37, 38). Critical windows in brain development have been described, during which neural circuits are particularly sensitive and even vulnerable to external factors, including gut microbiota composition (39, 40). Interestingly, early post-natal brain development overlap with gut microbiota establishment (33, 39, 40).

Animal models, in particular germ-free (GF) mice, have been crucial for the study of gut microbiota–brain axis in early phases of neurodevelopment (41). Seminal studies suggest that both the composition and the metabolic activity of gut microbiota at specific time points may influence HPA axis development (42) and have long-lasting impact on behavioral and neuroendocrine responses to stress (42–45). Gut microbiota may program the activity of multiple neurotransmitter systems in different brain regions inducing a long-term modulation of motor control and anxiety-like behavior in adult life (13, 35, 46). GF mice had a higher turnover rate of NA, DA, and serotonin 5-HT in the striatum compared with specific pathogen-free (SPF) mice (46). The serotonergic system seems to be particularly susceptible to early-life microbiota dynamics (47–50). Male GF animals showed a marked elevation in 5-HT and 5-hydroxyindoleacetic acid, its main metabolite, in the hippocampus compared with conventionally colonized control animals (48). Interestingly, post-weaning restoration of a normal flora failed to reverse the alterations in brain neurochemistry elicited by the lack of early life exposure to gut microbiota (48). Also, plasma 5-HT levels are affected by gut microbiota activity. In a metabolomics study, the colonization of GF mice induced a significant increase in plasma 5-HT (51), and bacterial metabolites were shown to stimulate 5-HT synthesis and secretion by enterochromaffin cells (20, 21). Intriguingly, the maternal separation in mice, an established model of early-life stress, induced profound changes in the gut microbiota that resulted in an anxiety-like phenotype (52).

The gut microbiota may also play a role in synapse maturation and synaptogenesis. In particular, GF animals when compared with SPF animals, showed higher striatal expression of synaptophysin and PSD 95, two markers of synaptogenesis and excitatory synapse maturation, respectively (46). Brain-derived neurotrophic factor (BDNF) is a key regulator of synaptic plasticity and neurogenesis in the brain and plays a crucial role in learning, memory, and mood regulation throughout life (53). In GF mice, *Bdnf* expression is significantly lower in the hippocampus, amygdala, and cingulate cortex compared with SPF mice (46). However, some inconsistency were reported about *Bdnf* expression in the hippocampus (42, 46, 48, 49).

Intriguingly, most of the reported neurodevelopmental alterations in GF mice occur differently in the two sexes (42, 46, 48, 49). Gut microbiota influence on neurogenesis is relevant for the normal gross morphology and ultrastructure of the amygdala and hippocampus (54, 55). While GF mice exhibit increased adult hippocampal neurogenesis in the dorsal hippocampus, subsequent post-weaning microbial colonization failed to reverse these changes, suggesting the existence of a critical developmental window in early life during which gut microbiota may program adult hippocampal neurogenesis (55). Gut microbiota may also be instrumental for the development of the blood–brain barrier (BBB). GF mice, starting from intrauterine life, displayed a life-long increased BBB permeability compared with mice with a normal gut flora that can partially be reverted by the exposure to pathogen-free gut microbiota during adult life (56).

Microglia, the macrophages that constitute the first-line immune defense of the CNS, play a central role in brain development, plasticity, and cognition and have been associated with the initiation or progression of several developmental and neurodegenerative diseases, including AD and PD (57, 58). Very recently, it was shown that microglia exhibited a time- and sex-specific susceptibility to gut microbiota depletion in mice (59). In particular, males seem to have their critical window during early *in utero* development, while females are more affected during adulthood. Microbiota alterations may have both acute and long-term effects on microglial functions. Remarkably, human fetal microglia showed significant similarities in the expression of key microglial genes when compared with murine counterparts (59). Finally, GF mice exhibited an increased myelination of neurons in the prefrontal cortex that could be reversed by colonization with a conventional microbiota following weaning (60).

Interventions on the early gut microbiota community (through the use of antibiotics, drastic changes in diet and/or pre/probiotic administration) may have profound effects on the gut–brain axis throughout life. For instance, antibiotic use during the first years of life was associated with neurocognitive outcomes later in life (e.g., depression, behavioral difficulties) (61).

In summary, several lines of evidence, although obtained mostly from animal models, suggest a relevant role played by the gut microbiota during the early phases of neurodevelopment, with possible long-standing effects later in life. The translatability of animal model findings to humans is obviously a priority but, also when ascertained, a comprehensive discussion should be started before implementing intervention strategies that could harm the mother–infant dyad in the first critical 1,000 days of life (62, 63).

THE ADULT "STEADY-STATE" MICROBIOTA AND CNS: COMMITTING TO A STABLE RELATIONSHIP

From birth till adulthood, bacterial diversity and functional capacity expand progressively, although at different rates across life stages (i.e., faster during infancy and slightly slower in early childhood) (64, 65).

In adulthood, gut microbial population fluctuates around a steady state (in terms of composition, diversity, and function) and remains quite resilient unless gross perturbations occur (e.g., major health conditions) (66). "Healthy" adult gut microbiota are consistently dominated by 2 main phyla (Bacteroidetes and Firmicutes), but more than 1,000 different bacterial species have been characterized and represent the vast human microbial collection (67–69). Each individual is characterized by a specific combination and proportion of different microbial species and subspecies (strains) that constitutes a unique microbial fingerprint (69). Despite this taxonomic inter-individual variability, adult gut microbiota display a relatively consistent functional capacity in healthy persons (70, 71). Importantly, microbial diversity and functional redundancy are positively associated with health, while decreased microbial richness and diversity and loss of functional redundancy characterize the microbiota in multiple disease conditions (66, 69, 72). Adult gut microbiota is influenced by several factors, including host genetics (73), nutrition and dietary habits (74, 75), xenobiotics (e.g., antibiotics) and other drugs (76–78), exercise (75, 79, 80), and circadian rhythm (81, 82).

Gut microbiota and brain dynamically interact also during adulthood. In adult mice, short-term oral administration of broad-spectrum antibiotics induced a decrease in anxiety and upregulated hippocampal expression of *Bdnf* (83). These changes were associated with a transient perturbation of microbiota but occurred independent of inflammatory status, vagal or sympathetic integrity, or alterations in gastrointestinal neurotransmitter levels (83). Adult neuroplasticity is sensitive to several environmental stimuli, including stress and gut microbiota alterations (84). Adult mice treated with antibiotics showed decreased hippocampal neurogenesis and memory retention (85). This effect was not completely rescued by the restoration of a normal flora by fecal transplant, unless supported by exercise or a probiotic cocktail administration (85).

Recent evidence suggests that complex microbiota-derived stimuli are requested for microglia maintenance also during adulthood (26, 59, 86). In particular, SCFAs, derived from bacterial fermentation processes, seem to regulate adult microglia homeostasis (26). Moreover, short-term antibiotic treatment in adult mice induce a rapid and sexually dimorphic (higher in females) change in microglial gene expression, reinforcing the concept that microbiota perturbations may have a relevant impact of microglia also during adulthood (59).

THE SECOND BRAIN AGING: LINKING GUT MICROBIOTA TO NEURODEGENERATION

Aging is a process characterized by progressive functional decline of all physiological systems. In the gastrointestinal tract, aging involves the degeneration of enteric nervous system (ENS), alterations in gastrointestinal motility, perturbations in small intestinal permeability and mucosal defense system, which may promote the development of gastrointestinal diseases, affect the local and systemic inflammatory status, and deeply influence both the composition and function of resident microbiota (87–89).

Aging is also associated with broad changes in brain and whole body physiology that may influence gut microbiota–brain axis. In particular, the HPA axis is deeply perturbed, through a self-reinforcing cycle mediated by the hyperactivation of the HPA axis that leads to increased basal glucocorticoid release and the impaired HPA negative feedback due to reduced central glucocorticoid receptor expression (90, 91). HPA axis dysfunctions have been associated with decline in hippocampal volume and cognitive performance, and increased risk of late-life depression and anxiety (92, 93). Also circadian rhythm disruption, which is typical of aging, may be involved in this process, due to the potential effect on both cortisol level fluctuations and gut microbial activities (94, 95).

The aging brain is also deficient in the synthesis of neurotrophic factors, including BDNF (96) as well as several neurotransmitters, including 5-HT and DA, all of which lead to neuronal and cognitive dysfunction (97, 98). BBB breakdown is an early event in the aging human brain that begins in the hippocampus and may contribute to cognitive impairment (99).

Aging is also characterized by the progressive decline in immune function (immunosenescence) associated with a chronic, low-grade inflammation (inflamm-aging) (100, 101). Both processes may have many effects on the CNS, such as microglial activation, BBB breakdown, and increase in oxidative damage that may contribute to neurodegenerative and neuropsychiatric diseases (100). Remarkably, recent data suggest that, in old mice, gut microbiota contribute to inflamm-aging, and that this inflammatory phenotype may be transferred to young GF mice (102).

Major taxonomic shifts and a consistent decrease in microbial richness and diversity have been reported in people 65 years of age and older and these changes were associated with worsening

of health status and frailty (89, 103). Similar findings were also obtained in mice (104).

The characterization of gut microbiota of centenarians revealed the presence of significant compositional differences across life stages till extreme ages (105). In particular, core microbiota (mostly composed by the members of Ruminococcaceae, Lachnospiraceae, and Bacteroidaceae families) seem to accompany human life, decreasing in abundance along with aging (105). In longevity and extreme longevity, an enrichment in some subdominant health-associated groups (e.g., *Akkermansia*, *Bifidobacterium*, and *Christensenellaceae*) occurs, even with the support of some opportunistic and allochthonous bacteria (105).

Recently, the effects of aging on the microbiota gut–brain axis were assessed in male mice (106). Aged mice showed significant shifts in gut microbiota that were associated with deficits in spatial memory and increases in anxiety-like behaviors compared with young adult mice (106). These changes were positively correlated with the abundance of bacteria from the Porphyromonadaceae family. Aged mice also exhibited increased gut permeability that was associated with elevations in peripheral pro-inflammatory cytokines (106).

These preliminary findings suggest that age-related changes in gut microbiota may impact behavioral and cognitive functions and support the relevance of the alteration in gut permeability and peripheral inflammation in mediating these effects.

As outlined earlier, the possible link between early gut microbiota–brain interactions and late onset neurological conditions, including AD and PD, is an intriguing area of research (15).

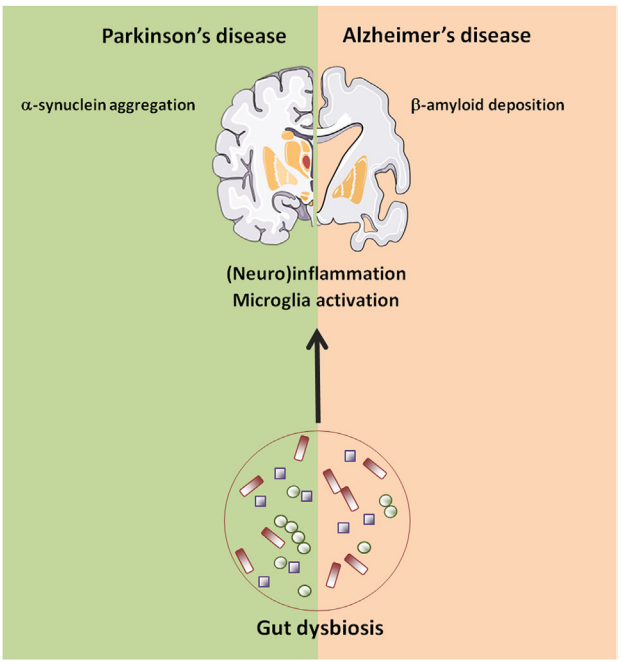

FIGURE 2 | Age-related changes in gut–brain axis possibly involved in neurodegeneration. Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease.

Alzheimer's Disease

In AD, the most common form of age-related dementia, deposition of protein aggregates composed of amyloid-β (Aβ) peptide and tau in brain tissues impairs cognitive function (107). Both host- and environmental factors that regulate these processes have been described, including a potential role for gut microbiota (108) (**Figure 2**).

In AD, reduced microbial richness and diversity were observed, with low abundance of Firmicutes and *Bifidobacterium* and increased Bacteroidetes that characterized the microbiome of AD patients (108). Correlations were found between the levels of *Bacteroides*, *Turicibacter*, and *SMB53* and the concentration of glial activation biomarkers in cerebrospinal fluid of AD (108).

An increase in the abundance of the pro-inflammatory *Escherichia*/*Shigella* taxon, and a corresponding reduction in the anti-inflammatory *E. rectale* was associated with higher levels of inflammatory mediators in patients with cognitive impairment and brain amyloidosis (109). Also in a mouse model overexpressing amyloid precursor protein and presenilin 1 (APPPS1), a distinct microbial signature was observed with an increase in *Rikenellaceae* and decreased *Allobaculum* and *Akkermansia* compared with age-matched wild-type controls (110).

Interestingly, reduced levels of *Akkermansia* characterize gut microbiota of mice with obesity and type 2 diabetes (111), two potentially modifiable risk factors for AD (107). Importantly, both young and old GF APPPS1 transgenic mice displayed a drastic reduction of cerebral Aβ pathology when compared with control mice, along with a reduced microgliosis (110). Further to this, colonization of GF-APPPS1 transgenic mice with microbiota from conventionally raised APPPS1 transgenic mice increased cerebral Aβ pathology, while colonization with microbiota from wild-type mice was less effective in increasing cerebral Aβ levels (110). Notably, GF-APPPS1 displayed increased levels of the Aβ-degrading enzymes insulin degrading enzyme and neprilysin degrading enzyme, suggesting a mechanism through which gut microbiota influence cerebral Aβ amyloidosis (110).

In the same mouse model of AD, life-long antibiotic treatment induced a considerable perturbation in gut microbial composition (including an expansion of *Akkermansia*) that was associated with marked changes in the circulating cytokine/chemokine network, a striking reduction in amyloid plaque deposition, and a concomitant increase in soluble Aβ (112). This was accompanied by alterations in neuroinflammatory milieu that lead to reduced plaque-localized gliosis and altered microglial morphology (112). Remarkably, early post-natal antibiotic treatment alone resulted in long-term alterations in gut microbial genera that were associated with changes in the inflammatory environment of serum and cerebrospinal fluid and attenuated Aβ amyloidosis in a manner similar to that observed in mice subjected to life-long antibiotic selection pressure (113). These findings corroborate the hypothesis of the presence of critical developmental periods in which the commensal microbiota manipulation may have long-lasting effects on host immunity and potential implications for neurodegenerative diseases.

In another model of AD, the 5xFAD transgenic mouse, elevated levels of APP were found not only in the brain but also in the different gut districts and this was associated with a distinct fecal

microbiota profile relative to wild-type animals, with an increase in pro-inflammatory species (e.g., *Clostridium leptum*) (114).

Alterations in gut microbiota composition together with the increase in intestinal permeability with age may lead to the translocation of microbes or microbial components [i.e., lipopolysaccharide (LPS)] from the gut to induce systemic and CNS inflammation (115). Interestingly, *in vitro* and *in vivo* studies have demonstrated a possible association between LPS and AD pathology. Coincubation of Aβ peptide with LPS potentiated amyloid fibril formation (116), and systemic administration of LPS in wild-type and transgenic AD mice induced neuroinflammation, amyloid deposition, and tau pathology (117–119). Moreover, in postmortem brain parenchyma and blood vessels from patients with AD, levels of LPS and Gram-negative *E. coli* fragments were greater compared with control brains and colocalized with amyloid plaques (120).

While the study of the microbiota gut–brain axis in AD is still in its infancy, promising preclinical data suggest that the modulation of gut microbiota through dietary ingredients or probiotics may provide a means to counteract the development or progression of neurodegenerative disease. For instance, in a triple-transgenic mouse model of AD (3xTg-AD), a formulation of lactic acid bacteria and bifidobacteria changed the composition of gut microbiota, stimulated the production of beneficial metabolites (e.g., increased SCFAs), reduced the levels of pro-inflammatory cytokines, increased gut hormones concentration and positively modulate quality control processes and proteolysis, reducing Aβ load and improving cognitive function (121). Moreover, the administration of the probiotic mixture VSL#3 to aged rats induced a robust perturbation in gut microbiota composition, that was accompanied by gene expression changes in the brain cortex, attenuated age-related deficits in long-term potentiation, decreased microglial activation, and increased BDNF and synapsin levels (122). In addition, 3-hydroxybenzoic acid and 3-(3-hydroxyphenyl)propionic acid, the phenolic products of microbial conversion of grape seed polyphenol extracts (and other dietary polyphenols), may potently interfere with the assembly of Aβ peptides into neurotoxic Aβ aggregates *in vitro* (123).

Despite these interesting preliminary findings, more work is needed to determine whether gut microbiota modulation may be employed for the prevention and/or treatment of AD pathogenic processes.

Parkinson's Disease

Parkinson's disease is the second most common neurodegenerative disorder, affecting 2–3% of the population ≥65 years of age (124, 125). Degeneration of the dopaminergic nigro-striatal pathway and widespread intracellular α-synuclein accumulation are the neuropathological hallmarks of PD that are associated with bradykinesia and other cardinal motor and non-motor features (126).

Gastrointestinal dysfunction, in particular in the form of constipation, is among the most frequent prodromal non-motor symptoms of PD that may precede motor symptoms by decades (126). At later disease stages, oral issues including drooling and swallowing problems and delays in gastric emptying further exacerbate gastrointestinal dysfunction (127). Aggregates of α-synuclein have been retrieved in the mucosal and submucosal nerve fibers and ganglia of the ENSs of PD patients at early disease stages (128, 129). In addition, some observations from experimental models support the intriguing hypothesis that intestinal α-synuclein may spread to the brain *via* postganglionic enteric neurons and the vagus nerve (130). Interestingly, the risk of developing PD was significantly decreased in patients who underwent a full truncal vagotomy compared with those who underwent selective vagotomy and in the general population (131).

Not surprisingly, gastrointestinal disturbances in people with PD are accompanied by alterations in fecal and mucosal microbial populations (31, 132–134). In particular, a reduced abundance of Prevotellaceae, mucin producers that regulate intestinal permeability, was commonly reported in PD patients (31, 132, 135, 136), while *Enterobacteriaceae* were positively associated with the severity of postural instability and gait difficulty (31). *Clostridium coccoides* group was high in early PD patients, while *Lactobacillus gasseri* subgroup was high in advanced PD patients (132). A pro-inflammatory dysbiosis, characterized by low counts of "anti-inflammatory" butyrate-producing bacteria from the genera *Blautia*, *Coprococcus*, and *Roseburia* and higher "pro-inflammatory" Proteobacteria of the genus *Ralstonia* was also reported in individual with PD (133). Individuals affected by PD also showed lower levels of SCFA concentrations, derived from host–microbiota cometabolism, that may have neuroactive and immunomodulating properties (135). Other evidence of microbiota dysregulation in PD includes small intestine bacterial overgrowth and high rates of *Helicobacter pylori* infection (137, 138). It is worth noting that this infection has also been involved in the pathogenesis of AD (139). Finally, the total abundance of intestinal bacterial was found to decrease during PD progression, with a low count of *Bifidobacterium* associated with worsening of PD symptoms (134).

Collectively, these findings suggest that perturbations in gut microbiota structure and function may be associated with the development and progression of PD through several potential mechanisms, including inflammation and bacterial translocation (**Figure 2**). However, findings in humans remain largely descriptive. Again, animal models provided some useful insights into the physiopathological mechanisms linking gut dysbiosis to PD. Under GF conditions, or when bacteria were depleted in post-natal life following antibiotic treatment, transgenic mice overexpressing α-synuclein showed reduced microglia activation, α-synuclein inclusions, gastrointestinal symptoms, and motor deficits compared with animals with a complex microbiota (140). Moreover, administration of a mixture of microbially derived SCFAs (acetate, propionate, and butyrate) restored all major features of PD in GF mice, suggesting that microbial metabolic mediators may promote microglia activation and α-synuclein aggregation and contribute to motor dysfunction in PD (140). Remarkably, mice transplanted with PD microbiota compared with mice who received microbiota from healthy human controls displayed enhanced motor dysfunction, suggesting that dysbiosis may be the environmental factor that combined with a genetic

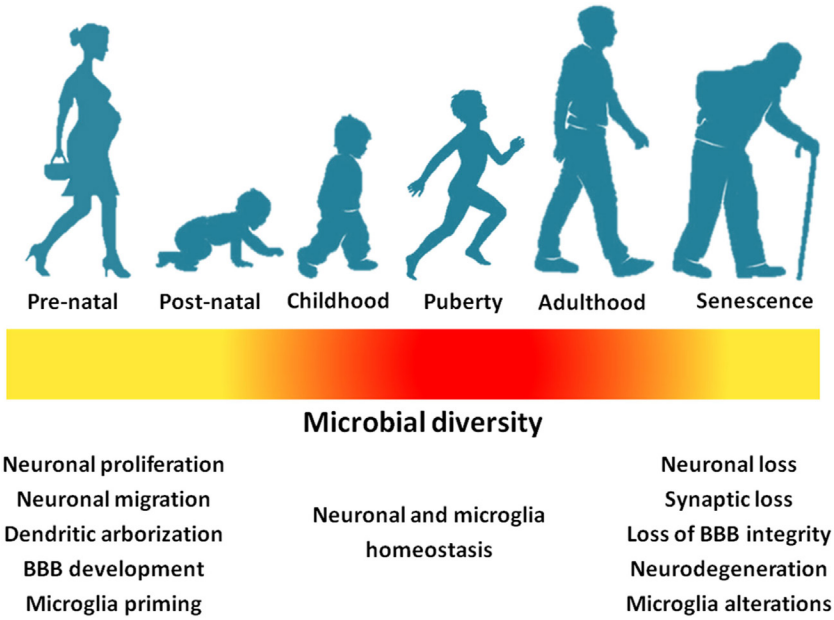

FIGURE 3 | Gut microbial richness and diversity across life stages impact neurodevelopment and the central nervous homeostasis (yellow: low richness/diversity; red: high richness/diversity). Abbreviation: BBB, blood–brain barrier.

predisposition (α-synuclein overexpression) influences disease outcomes in mice (140).

As already outlined for AD, in neurodegenerative diseases, including PD, the passage of bacterial products from the intestine to the circulation and into brain, or "molecular mimicry" processes induced by bacterial amyloids may trigger a persistent neuroinflammation (28, 141, 142) that in turn contributes to neuronal dysfunction and death (143). In this scenario, it has recently been proposed that Aβ production and aggregation may originally act as an antimicrobial defense and then infectious or sterile inflammatory stimuli may drive amyloidosis (144).

While it is currently recommended the use of fermented milk containing probiotics and prebiotic fiber in PD patients with constipation (145), the possible beneficial effects of the manipulation of gut microbiota (through diet, live bacteria, or microbiota transplantation) on the initiation or progression of the neurodegenerative process have not yet been explored. Further studies are also needed to assess the possible interactions among these interventions and levodopa uptake and availability.

CONCLUDING REMARKS

At the beginning of the twentieth century, the Nobel Prize winner Elie Metchnikoff theorized in his tracts, *The Nature of Man: Studies in Optimistic Philosophy* (1903) and *The Prolongation of Life: Optimistic Studies* (1907), that health status could be improved and senility delayed by replacing the native gut microbes with lactic acid bacteria such as those present in yogurt (146). In the past few decades, this idea was resumed and updated under the influence of methodological and technological advances in science (147). A more ecological perspective was then embraced and the concepts of complexity, (dis)harmony, (Nash)equilibrium, and personalization/precision were introduced to capture the dynamic aspects of gut microbiota–host relationship (66, 147–149).

While the study of microbiota gut–brain axis is still in infancy, a number of potential mechanisms (and, hence, plausible targets) have begun to be unveiled. Early-life interactions between host and colonizing gut microbes seem to influence the way in which the nervous system starts obtaining information about the external and internal environment in critical phases of neurodevelopment. BBB establishment and function, central inflammatory processes and neurogenesis may be differentially affected by the gut microbial assemblies and their metabolic products (**Figure 3**). Evidence is also accumulating for a role of life-long microbiota–host interactions in age-related disorders such as AD and PD.

Taken together, these data open up the possibility of developing interventions targeting the gut microbiota (in particular at the extreme ages of life) to improve brain health. Preclinical studies have suggested the efficacy of the modulation of the gut microbiota in ameliorating conditions such as depression and neurodegenerative diseases (150). A new term, "psychobiotics" (and related "psychobiotic properties"), was coined to define live bacteria (probiotics) and nutritional support for such bacteria (prebiotics), but also virtually any exogenous factor, such as diet, exercise, and drugs, acting on brain through bacterially mediated effects (19).

Despite the "optimistic nature" of this 100-year-old idea, future research should tackle several challenging questions before truly effective interventions in humans may be implemented. For instance, most of the published studies have only associated the gut

microbiota with diseases without proving any causation (1, 151). It is therefore crucial to assess whether changes in microbiota underpin disease pathophysiology or are just epiphenomena. Further to this, the microbial properties that are necessary to support proper neurodevelopment and prevent neurodegeneration should be clearly established. In addition, sufficiently powered, rigorous clinical trials should be conducted to assess the translatability of animal model findings to human conditions.

AUTHOR CONTRIBUTIONS

RC, EM, and AP conceived the manuscript. RC, MRLM, and AP drafted the paper. RB, FL, and EM supervised and edited the manuscript. All authors read and approved the final version of the paper.

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Getting Lost Behavior in Patients with Mild Alzheimer's Disease: A Cognitive and Anatomical Model

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Background: Getting lost behavior (GLB) in the elderly is believed to involve poor top-down modulation of visuospatial processing, by impaired executive functions. However, since healthy elderly and elderly with Alzheimer's disease (AD) experience a different pattern of cognitive decline, it remains unclear whether this hypothesis can explain GLB in dementia.

Objective: We sought to identify whether poor executive functions and working memory modulate the relationship between visuospatial processing and prevalence of GLB in healthy elderly and patients with AD. Complementary to this, we explored whether brain regions critical for executive functions modulate the relationship between GLB and brain regions critical for visuospatial processing.

Method: Ninety-two participants with mild AD and 46 healthy age-matched controls underwent neuropsychological assessment and a structural MRI. GLB was assessed using a semistructured clinical interview. Path analysis was used to explore interactions between visuospatial deficits, executive dysfunction/working memory, and prevalence of GLB, in AD and controls independently.

Results: For both healthy controls and patients with mild AD, visuospatial processing deficits were associated with GLB only in the presence of poor working memory. Anatomically, GLB was associated with medial temporal atrophy in patients with mild AD, which was not strengthened by low frontal gray matter (GM) volume as predicted. Instead, medial temporal atrophy was more strongly related to GLB in patients with high frontal GM volumes. For controls, GLB was not associated with occipital, parietal, medial temporal, or frontal GM volume.

Conclusion: Cognitively, a top-down modulation deficit may drive GLB in both healthy elderly and patients with mild AD. This modulation effect may be localized in the medial temporal lobe for patients with mild AD. Thus, anatomical substrates of GLB in mild AD may not follow the typical top-down modulation mechanisms often reported in the healthy aging population. Implications advance therapeutic practices by highlighting the need to target both working memory and visuospatial deficits simultaneously, and that anatomical substrates of GLB may be disease specific.

Keywords: Alzheimer's disease, getting lost, wayfinding, medial temporal lobe, top-down modulation

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INTRODUCTION

Getting lost behavior (GLB) is defined as the inability to find one's way in familiar or unfamiliar environments (1). GLB is highly prevalent in patients with Alzheimer's disease (AD), with an approximate 40% of patients reportedly experiencing some phenomenon of getting lost (2). This prevalence increases to 70% in patients with severe AD and often leads to institutionalization, increased risk of falls and even death (3). Despite its prevalence and devastating impact, the mechanisms underlying GLB in AD remain unclear.

Early assumptions on the underlying cause of GLB in patients with AD have focused on visuospatial processing problems, such as motion perception that guides self-movement and maintains spatial orientation (4). However, more recent speculations have centered around GLB as a problem with higher level cognition such as working memory, defined as the capacity to temporarily maintain and manipulate information in memory, and executive functions, which involve mental flexibility, problem solving and decision making (5).

One theory that integrates the functions of both visuospatial processing and higher level cognition is the top-down modulation hypothesis of cognitive aging. This hypothesis proposes that working memory and executive functions may exert modulatory control over the efficacy of visuospatial processing and its association with behavioral systems such as navigation (6). For example, if lost, selective attention is required to moderate visual perception toward relevant visual information and suppress attention toward irrelevant information competing for cognitive resources, additionally, mental flexibility is required to facilitate strategy switching and working memory is required to engage visual memory to manipulate information no longer in the environment (5).

The neural basis for higher level cognition and visuospatial processing are anatomically distinct, with the former localized in the frontal brain region (7, 8) and the latter localized in the occipital, posterior parietal and medial temporal brain regions (9). Despite the distinct locations, the regions for higher level cognition and visuospatial processing are functionally integrated (10). For instance, a fMRI study in healthy adults demonstrated that the frontal cortex modulated the magnitude of activity in the occipital cortex during a delayed visual recognition task (11). Following on from this, a subsequent study identified that the magnitude of this modulation predicted successful performance on a visuospatial processing task (12).

In healthy cognitive aging, frontal lobe structures are typically the first to deteriorate (13). As a result, the elderly demonstrate a pronounced deficit in suppressing cortical activity associated with task-irrelevant information processing, compared to younger adults (6). This deficit with top-down modulation of cortical activity is believed to be one substrate of GLB in the elderly (14). Compared to healthy cognitive aging, patients with AD experience early atrophy in structures critical for learning and memory, such as the parietal and medial temporal lobe, while structures important for top-down modulation, such as the frontal lobe, may become affected at later stages of the disease (15). Due to the different patterns of neurodegeneration associated with AD compared to healthy aging, it remains unclear whether the top-down hypothesis is suitable for explaining GLB in patients with mild AD.

We sought to identify whether deficits with higher order cognition, such as executive functions and working memory, moderate the effect of visuospatial deficits on prevalence of GLB. This hypothesis was explored in healthy controls and patients with AD to identify whether the same mechanisms are present in the normal and abnormal aging process. Complimentary to this, we sought to identify whether anatomical mechanisms of GLB in patients with mild AD involve top-down modulation deficits. Specifically, we predicted that reduced volume of frontal gray matter (GM) may strengthen the relationship between GLB and atrophy in regions critical for visuospatial processing, namely the occipital, parietal and medial temporal GM.

MATERIALS AND METHODS

Sampling, Screening, Procedure

In this cross-sectional study, patients with mild AD were recruited from a tertiary neurology center in Singapore (National Neuroscience Institute) between 2013 and 2016. Diagnosis of mild probable AD was based on the NIA-AA Criteria (16) and a full medical work-up, which involved medical and caregiver reports, structural MRI, a comprehensive cognitive evaluation and blood test to rule out cognitive impairment due to vitamin deficiency or thyroid abnormalities. Additional criteria for a diagnosis of mild AD included a Clinical Dementia Rating Scale (CDR) (17) of 1. Age-matched controls from the community were recruited at the National Neuroscience Institute from 2010 to 2016 and included elderly who were "cognitively normal," as determined by a comprehensive cognitive assessment, a MMSE score >28 and a CDR of 0. Recruitment of the clinical and control cohort was non-random and involved consecutive sampling methods.

Exclusion criteria for all participants included (a) major visual impairment, such as blindness, visual agnosia or cortical blindness, (b) a current diagnosis or history of neuropsychiatric conditions (e.g., psychosis, depression), (c) comorbid neurodegenerative diseases (e.g., Parkinson's disease), (d) a history of clinical strokes (e.g., CAA and prior clinical strokes), and (e) a current or history of alcohol or drug abuse.

Measures

Primary outcome measure, GLB, was indexed using a semi-structured clinical interview with a psychologist blinded to diagnosis. The interview queried the changes, if any, in the visuospatial abilities of the subject and involved responses from both the subject and their caregiver, or family member in the case of controls, for clarification purposes. The subject was queried on whether they still travel alone, how well they can recall travel routes (including travel route to the present location), whether they make wrong turns on familiar paths and whether they have experienced getting lost in the past 6 months. Caregiver/family member questions sought to

validate the subject's responses and focused on whether the subject still travels on their own and whether there has been instances of making wrong turns on familiar routes or getting lost in the past 6 months (see supplementary materials for full interview). After cross-referencing the accounts of the subject and caregiver/family member, the presence of GLB was then recorded as a yes or no by the psychologist based on clear indications that the subject was not able to orientate themselves in familiar environments, or that there have been instances of getting lost.

*Cognitive predictor variable*s included working memory, which was indexed using the composite score of Wechsler's forward and backward digit span tasks [WMS-IV; (18)]; executive function, which was indexed using the composite score of the Frontal Assessment Battery [FAB; (19)] and Color Trails 2 task (20); and visuospatial processing, which was indexed using the composite of Wechsler's block design [WAIS–IV; (21)] and Wechsler's immediate and delayed visual reproduction task [Wechsler Memory Scale-IV; (18)].

Image Acquisition and Processing

Anatomical predictor variables included the volumetric measure of frontal, parietal, medial temporal and occipital GM. Subjects underwent MRI in a whole body MR system which included a 3T Siemens Tim Trio system (Siemens, Erlangen, Germany) and a 3T Siemens Prisma system (Siemens, Erlangen, Germany). Voxel-based morphometry was conducted using the Computational Anatomy Toolbox (CAT12) package for the Statistical Parametric Mapping 12 (SPM12) software (http://www.fil.ion.ucl.ac.uk/spm) in MATLAB. Volumetric MPRAGE sequences were converted from DICOM to 3D NIFTI format and manually oriented to be within the standard Montreal Neurological Institute template space. Images were segmented into GM and cerebrospinal fluid maps using a unified segmentation pipeline (22), including affine regularization to the International Consortium for Brain Mapping space template for East Asian brains, bias corrections, and affine and non-linear modulated normalization. The generated GM maps were then smoothed (8 mm full width at half maximum) in SPM12. CAT12 was used to estimate the total intracranial volume for each subject, and the smoothed GM maps were used to generate global volumes of GM, and also regional volumes based on regions of interest defined using the Wake Forest University Pick Atlas v3.0 software toolbox (23).

Statistical Analysis

Group Comparisons

A *t*-test was used to identify the neuropsychological and anatomical deficits in the mild AD group as compared to age-matched healthy controls.

Path Analysis

The *a priori* cognitive and anatomical models, depicted in **Figure 1**, were assessed using moderation path analysis with SPSS Amos version 20 (24). Moderation analysis determined whether the effect of a predictor variable on an outcome was enhanced or attenuated in the presence of a third moderating variable. In our cognitive model, the predictor variables included visuospatial skills, the outcome included prevalence of GLB and the moderating variables included executive functions or working memory. In our anatomical model, the predictor variables included regions of visuospatial processing, namely the parietal, occipital or medial temporal GM, the outcome included prevalence of GLB and the moderating variable included the region for higher order cognition, namely frontal GM. The moderation effect was calculated by mean centering all variables, then multiplying each predictor variable with each moderating variable to obtain an "interaction variable."

Path analysis was conducted separately for both the cognitive and anatomical models and for each diagnostic group (mild AD or controls) by including diagnosis type as the multi-group variable. For each analysis, the primary independent variable was the interaction variable, the secondary independent variables were the target predictor and moderating variable, while the dependent variable was the presence of GLB (indexed as a binary variable). Each analysis also controlled for years of education (given it was different between mild AD and controls), gender and MMSE score (given they were different between mild AD patients with and without GLB). The path analysis model fit was revised using modification indices and assessed using previously published recommended criteria: (a) χ^2 p value > 0.05, (b) Bentler comparative fit index (CFI: >0.95), and (c) root mean error of approximation (RMSEA: <0.04) (25).

Due to our non-random sampling methods, we applied bias-corrected (BC) bootstrap estimation with 1,000 resamples as a non-parametric approach for estimating effect-sizes, SEs and biases (26). Bootstrapping is useful in regression because it measures the variability of the linear approximation of each path in the model and estimates the bias of this linear approximation to the population (27). BC bootstrap estimation has further been shown to be useful as a multiple comparison correction method for hypothesis testing (28–30). The significance of the BC bootstrap estimate was indicated by confidence intervals that did not contain 0. Effect sizes for the direct paths between independent and dependent variables were indexed using the standardized coefficient of the path, where 0.10 indicated a small effect, 0.30 indicated a medium effect and 0.50 indicated a large effect (31). Effect sizes for the path between the interaction and the dependent variable was indexed by squaring Cohen's (31) estimations because interaction effects represent a product of two effects (32). Thus, a small interaction effect size would be 0.01, moderate would be 0.09, and large would be 0.25.

RESULTS

Participants

The cohort consisted of 92 participants with mild AD and 46 healthy controls matched on age. **Table 1** shows that compared to the controls, the mild AD group overall had less years of education ($p = 0.00$), a higher prevalence of GLB ($p = 0.01$), lower global cognition ($p = 0.00$), performed worse on all cognitive domain tasks ($p = 0.00$) and had significant atrophy in the medial temporal ($p = 0.02$) and occipital GM region ($p = 0.00$). Within

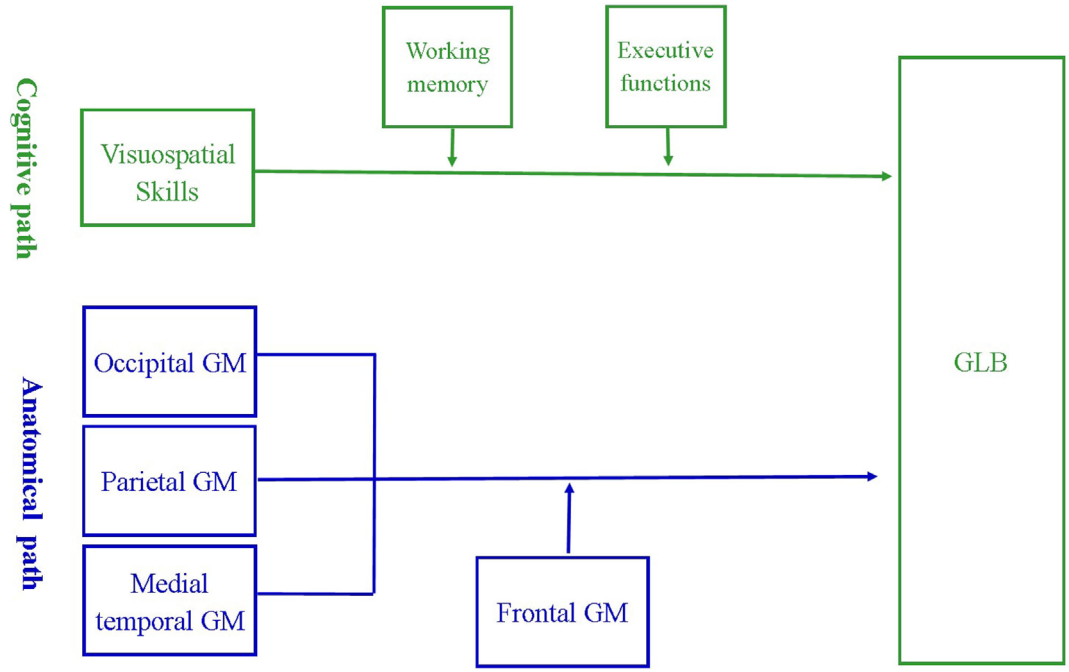

FIGURE 1 | *A priori* model of the cognitive and anatomical pathways associated with getting lost behavior (GLB). The cognitive model suggests that the relationship between visuospatial deficits and prevalence of GLB may be strengthened by poor working memory and executive dysfunctions. The anatomical model suggests that reduced volume of frontal gray matter (GM) may strengthen the relationship between GLB and atrophy in regions critical for visuospatial processing, namely occipital, parietal and medial temporal GM.

the mild AD group, those that experienced GLB were more likely to be male ($p = 0.01$), have lower global cognition ($p = 0.00$), poorer performance on executive function tasks (FAB, $p = 0.01$ and color trials, $p = 0.01$), poorer performance on visuospatial tasks (block design, $p = 0.001$) and visual reproduction (immediate recall, $p = 0.02$) and reduced volumes in the medial temporal ($p = 0.01$) and occipital GM regions ($p = 0.01$). For healthy controls, no differences were observed between those with and without GLB.

Path Analysis

Cognitive Model

The cognitive model had good model fit, with chi square (12) = 15.49, $p = 0.21$, CFI = 0.99 and RMSEA = 0.04. **Table 2** presents the characteristics of each path in the model, after controlling for covariates. GLB was not directly associated with working memory, executive functions or visuospatial skills in patients with mild AD or healthy controls. The interaction between working memory and visuospatial skills was significantly associated with GLB for both groups, suggesting that visuospatial deficits were associated with GLB only for those with poor working memory. This interaction was of a moderate effect size for patients with mild AD and of a moderate to large effect size for healthy controls. The interaction between executive functions and visuospatial skills was not significant for either group.

Anatomical Model

The anatomical model had good model fit, with χ^2 (6) = 2.49, $p = 0.47$, CFI = 0.99 and RMSEA = 0.00. **Table 3** depicts that for patients with mild AD, GLB was directly related to medial temporal GM, which was associated with a moderate to large effect size. GLB was not directly related to parietal, occipital or frontal GM ($p > 0.05$). The interaction between frontal and medial temporal GM was significant, see **Figure 2**. Frontal GM did not interact with parietal or occipital GM.

For healthy age-matched controls, GLB was not directly or indirectly related to frontal, parietal, medial temporal or occipital GM ($p > 0.05$).

DISCUSSION

Main Findings

Getting lost behavior in patients with mild AD and healthy age-matched controls was associated with visuospatial processing deficits only in the presence of poor working memory, while controlling for educational attainment, gender and global cognition. This suggests that for both AD and normal aging, visuospatial processing deficits may not be sufficient for GLB, and that impairments with higher cognitive functions, including working memory, may be necessary. This finding is consistent with the hypothesis that GLB may involve a deficit with top-down modulation of visuospatial processing, by impaired working memory.

TABLE 1 | Participant characteristics.

	Mild AD, mean (SD)			Healthy controls, mean (SD)		
	Total (*N* = 92)	**GLB+ (*N* = 26)**	**GLB− (*N* = 66)**	**Total (*N* = 46)**	**GLB+ (*N* = 4)**	**GLB− (*N* = 42)**
Demographics						
Age (years)	68.30 (9.28)	71.14 (8.05)	67.18 (9.55)	65.32 (6.04)	63.67 (7.19)	65.48 (5.99)
Gender (males, %)	45 (48)	18 (69)	27 (41)	22 (48)	2 (50)	20 (48)
Years of education	9.62 (3.88)	9.62 (3.5)	9.62 (4.02)	13.02 (2.91)	11.50 (3.87)	13.17 (2.87)
Race						
Chinese	86	23	63	43	39	4
Malay	3	3	2	0	0	0
Indian	2	2	1	3	3	0
Other	1	1	0	0	0	0
GLB prevalence	26 (28%)	–	–	4 (8%)	–	–
Cognitive measures						
Global cognition						
MMSE (score range 0–30)	24.47 (4.39)	21.46 (4.82)	25.65 (3.61)	28.70 (1.57)	28.25 (0.97)	28.74 (1.64)
Executive function						
FAB (score range 0–18)	14.34 (3.11)	13.08 (2.56)	14.83 (3.18)	17.33 (0.96)	17.50 (5.77)	17.31 (1.00)
Color Trails 2 (seconds)	732.98 (135.65)	671.26 (185.28)	757.30 (102.15)	830.11 (26.91)	833.73 (7.01)	829.76 (28.13)
Working memory						
Digitspan-forward (score range 0–16)	9.25 (2.44)	8.62 (2.11)	9.50 (2.53)	11.04 (2.22)	10.50 (3.00)	11.10 (2.71)
Digitspan-backward (score range 0–16)	7.42 (2.09)	7.00 (1.60)	7.59 (2.16)	9.89 (3.08)	10.25 (3.30)	9.86 (3.09)
Visuospatial skills						
Block design (score range 0–48)	28.26 (11.23)	22.15 (10.68)	30.64 (10.58)	37.13 (7.05)	38.00 (6.92)	37.05 (7.14)
Immediate VR (score range 0–43)	25.15 (10.90)	20.77 (11.48)	26.88 (10.25)	36.07 (3.89)	36.75 (3.09)	36.00 (3.98)
Delayed VR (score range 0–43)	14.60 (12.77)	10.69 (11.84)	16.14 (12.88)	27.35 (9.44)	30.50 (4.43)	27.05 (9.76)
Structural imaging (gray matter)						
Frontal	71.77 (6.83)	69.84 (6.31)	72.52 (6.92)	73.64 (7.11)	77.55 (9.89)	73.26 (6.84)
Parietal	32.35 (3.41)	31.40 (3.4)	32.72 (3.46)	33.03 (3.16)	34.12 (5.57)	32.93 (2.92)
Medial temporal	46.11 (5.11)	43.76 (4.79)	40.80 (4.39)	48.22 (4.24)	49.15 (5.53)	48.14 (4.17)
Occipital	23.41 (2.93)	22.17 (2.69)	23.91 (2.97)	25.06 (2.86)	25.79 (4.34)	24.99 (2.85)

AD, Alzheimer's disease; GLB+, getting lost behavior was prevalent; GLB–, getting lost behavior was not prevalent; MMSE, mini-mental state examination; FAB, frontal assessment battery; VR, visual recall.

TABLE 2 | Regression coefficients and significance of paths in the cognitive model for patients with AD and healthy controls.

Relationships	**Standardized *b***	**SE**	**BC 95% CI**
Mild AD			
Direct relationships			
Visuospatial skills → GLB	−0.17	0.14	−0.03 to 0.38
Working memory → GLB	−0.09	0.09	−0.22 to 0.04
Executive functions → GLB	−0.07	0.15	−0.33 to 0.17
Interactions			
Working memory × visuospatial skills → GLB	0.28	0.08	0.07–0.32*
Executive functions × visuospatial skills → GLB	−0.02	0.14	−0.28 to 0.82
Healthy controls			
Direct relationships			
Visuospatial skills → GLB	−0.22	0.26	−0.28 to 0.54
Working memory → GLB	−0.31	0.19	−0.67 to 0.01
Executive functions → GLB	−0.39	0.43	−0.10 to 1.4
Interactions			
Working memory × visuospatial skills → GLB	0.43	0.18	0.21–0.95**
Executive functions × visuospatial skills → GLB	−0.37	0.38	−0.83 to 0.43

*$p < 0.05$.
**$p < 0.01$.
SE, standard error; BC, bias corrected; CI, confidence interval; GLB, getting lost behavior; AD, Alzheimer's disease.

TABLE 3 | Regression coefficients and significance of the paths in the anatomical model for patients with Alzheimer's disease.

Relationships	**Standardized *b***	**SE**	**BC 95% CI**
Direct relationships			
Occipital GM → GLB	−0.28	0.18	−0.61 to 0.02
Parietal GM → GLB	0.14	0.23	−0.24 to 0.52
Medial temporal GM → GLB	−0.45	0.21	−0.79 to −0.12[a]
Frontal GM → GLB	0.29	0.21	−0.17 to 0.55
Interactions			
Frontal GM × occipital GM → GLB	−0.27	0.12	−0.46 to 0.00
Frontal GM × parietal GM → GLB	−0.07	0.19	−0.41 to 0.23
Frontal GM × medial temporal GM → GLB	−0.22	0.17	−0.41 to −0.05*

*$p < 0.05$.
SE, standard error; BC, bias corrected; CI, confidence interval; GLB, getting lost behavior; GM, gray matter.

The anatomical substrates of GLB were not consistent with the top-down deficit hypothesis for neither patients with mild AD or healthy controls. In patients with mild AD, GLB was directly associated with medial temporal atrophy; however, this association was not strengthened in the presence of reduced frontal GM as predicted. Instead, the relationship between medial temporal atrophy and GLB was strengthened in patients with

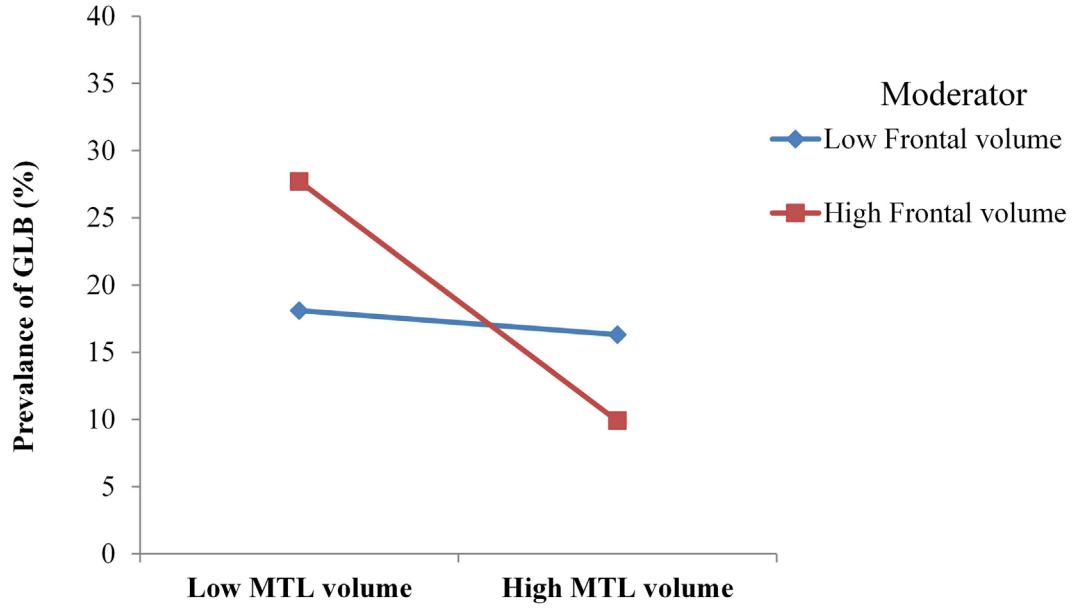

FIGURE 2 | For mild Alzheimer's disease patients with high volume of frontal gray matter (GM), medial temporal lobe (MTL) atrophy was more strongly associated with the prevalence of getting lost behavior (GLB). For patients with low frontal GM volume, no moderation was observed.

a high volume of frontal GM, indicating atypical modulatory mechanisms. Alternatively for healthy age-matched controls, GLB was not associated with occipital, parietal, medial temporal or frontal GM volumes, suggesting that the prevalence of GLB in this population may be associated with factors other than neural degeneration.

Cognitive Model

Getting lost behavior in patients with mild AD was not directly associated with general cognitive functions, such as working memory, executive functions or visuospatial processing, which converges with previous findings (33). Some (33) have interpreted this lack of association to suggest that GLB may not be a manifestation of generalized cognitive decline, rather a navigation specific decline. An alternative perspective identified by our moderation analysis suggested that the interaction between cognitive functions may be critical for understanding GLB in mild AD rather than independent associations. More specifically, general visuospatial processing deficits may become associated with GLB in the context of poor working memory, whereby poor working memory may impede the encoding and manipulation of information necessary for visuospatial processing. These findings are consistent with behavioral studies demonstrating that GLB in mild AD is a primary function of poor spatial working memory, and that visuospatial information processing deficits are secondary to these deficits (34, 35). Thus, one cognitive mechanism of GLB in patients with mild AD may involve altered top-down modulation of visuospatial processing by poor working memory.

Similar to patients with AD, healthy age-matched controls exhibited an association between GLB and visuospatial processing deficits only in the context of poor working memory. Interestingly, insights from previous studies indicate that the groups may differ with the function of working memory in top-down modulation. For instance, in healthy aging, the inability to suppress task-irrelevant information is a key substrate of GLB (6). Meanwhile for patients with AD, the inability to store and manipulate task-relevant visuospatial information is believed to be primary for GLB (36). Thus, we propose that while the functional role of working memory in GLB may differ between healthy elderly and patients with mild AD, the mechanisms by which working memory deficits affect GLB are similar across the groups.

Contrary to expectations, executive functions did not play a top-down modulatory role on the relationship between visuospatial processing and GLB. Executive functions have been implicated in way-finding, which involves spatial problem solving abilities when appropriate solutions are not available in memory (5, 36). Our findings suggest that the information source used to problem solve, namely working memory, may be more critical for GLB in elderly with mild AD than the problem solving skill itself. Given that working memory deficits are a primary diagnostic feature of AD, we propose that cognitive functions most implicated in the top-down effects of GLB may be the most vulnerable cognitive functions in each disease group.

Anatomical Model

Consistent with previous research (37), the medial temporal lobe was strongly associated with GLB in patients with mild AD. The effect size was moderate to large, suggesting that medial temporal atrophy may result in observable deficits with wayfinding in patients with mild AD. The medial temporal

region includes the hippocampus, the subicular complex and the parahippocampal cortical regions, which collectively play a critical role in the encoding, storage and active manipulation of cognitive maps (38). Accordingly, past research has demonstrated that patients with lesions to the medial temporal lobe exhibit deficits with spatial memory, including recalling locations, drawing maps of the environment and making judgments about the distance and proximity of locations (39). Similar spatial memory deficits have been observed in patients with AD (33). Thus, together with previous literature, our findings suggest that structures controlling memory functions may be a primary anatomical substrate of GLB in patients with mild AD.

To advance our understanding of the anatomical mechanisms of GLB in patients with AD, we proposed that the association between medial temporal atrophy and GLB may be strengthened by the top-down effects of reduced frontal GM volume. Contrarily to this hypothesis, we observed that the association between medial temporal atrophy and GLB was strengthened in the presence of healthy frontal GM volume. In our cohort, patients with AD exhibited comparable volumes of frontal GM to the healthy controls, which is consistent with previous findings that the frontal lobe in AD often begins to degenerate at later stages of the disease (15). This may be one reason why patients with mild AD did not exhibit typical anatomical top-down modulation mechanisms as observed in healthy aging (6). Given that our cognitive model indicated that poor working memory was necessary for poor visuospatial deficits to be associated with GLB, it is likely that this cognitive top-down modulation in patients with mild AD may be localized in the medial temporal lobe.

The medial temporal lobe and posterior parietal lobe have been argued to have overlapping but complimentary roles in spatial navigation (33). However, we only observed the medial temporal lobe to be associated with GLB in patients with mild AD. One reason for this may be that only the medial temporal lobe was reduced in volume for mild AD patients compared to healthy age-matched controls, while the parietal GM appeared healthy. Given the medial temporal lobe is one of the first regions to become affected in AD (15), our findings suggest that disease-related patterns of atrophy may contribute to the vulnerability of the spatial navigation network in patients with mild AD. Thus, anatomical markers of GLB may be disparate for patients with mild AD and healthy elderly, stressing the need for tailored assessment criteria and treatment strategies.

Strengths, Limitations, and Future Research

One strength of this study was that we used a real-world indicator of GLB, clinical interview. This measure was binary and future research may benefit from studying GLB as a continuous variable, which will allow the comparison of Alzheimer's patients with GLB and without GLB. Such comparisons will identify neural correlates for GLB not contributed by anatomical changes accounted for by typical cognitive deficits such as episodic memory loss. Another strength is that we applied path analysis to assess simultaneous relationships between variables in a multivariable pathway, however we note that our cross-sectional design did not allow us to infer causality. Future research may benefit from investigating the predictive value of the cognitive and anatomical mechanisms on the incidence of GLB. One limitation of the current study was the non-random sampling procedure, which may limit the generalizability of the results. We further note that we explored broad neural regions while specific regions such as the dorsal occipital cortex, the posterior parietal cortex and the dorsolateral prefrontal cortex have previously been implicated in GLB (9, 40, 41). The inclusion of broad regions in the current study was an important preliminary step for model building, paving the way for future research to specify the models in more detail. We further note that the cognitive assessments were not navigation specific, however the trends were consistent with previous studies (33) utilizing navigation specific memory and visuospatial tasks.

Conclusion

This study advanced our understanding of GLB by demonstrating that a cognitive top-down modulation deficit may drive GLB in both healthy elderly and patients with mild AD. Specifically, our findings suggest that visuospatial processing deficits may not be sufficient for GLB, and that its interaction with higher cognitive functions, including working memory, may be necessary. In patients with mild AD, GLB may be localized to disease-affected structures, such as the medial temporal lobe, and anatomical mechanisms of GLB may not involve typical top-down modulation. Implications of these cognitive and anatomical findings may advance the assessment and treatment of GLB in elderly with mild AD, including cognitive training, neurofeedback, neuromodulation, and pharmacological intervention. Specifically, intervention for GLB may be optimized by improving working memory simultaneously with visuospatial processing skills, as opposed to targeting only visuospatial skills. Additionally, research measuring visuospatial skills and GLB should consider controlling for working memory. Furthermore, assessment practices of GLB may be advanced by identifying that the anatomical mechanisms of GLB may be disease specific.

ETHICS STATEMENT

The study was approved by the SingHealth Centralized Institutional Review Board (CIRB) and conducted in accordance with Singhealth CIRB guidelines and the Declaration of Helsinki. Written informed consent was obtained from all subjects or their next of kin if they were mentally incapable of giving consent.

AUTHOR CONTRIBUTIONS

CY: study concept, study design, statistical analysis, interpretation of data, and preparation of manuscript; DL: study design,

data processing, and preparation of manuscript, LL: data collection and preparation of manuscript; JZ: revision of manuscript for intellectual content; NK: study concept and revision of manuscript for intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/article/10.3389/fmed.2017.00201/full#supplementary-material.

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Big Data and Dementia: Charting the Route Ahead for Research, Ethics, and Policy

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Emerging trends in pervasive computing and medical informatics are creating the possibility for large-scale collection, sharing, aggregation and analysis of unprecedented volumes of data, a phenomenon commonly known as big data. In this contribution, we review the existing scientific literature on big data approaches to dementia, as well as commercially available mobile-based applications in this domain. Our analysis suggests that big data approaches to dementia research and care hold promise for improving current preventive and predictive models, casting light on the etiology of the disease, enabling earlier diagnosis, optimizing resource allocation, and delivering more tailored treatments to patients with specific disease trajectories. Such promissory outlook, however, has not materialized yet, and raises a number of technical, scientific, ethical, and regulatory challenges. This paper provides an assessment of these challenges and charts the route ahead for research, ethics, and policy.

Keywords: dementia, big data, ethics, health policy, Alzheimer's disease, real-world evidence, mild cognitive impairment, m-health

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INTRODUCTION: BIG DATA, HEALTH, AND DEMENTIA

The predicted threefold increase in the prevalence of dementia in the coming decades (1) will put health-care systems and informal caregivers under an unmanageable pressure. This explains the current eagerness to find a cure, to slow down progression, and to develop better predictive tools to spot early signs of cognitive decline that may develop into full-blown dementias. The identification of biomarkers for Alzheimer's disease (AD) has paved the way for research into early determinants, with an emphasis on treating patients before the clinical manifestation of the disease (2). According to a study of the drug development pipeline for AD in 2017, current efforts focus mainly on disease-modifying therapies (DMTs) (3), and most of DMT agents in phase III AD trials (as reported on https://clinicaltrials.gov in 2017) address amyloid targets (15 out of 18) (idem). Yet, the failure rate for these kinds of trials is notoriously high (4).

Increased tau protein in the cerebrospinal fluid (CSF) is also used as a biomarker for patients affected by mild cognitive impairment (MCI) who are likely to transition to AD (5). Still, the very use of MCI as a prodromal phase of AD has recently come under attack, as MCI itself reverts to normal cognitive functioning in many patients (6, 7).

Genome wide association studies have identified genes associated with increased risk of late onset AD (idem). In particular, APOe4 has been shown to have some, but only limited predictive value in determining the progression from (MCI) to AD (8).

Further efforts are underway to establish other biomarkers—genetic, biological, and combinations thereof—in both CSF and plasma (2), as well as attempts to look at cognitive decline on longitudinally longer scales (9).

Multidimensional models integrating multiple biomarker data and etiological pathways are regarded as decisively more promising than reductionist approaches based on single explanatory hypothesis like those driving clinical research on the amyloid cascade (4, 10).

Integrative approaches to dementias are ideal candidates to test an incipient approach driven by the use of big data in dementia research. Recently, the global surge of interest around big data has spilled over into the field of dementia, as well as in many other domains of medicine and health research. Big data refers to unprecedentedly large amounts of data analyzed through novel data mining techniques for a variety of different purposes. Although the concept lacks an agreed-upon definition, it is generally assumed that big data is characterized by the so-called 3Vs: volume, velocity, and variety (11). This simplified definition captures some peculiar facts. For starters, the total amount of data stored in data centers in the world is estimated to reach 915 exabytes by 2020 (2.4-fold increase with respect to today) (12). In parallel the amount of data generated by networked end-user devices and appliances will be more than triple in the same period (12). Data are being generated at impressive velocity. Both structured and unstructured data contribute to this rapid growth. Biomedicine does its part too. Sequencing a whole human genome now take as little as few hours, and it is estimated that more than 35 petabytes of genomic data are produced every year (13). But genomic data are not the only reason why health care is predicted to be one of the domains in which big data will have a transformative effect (14). Electronic health records (EHRs)—comprehensive records of patient health history in electronic format—have now entered routine clinical practice in most advanced countries. Sensor-equipped mobile devices, wearables, and appliances keep track of physical activity, location, sleeping habits, and vital parameters in real time, 24 h a day. Mobile-based applications (hereafter apps), loyalty cards, credit cards, and smart objects register accurate data about our consuming habits. Biomedical research produces huge amounts of data that scientists can store and share for secondary use through a variety of data repositories and biobanks. The ability of such heterogeneous information to provide a multidimensional account of one's health state has led some to speak of it as our "digital phenotype" (15), and to introduce the notion of "digital health" (16). Interest is rapidly growing around the potential medical breakthroughs enabled by mining such unprecedented amounts of data.

Dementia research is among those fields in which big data are regarded as more promising. Leveraging the collection, aggregation, and predictive analysis of large data volumes could reboot dementia research and care as it holds the potential of casting new light on its etiology, enabling timelier diagnosis and prevention strategies, and possibly overcoming current therapeutic limitations. In particular, this potential is more likely to be realized by enabling the integration of EHRs, molecular biomarkers, neuroimaging biomarkers, and mobile health (mHealth) data.

In this contribution, we review the existing scientific literature on big data approaches to dementia including both original research articles and commercially available mHealth applications. Based on this synthesis, we identify some major promises and challenges associated with big data trends in dementia research and care and chart the route ahead for research, ethics, and policy (see **Figure 1**).

METHODS

In spite of their disruptive potential, big data trends in dementia still remain a relatively unexplored topic. In October 2017, we conducted a PubMed search [("big data" AND "dementia") OR ("big data" AND "cognitive decline")] with unrestricted time range. The search retrieved nine peer-reviewed articles and one conference paper. The nine scientific articles included editorials (17, 18) and commentaries aimed at introducing big data principles to the dementia community, examining the applicability of these principles to dementia research or discussing the level of preparedness of the dementia community for big data approaches (19). While most articles focused primarily on AD dementia, a recent commentary explored the use of big data resources to optimize data use in vascular dementia research (20).

The data sources examined in these studies included EHRs (20), Internet searches (21), and genetic data (22). Additional data sources such as mHealth data did not appear in the foreground of current scientific literature. However, a parallel search on the two main digital distribution services (app stores), namely, Google Play and iTunes (the latter screened through API search), indicated the current availability of 35 mobile apps aimed at screening dementia and cognitive decline through self-assessment tools or digital assistants for health professionals.

Further screening was performed through unstructured online search and retrieval of secondary sources. This second phase of analysis revealed that, besides traditional research models, big data approaches to dementia have also been pursued in the form of data analytics challenges. For instance, the DREAM Challenge for AD aimed at: (i) predicting changes in cognitive scores 2 years after initial assessment; (ii) understanding the biological basis of resilience to amyloid pathology; and (iii) classifying individuals into diagnostic groups using neuroimaging. The challenge capitalizes on large datasets such as the Alzheimer's Disease Neuroimaging Initiative's database and leverages multiple data sources including genetics, neuroimaging, cognitive assessment, and demographic information.

While research articles on big data and dementia still appear relatively rare, several policy documents produced by intergovernmental organizations focus on this topic. Between 2013 and 2015, the Organisation for Economic Co-operation and Development (OECD) released five policy papers addressing promises and challenges of big data trends in dementia care and research (23–27).

RESULTS

Promises

As often observed, dementia is "both a global problem and a pathological conundrum" (18). Therefore, the deployment of big data techniques should aim both at alleviating the global burden of dementia and at providing novel explanatory resources for the further understanding of the disease.

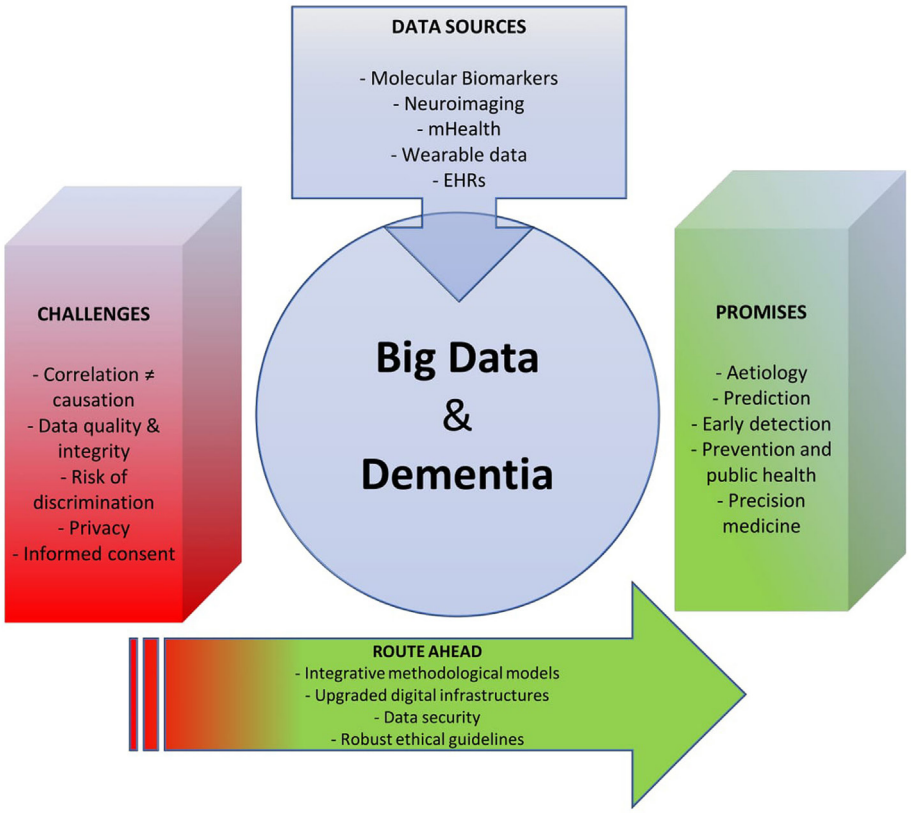

FIGURE 1 | Tackling the global dementia epidemic requires the deployment of all possible scientific and health policy means. Yet, success in this ongoing battle also depends, and in a crucial way, on targeting the right enemy and using available resources efficiently. As the big data turn starts to invest medicine, opportunities emerge to deploy new, effective weapons against this disabling condition. Our analysis revealed that the prospect of using big data for dementia research and care is still in its infancy, and that numerous challenges lie ahead on the way to furthering progress in this field. An integrative approach can overcome such obstacles and help reap the benefits of big data in dementia research and care.

Big data may in the future help in cracking the pathological conundrum of AD by shedding new light on its etiology. The use of single molecular biomarkers in isolation has so far not successfully predicted the functional and cognitive outcomes of dementia (28). Based on this observation, researchers have criticized the disproportionate focus on single molecular biomarkers such as amyloid-β and tau in dementia research, and called for more integrative approaches to the study of the etiology (10, 29). For this reason, big data trends could corroborate a multi-modal (having different modes of data acquisition from heterogeneous data sources) and multi-scalar (from the molecular to the behavioral and population scale) account of dementia, enabling statistical associations across different data types and scales. This might fix the lack of integration that currently affects different data levels, hence helping to "glimpse the big picture" (30)—from genes and molecules to cognition and behavior—in dementia research.

In recent years, attempts to integrate and statistically correlate information across large population groups have been used to achieve earlier detection of AD, ideally in the pre-symptomatic phase. Researchers have utilized multiple data sources including neuroimaging (31, 32), hand gesture tracking (33), and retinal scans (34), and developed machine learning algorithms to detect structural (e.g., changes in brain structure) or functional (e.g., changes in time response during the completion of tasks) anomalies years prior to the onset of symptoms. Some of these studies show prognostic and predictive potential (32, 33). In parallel, a number of smartphone-based apps claim the ability to detect early signs of cognitive decline through gaming behavior or digitalized mental examination. For example, the mobile app *Sea Hero Quest* (35) gamified virtual spatial navigation assessment techniques (36) to find correlations between levels of gaming performance and cognitive decline (37). With over 2.5 million users, the app can capitalize on larger datasets than most conventional clinical tools, hence leveraging the potential of big data analytics to improve screening and early detection. While Sea Hero Quest is designed for self-assessment, other apps such as *CogniSense* (38) and *ACEmobile* (39) provide digital assistance to clinicians during the cognitive screening of patients.

Employing big data to reduce the global burden of dementia (25) implies aggregating large sets of population-scale data to improve prevention and public health strategies. For example,

Doubal et al. have argued that the linkage of routine clinical data at a national or even international level might result in a better understanding of the risk factors of dementia, resulting in more effective prevention (20). In a similar fashion, Dacks et al. have argued that optimizing the use of observational data through data-pooling and Internet-based tools might support personal, clinical, or public health decision-making and contribute to the development of specific interventions that reduce modifiable risk factors (40). In parallel, as stated in an OECD report, integrating data from different size scales (from molecular to whole population) and information types (from neurophysiological to behavioral) might enable the development of precision medicine solutions (24). With recent unmet expectations regarding pharmacological therapy, this *personalized turn* can increase therapeutic effectiveness through the customization of treatments and medical decisions to each individual patient (41, 42). This is particularly relevant as evidence suggests that the "biological processes driving the clinical phenotype can differ remarkedly from patient to patient" (28) and can also depend on comorbidities, co-medications, and patient genotypes.

Challenges

Big data and digital health tools can streamline the detection of early signs of cognitive decline. MCI is a prominent example of a prodromal syndrome that, while not strongly debilitating, can develop into full-blown dementia (43).

Other entities have recently been suggested to have a similar predictive value, such as subjective cognitive decline and mild behavioral impairment (44, 45). Apps that monitor the clinical presentation of such conditions (such as users' mood and cognitive performance over time) can greatly facilitate spotting changes from baseline functioning levels. The ubiquity and ease-of-use of such tools may enable self-monitoring practices, thus leading to a widespread increase in the number of patients referred to neurologists. On the one hand, if this enhances early detection of patients at risk of developing dementia, such practices can inflate the number of false positive diagnoses. This is a concrete risk, especially in light of recent findings showing that conditions like MCI, for instance, are prone to stabilization or even spontaneous reversion to normal functioning (46). In the absence of adequate evidence and guidelines, excessive emphasis on preclinical syndromes can lead to over-diagnosis and unnecessary medicalization, with consequences for both health systems and patients. The latter face risks of insurance and employment discrimination, stigmatization, and direct psychological harm. Health systems, on the other hand, may have to cope with unnecessary financial and organizational costs in response to an upsurge of mild/preclinical syndromes (46–48).

These downstream effects of mHealth applications in dementia demonstrate the need to establish *ad hoc* regulatory pathways to validate apps that make medical claims. Regulators such as the US Food and Drugs Administration (49) and the UK Medicines and Healthcare Products Regulatory Agency (50) are starting to venture in this domain. Nonetheless, we observed that many developers present their applications in ambiguous ways, without offering sufficient information regarding either the evidence backing their products, or the way in which they will handle the personal data of their customers. More effective incentives and disincentives are still needed to ensure sufficient consumer protection in this area. In particular, there needs to be more stringent oversight regarding the health-related claims of apps.

Despite these drawbacks, early detection remains laudable, as it allows us to treat patients before degenerative trajectories compromise the odds of slowing or stabilizing cognitive decline. The collection and analysis of multiple data types describing the aging trajectory of individual patients can help isolate discrete stressors and molecular characteristics (including genetic ones), and cluster them with cognitive or neuro-psychiatric symptoms that lead to the clinical manifestation of dementia. This kind of knowledge will improve the clinical understanding of dementia, as well as the development of personalized therapeutic and preventive interventions. Creating the evidence base for such interventions will require large-scale personal data repositories, giving rise to regulatory challenges in terms of data management, protection, aggregation, interoperability, privacy, and informed consent for the collection, use, and sharing of such data. Such issues are currently being debated in ethics and regulatory circles (51). Yet, other pressing issues relate to the most adequate means to generate clinically reliable and usable evidence from heterogeneous "real-world data," such as EHRs, mobile device data, and socioeconomic data (52). Current discussions on pragmatic trial designs will likely turn out relevant to research in novel, data-driven approaches to prevention and therapy in dementia (53). In the case of a stigmatizing condition like dementia linking data from within and without the clinical setting to detect early signs of cognitive decline poses peculiar ethical challenges. At a minimum, patients (or their legal representatives, in case of advanced dementia) should be made aware of such activities and be given the option to opt out.

A WAY FORWARD: THE NEED FOR AN INTEGRATIVE APPROACH

Scientific Evidence and Theory

To overcome the above structural challenges and ensure the success of big data initiatives for dementia, there is a need for integrative approaches at the level of research methodology, digital infrastructures, and financing, as well as ethics and regulation.

At the scientific level, there is a need for clearly demarcating the explanatory power of big data driven research. Large-scale data collection and further mining through analytical tools could boost dementia research and care management, establishing reliable statistical correlations between heterogeneous data sources whose association could not be detected through small-scale methods. It is questionable, however, whether big data approaches alone would suffice to uncover the causal mechanisms of AD pathology. The idea that large datasets might *speak for themselves* (54), independent of explanatory hypotheses (55) has attracted praise as well as criticism (56, 57). Integrative approaches are needed to combine the predictive power of big data with theoretically robust and causally explanatory scientific models. A valid proposal for such integration has been advanced by Geerts

et al., who suggested that data-driven analytic approaches in AD research "need to be organically integrated into a quantitative understanding of the pathology" involving mechanism-based modeling and simulation approaches. In their view, this integration could enable a shift from big data to *smart-data*, i.e., from "information" to "actionable knowledge" (28). Similarly, DeKosky has called for the integration of big data approaches with basic neuroscience (18).

Integrative and theory-mediated big data approaches are well placed to overcome current limitations in dementia research. Taking a stance from systems biology and complexity theory, Geerts et al. argued that the integration of big data analytics with modeling and simulation might overcome the explanatory failures of reductionist biological approaches focused on single molecular biomarkers in isolation. In their view, this holistic approach has already shown benefits in PD-dementia, as it has led to a better understanding and optimization of deep-brain stimulation protocols (28).

Digital Infrastructure

Current digital infrastructures of dementia research and care need to be upgraded. As stated in a recent OECD report, secure infrastructures for data storage, processing, and access need to be sustained through complementary resources (27). While ongoing digitalization and automation in dementia care offer novel opportunities for large-scale data acquisition (58), further efforts are required to sustain the secure and reliable sharing of such information, and to guarantee the interoperability of different data-repositories (e.g., genetic biobanks, neuroimaging repositories, and eHealth data platforms). Active cooperation between public and private actors has been recognized as a viable strategy for increasing funding opportunities and favoring the digital transformation of dementia research and care (26). Yet, the appropriation of health data by large ICT corporation can cause public unease, thus undermining the development of data-driven medicine. A recent controversy over Google's access to NHS data through its AI subsidiary DeepMind shows that sufficient safeguards are not yet in place (59).

Ethical Guidelines

Ethically robust guidelines for the collection and sharing of personal health data would facilitate big data research while maintaining public trust and protecting data subjects. Existing oversight mechanisms (such as ethics review) and conventional informed consent models appear "ill suited" for large-scale data collections (60, 61). As far as research on large-scale repositories of structured and unstructured data is concerned, *ad hoc* criteria for assessing research protocols employing novel data analytics tools are urgently needed. Moreover, informed consent—in its current shape—does not grant data subjects (nor their legal representatives) sufficient control over highly sensible information regarding their cognitive state. This is a disincentive for people to make their data available for research in the first place. New mechanisms are being explored to enable more granular data control on the part of data subjects—for example by implementing data portability rights, or by introducing electronic consent management mechanisms and participatory forms of data governance (61). The longitudinal nature of studies based on big data and real-word evidence, however, poses issues relative to the validity of initial consent obtained from people whose cognitive functions may degrade over time. *Ad hoc* oversight mechanisms, such as advanced directives, shall be in place to safeguard the autonomy and wellbeing of those patients while at the same time enabling scientific progress.

Privacy and Data Security

As to privacy and data security, researchers and regulators need to acknowledge that not even anonymization of deep phenotypic data—such as those that are needed for the development of big data approaches in dementia—is a sufficient firewall. As demonstrated in the case of genomic (62) and electrophysiological data (63), maliciously re-identifying anonymous data is within reach of sufficiently skilled offenders. Given the sensitive nature of data regarding cognition (64) and given the frequency of spectacular health data breaches (65), data security represents a priority. It follows that efficient regulatory and technical measures to shore up data security are key to scientific progress in the field. Privacy-preserving techniques such as encryption and block chain need to be incorporated into the digital infrastructure of current data transmissions. These solutions will not only enhance data security but also facilitate and sustain the trust of individuals (both healthy subjects and people with symptomatic dementia) in the data collection and sharing (66).

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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