PSYCHOLOGICAL FRAILTY IN AGEING: LIFESPAN TRAJECTORIES AND EMERGING RISKS

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Editorial: Psychological frailty in aging: Lifespan trajectories and emerging risks

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frailty, aging, lifespan trajectories, multidimensional and dynamic perspective, integrated healthcare

Editorial on the Research Topic
Psychological frailty in aging: Lifespan trajectories and emerging risks

In the study of aging, "frailty" is the state that increases the individual's vulnerability to stress factors. In the context of biomedical sciences, the concept of frailty has been operationalized differently, and the most used is the frailty phenotype. However, different constructs have emerged in recent decades complementing the traditional one of physical frailty. From a biopsychosocial, gerontological outlook, multidimensional and dynamic perspectives that include physical, functional, cognitive, and psychosocial domains (e.g., cumulative deficit model), are currently more relevant (Rockwood and Mitnitski, 2007; Gobbens et al., 2010).

As people age and become frailer, their psychosocial circumstances seem to have a more direct impact on their health. For example, the concept of "cognitive frailty" includes the presence of physical frailty and mild cognitive impairment in the absence of dementia and/or disability (Facal et al.). "Social frailty" would be the risk of losing resources (e.g., social support, cohesive activities, and social participation) in the aging process to meet key social needs for human development. This lack of cognitive and social resources in old age can be accompanied by a withdrawal of vitality, as well as a loss in meaning of life and will-to-live (Bunt et al., 2017; Lozupone et al., 2020). Thus, "psychological frailty" (understood as a decrease in cognitive, social, and *transcendental* resources) would increase a person's vulnerability when exposed to stressful circumstances. In this way, there is no subordination between physical, psychological, and social areas, but rather these depend on different, interrelated developmental trajectories throughout the lifespan (Facal et al., 2019). Instead, what takes place is an interaction between socio-economic, familial, cognitive, and physiological factors present in aging (Navarro-Pardo et al., 2020). Similarly, the health crisis of COVID-19, as well as the psychosocial risks associated with the measures that

governments around the world have adopted to stop the spread of the virus, could have a significant impact directly on physical health, mental health and frailty, as well as indirectly, as a consequence of restrictions in mobility, activity, and social and family relationships, isolation, increased difficulties in performing physical exercise, delay in access to services health and loss of autonomy, to benefit from other services that have moved to the online space (Lozupone et al., 2020; Maltese et al., 2020; Pelicioni et al., 2020; Holland et al., 2021; Garner et al., 2022).

Regarding the role of affective factors across lifespan, depression and frailty present positive bidirectional associations in old adults, share common risk factors and may share pathophysiologic pathways. In the longitudinal study by Cao et al., prefrail or frail participants showed higher risks of depressive symptoms before and after adjusting for sociodemographic and health confounders, compared with the robust participants. In the cross-sectional study by Yuan et al., depression was a significant mediator of the relationship between frailty and the self-perception of the aging process, and so a significant psychological predictor of frailty of old adults. In the study by Yao, poor childhood experiences (poor self-reported health in childhood, poor mothers' and/or fathers' mental health) were associated with higher odds of depression in later adulthood, stressing the role of lifespan development in old adults' mental health.

Another topic of relevance is the relationship between frailty and motor signs of aging. In this Research Topic, Lin et al. shave examined the longitudinal transitions in the phenotypes of old adults with impairments in mobility, cognitive functioning and both, showing the potential for reversibility of these impairments and identifying the predictors of convertibility of transitions between phenotypes in question.

In terms of biological aspects, aging is often accompanied by an increase in inflammation. Pothier et al. confirm significant links between inflammation (especially higher levels of C-reactive protein and interleukin-6) and frailty status. In our Research Topic three reviews directly point out to biomarkers able to predict or operativize the relation between biological and psychological processes in frailty (Carini et al.; Moyse et al.; Pothier et al.). In this respect, although the research about this topic has increased considerably in recent years, no clear common pathways have been demonstrated for both frailty and cognitive impairment. Changes in microbiota, plasma biomarkers such as IGF-1 and IGFBP2, metabolic factors including low levels of vitamin E alpha tocopherol, omega-6 and 3 and albumin (Facal et al.) and neuroinflamation (Moyse et al.), may be all involved in cognitive frailty. Carini et al. also propose the potential role of microRNAs such as iR-92a-3p and miR-532-5p as biomarkers of cognitive frailty.

Finally, and regarding intervention studies, two papers show the effectiveness of interventions based on physical activity and multicomponent in long-term care centers (Facal et al.) and home-based individual cognitive stimulation programs (Silva et al.). The home-based individual cognitive stimulation program proved to be a promising non-pharmacological alternative to address age-related cognitive changes, also having a positive effect on strengthening the relationship between the caregiver and the cared person. However, as this approach requires continuous involvement of caregivers, its success may depend on adequately mobilizing community responses. It is expected that these types of interventions addressing psychological frailty will increase progressively and intervention programs will obtain evidence of their effectiveness and efficiency in parallel with the aging of the population.

The comprehensive analysis of quantitative and qualitative evidence from different scientific areas, presented in this Research Topic, confirmed that frailty is an emerging health and societal challenge that requires a holistic and lifecycle-centered approach and involvement of actors from different sectors, including old adults themselves and their families. By adopting this new approach, the possibility arises of offering health and social care that respond to people's real needs and adjust to their circumstances, increasing the acceptability and commitment to the proposed treatment and contributing to its success. We hope that reflection prompted by our Research Topic will relevantly contribute to efforts to involve, empower, and encourage the population to be an active part of this process.

Author contributions

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

Conflict of interest

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

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REVIEW
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The Potential Role of miRNAs in Cognitive Frailty

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Frailty is an aging related condition, which has been defined as a state of enhanced vulnerability to stressors, leading to a limited capacity to meet homeostatic demands. Cognitive impairment is also frequent in older people, often accompanying frailty. Age is the main independent risk factor for both frailty and cognitive impairment, and compelling evidence suggests that similar age-associated mechanisms could underlie both clinical conditions. Accordingly, it has been suggested that frailty and cognitive impairment share common pathways, and some authors proposed "cognitive frailty" as a single complex phenotype. Nevertheless, so far, no clear common underlying pathways have been discovered for both conditions. microRNAs (miRNAs) have emerged as key fine-tuning regulators in most physiological processes, as well as pathological conditions. Importantly, miRNAs have been proposed as both peripheral biomarkers and potential molecular factors involved in physiological and pathological aging. In this review, we discuss the evidence linking changes of selected miRNAs expression with frailty and cognitive impairment. Overall, miR-92a-5p and miR-532-5p, as well as other miRNAs implicated in pathological aging, should be investigated as potential biomarkers (and putative molecular effectors) of cognitive frailty.

Keywords: frailty, cognitive frailty, biomarkers, miRNA–microRNA, cognitive impairment, MCI (mild cognitive impairment)

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INTRODUCTION

The greatest achievement of public healthcare in the last several decades has been the large increase in lifespan. Yet the increasing aging population has brought about new challenges to the health system, with the mounting prevalence of geriatric conditions requiring a new general healthcare system for people afflicted by physical and mental impairment (Beard et al., 2016; Howdon and Rice, 2018).

In older people, frailty and cognitive impairment are commonly found together (Fabricio et al., 2020). Frailty is a clinical syndrome with different definitions, generally referred as a state of increased vulnerability to stressors that results from a decreased physiological reserve in multiple organs and systems, leading to a limited capacity to meet homeostatic demands (Clegg et al., 2013; Proietti and Cesari, 2020). Although frailty and cognitive impairment could be considered as

distinct clinical states, converging evidence has shown a close epidemiological association between these conditions (Halil et al., 2015; Kiiti Borges et al., 2019; Miyamura et al., 2019). This led to the generation of the term "cognitive frailty," defined as a heterogeneous clinical condition characterized by the concomitant presence of both physical frailty and cognitive impairment (Kelaiditi et al., 2013).

Nevertheless, the molecular mechanisms underlying cognitive frailty are still largely unknown. microRNAs (miRNAs) are a large family of conserved small (20–22 nucleotides) non-coding RNAs involved in post-transcriptional regulation of gene expression. Each miRNA targets hundreds of transcripts mainly repressing translation or inducing mRNA degradation of target transcripts through sequence-specific binding (Mohr and Mott, 2015). Compelling evidence suggests that miRNAs are both involved in physiological/pathological processes associated with aging (Williams et al., 2017) and in the regulation of brain functions (Kumar et al., 2017a; Nampoothiri and Rajanikant, 2017). Indeed, miRNAs act in several biological functions, such as proliferation, apoptosis, cell differentiation, embryogenesis, organogenesis, signal transduction and metabolism (Alvarez-Garcia and Miska, 2005; Kloosterman and Plasterk, 2006). Thus, it should not be surprising that miRNAs were recognized as key modulators of virtually all physiological processes and, consequently, miRNAs dysregulation have been reported in a multiplicity of diseases (**Figure 1**; Condrat et al., 2020). In addition to their presence inside the cells, miRNAs can be found also in extracellular fluids, forming the so-called circulating miRNAs, which are supposed to be involved in cell signaling and communication (Sohel, 2016). miRNAs presence in body fluids can be due to several concomitant processes, including tissue damage, cell apoptosis and necrosis, active release in exosomes and microvesicles, or association with proteins (O'Brien et al., 2018).

In the present manuscript, after introducing the multiple clinical aspects and the main cellular mechanisms proposed to be associated with frailty and cognitive impairment, we designed a narrative review on the studies in which miRNAs have been proposed as peripheral circulating biomarkers for frailty or cognitive impairment, with the final aim to identify miRNAs that might be associated with cognitive frailty.

CLINICAL, CELLULAR, AND MOLECULAR MECHANISMS OF FRAILTY: THE POTENTIAL ROLE OF miRNAs

Clinical Features of Frailty

Frailty is generally considered as a geriatric syndrome, characterized by an excessive vulnerability to endogenous and exogenous stressors, due to a decrease in physiological reserves, thus leading to a high risk of developing adverse health outcomes (Clegg et al., 2013; Proietti and Cesari, 2020).

The majority of studies are based on the definition of frailty introduced by Fried and collaborators in 2001. The Fried phenotype also known as the frailty phenotype model defines frailty as a clinical syndrome in which three or more of the following criteria are present: unintentional weight loss, fatigue or self-reported exhaustion, weakness (poor grip strength), slow walking speed, and reduced or absent physical activity (Fried et al., 2001). This definition, exclusively considering the physical domain, is most frequently used for determining "physical frailty." It should be mentioned that a key contribution to physical frailty comes from sarcopenia, defined as a progressive loss of skeletal muscle mass and strength (Ardeljan and Hurezeanu, 2021). Sarcopenia and frailty often co-exist in older patients, presenting a significant overlap of physical symptoms (Martin and Ranhoff, 2020). Indeed, sarcopenia is viewed as an essential correlate of the physical component of the frailty phenotype, although frailty can also be present in the absence of sarcopenia, suggesting the existence of several phenotypes of frailty (Davies et al., 2018).

In the same year in which Fried published the clinical criteria of physical frailty, other authors started to recognize that frailty was not exclusively characterized by physical impairments, but could be considered a more complex condition, involving other functional domains. Indeed, Rockwood and Mitnitski proposed the so-called Frailty Index (or Frailty Index of Deficit Accumulation) (Mitnitski et al., 2001), which is based on the concept that aging is a continuous process characterized by several deficits (including diseases, signs, symptoms, laboratory abnormalities, cognitive decline, and disabilities in activities of daily living), the accumulation of which may lead to frailty. Accordingly, the Frailty Index is defined as the proportion of accumulated deficits, thus representing the probability of an individual being frail (Martin and O'Halloran, 2020).

Other definitions of frailty exist, but the Fried Frailty Score and the Frailty Index are the most frequently used in clinical practice (Dent et al., 2016; Lekan et al., 2021).

More recently, a novel model of frailty has been proposed, based on a multidimensional evaluation considering the loss of harmonic interaction between multiple domains, including genetic, biological, functional, cognitive, psychological, and socio-economic dimensions, that ultimately leads to homeostatic instability (Pilotto et al., 2008, 2020). This multidimensional approach exploits the instruments of the comprehensive geriatric assessment (CGA). Operatively, CGA uses specific scales that explore functional disability, cognition, depression, nutritional status, comorbidities, number of drugs used, falls and pressure sores risk, cohabitation status, social and welfare context. This view, considering both multimorbidity and polypharmacy, allows for the evaluation of multidimensional impairment of the subject and promises to help the appropriateness of prescribing and intervention in frail older adults (Pilotto et al., 2018).

The prevalence of frailty has been assessed in many studies worldwide, although the results are highly variable, essentially depending on the definition used for indicating frailty. Overall, frailty has a prevalence estimated at around 11–16% in the population 60 years and older (Rohrmann, 2020; O'Caoimh et al., 2021). Frailty is more prevalent in women compared to men and as expected, prevalence increased with age, being the highest in subjects over 85 years (Collard et al., 2012; Rohrmann, 2020).

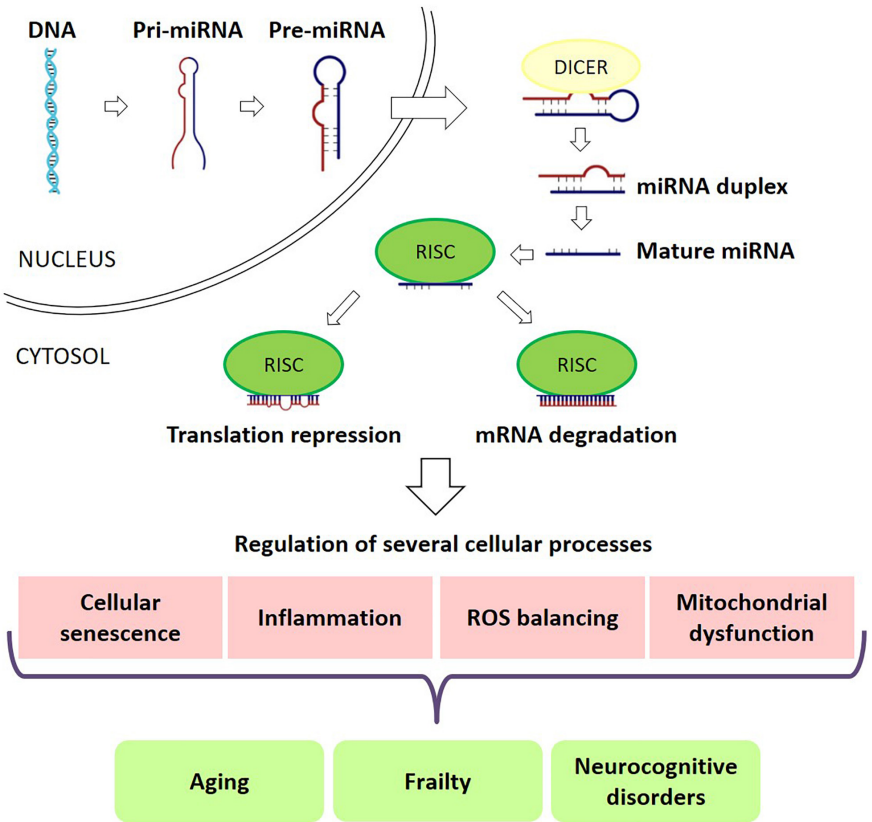

FIGURE 1 | miRNAs in frailty and cognitive deficits. miRNAs play a major role in RNA silencing and post-transcriptional regulation of gene expression. miRNAs target hundreds of transcripts to regulate various biological pathways and processes, repressing translation or inducing mRNA degradation of target transcripts through sequence-specific binding. miRNAs are key modulators of almost all physiological processes and, consequently, miRNA dysregulation is seen in a multiplicity of diseases, including frailty and cognitive deficits.

Cellular and Molecular Mechanisms of Frailty

In the last years, great efforts have been made to discover the molecular mechanisms underlying frailty. A gradual decrease in physiological reserve occurs with physiological aging but, in frailty, this decrease is accelerated, and homeostatic mechanisms start to fail (Clegg et al., 2013). Although lifelong accumulation of molecular and cellular damages is believed as a key element of both physiological aging and frailty, the interplay among dysfunctions in the brain, endocrine system, immune system, and skeletal muscle functions is recognized as a main factor in the development of frailty (**Figure 2**; Clegg et al., 2013). In the following paragraphs, we resume the main systemic and cellular processes recognized to be involved in frailty pathophysiology, including changes in the immune system, cellular senescence, and hormonal imbalance.

Changes in the Immune System and Related Musculoskeletal Consequences

Aging is associated with dramatic changes in the immune system, implying both immunosenescence (the decline in immune function with aging), and inflammaging (a state of chronic inflammation), which are considered to be main risk factors for age-related diseases (Franceschi et al., 2000; Fulop et al., 2015, 2018). Immunosenescence is characterized by altered T and B cells responses due to a modified naïve/memory cell ratio. Accumulation of memory T cells and reduction of peripheral blood naïve T cells are observed as a result of developmentally programmed thymic involution, increased serum levels of IgG and IgA, and a poor response to newly encountered microbial antigens (Pawelec, 2018). On the other hand, inflammaging is characterized by increasing circulating pro-inflammatory factors and decreasing circulatory anti-inflammatory factors (Franceschi et al., 2018). Remarkably, frail people have both immunosenescence (Lang et al., 2010) and inflammaging (Soysal et al., 2016).

The immune system plays, directly and indirectly, a role in age-associated muscle decline. Multiple immune cells have been implicated in muscle repair and regeneration, by controlling the local inflammatory responses and promoting muscle growth through releasing growth factors (Xu et al., 2020). Moreover, inflammatory cytokines have a major role in muscle homeostasis, activating muscle breakdown to generate amino acids for energy and cleave antigenic peptides. However, the overactive, insufficiently regulated inflammatory response that characterizes

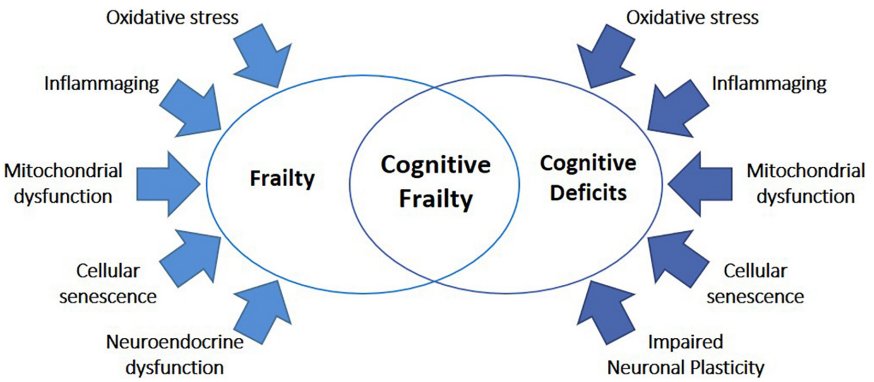

FIGURE 2 | Common mechanisms underlying frailty and cognitive deficits. The high majority of mechanisms known to be involved in frailty were also implicated in cognitive diseases, including oxidative stress, inflammaging, mitochondrial dysfunction, cellular senescence, neuroendocrine dysfunctions, and impaired neuronal plasticity.

aging and frailty could result in loss of muscle mass and strength, with an associated reduction in functional ability (Clegg et al., 2013; Wilson et al., 2017). Accordingly, as already mentioned in the introduction, sarcopenia is considered as a key component of frailty as well as a predictor of morbidity, disability, and death in older people (Cooper et al., 2012; Nascimento et al., 2018).

Cellular Senescence

Cellular repair and regeneration are key elements in tissue homeostasis (Lazzeri et al., 2012). Aging is characterized by the loss of tissue regenerative properties and the accumulation of senescent cells, which is a defense mechanism preventing genomic instability (Bisset and Howlett, 2019). Senescent cells are non-dividing cells, highly metabolically active, that gradually acquire a secretory phenotype called senescence-associated secretory phenotype (SASP) (Cardoso et al., 2018). SASP contains a variety of factors, including proinflammatory and matrix modifying peptides, which negatively influence tissue homeostasis and regeneration (Zampino et al., 2020) and are causally linked to increased inflammaging (Korolchuk et al., 2017). SASP has also been shown to be involved in the pathogenesis of several age-related diseases and conditions, including frailty (LeBrasseur et al., 2015; Schafer et al., 2020).

Senescence is associated with dysregulated mitophagy and mitochondrial dysfunction (Chapman et al., 2019), leading to enhanced levels of reactive oxygen species (ROS), which in turn contribute to the development of senescent phenotype (Korolchuk et al., 2017), age-related diseases, and frailty (El Assar et al., 2020; Ferrucci and Zampino, 2020).

Hormonal Imbalance

During aging, hormonal axes suffer significant changes. The endocrine system is considered particularly important in frailty, because of its complex inter-relationships with the brain, immune system, and skeletal muscle (Clegg and Hassan-Smith, 2018). Anabolic hormones, such as androgens and insulin-like growth factor-1 (IGF-1), play a key role in stimulating protein synthesis, muscle growth, and insulin secretion. Strong evidence suggested that the levels of these hormones decline with age (Bisset and Howlett, 2019) and their alteration have been associated with frailty (Morley and Malmstrom, 2013). Adrenocorticotropic Hormone (ACTH) and cortisol secretion are also altered during aging and frailty leading to an impaired ability to recover from stressful stimuli in older people (Yiallouris et al., 2019). The dysregulation of multiple hormones has been proposed as one potential mechanism underlying frailty since preliminary evidence indicates that the cumulative burden of hormone deficiencies in frailty may be more important than the type of hormonal change (Bisset and Howlett, 2019).

miRNAs and Frailty

miRNAs are emerging as promising non-invasive diagnostic and prognostic biomarkers, as well as potential therapeutic agents (Vatic et al., 2020). Indeed, they could be used both to help understand physiopathological processes, and as novel therapeutic strategies allowing the simultaneous targeting of different pathways (Cardoso et al., 2018).

The study of miRNAs is a growing area of interest in the aging field. miRNAs regulate several biological events related to the aging process but are also influenced by aging processes themselves (**Figure 1**). At the same time, miRNAs have been consistently linked with the main systemic and cellular processes discussed above as associated with frailty. Indeed, some miRNAs, defined as "inflamma-miRs," are involved in inflammatory pathways modulation and are differentially expressed during inflammaging (Quinn and O'Neill, 2011; Boldin and Baltimore, 2012; Olivieri et al., 2013, 2017). miRNAs play a pivotal role also in sarcopenia, regulating different aspects of muscle homeostasis (Sannicandro et al., 2019; Kinser and Pincus, 2020; Yin et al., 2020). Moreover, other miRNAs, the so-called senescence-associated miRNAs (SA-miRs) are involved in crucial biological processes of cellular senescence such as apoptosis, mitochondrial metabolism, and mitochondrial dynamics (Bu et al., 2017; Geiger and Dalgaard, 2017; Suh, 2018).

Several studies have reported differential miRNA expression between young and older individuals without discriminating for a frail phenotype (ElSharawy et al., 2012; Olivieri et al., 2012;

Serna et al., 2012; Noren Hooten et al., 2013; Smith-Vikos et al., 2016) reviewed in Chen et al. (2010) and Lai et al. (2019). Conversely, to the best of our knowledge, only two studies directly evaluated changes in blood plasma miRNAs in frailty (**Table 1**).

Ipson and collaborators examined the changes of plasma-derived exosome miRNA profiles in frailty, comparing young, old robust, and frail individuals. They identified eight miRNAs that were enriched in frailty: miR-10a-3p, miR-92a-3p, miR-185-3p, miR-194-5p, miR-326, miR-532-5p, miR-576-5p, and miR-760 (Ipson et al., 2018). The second study evaluated the levels of three inflammation-related miRNAs (miR-21, miR-146a, and miR-223) and one miRNA related to the control of melatonin synthesis (miR-483) in plasma samples of healthy adults, older robust, and frail patients. Frail subjects had higher miR-21 levels than controls, whereas miR-223 and miR-483 levels increased in both aged groups (Rusanova et al., 2018).

Although very preliminary, these two studies identified possible novel candidate biomarkers for frailty in old age. Intriguingly, some of these miRNAs were also related to cellular mechanisms involved in frailty pathogenesis. For example, miR-21 is counted among inflamma-miRs and is known to target a variety of molecules belonging to the NF-κB/NLRP3 pathways, thus modulating the "switch on/off of inflammation (Olivieri et al., 2013, 2021). miR-10a has been involved in inflammation as well (Tahamtan et al., 2018), while expression of miR-185-3p, miR-194-5p, and miR-760 have been associated with cellular senescence and ROS production (Lee et al., 2014; Bu et al., 2017; Xu et al., 2017; Suh, 2018; Li et al., 2020; Zhang et al., 2021). miR-194-5p and miR-92a-3p were reported to regulate muscle cell homeostasis (Morton et al., 2021; Shi et al., 2021a).

Moreover, some of these frailty-related miRNAs seem to play a major role also in neurons. Indeed, miR-326 inhibits neuronal apoptosis and attenuates mitochondrial damage (He et al., 2020; Huang et al., 2021). miR-532-5p showed a neuroprotective effect reducing apoptosis, ROS production, and inflammation in cerebral ischemia-reperfusion injury (Shi et al., 2021b), and ischemic stroke (Mu et al., 2020), while mir-92a-3p, belonging to the miR-17–92 family, is a synaptic-related miRNA (Siedlecki-Wullich et al., 2021), involved in neural cells proliferation, differentiation, and maturation (Zhang et al., 2013; Xia et al., 2020).

COGNITIVE IMPAIRMENT: THE POTENTIAL ROLE OF miRNAs

Clinical Features of Cognitive Impairment

As we age, some cognitive abilities, such as language, vocabulary, and verbal skills, remain largely unchanged but other abilities, such as conceptual reasoning, memory, and processing speed, can physiologically decline gradually over time (Harada et al., 2013). Although general knowledge and crystallized intelligence are mostly unaffected during aging, fluid intelligence, which is the ability to learn and use new information and use it to problem-solve, is more affected (Deary et al., 2009).

Cognitive disorders are a general umbrella term that describes a group of conditions characterized by impairment in cognitive abilities such as memory, problem solving, and perception (Sachdev et al., 2013). Cognitive abilities are usually assessed through the administration of specific tests, i.e., the mini-mental state examination (MMSE) (Folstein et al., 1975) and the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). Among cognitive disorders, mild cognitive impairment (MCI) is increasing in attention by researchers, as demonstrated by the introduction in the DSM-5. This entity can be identified in presence of: (1) modest cognitive decline from a previous level of performance in one or more cognitive domains, greater than expected for age, without falling into the dementia range, (2) no interference with capacity for independence in everyday activities, (3) cognitive deficits not occurring exclusively in the context of a delirium, and (4) cognitive deficits not explained by another mental disorder (Ganguli, 2013; Sachdev et al., 2013). MCI affects about 3–22% of the population over the age of 65 (Stokin et al., 2015; Sanford, 2017), symptoms may remain stable for years, with some cases may revert to normality (Sachdev et al., 2013), but it is estimated that about 50% of people affected by MCI can progress to dementia, particularly Alzheimer's disease (AD) (Gordon and Martin, 2013).

Cellular and Molecular Mechanisms Underlying Cognitive Impairment

Brain aging is the main predisposing factor for cognitive impairment (Yankner et al., 2008). As for frailty, the main mechanisms involved in cognitive disorders are also implicated in physiological aging (**Figure 2**). However, while a decline in cognitive features is expected during physiological aging, differently from pathological aging associated with cognitive decline, this does not result in any significant functional impairment (Schirinzi et al., 2020).

The pathophysiological mechanisms of cognitive disorders essentially comprise alterations of synaptic transmission, oxidative stress, cellular senescence, and increased inflammation.

Alterations of Synaptic Function

The maintenance of synaptic function requires the preservation of the proper synaptic structure, coordination of synaptic vesicle release and membrane excitability, and integration of retrograde signals from the postsynaptic terminal (Azpurua and Eaton, 2015). Aging is associated with physiological structural changes in the brain, including the reduction of the number and function of synapses in brain areas related to learning and memory (Burke and Barnes, 2006; Lupien et al., 2009; Cuestas Torres and Cardenas, 2020). However, beyond the physiological aging processes, more generalized synaptic deficits can induce cognitive disorders. The study of cellular mechanisms underlying cognitive impairment highlighted the role of synaptic dysfunction and synaptopathy, defined as an alteration of synaptic homeostasis leading to a high risk of degeneration and synaptic loss (Stephan et al., 2012; Skaper et al., 2017). Pathological changes identified in synaptic dysfunction include plaque and tangle

TABLE 1 | Summary of miRNAs associated with frailty and cognitive deficits.

miRNAs associated with frailty				
Main findings	**Participants**	**Sample**	**Technologies**	**Study**
miR-10a-3p, **miR-92a-3p**, miR-185-3p, miR-194-5p, miR-326, **miR-532-5p**, miR-576-5p, miR-760	Seven young control subjects (30.3 ± 5.3), seven robust older subjects (76.0 ± 6.5), seven frail older subjects (85.6 ± 3.8)	Exosome isolated from the plasma	RNA-Seq	Ipson et al., 2018
miR-21	22 control subjects (20.5 ± 2.4), 34 aged robust subjects (76.6 ± 5.3), 40 aged fragile subjects (84.4 ± 5.6)	Plasma	qPCR	Rusanova et al., 2018
miRNAs associated with cognitive impairment				
Main findings	**Participants**	**Sample**	**Technologies**	**Study**
miR-7, miR-9, **miR-125b**, miR-127-3p, **mir-128, miR-132, miR-134,** miR-181a, **miR-323-3p, miR-382, miR-370, miR-491-5p, miR-874**	Pilot study: 10 control subjects (71-85), 10 MCI subjects (75-87). Main study: 20 young control subjects (21-50), 20 age matched control subjects (71-85), 20 MCI subjects (75-87), 20 AD patients (63-89). Longitudinal study: 19 subjects (73-84)	Plasma	qPCR	Sheinerman et al., 2012
miR-128, miR-132, miR-134, miR-323-3p, miR-382, miR-370, miR-491-5p, miR-874	50 control subjects (50-82), 20 MCI subjects (51-82)	Plasma	qPCR	Sheinerman et al., 2013
miRNA-193b	Age- and gender-matched control subjects, 43 MCI subjects (23 females, 20 males, 63.8 ± 6.1), 51 AD patients (28 females, 23 males, 64.2 ± 6.5)	Exosome isolated from the serum	qPCR	Liu et al., 2014a
miR-384	50 control subjects (28 females, 22 males, 63.9 ± 5.7 years), 32 MCI subjects (13 females, 19 males, 63.2 ± 6.1 years), 45 AD patients (18 females, 27 males, 64.2 ± 5.8 years)	Plasma, Serum	qPCR	Liu et al., 2014b
miR-200b	30 control subjects (75.2 ± 6.5), 32 MCI subjects (72.8 ± 6.1), 38 AD patients (76.2 ± 6.8)	Serum	qPCR	Liu et al., 2014c
miR-93, miR-143, miR-146a	123 control subjects (79.5 ± 6.8), 30 MCI subjects (81.1 ± 6.8), 127 AD patients (79.3 ± 8.9)	Serum	RNA-Seq qPCR validation	Dong et al., 2015
miR-107	81 control subjects (71.7 ± 5.4), 116 MCI subjects (68.6 ± 5.3), 97 AD patients (70.1 ± 4.6)	Plasma	qPCR	Wang et al., 2015
miR-132, miR-206	76 control subjects (73.17 ± 6.16), 66 MCI subjects (72.89 ± 7.59)	Serum	qPCR	Xie et al., 2015
miR-210	42 control subjects (23 males, 19 females, 62-85), 30 MCI subjects (18 males, 12 female patients, 61-82), 26 AD patients (12 males,14 females, 60-84)	Serum	qPCR	Zhu et al., 2015
miR-613	40 control subjects (22 females, 18 males, 63.2 ± 6.3), 32 MCI (22 females, 20 males, 64.8 ± 7.2), 48 AD patients (26 females, 22 males, 65.5 ± 6.8)	Serum	qPCR	Li et al., 2016
miR-101, **miR-103, miR-125b**, miR-191, miR-222	30 control subjects (70.4), 23 MCI patients (72.8)	Plasma	miRNA qPCR array	Kayano et al., 2016
miR-455-3p, miR-4668-5p	14 control subjects, 16 MCI subjects, 10 AD patients	Serum	miRNA array qPCR validation	Kumar et al., 2017b
miR-30b-5p, miR-142-3p, miR-200a-3p, miR-483-5p, miR-486-5p, miR-502-3p	Pilot Study: six control subjects (66 ± 5), seven MCI subjects (64.3 ± 6), seven AD patients (73.7 ± 5). Main Study: nine control subjects (66 ± 3), eight MCI subjects (65.8 ± 7), 13 AD patients (67.5 ± 8)	Plasma	miRNA qPCR array qPCR validation	Nagaraj et al., 2017
miR-135a, **miR-193b, miR-384**	Age- and gender-matched control subjects, 101 MCI subjects (59 females, 42 males, 61.63 ± 7.32), 107 AD patients (66 females, 41 males, 74.15 ± 7.93)	Exosome isolated from the serum	qPCR	Yang et al., 2018
miR-16-5p, **miR-92a-3p**, miR-26b-5p, miR-106b-5p, **miR-93-5p, miR-20a-5p**, miR-320a, let-7a-5p, miR-484, miR-615-3p, miR-18a-3p 5, miR-7977, miR-17-5p, miR-155-5p, **miR-193b-3p**, miR-450a-1-3p, miR-887-5p	GSE63063: Cohort 1: 104 control subjects (65 +); 80 MCI subjects (65 +), 142 AD patients (65 +). Cohort 2: 136 control subjects (65 +), 109 MCI subjects (65 +), 139 AD patients (65 +). GSE97760: 10 healthy controls (females, 72.1 ± 13.1), nine AD patients (females, 79.3 ± 12.3). E-MTAB-6094: 13 control subjects (10 females, three males, 77.3 ± 6.2), 22 AD patients (14 females, eight males, 79.4 ± 6.6)	Blood	Meta-Analysis of microarray data	Bottero and Potashkin, 2019

(Continued)

TABLE 1 | (Continued)

miRNAs associated with cognitive impairment

Main findings	Participants	Sample	Technologies	Study
miR-206, miR-let-7b	Discovery cohort: 31 control subjects (75.0 ± 4.7), 30 MCI subjects (76.8 ± 4.0), 25 AD patients (84.6 ± 3.5). Longitudinal cohort: six control subjects (74.0 ± 3.2), six MCI to dementia subjects (77.3 ± 3.8), six stable MCI subjects (75.8 ± 3.6)	Plasma	miRNA qPCR array qPCR validation	Kenny et al., 2019
miR-20a, miR-27a, **miR-103a**	215 control subjects (138 females, 77 males, 60.9 ± 9.9), 122 lower SMMSE score subjects (55 females, 67 males, 67.6 ± 9.7)	Serum	qPCR	Kondo et al., 2019
miR-92a-3p, miR-181c-5p and **miR-210-3p**	14 control subjects (seven females, seven males, 68.29 ± 8.99), 26 MCI subjects (16 females, 10 males, 72.0 ± 8.49), 56 AD patients (41 females, 15 males, 77.77 ± 6.69),	Plasma	qPCR	Siedlecki-Wullich et al., 2019
miR-140-5p, miR-197-3p, miR-501-3p, miR-425-5p, **miR-532-5p**, miR-378a-5p, miR-411-3p, miR-181c-3p, miR-497-5p, miR-214-3p	94 control subjects (71.79 ± 9.46), 21 MoCA < 23 score subjects (72.29 ± 2.76)	Plasma	RNA-Seq	Gullett et al., 2020
miR-6764-5p, miR-6734-3p	Discovery cohort GSE120584: 288 control subjects (age 71.7 ± 6.3 years, 151 males and 137 females), 32 MCI subjects (age 75.5 ± 6.3 years, seven males and 25 females), 1,021 AD patients (age 79.2 ± 6.1 years, 307 males and 714 females). Validation cohort: four control subjects, five MCI subjects, six AD patients	Serum/Blood	Meta-Analysis of microarray data qPCR validation	Qin et al., 2021

miRNAs in red were found in at least one frailty study and one study assessing cognitive function and miRNAs in blue were found in at least two studies assessing cognitive function.
The participants column shows the demographic characteristics of the subjects included in the study in accordance with the data available in the cited works (mean age, mean age ± SD, min–max age).
MCI, mild cognitive impairment; AD, Alzheimer's disease; SMMSE, short Mini-Mental State Examination; MoCA score, Montreal Cognitive Assessment score.

formation, vascular pathologies, neurochemical deficits, cellular injury, oxidative stress, mitochondrial changes, inflammation, changes in genomic activity, disturbed protein metabolism (Stephan et al., 2012).

Oxidative Stress and Cellular Senescence

Neurons are postmitotic polarized cells with significant energy demands and mitochondria play a pivotal role in generating the ATP required to support electrochemical neurotransmission, synaptic plasticity, neural cell maintenance, and repair (Lejri et al., 2019). Defects in mitochondrial dynamics and quality control, together with inefficient mitochondrial transport and distribution in synaptic compartments, have been implicated in synaptic/neuronal degeneration and brain aging (Grimm and Eckert, 2017; Raefsky and Mattson, 2017). Apart from the production of energy, mitochondria are key modulators of brain cell survival and death by controlling calcium and redox equilibrium, producing ROS, and controlling cell apoptosis (Mattson and Arumugam, 2018). Cellular, biochemical, and molecular studies showed a clear link between oxidative stress and cognitive dysfunction during aging and age-associated neuronal diseases (Kandlur et al., 2020). Neurons are particularly vulnerable to oxidative insults: ROS may induce the activation of neuroinflammation and neuronal death, with mechanisms involving glutamate excitotoxicity, aspartate receptor signaling, and glucocorticoid receptor activation (Grimm and Eckert, 2017). Oxidative injury can alter brain plasticity, cell proliferation, neurogenesis, and synaptic neurotransmission while enhancing neuronal death and impairing normal synaptic neurotransmission (Castelli et al., 2019). Moreover, mitochondrial dysfunctions and ROS production trigger cell senescence of neurons and glial cells, which in turn contributes to changes in morphological and functional alterations associated with synaptopathy (Morley, 2018; Toricelli et al., 2021). Indeed, senescent cells secrete pro-inflammatory SASP factors and disrupt the cell-cell contacts needed for the structural and functional neuron–glial interaction that maintains neuronal homeostasis (Chinta et al., 2015).

Inflammation

The central nervous system is traditionally thought of as an immunologically privileged space, isolated from the immune system, and separated from peripheral immune cells that are unable to cross the blood-brain barrier. However, it is now accepted that there is a wide and constant bidirectional communication between the peripheral immune system and the central nervous system (Engelhardt et al., 2017). Indeed, it has been demonstrated that signals from a systemic inflammatory condition may contribute to brain immune cell population activation, which in turn may accelerate neuronal degeneration and/or cognitive decline, leading to exacerbation of a clinical condition (Perry, 2004). Although neuroinflammation serves several fundamental roles in the brain structure and function, chronic inflammation may instead cause an exaggerated response (Tangestani Fard and Stough, 2019). Resident glial cells, including microglia and astrocytes, become hyperactivated in response to

inflammatory stimuli and sustain a high-level production of proinflammatory cytokines, chemokines, secondary messengers, and ROS (Shabab et al., 2017; Slota and Booth, 2019). This altered inflammatory status may contribute to the onset of cognitive impairment in older people and enhances the state of vulnerability to environmental challenges (Brivio et al., 2019).

miRNAs and Cognitive Impairment

miRNAs have been shown to play a major role in the brain as key regulators of neuronal development from neural progenitor cells, cell migration, neuronal polarization, and synapse formation (Nampoothiri and Rajanikant, 2017; Rajman and Schratt, 2017; Esteves et al., 2020). miRNAs can also modulate neuroinflammation (Thounaojam et al., 2013; Sarkar et al., 2019; Slota and Booth, 2019), formation of ROS, mitochondrial function, and cellular senescence (Bigagli et al., 2016; Konovalova et al., 2019; Catanesi et al., 2020; **Figure 1**). Accordingly, it has been suggested that cognitive dysfunctions in aging may be predicted by selected alterations of miRNAs expression (Danka Mohammed et al., 2017; Hernandez-Rapp et al., 2017). Recently, the involvement of miRNAs in cognitive disorders has been extensively studied, measuring their levels in different body fluids, such as plasma, serum, urine, and cerebrospinal fluid (Grasso et al., 2014; Basak et al., 2016).

Changes in miRNA expression have been correlated with cognitive performance and decline.

Kondo and collaborators examined the association between cognitive function and serum levels of six miRNAs (miR-let-7d, miR-17, miR-20a, miR-27a, miR-34a, miR-103a) in 337 Japanese subjects who had never been diagnosed with dementia. This study identified a positive correlation between the serum levels of miR-20a, miR-27a, and miR-103a and MMSE scores. Thus, low serum miR-20a, miR-27a, and miR-103a levels were significantly associated with cognitive deficits and were proposed as markers of early-stage cognitive decline (Kondo et al., 2019).

A recent study utilized machine learning approaches as a broad cognitive screening instrument to determine whether miRNAs could be proposed as blood-based biomarkers of cognitive aging (Gullett et al., 2020). Top 10 most important miRNAs for predicting total cognitive performance include miR-140-5p, miR-197-3p, miR-501-3p, miR-425-5p, miR-532-5p, miR-378a-5p, miR-411-3p, miR-181c-3p, miR-497-5p, miR-214-3p. Instead, three miRNAs (miR-140-5p, miR-197-3p, miR-501-3p) were top-ranked predictors of multiple cognitive outcomes (including fluid, crystallized, and overall cognition).

Furthermore, several studies addressed alterations of miRNA profiles in the blood of MCI patients and proposed miRNAs as specific diagnostic and/or prognostic biomarkers of MCI (reviewed in Piscopo et al., 2019). Overall, more than forty miRNAs were reported to discriminate between MCI and healthy controls in different studies, although only miR-206 was consistently found as differentially expressed in at least two reports (Piscopo et al., 2019). Specific studies on MCI patients are reported in **Table 1**.

Moreover, a recent meta-analysis of six microarray datasets identified 17 miRNAs as dysregulated in both MCI and AD [miR-16-5p, miR-92a-3p, miR-26b-5p, miR-106b-5p, miR-93-5p, miR-20a-5p, miR-320a, let-7a-5p, miR-484, miR-615-3p,miR-18a-3p 5, miR-7977, miR-17-5p, miR-155-5p, miR-193b-3p, miR-450a-1-3p, miR-887-5p, suggesting a key involvement in the modulation of cognitive function (Bottero and Potashkin, 2019)].

Other miRNAs were instead proposed as early biomarkers of MCI in the preclinical stage, or for prodromal AD. miRNA pairs in the miR-132 family (miR-128/miR-491-5p, miR-132/miR-491-5p, and mir-874/miR-491-5p) and the miR-134 family (miR-134/miR-370, miR-323-3p/miR-370, and miR-382/miR-370), although not differentiating MCI from AD, were proposed as predictive markers for the onset of MCI (Sheinerman et al., 2012, 2013). On the other hand, Kenny and collaborators, based on a 4-year longitudinal evaluation, found increased miR-206 levels in MCI patients at high risk of dementia (tested with the Clinical Dementia Rating, CDR) and in MCI patients with deteriorating MMSE scores. Indeed, stable MCI subjects displayed little to no change in expression over the years, while MCI patients who progressed toward dementia displayed significantly higher levels of miR-206 (Kenny et al., 2019). Moreover, while upregulation of miR-92a, miR-181c, and miR-210 levels was reported in plasma of both MCI and AD patients, the signature values in the plasma of the MCI patients that progressed to AD were found to be significantly higher than the values found in the MCI patients that did not progress to dementia (Siedlecki-Wullich et al., 2019). Altogether, these data suggest that plasma levels of miR-206, miR-92a-3p, miR-181c-5p, and miR-210-3p could be used as molecular signatures of AD progression in MCI. Finally, very recently, Qin and collaborators, identified two miRNAs, miR-6764-5p and miR-6734-3p, as remarkably upregulated in both MCI and AD subjects compared to controls (Qin et al., 2021).

miRNAs reported in at least two studies as associated with cognitive function are highlighted in blue in **Table 1**.

COGNITIVE FRAILTY: THE POTENTIAL ROLE OF miRNAs

Cognitive Frailty: Definitions

Several shreds of evidence demonstrated that frailty and cognitive impairment are intrinsically related, since frailty is known to increase risk of cognitive decline, and cognitive decline may increase risk of frailty and have an impact on the trajectory of frailty (as recent reviews see Kiiti Borges et al., 2019; Welstead et al., 2020; Bu et al., 2021). The concept of simultaneous presence of frailty and cognitive impairment or cognitive frailty was initially proposed in 2013 by the International Institute of Nutrition and Aging and the International Geriatrics Association (IANA), defined by the presence of physical frailty and cognitive impairment, and exclusion of concurrent dementia (Kelaiditi et al., 2013). Although the concept of cognitive frailty is well accepted and has been shown to be associated with poor outcomes, there is yet no consensus on the actual definition (Merchant et al., 2021). Indeed, multiple definitions and terminologies have been proposed, including Motoric Cognitive Risk Syndrome (MCR),

defined as presence of both slow gait speed and subjective cognitive complaints and absence of concurrent dementia or mobility disability (Verghese et al., 2014), or Physio-cognitive Decline Syndrome (PCDS), defined by slowness and/or weakness and $\geq$ 1.5 SD below age/sex/education-matched norms in any cognitive function domain (Chen and Arai, 2020). Moreover, Ruan and collaborators proposed a new classification of cognitive frailty, in which they distinguish "reversible" from "potential reversible" cognitive frailty. Reversible cognitive frailty was defined by the presence of physical/pre-physical frailty and subjective cognitive decline and/or positive fluid and imaging biomarkers of amyloid accumulation and neurodegeneration, while potentially reversible cognitive frailty was defined by the presence of physical/pre-physical frailty and cognitive impairment (Ruan et al., 2015).

Nevertheless, recent evidence suggests that, regardless of the specific definition, cognitive frailty is a target for preventing disability and dementia through multi-domain interventions, considering physical, nutritional, cognitive as well as psychological domains, with the final aim to modify the trajectory of frailty and cognitive decline toward positive outcomes.

Even though epidemiological and clinical studies have demonstrated a close relationship between frailty and cognitive diseases, the common/concurring molecular mechanisms are still largely unknown. Nevertheless, it has been proposed that abnormalities in biological processes related to physiological aging could play a major role in both conditions (Ruan et al., 2015; Searle and Rockwood, 2015). In particular, chronic inflammation, immunosenescence, imbalanced energy metabolism, mitochondrial dysfunction, oxidative stress, and neuroendocrine dysfunctions may be all involved in cognitive frailty (**Figure 2**; Mulero et al., 2011; Robertson et al., 2013; Fulop et al., 2018; Sargent et al., 2018; Fabricio et al., 2020; Ma and Chan, 2020).

Putative Role of miRNAs in Cognitive Frailty

As regards the possible role of miRNAs in the pathogenesis of frailty with cognitive impairment and/or their potential use as biomarkers, to date, no studies are available considering cognitive frailty as a single condition. Furthermore, as reported above, there are only two studies analyzing changes in blood miRNAs specifically in frail subjects, while more evidence has been collected regarding cognitive impairment.

Although the limited information available makes it hard to depict a comprehensive picture of possible common miRNAs involved in both frailty and cognitive impairment, our review effort identified two miRNAs which were reported to be both differentially expressed in frail people and associated with cognitive deficits: miR-92a-3p and miR-532-5p (**Table 1**). Mature miR-92a-3p belongs to miR-17-92 cluster, located on chromosome 13 in the human genome. The miR-17-92 cluster, containing six miRNA precursors (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a), is highly conserved among vertebrates and has fundamental roles during development (Concepcion et al., 2012; Mogilyansky and Rigoutsos, 2013). miR-92a-3p is a synaptic-related miRNA (Siedlecki-Wullich et al., 2021), involved in neural cells proliferation, differentiation, and maturation (Zhang et al., 2013; Xia et al., 2020). Intriguingly, it has been recently identified as a peripheral biomarker in different diseases, among which systemic lupus erythematosus (Kim et al., 2016), schizophrenia (Ma et al., 2018), and amyotrophic lateral sclerosis (Joilin et al., 2020). Moreover, miR-92a-3p was reported to increase ROS in mice (Gou et al., 2018), to regulates cartilage development and homeostasis (Mao et al., 2018), to participate in age-related pathophysiological processes including atherosclerosis and lipid metabolism (Loyer et al., 2014), cerebral white matter impairment (He et al., 2017), and cancer (Reis et al., 2020; Wang et al., 2021).

Mature miR-532-5p derived from pre-miR-532 which is localized on chromosome X in the human genome. miR-532-5p showed a neuroprotective effect reducing apoptosis, ROS production, and inflammation in cerebral ischemia-reperfusion injury (Shi et al., 2021b), and ischemic stroke (Mu et al., 2020). Moreover it has been implicated in inflammation (Yan et al., 2020), osteoporosis (Guo et al., 2020), as well as in tumor progression (Kim et al., 2021; Yu et al., 2021).

CONCLUSION

In this review, we explored the possible use of miRNAs as both potential biomarkers and molecular effectors of frailty and cognitive impairment. We discussed the evidence linking changes in circulating miRNAs expression with these clinical conditions, with the final aim of shedding light on miRNAs that might be associated with cognitive frailty.

One of the limits of this study is that evidence giving a clear mechanistic link between frailty (or cognitive impairment) and miRNAs is still missing. Moreover. to date, only two works analyzed miRNAs expression in the plasma of frail patients, as potential peripheral biomarkers of frailty (Ipson et al., 2018; Rusanova et al., 2018). No further studies have been performed to evaluate the molecular mechanisms leading to changes in miRNAs expression in frail subjects, nor analyzing a possible involvement of these miRNAs in frailty etiopathogenesis. The same could be stated for studies linking miRNAs with cognitive impairment. Nevertheless, some of the miRNAs found to be differentially expressed in the blood of frail or cognitively impaired subjects have been reported to play a key role in cellular mechanisms associated with frailty and cognitive deficits, such as cellular senescence, oxidative stress, mitochondrial dysfunction, or inflammation (Thounaojam et al., 2013; Bigagli et al., 2016; Bu et al., 2017; Suh, 2018; Tahamtan et al., 2018; Konovalova et al., 2019; Sarkar et al., 2019; Slota and Booth, 2019; Catanesi et al., 2020). This suggests that miRNAs could be considered more than peripheral biomarkers, fostering the idea that miRNAs could be mechanistically involved in the etiogenesis of both frailty and cognitive impairment.

In this context, although more studies are needed, existing literature may suggest a potential use of iR-92a-3p and miR-532-5p not only as biomarkers of cognitive frailty, but also as

in the context of the study of molecular mechanisms of frailty and cognitive diseases. Besides miR-92a-3p and miR-532-5p, other miRNAs consistently implicated in cellular mechanisms underlying both frailty and cognitive dysfunction, such for instance inflamma-miRs, SA-miRs, and miRNAs regulating oxidative processes, could have potential as biomarkers and molecular effectors of cognitive frailty as well.

In conclusion, although many works have proposed miRNAs as biomarkers of frailty and cognitive decline, the study of differentially expressed miRNAs in frailty is at its infancy, and reports on cognitive frailty are still missing. The identification of selected miRNAs differentially modulated in cognitive frailty could pave the way for innovative diagnostic and prognostic strategies, which may help the clinical management of people suffering from this condition, improving their life expectancy and quality of life. Furthermore, the study of miRNAs involvement in etiological mechanisms of cognitive frailty represents a promising tool for the identification of new targets for the development of novel therapeutic approaches, thus modeling health trajectories toward positive outcomes.

AUTHOR CONTRIBUTIONS

GC, LM, and AB: conceptualization. GC, LM, NV, and AB: writing—original draft. GC, LM, FB, AC, CF, AI, SM, MP, NV, and AB: writing—review and editing. All authors contributed to the article and approved the submitted version.

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A Home-Based Individual Cognitive Stimulation Program for Older Adults With Cognitive Impairment: A Randomized Controlled Trial

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Objective: This study aims to assess the feasibility and meaningfulness of a home-based individual cognitive stimulation (iCS) program delivered by caregivers to persons with cognitive impairment (PwCIs). It also aims to assess whether the older adults receiving this program improved their cognitive, neuropsychiatric, and depressive symptoms and quality of life and whether their caregivers improved their mental and physical health.

Methods: A randomized controlled trial (RCT) was conducted with PwCI-caregiver dyads recruited from the community. Participants were allocated to two groups: intervention (n = 28) and control (n = 24). The intervention group received the European Portuguese version of the Individual Cognitive Stimulation Program—Making a Difference 3 (MD3-P). The control group received usual care. The iCS therapy program was implemented three times a week for 12 weeks. Caregivers were supported by the researchers to deliver the sessions at home. Participants were assessed at baseline and at the end of the intervention (week 13). Feasibility and meaningfulness were assessed through the attrition rate, adherence, and degree of satisfaction with the sessions. Four interviews were conducted (after week 13) to understand participants' experiences.

Results: The attrition rate was 23.1%. The dyads reported that they did not have high expectations about the iCS program before starting the study. Nevertheless, as the program evolved, caregivers noted that their family members had improved some areas of functioning. Intention-to-treat analysis based on group differences revealed a significant improvement in PwCIs' cognition, specifically in their orientation and ability to follow commands. The intervention had no impact on other variables such as caregivers' physical and mental health.

Conclusion: The iCS program implemented by caregivers showed promising results in improving PwCIs' cognition. The participants who completed the intervention attributed a positive meaning to the MD3-P, confirming it as a valid non-pharmacological therapeutic approach to reducing frailty in PwCIs in community settings.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier [NCT03514095].

Keywords: older adults, dementia, mild cognitive impairment, neurocognitive disorder, individual cognitive stimulation, caregiver

INTRODUCTION

Providing conditions that promote healthy aging in community settings is a social priority. Aging is associated with increased prevalence of cognitive disorders, such as mild cognitive impairment (MCI) or dementia, also known as major neurocognitive disorders (American Psychiatric Association [APA], 2013; Prince et al., 2015; Apóstolo et al., 2016; Livingston et al., 2017). Several factors influence the onset and progression of late-life cognitive disorders, namely demographic, genetic, cardiovascular, behavioral, and psychosocial factors (Apóstolo et al., 2016). A deeper understanding of these factors is crucial for creating and activating mechanisms to prevent and treat MCI and reduce the prevalence of its more evolved forms. However, effective disorders-modifying therapies are still lacking. Recent studies (Panza et al., 2015, 2017) have shown that the adverse effects of late-life cognitive disorders can be prevented or minimized through the successful management of other age-related conditions, such as frailty.

Frailty is a clinical state resulting from aging-associated physiological and biological declines. It is characterized by a decrease of the individual's homeostatic reserves, leading to diminished resistance to external agents and/or stressful events (Fried et al., 2001; Varadhan et al., 2008; Lang et al., 2009). Frailty consists of potentially reversible changes at different levels of individual functioning. According to the phenotypic model of frailty (Fried et al., 2001, 2004), these changes include (i) impaired mobility, strength, balance, and/or endurance, (ii) weight loss or undernutrition, and/or (iii) decrease in physical activity, representing a risk factor for adverse health outcomes such as falls, fractures, disability, dependency, hospitalization, institutionalization, or even death.

In alternative approaches, frailty is a multidimensional syndrome that can be measured by counting the number of health-related deficits, such as chronic comorbid and disabling illnesses, geriatric conditions, and disabilities (Deficit Accumulation Approach, Rockwood et al., 2005; Rockwood et al., 2007; Lacas and Rockwood, 2012) or examining the losses experienced in physical, psychological (mood and cognition), and social domains in combination with the effects of life-course determinants and multimorbidity (Integral Model of Frailty, Gobbens et al., 2010). Frailty-related cognitive losses can affect memory (Ruan et al., 2015), executive functions (Langlois et al., 2012; Robertson et al., 2013; Ruan et al., 2015), attention (Robertson et al., 2013; Ruan et al., 2015), language, visuospatial functions (Ruan et al., 2015), and processing speed (Langlois et al., 2012). However, in less severe cases, these losses may not be detected during cognitive screening due to older adults' compensatory efforts (Ruan et al., 2015).

In a recent study, physical frailty was associated with late-life cognitive disorders (Panza et al., 2015). On the other hand, cognitive impairment increases the risk of physical frailty, which suggests that both conditions can influence each other (Robertson et al., 2013). Indeed, it is not uncommon for physical frailty to coexist with changes in cognition, which, upon reaching a certain level of clinical significance, point to the existence of cognitive frailty (Kelaiditi et al., 2013). Cognitive frailty is reversible if cognitive impairment is pre-MCI subjective cognitive decline and potentially reversible if cognitive impairment reaches the MCI level (Panza et al., 2015).

In line with this idea, a recent systematic review on the effectiveness of interventions in preventing pre-frailty and frailty progression in older adults showed that cognitive impairment is a major risk factor for vulnerability (Apóstolo et al., 2018). Studies have shown the benefits of a proximity multimodal care approach (both cognitive and physical activities) in preventing frailty (Panza et al., 2015). MCI is sensitive to a set of interventions that can slow down its progression into a potentially irreversible state, such as dementia (Apóstolo et al., 2016). Therefore, older adults with cognitive impairment require continuous care to meet their needs, delay the progression of frailty (Orrell et al., 2012a; Yates et al., 2014; Apóstolo et al., 2018), and increase their potential for self-care, autonomy, and independence (Milders et al., 2013).

Systematic reviews have shown that non-pharmacological interventions are an effective therapeutic option for maintaining cognitive performance, controlling neuropsychiatric symptoms (NPS), and improving quality of life (Olazarán et al., 2010; Woods et al., 2012; Silva et al., 2018, 2020). These interventions include reminiscence, training, cognitive stimulation, rehabilitation, and multisensory stimulation (Olazarán et al., 2010; Woods et al., 2012; Silva et al., 2018, 2020). Most of these therapeutic approaches are effective and can be used in conjunction with pharmacological treatments (Spector et al., 2008; Olazarán et al., 2010). Cognitive stimulation (CS) is a psychosocial approach that focuses on intellectual and social stimulation through relevant interaction activities and discussions in group or individual sessions (Spector et al., 2008; Woods et al., 2012; Apóstolo et al., 2014a). However, individual CS (iCS) has been underexplored (Quayhagen et al., 2000; Milders et al., 2013; Silva et al., 2020).

This individual approach can be developed at home at reasonable cost, and constitutes an innovative instrument in the context of *aging in place*. The development of caregiver-led iCS programs has attracted increasing research interest (Zientz et al., 2007; Yates et al., 2014, 2015a; Orgeta et al., 2015). Previous studies have shown that this therapeutic option is easy to apply and adapt to other settings besides the home environment (Quayhagen et al., 2000; Orrell et al., 2012a). Furthermore, iCS programs represent an alternative therapeutic approach in cases of impaired mobility or limited access to group CS programs (Orrell et al., 2012b). They are designed to be partially or fully delivered by the caregivers, who receive training, guidance, or supervision from a healthcare professional (Milders et al., 2013; Silva et al., 2020).

Caregivers can be spouses, family members, or friends interested in implementing the intervention (Quayagen et al., 1995; Milders et al., 2013; Aguirre et al., 2014; Yates et al., 2014, 2015a,b). A recent systematic review (Silva et al., 2020) found that caregiver-led individual cognitive intervention programs, including the iCS program, have improved cognitive performance, including immediate memory, attention, and problem-solving ability. Other authors have also reported that individual cognitive interventions have helped delay the institutionalization of persons with cognitive impairment (PwCIs; Moniz-Cook et al., 1998; Zientz et al., 2007; Orrell et al., 2012b).

In a systematic review, Silva et al. (2020) found few iCS programs in the literature, with the Making a Difference 3 (MD3) Individual Cognitive Stimulation Therapy being one of the most structured programs. The development of MD3 followed the guidance of the Medical Research Council framework for developing complex interventions and was funded by the United Kingdom's National Institute of Health Research—Health Technology Assessment Program (Orrell et al., 2012b; Yates et al., 2014, 2015a, 2016; Orgeta et al., 2015; Yates, 2016).

During a 25-week administration of MD3, Orgeta et al. (2015) found that people with dementia in the iCS group experienced better communication and relationship quality with their caregivers. Compared to the usual care (UC) group, caregivers in the iCS group also improved their health-related quality of life and had fewer depressive symptoms as they completed more MD3 sessions. However, other outcomes such as cognition, NPS, and quality of life were not statistically significant.

Therefore, further studies are needed to assess the impact of iCS, particularly the MD3 program, on PwCIs and their caregivers in different settings and cultures.

OBJECTIVE

This study aims to assess the effectiveness of the European Portuguese version of the MD3 (MD3-P) in improving the cognition (and its domains), quality of life, and neuropsychiatric and depressive symptoms of PwCIs. It also aims to compare the mental and physical health of caregivers of older adults who participated in the iCS activities to that of those who received UC. Finally, it aims to assess the feasibility and meaningfulness attributed to the MD3-P by PwCIs and their caregivers.

MATERIALS AND METHODS

This randomized controlled trial (RCT) had two arms: a UC group and a MD3-P group. There were two moments of blind assessment: at baseline (pre-intervention) and post-intervention at week 13 (outcome assessors were unaware of participant allocation). This study was approved by the Ethics Committee of the Regional Health Administration of Northern Portugal (number 27/2017). All ethical principles were observed in this study. All dyads (PwCI and caregiver) contacted by the research team were informed about the study's objectives, the methodology, and the voluntary nature of their participation. They were also informed that they could withdraw at any time and that this decision would not affect the care being provided by the local healthcare units. All participants signed an informed consent form.

This RCT was registered on clinicaltrial.gov (record NCT03514095).

Procedures

Participants were recruited in primary healthcare units of the Regional Health Administration of Northern Portugal. Before the study began, 11 formal meetings were held: four with the management team and seven with local clinicians (primary care nurses and general practitioners). The meetings aimed to prepare the team to refer the dyads. These professionals were explained the purpose of the study, including the MD3-P program and the RCT design, and the referral criteria.

First, the healthcare professionals selected potential participants and explained the study's main objective to at least one member of the dyad. If the dyad showed interest in participating in the study, the healthcare professionals obtained their consent to be subsequently contacted by the research team. Then, a research team member met the dyad and screened both members for eligibility using inclusion/exclusion criteria. If the dyad met the inclusion criteria, they were given more information on the study and asked to read and sign a formal consent form. They were explained that they would be allocated to different groups and that if they were allocated to the control group, they could benefit from the intervention after study completion.

Inclusion Criteria

All participants met the following inclusion criteria:

(a) Aged 60 years or older;
(b) Diagnosed with MCI or dementia by a neurologist, psychiatrist, or general practitioner. If diagnosed by a general practitioner, the presence of diagnostic criteria as defined by the International Working Group on Mild Cognitive Impairment (Portet, 2006), the Diagnostic and Statistical Manual of Mental Disorders—Fourth or Fifth edition, or the ICD-9/10 (World Health Organization [WHO], 1977, 2004) was required (American Psychiatric Association [APA], 1994, 2002, 2013);

(c) Scored 2–20 points on the 6-item Cognitive Impairment Test (6-CIT; Brooke and Bullock, 1999; Portuguese version by Apóstolo et al., 2017);
(d) Were able to communicate effectively with others;
(e) Had no physical illness or disability affecting their participation;
(f) Lived in a community setting, either at their own home or in a family member's home, and should not attend an adult day care center or any other institution of the same nature, such as a cognitive rehabilitation center/occupational therapy center;
(g) Had a caregiver (informal or formal) who completed, at least, primary school (1st–4th grade), available and willing to deliver the MD3-P program.

Exclusion Criteria

The following exclusion criteria were applied:

(a) Older adult/caregiver with a history of severe psychiatric illness, diagnosed before the age of 60; (b) Caregiver with cognitive impairment, even if a mild Neurocognitive Disorder according to DSM-5 criteria (American Psychiatric Association [APA], 2013), assessed by healthcare professionals when selecting potential participants.

Randomization and Stratification

Data were collected at the participants' homes. It included two moments of blind assessment: (i) At baseline, after inclusion in the study and before the randomization process (week 0, carried out by RS—member of the research team—and a psychologist hired for this task); (ii) 13 weeks after the intervention (week 13, carried out by ARC—member of the research team -, and another psychologist hired for this task).

Stratified randomization was performed by one member of the research team (PSC), who was blinded to the dyads. The variables for the stratification process were the PwCI's sex and degree of cognitive impairment (mild or moderate, assessed using the 6-CIT). Participants were randomized using a randomization website.[1]

Data Collection

The assessment tools administered at weeks 0 and 13 are presented below.

Assessment Tools

– Sociodemographic questionnaire developed by the research team to collect information on the PwCIs and caregivers, such as: age, sex, education level, type of relationship between dyad members, and marital status.

Primary Outcomes for the Persons With Cognitive Impairment

– Cognition: the Alzheimer's Disease Assessment Scale (ADAS-Cog) by Rosen et al. (1984), European Portuguese version by Guerreiro et al. (2008). The ADAS-Cog comprises 11 tasks that evaluate the severity of cognitive and non-cognitive behavioral dysfunctions such as those related to memory, language, praxis, constructional praxis, and orientation. The higher the score, the greater the severity of cognitive impairment.
– Quality of life: the Quality of Life Scale—Alzheimer's Disease (QoL-AD) by Logsdon et al. (1999), European Portuguese version by Bárrios (2012). This 13-item measure focuses on the different domains of patients' lives, combining the information reported by them and their caregivers. The life domains assessed by the QoL-AD include physical condition, mood, interpersonal relationships, ability to participate in meaningful activities, financial situation, and overall perception of self and quality of life.

Secondary Outcomes for the Persons With Cognitive Impairment

– Neuropsychiatric symptoms (NPS): the Neuropsychiatric Inventory by Cummings et al. (1994), European Portuguese version by Leitão and Nina (2008). It was designed to assess the frequency and severity of behavioral disturbances in older adults with major neurocognitive disorders, such as delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, and aberrant motor activity.
– Depressive symptoms: the Geriatric Depression Scale (GDS-15) by Yesavage and Sheikh (1986), European Portuguese version by Apóstolo et al. (2014b). This brief self-report measure, developed from the GDS-30, evaluates the presence of depressive symptoms in older adults in the last 2 weeks. The higher the score, the higher the severity of symptoms.
– Quality of the Relationship between dyad members: the Quality of the Carer–Patient Relationship (QCPR) scale—PwCI version by Spruytte (2016), European Portuguese version by Silva et al. (2021). The QCPR scale includes two equal versions, one for PwCIs and another for caregivers. Each version assesses two dimensions of the emotion expressed: warmth/affection, the positive dimension; and conflict/criticism, the negative dimension. The total score ranged from 14 to 70 points. A score over 56 indicates a good quality relationship, a score between 56 and 42 indicates that the relationship is common, that is, a standard relationship, and a score under 42 reflects a poor quality relationship (Spruytte, 2016; Silva et al., 2021).

Outcomes for Caregivers

– Health status: the 12-Item Short Form Health Survey (SF-12) by Ware et al. (1995), European Portuguese version by Pais-Ribeiro (2005). The SF-12 is a self-reported measure assessing physical and mental health.
– Quality of the Relationship between dyad members: the QCPR scale—carer version by Spruytte (2016), European Portuguese version by Silva et al. (2021). For more details, see the QCPR—PwCI version described above.

[1] http://www.random.org

Intervention and Control Groups

Participants were randomly assigned to one of two arms: (i) intervention group receiving the iCS program MD3-P; (ii) control group receiving UC. Caregivers delivered the MD3-P sessions at home, three times, a week over 12 weeks. Concerning the UC group, participants maintained their usual activities at home or in other social/leisure settings, and no additional intervention was provided. Participants in both groups were asked to report all changes to the activity plan during the 12-week follow-up. None of the participants could be engaged in additional mentally stimulating activities (e.g., none of them attended a cognitive rehabilitation center, occupational therapy center, or adult day care center).

Intervention

The MD3 was translated, adapted, and validated for the Portuguese language and culture (Apóstolo et al., 2019; Silva, 2019). This iCS program is designed to be applied individually, three times a week, in 30-min sessions. The MD3 manual is divided into two parts. The first part of the manual teaches the caregiver how to use the manual and puts forward 13 principles for implementing the iCS program. The second part corresponds to the iCS sessions (Yates et al., 2015a; Apóstolo et al., 2019).

Caregiver Training

Caregiver training was developed in two moments. In the first moment, (a) a research team member delivered a 60-min theoretical-practical training session; (b) the dyad member received the MD3-P manual; (c) the caregiver was asked to read the 13 key principles and clarify any doubts with the research team.

In the second moment, a research team member was present during the first session of the MD3-P program delivered by the caregiver to assess their ability to implement the intervention, using a checklist with items reflecting the 13 key principles. The caregiver was considered fit to deliver the intervention if the session had run smoothly and followed more than seven of the 13 key principles. If the caregiver was unable to deliver the intervention, another theoretical-practical training session was scheduled between the caregiver and the research team.

Dyad Monitoring

During the 12 weeks, the dyads in the MD3-P group were contacted twice a week by telephone or in-person. This follow-up aimed to collect information on the number of completed sessions, average time per session, and difficulties experienced by the caregiver, provide support, and introduce complementary strategies. The research team also monitored the UC group through monthly telephone calls. This activity aimed to maintain contact with the dyads and record any changes in their dynamics.

Feasibility and Meaningfulness of the Individual Cognitive Stimulation Program

During the study, caregivers were asked to record each session's details (e.g., time spent preparing the session, topic covered in the session, interaction during the session) to monitor the acceptability and applicability of the MD3-P program. Caregivers recorded their level of satisfaction using parameters such as the PwCIs' ability to perform the tasks, the clarity of the instructions, or the session's overall level of difficulty.

The attrition rate and the dyad's adherence to the sessions were also analyzed. Finally, four interviews were conducted (after week 13) to explore the meanings attributed to the MD3-P program and understand the participants' perceptions of the acceptability and applicability of the program. The following questions were asked: Do you think your involvement in this program was important? And if so, why? What did you like the most, and the least about the sessions? How did you benefit from this experience?

Participants who demonstrated involvement in the program were chosen to participate in the interview, in a total of two PwCIs and two caregivers.

ANALYSIS OF RESULTS

The significance level (p-value) was set at 5% for inferential analysis. Mann-Whitney U-test and Chi-Square test were used to compare the distribution of continuous and categorical variables between groups, respectively. The overall attrition rate (outcomes data in analysis/number of participants randomized) was calculated. Data on participants who dropped out of the study were subjected to intention-to-treat (ITT) analysis. Thus, all eligible individuals who received at least one session of iCS were included.

To determine the effect of the intervention, the pre- and post-intervention mean differences were calculated, as well as a non-standardized estimate (magnitude) of the intended outcomes. Thus, in addition to the significance level (p-value), the effect size (Cohen's d) was considered. The statistical measure of the effect size (ES) Cohen's d was calculated as a measure of effect size (ES) using the Z score resulting from the Mann-Whitney U-test, with the support of an online ES calculator for non-parametric tests (available at www.psychometrica.de/effect_size.html). The following formula was used: $r = Z/\sqrt{N}$. Subsequently, r-values were transformed to Cohen's d at: https://www.psychometrica.de/effect_size.html#transform (Transformation of the ES d, r, f, Odds Ratio, and η^2). The numbers needed to treat (NNT) were calculated based on the tables that support the conversion of Cohen's d into these parameters (Santo and Daniel, 2017). Data were analyzed using IBM SPSS Statistics software (version 24, IBM SPSS, New York).

Following Bardin's content analysis approach (Bardin, 2004), the qualitative data from the interviews were analyzed based on the categories established by combining inductive and deductive approaches.

RESULTS

The primary healthcare units of the Regional Health Administration of Northern Portugal referred 113 dyads. Of these, 61 dyads (53.9%) were excluded mostly for not meeting the inclusion criteria (see **Figure 1**). Thus, 52 dyads were

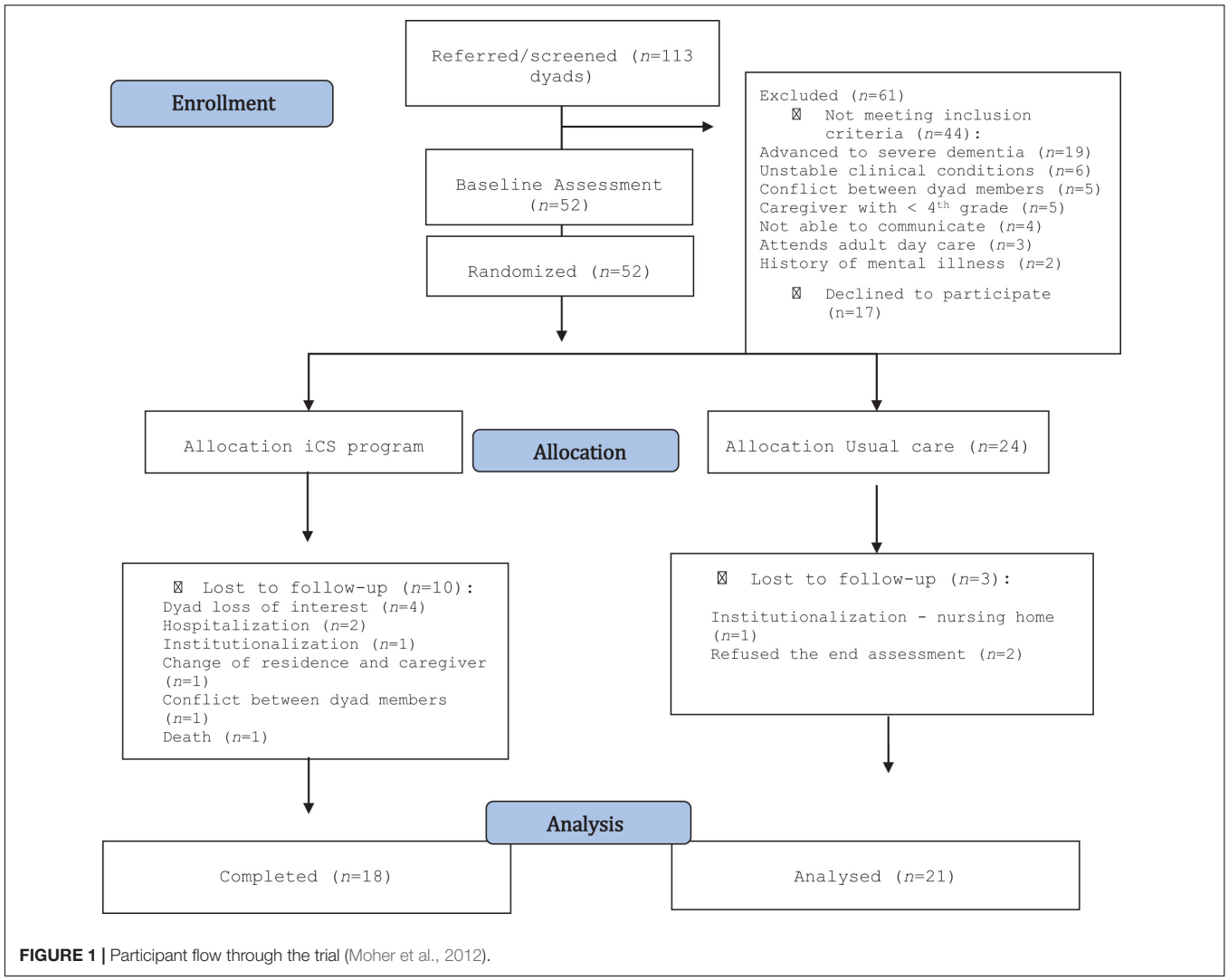

FIGURE 1 | Participant flow through the trial (Moher et al., 2012).

randomized: 28 were allocated to the MD3-P group and 24 to the UC group. **Figure 1** shows the number of dropouts and completers in each arm.

The baseline characteristics of the participants who did not complete the study (n = 13 dyads) were compared to those of the participants who completed it (n = 39 dyads) through the Mann-Whitney U-test. None of the sociodemographic characteristics and respective outcomes showed significant differences ($p > 0.05$).

At the end of the intervention, the overall attrition rate was 25.0% (n = 13), falling to 23.1% (n = 12) if death was not considered. Attrition rates were 12.5% in the UC group (n = 3) and 35.7% in the MD3-P group (n = 10), decreasing to 32.1% (n = 9) if death was excluded. **Figure 1** shows the reasons for the losses.

The baseline characteristics of the participants who dropped out (n = 13 dyads) were compared to those of the participants who completed the study (n = 39 dyads) to assess whether sociodemographic characteristics (e.g., age, gender, education level) or clinical outcomes (e.g., cognitive status or mood) influenced participants' intention to complete or drop out of the study (**Tables 1**, **2**).

None of the sociodemographic characteristics or respective clinical outcomes showed statistically significant differences ($p > 0.05$), confirming that the participants' characteristics did not influence the intention to drop out of the study.

Sociodemographic Characteristics

Table 3 shows the sociodemographic characteristics of the PwCIs and their caregivers by group (MD3-P and UC) and the baseline assessment results.

The randomization process ensured that both groups (MD3-P vs. UC) were similar in terms of sex and degree of cognitive impairment. The groups were also similar in terms of the other sociodemographic variables (age, education level, marital status, $p > 0.05$).

The analysis of differences in the sociodemographic variables of caregivers by group, using the Mann-Whitney U and Chi-Square tests, showed no significant differences ($p > 0.05$), except for age which was higher in the control group [Mean

TABLE 1 | Sociodemographic characteristics of PwCI and caregiver by lost and completed.

	PwCI			Caregiver		
	Completed (*n* = 39)	**Lost (*n* = 13)**	***p*-value**	**Completed (*n* = 39)**	**Lost (*n* = 13)**	***p*-value**
Age (years), Mean (± SD) Range	79.28 (± 9.67) 60–97	78.77 (± 6.43) 64–90	>0.05	51.54 (± 15.78) 20–82	53.53 (± 17.05) 26–79	>0.05
Women, *n* (%) Men, *n* (%)	28 (71.8) 11 (28.2)	9 (69.2) 3 (30.8)	>0.05	32 (82.1) 7 (17.9)	9 (69.2) 4 (30.8)	>0.05
Married, *n* (%)	27 (69.2)	8 (61.5)	>0.05	30 (76.9)	10 (76.9)	>0.05
Widowed, *n* (%)	12 (30.8)	5 (38.5)		1 (2.6)	–	
Divorced, *n* (%)	–	–		2 (5.1)	2 (15.4)	
Not married, *n* (%)	–	–		6 (15.4)	1 (7.7)	
Education level, Mean (± SD) Range	4.01 (± 2.60) 0–15	3.97 (± 3.20) 1–12	>0.05	8.05 (± 3.84) 4–17	7.4 (± 4.70) 4–15	>0.05
6-CIT, Mean (± SD) Range	13.53 (± 5.69) 4–20	13.46 (± 5.46) 6–20	>0.05	–	–	–
Degree of CI mild, *n* (%) Moderate, *n* (%)	23 (59.0) 16 (41.0)	7 (58.8) 6 (46.2)	>0.05	–	–	–
Son or daughter, *n* (%)	–	–	–	23 (59.0)	5 (38.5)	>0.05
Spouse, *n* (%)				9 (23.1)	5 (38.5)	
Granddaughter, *n* (%)				3 (7.7)	1 (7.7)	
Formal caregiver, *n* (%)				2 (5.1)	2 (15.4)	
Daughter in law, *n* (%)				2 (5.1)	1 (7.7)	
Main caregiver, *n* (%)	–	–	–	24 (61.5)	9 (69.2)	>0.05
Cohabitation, *n* (%)	–	–	–	27 (69.2)	7 (53.8)	>0.05

MD3-P, intervention group (Making a Difference 3—European Portuguese version); PwCI, Person with Cognitive Impairment; UC, control group (usual care); SD, standard deviation; 6-CIT, 6-item Cognitive Impairment Test.

TABLE 2 | Clinical outcomes of PwCI and caregiver by lost and completed.

Outcomes	PwCI			Caregiver		
	Completed (*n* = 39) Mean (± SD)	**Lost (*n* = 13) Mean (± SD)**	***p*-value**	**Completed (*n* = 39) Mean (± SD)**	**Lost (*n* = 13) Mean (± SD)**	***p*-value**
ADAS-Cog	19.43 (± 7.61)	20.69 (± 7.68)	>0.05	–	–	–
QoL-AD	26.41 (± 5.53)	24.64 (± 6.11)	>0.05	–	–	–
NPI	12.87 (± 11.15)	11.84 (± 13.72)	>0.05	–	–	–
GDS	5.9 (± 3.42)	7.46 (± 4.50)	>0.05	–	–	–
QCPR	56.13 (± 7.40)	55.15 (± 7.06)	>0.05	54.00 (± 9.94)	55.00 (± 7.55)	>0.05
$SF12_{Mental}$	–	–	–	53.33 (± 15.24)	46.45 (± 19.50)	>0.05
$SF12_{Physical}$	–	–	–	55.79 (± 17.17)	55.17 (± 17.77)	>0.05

ADAS-Cog, Alzheimer's Disease Assessment Scale; GDS, Geriatric Depression Scale; NPI, Neuropsychiatric Inventory; PwCI, Person with cognitive impairment; QCPR, Quality of the Carer–Patient Relationship (QCPR) scale; QoL-AD, Quality of Life Scale—Alzheimer's Disease; SD, standard deviation; SF-12, Short Form-12 Health Survey; UC, control group (usual care).

MD3 = 53.5 (± 15.69); Mean UC = 60.58 (± 14.88); U = 229.00; $p = 0.049$].

Impact of the Intervention on Persons With Cognitive Impairment

Pre-intervention assessment (ADAS-Cog, QoL-AD, NPI, GDS, QCPR) found no significant differences between groups, except for the quality of life outcome [Mean MD3-P = 28.90 (± 5.27); Md = 26.66; Mean UC = 4.56 (± 5.38); Md = 23.83]. The scores in the QoL-AD scale were higher in the MD3-P group than in the UC group (U = 224.50; $p < 0.05$).

Table 4 shows the mean outcome scores and the total mean difference obtained in the pre- and post-intervention assessments ($M_{pos-Int}$—$M_{pre-Int}$) for each group and each outcome.

ADAS-Cog scores in the MD3-P group increased by more than one point from pre- to post-intervention and decreased by more than three points in the UC group, with the difference between the statistically significant (U = 214.50; $p = 0.02$).

Concerning the ES of the MD3-P for cognition, the results suggest that the program had a medium to large ES ($d_{cohen} = 0.651$). Five PwCIs needed to be treated (NTT) to obtain gains in cognitive performance (in contrast to the control group).

In the ITT analysis, the results on the assessment of the cognitive domains using ADAS-Cog revealed a significant improvement in older adults' cognition. More specifically, the MD3-P had a more significant positive impact on following commands (U = 103.50; $p = 0.015$) and orientation (U = 89.00; $p = 0.004$). A large ES was found in the orientation domain ($d_{Cohen} = 0.88$) and a medium ES was found in following commands ($d_{Cohen} = 0.75$).

The total QoL-AD score (U = 239.00; $p = 0.07$) revealed a marginally significant value for the PwCIs' quality of life. The

TABLE 3 | Sociodemographic characteristics of PwCI and caregiver.

	PwCI			Caregiver		
	MD3-P (*n* = 28)	**UC (*n* = 24)**	***p*-value**	**MD3-P (*n* = 28)**	**UC (*n* = 24)**	***p*-value**
Age (years),Mean (± SD)Range	79.5 (± 8.80)60–97	78.75 (± 9.32)60–93	>0.05	53.5 (± 15.69)20–79	60.58 (± 14.88)20–82	<0.05
Women, *n* (%)Men, *n* (%)	21 (75.0)7 (25.0)	16 (66.7)8 (33.3)	>0.05	24 (85.7)4 (14.3)	17 (70.8)7 (29.2)	>0.05
Married, *n* (%)	16 (57.1)	19 (79.2)	>0.05	19 (67.9)	21 (87.5)	>0.05
Widowed, *n* (%)	12 (42.9)	5 (20.8)		1 (3.6)	0 (0)	
Divorced, *n* (%)	–	–		3 (10.7)	1 (4.2)	
Not married, *n* (%)	–	–		5 (17.9)	2 (8.3)	
Education level,Mean (± SD)Range	4.07 (± 2.50)0–15	4.04 (± 2.46)0–9	>0.05	8.53 (± 4.14)4–17	7.17 (± 4.14)4–16	>0.05
6-CIT,Mean (± SDMdRange	13.68 (± 5.72)6–20	13.33 (± 5.55)4–20	>0.05	–	–	–
Degree of CI Mild, *n* (%) Moderate, *n* (%)	16 (57.1)12 (42.7)	14 (58.3)10 (41.7)	>0.05	–	–	–
Son or daughter, *n* (%)	–	–	–	15 (53.6)	13 (54.2)	>0.05
Spouse, *n* (%)				6 (21.5)	8 (33.3)	
Granddaughter, *n* (%)				2 (7.1)	2 (8.3)	
Formal caregiver, *n* (%)				4 (14.3)	0 (0)	
Daughter-in-law, *n* (%)				1 (3.6)	1 (4.2)	
Main caregiver, *n* (%)	–	–	–	18 (64.3)	15 (62.5)	>0.05
Cohabitation, *n* (%)	–	–	–	16 (57.1)	18 (75)	>0.05

MD3-P, intervention group (Making a Difference 3—European Portuguese version); Md, Median; PwCI, Person with Cognitive Impairment; UC, control group (usual care); SD, standard deviation; 6-CIT, 6-item Cognitive Impairment Test.

TABLE 4 | Mean outcome scores for MD3-P and UC groups and total pre- and post-intervention mean differences for PwCI.

Outcomes (PwCI)	**Pre-intervention assessment**		**Post-intervention assessment**		**Mpost-Int—Mpre-Int**		
	MD3 –P (*n* = 28) Mean (± *SD*)	**UC (*n* = 24) Mean (± *SD*)**	**MD3-P (*n* = 28) Mean (± SD)**	**UC (*n* = 24) Mean (± *SD*)**	**Total (*n* = 52) MD (± *SD*) CI**	***p*-value**	d_{cohen}
ADAS-Cog	18.88 (7.11)	19.12 (9.39)	17.94 (8.53)	21.69 (9.73)	0.80 (± 6.20) –0.92–2.53	<0.05	0.651
QoL-AD	28.90 (5.27)	24.56 (5.38)	31.43 (4.13)	25.44 (5.96)	1.87 (± 4.46) 0.61–3.59	>0.05	0.510
NPI	15.88 (13.84)	10.56 (8.25)	9.71 (10.07)	10.37 (8.52)	–1.79 (± 1.78) –5.08–1.48	>0.05	0.320
GDS	5.29 (3.46)	6.37 (3.30)	4.88 (3.69)	5.50 (3.44)	–0.83 (± 3.57) –1.83–0.18	>0.05	0.011
QCPR	59.88 (6.61)	52.50 (7.37)	57.65 (5.96)	52.31 (8.43)	–1.16 (± 6.01) –2.84–0.51	>0.05	0.082

ADAS-Cog, Alzheimer's Disease Assessment Scale; CI, 95% confidence interval of the mean of the difference; MD, mean difference; MD3-P, intervention group (Making a Difference 3—European Portuguese version); GDS, Geriatric Depression Scale; NPI, Neuropsychiatric Inventory; Md, median; PwCI, Person with cognitive impairment; QCPR, Quality of the Carer–Patient Relationship (QCPR) scale; QoL-AD, Quality of Life Scale—Alzheimer's Disease; UC, control group (usual care); SD, standard deviation.

mean difference in both groups revealed that the UC group increased its score by one point and that the MD3-P group increased its score by more than two points [MD = 2.60 (± 4.22); Md = 2.67]. The MD3-P intervention had a medium ES on quality of life (d_{cohen} = 0.51). These results show that six PwCIs need to be treated (NTT) for one patient to improve his or her quality of life.

Although NPS improved slightly in the MD3-P group (see **Table 4**), the differences between groups were not significant (U = 274.00; p = 0.25). Depressive symptoms, assessed by GDS-15, improved in both groups, with the UC group showing a greater improvement, although not significant (U = 322.00; p = 0.97; d_{cohen} = 0.01). According to the PwCIs version's QCPR, the quality of the caregiver-PwCI relationship, improved in both groups, being slightly better in the MD3-P group. However, the differences were not statistically significant (U = 297.50; p = 0.48; d_{cohen} = 0.082).

Impact of the Intervention on the Caregiver

The Mann-Whitney *U*-test revealed no significant differences in the health status scores (SF-12) at baseline between both groups (MD3-P vs. UC). In the QCPR scale—caregiver's version, the scores were significantly higher in the MD3-P group than in the UC group (U = 210.00; $p < 0.05$). Thus, caregivers in the MD3-P group had a better relationship before the intervention than those in the UC group.

TABLE 5 | Mean outcome scores for the MD3-P group and total pre- and post-intervention mean differences for caregiver.

Outcomes (caregiver)	Pre-intervention assessment		Post-intervention assessment		Mpost-Int—Mpre-Int		
	MD3-P (*n* = 28) Mean (± *SD*)	UC (*n* = 24) Mean (± *SD*)	MD3-P (*n* = 28) Mean (± *SD*)	UC (*n* = 24) Mean (± *SD*)	Total (*n* = 52) MD (± *SD*) CI	*p*-value	d_{Cohen}
$SF12_{Mental}$	53.57 (± 16.37)	50.40 (± 17.19)	66.39 (± 8.33)	52.08 (± 12.35)	6.04 (± 15.80) 1.64–10.44	>0.05	0.437
$SF12_{Physical}$	58.00 (± 17.35)	52.88 (± 16.84)	67.50 (± 10.78)	56.88 (± 15.49)	6.96 (± 16.19) 2.45–11.47	>0.05	0.353
QCPR	57.76 (± 10.16)	49.81 (± 9.03)	58.41 (± 8.43)	49.56 (± 9.88)	–0.25 (± 5.36) –1.74–1.24	>0.05	0.27

CI, 95% confidence interval of the mean of the difference; MD, mean difference; MD3-P, intervention group (Making a Difference 3—European Portuguese version); QCPR, Quality of the Carer–Patient Relationship (QCPR) scale; SD, standard deviation; SF-12, 12-Item Short Form Health Survey; UC, control group (usual care).

Table 5 shows the results of the outcomes evaluated by the caregivers and the total mean differences ($M_{post-Int}$—$M_{pre-Int}$) by group and outcome.

The analysis revealed no statistically significant differences in the outcomes between groups.

Adverse Events

During the study, some adverse events occurred: (i) one death in the MD3-P group; (ii) a participant in the UC group was institutionalized due to the worsening of psycho-behavioral symptoms; (iii) three participants were hospitalized, two of whom due to worsening of the PwCIs' health status, and the other due to a fall (one in the MD3-P group; and two in the UC group). These adverse events were not associated with this study. However, immediately after starting the iCS sessions, one caregiver noticed that the family member showed depressive symptoms. This event may have been associated with the intervention because it may have increased the PwCI's awareness of difficulties in performing the activities. Due to the PwCI's lack of interest, this dyad dropped out of the study. Three more dyads lost interest in the intervention but provided no justification (see **Figure 1**).

Making a Difference 3 Feasibility and Meaningfulness

The attrition rate is an indicator of the acceptability of the iCS program (MD3-P). The attrition rate in the MD3-P group was almost three times higher than that in the UC group [32% (*n* = 9) vs. 12.5 (*n* = 3)]. The main reason reported by the participants for abandoning the program was the loss of interest (30.77%).

Over the 12 weeks, participants had two to 36 sessions. The dyads who completed the study (*n* = 18) had, on average, three weekly sessions (44.4%), two weekly sessions (38.9%), and one and a half weekly sessions (16.7%). Of the eligible participants who did not complete the study, seven had one to 10 sessions, two had 10–20 sessions, and one (one of the hospitalized participants) had 20–30 sessions.

The dyads' level of satisfaction with the MD3-P sessions was also assessed, ranging from satisfied to very satisfied, and no session was expressively less appreciated.

Interviews

Interviews (*n* = 4) were conducted to explore the meaningfulness attributed by the dyads to the iCS program (MD3-P) and their perception of their relationship. The content analysis of the interviews showed the dyads' opinions about the MD3-P and its impact on their relationship and daily life.

The dyad members recognized that, at an early stage, they did not have high expectations about the MD3-P. However, as the program evolved, the caregivers reported that the PwCIs had improved their spontaneous speech, interaction skills, mood, and were more willing to socialize. Caregivers also recognized that the training helped them implement specific strategies to promote cognitive stimulation in their everyday lives and improve their relationship quality.

". . . This is very important, he's a lot better. . . no doubt, my father is a more active person now" [Caregiver_1]

". . . she always did the exercises, I think she was engaged during those moments, and she took them seriously "[Caregiver_2]

The PwCIs recognized that participation in this study was beneficial, regretting that no more sessions were available after the program ended. One participant was not satisfied with the degree of complexity of some sessions but recognized the need for different levels of difficulty. Both interviewed PwCIs reported that, although their cognitive performance had not improved, their mood had improved, and they were more willing to leave the house and socialize.

"It was good, I had the company of my granddaughter. . ., I made her lunch, and then, we did the exercises" [PcPNC_1]

"I enjoyed the exercises, I don't think I always answered correctly, but I did not feel overwhelmed" [PcPNC_2]

DISCUSSION

This study aimed to assess the effectiveness of the European Portuguese version of the iCS program—MD3, and explore the feasibility and meaningfulness attributed to it by PwCIs and their caregivers. As in similar studies, participants who completed the iCS intervention had greater improvements than those who received UC (Quayagen et al., 1995; Orgeta et al., 2015).

With a sample of 52 dyads, the attrition rate was 23.1%, which is justified by the dyads' loss of interest (30.8%) in the sessions. However, these values are in line with those found in previous studies (Orgeta et al., 2015; Yates, 2016). Of the dyads who completed the study, 44.4% had an average of three weekly sessions. These attrition and low adherence rates can also be explained by the dyads' low level of knowledge about cognitive impairment and its evolution, lack of information about CS interventions and their role as stabilizers of cognitive disease, and also the caregivers' burden and low education level (Silva et al., 2020).

Nonetheless, this study revealed significant cognitive improvements in older adults. After the intervention, the PwCIs had improved their cognitive function, namely their orientation and ability to follow commands. The positive effect of the MD3-P on cognition is consistent with previous studies on iCS (Quayagen et al., 1995; Onder et al., 2005). These results suggest that participants may have responded positively to the intervention because they were under-stimulated. Many of their cognitive skills could be preserved but were only minimally manifested due to lack of social stimulus, occupation, and involvement in decision-making. Thus, a pleasant and meaningful interaction with the caregiver during the intervention may have triggered a positive response, translating into health gains (Quayagen et al., 1995; Onder et al., 2005; Valenzuela and Sachdev, 2005).

MCI's response to intervention should also be explored because older adults with this condition may be more sensitive to an individualized intervention, unlike those with more severe dementia (Mierlo et al., 2010). In this study, about 57% of the participants in the intervention group had MCI or mild dementia, which can explain the more positive response to the intervention. Concerning neuroplasticity and neurogenesis, current evidence suggests that the lower the cognitive damage, the greater the neuroplastic capacity (brain adaptation) and the ability to learn and promote neurogenesis (Valenzuela and Sachdev, 2005; Livingston et al., 2017). The results of this study are promising, so the authors recommend the implementation of cognitive interventions at the earliest stages of cognitive impairment (Livingston et al., 2017). Nevertheless, older adults with more severe cognitive impairment require more differentiated interventions, which may explain the low effectiveness of iCS programs delivered by caregivers to older adults with severe cognitive impairment (Silva et al., 2020).

Unlike the study by Yates (2016), this study found no statistically significant changes in the quality of the relationship between the dyad members. However, qualitative data from the interviews indicate that the relationship improved after the study. Finally, although the implementation of the iCS could have worsened the caregivers' burden, it had no significant impact on their physical and mental health, which is consistent with Yates (2016). In fact, qualitative data revealed that the caregivers were satisfied with their contribution to their family members' well-being.

The data obtained for the dyads who completed the 12-week program, showed that the caregivers understood that intellectual activities are vital for the PwCIs' well-being. Thus, a positive perception of the intervention promotes greater adherence. These results highlight the good feasibility of the MD3-P program, with attrition and adherence rates similar to previous studies on iCS (Orgeta et al., 2015; Yates, 2016).

Both pharmacological and non-pharmacological interventions must take into account the characteristics of their target group (Mierlo et al., 2010). There is no single intervention for all cases, and proper interventions must be designed for each older adult (Mierlo et al., 2010). A tailored intervention can be very effective but only if it is significant enough for its users. Therefore, a significant increase in the number of frail older adults with cognitive impairment requires societal resources/responses and quality services, but above all more differentiated and tailored evidence-based care programs (Prince et al., 2016; Alzheimer's Disease International [ADI], 2018; Apóstolo et al., 2018).

Strengths of the Study

The pre-intervention groups were homogeneous, except for the PwCI's quality of life and the caregivers' age. Caregivers were significantly younger in the intervention group than in the control group. Before the intervention, caregivers in the iCS program group perceived a better relationship quality than those in the UC group.

The caregivers' mean age in this study was lower than that found in international studies (Silva et al., 2020). Involving younger caregivers in the delivery of iCS sessions may contribute to the program's success, given that younger adults tend to have a better understanding of the PwCIs' difficulties, differentiated skills to conduct CS activities, and better health literacy (Silva et al., 2020).

Blinded outcome assessment was used in this RCT. Dyads from both groups were instructed not to give the assessor any indication of the group to which they were allocated during the study. Another strength of this study was the use of translated and culturally adapted instruments with robust psychometric properties that had already been used in similar research studies (Moniz-Cook et al., 1998; Yates, 2016).

Limitations of the Study

Although experimental studies allow the identification of causal relationships, they are not exempt from bias. This study should be replicated involving a larger and more diversified sample.

Treatment and control group participants had similar sociodemographic and clinical characteristics at baseline, except for the PwCIs' quality of life and the caregivers' age. These differences between groups may threaten the study's internal validity. Other limitations of this study include its non-representative sample and the high attrition rate. Except for Yates's study (2016), most of the previous studies focused on iCS, had small samples, justifying it with the complexity of conducting an RCT and the human and economic resources required (Davis et al., 2001; Quayhagen and Quayhagen, 2001; Milders et al., 2013). Although statistical inference is compromised due to the

non-representative sample, the magnitude of the intervention effect confirms the clinical importance of these results. Another limitation is the lack of a long-term follow-up assessment. A few studies have found positive long-term effects in similar interventions, which have implications for clinical practice (Silva et al., 2018). Therefore, future studies should address the long-term assessment of the effects of iCS.

Despite these limitations, the methodological design (RCT), the blinded randomization process, the existence of a control group, and the blinded pre- and post-intervention outcome assessments strengthen the study's internal validity.

CONCLUSION

Providing conditions that promote healthy aging in community settings is a social priority. This study focused on individual cognitive stimulation (iCS) as a home intervention conducted by the caregiver for older adults with cognitive deterioration. Three-month intervention was implemented using the European Portuguese version of the iCS therapy program—MD3-P. The intervention was feasible and well accepted by a considerable proportion of older adults and caregivers and produced immediate cognitive benefits at reasonable cost (i.e., two training home visits plus continuous telephone support). This preliminary data extends the benefits of the MD3 to non-English speaking people, giving further support to the value of this therapy program as an innovative and promising instrument in the context of aging in place. Future studies should explore the characteristics of the target population who will benefit most from this type of intervention. This study suggests that the successful implementation and adherence to the MD3-P program require a set of conditions, such as the existence of a good carer-patient relationship, the caregiver's availability, reasonable levels of health literacy, and the diagnosis of MCI. Hence, the studies should explore these conditions, given their implications for practice.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Regional Health Administration of Northern Portugal (number 27/2017). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RS, PS-C, and JA: conceptualization. RS and JA: methodology and funding acquisition. RS and EB-C: formal analysis. RS, EB-C, PS-C, and ARC: investigation and data curation. RS: writing—original draft preparation. RS, EB-C, PS-C, ARC, and JA: writing—review and editing. JA: supervision and project administration. All authors have read and agreed on the published version of the manuscript.

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Relationships Between Childhood Health Experience and Depression Among Older People: Evidence From China

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The assessment of childhood health experience helps to identify the risk of depression among older people. Poor childhood experience is generally associated with depression in adulthood. However, whether such association can be extended to older people' life remains unclear. The history of parental mental health was obtained from 2014 CHARLS Wave 3 (Life History Survey) data while other data from 2011 CHARLS Wave 1 baseline data. The study involves 4,306 respondents. The depression was assessed by the Chinese version of Center for Epidemiologic Studies Depression scales (CES-D) using logistic regression model. More than 40% of older people suffered from depression, 25% of whom experienced poor childhood self-reported health. Nearly 20% of their mothers and more than 10% of their fathers had a history of poor mental health. Poor childhood health experiences have shown to be associated with higher odds of depression (good self-reported health OR: 0.732, $p = 0.000$, 95% CI: 0.633–0.847; poor mother's mental health OR: 1.391, $p = 0.001$, 95% CI: 1.138–1.699; poor father's mental health OR: 1.457, $p = 0.003$, 95% CI: 1.141–1.862). There is a high rate of depression among the older adults in China. In China, older people with poor childhood health experiences are more likely to suffer from depression.

Keywords: childhood health experience, depression, CHARLS, aging, mental health

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INTRODUCTION

Depression is a common psychiatric disorder among middle-aged and older adults people, affecting an estimated 322 million people worldwide (World Health Organization, 2017). Depression is accompanied with substance abuse (Hjorthøj et al., 2015), chronic pain (Gadermann et al., 2012), impaired quality of life (Ibrahim et al., 2013), reduced life expectancy, and increased risk of suicide (Laursen et al., 2016). Depression is a serious public health issue in both developed and developing countries. Moreover, given the rapid rate of aging worldwide, late-life depression has become a critical concern around the world (Moussavi et al., 2007; Gertner et al., 2017), with its prevalence rising from 4.7% to 16% (Blazer, 2003). According to data from baseline data of the China Health and Retirement Longitudinal Study (CHARLS), 30% of men and 45% of women aged 45 and above in China suffered from depression (Lei et al., 2014), which indicates that depression has become a prominent problem in China. It is suggested that the timely identification of people at high risk

of depression helps doctors diagnose the disorder earlier (Cairns et al., 2014). Therefore, the early detection of depression poses a challenge for health improvement.

However, early detection of depression is inseparable from consideration of childhood experiences (Colman and Ataullahjan, 2010), because depression is jointly caused by biological, psychological, and social factors (Urrea and Pedraza, 2000). The retrospective and prospective studies have demonstrated that childhood experiences are related to higher prevalence of late-life depression (Betts, 2014). Furthermore, the life course indicates that early life experiences will produce an enduring impact on the consequences throughout the whole life course (Elder, 1998, 2018; Zheng and Hu, 2018).

Childhood experiences describes experiences which are out of the child's control such as loss of a parent (Tiet et al., 1998). Childhood is a critical and sensitive period in determining an individual's later health. Childhood experiences are often linked to physical abuse, sexual abuse, poverty or household dysfunction. Evidences suggest that childhood experiences have accumulative effects on an individual's health outcomes (Scott et al., 2012). Childhood may shape neurobiological and immunes system development and these changes may persist over the whole life course (Teicher et al., 2003). Currently, many researches focus on the relationship between poor childhood experiences and depression (Chapman et al., 2004; Ford et al., 2011; Nakai et al., 2014; Maclean et al., 2016; Björkenstam et al., 2017; Green et al., 2018) and a negative relationship is observed. However, there is still a research gap in this regard. First, most studies have looked at adults, and it remains unclear whether the relationship extends to older adults. Second, existing studies about childhood experiences do not cover childhood health experiences. Currently, most of the literature concerning the association between childhood experiences and depression focus on childhood neighborhood quality, friendship (Chen et al., 2020), early peer relationship (Jiang and Wang, 2020), etc. However, such research does not take the childhood health into consideration. It is known to all that in China, the older people are the target population, born between 1940s and 1960s. What they have in common is that they all experienced a period of poor childhood health as they were born during war, famine and baby boom (Jiang and Wang, 2020). From the life course perspective, their poor childhood health experience could have a non-negligible and enduring impact on their later psychological health (George, 2014). But the relevant research remains unclear. Therefore, in this paper we aim to fill this research gap by exploring the association between childhood health experiences and depression among older people in China. As noted above, the effects of childhood may persist throughout the life course, and we hypothesize that poor health experiences in childhood may negatively affect depression among older Chinese adults.

MATERIALS AND METHODS

Design and Sample

The China Health and Retirement Longitudinal Study (CHARLS) was conducted to collect a high quality nationally representative sample of Chinese residents aged 45 and above in 2011, which was supported by Peking University, the National Natural Science Foundation of China, the Behavioral and Social Research Division of the National Institute on Aging and the World Bank. The data collection has been approved by the institutional review board at Peking University and the data will be updated annually. About 10,000 households and 17,500 individuals in 150 counties/districts and 450 villages/resident committees were included in the baseline survey. Multi-stage stratified PPS sampling was adopted in CHARLS (Zhao et al., 2014). CHARLS 2011 baseline survey data and 2014 CHARLS Wave 3 (Life History Survey) data were used in this research. Childhood parental health was extracted from 2014 CHARLS Wave3 (Life History Survey) data. All other data were obtained from CHARLS 2011 baseline survey data. People whose age $\geq$ 60 were included, since 60 years old was the cut-off point between mid-aged people and older people in China. The data processing flow chart is demonstrated in **Figure 1**.

Measures

Childhood Self-Reported Health

Health is a complex concept and it is difficult to grasp all the relevant aspects. Most of the time, people tend to reflect it on self-reported health status, which is a valuable source of data on various aspects of overall health (Idler and Benyamini, 1997) and is easy to implement. Now it is widely collected in almost all countries. In this research, we adopted childhood self-reported health to reflect the respondents' heath conditions during childhood. Older people were asked about the following question to assess their childhood self-reported health: how do you evaluate your health during childhood, up to and including age 15? The respondents selecting "excellent," "very good" or

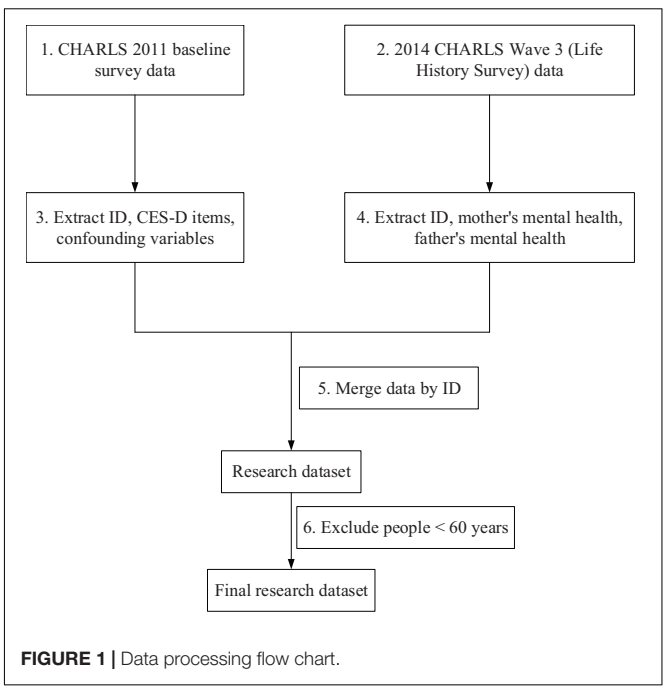

FIGURE 1 | Data processing flow chart.

"good" was considered that its childhood self-reported health was good and was coded as 1. Those who answered "fair" or "poor" were considered to have had poor self-reported health as children and were set to 0.

Parental Mental Health

Parental mental health has proven to be an important factor affecting the health experience for people's depression development (Gundel et al., 2018). We included a history of both mother's and father's mental health in this paper. The respondents were asked "during the years when you were growing up, did your father/mother show continued signs of sadness or depression that lasted 2 weeks or more." Those who reported "yes" were considered that his father's/mother's mental health was poor and were set as 1 while answer of "no" was set as 0.

Health Outcome: Depression

Depression was assessed through the Chinese version of scale items developed by the Center for Epidemiologic Study, with 10 short-form scale items (CESD-10) (Andresen et al., 1994). The CESD-10 contains response options varying from 0 to 4 [0 = Rarely or none of the time (less than 1 day); 1 = Some or a little of the time (1–2 days); 3 = Occasionally or a moderate amount of the time (3–4 days); 4 = Most or all of the time (5–7 days)] (Amtmann et al., 2014). The minimum total score of CESD-10 was 0 and the maximum was 30. The respondents with higher CSED-10 score indicated that he/she had a higher level of depressive symptoms. CES-D score of 10 was the cut-off point to identify whether the respondents experienced significant depressive symptoms. The respondents who were likely to suffer from depression had a CES-D score of $\geq$ 10 (Lei et al., 2014).

Potential Confounding Variables

CHARLS collected data about the respondent's age, gender, place of residence, marital status and educational level. These variables were potential confounding variables commonly seen in previous studies (Whitaker et al., 2014; Bareis and Mezuk, 2018; Gundel et al., 2018). We included them in this research. In addition, studies have shown that job position (Whitaker et al., 2014) and income (Campbell et al., 2016; Fang and McNeil, 2017) are also potential confounding variables. Therefore, respondent's retirement status and pension status were included in this research based on the fact that older people's employment status was dependent on their retirement status and that their income is mainly affected by their pension.

Analytic Strategy

Continuous variables were displayed through means and standard deviation while categorical variables were described with percentage. A series of logistic regression models were used to assess the association between childhood health experience and depression among Chinese older people: in Model I, we solely accounted for childhood self-reported health; in Model II, we adjusted childhood mother's mental health separately; Model III was similar to Model II, in which childhood father's mental health was taken into the model; in Model IV, we included childhood self-reported health, childhood mother's mental health and childhood father's mental health simultaneously. The odds ratio (OR) and confidence interval (CI) of 95% were calculated. All models were adjusted for all potential confounding variables mainly including age, gender, place of residence, marital status, educational level, retirement status and pension status. If the *p*-value was less than 0.05, it would be considered as statistically significant. All the work was conducted in Stata, version 13.1 (StataCorp. College Station, TX: Stata Corp LP).

RESULTS

Descriptive characteristics of the respondents are presented in **Table 1**. The average age of the population was 67.09 years. Men were slightly older on average than women (Male: 67.11; Female: 67.06). 75% of them experienced good childhood self-reported health. Among males, their fathers (12.3%) were more likely to have a poor mental health than females (11.7%) during their childhood, while among females, their mothers (21.1%) had a higher likelihood to experience bad mental health. In terms of depression prevalence, 40.6% of them suffered from depression. Female older people had a higher depression prevalence than male ones. Depression prevalence for females was 44.5% while

TABLE 1 | Descriptive characteristics of the participants.

	Total (4,306)		Female (2,151)		Male (2,155)	
Variables	**Mean**	**Std**	**Mean**	**Std**	**Mean**	**Std**
Childhood health experience						
Self-reported health (good)	75.0		74.5		75.5	
Mother's mental health (poor)	19.7		21.1		18.3	
Father's mental health (poor)	12.0		11.7		12.3	
Age	67.09	5.97	67.06	6.12	67.11	5.81
Gender (male)	50.0					
Place of residence						
Rural	63.8		62.6		65.0	
Marital status						
Married	78.4		71.6		85.2	
Partnered	2.3		2		2.6	
Separated	0.7		0.6		0.7	
Divorced	0.6		0.4		0.8	
Widowed	17.1		25.2		9.0	
Never married	0.8		0.1		1.6	
Education level						
Primary school	26.5		17.8		35.2	
Middle school	12.7		8.1		17.4	
High school	5.0		2.7		7.2	
College and above	1.6		0.7		2.6	
Illiteracy	54.1		70.8		37.5	
CES-D score	8.93	6.39	10.11	6.73	7.75	5.81
CES-D score $\geq$ 10	40.6		49.4		31.9	
Retirement status						
Retired	39.3		44.5		34.0	
Pension status						
Received	33.3		32.4		34.2	

for 34.0% for males. Among them, more than 50% still lived in rural areas, nearly 40% retired and about 33% enjoyed pension.

Table 2 shows the results of logistic regression analyses. First, we assessed the relationship between childhood self-reported health and depression among older people by Model I. Older people with good self-reported health in childhood significantly had lower likelihood of suffering from depression than those with poor childhood self-reported health as the OR was less than 1 (OR = 0.719***, 95% CI: 0.622–0.830). Next, we evaluated the association between parental mental health in childhood and depression among older people by Model II and Model III. The results indicate that poor parental mental health is associated with a greater probability of having depression, since "mother's mental health" had an OR of 1.696*** (95% CI: 1.449–1.986) and "father's mental health" had an OR of 1.892*** (95% CI: 1.559–2.296). Finally, when we put the three childhood health

TABLE 2 | Associations between childhood self-reported health, parental mental health and depression among Chinese older people.

	Model I	Model II	Model III	Model IV
Childhood health experience				
Self-reported health (good)	0.719***			0.732***
	[0.622, 0.830]			[0.633, 0.847]
Mother's mental health (poor)		1.696***		1.391**
		[1.449, 1.986]		[1.138, 1.699]
Father's mental health (poor)			1.892***	1.457**
			[1.559, 2.296]	[1.141, 1.862]
Age	0.994	0.995	0.994	0.995
	[0.982, 1.006]	[0.983, 1.006]	[0.983, 1.006]	[0.984, 1.007]
Gender	0.539***	0.539***	0.529***	0.533***
	[0.469, 0.619]	[0.469, 0.620]	[0.460, 0.608]	[0.463, 0.613]
Place of residence				
Rural	1.464***	1.440***	1.446***	1.421***
	[1.267, 1.691]	[1.246, 1.664]	[1.251, 1.671]	[1.229, 1.644]
Marital status				
Married	0.299***	0.278***	0.289***	0.295***
	[0.147, 0.606]	[0.137, 0.564]	[0.142, 0.587]	[0.145, 0.601]
Partnered	0.334**	0.305**	0.319**	0.325**
	[0.148, 0.752]	[0.135, 0.688]	[0.141, 0.720]	[0.143, 0.736]
Separated	0.746	0.619	0.636	0.641
	[0.264, 2.112]	[0.218, 1.763]	[0.224, 1.806]	[0.225, 1.828]
Divorced	0.519	0.488	0.515	0.535
	[0.180, 1.497]	[0.169, 1.406]	[0.179, 1.486]	[0.184, 1.550]
Widowed	0.394*	0.368**	0.381**	0.389*
	[0.191, 0.812]	[0.178, 0.761]	[0.185, 0.788]	[0.188, 0.806]
Education level				
Primary school	0.866	0.892	0.892	0.901
	[0.742, 1.012]	[0.763, 1.042]	[0.764, 1.043]	[0.770, 1.053]
Middle school	0.606***	0.631***	0.626***	0.638***
	[0.488, 0.754]	[0.507, 0.785]	[0.504, 0.779]	[0.512, 0.794]
High school	0.471***	0.481***	0.485***	0.490***
	[0.331, 0.670]	[0.338, 0.685]	[0.341, 0.690]	[0.344, 0.698]
College	0.251***	0.245***	0.253***	0.246***
	[0.118, 0.535]	[0.115, 0.522]	[0.119, 0.538]	[0.116, 0.525]
Retirement status				
Retired	0.998	1.003	1.007	1.015
	[0.863, 1.154]	[0.867, 1.160]	[0.871, 1.165]	[0.877, 1.175]
Public pension status				
Received	0.796**	0.801**	0.799**	0.803**
	[0.695, 0.912]	[0.699, 0.918]	[0.697, 0.916]	[0.700, 0.920]
R^2	0.0549	0.0589	0.0587	0.0636
N	4,306	4,306	4,306	4,306

Exponentiated coefficients; 95% confidence intervals in brackets.
$^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.
Reference level: gender (female); marital status (unmarried); education level (illiteracy); place of residence (urban).

experience factors into Model IV together, these significant relationships still existed.

DISCUSSION

Former studies concentrate more on the enduring health effect of early childhood adversities, and the enduring health effect of childhood health experience has received little attention. Drawing on the life course theory, this is the first study to assess the enduring health effect of multidimensional childhood health experiences, including childhood self-reported health and parental mental health. Using a representative sample of 4,306 individuals, this study examined whether childhood health experience was associated with depression among older people in China. The results confirm our hypothesis that after adjusting for several confounding variables, both poor childhood self-reported health and poor childhood parental mental health are associated with higher likelihood of suffering from depression among older people. Thus, more attention should be paid to older people who had poor childhood health experience to actively cope with the high prevalence of depression among older people in China. This study is a comprehensive research to explore the childhood health experience factors influencing older people's depressive symptoms.

Generally speaking, the results of this study support the view of life course theory that early life experiences will produce an enduring impact on the consequences throughout the whole life course (Elder, 1998, 2018; Zheng and Hu, 2018). The findings demonstrate that poor childhood self-reported health experience had a strong positive correlation with depressive symptoms, which is in line with the results of Danese and McEwen (2012). Childhood experiences covered different aspects, such as physical abuse, parental separation, low family socioeconomic status and malnutrition. It is reported that a history of poor childhood experience is a high-risk group with respect to depression in young adulthood (Björkenstam et al., 2017). Our findings are consistent with those of the study on childhood experience, implying that poor childhood experience is correlated with depression. Prior studies looking at the childhood experiences related to mental health also support this relationship. Anda et al. (2002) point out that the number of poor childhood experiences had a graded relationship to depression (Anda et al., 2002). In their study, one of the poor childhood experiences that they used was mentally illness, as an aspect of childhood health. They were assessed for depression in adulthood. Another similar research confirms this negative relationship. Gundel et al. (2018) indicate that children and adolescents with non-affective mental disorders are at substantially increased absolute and relative risk of developing depression in young adulthood. And an increased relative risk for depression in children with anxiety disorders has also been observed (Copeland et al., 2013). The results of poor childhood self-reported health in this study are consistent with theirs. But childhood self-reported health reflects a more comprehensive health status in childhood than mental health used in other studies, and we extended the negative relationship to older people, which was more specific. This can be explained by the following reasons based on the life course perspectives. Many literatures have suggested that nutritional adversity in childhood will have a lasting impact on people's health throughout the life course (Gluckman et al., 2005; Kesternich et al., 2014). As mentioned earlier, older people suffered from malnutrition in childhood because they were born during the war, the famine and the baby boom (Jiang and Wang, 2020). The consequences caused by poor childhood health may accumulate over time and can finally lead to chronic diseases later in life, while chronic diseases may increase risk of depression.

History of parental health status is an important childhood experience for everyone. Our results demonstrate that children whose parents suffer from mental health problems are associated with a higher risk of depression in the older age. Previous studies examined the impact of different factors such as psychopathology, morbidity, and mortality on the offspring of parents with depression from birth to adulthood, and found that people whose parents had poor mental health status were more likely to have depression (Weissman et al., 1997, 2016, 2006). Chapman et al. (2018) indicate that exposure to mental illness during childhood has an effect on the risk of depressive disorders. Prior studies have shown that history of adverse parental status contributes to depression (Björkenstam et al., 2017). It is suggested that parental death, parental substance abuse, substantial parental criminality, parental psychiatric morbidity and parental separation help to predict depression in early adulthood (Green et al., 2010; Sareen et al., 2013; Björkenstam et al., 2017; Dahl et al., 2018). In particular, parental psychiatric morbidity has been reported to be a key factor for depression (Chapman et al., 2018). In this research, we used history of parental mental health status as an indicator for childhood health experience. Our results are in line with theirs. We found that individuals who had history of poor parental mental health were at a high risk of depression, as suggested by previous literature (Björkenstam et al., 2017). This can also be rationally explained by the life course theory that parental mental health has an enduring effect on offspring's mental health outcomes (Ferraro and Shippee, 2009). When living with their parents with poor mental health status, people in their childhood were easily affected by negative emotions, such as depression, anxiety and fear. Additionally, they could not receive adequate health care and emotional support from their parents. Thus, they were surrounded with a poor health status atmosphere. The long-term surroundings will promote their depressive symptoms development, which can lead to life-long consequences.

This study has the following limitations. First, we relied on self-reported data on childhood health experience. However, the low prevalence of adverse childhood health experiences in this population sample may reflect recall bias. A common fact is that most of the population in this sample was born 60 years ago while they possibly lived through the Great Chinese Famine at that time or they may be malnourished. And at that time the death rate was very high (Feng and Johansson, 2018). However, only a quarter of them reported that their childhood health was

poor. Therefore, our results may be underestimated. Another drawback is that we only used CES-D to assess depression. Although CES-D has been widely used to assess depression, it is not a golden rule to diagnose depression and CES-D may result in an underestimation or overestimation for depressive symptoms. Finally, we only included three childhood health indicators in our research because we hoped to conduct our research from the perspective of childhood health experience. Other childhood experiences like childhood neighborhood quality and relationships with parents may also influence depression among older people. Further research is needed to explore the impact of other potential factors on depression.

CONCLUSION

In conclusion, we find that having poor childhood health experience is associated with depression in older people. The results show that individuals with poor childhood health experience are at high risk of depression in older life. Given the importance of childhood, early and enough support for older people of having poor childhood health is important to improve their mental health. And early preventive interventions should invest in children with a history of poor childhood health experience.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: charls.pku.edu.cn/.

ETHICS STATEMENT

The study was reviewed and approved by the Institutional Review Board of Peking University with ethical approval no. (IRB00001052-11014). Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Cognitive Frailty: An Update

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This review article provides an update of the empirical research on cognitive fragility conducted in the last four years. The studies retrieved were classified in four different categories. The first category includes articles relating cognitive frailty to cognitive reserve and which continue to highlight the importance of educational level. The second category includes recent research on cognitive fragility biomarkers, involving neuroimaging, metabolism and, in a novel way, microbiota. The third category includes research on how cognitive frailty is related to motor development and physical functioning, exploring e.g. the use of technology to study motor markers of cognitive frailty. Finally, in the fourth category, research clarifying the difference between reversible frailty and potentially reversible cognitive frailty has led to new interventions aimed at reducing cognitive frailty and preventing negative health outcomes. Interventions based on physical activity and multicomponent interventions are particularly emphasized. In addition, recent research explores the long-term effects of dual interventions in older adults living in nursing homes. In summary, research on cognitive frailty has increased in recent years, and applied aspects have gained importance.

Keywords: frailty, subjective cognitive decline, cognitive reserve, biomarkers, physical activity, dual-task intervention, multicomponent intervention programs, mild cognitive impairment

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INTRODUCTION

The International Academy on Nutrition and Aging (I.A.N.A) and International Association of Gerontology and Geriatrics (I.A.G.G) consensus group has defined cognitive frailty as the simultaneous presence of physical frailty (PF) and mild cognitive impairment (MCI) in the absence of dementia or other pre-existing brain disorders (Kelaiditi et al., 2013). Facal et al. (2019) conducted a systematic review with the aim of analyzing the definition of the term "cognitive frailty" in the empirical literature published up to August 2017. The authors concluded that a more comprehensive definition of the potential relationships between PF and MCI was needed. They also indicated some limitations regarding the scarcity of specific markers of cognitive reserve and motor impairment and the lack of interventions studies.

Since then, research on cognitive frailty has increased exponentially. This review study aims to provide an update of research on the topic published in the empirical literature. Two independent authors conducted an empirical literature search in Medline, Web of Science, PsycINFO and Cochrane databases from September 2017 to December 2020, with the term "cognitive frailty". All original empirical studies in English, Spanish or Portuguese that explicitly used the term "cognitive frailty" were included. In total, 64 records were obtained from Medline, 73 from Web of Science, 9 from PsycINFO and 15 from Cochrane. After removal of duplicates, 80 articles were

considered. Two independent authors reviewed the title, abstract and keywords and evaluated their suitability for inclusion. Any conflicts were discussed until consensus was reached. According to the structure proposed by Facal et al. (2019), only articles that explicitly measured cognitive reserve, biological markers, motor capacity or that involved intervention studies were included. In their 2019 systematic review, Facal et al., analyzed all scientific research including the term "cognitive frailty" up to August 2017, and extracted these four thematic areas as the most relevant in the study of cognitive frailty as an applied concept in psychogerontology. As an update, in this mini-review we have decided to continue with this structure, and also to incorporate it as an inclusion criteria in order to maximize its potential for explanation. Finally, 4 articles concerning the relationships between cognitive frailty and cognitive reserve, 6 articles on the associations between cognitive frailty and biomarkers, 10 articles about motor signs and 8 articles analyzing the effects of interventions against cognitive frailty were selected (see **Supplementary Material**).

RELATIONSHIP BETWEEN COGNITIVE FRAILTY AND COGNITIVE RESERVE

Although the I.A.N.A-I.A.G.G definition indicates that cognitive frailty is characterized by reduced cognitive reserve, to date educational level has been the only proxy for this measure that has been systematically included in studies on cognitive frailty (Facal et al., 2019). We found that this trend continues in the most recent literature. Niederstrasser et al. (2019) detected a protective effect against early development of frailty and for frailty progression in individuals with any type of formal education, relative to individuals with no educational qualifications. Ruan et al. (2020) observed lower rates of physical and cognitive frailty in participants with an intermediate educational level (6–12 years) than in participants with a lower educational level. Similarly, Gallucci et al. (2020) reported that education seems to be a protective factor in the incidence of frailty, with more years of education associated with robust or pre-frailty and low education associated with frailty. Wongtrakulruang et al. (2020) associated low education level (primary school or less) a with higher risk of MCI and PF/pre-frailty.

Recent evidence reinforces the role of low educational level in the early stages of life as a strong, non-modifiable risk of cognitive frailty (Niederstrasser et al., 2019), highlighting the relationships between low wealth, low educational attainment and negative health outcomes, especially at the end of the lifespan, when older adults are more vulnerable to stressors. However, the relationship between cognitive frailty and cognitive reserve remains to be well established, by including not only measures related to years of formal education but also to proxies for work complexity or intellectually active lifestyles.

ROLE OF BIOMARKERS

Identification of biomarkers of CF is difficult as the syndrome is multidimensional. In the context of neuroimaging evidence, several recent papers have addressed the structure of certain areas and the damage caused by cerebrovascular diseases. Sugimoto et al. (2019) describe the relationship between inflammatory markers as a risk factor for white matter hyperintensity (WMH). By examining hyperintensity in T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, these researchers demonstrate increased volumes of WMH in CF and prefrail (PF) participants. At the structural level, Wan et al. (2020) describe a significant reduction in five subcortical nuclei (bilateral thalami, left caudate, right pallidum, accumbens area and the bilateral thalami). The data reported suggest that CF is associated with loss of structure of the thalamus and hippocampus and changes in WMH, and that possible volumetric biomarkers in these areas could thus potentially act as biomarkers of CF and its progression.

Consideration of the microbiota is a new aspect in the development of age-related biomarkers. Changes in the microbiota during aging are increasingly being studied, and it has been suggested that potentially important changes occur during the development of CF. In a recent study, He et al. (2020) demonstrated that CF patients have elevated levels of trimethylamine N-oxide (TMAO), a stable metabolite of the intestinal microbiota.

At the metabolic level, plasma biomarkers that are easily identifiable in a routine blood test are being studied. After longitudinal analysis of a population of 7,769 individuals included in the Doetinchem Cohort Study, Rietman et al. (2019) found that none of the following parameters were predictive of CF: high-density lipoprotein (HDL) cholesterol, triglycerides, alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), C-reactive protein (CRP), albumin, uric acid, cystatin C or creatinine. Royal and Plamen (2019) found that insulin-like growth factor 1 (IGF-1) and IGF-binding protein 2 (IGFBP2) were implicated in CF and potentially in the cause of age-related cognitive decline and physical frailty.

Regarding metabolism, recent research has examined the importance of lipids both in cell structure and at the nutritional level. Considering that lipids are a major component (70%) of the composition of the human brain, variations in these compounds could potentially be used as biomarkers of cognitive problems. In recent research, Sargent et al. (2020) found that low levels of vitamin E alpha tocopherol, omega-6 and 3 and albumin were associated with CF. In addition, these researchers observed a second pattern of association characterized by a low level of trans fats, as indicated by measuring low and high density lipoproteins (LDL and HDL).

RELATIONSHIP WITH MOTOR SIGNS OF AGING

Considering the importance of motoric aspects in the interplay between cognitive performance, cognitive impairment and PF, different studies on cognitive frailty have focused on motor decline and gait variables. Although Facal et al. (2019) pointed out that motor decline and gait variables were not systematically included in protocols for assessing cognitive frailty, more recent

studies frequently include these aspects. For example, Armstrong et al. (2019) associated cognitive performance measured by a computerized Stroop with physical functioning in a randomized sample of 607 old adults in the Baltimore Experience Corps Trial. Slower initial performance in the computerized test, but not lower learning rate, was associated in this study with poorer performance in the short physical performance battery (SPPB). Simpler physical performance assessment tools such as the Timed Up and Go (TUG) test are also good indicators of cognitive frailty. A decrease in functional mobility measured with this test has been shown to be a significant predictor of both prevalence (Kim et al., 2019) and incidence of cognitive frailty (Rivan et al., 2020). In the latter study, a one-unit increase in TUG was found to significantly increase the risk of developing cognitive frailty in an older population. Wanaratna et al. (2019) reported a high prevalence of frailty and pre-frailty in community-dwelling older patients with osteoarthritis of the knee, and severe symptoms of osteoarthritis measured by Oxford knee score were also associated with cognitive frailty.

The incidence of falls in frail old adults is high, and the negative consequences of falls increase with age. Recent studies associate cognitive frailty with a higher risk of falls. Tsutsumimoto et al. (2018) reported a higher risk of falls and also an increase in the fracture risk after falling in cognitively frail old adults than in old adults with normal cognition. According to the findings of the study, cognitive frailty is associated with a greater risk for fall-related fractures than cognitive impairment or PF alone. Zhao et al. (2020) reported that the relationship between cognitive frailty and falls may be mediated by engagement in activity, considered as a lifestyle factor which decreases the risk of falling. In this regard, risk of falling may lead to reduced physical activity, but also to reduced engagement in social activities and increased social isolation, which could lead to further cognitive and functional impairment.

Adequate assessment of motor performance is important in the context of cognitive frailty. Common approaches for assessing cognitive frailty use tools with a limited capacity to track changes over time and that may not be suitable for older adults living in remote, rural areas. Wearable sensors have thus been proposed as a possible means of measuring daily activity, as they are practical and reproducible. Recent studies have shown the feasibility and effectiveness of using remote physical activity and sleep monitoring recorded via a pendant sensor worn on the chest to identify old adults with cognitive frailty (Razjouyan et al., 2020), and using remote physical activity monitoring to identify pre-frail old adults (Razjouyan et al., 2018). Zhou et al. (2018) went a step further and evaluated a wearable platform to demonstrate the feasibility and efficacy of detecting cognitive impairment via an ankle-worn sensor in a series of interactive, instrumented trail-making tasks. The authors used trail-making tasks to quantify motor planning errors, by analyzing patterns of actual and optimal ankle velocity. The authors suggest that this procedure may be a substitute for dual-tasking walking tests when gait assessment is not possible.

COGNITIVE FRAILTY AS A REVERSIBLE CONDITION AND PREVENTIVE INTERVENTIONS

Recent research studies have attempted to differentiate between reversible and potentially reversible cognitive frailty. Cognitive frailty is considered reversible in the combined presence of physical pre-frailty (PF) and pre-MCI subjective cognitive decline (SCD), and potentially reversible in the combined presence of physical PF and MCI (Ruan et al., 2020). Reversible cognitive frailty is the ideal target to prevent asymptomatic, pre-clinical cognitive impairment. For this reason, and because it would be a central part of this pattern of reversible frailty, SCD has been the subject of recent research in the study of cognitive frailty. Hsieh et al. (2018) reported that old adults with SCD were more likely to be identified as pre-frail or frail than old adults with normal cognitive aging, regardless of potential confounding factors such as age, gender, education level, comorbidity, nutritional status, kidney function and biochemical-related factors. Okura et al. (2019) found that the impact of self-reported mobility decline (SR-MD) and self-reported cognitive decline (SR-CD) on adverse health outcomes depended on the moderating role of age and sex. For community-dwelling old men, SR-MD and non-SR-CD significantly predicted adverse health outcomes, with earlier negative outcomes than in non-SR-MD and SR-CD. For women, similar results were observed for respectively non-SR-MD and SR-CD, relative to SR-MD and non-SR-CD. Ruan et al. (2020) also observed gender differences, concluding that females with higher levels of education had a significantly increased risk of reversible cognitive frailty. Interestingly, in this study SCD was positively associated with physical pre-frailty but negatively associated with PF.

Although intervention studies in cognitive frailty are recent and relatively scarce, there is a growing consensus that interventions can be effective and beneficial in reducing cognitive frailty and/or preventing negative health outcomes. Interventions focused on physical activity and multicomponent interventions are highlighted. Regarding interventions based on physical activity, moderate-to-vigorous physical activity has been found to have a positive effect on cognitive frailty. Liu et al. (2018) reported that a 24-month structured programme of moderate-intensity physical activity was associated with a lower probability of worsening cognitive frailty. Similarly, an eHealth physical activity programme conducted over 12 weeks, promoting exercise in the form of brisk walking, was shown to reduce frailty and had a positive effect on mobility, improving cognitive function, walking time, step count, brisk walking time, peak cadence and moderate-to-vigorous activity time after the intervention (Kwan et al., 2020). Yoon et al. (2018) tested the effects of a high-speed resistance training programme conducted over 16 weeks in cognitively frail community-living older adults. The results showed that the exercise involved in the intervention improved cognitive function, physical function and muscle strength.

Adding cognitive intervention to physical exercise and due to the mutual influence between physical and cognitive

decline, multicomponent programmes appear to be important for preventing and reducing cognitive frailty. Gallucci et al. (2020) found that frailty status was likely to improve by more than three times in participants of a 12-months structured programme including two/days week physical activity and a bimonthly group reading activity than in a control group who decided not to engage in the programme. Romera-Liebana et al. (2018) found that a multifaceted intervention including exercise training, intake of hyperproteic nutritional shakes, memory training and medication review was effective in reversing frailty 3 and 18 months after the intervention, improving mobility, balance, stretching, muscle strength and all dimensions of a neuropsychological battery and also reducing the number of medication prescriptions.

Finally, recent research has explored dual-task interventions in older adults living in long-term nursing homes. The ability to perform dual or multiple tasks decreases with age, particularly in the presence of cognitive impairment. According to Rezola-Pardo et al. (2019), dual-task interventions require greater cognitive and motor resources, are more complex in terms of control and coordination demands, and they may prevent or reverse frailty in older adults living in long-term nursing homes by improving cognitive function, gait and dual-task performance. These researchers compared a dual-task training intervention and a multicomponent exercise programme. In the dual-task training, the exercise component, based on the same physical exercises done by the groups undertaking the multicomponent exercise programme, was implemented with simultaneous progressive cognitive training. Cognitive exercises, including attentional, executive and semantic memory tasks, were individually tailored by adapting the difficulty for different cognitive domains for each participant. Both programmes were effective in improving gait and maintaining cognitive performance, and frailty status tended to improve. Nevertheless, the addition of simultaneous cognitive training did not provide additional benefits.

DISCUSSION

It has been possible to verify some important advances in research on cognitive frailty in the scientific literature. Links between cognitive frailty and years of education continue to highlight the relationships between low wealth, low educational attainment and negative health events (Gallucci et al., 2020; Ruan et al., 2020; Wongtrakulruang et al., 2020), and the mediational role of active engagement in the relationship between cognitive frailty and falls (Zhao et al., 2020) appears as an emerging research topic. It is desirable that research on cognitive frailty progressively incorporates other relevant proxies of cognitive reserve, such as leisure activity and work complexity, as well as global measures of the cognitive reserve construct.

The articles included in this review also support the relationship between cognitive development and motor development in cognitive frail older adults. The findings reported by Kim et al. (2019) and Rivan et al. (2020) highlight the importance of simple mobility tests such as TUG in the context of cognitive frailty. Decline in physical function can lead to reduced physical activity and socialization, which could lead to further functional decline and cognitive frailty. According to these authors, the interventions required to improve TUG performance may also be effective in preventing cognitive frailty and subsequent falls. Innovative devices such as portable sensors are also proposed as a possible alternative means of measuring daily activity in these populations.

Recent research also shows that a combination of clinical, inflammatory and neuroimaging markers could be included in a panel of clinically useful biomarkers for CF and the possibility of intervening at the nutritional and/or psychosocial level to reduce incident dementia. Lifestyle aspects such as physical activity and nutrition have been considered in preventive intervention measures aimed at mitigating physical and cognitive decline.

Finally, recent research provides the first evidence supporting the effectiveness of interventions designed to reduce cognitive frailty and prevent related negative health outcomes. These include interventions focused on physical activity and also multicomponent interventions. Interestingly, a dual task programme was effective in improving gait and maintaining cognitive function, but it did not produce better results than an equivalent, exercise-only programme (Rezola-Pardo et al., 2019). This result stress the protective role of physical exercise. It also suggest us that dual-task interventions must be tailored on the basis of physical performance under single-task conditions but also on the cognitive abilities and preferences of the participants in order to maximize their potential efficacy.

According to the promising results in intervention studies, reversibility remains an important aspect of research on CF, and this importance is expected to increase with successive research on preventive interventions and the role of SCD in the study of cognitive frailty. The development of clinical, inflammatory and neuroimaging markers of CF would also help in differentiating between reversible and potentially reversible CF and in designing more precise preventive studies.

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

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SUPPLEMENTARY MATERIAL

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Bidirectional Longitudinal Study of Frailty and Depressive Symptoms Among Older Chinese Adults

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Objective: Frailty and depression, as two common conditions among older adults in China, have been shown to be closely related to each other. The aim of this study was to investigate the bidirectional effects between frailty and depressive symptoms in Chinese population.

Methods: The bidirectional effect of frailty with depressive symptoms was analyzed among 5,303 adults ≥ 60 years of age from the China Health and Retirement Longitudinal Study (CHARLS). Phenotype and a frailty index were used to measure frailty. Depressive symptoms were evaluated using the Epidemiological Studies Depression Scale (CES-D). Logistic regression and Cox proportional hazard regression models were used to determine the bidirectional effects of frailty and depressive symptoms in cross-sectional and cohort studies, respectively. Subgroup and sensitivity analyses were further used to further verify the associations.

Results: In the cross-sectional study, the multivariate-adjusted ORs (95% CIs) for depressive symptoms among pre-frail and frail adults, as defined by the frailty index and phenotype, were 3.05 (2.68–3.49), and 9.78 (8.02–12.03), respectively. Depressed participants showed higher risks of pre-frailty and frailty [frailty index, 3.07 (2.69–3.50); and phenotypic frailty, 9.95 (8.15–12.24)]. During follow-up, the multivariate-adjusted HRs (95% CIs) for depressive symptoms among pre-frail and frail participants, as defined by the frailty index and phenotype, were 1.38 (1.22–1.57), and 1.30 (1.14–1.48), respectively. No significant relationship existed between baseline depressive symptoms and the incidence of frailty. Moreover, the results from subgroup and sensitivity analyses were consistent with the main results.

Conclusion: Although a cross-sectional bidirectional association between depressive symptom and frailty has been observed in older (≥60 years old) Chinese adults, frailty may be an independent predictor for subsequent depression. Moreover, no effect of depressive symptoms on subsequent frailty was detected. Additional bidirectional studies are warranted in China.

Keywords: depressive symptoms, frailty, bidirectional association, China, older people

INTRODUCTION

The aging population is a global phenomenon, with 1 billion adults ≥ 60 years of age. This number is estimated to reach 1.4 billion by 2030, and will be on the rise in the ensuing decades (World Health Organization, 2018, 2019). The old adults are more likely to have age-related disorders, including mental health and physical fitness, given the limited regenerative abilities. Moreover, the old adults are more likely to have more than one co-morbidity at the same time (World Health Organization, 2019). Indeed, depression, a common mental illness, has a prevalence ranging from 10 to 20% in the older population (Rodda et al., 2011). In addition, depression is associated with a 6–10%, and 30% rate of disability in the primary care setting, and in medical and long-term care settings, respectively (Reynolds et al., 2012). Frailty is a common physical condition among older adults, and is characterized by a functional decline in multiple physiologic systems that causes an increased susceptibility to stressors (Hoogendijk et al., 2019). As reported, the prevalence of frailty has been estimated to range from 10% among community-dwellers (Collard et al., 2012) to 18–40% in hospitalized patients (Cunha et al., 2019). When stressors, such as acute illness, occur, a person with frailty rapidly has a deterioration in functional capacity. Generally, several instruments have been established to identify frailty. The two most common frailty instruments used in studies and clinical settings are the phenotypic and the frailty indices. The phenotype model of frailty considers frailty as a biological syndrome, defined by a set of five specific symptoms: weakness; slowness; exhaustion; low physical activity; and shrinking (Fried et al., 2001). The frailty index is based on the cumulative deficit model, and covers non-specific diseases, deficits, signs, symptoms, disabilities, and mental factors (Rockwood and Mitnitski, 2007).

Notably, frailty and depression may share common risk factors and pathophysiologic pathways, including inflammation and mitochondrial dysfunction (Franceschi et al., 2018). As a result, frailty and depression also contribute to a range of harmful consequences of old age, such as poor quality of life, and increased health care needs, morbidity, and mortality (Rodda et al., 2011; Clegg et al., 2013; Shamliyan et al., 2013; Hare et al., 2014). Moreover, co-existing frailty and depressive symptoms have been reported to be associated with impaired cognitive functioning and disability based on a cross-sectional study from the Neurocognitive Outcomes of Depression in the Elderly study (Potter et al., 2016). To date, previous studies have demonstrated a strong link between frailty and depressive symptoms (Nabi et al., 2008; Surtees et al., 2008). As summarized by a meta-analysis based on 16 cross-sectional and 23 cohort studies in 2012, a positive association between depression and frailty was observed in cross-sectional studies, whereas findings from cohort studies were inconsistent (Mezuk et al., 2012). A 2017 meta-analysis from multiple countries reported that frail individuals have a 4.42-fold increased probability of being depressed and the likelihood of being frail is 4.07-fold higher in depressed patients (Soysal et al., 2017). Similarly, the increased likelihood of being frailty is 4.07-fold higher in depressed patients. In addition, the incidence of frailty among depressed patients is 2.72-fold higher than non-depressed patients, whereas the increased probability of being depressed was 0.90-fold higher in frail patients (Soysal et al., 2017). These findings suggest that frailty and depression may have an influence on each other, but no such data are available in China.

Currently, China has approximately 250 million old adults, accounting for 17.9% of the total 1.4 billion people (Jia et al., 2020). As expected, 27% of the population will be old populations by 2050 (United Nations, 2019). Hence, investigating the bidirectional association between frailty and depressive symptoms is older Chinese adults is warranted. To fill this gap in knowledge and provide the evidence, we conducted this study to analyze the bidirectional effect between frailty and depressive symptoms among older adults from the China Health and Retirement Longitudinal Study (CHARLS) using a cross-sectional and cohort design.

MATERIALS AND METHODS

Study Participants

The study sample was obtained from the (CHARLS), a representative national cohort with middle-aged and older adults in China, as described previously (Zhao et al., 2014). At baseline, 17,708 participants from 450 urban and rural areas of 28 provinces were recruited in 2011, with follow-up evaluations in 2013, 2015, and 2018. During each survey, information on age, sex, marital status, educational level, family income, residence, social activities, retirement, cigarette smoking, alcohol consumption, sleep duration, number of chronic diseases, and body mass index (BMI) was collected from structured questionnaires and physical examinations by trained interviewers and physicians, respectively. Adults ≤ 60 years of age (N = 10,255), and those with missing depressive symptom assessments (N = 454) and demographic data (N = 50) were excluded. In addition, 1,646 or 1,361 participants without sufficient evaluation data on the frailty index or phenotypic frailty were excluded, respectively. Thus, using the baseline data in 2011, 5,303 or 5,117 participants underwent a cross-sectional analysis between frailty, as defined by a frailty index or phenotype, respectively, and depressive symptoms, using the baseline data in 2011. In the cohort study (2011–2018), we further excluded those participants with baseline frailty or depressive symptoms and those lost to follow-up. Therefore, 3,157 or 3,082 participants remained in the cohort analysis with baseline frailty, as defined by a frailty index or phenotype, respectively, and the incidence of depressive symptoms, while 2,086 or 1,491 participants were included for the cohort analysis between baseline depressive symptoms and incidence of frailty assessed by a frailty index or phenotype, respectively. Additionally, with the limited information, such as physical examination indicators, for the definition of phenotypic frailty in 2018, the association between baseline depressive symptoms and the incidence of phenotypic frailty was only evaluated during follow-up from 2011 to 2015. The flow chart of the selection process for participants is shown in **Supplementary Figure 1**.

This study was approved by the Peking University Ethical Committee. Informed consent was obtained from all participants.

Assessment of Depressive Symptoms

The 10-item Center for Epidemiological Studies Depression Scale (CES-D) was used to evaluate depressive symptoms (Andresen et al., 1994). As reported elsewhere, the CES-D includes 10 items with four answers for each item, as follows: "rarely (<1 day/week);" "some days (1–2 days/week);" "occasionally (3–4 days/week);" "most (5–7 days/week)." For the negative items, the score was assigned 0, 1, 2, and 3 points for "rarely," "some days," "occasionally," and "most," respectively; whereas for the positive items, the score was defined as 3, 2, 1, and 0 points for "rarely," "some days," "occasionally," and "most," respectively. Then, the total score was summed for the 10 items, ranging from 0 to 30. In agreement with a prior study verified the validity of CES-D in CHARLS (Chen and Mui, 2014), the study participants were classified as depressed with a CES-D score $\geq$ 12 and non-depressed with a CES-D score < 12.

Assessment of Frailty

Frailty was assessed by both phenotype and a frailty index. As reported elsewhere, phenotypic frailty was determined by the physical frailty phenotype (PEP) scale, which includes weakness, slowness, exhaustion, inactivity and weight loss (Wu et al., 2017). Weak was defined as a maximum handgrip strength for either hand less than the 20th percentile for the sex- and BMI- adjusted weighted population distribution. Slow was the average time of repeated walking tests over a 2.5-m course that exceeded the 80th percentile for the sex- and height-adjusted weighted population distribution. Exhaustion occurred when subjects felt that anything they did was an effort or they could not get going. Inactivity was defined as subjects who walked continuously for < 10 min in a typical week. Weight loss was defined as a self-rated loss of $\geq$5 kg in the previous year or a BMI $\leq$ 18.5 kg/m^2. Using the above information, phenotypic frailty was categorized into three levels, as follows: robust (meeting none of the five domains); and prefrail and frail (meeting any one or more criteria).

The modified procedure of the China Kadoorie Biobank was used to evaluate the frailty index (Fan et al., 2020), and included 20 deficits, including chronic diseases (i.e., hypertension, heart disease, stroke, emphysema or bronchitis, tuberculosis, asthma, peptic ulcer, gallstone diseases, rheumatoid arthritis, fracture, neurasthenia, diabetes, cancer, and chronic kidney diseases), symptoms and signs (i.e., sleep disturbances, body pain or discomfort, unintentional weight loss, feeling sad or depressed, and poor health status), and physical measurements (i.e., BMI). Each deficit was dichotomized or mapped from 0 (the healthiest status) to 1 (the unhealthiest status). The frailty index was calculated as a ratio of the number of deficits for each participant to the total number of deficits, with a range from 0 to 1. Two subgroups were created, as follows: robust ($\leq$0.10); and pre-frailty and frailty (>0.10). Because the number of frail people over 60 aged in the CHARLS is limited, we had to combine the prefrailty and frailty conditions.

Statistical Analysis

The distributions of the study sample were determined by frailty status. Means $\pm$ standard deviations (SDs) or numbers (percentages) were calculated to perform continuous or categorical variables, respectively. Student's *t*-test, the Mann-Whitney *U*-test and the chi-square test were used to compare the distribution of covariates in univariate analyses. Logistic regression models were used to determine the bidirectional associations between frailty and depressive symptoms with a cross-sectional design. Cox proportional hazard regression models were used to determine the relationship between frailty and the incidence of depression, as well as the relationship between depression and the incidence of frailty. For example, in the association between frailty index and the incidence of depressive symptoms, if individuals without depressive symptoms at baseline (2011), but were evaluated to be with depressive symptoms in 2013, then the time interval in Cox proportional hazards model was considered as 2 years. Similarly, if participant without depressive symptoms in 2011 and 2013, but were assessed to be with depressive symptoms in 2015, then the time interval was defined as 4 years; if individuals without depressive symptoms in 2011, 2013, and 2015, but were evaluated to be with depressive symptoms in 2018, then the time interval was considered as 7 years. Additionally, to ensure the reliability of the results, we further calculated the per SD change value after zero-mean normalization of the continuous independent variable. The standardization process was calculated according to the following formula:

$$z_{ij} = \left(x_{ij} - x_i\right) / s_i$$

where z_{ij} represents the standardized independent variable, x_{ij} represents the original independent variable, x_i represents the mean value of the independent variable, and s_i represents the SD of the independent variable.

Moreover, subgroup analyses based on sex and residence were both performed to verify such associations, either in a cross-sectional or prospective study. In addition, a series of sensitivity analyses were further conducted. Firstly, because the definition of frailty might involve depressive symptoms-related factor ("Overall in the last month, how much of a problem did you have with feeling sad, low, or depressed?"), we excluded the associated factors and performed sensitivity analyses. Secondly, since the age limit established for old age is 65 years, we conducted the sensitivity analyses among people over the age of 65, as well. Thirdly, the survival time is unlikely to be precisely observed in the queuing setting, and thus at best it is known only to fall within an interval between two consecutive surveys, that is interval-censoring. Briefly, it treats the right-truncated observation value as a special interval with an infinite right boundary and the exact event time as a zero-length interval. The PROC ICLIFETEST (Guo et al., 2014) provides a non-parametric statistical method for estimating survival functions and a statistical test of interval-censored data. Therefore, we used this procedure to investigate the association between baseline frail status and incidence of depressive symptoms, as well as the association between baseline depressive symptoms and the incidence of frailty.

In the present study, the crude model was used to evaluate the odd ratio (OR) or hazard ratio (HR) and the 95% confidence interval (CI) without any adjustment. Model 1 adjusted for age and sex, and model 2 additionally adjusted for education level, smoking status, alcohol consumption, marital status, place of residence, income, participation in social activities, number of chronic diseases, retirement status, and sleep duration. All statistical analyses were conducted using SAS (version 9.4; SAS Institute Inc., Cary, NC, United States). All *P*-values were two-tailed, and a $P < 0.05$ was considered statistically significant.

RESULTS

Basic Characteristics

Table 1 shows the basic characteristics of the study population. As calculated by the frailty index, greater than one-half of 5,303 participants (53.84%) were pre-frail or frail, primarily affecting the majority of women and retirees. These subjects tended to have a higher BMI, lower educational level and family income, shorter sleep duration, and several chronic diseases. In addition, the prevalence of depressive symptoms among pre-frail and frail subjects was significantly greater than the robust subjects. Indeed, 65.88% of subjects had pre-frailty and frailty when determined based on phenotype. Specifically, the pre-frail and frail subjects were more likely to be older, females, no alcohol consumption, countrymen, and retirees. Furthermore, the pre-frail and frail subjects tended to have several chronic diseases, but a lower BMI, educational and income levels, and shorter sleep duration. The prevalence of depressive symptoms in pre-frail and frail subjects was significantly greater than the robust subjects.

Bidirectional Relationship of Frailty With Depressive Symptoms in the Cross-Sectional Study

Figure 1 presents the association of frailty with depressive symptoms in the cross-sectional study. Pre-frail and frail participants had higher risks of depression before and after adjustments for confounders when compared to the robust participants. As shown in **Supplementary Table 1**, the crude ORs (95% CIs) for depressive symptoms among pre-frail and frail participants, as defined by the frailty index and phenotype, were 3.25 (2.87–3.69) and 10.56 (8.73–12.89), respectively. The ORs (95% CIs) for depressive symptoms for each incremental increase in the standard deviation of the frailty index and phenotypic frailty scores were 2.03 (1.91–2.17), and 2.58 (2.41–2.77), respectively. The ORs (95% CIs) for depressive symptoms among pre-frail and frail participants, as defined by the frailty index and phenotype were 3.19 (2.82–3.62) and 10.86 (8.95–13.29) after adjustment for age and sex, respectively. The ORs (95% CIs) for depressive symptoms for each incremental increase in the standard deviation of the frailty index and phenotypic frailty scores were 2.01 (1.88–2.14), and 2.76 (2.56–2.97), respectively. The full-adjusted ORs (95% CIs) for depressive symptoms among pre-frail and frail people defined by index and phenotype were 3.05 (2.68–3.49) and 9.78 (8.02–12.03), respectively. The ORs (95% CIs) for depressive symptoms for each incremental increase in the standard deviation of the frailty index and phenotypic frailty scores were 1.95 (1.82–2.08), and 2.61 (2.42–2.82), respectively.

When assigning depressive symptoms as an independent variable, as shown in **Supplementary Table 2**, depressed patients had higher risks of pre-frailty and frailty, with crude ORs (95% CIs) of 3.25 (2.87–3.69) for the frailty index and 10.56 (8.73–12.89) for phenotypic frailty. The ORs (95% CIs) for pre-frailty and frailty, as assessed by the frailty index and phenotype, for each incremental increase in the standard deviation of the depressive symptoms score were 1.90 (1.79–2.02) and 3.78 (3.46–4.16), respectively. After adjusting for age and sex, depressed patients had higher risks of pre-frailty and frailty, with ORs (95% CIs) of 3.19 (2.81–3.62) for the frailty index; and 10.88 (8.97–13.31) for phenotypic frailty. The ORs (95% CIs) for pre-frailty and frailty, as assessed by the frailty index and phenotype, for each incremental increase in the standard deviation of the depressive symptoms score were 1.89 (1.77–2.01) and 3.90 (3.55–4.29), respectively. Moreover, depressed patients had higher risks of pre-frailty and frailty, with ORs (95% CIs) of 3.07 (2.69–3.50) for the frailty index and 9.95 (8.15–12.24) for phenotypic frailty, after adjusting for age, sex, education level, smoking status, alcohol consumption, marital status, place of residence, income, participation in social activities, number of chronic diseases, retirement status, and sleep duration. The ORs (95% CIs) for pre-frailty and frailty, as assessed by the frailty index and phenotype, for each incremental increase in the standard deviation of the depressive symptoms scores were 1.89 (1.77–2.02) and 3.97 (3.59–4.40), respectively.

Sensitivity Analysis Between Frailty and Depressive Symptoms in the Cross-Sectional Study

Because the definition of frailty might involve depressive symptom-related factors, sensitivity analysis was performed after excluding the related factors, as shown in **Supplementary Table 3**. The results were similar to that of the entire population. Pre-frail and frail participants had higher risks of depressive symptoms before and after adjustments for confounders, when compared to the robust participants. In the crude model, pre-frail and frail participants were at higher risk of depressive symptoms when assessed by the frailty index and phenotype [ORs (95% CIs), 3.46 (3.00–4.00) and 1.69 (1.51–1.91), respectively], compared to robust subjects. In addition, the ORs (95% CIs) for depressive symptoms per each incremental increase in the standard deviation for the frailty index and phenotypic frailty scores were 1.95 (1.83–2.08) and 1.32 (1.25–1.40), respectively. After adjusting for age and sex, pre-frail and frail participants were at higher risk of depressive symptoms when assessed by the frailty index and phenotype [ORs (95% CIs), 3.32 (2.87–3.84) and 1.73 (1.53–1.95), respectively], respectively, compared to robust subjects. In addition to the ORs (95% CIs) for depressive symptoms per each incremental increase in the standard deviation for the frailty index and phenotypic frailty scores were 1.93 (1.81–2.06), and 1.35 (1.27–1.43). In

TABLE 1 | The basic characteristic of the study population in the cross-sectional study.

Characteristics	Total	Frailty index		*P*-value	Total	Phenotypic frailty		*P*-value
		Robust	Pre-frailty/frailty			Robust	Pre-frailty/frailty	
N (%)	5,303	2,448 (46.16)	2,855 (53.84)		5,117	1,746 (34.12)	3,371 (65.88)	
Males (N, %)	2,717 (51.24)	1,343 (54.86)	1,374 (48.13)	<0.001	2,639 (51.57)	983 (56.30)	1,656 (49.12)	<0.001
Age (Mean ± SD, years)	67.70 ± 6.40	67.57 ± 0.13	67.81 ± 0.12	0.18	67.62 ± 6.36	66.26 ± 0.15	68.33 ± 0.11	<0.001
BMI (Mean ± SD, years)	22.93 ± 3.99	22.43 ± 0.08	23.37 ± 0.07	<0.001	22.92 ± 3.92	23.71 ± 0.09	22.51 ± 0.07	<0.001
Marital status (Married, N, %)	4,192 (79.05)	1,959 (80.02)	2,233 (78.21)	0.11	4,051 (79.17)	1,464 (83.85)	2,587 (76.74)	<0.001
Residence (Rural, N, %)	3,337 (62.93)	1,566 (63.97)	1,771 (62.03)	0.15	3,255 (63.61)	988 (56.59)	2,267 (67.25)	<0.001
Educational level (Illiterate, N, %)	1,887 (35.58)	865 (35.33)	1,022 (35.80)	<0.001	1,811 (35.39)	470 (26.92)	1,341 (39.78)	<0.001
Income (≥mean value, N, %)	415 (7.83)	233 (9.52)	182 (6.37)	<0.001	406 (7.93)	211 (12.08)	195 (5.78)	<0.001
Participation in social activities (Yes, N, %)	2,426 (45.75)	1,135 (46.36)	1,291 (45.22)	0.40	2,357 (46.06)	913 (52.29)	1,444 (42.84)	<0.001
Retired (Yes, N, %)	2,219 (41.84)	943 (38.52)	1,276 (44.69)	<0.001	2,091 (40.86)	669 (38.32)	1,422 (42.18)	0.01
Smoking status (N, %)				<0.001				0.09
Non-smoker	3,001 (56.59)	1,382 (56.45)	1,619 (56.71)		2,884 (56.36)	948 (54.30)	1,936 (57.43)	
Ex-smoker	650 (12.26)	242 (9.89)	408 (14.29)		626 (12.23)	220 (12.60)	406 (12.04)	
Current smoker	1,652 (31.15)	824 (33.66)	828 (29.00)		1,607 (31.41)	578 (33.10)	1,029 (30.53)	
Drinking status (N, %)				0.17				<0.001
Never	3,678 (69.36)	610 (24.92)	651 (22.80)		3,525 (68.89)	1,119 (64.09)	2,406 (71.37)	
<1 Time/month	1,261 (23.78)	170 (6.94)	194 (6.80)		1,238 (24.19)	486 (27.84)	752 (22.31)	
≥1 Time/month	364 (6.86)	1,668 (68.14)	2,010 (70.40)		354 (6.92)	141 (8.08)	213 (6.32)	
Sleep duration (Mean ± SD, hours/per day)	6.17 ± 2.00	6.46 ± 0.04	5.91 ± 0.04	<0.001	6.17 ± 1.99	6.41 ± 0.05	6.04 ± 0.03	<0.001
Number of chronic diseases (N, %)				<0.001				<0.001
0	1,329 (25.06)	1,187 (48.49)	142 (4.97)		1,298 (25.37)	530 (30.36)	768 (22.78)	
1	1,586 (29.91)	999 (40.81)	587 (20.56)		1,528 (29.86)	544 (31.16)	984 (29.19)	
≥2	2,388 (45.03)	262 (10.70)	2,126 (74.47)		2,291 (44.77)	672 (38.49)	1,619 (48.03)	
Frailty scores (Mean ± SD)	0.14 ± 0.09	0.06 ± 0.03	0.21 ± 0.07	<0.001	1.04 ± 0.97	0	1.57 ± 0.77	<0.001
Depressive symptoms (N, %)	1,712 (32.28)	469 (19.16)	1,243 (43.54)	<0.001	1,630 (31.85)	124 (7.10)	1,506 (44.68)	<0.001
Depressive symptoms score (Mean ± SD)	9.09 ± 6.45	7.07 ± 5.62	10.81 ± 6.61	<0.001	9.02 ± 6.43	5.10 ± 3.86	11.05 ± 6.55	<0.001

BMI, body mass index; SD, standard deviation.

the full-adjusted model, pre-frail and frail participants were at higher risk of depressive symptoms when assessed by an index and phenotype [ORs (95% CIs), 3.12 (2.68–3.63) and 1.59 (1.40–1.82), respectively], compared to robust subjects. The ORs (95% CIs) for depressive symptoms per each incremental increase in the standard deviation for the frailty index and phenotypic frailty scores were 1.88 (1.76–2.01) and 1.28 (1.20–1.37), respectively.

When assigning depressive symptoms as an independent variable, as shown in **Supplementary Table 4**, depressed participants had a higher risk of pre-frailty and frailty before and after adjustments for confounding factors, including age, sex, education level, smoking status, alcohol consumption, marital status, place of residence, income, participation in social activities, number of chronic diseases, retirement status, and sleep duration, when compared to the non-depressed participants. In the crude model, the ORs (95% CIs) for pre-frailty and frailty, as defined by the frailty index and phenotype among depressed patients, were 3.46 (3.00–4.00) and 1.69 (1.51–1.91), respectively. The ORs (95% CIs) for pre-frailty and frailty, as assessed by the frailty index and phenotype, for each incremental increase in the standard deviation for the depressive symptoms scores were 1.98 (1.84–2.11) and 1.34 (1.27–1.42), respectively. After adjusting for age and sex, the ORs (95% CIs) for pre-frailty and frailty, as defined by the frailty index and phenotype among depressed patients, were 3.31 (2.87–3.84) and 1.73 (1.53–1.95), respectively. The ORs (95% CIs) for pre-frailty and frailty, as assessed by the frailty index and phenotype, for each incremental

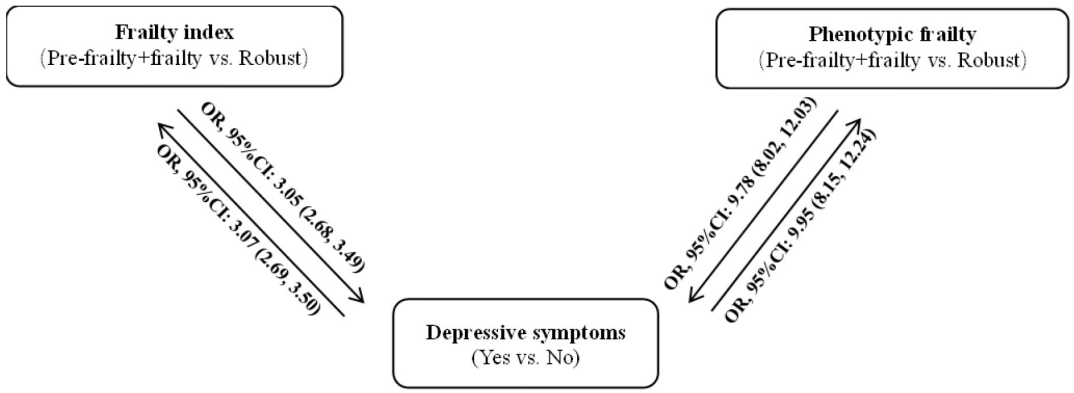

FIGURE 1 | Bidirectional association between frailty and depressive symptoms in the cross-sectional study.

increase in the standard deviation for the depressive symptoms scores were 1.93 (1.80–2.07) and 1.36 (1.28–1.44), respectively. The full-adjusted ORs (95% CIs) for pre-frailty and frailty, as defined by the frailty index and phenotype among depressed patients were 3.15 (2.71–3.67) and 1.59 (1.40–1.82), respectively. The ORs (95% CIs) for pre-frailty and frailty, as assessed by the frailty index and phenotype, for each incremental increase in the standard deviation for the depressive symptoms scores were 1.92 (1.79–2.08) and 1.31 (1.23–1.40), respectively.

Consistently shown in **Supplementary Figure 2**, after adjusting for age, sex, education level, smoking status, alcohol consumption, marital status, place of residence, income, participation in social activities, number of chronic diseases, retirement status, and sleep duration, pre-frail and frail participants (>65 years) were at higher risk of depressive symptoms when assessed by an index and phenotype [ORs (95% CIs), 2.78 (2.35–3.30) and 11.03 (8.31–14.94), respectively], compared to robust subjects. In contrast, the full-adjusted ORs (95% CIs) for pre-frailty and frailty, as defined by the frailty index and phenotype among depressed patients were 2.79 (2.36–3.31) and 11.23 (8.45–15.22), respectively.

Bidirectional Effect Between Frailty and Depressive Symptoms in the Cohort Study

The incidence of depressive symptoms was 56 per 1,000-person years. The association between frailty and the incidence of depressive symptoms is shown in **Table 2**. Compared with the robust participants, prefrail or frail participants had higher risks of depressive symptoms before and after adjusting for confounders, including age, sex, education level, smoking status, alcohol consumption, marital status, place of residence, income, participation in social activities, number of chronic diseases, retirement status, and sleep duration. The crude HRs (95% CIs) for depressive symptoms among prefrail and frail participants, as defined by the frailty index and phenotype, were 1.39 (1.23–1.58) and 1.38 (1.21–1.56), respectively. The HRs (95% CIs) for the incidence of depressive symptoms for each incremental increase in the standard deviation of the frailty index and phenotypic frailty scores were 1.24 (1.17–1.31), and 1.19 (1.12–1.26), respectively. After adjusting for age and sex, the HRs (95% CIs) for depressive symptoms among prefrail and frail participants, as defined by the frailty index and phenotype, were 1.38 (1.22–1.57) and 1.38 (1.21–1.57), respectively. The HRs (95% CIs) for the incidence of depressive symptoms for each incremental increase in the standard deviation of the frailty index and phenotypic frailty scores were 1.23 (1.16–1.30), and 1.19 (1.12–1.27), respectively. The full-adjusted HRs (95% CIs) for depressive symptoms among prefrail and frail people, as defined by an index and phenotype, were 1.38 (1.22–1.57), and 1.30 (1.14–1.48), respectively. The HRs (95% CIs) for the incidence of depressive symptoms for each incremental increase in the standard deviation of the frailty index and phenotypic frailty scores were 1.23 (1.16–1.30), and 1.15 (1.08–1.30), respectively.

When setting depressive symptoms as an independent variable, the incidences of frailty defined by phenotype and index were 45 per 1,000 person years and 94 per 1,000-person year. As shown in **Table 3**, depressed participants had a higher risk of pre-frailty and frailty when assessed by the frailty index, although

TABLE 2 | Association between frailty and incidence of depressive symptoms.

	HR (95% CI)		Per SD increase
	Robust	Pre-frailty/frailty	
Frailty index			
Unadjusted	1 (Reference)	1.39 (1.23–1.58)	1.24 (1.17–1.31)
Model 1	1 (Reference)	1.38 (1.22–1.57)	1.23 (1.16–1.30)
Model 2	1 (Reference)	1.38 (1.22–1.57)	1.23 (1.16–1.30)
Phenotypic frailty			
Unadjusted	1 (Reference)	1.38 (1.21–1.56)	1.19 (1.12–1.26)
Model 1	1 (Reference)	1.38 (1.21–1.57)	1.19 (1.12–1.27)
Model 2	1 (Reference)	1.30 (1.14–1.48)	1.15 (1.08–1.22)

CI, confidence interval; HR, hazard ratio; SD, standard deviation. The crude model was conducted without any adjustment; Model 1 was adjusted for age, and sex; Model 2 was additionally adjusted for education level, smoking status, alcohol consumption, marital status, place of residence, income, participation in social activities, number of chronic diseases, retirement status, and sleep duration.

the risk was not statistically significant. The crude HRs (95% CIs) for the incidence of pre-frailty and frailty, as defined by the frailty index and phenotype among depressed patients, were 1.17 (0.98–1.39) and 1.47 (0.95–2.28), respectively. The HRs (95% CIs) for the incidence of pre-frailty and frailty, as assessed by the frailty index and phenotype, for each incremental increase in the standard deviation of the depressive symptoms scores, were 1.06 (0.996–1.12) and 1.33 (1.17–1.53), respectively. With adjustment for age and sex, the adjusted HRs (95% CIs) for the incidence of pre-frailty and frailty, as defined by the frailty index and phenotype among depressed patients, were 1.15 (0.96–1.37), and 0.98 (0.63–1.52), respectively. The HRs (95% CIs) for the incidence of pre-frailty and frailty, as assessed by the frailty index and phenotype, for each incremental increase in the standard deviation of the depressive symptoms scores, were 1.05 (0.99–1.11) and 1.14 (0.995–1.31), respectively. Moreover, the full-adjusted HRs (95% CIs) for the incidence of pre-frailty and frailty, as defined by the frailty index and phenotype among depressed patients, were 1.18 (0.98–1.41) and 0.96 (0.61–1.50), respectively. The HRs (95% CIs) for the incidence of pre-frailty and frailty, as assessed by the frailty index and phenotype for each incremental increase in the standard deviation of the depressive symptoms scores were 1.06 (0.99–1.13) and 1.12 (0.96–1.29), respectively.

Sensitivity Analysis Between Frailty and Depressive Symptoms in the Follow-Up Study

In agreement with the results from the entire study population, the sensitivity analysis showed that pre-frail or frail participants had a higher risk of depressive symptoms before and after adjustments for confounding factors, including age, sex, education level, smoking status, alcohol consumption, marital status, place of residence, income, participation in social activities, number of chronic diseases, retirement status, and sleep duration, when compared with the robust participants (**Supplementary Table 5**). The crude HRs (95% CIs) for depressive symptoms among pre-frail and frail participants, as assessed by the frailty index and phenotype, were 1.58 (1.39–1.81) and 1.17 (1.03–1.34), respectively. The depressive symptom HRs (95% CIs) for each incremental increase in standard deviation of the frailty index and phenotypic frailty scores were 1.22 (1.15–1.30) and 1.09 (1.03–1.16), respectively. After adjusting for age and sex, the HRs (95% CIs) for depressive symptoms among pre-frail and frail participants, as assessed by the frailty index and phenotype were 1.55 (1.36–1.77) and 1.19 (1.04–1.35), respectively. The depressive symptom HRs (95% CIs) for each incremental increase in standard deviation of the frailty index and phenotypic frailty scores were 1.21 (1.15–1.29) and 1.10 (1.03–1.17), respectively. The multivariate-adjusted HRs (95% CIs) for depressive symptoms among pre-frail and frail participants, as assessed by the frailty index and phenotype, were 1.55 (1.35–1.77) and 1.16 (1.02–1.32), respectively. The depressive symptoms HRs (95% CIs) for each incremental increase in standard deviation of the frailty index and phenotypic frailty scores were 1.22 (1.15–1.29) and 1.09 (1.02–1.16), respectively. When depressive symptoms were set as an independent variable (**Supplementary Table 6**), no significant relationship of existed between depressive symptoms and the incidence of frailty.

Using the ICLIFETEST procedure, the results were consistent with that of the main analysis. As shown in **Supplementary Table 7**, the crude HRs (95% CIs) for depressive symptoms among pre-frail and frail participants, as assessed by the frailty index and phenotype, were 1.44 (1.27–1.63) and 1.41 (1.24–1.60), respectively. With adjustment for age and sex, the HRs (95% CIs) for depressive symptoms among pre-frail and frail participants, as assessed by the frailty index and phenotype were 1.43 (1.26–1.62) and 1.42 (1.24–1.61), respectively. Moreover, the multivariate-adjusted HRs (95% CIs) for depressive symptoms among pre-frail and frail participants, as assessed by the frailty index and phenotype, were 1.44 (1.27–1.63) and 1.35 (1.19–1.54), respectively. However, considering the depressive symptoms as an independent variable, no significant relationship of existed between depressive symptoms and the incidence of frailty (**Supplementary Table 8**).

Moreover, for participants aged over 65, we got a similar result. As shown in **Supplementary Figure 3**, the multivariate-adjusted HRs (95% CIs) for depressive symptoms among pre-frail and frail participants (age over 65), as assessed by the frailty index and phenotype, were 1.25 (1.05–1.49) and 1.27 (1.06–1.53), respectively. Whereas considering depressive symptoms as an independent variable, the full-adjusted HRs (95% CIs) for the incidence of pre-frailty and frailty, as defined by the frailty index and phenotype among depressed patients, were 1.22 (1.00–1.49) and 0.92 (0.43–1.97), respectively.

TABLE 3 | Association between depressive symptoms and incidence of frailty.

	HR (95% CI)		Per SD increase
	Normal	Depression	
Frailty index			
Unadjusted	1 (Reference)	1.17 (0.98–1.39)	1.06 (0.996–1.12)
Model 1	1 (Reference)	1.15 (0.96–1.37)	1.05 (0.99–1.11)
Model 2	1 (Reference)	1.18 (0.98–1.41)	1.06 (0.99–1.13)
Phenotypic frailty			
Unadjusted	1 (Reference)	1.47 (0.95–2.28)	1.33 (1.17–1.53)
Model 1	1 (Reference)	0.98 (0.63–1.52)	1.14 (0.995–1.31)
Model 2	1 (Reference)	0.96 (0.61–1.50)	1.12 (0.96–1.29)

CI, confidence interval; HR, hazard ratio; SD, standard deviation. The crude model was conducted without any adjustment; Model 1 was adjusted for age, and sex; Model 2 was additionally adjusted for education level, smoking status, alcohol consumption, marital status, place of residence, income, participation in social activities, number of chronic diseases, retirement status, and sleep duration.

Subgroup Analysis Between Frailty and Depressive Symptoms in the Cohort Study

Tables 4, **5** present the subgroup analysis of the association between frailty and incidence of depressive symptoms, according to sex and place of residence. No significant interaction effects of frailty were detected with sex, or the place of residence. Pre-frailty and frailty participants, as assessed by the frailty index,

TABLE 4 | Subgroup analysis of the association between frailty and incidence of depressive symptoms according to the sex.

	HR (95% CI)		$P_{interaction}$	Per SD increase	$P_{interaction}$
	Robust	Pre-frailty/frailty			
Frailty index					
Males	1 (Reference)	1.27 (1.05–1.53)	0.25	1.28 (1.15–1.42)	0.71
Females	1 (Reference)	1.48 (1.24–1.76)		1.28 (1.16–1.42)	
Phenotypic frailty					
Males	1 (Reference)	1.45 (1.19–1.75)	0.17	1.26 (1.13–1.41)	0.87
Females	1 (Reference)	1.25 (1.05–1.50)		1.16 (1.05–1.29)	

CI, confidence interval; HR, hazard ratio; SD, standard deviation. The model was adjusted for age, education level, smoking status, alcohol consumption, marital status, place of residence, income, participation in social activities, number of chronic diseases, retirement status, and sleep duration.

TABLE 5 | Subgroup analysis of the association between frailty and incidence of depressive symptoms according to the place of residence.

	HR (95% CI)		$P_{interaction}$	Per SD increase	$P_{interaction}$
	Robust	Pre-frailty/frailty			
Frailty index					
Urban	1 (reference)	1.53 (1.21–1.94)	0.37	1.37 (1.20–1.56)	0.36
Rural	1 (reference)	1.33 (1.14–1.55)		1.25 (1.14–1.36)	
Phenotypic frailty					
Urban	1 (reference)	1.35 (1.07–1.72)	0.65	1.18 (1.02–1.36)	0.80
Rural	1 (reference)	1.28 (1.10–1.50)		1.18 (1.08–1.29)	

CI, confidence interval; HR, hazard ratio; SD, standard deviation. The model was adjusted for age, sex, education level, smoking status, alcohol consumption, marital status, income, participation in social activities, number of chronic diseases, retirement status, and sleep duration.

had a higher risk of depressive symptoms [HRs (95% CIs), 1.27 (1.05–1.53) for males; 1.48 (1.24–1.76) for females; 1.53 (1.21–1.94) for urban residents; and 1.33 (1.14–1.55) for rural residents]. The HRs (95% CIs) for the incidence of depression for each incremental increase in the standard deviation for frailty index scores were 1.28 (1.15–1.42) for males, 1.28 (1.16–1.42) for females, 1.37 (1.20–1.56) for urban residents, and 1.25 (1.14–1.36) for rural residents. Pre-frail and frail participants assessed by phenotype had a higher risk of depressive symptoms [HRs (95% CIs), 1.45 (1.19–1.75) for males; 1.25 (1.05–1.50) for females; 1.35 (1.07–1.72) for urban residents; and 1.28 (1.10–1.50) for rural residents). The HRs (95% CIs) for the incidence of depressive symptoms for each incremental increase in the standard deviation for phenotypic frailty scores were 1.26 (1.13–1.41) for males, 1.16 (1.05–1.29) for females, 1.18 (1.02–1.36) for urban residents, and 1.18 (1.08–1.29) for rural residents. The results of subgroup analysis between depressive symptoms and the incidence of frailty were consistent with the entire population (data not shown). Thus, no significant interaction effects of depressive symptoms were detected with sex, or the place of residence.

DISCUSSION

The current cohort study first explored the bidirectional relationship between frailty and depressive symptoms in older Chinese adults. The cross-sectional study showed a bidirectional association between frailty and depressive symptoms, but the cohort study only reported that frailty was a risk predictor for subsequent depressive symptoms.

As previously reported, frailty is associated with increased mortality, hospitalization, falls, and admission to long-term care facilities, all of which may lead to disability or functional dependence, which in turn may contribute to the development of depressive symptoms (Woods et al., 2005; Hoogendijk et al., 2019). In agreement with our findings, Brown et al. (2020) reported that phenotypic frailty was related to depressive symptoms among 134 US residents. Similarly, an increased odds of depressive symptoms were shown in pre-frail [OR (95% CI), 3.82 (3.72–3.93)] and frail [OR (95% CI), 11.23 (10.89–11.58)] older Mexican adults (≥60 years of age) than non-frail older Mexican adults (Sánchez-García et al., 2014). Moreover, several prospective studies have shown that the presence of frailty at baseline predicts new-onset incident depressive symptoms (Feng et al., 2014; Collard et al., 2015; Makizako et al., 2015). In contrast, physical activity protects against depressive symptoms among older adults from south and southeast Asia (Kadariya et al., 2019). As a result, these findings suggest that frailty is a longitudinal predictor of depressive symptoms.

Depressive symptoms, in contrast, is often accompanied by a sedentary lifestyle, physical inactivity, poor social relationships, slow gait speed, risk of falls, weight loss, and malnutrition, thus making depressive symptoms a predictor of frailty, which in turn can exacerbate the typical emotional symptoms of depression, including sadness, anhedonia, and helplessness (Paulson and Lichtenberg, 2013; Soysal et al., 2017). Using a cross-sectional design, studies from Europe and the United States have also indicated that older people with depressive symptoms are more likely to be frail than those without depressive symptoms (Chang et al., 2010; Gurina et al., 2011; Jurschik et al., 2012; Collard et al., 2014; Lohman et al., 2014; Pegorari and Tavares, 2014; Sanchez-Garcia et al., 2014; Espinoza and Hazuda, 2015), whereas one study from northeast Brazil showed a negative association between depressive symptoms and frailty in community-dwelling older adults [OR (95%

CI), 1.782 (0.820–3.870)] (Sousa et al., 2012). The discrepancy in findings may vary with different methods of assessing depressive symptoms and frailty, and the composition of the study population. Moreover, prospective studies from Australia, the United States, and six Latin American countries have shown that depressive symptoms might be an adverse consequence of frailty among older adults (Woods et al., 2005; Lakey et al., 2012; Lohman et al., 2014; Almeida et al., 2015; Prina et al., 2019). A study from the Rugao Longevity and Aging Study conducted in China investigated the association between depression symptoms and frailty among 1,168 Chinese adults > 70 years of age with a cross-sectional and 3-year follow-up analysis (Zhang et al., 2020). It was found that depressive symptoms are associated with the prevalence of pre-frailty and frailty. In addition, depressive symptoms were related to a 2.79-fold increased risk of the 3-year incidence of frailty. We also reported a positive relationship between depressive symptoms and frailty in the cross-sectional study, but no significant association existed between baseline depressive symptoms and incidence of frailty for phenotypic frailty or frailty index. The inconsistent findings may be partially attributed to ethnicity and population differences, as well as the assessment of frailty. Further studies with large sample are warranted, especially in China.

Frailty and depressive symptoms often independently reflect the physical and mental health of individuals. A strong link has been demonstrated between physical and mental health (Mezuk et al., 2012). In a sense, depressive symptoms is a sign of psychological frailty (Fitten, 2015). Depressive symptoms and physical frailty share several clinical characteristics, such as loss of energy, fatigue, poor sleep, and reduced interest, which may attribute to common risk factors and pathophysiologic pathways. Aging, is often accompanied by the appearance of chronic, sterile, low-grade inflammation, which may be involved in the pathogenesis of age-related diseases (Franceschi et al., 2018). Increased inflammatory cytokines are not only closely related to decreased muscle mass and strength, but also have a negative impact on central dopaminergic function, which may lead to fatigue, motor slowing, and depressive symptoms (Brown et al., 2016). Growing evidence has shown that higher levels of circulating inflammatory cytokines (C-reactive protein and IL-6) have been confirmed in pre-frailty and frailty participants (Soysal et al., 2016; Ma et al., 2018), as well as depressed patients (Howren et al., 2009; Valkanova et al., 2013). Moreover, mitochondrial dysfunction, which has been reported in several neurodegenerative diseases, including depressive symptoms, might be another explanation for the increased circulating cytokines (Bansal and Kuhad, 2016). Muscle biopsies obtained from depressed participants were been shown to have decreased ATP production. Impaired mitochondrial respiration in peripheral blood mononuclear cells has also been reported in depressed patients (Brown et al., 2016). Taken together, these markers have a strong relationship with frailty syndrome symptoms (Arauna et al., 2020).

This study had several strengths. First, the bidirectional longitudinal association between frailty and depressive symptoms we analyzed added the evidence in Chinese old adults, which helps identifying the sequence of physical and psychological frailty and thus provide insights into interventions for adverse health outcomes. Second, two definitions were used to evaluate frailty in the present study (phenotype and an index), which may reflect different dimensions of frailty. Third, because there may be an overlap between frailty and depressive symptoms, we further excluded those items and performed subgroup analyses. The findings were consistent with the entire population, suggesting the reliability of the results. Some limitations should be acknowledged. First, although depressive symptoms was assessed by a self-rated questionnaire (CES-D), the CES-D has been validated (Chen and Mui, 2014) and widely applied (Ni et al., 2017; Luo et al., 2018; Liu et al., 2020; Shao et al., 2021) in this cohort. Second, the frailty index items were modified based on the questionnaire because an evaluation can be performed if a questionnaire contains health variables and sufficient valid health variables (Searle et al., 2008). Third, due to the limited information (physical examination indicators) for the definition of phenotypic frailty in 2018, the association between baseline depressive symptoms and the incidence of phenotypic frailty was only evaluated in follow-up appointments from 2011 to 2015. Thus, whether the findings in our study can be extended to clinical practice remains to be explored. Moreover, the exclusion of a large number of adults makes the study sample may not be representative of Chinese adults. Prospective studies among Chinese adults are still warranted. Additionally, the time points of frailty or depressive symptoms incidents were only calculated by the time interval of follow-up, which may not be the exact time of points and makes the results misestimated, given that limited manpower and resources make it difficult to conduct more frequent follow-up investigations.

CONCLUSION

A positive bidirectional association between depressive symptoms and frailty status has been demonstrate in older Chinese adults. More importantly, given that frailty is a risk factor for later depression, healthcare practitioners should be increasingly aware of the relationship, to avoid the co-existing conditions of frailty and depressive symptoms. Further researches are still warranted to clarify the causal relationship between these two conditions among Chinese adults.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: http://charls.pku.edu.cn/index.html.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Peking University's Ethical Committees. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LC: conceptualization, formal analysis, visualization, and writing – original draft. YZ, HL, and MS: writing – review and editing. YW: conceptualization, resources, writing – review and editing, supervision. YX: conceptualization, resources, writing – review and editing, supervision, funding acquisition. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.791971/full#supplementary-material

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Associations Between Frailty and Inflammation, Physical, and Psycho-Social Health in Older Adults: A Systematic Review

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Frailty is a complex geriatric syndrome with multifactorial associated mechanisms that need to be examined more deeply to help reverse the adverse health-related outcomes. Specific inflammatory and physical health markers have been associated with the onset of frailty, but the associations between these factors and psycho-social health outcomes seem less studied. This systematic review aimed to identify, in the same study design, the potential associations between frailty and markers of inflammation, and physical or psycho-social health. A literature search was performed from inception until March 2021 using Medline, Psycinfo, and EMBASE. Three raters evaluated the articles and selected 22 studies, using inclusion and exclusion criteria (n = 17,373; 91.6% from community-dwelling samples). Regarding biomarkers, 95% of the included studies showed significant links between inflammation [especially the higher levels of C-reactive protein (CRP) and interleukin-6 (IL-6)], and frailty status. Approximately 86% of the included studies showed strong links between physical health decline (such as lower levels of hemoglobin, presence of comorbidities, or lower physical performance), and frailty status. At most, 13 studies among the 22 included ones evaluated psycho-social variables and mixed results were observed regarding the relationships with frailty. Results are discussed in terms of questioning the medical perception of global health, centering mostly on the physical dimension. Therefore, the development of future research studies involving a more exhaustive view of frailty and global (bio-psycho-social) health is strongly encouraged.

Keywords: frailty, older adults, biomarkers, physical health, psycho-social health

INTRODUCTION

Frailty is commonly defined as a biologic syndrome correlated with the loss of homeostasis and increased vulnerability to stressors (Fried et al., 2001). While other conceptual models have been suggested (Rockwood and Mitnitski, 2007; Panza et al., 2015), Fried's phenotype represents the most frequently used one to measure frailty (Fried et al., 2001). Fried's phenotype focuses on a

unidimensional physical construct and defines frailty by the presence of at least three of the five following elements: unintentional weight loss, low grip strength, exhaustion, slow gait speed, and low physical activity level (pre-frailty status is defined by the presence of one or two criteria). According to this phenotype, approximately 10% of people over 65 years old and 25–50% of those over 85 years are being frail (Fried et al., 2001). A more recent meta-analysis suggested that community-dwelling older adults were prone to developing frailty, with a pooled incidence rate being 43.4 cases per 1,000 person-years (Ofori-Asenso et al., 2019). This frequent age-related syndrome has an important negative impact on health outcomes as it is commonly associated with an increased risk of incident falls, worsening mobility or disability, hospitalization, and death (Fried et al., 2001). On a positive note, research studies have shown that frailty was a dynamic process, with possible fluctuations between frailty states for individuals (Pollack et al., 2017; Trevisan et al., 2017). The influence of the life trajectories of older adults will influence the emergency and impact of frailty situations, increasing the inter- and intra-individual variability. To better understand frailty mechanisms is then crucial to identify as early as possible relevant modifiable factors and help create efficient and personalized interventions (mostly including physical exercise, but also nutritional and cognitive trainings) to delay or reverse frailty.

Regarding biological mechanisms, the development and progression of frailty have often been associated with a systemic inflammatory state. The recent systematic review and meta-analysis from Soysal et al. (2016) compared the inflammatory profile of frail and pre-frail with non-frail older subjects (n = 23,910, mean age of 75.2 $\pm$ 6.1 years). Results of cross-sectional studies highlighted specific biomarkers associated with frailty: frail and pre-frail individuals had significantly higher levels of pro-inflammatory cytokines, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), as well as the higher levels of fibrinogen and white blood cells (WBC) counts vs. non-frail participants. Specific pathways leading to frailty and involving these pro-inflammatory biomarkers have been studied (e.g., metabolically active fat depots, activation of common molecular pathways in several interactive physiological systems, and inflammatory cascades; as shown in ref. Walston et al., 2006) indicating that inflammation seems to be an important pathophysiological change associated with frailty.

Inflammatory biomarkers could also play an indirect role in the presence of physical declines associated with frailty (more specifically with physical frailty according to Fried's phenotype). Among these age-related declines, sarcopenia (i.e., reduced muscle mass associated with limited mobility; Morley et al., 2011) has been considered as an important parameter of physical frailty. As noted by Landi et al. (2015), sarcopenia might be considered both as the biological substrate for the development of physical frailty (particularly low grip strength, slow gait speed, and low physical activity level), and the physiopathologic pathway which could result in future adverse health outcomes (mobility disability, falls, loss of independence, . . .). Moreover, previous research studies have shown that sarcopenia was characterized by the increased levels of pro-inflammatory cytokines, such as TNF-α, IL-6, or CRP (Vatic et al., 2020), which could directly or indirectly speed up frailty. Inversely, the age-related significant rise of inflammatory markers (also known as "*inflammaging*," as shown in ref. Franceschi et al., 2000) could predispose older individuals to sarcopenia (Liguori et al., 2018) and frailty.

The associations between physical frailty, inflammation, and physical health, while being not fully understood yet, are well-documented in the aging literature. Nevertheless, frailty is more than just physical declines. It represents a multidimensional syndrome involving physical, functional, cognitive, and psychosocial interactions (e.g., cumulative deficit model by Rockwood and Mitnitski, 2007). Psycho-social health markers do need to be taken into greater account in studies examining the markers of (physical) frailty. In their review, Zaslavsky et al. (2013) mentioned various psycho-social indicators associated with frailty, such as cognition, depressive symptoms, or lifestyle factors (such as low-educational level and poor socioeconomic conditions). Frailty and specific psycho-social health outcomes (such as cognitive decline, as shown in ref. de Morais Fabrício et al., 2020 or depressive symptoms, as shown in ref. Zalli et al., 2016) do share common risk factors, such as increased pro-inflammatory cytokines but future studies would be needed to specifically evaluate the potential associations between inflammatory markers and various psycho-social outcomes in frail older adults. This is particularly important considering the protective role of some psychosocial factors against the onset and the worsening of frailty among older adults. For example, a recent review (Sardella et al., 2020) showed that education, occupation, premorbid intelligence quotient, and leisure time activities (as cognitive reserve factors) were able to interact with the frailty status of older adults.

Frailty is a complex geriatric syndrome with multifactorial associated mechanisms that need to be more deeply examined. One possible and innovative avenue of research to better understand the direct and indirect contributions to and of frailty would be to observe the relationships between this syndrome and inflammation/physical health/psycho-social health in the same study design. Therefore, the purpose of this original study was to perform a systematic review on cross-sectional studies about frailty in older adults to identify potential associations with the markers of inflammation, and with physical or psycho-social health.

METHODS

Study Design

A systematic review was conducted, following Mulrow's recommendations (Mulrow, 1994), to describe the current state of knowledge regarding the associations between frailty and inflammatory, physical, and psycho-social outcomes to provide recommendations for future research studies.

Search Strategy

Systematic literature research from inception until March 2021 was conducted using Medline, Psycinfo, and EMBASE with the following search terms: (frail* [MeSH Terms]) AND

((“inflam*”[MeSH Terms] OR “inflam*”[All Fields])) AND (((Health) OR (Health Status) OR (Mental Health))).

Selection of Studies

Study selection was conducted in two steps. First, three independent authors (KP, WG, and NB) reviewed all titles and abstracts using the following inclusion and exclusion criteria. Studies involving: (1) older adults (population with a mean age >65 years old), (2) a specific measure of frailty, and (3) specific inflammatory biomarkers were included. Duplicates, studies that were not in English or French, and studies that were not cross-sectional (longitudinal, interventional or protocol studies, reviews, book chapters, comments, or editorials) were excluded. Second step involved retrieving the full text of the selected papers, and filtering them for relevance using an additional criterion: to be included, papers must evaluate the potential associations between frailty and either inflammation or physical health or psychosocial health. Finally, the three reviewers discussed the papers and agreed on final inclusion.

Data Collection

The following information has been extracted from the selected studies: author(s) and year of publication, characteristics of participants (such as, size, mean age, and percentage of men and women), and measures used to characterize frailty, types of inflammatory biomarkers, and physical and/or psycho-social health (data summarized in **Supplementary Table 1**). Two of the co-authors (WG and KP) screened all the markers used in the included studies to highlight specific inflammatory biomarkers. Other biomarkers having a role in the inflammatory process (such as oxidative stress markers or muscle protein turnover) were then considered as the markers of older adults' general physical health. The inter-judge procedure (involving the three co-authors WG, NB, and KP) was also performed for all physical and psychosocial health outcomes included in the studies. Mean results on the potential associations between the three outcomes (inflammation, physical health, and psycho-social health) with frailty, and specific relationships among the three outcomes (when data were available) are presented in **Supplementary Table 2**.

RESULTS

The flowchart (**Figure 1**) shows the number of studies identified from databases (n = 650). After removing duplicates and screening articles based on abstracts, 90 records remained. The full-text articles reading led to the exclusion of 68 studies (2 duplicates, 9 off-topic, and 57 studies that did not evaluate the potential associations between frailty and inflammation/physical health/psycho-social health). Accordingly, 22 studies met the pre-established criteria and were included in this systematic review.

Main Characteristics of the Studies Included

Supplementary Table 1 shows the main characteristics (population and measurements) of the studies included.

Thirteen of the 22 included studies (59%) involved a community-dwelling sample. Six studies involved vulnerable older adults, such as followed-up for chronic diseases (Boxer et al., 2008; Wu et al., 2009; Lee Y. P. et al., 2016; Huang et al., 2020), veteran (Van Epps et al., 2016), and socially vulnerable older adults (Nascimento et al., 2018). The three remaining studies involved institutionalized (Fernández-Garrido et al., 2014) and hospitalized (Ma et al., 2018; Yang et al., 2018) older adults.

Included studies represent a total of 17,373 older adults [n ranging from 30 (Leng et al., 2002) to 4,735 (Walston et al., 2002)]. The community-dwelling sample contains 15,912 older adults (91.6%), while the total number of vulnerable older adults and inpatients were respectively 854 (4.9%) and 607 (3.5%).

It should be noted that five studies (Blaum et al., 2009; Fried et al., 2009; Chang et al., 2012; Silva et al., 2014; Van Epps et al., 2016) did not specify the mean age of their samples. Taking into account the 17 other studies, the total mean age of the included older adults was 75.34 years [means ranging from 65.5 (Lee W. J. et al., 2016) to 84.9 years (Leng et al., 2002)]. The total mean age of inpatients and institutionalized older adults (79.53, n = 3 studies) were higher than the vulnerable older adults one (75.67; n = 5 studies), which was also higher than the total mean age of the community-dwelling older adults (74.24; n = 9 studies).

Regarding sex ratio, included studies involved a small majority of older women, with a total mean percentage of women of 58.4%. Of important note, five studies (Leng et al., 2007; Blaum et al., 2009; Fried et al., 2009; Chang et al., 2012; Fernández-Garrido et al., 2014) included a 100%-women sample while only one included a 100%-men sample (Lee W. J. et al., 2016). Comparing sex ratio between the different samples, a lower percentage of older women in the studies involving vulnerable older adults (39.3% of women) compared with inpatients (54.6%) and community-dwelling older adults (67.8%) studies was noted.

Measures

Data regarding measurements are summarized in **Supplementary Table 1**.

While measures of frailty and inflammation were mandatory for studies to be included in this systematic review (first step of the studies selection), physical and psychosocial health measures were optional (second step of the studies selection). Data are summarized in **Supplementary Table 1**.

Regarding frailty, 100% of the studies used Fried criteria (weight loss, exhaustion, weakness, slow walking speed, and low physical activity; Fried et al., 2001) to characterize frailty. A large majority of the studies (17/22, 77.3%) divided their sample into three groups: non-frail, pre-frail (one or two criteria), frail (≥three criteria) based on the Fried phenotype of frailty (Fried et al., 2001). Three studies (Leng et al., 2002; Chang et al., 2012; Yang et al., 2018) divided their sample into two groups (non-frail vs. frail older adults) with two of them (Chang et al., 2012; Yang et al., 2018) considering non-frail status as having from 0 to 2 Fried criteria. One study divided the included sample into four frailty groups (sub-dividing the pre-frail group into a low frailty group—older adults having one criterion—and a medium frailty group—two criteria—Boxer et al., 2008). Last, one included study

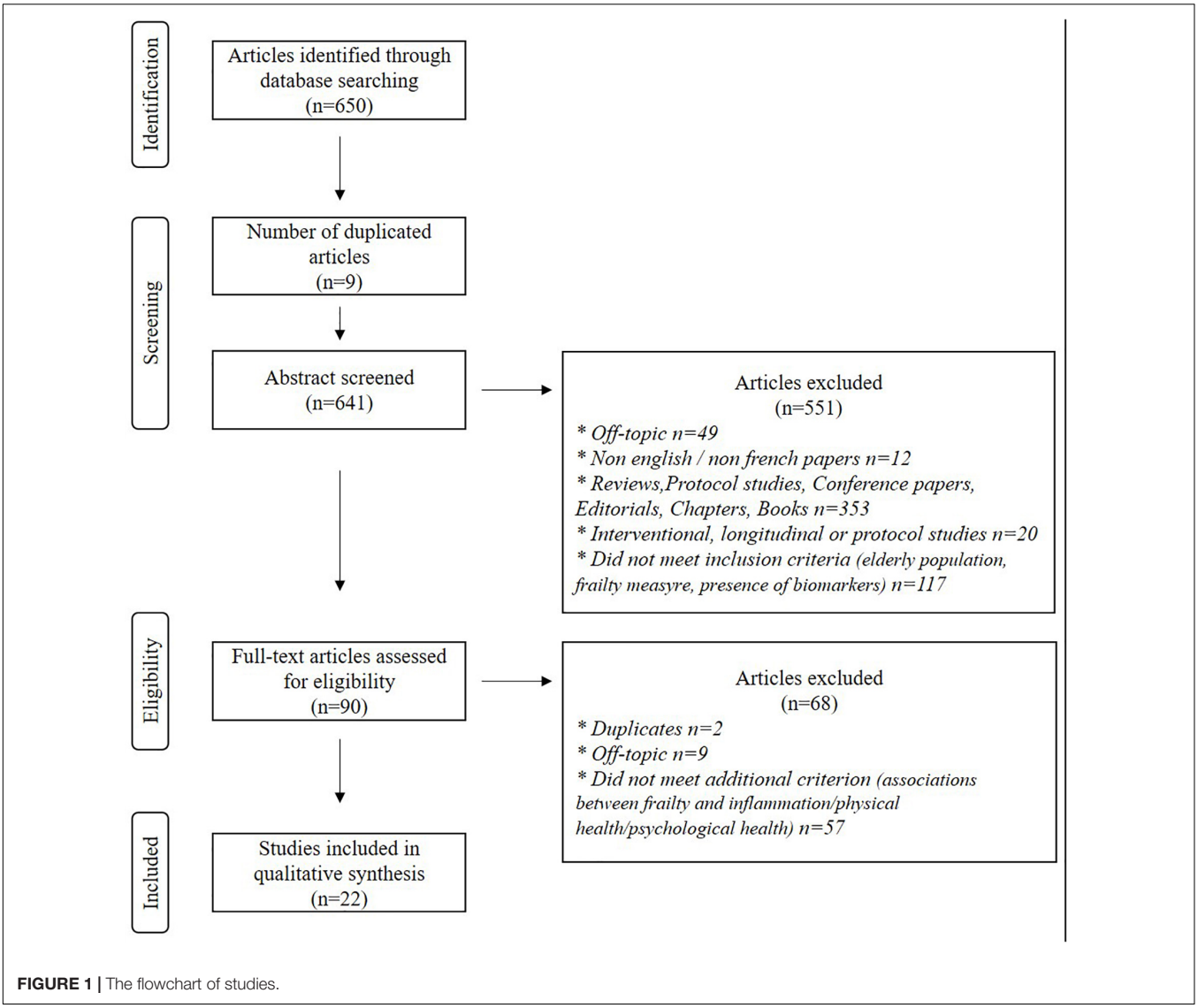

FIGURE 1 | The flowchart of studies.

(Fernández-Garrido et al., 2014) chose to specifically consider frailty score as a continuous variable only, and five individually examined the five frailty criteria (Fernández-Garrido et al., 2014; Silva et al., 2014; Ma et al., 2018; Semmarath et al., 2019; Huang et al., 2020).

Regarding inflammation, among the 22 included studies, 15 (68.2%) studies measured Interleukin (IL; mostly IL-6) levels, and/or C-reactive protein (CRP), or high sensitive CRP (hsCRP) levels, 8 (36.4%) studies included a white blood cell (WBC) count, 5 (22.7%) studies examined tumor necrosis factors (TNFs; mostly TNF-α), and 3 studies (13.6%) included measures of hemostatic factors (fibrinogen, Factor VII, Factor VIII, transferrin, and haptoglobin). More sporadically, vascular adhesion protein-1 (VAP-1; Huang et al., 2020) and erythropoietin (EPO; Silva et al., 2014) were also measured. Of important note, 3 studies also calculated an inflammation index score (Chang et al., 2012; Van Epps et al., 2016; Ma et al., 2018).

The totality of the included studies evaluated physical health. The following measurements were considered falling under physical health: biochemical measurement (n = 17 studies, 77.3%), anthropometric measures (n = 13, 59%), comorbidities (n = 14, 63.7%), smoking and alcohol status (n = 10, 45.5%), medications (n = 6, 27.3%), physical performance (physical activity, grip strength, gait speed, energy level, and fine motor speed; n = 4, 18.2%), blood pressure (n = 2; Lee Y. P. et al., 2016; Ma et al., 2018), past medical history (n = 2; Hsieh et al., 2018; Semmarath et al., 2019), nutritional status (n = 1; Hsieh et al., 2018), falls or the risk of falls (n = 2; Fernández-Garrido et al., 2014; Darvin et al., 2014), overnight hospital admissions (n = 1; Zhu et al., 2016).

In the 22 included studies, 13 (59%) studies involved psychosocial variables. Among them, 10 (77%) included lifestyle characteristics (years of education, marital status, and capital income) of older adults, 7 (53.8%) effective measures, and 6 (46.1%) measured cognition (MMSE, memory loss, and

subjective cognitive decline). Behavioral disorders and autonomy (i.e., functional status) were also evaluated in one study (Fernández-Garrido et al., 2014).

Significant Associations Between Frailty and the Three Specific Outcomes

Supplementary Table 2 shows all the found associations between frailty and specific outcomes included in this systematic review.

Associations Between Frailty and Inflammatory Biomarkers

Only one study did not find a significant relationship between frailty and inflammation (Lee Y. P. et al., 2016). Among the 21 left studies, 13 of them (62%) found significant links between frailty and the totality of the used inflammatory biomarkers; the remaining studies showed links between frailty and specific inflammatory biomarkers. IL-6 and CRP levels were significantly and positively associated with frailty in, respectively, 15 (100%) and 12 (80%) of the studies using these cytokines biomarkers. Four studies over the 8 including WBC levels significantly and positively linked this inflammatory measure with frailty (50%). TNFs were significantly and positively associated with frailty in 2 of the 5 studies (40%) using these biomarkers. Two studies over the three measuring hemostatic factors found a significant and positive association with frailty (66%). The studies using more sporadic inflammatory measures found mixed results: while VAP-1 was significantly and positively associated with frailty in Huang et al. (2020), EPO did not correlate with frailty in Silva et al. (2014). All the studies using an inflammation index score showed significant and positive relationships with frailty.

A large majority of studies comparing an inflammation between frailty groups (n = 12/13) showed that frail individuals had significantly higher levels of pro-inflammatory cytokines (CRP, IL-6, and TNF), WBC, hemostatic factors, and VAP-1 levels, compared with non-frail, and, to a less extent, pre-frail older adults.

Nine studies evaluated the potential links between frailty and inflammation with correlations and regressions analyses. All of them showed significant positive correlations between specific biomarkers and a higher frailty phenotype score (Boxer et al., 2008; Fernández-Garrido et al., 2014) or and the likelihood of being pre-frail or frail (Leng et al., 2007; Blaum et al., 2009; Wu et al., 2009; Chang et al., 2012; Darvin et al., 2014; Silva et al., 2014; Lee W. J. et al., 2016).

Among the five studies evaluating individual frailty criteria, three of them found direct links between the low grip strength criterion and specific biomarkers (IL-6 and CRP in Semmarath et al., 2019; WBC count in Fernández-Garrido et al., 2014; VAP-1 levels in Huang et al., 2020), and two of them between the exhaustion criterion and specific biomarkers (IL-6 and IL-1ra levels in Silva et al., 2014; VAP-1 levels in Huang et al., 2020). A study also linked the low physical activity level criterion with WBC count (Fernández-Garrido et al., 2014). Finally, one study associated the slow gait speed criterion with higher IL-6 levels (Ma et al., 2018).

Associations Between Frailty and Physical Measures

Among the 22 studies evaluating physical health outcomes, 3 of them did not find any significant association with frailty at all (Leng et al., 2007; Fernández-Garrido et al., 2014; Van Epps et al., 2016).

Regarding biochemical measures, over 17 studies including them, 14 reported significant associations with frailty (82.3%). These studies mainly showed that frail older adults had lower levels of red blood cell (n = 4), albumin (n = 3), vitamin D (n = 1), AST and ALT (n = 2), urea (n = 1), reticulocyte (n = 1), intracellular adhesion molecule-1 (n = 1), and higher levels of creatinine (n = 2), cholesterol (n = 2), procalcitonine (n = 1), oxidative stress (8-OHdG, dROM, TTL; n = 2), zinc alpha2-glycoprotein (n = 1), triglyceride (n = 1), compared with non-frail older adults. Mixed results were found for hemoglobin but a majority of the studies (4/7) showed lower levels for frail patients, compared with non-frail older adults (one reported higher levels of hemoglobin for frail individuals, the other two did not find significant differences). Among the 13 studies taking into account of the anthropometric measures, 4 reported a significant relationship with frailty (30.8%), with higher BMI values associated with frail status. Twelve of the fourteen studies measuring comorbidities reported a link between the presence of specific diseases (mostly cardiovascular disease, diabetes, hypertension, arthritis, and stroke) and frailty (85.7%). Among the 10 studies measuring smoking and alcohol status, 3 reported significant associations (30%), with more current and former smokers in the frail groups (Saum et al., 2015; Lee W. J. et al., 2016) and more drinkers in non-frail and pre-frail older adults (Saum et al., 2015; Semmarath et al., 2019). Two studies over the six measuring number of medications (33.3%) reported a significant relationship with frailty (statins and thiazolidinediones; Lee Y. P. et al., 2016; Huang et al., 2020). Over the four studies evaluating specific physical measures, all of them (100%) reported a significant association with frailty, with a global lower physical performance associated with frailty status (Fried et al., 2009; Darvin et al., 2014; Ma et al., 2018; Nascimento et al., 2018). More sporadically, the few studies evaluating past medical history (n = 2), nutritional status (n = 1), and overnight hospital admissions (n = 1), all showed a significant relationship with frailty.

Regarding analyses performed on individual frailty criteria (n = 5 studies), only one reported a significant relationship with physical health measures (Silva et al., 2014). Higher values of Red blood cell Distribution Width (RDW) (measuring the variation in red blood cell size) were associated with the presence of exhaustion and slow gait speed criteria while the lower levels of reticulocyte increasing the change of being positive for the low physical activity criterion.

Associations Between Frailty and Psycho-Social Measures

Among the 13 studies measuring psycho-social variables, 3 of them did not find any significant association with frailty at all (Darvin et al., 2014; Fernández-Garrido et al., 2014; Ma et al., 2018); 6 studies linked all their used measures with frailty (Leng et al., 2007; Wu et al., 2009; Chang et al., 2012;

Lee W. J. et al., 2016; Hsieh et al., 2018; Yang et al., 2018), and 4 studies found partial links (associations between frailty and specific psycho-social measures; Blaum et al., 2009; Zhu et al., 2016; Nascimento et al., 2018; Semmarath et al., 2019).

Regarding lifestyle characteristics, 5 of the 10 studies including these measures (50%) found significant relationships with frailty. Results showed that frail and pre-frail participants were less educated than non-frail older adults, but mixed results were found considering marital status (only one over the five studies measuring this variable found that frail older adults were more likely to be unmarried compared with non-frail individuals; Yang et al., 2018). Regarding affective status, three of the seven studies including this variable (43%) found significant differences in the prevalence of depressive symptoms between frailty groups (Wu et al., 2009; Chang et al., 2012; Nascimento et al., 2018, with more depressive symptoms in frail compared with non-frail older adults). Among the six studies evaluating the cognitive status, three of them (50%) found significant differences between frailty groups, with frail participants having lower cognitive scores (Chang et al., 2012; Hsieh et al., 2018; Semmarath et al., 2019) or higher cognitive subjective decline (Hsieh et al., 2018) than non-frail older adults.

Total Number of Associations Between Frailty and Specific Outcomes

Among the 22 included studies, 9 of them (41%) found significant associations between frailty status and the 3 inflammatory/physical/psycho-social measures. Ten studies (45.5%) found a double-association with nine of them significantly linked frailty with inflammation and physical health measures while only one linked frailty with inflammation and psycho-social health measures (Leng et al., 2007). Finally, three studies found a single significant association, with two studies showing a relationship between frailty and inflammation (Fernández-Garrido et al., 2014; Van Epps et al., 2016) while the other one found a link between frailty and physical health markers (Lee Y. P. et al., 2016). Of important note, these three studies included samples composed of vulnerable outpatients or institutionalized older adults.

Relationships Between Inflammation, Physical, and Psycho-Social Health Outcomes

When available, data regarding relevant associations between specific outcomes included in this systematic review have been summarized in **Supplementary Table 2**.

Among the 22 included studies, 7 (31.8%) studies reported results on relationships between inflammation, physical health, or psycho-social health (associated or not with the relationship with frailty). Independency between specific factors was found in three studies (subjective cognitive decline and inflammation in Hsieh et al., 2018; ICAM-1 and IL-6 in Lee W. J. et al., 2016; and WBC and all geriatric assessments in Fernández-Garrido et al., 2014). Significant relationships were found between inflammatory and physical health markers in three studies (Boxer et al., 2008: lower hsCRP and IL-6 levels correlated with intact parathyroid hormone levels; Saum et al., 2015: positive correlations between markers of oxidative stress; Zhu et al., 2016: the higher levels of hsCRP associated with overnight hospital admission) while a physical health outcome (HbA1c) was negatively correlated with life-style characteristics (educational level) in one study (Blaum et al., 2009).

DISCUSSION

This original systematic review of the aging literature examined the potential associations between frailty states and inflammatory, physical, and psycho-social markers of health.

The population included in this review is largely composed of community-dwelling older adults (over 90%). The main focus of cross-sectional studies on this specific elderly population is not surprising: due to its dynamic process, the frailty syndrome can be more easily reversed if interventions target older adults before major clinical events (such as emergency room admissions or hospitalizations; as shown in ref. Vellas et al., 2013). To better understand frailty mechanisms in this key population is thus of great interest. Nevertheless, more studies involving frail older adults with multi-system impairments would also be helpful to further propose the best treatment, related to each independent prognosis' condition (i.e., frailty syndrome vs. other specific comorbidities; Fried et al., 2004; Hoogendijk et al., 2019).

While, decades ago, the World Health Organization (WHO) defined health as "a state of complete physical, mental, and social wellbeing and not merely the absence of disease or infirmity" (Shimkin, 1946), aging research and clinical studies still perceive health from a medical point of view, centering mostly on the physical dimension of health. This medical view is represented in included measures of the main outcomes of this systematic review. While different tools exist to clinically measure frailty in older adults (depending on frailty approaches; e.g., Rockwood and Mitnitski, 2007; Panza et al., 2015), all the included studies have used Fried's criteria, a fast and easy-to-use frailty measure, frequently employed in medical care. Regarding inflammatory biomarkers, a large majority of the included studies, whatever the sample of older adults, measured pro-inflammatory cytokines (CRP, IL-6, and TNF) and WBC, also frequently quantified in medical units. Moreover, the totality of the included studies measured physical health through various domains (e.g., biochemical measurement, anthropometric measures, comorbidities, and physical performance), while a lower number of studies (59%) included a psycho-social health assessment.

Main results on the associations between *frailty and inflammation* highlighted the central role of specific cytokines in this geriatric syndrome. The totality of included studies measuring IL-6 level and 80% of the studies involving CRP showed that frail older adults had higher levels of both of these biomarkers compared with non-frail participants. These results were confirmed in studies with regression analyses, even if the different methods involved in the odd-ratios (*OR*s) calculations made the comparisons more complex to do (as shown in refs. Leng et al., 2007 vs. Lee W. J. et al., 2016). These overall results regarding specific inflammatory biomarkers,

also found in a recent meta-analysis (Marcos-Pérez et al., 2020), confirmed the existing literature on the inflamm-aging paradigm in frailty older adults (as shown in ref. Vatic et al., 2020 for a review) and support the role of age-related chronic inflammation in frailty development. Results on *physical health measures* showed important relationships with frailty. Regarding biochemical measurement, results mostly showed that, compared with non-frail older adults, frail individuals had lower levels of red blood cells, especially hemoglobin (more than 50% of the studies reported a significantly negative relationship with frailty). Of important note, one study analyzing individual Fried's criteria reported a significant relationship between red blood cells and two frailty criteria (exhaustion and slow gait speed; Silva et al., 2014), and another one reported increasing BMI values associated with increasing hemoglobin levels (Blaum et al., 2009). Taken together, these results could be in line with previous studies linking red blood indices to frailty through sarcopenia (Silva et al., 2014; Vatic et al., 2020), even if more studies would be needed to confirm this hypothesis. This review confirmed the strong links between comorbidities and frailty: the older adults suffer from specific diseases, the more they are at risk of being frail. The inter-relationships between comorbidity and frailty has often been reported (as shown in Ref. Gobbens et al., 2010) even if research studies still lack to determine whether comorbidities act as a cause or as a consequence of adverse outcomes related to frailty. Few studies measured physical performance (4/17), but all of them reported significant links with frailty. These results are not surprising considering how included studies defined and measured frailty in older adults. Fried's criteria, and especially low grip strength, slow gait speed, and low physical activity level, will automatically imply a significantly reduced physical performance in frail individuals. Finally, in this review focusing on frailty and inflammatory biomarkers (two medical concepts), *psycho-social health* has been under-measured comparing with a physical assessment and studies produced mixed results. Less than 50% of the included studies found significant associations among educational level, marital status, cognition, or depression and frailty status. It could be hypothesized that frailty, and especially physical frailty, impacts to a less extent psycho-social health, compared with physical health or inflammation. Nevertheless, previous reviews of the literature have linked frailty to psycho-social measures in older adults. For instance, poor mental health (and especially the presence of depressive symptoms, usually measured with Center for Epidemiologic Studies-Depression (CES-D) or Geriatric Depression Scale (GDS) scales) is frequent in frail older adults (as shown in ref. Buigues et al., 2015, for a systematic review). It has been hypothesized that physiological dysregulation associated with frailty (generating low-grade inflammation, for example) could predispose or precipitate depression in aging (as shown in ref. Buigues et al., 2015). Regarding cognitive status, a recent meta-analysis did show that frail older adults were at a higher risk of incident cognitive disorders (measured through neuropsychological testing) than non-frail elders (pooled $OR = 1.80$, 95% $CI = 1.11–2.92$; $p = 0.02$; Borges et al., 2019). Mixed findings observed in this systematic review could be the result of the simple tools used in lots of included studies to measure complex psycho-social concepts. For instance, the MMSE test is frequently used in frailty studies to measure cognitive impairment. Nevertheless, when studying cognition in community-dwelling samples, the use of more complex tests, evaluating executive functions for instance (one of the first cognitive functions to be early affected in normal aging; Amieva et al., 2003) could provide interesting avenues of research in the field of frailty. This rationale is also true for mental health, a complex concept involving both environmental (e.g., social support) and personal (e.g., self-efficacy) factors, and not just the absence of depressive symptoms (which are assessed here in a variety of ways). Future research studies analyzing the various causes and effects of frailty should also include precise measures of psychological variables to not miss out on an important part of older adults' health.

In addition, this systematic review raised some important remarks in the research field of frailty. First, the importance of intermediate states could be underestimated, at least, by few frailty studies exploring inflammatory biomarkers. For instance, two included studies considered participants as being non-frail when having from 0 to 2 Fried's criteria (Chang et al., 2012; Yang et al., 2018) while pre-frail status has been associated with specific patterns of results (on some measures, pre-frail older adults acted similarly as non-frail individuals whereas, on others, they acted like frail individuals). Moreover, on some specific physical health measures, the pre-frail group was the only one showing signs of poorer health [higher hypercholesterolemia levels or lower grip strength (Darvin et al., 2014), or higher hyperlipidemia (Huang et al., 2020), in pre-frail individuals compared with the two other groups]. Pre-frail individuals could then represent a target population, between prevention and intervention, to focus on delay or avoid adverse health outcomes related to frailty. Second, this systematic review highlighted the fact that frailty studies, when exploring inflammatory biomarkers, still lack a holistic approach of health. Future studies would be needed to specifically explore psycho-social health and its relationship with inflammation and frailty. The use of other conceptual models on frailty, such as the accumulation of age-related deficits, proposed by Rockwood and Mitnitski (2007), would be interesting to explore deeper frailty and inflammation impact on physical and psycho-social health in future studies. The underlying idea would be to further investigate the bidirectional links between psychological and physical health (e.g., is subjective well-being a cause or effect of physical health? As shown in ref. Gana et al., 2013), particularly in frail older adults, and using inflammatory biomarkers as potential mediators.

While innovative and exploratory, this systematic review contains some limitations worth pointing out. First, the associations between frailty and inflammation, physical health, and psycho-social health, were only observed in cross-sectional studies, limiting the findings impact. Previous longitudinal studies have shown strong links among inflammatory markers (Gale et al., 2013), physical decline (Gobbens and van Assen, 2014), and psycho-social (specifically, cognitive impairment; Samper-Ternent et al., 2008), and the onset of frailty but a recent meta-analysis on inflammation and frailty (Soysal et al., 2016) pointed out methodological bias (paucity of data, over-adjustment of the analyses due to various baseline

potential confounders in the included studies, . . .). Therefore, this systematic review voluntarily focused on cross-sectional studies only. Second, data regarding specific multiple associations among frailty, inflammation, physical health, and psycho-sociological health were hard to retrieve in the studies because the studies analyses mainly focused on frailty status differences (group comparisons or multivariate regressions). This made the comparisons between studies harder but inclusion criteria used in this systematic review were partly responsible for it. Third, the use of unspecific MeSH Terms regarding frailty and inflammation may have led to miss few specific references. However, this broad search strategy was voluntarily employed to retrieve as many as possible medical or physiological studies, and study how they included any physical or psycho-social health evaluation.

This systematic review is the first one, to the best of our knowledge, to explore, in the same study design, the relationships between frailty and three markers of health (inflammation, physical health, and psycho-social health). While results have mostly confirmed existing literature regarding the strong links between frailty status and inflammation or physical health decline, studies evaluating psycho-social health of frail older adults still lack when inflammatory biomarkers and Fried's criteria (two medical concepts) are involved. Therefore, the development of future research studies is strongly encouraged: (1) to deeper explore the causal relationships between all these markers (top-down vs. bottom-up approaches), and (2) with a more exhaustive view of frailty and global health.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

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

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.805501/full#supplementary-material

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REVIEW
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Neuroinflammation: A Possible Link Between Chronic Vascular Disorders and Neurodegenerative Diseases

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Various age-related diseases involve systemic inflammation, i.e. a stereotyped series of acute immune system responses, and aging itself is commonly associated with low-grade inflammation or inflamm'aging. Neuroinflammation is defined as inflammation-like processes inside the central nervous system, which this review discusses as a possible link between cardiovascular disease-related chronic inflammation and neurodegenerative diseases. To this aim, neuroinflammation mechanisms are first summarized, encompassing the cellular effectors and the molecular mediators. A comparative survey of the best-known physiological contexts of neuroinflammation (neurodegenerative diseases and transient ischemia) reveals some common features such as microglia activation. The recently published transcriptomic characterizations of microglia have pointed a marker core signature among neurodegenerative diseases, but also unraveled the discrepancies with neuroinflammations related with acute diseases of vascular origin. We next review the links between systemic inflammation and neuroinflammation, beginning with molecular features of respective pro-inflammatory cells, i.e. macrophages and microglia. Finally, we point out a gap of knowledge concerning the atherosclerosis-related neuroinflammation, which is for the most surprising given that atherosclerosis is established as a major risk factor for neurodegenerative diseases.

Keywords: inflammation, neuroinflammation, microglia, astrocytes, macrophages, ischemia-reperfusion, Alzheimer's disease

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INTRODUCTION

Psychological disturbances are part of the "sickness syndrome" triggered by episodes of inflammation (Dantzer et al., 2008) and their occurrence has been correlated with increased morbidity in elderly people (Majnaric et al., 2021). Aging is commonly associated with increased inflammatory tone at the systemic level, which is summarized in the modern concept of inflamm'aging and is a risk factor for cognitive decline pathologies in aging (Fülop et al., 2018). Psychological frailty assessments must therefore include the inflammatory status of each subject.

Inflammation is defined as a stereotyped series of acute responses of the immune system in response to tissue injury or infection by pathogens, resulting in tissue repair and/or pathogen

elimination (Okin and Medzhitov, 2012). Initial inflammatory response occurs in the context of innate immunity based on the detection of danger signal molecules (DAMP: damage-associated molecular pattern, and PAMP: pathogen-associated molecular pattern) by circulating or tissue-hosted sentinel cells (monocytes/macrophages, resident macrophages, mast cells, dendritic cells) *via* pattern recognition receptors (PRR). Activation of PRR yields production of microbe-destroying molecules such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), phagocytosis of cell and tissue debris by macrophages and release of a plethora of immune cell-modulating chemical messengers (cytokines, chemokines, growth factors) (Takeuchi and Akira, 2010). Efficiency of the inflammatory response is due to its rapidity of setting but also on its transiency. A non-resolved acute inflammatory response can switch to a state of chronic inflammation, which involves recruitment of circulating leukocytes, notably B- and T- lymphocytes *via* the activation of the adaptive immune system (Chovatiya and Medzhitov, 2014). There is growing evidence that chronic systemic inflammation, even at low grade, is a detrimental process and a risk factor for many chronic diseases such as neurodegenerative and cardiovascular diseases (Ferrucci and Fabbri, 2018).

Neuroinflammation comprises inflammation-like processes inside the parenchyma of the central nervous system (CNS). It is currently well accepted that these inflammatory processes could take place locally within the CNS despite "the immune privilege of the brain," i.e., absence of direct interaction of CNS parenchyma with systemic circulation-borne cells and soluble cell-communication messengers due to the blood-brain-barrier (BBB; DiSabato et al., 2016). Neuroinflammation is currently considered as a driving force in progression and likely etiology of numerous neurological diseases, including neurodegenerative ones. Some common mechanisms behind neuroinflammation characterizing a variety of neurological and neurodegenerative conditions are now emerging and may support novel therapeutic developments. However, such perspective is hampered by discrepant terminologies and experimental conditions used to study neuroinflammation. The present review aims to highlight (i) the common features of neuroinflammation beyond the diversity of physio-pathological models that have been addressed, (ii) the relationship between systemic inflammation and neuroinflammation, and (iii) the systemic inflammation and neuroinflammation cross-talk in the particular case of the age-related chronic cardio-vascular disorder, atherosclerosis.

NEUROINFLAMMATION: THE INNATE IMMUNE REACTION OF THE CENTRAL NERVOUS SYSTEM

Mechanisms and Effectors of Neuroinflammation

Innate immunity processes inside the CNS parenchyma occur in various neurological pathologies where they manifest by increased tissue levels of chemical messengers that are commonly correlated with peripheral inflammation (Layé et al., 1994; Dantzer, 1996; Quan et al., 1997). However, in the case of neuroinflammation, these chemical messengers are produced locally in the nervous parenchyma by specialized cells of the CNS (brain and spinal cord) such as glial cells and even by neurons. These chemical messengers participate to cell-to-cell communication and activation.

Neuroinflammation Typically Involves Four Categories of Stereotyped Mechanisms

(i) Increased tissue concentrations of chemical mediators like: cytotoxic molecules (ROS, produced along the mitochondrial respiratory chain, RNS including nitric oxide [NO], biosynthesis of which is catalyzed by inducible nitric oxide synthase [iNOS]; Chitnis and Weiner, 2017) prostaglandins, pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL6), anti-inflammatory cytokines (e.g., IL4, IL10, TGFβ), chemokines (CCL2, CCL5, CXCL1. . .), ATP and matrix metalloproteases (MMP2, MMP9. . .). The balance between production of pro- and anti-inflammatory cytokines depends upon pathological context and its time-course.

(ii) Functional activation and proliferation of microglia and astrocytes (the latter being the most abundant type of neural cells) in pathology-specific regions of the CNS (Radenovic et al., 2020).

(iii) Infiltration of peripheral immune cells from the systemic circulation: monocytes-macrophages, T-lymphocytes (including T-regulators; Dansokho et al., 2016) which is associated with permeabilization of the blood-brain-barrier (BBB) (Estes and McAllister, 2014).

(iv) Neuronal cell death, caused by the resulting neurotoxic context (Skaper et al., 2018).

The involvement of glial cells in neuroinflammation deserves to be clarified in terms of clear distinction between glial cells of neural origin (i.e., astrocytes) and those related to immune system (i.e., microglia) to avoid confusion (**Figure 1**).

Microglia

Microglial cells play a central role in neuroinflammation by: i) sensing "danger signals" coming from pathogens or damaged "self" cells throughout the CNS parenchyma *via* their PRRs; ii) phagocytosis of tissue remnants issued from neural lesions; iii) production of chemical messengers and recruitment of other cellular effectors (DiSabato et al., 2016). Microglial cells belong to the hematopoietic lineage since they derive from monocyte/macrophage precursors that migrated from the yolk sac of early embryo to the neural tube before the establishment of the BBB (Prinz et al., 2021). Microglia is thus a non-neural glia: it shares many phenotypic and functional properties with peripheral macrophages but remains a distinct cell type (Prinz et al., 2021). Consistently, all microglia express constitutively the markers such as Iba1, CD11, HexB which are common with other cells of monocyte/macrophage lineage. In healthy adult CNS, microglial cells spread homogeneously throughout the parenchyma but display a panoply of both brain-region and sex-specific morphological features (Grabert et al., 2016).

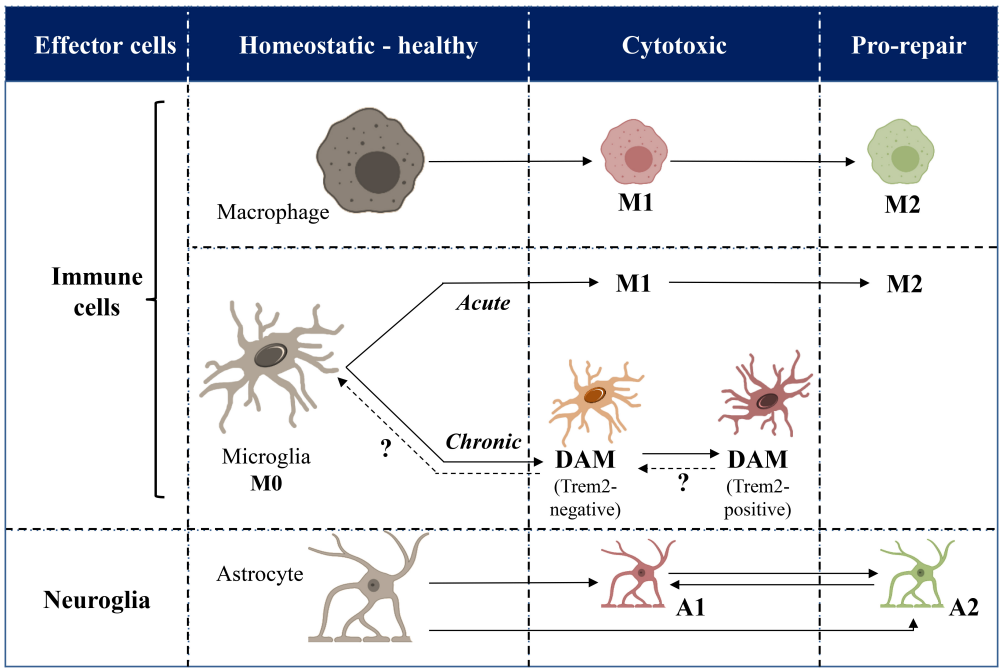

FIGURE 1 | Cellular mechanisms of inflammation and neuroinflammation: a schematic picture. Immune and neural effector cells of inflammation and neuroinflammation are represented in horizontal rows. Healthy and pathological phenotypes are categorized in columns. Plain vs. dashed arrows indicate demonstrated vs. hypothetical switches from one phenotype to another. Acute vs. chronic diseases are indicated in italic. DAM, disease-associated microglia.

Microglial cells are characterized cytologically by a small size (cell body 15–30 mm diameter; Leyh et al., 2021), thin ramified expansions, expression of danger/damage sensors (scavenger receptors, DAMP and PAMP receptors, purinergic receptors P2Y12, P2×4, P2×7) and low phagocytic activity. These features globally qualify the "homeostatic phenotype" of microglia in healthy adult CNS (Butovsky and Weiner, 2018; Jiang and Roger, 2020; Masuda et al., 2020a).

Astrocytes

Neuroinflammation also involves activation of astrocytes, i.e., the predominant neural type of glia in the CNS, originating from the embryonic neurectoderm like neurons and myelin-elaborating glial cells (oligodendrocytes in the CNS and Schwan cells in the periphery). Astrocytes therefore cannot be designated as being "immune cells" even though they do participate in some immune processes; like in many other examples, the cell lineage must not be confounded with physiological function. It is, however, of utmost importance to recall that astrocytes and microglial cells are homogeneously intermingled throughout the tissue parenchyma of the CNS where they tightly cooperate functionally both in homeostatic and pathological conditions. Astrocytes are highly ramified cells that extend long and thin leaflets between neuronal processes and especially around synapses, which supports their well-known roles in regulation of neuronal activity and in metabolic support to neurons, extracellular fluid homeostasis and electrical isolation of excitable cells (Sofroniew, 2020). Their specific, genuine phenotypic marker is the glial fibrillary acidic protein (GFAP). Astrocytes express various DAMP and PAMP receptors, among which several Toll-like receptors (TLR) and purinergic receptors such as P2×7, which when activated by extracellular ATP, elicits neurodegeneration (Sidoryk-Wegrzynowicz and Struzinska, 2021; Territo and Zarrinmayeh, 2021; Zhao et al., 2021). Beyond relative cyto-morphological uniformity of astrocytes throughout the CNS, region-specific subpopulations are being unraveled with transcriptomic approaches (Khakh and Deneen, 2019; Diaz-Castro et al., 2021).

Remarkably, both microglia and astrocytes are characterized by their phenotypic plasticity which began to be uncovered in the last few years, particularly in pathological contexts of injuries or diseases. Such characterization has been long hampered because these two cell types are exquisitely sensitive to microenvironment and display phenotypic changes in primary cultures, which complicates the interpretation of *in vitro* studies in general, and characterization of their pathology-related plasticity, in particular.

Pathological Contexts of Neuroinflammation: A Comparative Survey

Neuroinflammation has been reported as associated to acute lesions subsequent to trauma or to vascular obturation and/or rupture (causing, respectively ischemia and/or hemorrhage), and in relation with chronic neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, Huntington's, amyotrophic lateral sclerosis) and multiple sclerosis (Muzio et al., 2021).

Neuroinflammation also occurs in relation with systemic inflammatory diseases as for instance type II diabetes (Moyse et al., 2019).

Differential Cellular and Molecular Mechanisms of Neuroinflammation

At the cellular level, microglia have been histologically characterized to undergo "activation" in the above pathological contexts, as early as by pioneering description by Del Rio Hortega one century ago (Leyh et al., 2021). Following either of above-mentioned pathological conditions, both in animal models and in post-mortem human brains, microglial cells in the affected area have been found to retract their ramifications toward a more roundish morphology, proliferate, acquire migration capacity by amoeboid motility, increase their phagocytic activity and switch their secretome to pro-inflammatory cytokines (IL1β, IL6, TNFα) and cytotoxic compounds (RNS, ROS) (Prinz et al., 2021; Wieronska et al., 2021). In parallel, astrocytes also proliferate and secrete matrix components which builds-up a "glial scar" around the affected area, and alter their secretome toward production of pro-inflammatory and chemotactic mediators (Giovannoni and Quintana, 2020). Astrocytes' activation occurs in the anatomical vicinity of microglial activation in various neuropathological states *in vivo*, as analyzed by combined immunohistochemistry of their respective markers GFAP and Iba1 (Zamanian et al., 2012). Neuroanatomical location and time-course of these micro- and astro-glial changes nevertheless vary depending upon type of injury or disease (see below). Besides, it has to be stressed that other cell types are also involved in neuroinflammation, namely neurons through their constitutive communication with microglia *via* interaction of neuronal membrane-expressed fractalkine (CX3CL1) and its microglial receptor CX3CR1, but also endothelial cells and pericytes of CNS blood vessels (Estes and McAllister, 2014; DiSabato et al., 2016). Interestingly, endothelial cells use the neuroinflammation effector NO as a paracrine relay for physiological regulators of vasomotricity (Tousoulis et al., 2012).

At the molecular level, mechanisms of neuroinflammation have been unraveled in the last few years by *ex vivo* transcriptomic comparisons of microglial subpopulations (or single cells) dissociated after micro-dissection of the damaged brain regions in experimental animal models of disease or injuries at critical stages, as compared to analogous samples coming from the respective controls. Microglia was purified from primary cell suspensions by fluorescence-activated cell sorter (FACS) using for instance CD11b-fluorescent immunolabeling, and subjected to RNA-sequencing (Keren-Shaul et al., 2017; Krasemann et al., 2017; Madore et al., 2020; Masuda et al., 2020b; Li et al., 2021; Liu et al., 2021; Lu et al., 2021; Muzio et al., 2021; Yusuying et al., 2021). The key results of these approaches are summarized in **Table 1** to facilitate comparison between the different pathological contexts of neuroinflammation. Overall, these data reveal both unity and diversity of mechanisms underlying neuroinflammation, as discussed below.

Activated astrocytes could also be profiled by DNA-microarray or RNAseq on primary cells dissociated from rodent brain and purified by immunopanning (elimination of non-astrocyte cells by sequential incubations on plaques, respectively coated with antibodies directed against the cell-specific markers and/or astrocyte selection with antibody against a cell-surface marker like integrin subunit beta5 [Itbg5]). These approaches led to identify the genes that are upregulated in activated astrocytes from diverse neuroinflammation-linked pathologies in rodents, like the acute phase protein Lcn2 and the proteinase inhibitor SerpinA3N; however, most of astrocyte transcriptomic signatures were specific to the pathological context (ischemia and LPS exposure; Zamanian et al., 2012). Transcriptomic signatures of astrocytes purified *ex vivo* from animal models were defined as a proinflammatory "A1" phenotype in the context of acute CNS injury, LPS-induced neuroinflammation, neurodegenerative models and a pro-repair "A2" phenotype in the context of ischemia *in vivo* (Liddelow et al., 2017). However, further characterizations of purified astrocytes revealed a number of different pathology- and region-specific phenotypes that presently preclude generalization (Escartin et al., 2021).

Transient Vs. Chronic Neuroinflammatory States

In transient states of neuroinflammatory pathologies like ischemia-reperfusion (ischemia being triggered by 1-hour-long occlusion of the middle cerebral artery [MCAO] followed by reperfusion), CD11-positive microglia switches from the homeostatic phenotype (called M0) to a M1 phenotype characterized by pro-inflammatory properties, which converts 1 week later to a M2 resolutive phenotype with anti-inflammatory features and favoring tissue-repairing (Perego et al., 2011). Specific markers of M1 and M2 phenotypes have been characterized, in addition to the upregulation of genes encoding, respectively pro-inflammatory- (IL1β, TNFα, IL6) or anti-inflammatory (TGFb, IL10) cytokines (**Table 1**). Depending on *in vivo* context, M1 and M2 microglial phenotypes are mutually interconvertible, and each one can switch from M0 state. These microglial phenotypes are strikingly reminiscent of the M0, M1 and M2 phenotypes that had been characterized previously in peripheral monocytes/macrophages in the course of systemic inflammation (**Table 2**).

In chronic states of neuroinflammation associated with neurodegenerative diseases (Alzheimer's disease, amyotrophic lateral sclerosis [ALS]) and with aging, a pro-inflammatory phenotype of microglia has been characterized and designated "disease-associated microglia" (DAM). This phenotype shares some common features with the M1 phenotype above, in particular down-regulation of homeostatic microglia markers (the anti-inflammatory cytokine TGFb, the transcription factors Sall1 and Egr1). However, as far as available bibliography allows comparison, the down-regulation of microglial M0 markers is more extensive in the DAM phenotype than in the post-ischemic M1 above (**Table 1**). In addition, two sequential pro-inflammatory stages of DAM have been characterized in murine models of Alzheimer's disease, according to the sequential up-regulation of the TREM2-ApoE pathway. Besides, ApoE, apart its function as the major apolipoprotein of the CNS interstitial

TABLE 1 | Microglia phenotypes in health and disease.

Physio-pathology	Homeostatic microglia *DAMP sensing via PRR*	M1 phenotype *proinflammatory*	M2 phenotype *antiinflammatory*	DAM stage1	DAM stage2
				pro-inflammatory	*pro-inflammatory, neurotoxic*
Health	P2ry12, PY2ry13, P2X7R, Tmem119, SiglecH, Gpr34, Socs3, Olfml3, Fcrls, Cts3, Ctsd, Ctss, Sparc, C1qa, Tmsb4x, C1qb; **Sall1, Egr1** *Common with monocytes/macrophages*: CX3CR1, Fc, CD200R1, ITGAM (a-integrin=CD11b), CSF1R (=CD115), Iba1, ADGRE, SIRPA (=CD172a) ***IL10, TGFβ, (IL4)***				
Ischemia-reperfusion (mouse)		CD86, CD16/32, CD68, iNOS^{high} ***IL1β, TNFα, IL6, NO, ROS***	CD206, Arg1, Ym1 iNOS^{low} ***TGFβ, IL10, BDNF, VEGF, MMP-9***		
Alzheimer's disease *Plaque-containing brain regions (tg mouse 5xFAD)*				↘ CX3CR1, P2ry12, HexB Tmem119, TGFβR1, P2ry13, Gpr34, Olfm13; **Jun, Sall1, Egr1** ↗ ApoE, Tyrobp, Ctsb, Ctsd, B2m, Fth1, Lyz2 ↘ ***TGFβ***	↗ Trem2, ApoE,Axl, Csf1, Clec7a, Lgals3, Itgax, Timp2, Cst7, Ctsl, Cd9, Ccl6, Ccl2, Lpl, Gpnmb, Ch25, Lilrb4, Spp1, Fabp5, P2X7R ; **miR-155** ↗ ***IL1β, TNFα, IL6, IL4, NO, ROS***
ALS *Spinal cord (tg mouse SOD1-/-)*				↘ CX3CR1, P2ry12, Tmem119, Csf1r; **Olfml3, Sall1** **Up:** Trem2, ApoE, Axl, Clec7a, Itgax, Spp1; **miR-155** ↘ ***TGFβ; ↗ IL1b, IL6, TNFα***	
Aging				↘ P2ry12, P2ry13, SiglecH, Adora3 ↗ Trem2, ApoE, Tyrobp, Ctsd, Lpl ↘ ***TGFβ*** ↗ ***IL1b, IL6, TNFα, TGFβ1***	
Parkinson's disease					
Pan-markers	Iba1, CD11b, HexB				

Summarized from (i) Li et al., 2021; Liu et al., 2021; Lu et al., 2021; Yusuying et al., 2021 (for ischemia-reperfusion), (ii) Keren-Shaul et al., 2017; Krasemann et al., 2017; Butovsky and Weiner, 2018; Madore et al., 2020 (for Alzheimer'disease and amyotrophic lateral sclerosis), (iii) Muzio et al., 2021 (for aging); (iv) Madore et al., 2020; Li et al., 2021 (for Parkinson's disease). Bold-italic: messengers secreted by microglial cells. Bold-underlined: genomic expression-controlling transcription factors and miRNA.

fluid, is also expressed intracellularly in microglial cells and acts as a downstream mediator of the membrane receptor TREM2, to trigger further pro-inflammatory switch of microglia. The DAM "stage 2" (TREM2 + /ApoE +) is distinguished from "stage 1" (TREM2-/ApoE +) by upregulated expression of TREM2 and globally increased pro-inflammatory secretome and neurotoxicity (Keren-Shaul et al., 2017; Krasemann et al., 2017; Madore et al., 2020). The same approach on a murine transgenic model of another neurodegenerative disease (ALS) yielded a conserved core of transcriptomic signature in respective degenerating regions of the CNS, i.e.,: down-regulation of the M0-specific markers CX3CR1, P2Y12, Tmem119, Csf1r, Olfm13, Sall1; up-regulation of the DAM-specific markers Trem2, ApoE, Axl, Clec7a, Itgax, Spp1, miR-155; up-regulation of the pro-inflammatory secretome (IL1β, IL6, TNFα) (**Table 1**; Keren-Shaul et al., 2017; Krasemann et al., 2017) which led to postulate a "neurodegenerative signature" of microglia (Madore et al., 2020). It is striking to uncover such common features of microglia properties between two diseases with such different neurological outcomes and specific neuro-anatomic lesion (hippocampus and discrete neocortex areas in Alzheimer's disease vs. ventral horn of spinal cord in

TABLE 2 | Monocytes/macrophages phenotypes.

	Monocyte/peripheral macrophage M0	**M1 macrophage *Pro-inflammatory; "classical" activation by IFNg or LPS***	**M2 macrophage *anti-inflammatory, pro-repair; "alternative activation" by IL4***
Healthy adult mouse donor	*Common with homeostatic microglia*: Fc, ITGAM (a-integrin=CD11b), CD200R1, CSF1R (=CD115), Iba1, ADGRE, SIRPA (=CD172a), CX3CR1		
Adult mouse macrophages from bone marrow		Primary culture 1 week in GM-CSF and last 24h in LPS CD80, CD86, CD 40 ***IL1β, TNFα, IL6, NO, ROS, IL12, IL23, MMP1, MMP3, MMP13, ADAMTS***	Primary culture 1 week in M-CSF and last 24h in IL4 CD206, CD163, Arg1, PD-L2, RELMa ***TGFβ, IL10, IL1-RA, IGF, MMP-1, MMP12***

*Summarized from Shapouri-Moghaddam et al., 2018; Orecchioni et al., 2019; Spittau et al., 2020; Miyamoto et al., 2021. **Bold-italic:** messengers secreted by macrophages.*

ALS) (Keren-Shaul et al., 2017; Krasemann et al., 2017; Madore et al., 2020). However, to fully support the postulated generalization, the "neurodegenerative microglial signature" should now be assessed in the respective lesioned areas of other neurodegenerative diseases: substantia nigra and striatum in Parkinson's disease, striatum in Huntington's disease, hippocampus and lesioned areas of cerebral neocortex in Creutzfeld-Jacob disease. On the basis of already published studies, this aim could be performed merely by RT-qPCR of DAM vs. M0 markers on RNA extracts from micro-dissected explants of the respective lesioned area in murine models of these diseases.

Nevertheless, it has to be stressed that DAM phenotype, although displaying some dissimilarities with the M1 phenotype (e.g., ApoE is down-regulated in M1 but up-regulated in DAM), also presents some analogies with the M2 phenotype (e.g., up-regulated Arg-1 expression found in both DAM and M2), (Krasemann et al., 2017). By contrast, the relationship between the M1-M2 and putative DAM microglial phenotypes in models of acute, transient neuroinflammation (e.g., ischemia/reperfusion, see above), has not been assessed so far.

Interestingly, the transcriptomic approach on *ex vivo* brain tissue from a murine model of Alzheimer's disease recently led to characterization of a novel phenotype of activated microglia, distinct from Trem2-ApoE-Clec7a-expressing DAM, but still increasing (as DAM) along disease progression. This new sub-population of microglia has been designated as "interferon response microglia" (IRM), and (as DAM) was identified in the vulnerable brain areas (hippocampus and cortex in the studied model of Alzheimer's disease). The IRM upregulate a subset of genes characteristic for monocytes/microglia response to interferon-γ exposure (C1qa, C1qb, C1qc, Ctsb, Ctsd, Fth1, Lyz2) (Sala Frigerio et al., 2019). By analogy to interferon-γ (IFNγ) - dependent phenotypic switch in monocyte-macrophage lineage classically observed *in vitro*, and in the light of reported IFNγ increase the hippocampus after global transient ischemia in a rat model (Yasuda et al., 2011), an exciting hypothesis to test in the future studies is whether IRM might be induced in models of acute, transient neuroinflammation associated with ischemia/reperfusion.

Altogether, neuroinflammation thus displays both common and distinct features in different physio-pathological contexts (**Figure 1**). On the basis of the molecular profiling of microglia that has been recently achieved in a limited number of animal models, the translation of knowledge is now needed to fill the gaps in additional pathological models of neurological and neurodegenerative diseases associated with neuroinflammation in the chronical context. Furthermore, the transcriptomic assessment of neuroinflammatory profile of microglia in the acute settings such as ischemia/reperfusion models, never performed before, is also urgently warranted.

RELATIONSHIP BETWEEN SYSTEMIC INFLAMMATION AND NEUROINFLAMMATION

During the last two decades, systemic inflammation has been extensively documented to trigger neuroinflammation as an indirect consequence of inflammation signaling to the CNS parenchyma. Four major routes have been identified for such signaling (Dantzer et al., 2008; Barbosa-Silva et al., 2021):

- Activation of autonomic afferent nerves (vagal and trigeminal cranial ones) by the circulating pro-inflammatory cytokine IL1β, *via* its specific receptors at the surface of sensory fibers; in line, peripheral inflammation-induced sickness behavior is blocked by experimental vagotomy in rodents (Bluthé et al., 1996);
- Neurohumoral activation of PAMP- and DAMP-receptors of macrophages and resulting secretion of pro-inflammatory mediators in the BBB-devoid circumventricular organs and choroid plexus (Konsman et al., 2004);
- "IL-1β pathway" *via* specific receptor-mediated uptake of some cytokines in the BBB of the CNS microvasculature and activation of its endothelium (Erickson and Banks, 2018);
- Blood-brain-barrier disruption, which allows systemic pro-inflammatory mediators and immune cells to infiltrate the CNS parenchyma (Banks and Erickson, 2010).

In addition, the microvasculature in meninges and choroid plexus harbors a variety of myeloid cells: monocytes, macrophages, dendritic cells, granulocytes. However, the contribution of these cells to neuroinflammation *via* cross-talk with systemic inflammation is presently still controversial (reviewed in Herz et al., 2021).

Nevertheless, the inter-play between systemic and CNS inflammation is increasingly recognized. One of the broadly studied examples of such cross-talk is sepsis. Indeed, sepsis and, more generally, various pathogenic infections, yielding a "cytokine storm," were documented to trigger encephalopathies and neuroinflammation which can be alleviated by peripheral anti-inflammatory therapies (Barbosa-Silva et al., 2021).

Besides, peripheral inflammation has been established as a risk factor for neurodegenerative diseases, especially Alzheimer's disease. Of note, neurodegenerative lesions and cognitive deficits in this disease are preceded by neuroinflammation in animal models (Moyse et al., 2019). Moreover, at least in murine models of Alzheimer's disease, recent studies demonstrated that both neuropathological lesions and cognitive deficits can be prevented or delayed by peripheral anti-inflammatory treatments (Bettcher et al., 2021).

Concerning acute injury settings, in a recent clinical trial, neuroinflammatory response to traumatic brain injury (TBI) has been alleviated by a peripheral treatment with an IL1β receptor antagonist, anakinra (Kineret), while peripheral inflammation markers remained unaffected (Lassaren et al., 2021). This clinical study indicates the causal role of systemic mediators in modulating TBI-linked neuroinflammation.

In spite of the great achievements accomplished during the last decades in terms of understanding the inter-play between systemic- and central (neuro)-inflammation, the biggest challenge for the future remains to decipher the underlying mechanisms and uncover putative common effectors. In this light, the purinergic P2×7 receptor, has recently attracted much interest since it has been causally involved in inflammatory changes, as well as in some psychiatric diseases like depression, both in human (Roger et al., 2010; Meyer et al., 2020) and in murine models (Chen et al., 2017; Bhattacharya and Jones, 2018; Martinez-Frailes et al., 2019; Troubat et al., 2021).

THE CASE OF CHRONIC VASCULAR DISEASES

Atherosclerosis is a chronic disease characterized by progressive development of lipid-rich fibrotic deposits (atheroma plaques) inside the intima of large- and medium-sized arteries (Taleb, 2016). Increasing evidence points to the chronic inflammation, occurring either locally or at the systemic level, as a key factor in progression of atherosclerotic lesions and related acute cardiovascular events. Relevantly, various serum biomarkers of inflammation have been proposed as predictors of cardiovascular complications both in patients suffering from chronic vascular diseases (CVD) and in healthy adults, independently of CVD risk factors (Moriya, 2019). Notably, inflammatory biomarkers such as C-reactive protein (CRP) and interleukins (IL) -1 and -6 have been widely explored as biomarkers of endothelial dysfunction and inflammation in clinical studies (Libby, 2021a). The serum CRP, although relatively low in atherosclerotic patients, has been reported to be on average above the gauge of systemic inflammation (plasma level of 2 mg/L). Furthermore, IL-1-neutralizing treatment could reduce serum CRP levels and the risk of cardiovascular death (Libby, 2021b). Combined, these recent data suggest that atherosclerosis should be considered as a chronic inflammatory disease.

Given the growing evidence pointing to the impact of systemic inflammation as a trigger of neuroinflammation, and the fact that neuroinflammation is recognized as being associated with neurodegenerative diseases such as Alzheimer's disease, it is important to assess neuroinflammation in the specific context of atherosclerosis in future studies.

Indeed, the mechanistic link between atherosclerosis and neuroinflammation has barely been addressed so far, except in one experimental study on the animal model of atherosclerosis: the ApoE-knockout (ApoE-/-) adult mouse fed for 2 months with a hyperlipidic diet (Denes et al., 2012). In the brain of this atherosclerosis mouse model, Iba1-immunoreactive microglial cells and CD45-immunopositive infiltrated leukocytes significantly outnumbered microglia and leukocytes seen in age-matched, wildtype mice (Denes et al., 2012). Moreover, *in vivo* IL-1β neutralization in ApoE-/- mice exposed to an atherogenic diet (either by administration of an IL-1β antibody, or by genetic crossing with IL1R1-/- mouse) could block neuroinflammatory features (VCAM-labeled vascular inflammation, increased number of Iba1-immunoreactive activated microglial cells, decreased intracerebral accumulation of CD45 + leukocytes in the brain) and reduced the atheroma burden in large arteries (Denes et al., 2012). Besides, the latter study explicitly demonstrated that IL-1β is causally related to atherosclerosis-associated neuroinflammation, and that systemic inflammation and neuroinflammation are inter-related. However, these data need to be extended by detailed characterization of microglia and astrocytes transcriptomic signatures in this model of atherosclerosis.

Epidemiological, genetic and clinical data indicate a consistent association between CVD and dementia. Alzheimer's disease, the major cause of dementia world-wide, and CVD affect the same population of patients that shares many common risk factors. Accordingly, two recent autopsy studies showed an increased prevalence of CVD (Toledo et al., 2013) and atherosclerotic lesions (Arvanitakis et al., 2016) in Alzheimer's disease patients, as compared to healthy controls. A correlation was also established between Alzheimer's disease progression and the severity of atherosclerotic lesions, suggesting that CVD could be considered as a risk factor for development of Alzheimer's disease. Moreover, cardioprotective treatments, such as angiotensin receptor antagonists and diuretics, yielded significantly reduced amyloid-β accumulation (the latter is a key histopathological feature of Alzheimer's disease) (Glodzik et al., 2016). In addition, allele ε4 of the apolipoprotein E gene (*APOE*) is a risk factor for both Alzheimer's disease (Wang et al., 2014) and CVD (Schächter et al., 1994). There is also a significant overlap between the mechanisms involved in Alzheimer's disease and CVD. Indeed, decreased cerebral blood flow, morphological changes in the vascular system similar to those observed during

arterial aging, permeability of the blood-brain barrier and cholinergic neurodegeneration are all found in both pathologies (Santos et al., 2017). Of note, systemic hypertension that is also linked to cognitive impairment, has been suggested to be both a trigger and consequence of neuroinflammation through activation of the renin-angiotensin system (Winklewski et al., 2015). These pathological processes could be synergistic, so that the pathological alterations of one accelerates the progression of the other. This view remains controversial and clinical data suggest rather additive effects.

More studies are clearly needed to further assess the putative analogy between CVDs and Alzheimer's disease, notably regarding neuroinflammatory changes and though beyond chronic, progressive and age-related character of both pathologies. Indeed, neuroinflammation has been extensively characterized in the context of Alzheimer's disease, especially by using transgenic murine models, but much less is known in relation with chronic CVDs like atherosclerosis. Neuroinflammation therefore deserves extensive characterization in the context of atherosclerosis. These future studies will help answering whether CVD-associated neuroinflammation displays a chronic feature and is closer to the neuroinflammation seen in Alzheimer's disease rather than acute, transient context of ischemia-reperfusion.

CONCLUSION

Neuroinflammation has been discovered some 30 years ago and first described as innate immunity response triggered inside the CNS parenchyma by systemic infection or CNS injury. More recently, data coming from a variety of pathological and physiological contexts in mammals, including human, has unraveled neuroinflammation as a pathophysiological process displaying many similarities with peripheral inflammation. Among these similarities, there is for instance the phagocytosis by circulating- or brain resident macrophages and use of common chemical messengers (e.g., cytokines and chemokines) for intercellular communication. Neuroinflammation, however, displays many specificities, related for example to the anatomical structure of the brain. Thus, specialized effector cells that are intermingled inside the brain parenchyma, are locally conditioned by their mutual interaction. These effector cells include: (i) microglia, i.e., resident macrophages deriving from non-neural hematopoietic lineage and thus belonging thus to the "immune cells" of the organism, and (ii) astrocytes from neuroectodermal (neural) lineage. Each of these cell types can undergo context-dependent switch between different phenotypes, from "homeostatic" states in physiological conditions to "disease-associated" ones in pathological contexts. These switches can be reversible in acute aggressions or definitive in chronic diseases like neurodegenerations. Molecular characterization of these phenotypes in animal models of a few pathologies, especially ischemia paradigms and Alzheimer's disease, has revealed respective transcriptomic signatures that are different between acute and chronic diseases (**Figure 1**). In this light, the mechanisms behind the atherosclerosis-related neuroinflammation still remain poorly understood, since the phenotypes of effector cells and the transcriptomic variations of inflammatory mediators have not been addressed so far. The only exception is a single study published a decade ago (Denes et al., 2012), before discovery of the transcriptomic diversity of glial cells. It is urgent to fill this gap, since atherosclerosis is increasingly recognized as a major risk factor for neurological and neurodegenerative diseases which are ever-increasing in the aging populations world-wide.

LIST OF TRANSCRIPTOMIC MARKERS CITED

ADGRE: Adhesion G protein coupled receptors, i.e., a family of G protein-coupled receptor with seven transmembrane domains and an extracellular domain containing repeated Epidermal Growth Factor (EGF)-like calcium binding domains. ADGRE1 is a monocyte-macrophage marker (Waddell et al., 2018).
ApoE: Apolipoprotein E, i.e., the predominant member in central nervous system of the apolipoprotein family. These amphiphilic proteins bind cholesterol and transport it in extracellular fluids as lipoproteic particles. ApoE in addition, can be expressed inside activated microglial cells and transduces TREM2-detected signals (Krasemann et al., 2017). ApoE occurs under several isoforms, the e4 of which is a strong genetic risk factor of Alzheimer's disease.
Arg1: Arginase-1.
Axl: A receptor tyrosine kinase (RTK) that specifically binds Growth-Arrest-Specific protein 6 (Gas6) and is expressed on microglia. Axl signaling reduces expression of the pro-inflammatory cytokine TNFα and thus dampens immune-mediated insult to the central nervous system (Weinger et al., 2011). Axl belongs to the TAM sub-family of RTKs along with Tyro3 and Mer, defined by pivotal roles in innate immunity (Lemke and Rothlin, 2008; Fourgeaud et al., 2016).
C1q (a,b,c): the initial, antigen-binding element of the "complement cascade" that triggers clearing of microbes or damaged endogenous cells in the frame of innate immune reaction.
CD: Cluster of Differentiation, followed by a number between 1 and 371, i.e., a cell surface glycoprotein used for immunophenotyping of immune cells.
Clec7a: C-type Lectin domain containing protein family 7 member A (or Dectin-1).
Csf1r: Colony stimulating factor-1 receptor, i.e., the transmembrane tyrosine kinase receptor for the macrophage growth factor CSF-1 (colony stimulating factor-1).
Cts (b, d, s, 3): Cathepsines, i.e., lysosomal proteases.
CX3CL1: Fractalkine, a member of the CX3C chemokine family. It is constitutively expressed by neurons and can be induced in astrocytes, microglia and endothelium (Pawelec et al., 2020). Fractalkine exists as either a membrane-integrated glycoprotein or a soluble, metalloprotease-cleaved isoform which, respectively mediate cell adhesion or chemotaxis.
CX3CR1: the fractalkine receptor, exclusively expressed by microglia (Pawelec et al., 2020).

Egr1: a transcription factor driving coordinate expression of diverse genes altogether defining the homeostatic M0 phenotype of microglia.
Fc: crystallizable fragment of antibody molecules, i.e., the immunoglobulin region that binds immune cells'activating receptor-Fc when complexed with antigen.
Fcrls: Fc receptor-like S, a transmembrane scavenger receptor.
Fth1: Ferritin Heavy chain-1
Gpr34: A G protein-coupled transmembrane receptor, once orphan, now related with the P2Y family of purinergic receptors (Schönberg et al., 2018). Gpr34 binding maintains microglia in its homeostatic (M0) state.
HexB: Hexosaminidase-B, i.e., a subunit of a lysosomal enzyme in microglia (Masuda et al., 2020a).
Iba1: Ionized calcium-binding adaptor molecule 1, a pan-marker of both microglia and systemic macrophages.
iNOS: inducible nitric oxide synthase (Sierra et al., 2014).
Itgam (= CD11b): Integrin Subunit Alpha M, i.e., an heterodimeric transmembrane protein that mediates the phagocytosis of complement-coated particles by macrophages and combines with Itgax in mediating adherence of monocytes and neutrophils to activated endothelial cells.
Itgax (= CD11c): Integrin Subunit Alpha X, i.e., an heterodimeric transmembrane protein combining with Itgam in mediating adherence of monocytes and neutrophils to activated endothelial cells.
Lgals3: Galectine-3, i.e., a ubiquitous immunoglobulin-E with glycan-binding property in both intra- and extra-cellular compartments, which modulates proliferation, cell death and survival, cell adhesion and cell migration (Ramirez et al., 2019). Lgals3 is expressed by both astrocytes and microglia, and its genetic deletion in mouse protects brain against injury. Lgals3 is a ligand of TREM2.
Lyz2: a lysosomal precursor (lysozyme) for a transglycolase-hydrolase enzyme of monocytes-macrophages, that targets peptidoglycans and chitin-oligosaccharides of bacterial walls.
miR: microRNAs are non-coding, short (around 20-nucleotide-long) RNAs that regulate expression of target proteins by specific hybridization to their mRNAs.
NO: nitric oxide, i.e., a gaseous liposoluble messenger with a very short half-life, that elicits its biological actions *via* direct binding to intracellular, second messenger-producing guanylate cyclase enzyme without specific receptor. NO can elicit toxicity on cells indirectly *via* its oxidized metabolites.
Olfm13: a member of the olfactomedins family, i.e., glycoproteins sharing an adhesive protein-protein domain, the prototype of which was discovered in olfactory epithelium and later expanded into diversified regulators of neural and immune development and plasticity (Anholt, 2014). Olfactomedin-13 is expressed in microglia but not in monocytes-macrophages.
P2Y12, P2Y13: G protein-coupled metabotropic ATP receptors.
P2×4, P2×7: Ionotropic ATP-gated receptors.
Sall1: a transcription factor driving expression of diverse genes defining the homeostatic M0 phenotype of microglia.
Siglec: Sialic acid binding immunoglobulin-like lectin, i.e., a family of receptors (16 members) recognizing the sialic groups in tissue glycocalyx structures. Siglec receptors are expressed specifically in immune cells, where they transduce inhibitory signals (Siddiqui et al., 2019).
Socs3: Suppressor Of Cytokine Signaling-3, i.e., a retro-inhibitor of ligand-bound cytokine receptors, promoting acute arrest of the cytokine message and long-term desensitization of cytokine receptors.
Sparc: Secreted protein acidic and rich in cysteine, i.e., a cell-matrix modulating protein involved in blood-brain-barrier function and in angiogenesis.
Spp1: osteopontine, i.e., an adhesion protein of bone tissue being expressed by bone resident macrophages (osteoblasts) and by microglia.
Tmem119: A transmembrane protein specifically expressed by microglia, to the exclusion of other immune cells and of neural cells (Bennett et al., 2016).
Tmsb4x: Thymosin beta 4 X-linked, i.e., an actin sequestering protein involved in regulation of actin polymerization and, as such, in cell division, migration and differentiation.
TREM2: Triggering Receptor Expressed on Myeloid cells-2, a phagocytic receptor expressed specifically in cells of the myeloid hematopoietic lineage (monocytes-macrophages, osteoclasts, dendritic cells and microglia). TREM2 senses phospholipids, apoptotic cells and lipoproteins. TREM2 mutations are risk factor for sporadic Alzheimer's disease, and transgenic TREM2 deficiency in an AD murine model accelerates amyloid plaque deposition and neuron loss (Colonna and Wang, 2016; Herz et al., 2021). Mutation in TREM2 gene is a strong risk factor of Alzheimer's disease.
Tyrobp: Tyro protein tyrosine kinase binding protein, forming a signaling complex with TREM2.
Ym1: Chitinase-3-like protein, i.e., a member of the glycosyl-hydrolase family that is activated during injury and inflammation, inhibits apoptosis and favors tissue repair and protection along with anti-inflammatory effects (Lee et al., 2011).

AUTHOR CONTRIBUTIONS

EM: cellular and molecular neurobiology and first draft writing. SK: neuroinflammation in Alzheimer's disease. ND: transcriptomic assays of microglia in an animal model of neuroinflammation. SR: molecular effectors of inflammation in ischemia/reperfusion. DA: cardiovascular pathophysiology and inflammation. CD: neurocognitive pathologies in clinics. VL: neurocognitive pathologies and education and ethics in health. BF: aging-related frailty and systemic inflammation. AA: atherosclerosis, inflammation, and vaccination. All authors contributed to the article and approved the submitted version.

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The Flexibility of Physio-Cognitive Decline Syndrome: A Longitudinal Cohort Study

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The mutual presence of impairments in physical and cognitive functions in older adults has been reported to predict incident disability, dementia, and mortality. The longitudinal transitions of phenotypes between these functional impairments, either individually or in combination, remain unclear. To investigate the natural course and prevalence of physical and/or cognitive impairments (CIs), we enrolled participants from a community-based population. Data were retrieved from the first (August 2011 and December 2012) and second wave (August 2013 and June 2015) of the I-Lan Longitudinal Aging Study (ILAS). All participants were classified into four groups: robust, mobility impairment (MI), CI, and physio-cognitive decline syndrome (PCDS). MI was diagnosed with weakness and/or slowness. CI was diagnosed if a subject met a cutoff below 1.5 standard deviations (SDs) of age-, sex-, and education-matched norms of any neuropsychological assessments. PCDS was combined with MI and CI. Our results showed that 38, 14, 30, and 18% of the participants were on the robust, MI, CI, and PCDS at the first wave, respectively. After 2.5 years, 17% robust, 29% MI, and 37% CI progressed to PCDS. In contrast, 33% of PCDS was reversed to non-PCDS. Predictors of conversion to PCDS included worse memory and language functions, older age, lower muscle mass, and the presence of diabetes. In PCDS, a stronger hand-grip strength, younger age, and better memory functions predicted reversion to non-PCDS status. In summary, we probed the transition of PCDS. The skeletal muscle mass/function and memory function are crucial factors associated with PCDS reversion or progression.

Keywords: flexibility, reverse, cognitive decline, physical frailty, cognitive frailty

INTRODUCTION

Physical frailty is a state of vulnerability characterized by reduced muscle strength, endurance, slowness, and reduced physiologic reserve (1), which affects 11–14% of people aged 65 years and older and predicts falls, disability, institutionalization, mortality (2, 3), and cognitive impairment [CI; (4–7)]. A meta-analysis study has shown that the risk for dementia was higher among those with the co-occurrence of physical frailty and CI than among those with CI alone (7).

The co-occurrence of impairments in physical and cognitive functions is clinically common, and several terms have been proposed for this specific phenotype, such as cognitive frailty and motoric cognitive risk (MCR) syndrome. The major difference between these terms is the operational definition of impairments in physical and cognitive functions. Our research group defined this unique phenotype as physio-cognitive decline syndrome (PCDS) (8).

The operational definition of PCDS was based on the findings of our previous cohort studies. We found that the mobility components of frailty (slowness and weakness cluster) were associated with poorer cognitive performance and higher mortality risk than the non-mobility components of frailty (fatigue and weight loss cluster) (9, 10). Therefore, we defined PCDS as a certain condition with slowness and/or weakness as mobility impairment (MI) as well as cognitive performance a minimum of 1.5 standard deviation (SD) below the mean for age-, sex-, and education-matched norms in any cognitive domain. We also identified the specific neuroanatomical signatures of PCDS with low skeletal muscle mass, and those with frailty had gray matter deficits in the hippocampus, cerebellum, and middle frontal gyri in the magnetic resonance imaging (MRI) study (10, 11).

Physio-cognitive decline syndrome affects 10–15% of community-dwelling older adults and deserves further research (10). The pathophysiology between CIs only and the concomitant presence of impairments in physical and cognitive functions may be different, which is still unclear. A recent post-mortem pathological study further demonstrated that the neuropathologic burden was related to frailty and mild CI, or dementia. This study showed that neuropathologic features, including β-amyloid deposition, hippocampal sclerosis, Lewy bodies, tangle density, TDP-43, cerebral amyloid angiopathy, arteriolosclerosis, atherosclerosis, and gross and chronic cerebral infarcts (12), are different from β-amyloid and tangle density in Alzheimer's dementia (13). These findings suggest that there is an extraordinary pathophysiological relationship between physical frailty and related cognitive decline, which may differ from the well-recognized neurodegenerative Alzheimer's disease (AD). The clinical outcomes of PCDS may also differ from those of mild CI or prodromal AD without physical frailty.

Hence, this study aimed to evaluate longitudinal transitions in the phenotypes of older adults with MI, CI, and PCDS to explore the potential reversibility of PCDS (1, 14–16), and to identify factors associated with phenotypic transitions using the data from the I-Lan Longitudinal Aging Study (ILAS).

MATERIALS AND METHODS

Study Design and Participants

The ILAS was a community-based aging cohort study in I-Lan County, Taiwan, which was designed to evaluate the complex interrelationship between aging, frailty, and cognitive function (9). ILAS enrolled community-dwelling adults aged 50 years and above from I-Lan County with the following inclusion criteria: (1) inhabitants of I-Lan County, (2) aged 50 years or above, and (3) no recent plans to move to other counties. ILAS excluded people with the following conditions for participation: (1) inability to communicate and complete an interview, (2) unable to complete assessments due to poor functional status, (3) having a life expectancy <6 months due to a major illness, and (4) being institutionalized. Data retrieved for this study further excluded participants with major neuropsychiatric diseases such as dementia, stroke, brain tumor, or major depression based on self-report or assessment results. Data of the first (baseline) and second wave (follow-up) were included for analysis in the present study. All participants provided written informed consent. This study was approved by the institutional review board of the National Yang-Ming Chiao-Tung University.

Demographic Data and Functional Assessments

Demographic information, including age, sex, years of education, body weight, and height, were collected in both first and second waves of evaluation. The medical history of each participant was assessed by trained research nurses, including diabetes mellitus (DM), hypertension, hyperlipidemia, and cardiovascular disease. According to Fried's criteria, physical frailty is defined by five components: weight loss, exhaustion, low physical activity, weakness, and slowness (17). In this study, weight loss was identified as an unintentional weight loss >5% in the past year or >3 kg in the last 3 months, and exhaustion was defined using the Center for Epidemiologic Studies Depression Scale (18). Physical activity was assessed using the International Physical Activity Questionnaire-Taiwan edition (19), and low physical activity was defined as the lowest quintile within sex. Handgrip strength was measured using a digital dynamometer (Smedlay's Dynamo Meter; TTM, Tokyo, Japan) of the dominant hand, and the best result of the three trials was recorded as the muscle strength. The 6-m usual walking speed with static start and without deceleration was used to define slowness. The lowest quintile of walking speed was defined as the cutoff for slowness, and the sex-specific lowest quintile of handgrip strength was defined as weakness. We used the appendicular skeletal muscle mass (ASM) index to represent the amount of muscles in individuals (20).

Cognitive Function Assessment

In addition to the Chinese version of the Mini-Mental Status Examination (MMSE), all participants underwent comprehensive neuropsychological assessments across multiple cognitive domains in both first and second waves of evaluation, which included (1) verbal memory: a delayed recall in the Chinese Version Verbal Learning Test (CVVLT) (21), (2) language: Boston Naming Test (BNT) (22), and category

(animal) Verbal Fluency Test (VFT) (3, 23) Visuospatial function: Taylor Complex Figure Test (CFT) (24); and (4) executive function: Clock Drawing Test (CDT) (25). All these neuropsychological assessments were culturally adapted and validated (21, 26–29).

Definition of MI, CI, and PCDS

In this study, MI was defined as the presence of weakness and/or slowness of participants, where the cutoffs recommended by the Asian Working Group for Sarcopenia were used (30). CI was defined as 1.5 SD below the mean for age-, sex-, and education-matched norms in any cognitive domain; however, without global CI. PCDS was defined as the concomitant presence of MI and CI (10). According to the epidemiological studies on the Taiwanese population, global CI was indicated as MMSE $<$ 24 in the well-educated participants (education years $\geq$6) or $<$14 in less-educated participants (education years $<$6) (31). In this case, we excluded participants who had the above conditions for possible global CI or dementia.

Statistical Analysis

All participants in the first and second wave were classified into four clinical phenotype categories: robust, MI only, CI only, and PCDS. Continuous variables are expressed as mean $\pm$ SD and categorical variables as numbers (proportions). To compare the characteristics of study participants across the different groups (robust, MI, CI, and PCDS groups), we used the chi-squared test for dichotomous variables and one-way analysis of variance (ANOVA) for continuous variables. To explore the possible predictors for the transition of phenotypes, Tukey' test was used for *post hoc* analysis due to its sensitivity for multiple comparisons. The cumulative probability (95% confidence interval) of transitions among the four groups in a 2.5 year follow-up was calculated using the cumulative distribution function of the standard normal distribution.

To investigate the factors that influence the categorical transition of four different groups, we first used the chi-squared test for dichotomous variables and one-way ANOVA for comparisons of continuous variables of four transitioned groups in a 2.5-year follow-up in each category classified at baseline (the first wave of assessment). Variables showing statistical significance after *post hoc* analyses between those who remained in the same group and who progressed to a more severe group or reversed to a milder group were included in the following multivariate binomial logistic regression models. For example, in the robust group classified at baseline, the variables that showed statistically significant differences between those who remained in the robust group and those who progressed to the PCDS group in a 2.5 year follow-up in *post hoc* analyses were put into the multivariate binomial logistic regression model (transition vs. maintenance) to determine whether the factors were the significant predictors of PCDS transition in the robust subjects. SPSS software (version 15.0; SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. All tests were two-sided, and the value of $p < 0.05$, was considered significant.

RESULTS

Demographic Characteristics

In the first wave of the ILAS, data from 1,223 participants were eligible for analysis. Due to funding and administrative limitations, the second wave of the ILAS was applied to a smaller random sample using the simple random sampling method. Overall, 531 participants, aged 51–87 years, completed both the first and second wave assessments with a mean follow-up of 2.5 years. Comparisons between participants from both the waves ($n = 531$) and wave 1 only ($n = 692$) are shown in **Supplementary Table 1**. Participants who received assessments in both the waves were older (64.46 $\pm$ 8.58, vs. 61.61 $\pm$ 8.82, $p < 0.001$), had fewer educational years (5.88 $\pm$ 4.72 vs. 7.67 $\pm$ 5.08, $p < 0.001$), slower walking speeds (1.49 $\pm$ 0.44 vs. 1.68 $\pm$ 0.46, $p < 0.001$), a lower BNT score in language function (9.51 $\pm$ 2.93, vs. 14.69 $\pm$ 2.79, $p < 0.001$), and a lower CDT score in executive function (7.28 $\pm$ 2.59, 8.08 $\pm$ 2.53, $p < 0.001$) than those who were not selected in the second wave study.

In this study, we only included data from participants who attended both wave assessments for further analyses. **Table 1** summarizes the baseline characteristics and comparisons between the groups. There are no significant differences in gender and past medical history. There are significant changes in age, education, weight, height, physical functions (walking speed and grip-strength), cognitive tests (CVVLT, BNT, VFT, CFT, and CDT), MMSE, and muscle mass index (ASM). *Post hoc* analysis showed that the MI group had significantly lower height and lower ASM compared with the robust group. In contrast, the CI group had significantly older age and weaker handgrip strength than the robust group. Notably, the PCDS group was older than the MI group and had less education and poorer performance in several cognitive domains and MMSE than the CI group.

The Phenotypic Transition During Follow-Up

At baseline, the prevalence of robust, MI, CI, and PCDS groups was 38, 14, 30, and 18%, respectively (**Figure 1B**). After 2.5 years, the PCDS group had a higher risk of developing dementia (4.0%), which was similar to the CI group (3.75%, $p = 0.889$); however, it was higher than the robust group (0.48%, $p = 0.04$). However, no participant in the MI group had a high risk of dementia during follow-up (**Figure 1A**). As dementia is an irreversible state, this study focused on the flexibility of PCDS. Next, we examined the transition among these four groups after excluding participants who were already demented at the second wave.

In the second wave, the distribution of the four groups was 20, 29, 16, and 33%, respectively (**Figure 1B**). About 2% of the participants progressed to dementia after 2.5 years. More than half (63%) of the PCDS participants remained in PCDS at a follow-up. Moreover, 4.0% of PCDS participants returned to be robust, 19.0% became MI only, and 10.0% became CI only. In contrast, 17.4% of robust, 29.3% of MI, and

TABLE 1 | Demographic characteristics of four categories at baseline.

	Total	Robust	MI	CI	PCDS	*p*-Value
n	531	206	75	154	96	
Sex, Female, *n* (%)	246 (46%)	91 (44%)	35 (47%)	68 (44%)	52 (54%)	0.385
Age, year	64.38 ± 8.57	62.51 ± 8.06	63.18 ± 8.52	65.94 ± 8.55[b]	66.81 ± 8.78[ce]	0.001
Education, year	5.88 ± 4.72	6.84 ± 4.88	5.89 ± 4.82	5.69 ± 4.40	4.09 ± 4.29[cf]	0.001
Weight, kg	62.79 ± 11.03	63.88 ± 11.31	61.56 ± 10.39	63.46 ± 10.02	60.36 ± 12.08[c]	0.042
Height, cm	159.03 ± 8.00	160.50 ± 8.29	157.56 ± 7.72[a]	159.72 ± 7.10	155.91 ± 7.97[cf]	0.001
Physical function assessments						
Walking- speed, m/s	1.49 ± 0.44	1.65 ± 0.41	1.25 ± 0.39[a]	1.56 ± 0.43[d]	1.21 ± 0.35[cf]	0.001
Grip- strength, KGs	29.44 ± 9.41	32.90 ± 8.96	26.07 ± 9.38[a]	30.31 ± 7.84[bd]	23.25 ± 8.88[cf]	0.001
Cognitive function assessments						
CVVLT						
Score	6.79 ± 2.14	7.70 ± 1.18	7.64 ± 1.19	6.04 ± 2.39[bd]	5.38 ± 2.64[cef]	0.001
Impairment, *n* (%)	91 (17.1%)	0 (0%)	0 (0%)	54 (35.1%)	37 (38.5%)	0.001
BNT						
Score	9.51 ± 2.93	10.92 ± 2.38	10.21 ± 2.05	8.50 ± 2.95[bd]	7.56 ± 2.88[cef]	0.001
Impairment, *n* (%)	93 (17.5%)	0 (0%)	0 (0%)	53 (34.4%)	40 (41.7%)	
VFT						
Score	14.81 ± 4.66	16.65 ± 4.50	15.68 ± 4.08	13.24 ± 4.39[bd]	12.70 ± 4.16[ce]	0.001
Impairment, *n* (%)	54 (10.2%)	0 (0%)	0 (0%)	38 (24.7%)	16 (16.7%)	0.001
CFT						
Score	30.86 ± 5.95	33.01 ± 3.43	31.88 ± 4.41	29.69 ± 6.25[bd]	27.33 ± 8.28[cef]	0.001
Impairment, *n* (%)	43 (8.1%)	0 (0%)	0 (0%)	28 (18.2%)	15 (15.6%)	0.001
CDT						
Score	7.28 ± 2.59	8.54 ± 1.58	8.07 ± 1.76	6.49 ± 2.72[bd]	5.25 ± 2.96[cef]	0.001
Impairment, *n* (%)	112 (21.1%)	0 (0%)	0 (0%)	63 (40.9%)	49 (51.0%)	0.001
MMSE Score	26.15 ± 3.44	27.29 ± 2.65	27.12 ± 2.40	25.71 ± 3.42[bd]	23.63 ± 4.16[cef]	0.001
Muscle mass index						
ASM	18.22 ± 4.07	18.84 ± 4.32	17.40 ± 3.96[a]	18.47 ± 3.76	17.14 ± 3.83[c]	0.002
Medical history						
HTN	41%	39%	44%	40%	45%	0.732
DM	17%	18%	21%	16%	16%	0.710
HLD	11%	12%	12%	9%	14%	0.131
CAD	4%	2%	1%	7%	3%	0.133

ASM, appendicular skeletal muscle mass index; BNT, Boston Naming Test; CAD, cardiovascular disease; CDT, Clock Drawing Test; CFT, Taylor Complex Figure Test; CI, cognitive impairment; CVVLT, Chinese Version Verbal Learning Test; DM, diabetes mellitus; HLD, hyperlipidemia; HTN, hypertension; MI, mobility impairment; MMSE, Mini-Mental State Examination; PCDS, physio-cognitive decline syndrome; VFT, Verbal Fluency Test.

Data showed mean ± standard deviation (SD).

Significant after post hoc analyses between groups. a: significance between MI and robust group; b: significance between CI and robust group; c: significance between PCDS and robust group; d: significance between MI and CI; e: significance between MI and PCDS; f: significance between CI and PCDS.

Chi-squared test for dichotomous variables and ANOVA for continuous variables, significantly ($p < 0.05$).

36.9% of CI participants progressed to PCDS in a follow-up (**Figure 1C**).

Factors Associated With Phenotypic Transitions

One-way ANOVA with *post hoc* Tukey' test was used to identify variables with significant differences at baseline between each group of phenotypic transitions (**Table 2**, **Supplementary Tables 2–4**), and those variables that reached statistical significance were then entered into the multivariate binomial logistic regression model as independently associated factors (**Table 3**).

Transition of Baseline Robust Group and the Predictive Factors for Transition

Compared to participants who remained robust, participants progressed to CI were older and had a lower CVVLT score in memory function at baseline, and those progressed to PCDS group had lower education years, a lower CVVLT score in memory function, and a lower VFT score in language function (**Supplementary Table 2**). Multivariate binomial logistic regression showed that a lower CVVLT score in memory function was a significant predictor of CI conversion (odds ratio [OR] = 0.55, $p = 0.004$), and a lower CVVLT score in memory function (OR = 0.63, $p = 0.03$) or a VFT score in language

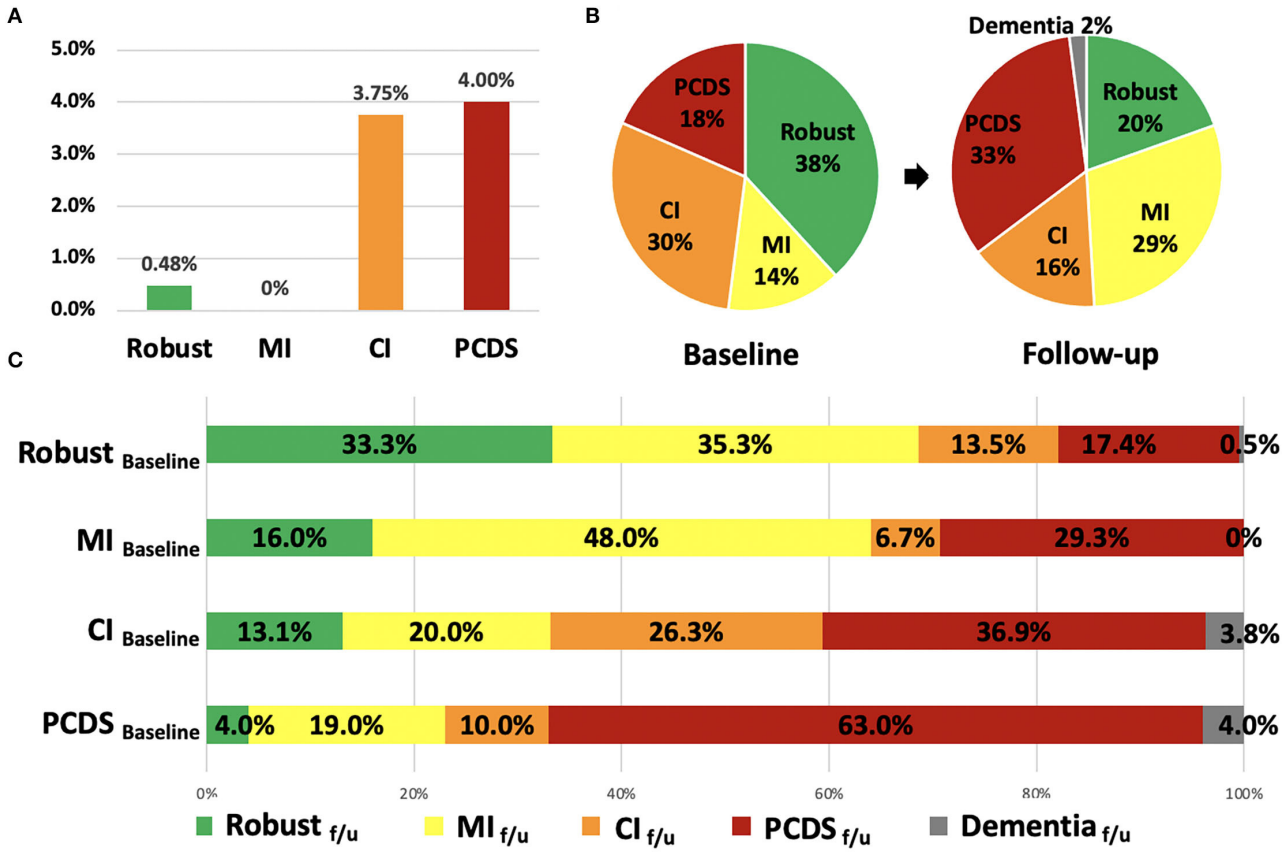

FIGURE 1 | The incidence of dementia, the distribution and transitions of robust, physical frailty, CI, and PCDS groups at the first and follow-up visit. **(A)** The incidence of dementia in the four groups after 2.5 years. **(B)** The distribution of robust, physical frailty, CI, and PCDS groups at the first and follow-up visits. **(C)** The categorical transitions at the follow-up visit in four categories. CI, cognitive impairment; MI, mobility impairment; PCDS, physio-cognitive decline syndrome.

function (OR = 0.83, $p = 0.01$) were significant factors for PCDS conversion in the robust group (**Table 3**).

Transition of Baseline MI Group and the Predictive Factors for Transition

Compared to participants who remained in MI, those who progressed to PCDS were older, had fewer years of education, slower walking speed, weaker hand-grip strength, lower ASM, lower BNT and VFT scores in language function, the CDT score in executive function, and the MMSE score compared to those in the MI group (**Supplementary Table 3**). Only older age and lower ASM were significantly associated with PCDS conversion in MI participants (age: OR = 1.13, $p = 0.004$; ASM: OR = 0.76, $p = 0.01$) (**Table 3**). In the MI group, no associated factors were identified among MI to become CI.

Transition of Baseline CI Group and the Predictive Factors for Transition

Compared to participants who remained in CI, those who reversed CI to robust were younger and had a higher BNT score in language function (**Supplementary Table 4**), which remained statistically significant in the binomial regression model (age: OR = 0.83, $p = 0.002$; BNT: OR = 1.47, $p = 0.01$) (**Table 3**). And those who converted to MI were younger and had a higher CVVLT score in memory function at baseline than those who remained in CI (**Supplementary Table 4**). Further logistic regression showed that only older age was an independent factor associated with CI to MI conversion (OR = 1.25, $p = 0.0001$) (**Table 3**). In CI participants, those who progressed to PCDS had DM (**Supplementary Table 4**). Moreover, DM was an independent factor associated with progression to PCDS (OR = 6.82, $p = 0.01$) (**Table 3**).

Transition of Baseline PCDS Group and the Predictive Factors for Transition

Compared to participants who remained in PCDS, those who reversed to robust had stronger hand-grip strength (**Table 2**), and better hand-grip strength remained to be an independent associated factor in the binomial regression model (OR = 1.36, $p = 0.01$) (**Table 3**). And those who reversed PCDS to the CI group had a higher CVVLT score in memory function, and those who reversed to MI had a younger age (**Table 2**). Younger age was an independent associated factor for PCDS to MI, a higher CVVLT score in memory function was an independent associated factor

TABLE 2 | Comparisons of the baseline physical and cognitive performance of four groups transited from participants with PCDS ($n = 96$).

	Baseline: PCDS				*p*-value
2.5 years of follow-up	**Robust**	**MI**	**CI**	**PCDS**	
n	4	19	10	63	
Sex (F)	50%	58%	50%	54%	0.981
Age	60.13 ± 5.05	62.27 ± 5.76[e]	66.97 ± 6.25	68.58 ± 9.44	0.022
Education	6.75 ± 1.50	5.68 ± 4.85[e]	3.90 ± 2.85	3.48 ± 4.30	0.143
Weight	57.23 ± 9.84	60.1 ± 9.80	67.52 ± 18.89	59.50 ± 11.38	0.248
Height	157.60 ± 8.18	157.22 ± 8.10	154.48 ± 8.29	155.63 ± 7.99	0.789
Walking speed	1.02 ± 0.13	1.30 ± 0.42	1.33 ± 0.38	1.18 ± 0.32	0.251
Hang grip strength	35.75 ± 11.53[c]	24.90 ± 10.80[e]	23.60 ± 7.49	21.91 ± 7.72	0.024
CVVLT	5.00 ± 3.56	6.53 ± 1.87[e]	7.00 ± 1.49[f]	4.79 ± 2.75	0.010
BNT	10.25 ± 1.71[c]	8.79 ± 2.32[e]	6.80 ± 2.74	7.14 ± 2.95	0.031
VFT	11.50 ± 4.80	14.21 ± 3.61	12.50 ± 4.50	12.35 ± 4.21	0.347
CFT	34.75 ± 1.50[c]	29.97 ± 5.21	28.35 ± 8.85	25.91 ± 8.82	0.056
CDT	7.25 ± 1.50	6.21 ± 2.74	5.90 ± 2.77	4.73 ± 3.02	0.101
MMSE	27.00 ± 2.45[c]	25.32 ± 3.46[e]	24.00 ± 3.74	22.84 ± 4.30	0.043
ASM	17.76 ± 3.91	17.76 ± 4.31	17.52 ± 4.39	16.85 ± 3.65	0.800
HTN	0%	26%	60%	51%	0.051
DM	0%	0%	20%	21%[e]	0.143
HLD	0%	5%	10%	18%	0.458
CAD	0%	0%	0%	5%	0.666

ASM, appendicular skeletal muscle mass index; BNT, Boston Naming Test; CAD, cardiovascular disease; CDT, Clock Drawing Test; CFT, Taylor Complex Figure Test; CI, cognitive impairment; CVVLT, Chinese Version Verbal Learning Test; DM, diabetes mellitus; HLD, hyperlipidemia; HTN, hypertension; MI, mobility impairment; MMSE, Mini-Mental State Examination; PCDS, physio-cognitive decline syndrome; VFT, Verbal Fluency Test.

[*] Significant after post hoc analyses between groups. a: significance between the MI and robust group; b: significance between the CI and robust group; c: significance between the PCDS and robust group; d: significance between MI and CI; e: significance between MI and PCDS; f: significance between CI and PCDS.

[**] Chi-squared analysis using Tukey' test with corrected p-value, significantly ($p < 0.05$).

for PCDS to CI (age: OR = 0.92, $p = 0.01$; CVVLT: OR = 1.57, $p = 0.03$) (**Table 3**).

DISCUSSION

Overall, our study demonstrated that the phenotypes of physio-cognitive decline are potentially reversible. It included 18% robust, 29% MI, and 39% CI groups that progressed to PCDS. Notably, 34.4% of the PCDS participants reversed their phenotypes into robust (4.2%), MI (19.8%), and CI (10.4%). In our studies, we probe the trajectories of PCDS. Skeletal muscle mass and mobility function are the most important factors for the phenotypic transitions of physical and CI. A lower appendicular skeletal muscle mass index (ASM) in MI participants was more likely to progress to PCDS, and PCDS participants with stronger handgrip strength, younger age, and better verbal fluency were more likely to revert to the non-PCDS status.

Mobility impairment and skeletal muscle mass loss are important in PCDS progression. These findings persisted not only in our epidemiological study but also in our basic research results. In our aging cell and animal model study, exosomal miR-29b-3p secreted by atrophic skeletal muscle impairs the development of neurons and induces neuronal senescence (32). Our previous neuroimaging study also demonstrated that individuals with physical prefrailty or frailty were present with gray matter deficits in the hippocampus, cerebellum, and middle frontal gyri (8, 11, 33). All of these evidences reinforce that phenotypic transitions in the physio-cognitive decline phenomenon are associated with a skeletal muscle–brain crosstalk.

Studies have reported that people with cognitive frailty have a poor cognitive function in some specific cognitive domains, such as working memory, verbal fluency, and processing speed (34, 35). Few studies have reported sequential changes in the specific cognitive function of PCDS (or cognitive frailty) (36, 37). Our previous study revealed that both non-memory and memory domains are associated with physical frailty (9). In this study, we also found that both memory and non-memory cognitive functions (CVVLT and VFT scores) could predict the progression from robustness to PCDS. Non-memory cognitive functions are involved earlier in physical frailty-related CI in our previous study (9). People with physical frailty tend to progress and develop PCDS during the decline of the memory function. The memory function (CVVLT score) appears to be a significant predictor of PCDS conversion in our study. In contrast, patients with PCDS with a good memory function are more likely to revert.

TABLE 3 | Statistically significant factors affecting categorical transitions in a 2.5-year follow-up revealed by multivariate binomial logistic regression.

	Factors	OR	95% CI	*p*-value
Baseline Robust				
Transition to:				
MI	None detectable			
CI	CVVLT	0.55	0.37–0.82	0.004
PCDS	CVVLT	0.63	0.41–0.96	0.030
	VFT	0.83	0.73–0.95	0.011
Baseline MI				
Transition to:				
Robust	None detectable			
CI	None detectable			
PCDS	Age	1.13	1.04–1.22	0.004
	ASM	0.76	0.61–0.94	0.012
Baseline CI				
Transition to:				
Robust	Age	0.83	0.74–0.94	0.002
	BNT	1.47	1.11–1.93	0.014
MI	Age	1.25	1.12–1.38	0.0001
PCDS	DM	6.82	1.47–31.69	0.012
Baseline PCDS				
Transition to:				
Robust	Hand-grip strength	1.36	1.07–1.73	0.011
MI	Age	0.92	0.86–0.98	0.013
CI	CVVLT	1.57	1.05–2.35	0.032

ASM, appendicular skeletal muscle mass index; BNT, Boston Naming Test; CI, cognitive impairment; CVVLT, Chinese Version Verbal Learning Test; DM, diabetes mellitus; MI, mobility impairment; PCDS, physio-cognitive decline syndrome; VFT, Verbal Fluency Test.

In our study, the PCDS group had a higher incidence of dementia (4.0%) than the robust group (0.48%). Based on our study, PCDS may be one of the main contributors to frailty-related incidental dementia instead of physical frailty alone. Our findings are in line with previous reports that CI and frailty were found to be significant risk factors for dementia instead of physical frailty (38). Alternatively, those with a combination of physical frailty and CI had a higher risk of dementia than those with physical frailty or CI alone. Therefore, CI in the MI group should be assessed for detecting PCDS. These findings also support the hypothesis that PCDS may differ from dementia in its patho-etiology (39, 40).

The criteria of original cognitive frailty are defined as physical frailty and the Clinical Dementia Rating scale 0.5 scores (41). Moreover, the following criteria further define "potentially reversible cognitive frailty" and "reversible cognitive frailty" based on the presence of objective or only subjective cognitive decline (42). Additionally, MCR was recognized as a state of concurrent physical frailty and CI. It is defined as a predementia syndrome characterized by slow gait and cognitive complaints (43, 44). Both cognitive frailty and MCR have been associated with a higher risk of incident dementia and all-cause mortality.

Compared to cognitive frailty and MCR, PCDS defines physical decline as weakness and/or slowness, but not the other components of physical frailty, and CI as objective CI in any domain. This definition is based on our previous findings that CI is more likely to be associated with MI (weakness and slowness) (9–11). MI was a good predictor of low survival rate (hazard ratio: 6.82) and poorer overall health outcomes (hazard ratio: 1.67) in our previous study (45). A recent longitudinal cohort study showed that MI was associated with a functional decline and the progression of multimorbidity, compared with the subtypes of no mobility and low physical activity (46). MI was also associated with a fast clinical decline using a data-driven approach (47). MI is an important predictor of cognitive frailty. Additionally, only subjective cognitive decline in the MCR criteria is not sufficient for CI (8). Therefore, the criteria of PCDS, including MI (weakness and/or slowness) and CI, are suitable for further studies.

Regarding comorbidities, we found that DM (48) was an independent factor for CI participants to progress to PCDS. DM has been reported to be associated with the development of frailty and dementia (49, 50). DM was at a greater risk of developing cognition impairment (49, 51); therefore, older patients with diabetes may experience CI earlier than PCDS. However, more studies are needed to confirm the pathophysiological roles of DM in the development of PCDS. Additionally, other comorbidities, including hypertension, hyperlipidemia, and cardiovascular disease, were not significantly associated

with PCDS progression in our study. This might be related to the fact that most of our participants were on medications for these comorbidities. In such cases, the risk of PCDS may be low.

We have demonstrated that PCDS is a variable status with flexibility. In addition to its ability to predict poor physical and cognitive functions after 2.5 years, its flexibility was also shown in the present study. Recently, people with cognitive frailty underwent multidomain interventions, including physical, nutritional, cognitive, and psychosocial aspects, showed improvements in physical and psychosocial functions, which indicated the flexibility of cognitive frailty (52, 53). Several studies have showed factors that are associated with the reversal of frailty progression, including exercise (muscle strength training), protein supplementation, and high self-rated health (54–57). Accumulating evidences also showed the reversion from mild CI to normal cognition (58–60). Although the relationship between frailty and cognitive function impairment and how they interacted with each other are still lacking, the present study showing the factors associated with the reversion of PCDS provided clues to understand the pathophysiology of physical frailty-related CI. In addition, this study provided the nature of the flexibility of PCDS, which highlighted that early intervention is important to prevent falls, disability, institutionalization, and mortality (2, 3).

Our result suggests that, although PCDS is supposed to be a prodromal accelerated aging phenotype, it is also an important potential intervention target to prevent poor prognosis in older adults. Although in our study, there was no further intervention such as care program, policy implementations, or treatment process. Only those with chronic diseases such as hypertension, DM, or hyperlipidemia used medication. We showed that factors associated with the reversion and progression of PCDS also provided directions for interventions. We anticipate our criteria to define a high-risk PCDS group, which has the possibility of reversion for further intervention studies. Our PCDS definition supports the efficacy of a multidomain intervention to improve the function of individuals with PCDS, who are vulnerable but reversible and flexible (61–63). In addition, our study demonstrated that skeletal muscle mass and function are key factors associated with the reversion or progression of PCDS, which indicated that exercise training may be a good intervention to prevent physical and CIs (15, 52, 53, 64).

This study has some limitations. First, the participants in this study were living in rural communities and had lower educational status and good physical function, which may have overestimated the extent of CI and underestimated the extent of MI in our study population. We would need another cohort of different backgrounds to validate the present results. Second, the present longitudinal study only analyzed the follow-up data at 2.5 years. Because age-related physical or/and cognitive decline is a long-term process, we would need a longer follow-up duration to elucidate the entire disease course of PCDS. Third, this study did not record the medication used in our participants. We did not know the effect of medication on PCDS. Fourth, we did not have the data of intermediate status changes, which are important for a convertible or reversible process. Finally, we did not check for biomarkers related to degenerative dementia. According to a recent study, the potential for reversibility of cognitive frailty should be supported by the evidence of biomarkers of amyloid, tau, and neuronal damage (65). Further studies involving these biomarkers and a revised definition of cognitive frailty according to multidimensional subtyping may be needed.

In conclusion, our study showed that the phenotypes of physio-cognitive decline are potentially convertible and reversible. In the first wave, 38, 14, 30, and 18% of the participants were in the robust, MI, CI, and PCDS, respectively. After 2.5 years, 17% robust, 29% MI, and 37% CI progressed to PCDS. Skeletal muscle mass and mobility function are the most important factors for the phenotypic transitions of physical and CI. Lower ASM in MI participants was more likely to progress to PCDS, and PCDS participants with stronger handgrip strength, younger age, and better verbal fluency were more likely to revert to the non-PCDS status. We probed the transition of PCDS. Skeletal muscle mass/function and memory function are crucial factors associated with the reversion or progression of PCDS.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the National Yang-Ming Chiao-Tung University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

P-NW designed the experiments. P-NW, K-HC, L-HC, and Y-JL enrolled the participants. P-LL, Y-CL, S-YL, and C-PL analyzed the data. Y-CL, C-PC, and P-NW wrote this manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.820383/full#supplementary-material

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Depression and Cognition Mediate the Effect of Self-Perceptions of Aging Over Frailty Among Older Adults Living in the Community in China

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Objectives: The aims of the study were first to investigate the association between self-perceptions of aging and frailty and second to determine whether self-perceptions of aging affects frailty *via* depressive symptoms and cognitive status among older adults living in the community in China.

Methods: Among 850 older adults who participated in this cross-sectional study, 822 older adults made valid responses to Tilburg Frailty Indicator, Brief Aging Perceptions Questionnaire, UCLA loneliness scale-8, Mini-Mental State Examination, and Patient Health Questionnaire-9 between March to December 2019. The possible pathways of self-perceptions of aging affecting frailty were analyzed based on the structural equation modeling analysis.

Results: A total of 21.53% of older adults reported frailty. Correlation analyses showed that higher degrees of frailty were related to greater loneliness, more depressive symptoms, more negative self-perceptions of aging, worse locomotive function, and cognitive status ($r = 0.267$, $r = 0.440$, $r = 0.481$, $r = 0.451$, $r = -0.337$; $p < 0.001$). Multiple regression analysis showed that loneliness, depressive symptoms, self-perceptions of aging, locomotive function, and cognitive status were the five factors to be entered the regression equation, and the variance of joint explanation was 46.60%. SPA had a direct effect on frailty ($\beta = 0.306$ and $p < 0.001$), and SPA indirectly affects frailty by independently affecting depressive symptoms ($\beta = 0.391$, 95% CI [0.027, 0.061], and $p < 0.001$) or cognitive status ($\beta = 0.148$, 95% CI [0.009, 0.024], and $p < 0.001$) of older adults.

Conclusion: These findings help explain the potential psychological mechanisms through which SPA impacts frailty and may aid community healthcare providers in China in identifying individuals at high risk of frailty. The results suggest that health staff should help older adults improve their perspectives on aging, alleviate or prevent depressive symptoms, and improve cognitive status to delay the progress of frailty and promote healthy aging.

Keywords: self-perceptions of aging, depressive symptoms, cognitive status, frailty, older adults

INTRODUCTION

An aging population is an inevitable part of social development. However, the current acceleration of population aging is having a far-reaching impact on the planning and provision of health and social care worldwide (Wu et al., 2017). China has the world's largest population of adults over 60 years old. The growing number of adults entering old age demonstrates the importance of understanding the processes in and around older adults to ensure that older adults are able to participate actively and not become frailty and/or ill. Frailty is recognized as a clinical syndrome which increased vulnerability and decreased ability to cope with stress caused by the decline of physiological reserves or multiple functional abnormalities that arise in older people, manifested in multiple aspects physically, psychologically, and socially (Walston et al., 2006; Puts et al., 2017). The incidence of frailty among China's older population is relatively high, and the phenomenon tends to increase with age (Ye et al., 2020). Frailty is an important risk factor leading to various adverse health consequences for older adults, including an increase in the incidence of falls and disability (Kojima, 2015; Makizako et al., 2015). It can also affect their health status, functional integrity, and quality of life-all while bringing a heavy burden to families and society (Arjunan et al., 2018). Since frailty is composed of a constellation of symptoms, it is likely that no single biomarker can perfectly predict this syndrome. Instead, frailty exists in the complex interaction of various factors. In addition, according to the frailty dynamic equilibrium hypothesis, frailty is a potentially reversible process, which can change in either direction with the passage of time (Junius-Walker et al., 2018). Therefore, given the high incidence and prevalence of frailty and the negative health conditions and associated factors, modifiable factors and underlying mechanisms associated with frailty progression need to be explored to reverse the course of frailty in older adults.

According to stereotype embodiment theory (SET), as people age, internalized age-related stereotypes, whether positive or negative, are eventually applied to the ego and translated into expectations and attitudes about a person's aging process (Levy, 2009). This introspective belief is called self-perceptions of aging (SPA) and appears to have effects on psychological, behavioral, and physiological pathways (Levy, 2009). Previous studies have shown that more negative SPA was associated with adverse health outcomes (frailty, falls, hospitalizations, and decrease in activities of daily living; Moser et al., 2011; Sun et al., 2017), higher risk of death and shorter longevity (Sargent-Cox et al., 2014), higher depressive symptoms (Freeman et al., 2016). and worse cognitive functioning (Siebert et al., 2020). For older people who are in poor health, their attitude toward aging is likely to be more negative, which may put their health at even greater risk (Wurm et al., 2017). This study aimed to better understand how SPA is associated with frailty in a community-based sample of older adults to increase understanding of the underlying mechanisms that may exacerbate or delay the progression of frailty. Previous studies have shown that frailty is strongly associated with psychological, cognitive, and physical outcomes, such as depressive symptoms (Soysal et al., 2017), cognitive status (Searle and Rockwood, 2015), loneliness (Herrera-Badilla et al., 2015), and exercise (Kelaiditi et al., 2014). Depression is one of the most prevalent psychological distress in later life (Alexopoulos, 2005), and has been described as an antecedent of frailty (Chu et al., 2019). Furthermore, cognitive status and frailty were found to interact in an aging-related decline cycle (Robertson et al., 2013), the frailty among older adults is associated with the worse cognitive performance (Aguilar-Navarro et al., 2019). It is essential that higher levels of psychological health may help protect frailty and delay onset of frailty (Gale et al., 2014). Therefore, considering that depressive symptoms and cognitive status are strongly associated with SPA and frailty, depressive symptoms and cognitive status may also be the underlying psychological and cognitive pathways through which SPA affects frailty.

In the light of the above, the aim of this study is to conduct a cross-sectional study of older adults to determine the effect of self-perceptions of aging on frailty and internal relation mechanism using the SET as a framework. We performed this study to examine three hypotheses as follow: (a) SPA, loneliness, depressive symptoms, and locomotive function was positively associated with frailty. Cognitive status was negative associated with frailty. (b) SPA can influence frailty through depressive symptoms or cognitive status. To our knowledge, these possible mediators have not been studied in the Chinese context. Therefore, this study provides an opportunity to identify unique positive or negative aspects of Chinese older adults' expectations and attitudes about their own aging, namely, SPA, to predict frailty, and explore the potential mechanisms between these two variables. Our research provides support for the consequences of aging stereotypes, providing support for Levy's SET.

MATERIALS AND METHODS

Participants and Procedure

From March to December 2019, a convenience sampling survey was conducted among people over 65 years old in the Xinxiang city community in Henan Province, China. All participants were older adults aged 65 years and above, taking part in the annual physical examination in the communities of the designated community health centers in Xinxiang, China. Individuals diagnosed with dementia by a doctor and participants who were unable to agree to participate in the study in person due to serious visual, auditory, or speech barriers were not included in this study.

Prior to the formal investigation, we introduced the research plan and specific procedures to the community health Service Center of Xinxiang City and obtained the approval of the institution. The investigators (8 postgraduate students in psychological and geriatric care) all underwent uniform standardized training prior to conducting the investigation. The investigators systematically described the purpose and process of the study to the participants to ensure that all participants knew the purpose of the survey and agreed to participate in the survey. During the formal investigation, investigators collected data through in-depth interviews. If a

volunteer agreed to participate but had difficulty with reading or writing, the investigator assisted the respondent in filling out the form according to his/her wishes. Following testing, participants were thanked and compensated for their time. As compensation, each participant received a free breakfast.

Sample Size

Depending on the requirements of the structural equation model (SEM), the sample size (N) and the amount of estimated limitations (parameters) need to be in the right proportion (McDonald and Ho, 2002). Kline believes the N:q ratio should be above 10 or even 20 (Kline, 1998). In this study, the N:q ratio rule was identified to be 20/1, q was identified to be 10. Therefore, a minimum sample size of 240 was calculated under the consideration of 20% invalid questionnaires. In this survey, we investigated 850 older adults. Due to lack of data, 28 participants were excluded. Thus, the final sample size was 822 (96.71%). The sample size met the requirements for SEM analysis.

Measures

Socio-Demographic Variables

We assessed participants' social demographic information (i.e., age, gender, educational level, marital status, and monthly income), health-related status (i.e., physical exercise, nutritional status, smoking history, and drinking history), and health conditions (i.e., anthropometric data and number of concurrent chronic diseases) through a demographic questionnaire devised by the researchers.

Self-Perceptions Assessment

SPA were assessed using the Chinese version of the Brief Aging Perceptions Questionnaire (B-APQ; Wang et al., 2021). The B-APQ is composed of 17 items that evaluate individuals' understanding of aging along five different dimensions to determine whether a person's attitudes are positive or negative (Sexton et al., 2014). Scores ranged between 17 and 85; the higher the overall score, the more negative an individual's attitude toward aging. The Chinese version of the B-APQ was internally consistent and reliable (Cronbach's α of 0.91; Wang et al., 2021).

Cognitive Status Assessment

Cognitive status was assessed using the Chinese version of the Mini-Mental State Examination (MMSE; Xiao-xuan et al., 2016), which consists of 30 items evaluating global cognition along the following dimensions: place and time orientation, attention and calculation, and memory recall. An MMSE score of 24 or lower usually indicates suspected cognitive impairment (Brown et al., 2020). The Chinese version of the MMSE was internally consistent and reliable (Cronbach's α of 0.83; Xiao-xuan et al., 2016).

Loneliness Assessment

Loneliness was assessed using the Chinese version of the UCLA loneliness scale-8 (ULS-8; Zhou et al., 2012), an eight-item scale assessing an individual's experience of loneliness. Total scores for this questionnaire range between 8 and 32. ULS-8 has shown satisfactory reliability and validity in evaluating loneliness among older Chinese adults, with a Cronbach α of 0.83 (Zhou et al., 2012).

Depressive Symptoms Assessment

Depressive symptoms were assessed using the Chinese version of the Patient Health Questionnaire-9 (PHQ-9; Wang et al., 2014). It was used to assess whether respondents had experienced sadness or depressive symptoms in the 2 weeks preceding the questionnaire survey. The sum of scores ranged from 0 to 27. A PHQ-9 score of ≥10 is considered to be the positive screening cutoff (Levis et al., 2019). PHQ-9 has been widely verified in different Chinese populations, with a Cronbach α of 0.86 in the general Chinese population (Wang et al., 2014).

Locomotive Function Assessment

The Japanese Orthopedic Association proposed the concept of "locomotive syndrome" for the prevention and treatment of locomotive organ diseases in 2007 (Nakamura, 2008). Locomotive syndrome is a condition in which damage to the locomotive organs (i.e., muscles, bones, and joints) leads to a decline in activities of daily living. Locomotive syndrome was assessed using the Chinese version of the Geriatric Locomotive Function Scale (GLFS-25; Ning et al., 2016). The sum of scores ranged from 0 to 100. A respondent with a GLFS-25 score of 16 or above is usually considered to be suffering from locomotive syndrome (Shinichi et al., 2014). The Chinese version of the GLFS-25 was internally consistent and reliable (Cronbach's α of 0.92; Ning et al., 2016).

Frailty Assessment

Frailty was assessed using the Chinese version of the Tilburg Frailty Indicator (TFI; Dong et al., 2017), a self-rating scale developed based on the integral frailty model (Gobbens et al., 2010b). The scale measures three domains of frailty: physical frailty, psychological frailty, and social frailty. TFI is characterized by multi-dimensional structure, fast and easy to use, and accurate risk prediction of frailty adverse outcomes (Gilardi et al., 2018). Furthermore, TFI can better predict the overall functional status of older people's bodies and provide evidence for clinical prevention and treatment of disease (Vrotsou et al., 2018). TFI is considered to be an appropriate instrument for assessing the frailty of older adults in the community (Sutton et al., 2016; Gilardi et al., 2018). TFI scores can range between 0 and 15, with the frailty cutoff being 5 (Gobbens et al., 2010a). TFI has been validated in populations from many countries all over the world, including Chinese older adults, with a Cronbach coefficient of 0.71 (Dong et al., 2017).

Statistical Analysis

Our analytic approach involved two steps. First of all, descriptive statistics and univariate analysis were conducted with all

variables by SPSS version 23.0. Spearman's rank correlation analysis and multiple regression analysis were conducted to examine the relations between loneliness, depressive symptoms, self-perceptions of aging, locomotive function, cognitive status, and frailty. Then, the mediation model was tested using AMOS 23.0. A two-step procedure was used to analyze the mediation effect (Anderson and Gerbing, 1988). Firstly, the measurement model, which involved four latent variables, was tested to assess the goodness of fit represented by its explicit indicators. This study used several goodness-of-fit indices to evaluate model fit: Chi-square/degrees of freedom (χ^2/df), root mean square error of approximation (RMSEA), goodness-of-fit index (GFI), comparative fit index (CFI), and the Tucker–Lewis index (TLI). A structural equation modeling (SEM) was considered acceptable when χ^2/df was <5; RMSEA was <0.08; and GFI, CFI, and TLI were ≥ 0.90 (Schermelleh-Engel et al., 2003). Secondly, if the index of measurement model met the requirements, the maximum likelihood estimation examined the SEM. Besides the goodness-of-fit index, a bias-corrected percentile Bootstrap test was used to test the significance of the indirect effect, 5,000 repeated sampling with replacement was performed in the original data ($n = 822$), estimated 95% Confidence Interval (CI) for the indirect effect using a 2.5 percentile and a 97.5 percentile. When the bias-corrected 95% CI of bootstrap generated non-parametric estimation does not contain the number 0, the Point estimate is considered statistically significant (Hayes, 2013). When the value of $p < 0.05$, the result is considered to be statistically significant.

Ethics Consideration

This study was conducted is in accordance with the Declaration of Helsinki. Before implementation of the research scheme, the study was approved by the local ethics committee (2019-HLPY-A001). Written informed consent was obtained from all participants in this study.

RESULTS

Sample Characteristics

The participants' socio-demographic data are presented in **Table 1**. The median age of the total sample was all around 70 years, and over half of the total sample was female (57.06%). The participants' median body mass index (BMI) was $M_{BMI} = 25\,kg/m^2$. Normal BMI was reported in 305 (37.11%) cases. More than half of participants had obtained a high school education or above (52.80%). There were 396 (48.18%) cases of participants who were suffering from more than two chronic diseases simultaneously.

Overall, the average B-APQ score was (40.95 ± 9.18). The median score of TFI, ULS-8, PHQ-9, GLFS-25, and MMSE were 3, 9, 1, 3, and 28, respectively. Among all participants, 21.53% reported frailty and 2.80% reported depressive symptoms. Cognitive impairment was found in 8.76% of respondents, and 8.27% showed signs of locomotive syndrome.

TABLE 1 | Frailty among older adults with different sample characteristics ($N = 822$).

Characteristics	*Frequency (%)/Mean (SD)/ [M(P75-P25)]*	TFI Univariate Analysis		
		Mean rank	*Z/χ²*	*P*
Age[a], yr	70(7)			
Age group			34.280	<0.001[b]
60–69	390(47.45)	381.02		
70–79	362(44.03)	416.51		
≥80	70(8.52)	555.38		
Height (cm)	163.10(7.83)			
Weight (kg)	65(13)			
Waistline (cm)	84(10)			
BMI (kg/m²)	25(4)			
BMI group			5.999	0.112[b]
≤18.4	20(2.43)	521.63		
18.5–23.9	305(37.11)	413.00		
24.0–27.9	386(46.96)	412.10		
≥28.0	111(13.50)	385.47		
Gender			−4.463	<0.001[a]
Male	353(42.94)	370.15		
Female	469(57.06)	442.62		
Marital status			−5.033	<0.001[a]
Married	692(84.18)	393.97		
Divorced/Widowed/ Unmarried	130(15.82)	504.83		
Educational level			32.451	<0.001[b]
Primary and below	154(18.73)	505.03		
Secondary	234(28.47)	403.45		
High and above	434(52.80)	382.65		
Monthly income (CNY)			21.048	<0.001[b]
<2,000	46(5.60)	502.48		
2,000–2,999	347(42.21)	416.06		
3,000–3,999	184(22.38)	443.05		
≥4,000	245(29.81)	364.26		
Physical exercise			−2.909	0.004[a]
Long-term adherence	722(87.83)	402.80		
Never or occasionally	100(12.17)	474.34		
Nutritional status			−3.529	<0.001[a]
Well-nourished	626(76.16)	395.63		
malnutrition	196(23.84)	462.19		
Smoking history			−2.026	0.043[a]
Yes	175(21.29)	380.19		
No	647(78.71)	419.97		
Drinking history			−1.954	0.051[a]
Yes	259(31.50)	388.34		
No	563(68.50)	422.15		
Number of concurrent chronic diseases			−4.196	<0.001[a]
≤1	426(51.82)	378.99		
≥2	396(48.18)	446.48		

M, Mean; SD, Standard deviation;

[a]range = 60–95 yr; BMI, Body Mass Index; CNY, Chinese Yuan.

[a]P derived from Mann-Whitney U-test;

[b]P derived from Kruskal–Wallis H-test.

Spearman's Rank Correlation Analyses and Multiple Regression Analyses

We designed **Table 2** to display the relationships of loneliness, depressive symptoms, self-perceptions of aging, locomotive function, cognitive status, and frailty. The results of Spearman's rank correlation analyses suggested that all the variables were

TABLE 2 | Spearman correlations for loneliness, depressive symptoms, self-perceptions of aging, locomotive function, cognitive status, and frailty.

Variable	*Mean (SD)/ [M(P75-P25)]*	1	2	3	4	5	6
1. Frailty	3(2)	1					
2. Loneliness	9(3)	0.267**	1				
3. Depressive symptoms	1(3)	0.440**	0.269**	1			
4. Self-perceptions of aging	40.95(9.18)	0.481**	0.231**	0.327**	1		
5. Locomotive function	3(5)	0.451**	0.170**	0.426**	0.439**	1	
6. Cognitive status	28(3)	−0.337**	−0.057	−0.142**	−0.175**	−0.194**	1

**$p < 0.001$.

significantly correlated with one another. Frailty was significantly positively correlated with loneliness, depressive symptoms, self-perceptions of aging, and locomotive function ($r = 0.267$, $r = 0.440$, $r = 0.481$, $r = 0.451$; $p < 0.001$), and it also showed a significant negative correlation with cognitive status ($r = -0.337$, $p < 0.001$). SPA was significantly positively correlated with depressive symptoms ($r = 0.327$, $p < 0.001$), and it also showed a significant negative correlation with cognitive status ($r = -0.175$, $p < 0.001$).

The statistically significant ($p < 0.05$) variables in the participants' demographic variables and Spearman's rank correlation analyses were entered into a multiple regression analysis for TFI using a stepwise selection procedure. The results showed that loneliness, depressive symptoms, self-perceptions of aging, locomotive function, and cognitive status were the five factors to be entered the regression equation, and the variance of joint explanation was 46.60%. Loneliness, depressive symptoms, self-perceptions of aging, locomotive function, and cognitive status were shown to explain frailty among older adults by 8.30, 31.0, 18.0, 25.30, and 17.30%, respectively. None of the participants' social or demographic variables was an independent predictor of frailty in the multiple regression analysis (**Table 3**).

TABLE 3 | Multiple regression results for frailty.

Variable	*Standardized β*	*SE*	*95% CI*
Loneliness	0.083	0.013	[0.014, 0.067]
Depressive symptoms	0.310	0.014	[0.124, 0.180]
Self-perceptions of aging	0.180	0.005	[0.019, 0.038]
Locomotive function	0.253	0.006	[0.039, 0.063]
Cognitive status	−0.173	0.015	[−0.120, −0.060]

$R^2 = 0.475$, *Adjusted* $R^2 = 0.466$; $F = 52.183$, $P < 0.001$.

Structural Equation Modeling

We first constructed the relationship structure of all variables according to the results of the correlation matrix and multiple regression analyses. We further analyzed the influence of mediating latent variables on the relationship between independent variables and outcome variables, to determine whether they had weakened, strengthened, or no influence. The model of the relationships between self-perceptions of aging and frailty, as mediated by depressive symptoms and cognitive status, is shown in **Supplementary Figure 1**. The results show that the model has acceptable fit indices: $\chi^2 = 303.398$ (df = 85, $p < 0.001$), $\chi^2/df = 3.569$, GFI = 0.953, AGFI = 0.934, CFI = 0.939, TLI = 0.941, RMSEA = 0.056 (90% CI: 0.049, 0.063). **Table 4** presents the bootstrap results, showing all the model's standardized direct and indirect effects to be statistically significant.

As illustrated in **Supplementary Figure 1A**, SPA ($\beta = 0.306$ and $p < 0.001$) and depressive symptoms ($\beta = 0.714$ and $p < 0.001$) had direct positive effects on frailty. Cognitive status ($\beta = -0.483$ and $p < 0.001$) had direct negative effects on frailty. The results from the bootstrap test for the significance of all pathways are shown in **Table 4**. Results for indirect pathways indicated that the indirect pathways between SPA and frailty through depressive symptoms were statistically significant ($\beta = 0.391$, 95% CI [0.027, 0.061], and $p < 0.001$). Furthermore, the indirect pathways between SPA and frailty through cognitive status were statistically significant ($\beta = 0.148$, 95% CI [0.009,0.024], and $p < 0.001$). Overall, the total effect of SPA on frailty was 0.539 through two indirect pathways (95% CI [0.421, 0.695] and $p < 0.001$). Based on these outcomes, it can be stated that depressive symptoms and cognitive status mediated the relationship between SPA and frailty and that this total mediating effect explains 63.67% of the total effect.

DISCUSSION

The burden of debilitating older people is expected to increase in low- and middle-income countries around the world due to rapidly aging populations (Hoogendijk et al., 2019). Therefore, it is imperative to clarify the potential mechanism of frailty in older adults, it is the main concern of healthcare policy and provision to formulate more effective intervention programs to prevent or slow down the development of frailty before it leads to substantial functional decline (Dent et al., 2019). The research purpose was to examine the effect of SPA on frailty and the mediating effect of depressive symptoms and cognitive status in this relationship.

Our study found that 177 older people in the community we sampled suffered from frailty (according to TFI score), and the prevalence of frailty was 21.53%. The results exceed the 18.0% prevalence of frailty previously detected by TFI among Chinese community-dwelling older people (Dong et al., 2017). This study shows that higher TFI scores were found among older women, those with low levels of education and low monthly incomes, those whose marital status is divorced or widowed or unmarried, those who have smoking history,

TABLE 4 | Bootstrapping total, direct, and indirect effects and 95% Confidence Interval (CI) for the mediation model.

Model pathways (SPA Frailty)	Point estimate	Product of coefficients		Bias-corrected *95% CI*		Two-tailed Significance	Ratio of total effect
		SE	*Z*	Lower	Upper		
Total effect	0.845	0.060	14.083	0.735	0.969	<0.001	
Direct effect	0.306	0.079	3.873	0.148	0.456	<0.01	36.21%
Indirect effect	0.539	0.068	7.927	0.421	0.695	<0.001	63.79%

those who never or only occasionally took part in physical exercise, those suffering from malnutrition, and those with two or more concurrent chronic diseases. This suggests that medical personnel should pay attention to the above characteristics in the population as they are possible frailty intervention targets.

According to SET, frailty was significantly positively correlated with loneliness, depressive symptoms, self-perceptions of aging, and locomotive function, and it also showed a significant negative correlation with cognitive status. Further multiple regression analysis showed that loneliness, depressive symptoms, self-perceptions of aging, locomotive syndrome, and cognitive status are key factors affecting the occurrence and development of frailty. This result further supports the previous research on frailty and its related factors (Kelaiditi et al., 2014; Herrera-Badilla et al., 2015; Searle and Rockwood, 2015; Carneiro et al., 2017). Therefore, health providers should pay more attention to these adjustable psychological and physical factors in order to delay the onset of frailty in older people.

By measuring individuals' depressive symptoms and cognitive status levels, this study provides evidence of the internal mechanism of the influence of SPA on frailty. In this model of parallel multiple mediators for frailty, depressive symptoms and cognitive status played mediating roles, and weakened the effects of SPA. Our study found that older people with negative views of aging are more likely to suffer from frailty. This conclusion is consistent with that of Levy's view on Aging Self-Stereotypes research (Levy, 2003). In addition, a longitudinal study also confirmed that people with a negative self-perceptions of aging were more likely to be frailer after 6 years (Warmoth et al., 2018). Therefore, this study suggests that perception of aging may be a contributing factor in the development of frailty and that promoting and maintaining positive perception of aging may provide a way to help individuals cope with health and frailty conditions.

The process of aging is a risk factor for frailty, cognition, and psychosocial function (Panza et al., 2018). Depressive symptoms are one of the most severe and prevalent mental disorders among older people (Gonçalves-Pereira et al., 2019). In this study, 2.80% of the community older adults sampled had depressive symptoms. We find that depressive symptoms play an important role in explaining the relationship between SPA and frailty. Psychological pathways suggest that more positive SPA is beneficial to relieve depressive symptoms, and thus delay the deterioration of frailty. On the contrary, when older adults have more negative attitudes toward aging, depressive symptoms have greater intrinsic psychological significance, which is a subjective unpleasant experience, which will trigger frailty worsening. As we introduced earlier, older people with passive SPA have an increased probability of future depressive symptoms (Freeman et al., 2016). In addition, consistent with previous findings, depressive symptoms conferred a higher risk for frailty worsening (Soysal et al., 2017), mainly due to their shared physiological etiology and the unhealthy lifestyle caused by depressive symptoms. Therefore, paying attention to and preventing depressive symptoms is of great significance for delaying frailty among older people.

Considering the various neurobiological mechanisms of aging and the changes in brain structure and function that occur with aging, human cognitive abilities will undoubtedly change with aging. In our study, the effect of SPA on frailty was also partly influenced by cognitive status. This result is supported by a previous study, which showed that the more positive a person's attitude toward aging, the better their cognitive status, and the lower the risk of developing or forming frailty (Robertson and Kenny, 2016). We report that positive SPA may be a better predictor of cognitive health in older adults. This is consistent with the explanation in positive psychology including "how optimism and hope affect health" (Seligman and Csikszentmihalyi, 2000). In addition, Fredrickson's broaden-and-build theory (Fredrickson, 1998) provides a mechanism by which positive beliefs and emotions may confer benefits to cognitive abilities. The correlation between frailty and cognitive impairment may be related to a common occurrence mechanism of both, such as genetic inheritance, chronic inflammation, malnutrition, mitochondrial dysfunction, oxidative stress, hypothalamic–pituitary–adrenal axis dysfunction, endocrine disorders, energy metabolism imbalance, and so on (Howrey et al., 2020). Therefore, good cognitive status can be considered a protective factor that can improve adverse effects in the pathway between self-perceptions of aging and frailty.

This study has some potential limitations that should be further interpreted. First, this study presents us with cross-sectional data, which does not allow us to determine causality. Second, we cannot track the health of patients, especially those with poor health outcomes (e.g., non-adaptive self-perceptions of aging, cognitive impairment, loneliness, depressive symptoms, and/or locomotive syndrome). These factors need further longitudinal study. Furthermore, physical frailty and mild cognitive impairment (MCI) often coexist, as these two syndromes share many common neuropathologies (Kwan et al., 2019). Therefore, future exploration of risk factors for cognitive frailty may lead to reversal of cognitive frailty outcomes. Despite these limitations, the current research helps us to understand the complex relationship between old people's views on aging and frailty, giving it its value. The findings suggest that, in

the context of China, depressive symptoms and cognitive status play a partial mediating role between SPA and frailty and that SPA, depressive symptoms, and cognitive status can be used as the targets of frailty intervention. This could provide a theoretical basis for improving frailty in future intervention studies. Future research must identify the predictive value of these determinants using longitudinal surveys in order to assess their usefulness within the context of intervention studies.

CONCLUSION

This study first shows that the overall prevalence rate of frailty was 21.53%, and older people who view aging negatively tend to fall into a vicious spiral of frailty, depressive symptoms, and cognitive disorder. Degeneration is the result of the body's natural development. It is worth noting that frailty is dynamic and reversible, and early screening and preventive intervention can delay or even reverse signs of frailty among older people. Our results suggest that community health service providers should implement timely evaluation of frailty status in older adults, help older adults revise their passive perspectives on aging, alleviate or prevent depressive symptoms, and improve cognitive status. This should be done to further delay the progress of frailty, improve clinical outcomes in older adults with frailty syndrome, and promote healthy aging.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The First Affiliated Hospital of Xinxiang Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YL, KY, JS, and HC participated in the concept and design of the study. KY and HH collected data and controlled quality. KY, YL, and JS drafted and edited the manuscript. KY, HH, and BZ performed the statistical analyses. All authors made substantial contributions to interpret data and revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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