PHYSICAL AND COGNITIVE FRAILTY IN THE ELDERLY: AN INTERDISCIPLINARY APPROACH

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PHYSICAL AND COGNITIVE FRAILTY IN THE ELDERLY: AN INTERDISCIPLINARY APPROACH

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EDITORIAL
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Editorial: Physical and Cognitive Frailty in the Elderly: An Interdisciplinary Approach

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Keywords: physical and cognitive frailty, aging, mild cognitive impairment, major neurocognitive disorders, assessment, interventions

Editorial on the Research Topic

Physical and Cognitive Frailty in the Elderly: An Interdisciplinary Approach

INTRODUCTION

The scientific contributions published in the Research Topic emphasize frailty as a complex and heterogeneous clinical state which is described as the loss of harmonious interactions among various dimensions, such as biological, functional, psychological, cognitive, and social domains leading to homeostatic instability.

Data and inferences derived from different models currently in use to study frailty in aging individuals are presented: (1) the *biomedical approach*—represented by the Fried's frailty phenotype model (Fried et al., 2001)—which highlights a reduction in the ability to preserve homeostasis and respond to environmental changes appropriately; (2) the *bio-psycho-social model* (Gobbens et al., 2010), which defines the importance of a multidimensional approach to frailty, considering it no longer just a pathophysiological syndrome, but assessing its neuropsychological and social implications, especially considering different frailty states in individuals with neurocognitive disorders. Indeed, a fundamental question that needs to be clarified regards the relationship between neuropsychological dysfunctions and physical frailty. Up to now, this relationship is described as a "feedback loop relationship." However, there is still a lack of knowledge about the mutual relationship between neuropsychological dysfunctions and physical frailty when considering the continuum from physiological aging to major neurocognitive disorders.

Three different reviews emphasized the different approaches by outlining:

(1) A possible association between frailty and executive dysfunction in mild and major neurocognitive disorders due to Alzheimer's and Parkinson's diseases (Bartoli et al., 2020);
(2) The critical determinants of frailty syndrome from a multidimensional perspective in cardiological conditions (Wleklik et al.);
(3) A possible intervention model based on an integrated approach to proactively manage community-dwelling older people with suspected frailty (Lauretani et al.).

Indeed, the literature emphasizes the importance of developing programs that reverse the course of frailty while reducing the health, psychological, social, and economic costs of its negative consequences.

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THE BIOMEDICAL APPROACH

Two original research are contextualized within the Fried's frailty phenotype model, which, based allows individuals to be classified as robust, pre-frailty or frailty on the number of lacking factors out of the five main components (weakness, sluggishness, involuntary weight loss, exhaustion, and low physical activity).

The first article investigates the specific contribution of each of the Fried's frailty components in a sample of 142 oldest old community-dwelling people. A multiple correspondence analysis has made it possible to identify two main facets of frailty: one related with physical components and the second related with intrinsic conditions (Alves et al.).

The second article investigates whether the frailty phenotype has a different association with hearing loss (HL) and tinnitus in 429 community-dwelling older adults. Authors found that frailty phenotypes showed divergent association with HL and tinnitus (Ruan, Chen, Zhang, Ruan et al.).

THE MULTIDIMENSIONAL APPROACH—VALUING COGNITIVE FRAILTY

Cognitive decline and impaired global cognition have been mostly linked to frailty in the elderly. *Cognitive frailty* refers to the co-occurrence of mild cognitive impairment and physical frailty in the absence of a diagnosed major neurocognitive disorder (MND).

Two original articles suggest the importance of:

(1) *screening cognitive frailty* with short cognitive screening instruments, analyzing their diagnostic accuracy in a Chinese population of 95 outpatients in rehabilitation clinics and suffering from subjective cognitive disorder, mild cognitive impairment and major neurocognitive disorder (Xu et al.).
(2) *applying objective assessments* for the diagnosis of cognitive frailty subtypes, analyzing it in 335 community-dwelling older adults suffering from subjective cognitive decline and mild cognitive impairment compared to 144 robust elderly with normal cognition (Ruan, Chen, Zhang, Zhang et al.)

The general concept of looking more deeply into the cognitive correlates of frailty is interesting and may shed light on a more comprehensive model of cognitive frailty. This aspect becomes even more pervasive in the case of MND. This aspect is addressed by an original research which aims to identify predictors of those severe conditions in a sample of 250 adults, 30.4% of whom were classified as having probable major neurocognitive disorder (Sousa et al.). Authors found that advanced age, school education, physical activity, and hand strength are major predictors of MND.

These findings support the findings of previous literature, which has shown that pre-frailty already impact on executive-metacognitive functions and behavior in minor and major neurocognitive disorders (Amanzio et al., 2017). Moreover, a correlation between a specific pattern of co-occurring gray matter atrophy and hypometabolism with pre-frailty has been found in behavioral variant frontotemporal dementia (Amanzio et al., 2021), paving the way for this type of investigation in other types of neurodegeneration as well.

THE MULTIDIMENSIONAL APPROACH—VALUING PHYSICAL ACTIVITY

Inadequate physical activity is associated to higher probability for frailty in the elderly (da Silva et al., 2019). Four original articles address this matter.

A first study aims to determine whether grip strength loss is a convincing predictor of impairment in cognitive performance and social functioning in 30 patients with type-2 diabetes mellitus and 107 subjects with severe mental illnesses (35 major depressive disorder, 42 bipolar disorder, 30 schizophrenia) in a 1-year longitudinal study (Aliño-Dies et al.). Authors concluded that interventions aimed to improve the overall physical conditions of patients who have poor grip strength could have beneficial effects on global cognition and social functioning.

A second original research sought to investigate the possible long-term association between activity, physical and cognitive functions in 10,240 middle-aged and elderly people through a multivariate latent growth modeling (Bae). Moreover, it was verified whether there is a long-term mediating effect of physical activity on the relation between social activity and cognitive function. The author suggested that social activity had a positive impact on cognitive function and negative impact on physical function decline. Furthermore, a decline in physical activity affected cognitive function through the indirect action of social activity.

A cross-sectional study aims to explore the interactive relation between physical frailty and psychological well-being on 358 older Portuguese women, finding that emotional well-being and global cognitive performance are strongly associated with physical frailty (Furtado, Caldo et al.). Authors concluded that the implementation of active lifestyle interventions to enhance positive psychological outcomes could help in the physical and mental health care of institutionalized elderly patients.

Finally, a clinical trial verified the potential beneficial impact of a 14-week combined chair-based exercise program (CEP) on immune/anti-microbial functions, salivary steroid hormones, functional fitness, and mental well-being in 47 pre-frail older women. Authors concluded that CEP is effective in improving performance in static balance and gait speed, immune and anti-microbial response, and happiness, while decreasing feelings of stress (Furtado, Letieri et al.).

An increasingly significant number of people find themselves in a condition of frailty, making this a hot topic. Just for an example, physical and cognitive frailty have proved to be more useful than ever in understanding the impact of the SARS-CoV-2 pandemic on the elderly population (Maltese et al., 2020; Bartoli et al.) and in guiding clinical vaccine trials principles (Palermo, 2020).

Research and attention to the issues proposed in this Research Topic will be increasingly necessary to ensure effective public health and welfare policies.

AUTHOR CONTRIBUTIONS

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

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REVIEW
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Multidimensional Approach to Frailty

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The concept of frailty syndrome (FS) was first described in the scientific literature three decades ago. For a very long time, we understood it as a geriatric problem, recently becoming one of the dominant concepts in cardiology. It identifies symptoms of FS in one in 10 elderly people. It is estimated that in Europe, 17% of elderly people have FS. The changes in FS resemble and often overlap with changes associated with the physiological aging process of the body. Although there are numerous scientific reports confirming that FS is age correlated, it is not an unavoidable part of the aging process and does not apply only to the elderly. FS is a reversible clinical condition. To maximize benefits of frailty-reversing activities for patient with frailty, identification of its determinants appears to be fundamental. Many of the determinants of the FS have already been known: reduction in physical activity, malnutrition, sarcopenia, polypharmacy, depressive symptom, cognitive disorders, and lack of social support. This review shows that insight into FS determinants is the starting point for building both the comprehensive definition of FS and the adoption of the assessment method of FS, and then successful clinical management.

Keywords: cardiology, determinants, disability, elderly, frailty syndrome, multi-morbidity

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INTRODUCTION

There are an increasing number of research reports on frailty syndrome (FS) showing its importance in cardiology and evidence-base clinical practice. Guidelines for clinical management in cardiology emphasize the need to monitor FS and search for its reversible causes in the elderly (Ponikowski et al., 2016). Despite the widespread importance of FS in clinical management, there are no explicit cardiological guidelines adopting a specific definition of FS and requirements for applying methods of its identification (Vogt et al., 2018). In cardiology, there are no standardized methods in clinical decisions-making based on FS, as it is still being diagnosed with the patient's foot-of-the-bed assessment or the so-called "eyeball test" (Bridgman et al., 2015). The Task Force of the International Conference of Frailty and Sarcopenia Research (ICFSR) has developed clinical practice guidelines for identification and management of physical frailty. These recommendations recognize that older adults over age 65 should be screened for FS rapidly based on the validated instrument adapted for the specific patient's conditions. All patients who passed a positive screening test for frailty and patients classified as pre-frail should receive further assessments for clinical frailty (Dent et al., 2019).

According to the phenotypic approach, older adults are diagnosed as pre-frail when there are one or two components: weakness, slowness, weight loss, low physical activity, or exhaustion. Frailty is a dynamic condition, whereby pre-frail symptoms may develop into a full-blown frailty with the presence of three or more components, but may also be prevented by appropriate clinical measures (Hanlon et al., 2018). An optimal screening for FS in cardiovascular disease should be practical, sensitive, and approved for a specific patient population (Kim et al., 2016). In the literature, there are one-dimensional tools for assessing FS most often intended to screen for physical frailty, but multidimensional tools are becoming popular in clinical practice. The most frequently cited assessment of FS includes Frailty Phenotype, Frailty Index, and Clinical Frailty Scale (Khezrian et al., 2017). Multidimensional measures of FS can provide clinicians with more data on patients' needs, their initial vulnerability, and also enable individualized therapeutic management. There is empirical evidence in support that FS is reversible. Thus, planned cardiac rehabilitation programs can help improve patients' functional fitness, their ability to perform exercises, enhance psychosocial well-being, nutritional status, independence, and reduce the risk of death (Sepehri et al., 2014). Such multidimensional interventions of FS by focusing on several frailty components provide greater efficiency in the treatment and diagnosis of cardiological patients (Uchmanowicz et al., 2018).

The ICFSR guidelines include a recommendation for implementing comprehensive care with physical frailty that handles sarcopenia, treatable causes of weight loss, and the causes of exhaustion (depression, anemia, hypotension, hypothyroidism, and vitamin B12 deficiency) (Dent et al., 2019). To maximize benefits of frailty-reversing activities for patient with frailty, identification of its determinants appears to be fundamental. This multi-dimensional holistic approach is in favor of better diagnosis FS symptoms than the pure physical phenotype approach. The identification and further treatment of patients with cardiovascular disease based on the modified or reversed FS parameters directly translate into better treatment outcomes.

The main goal of this review is to provide a detailed scrutiny of the frailty determinants presented in the recent literature on cardiology and cardiological nursing. We argue in this review for determinants, favoring a multidimensional assessment of FS in both research and clinical practice. As illustrated in **Figure 1**, we classified the determinants into several domains: clinical, physical, psychological, cognitive, and social ones. We complemented classification of each determinant with information necessary for its identification. This review emphasizes a multidimensional approach accommodating complexity of FS phenomena in research and clinical practice as a holistic approach to FS diagnosis and individualized therapeutic strategies that reduce the adverse effects of FS.

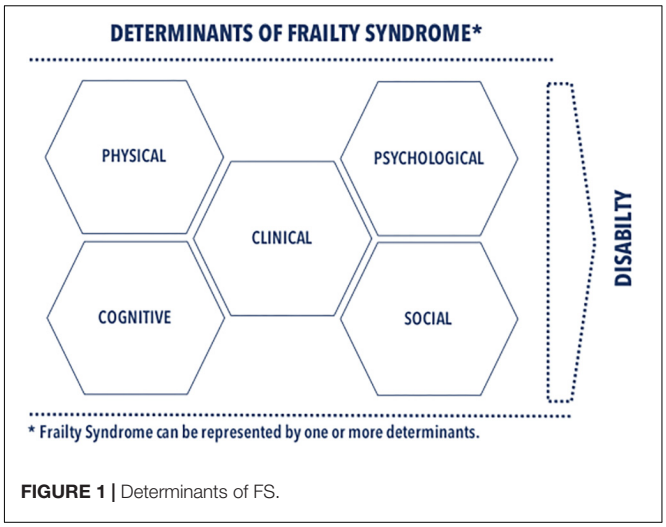

FIGURE 1 | Determinants of FS.

DEFINITION

The word frailty comes from the French language from the word *frêle*, which means: fragile, weak, delicate (Diaz et al., 2015). The notion of FS one usually understands as a syndrome of weakness, fragility, or exhaustion of reserves. In the past, FS was only a determinant of biological age until clinical observations that patients' responses to the disease, their functional state, and survival depend not solely on the age factor, but by the physiological resources of the organism. Although there are many reports confirming that there is a relationship between FS and age, today's view suggests FS to be not an unavoidable part of the aging process and does not apply only to the elderly. Therefore, FS goes beyond the physiological process of organism aging. For instance, FS affects younger patients with chronic diseases or cognitive dysfunctions (Bagshaw et al., 2014). In clinical medicine, there is still no common definition of FS, which is often referred to as a syndrome or condition.

One definition of FS states that it is: "*a physiological syndrome, characterized by a reduction in reserves and resistance to stressors, resulting from the accumulation of reduced performance of different physiological systems, which in turn leads to susceptibility to adverse consequences*" (Fried et al., 2001).

According to another definition, FS is: "*a multidimensional syndrome of homeostatic reserve loss (energy, physical and mental abilities), which promotes the accumulation of deficits, increasing the patient's sensitivity and risk to adverse medical consequences*" (Clegg et al., 2013; Rajabali et al., 2016).

In the 2013 consensus of six geriatric societies assumed that FS is: "*a multi-causal clinical syndrome, characterized by a decrease in strength, endurance and reduction in physiological processes, increasing an individual's susceptibility to development of dependency and/or death*" (Morley et al., 2013).

There are two dominant approaches to defining FS, a phenotypic definition of weakness and a definition based on the accumulation of deficits. Fried et al. (2001) proposed the first one based on data from the Cardiovascular Health Study. The second approach uses the frailty index from a Canadian study by Rockwood et al. Both approaches show a similar predictive accuracy in the identification of FS (Graham and Brown, 2017). Phenotypic frailty arises from age-related biological changes that shape the physical features of frailty

(unintentional weight loss, weakening of muscle strength and mass, slower walking, reduced energy, decreased level of physical activity). The frailty model based on the accumulation of deficits recognizes that frailty results from an accumulation of abnormal, not only physical, clinical features including cognitive disorders, depressive symptoms, reduced functionality, multiple diseases, malnutrition, social isolation; their high accumulation speeds up the aging of the body. Phenotypically, physical features are a manifestation of frailty, whereas in terms of the accumulation of deficits are considered as a cause of frailty. The phenotypic approach is one-dimensional, and the one based on the accumulation of deficits is multidimensional (Robinson et al., 2013, 2015).

Multidimensional definitions are becoming increasingly important because FS results from negative effects of various factors on the body's physiology, which increase its vulnerability to even potentially harmless stressors (Kovacs et al., 2017). Therefore, the definition of FS should consider not only the functional state but also the psychosocial weakness, and explicitly shows that a patient with concomitant FS is at risk of complications and susceptible to poor clinical outcomes (Robinson et al., 2013). The literature on FS also defines a pre-frail condition, which identifies individuals at risk of FS (Fried et al., 2001). Since frailty is a reversible state, several targeted interventions can prevent the transition from the pre-frail condition to fully symptomatic FS (Summers et al., 2018). The formulation of a single, common definition of FS appears to be important from both a scientific and clinical point of view. It will enable more accurate assessments of the prevalence of frailty in specific patient populations, facilitate comparisons of research findings and the better availability of meta-analytic scientific data. A single, common definition of FS in clinical practice would also help clinicians to select screening methods.

EPIDEMIOLOGY

In the literature, there are various epidemiological data on the prevalence of FS, because of different research methods to identify it and the patient population assessed (Chen, 2015). Symptoms of FS occur in one in 10 elderly people (Goldfarb et al., 2015). Recent reports suggest that in Europe, 17% of elderly people have FS, while in Poland, the figure stands at 6.7%. In people over 80 years of age, the prevalence of FS in Poland increased up to 50% (Łęgosz et al., 2018). The meta-analysis and systematic review of studies of frailty in 22 European countries in the program of ADVANTAGE Joint Action showed that FS is widespread in Europe, and its actual prevalence varied across the studies and strictly depended on an operational definition of FS. For example, one study included in the analysis showed that the prevalence of FS in a patient population $\geq$80 years in the community is 7.2% (O'Caoimh et al., 2018). A recent study based on the phenotypic frailty model showed the prevalence of FS at 9.9%, while that of the pre-frail condition at 44% (Furukawa and Tanemoto, 2015). In a study on the accumulation of deficits in surgical patients, FS was in 28% of patients and the pre-frail condition in 20% of patients (Robinson et al., 2013). In a systematic review of 15 FS studies involving 44,894 patients, frailty was found in 9.9% of patients.

The prevalence of FS increased with age and was more common in women than in men (Oresanya et al., 2014). The Women's Health and Aging study identified frailty in 11.3% of women. FS is more common in African-Americans and Asians than in Caucasians, single people and those with lower levels of education (Chen, 2015). FS patients are older, more often female, have more co-morbidities and a higher perioperative risk. In addition, they have a lower New York Heart Association (NYHA) class, poorer kidney function, higher NTProBNP (N-terminal pro-brain natriuretic peptide), more depressive symptoms, higher frequency of mobility restrictions in basic and complex everyday activities, and poorer results in quality of life studies (Rodríguez-Pascual et al., 2016). After over 4 years of observation, out of 54.4% of elderly patients without FS, but almost half of the patients suffered from pre-frail status (Chen, 2015). Pre-frail status indicates a fourfold higher risk of developing FS within 4 years of observation (Sergi et al., 2015). In patients with cardiovascular diseases, the incidence of FS ranges from 10 to 60%, whereas in patients undergoing cardiac surgery in old age, it is even 50% (Graham and Brown, 2017; Zuckerman et al., 2017). In the Frailty Assessment Before Cardiac Surgery (ABCS), 46% of patients aged 70 years or older undergoing coronary artery bypass and/or heart valve surgery were frail in a 5-m gait rate test (Afilalo, 2011). A recent report suggests that preventing FS could delay 2–5% of deaths (Łęgosz et al., 2018).

PATHOPHYSIOLOGY

Frailty syndrome pathophysiology arises primarily from a metabolic imbalance of the body and impaired functioning of the immune and endocrine systems. There is a hypothesis that combined processes of apoptosis, aging, autophagy, and mitochondrial dysfunction play a key role at the cellular and molecular levels. Disturbed cellular processes influence the development of FS through changes in the functioning of organs and systems (Graham and Brown, 2017). The changes in FS resemble and often overlap with the physiological aging process, but in FS they are mainly concentrated on a disturbed energy metabolism, which is the imbalance between the anabolic state and the catabolic state. Thus, frailty is often associated with metabolic deficiencies, increased nutritional risk, and sarcopenia, which is defined as a decrease in muscle mass, strength, and capacity (Joyce, 2016; Cruz-Jentoft et al., 2019).

In cardiovascular diseases, inflammation plays a key role in lipoprotein oxidation and platelet activation. Chronic inflammation in FS induces catabolism, which results in a redistribution of amino acids from skeletal muscles, leading to a deep loss of muscle mass. As muscles are the main reservoir of amino acids, losing muscle mass and change in their metabolism impair the body's ability to repair itself when confronted with stressors. Hence, muscle mass loss is an essential component of FS (Afilalo, 2011). The presence of chronic diseases, such as heart failure, and surgical procedures additionally contribute to the stimulation of the immune and sympathetic systems,

causing inflammation manifested by high levels of C-reactive protein (CRP), elevated white blood cell count, and interleukin 6 (IL-6) (Soysal et al., 2016). Pro-inflammatory cytokines may affect frailty either directly, promoting protein degradation, or indirectly affecting important metabolic pathways. In their meta-analysis of 32 cross-sectional studies (23,910 elderly people), Soysal et al. (2016) observed that frailty and pre-frail status were associated with a significant increase in serum inflammatory factors, in particular with a high increase in CRP and IL-6. In patients with frailty and pre-frail status, disability and obesity were more frequent as coexisting factors increasing inflammatory parameters. Individuals with coexisting FS are characterized by weakened immune system, reduced T-cell activity, and antibody production, and an increase in oxidative stress products, which ultimately leads to increased inflammatory parameters in the blood serum. Apart from CRP and IL-6, patients with FS experience an increase in tumor necrosis factor (TNFα), fibrinogen and D-dimers, low vitamin D concentration, decreased concentration of sex hormones and growth hormone, abnormal secretion of cortisol, or high level of C-glycosyl tryptophan (Życzkowska and Grądalski, 2010; Soysal et al., 2016; Koh and Hwang, 2019).

DETERMINANTS

Reduction in Physical Activity

The decrease in physical activity, which is one of the determinants of FS in combination with the coexistence of chronic diseases, contributes to the acceleration of catabolic processes and consequently leads to disability. In cardiac surgery, a decrease in functional efficiency is observed in 16% of elderly patients and 20% of patients aged ≥70 years (Hoogerduijn et al., 2014). Decreased functional efficiency in cardiac patients often results in a loss of autonomy, increased dependence on others, and reduced quality of life. Moreover, it is associated with longer hospital stays, increased use of health care resources, institutionalization, and mortality (Hoogerduijn et al., 2014). In a randomized surgical treatment for ischemic heart failure (STICH) study, patients qualified for CABG with improved functional performance showed a lower perioperative risk and lower mortality during 5 years of follow-up (Singh et al., 2014). Patient mobility as one of the components of FS, assessed by the walking speed test, is a recognized, sensitive indicator and predictor of institutionalization, disability, and mortality after cardiac surgeries (Gobbens and van Assen, 2014; Kim et al., 2016). In patients with reduced walking speed and high perioperative risk, the incidence of mortality was 43% compared to patients with normal gait rate and medium and low perioperative risk, where it was 6%. Meta-analytic data based on nine prospective studies showed that an improvement in gait rate by 0.1 m/s leads to a 10% improvement in survival (Afilalo et al., 2014). Patients' dependence with respect to basic vital functions or the use of auxiliary devices are independent predictors of test results after cardiac surgeries (Neupane et al., 2017).

The walking speed test also has a positive prognostic value in predicting disability in the areas of activities of daily living (ADL) and instrumental ADL (IADL) (Gobbens and van Assen, 2014). Hospitalization often leads to the impairment of functional performance and development in one-third of patients with disabilities, especially with problems with early activation of patients after medical procedures. When activating patients after cardiac surgery for an average of 43 min a day, there is a risk of losing 1–5% of muscle strength every day, which significantly increases the risk of developing disability, especially in patients with concomitant FS (O'Neill et al., 2016). The gait speed is a clinical marker of physical frailty, often used in cardiac surgery for predicting the risk of perioperative complications in elderly patients. A cut-off for slow gait speed is present in a walk slowdown on a distance of 5 m in ≥6 s (walking speed of ≥0.83 m/s) (Afilalo et al., 2010).

Malnutrition

Abnormal nutrition status of the patient plays an important role among FS determinants. Malnutrition contributes to the reduction of muscle mass and strength, thus impairing the physical performance of the body. Moreover, it increases the dysfunction of the immune system, thus reducing the resistance to infection. In general, it seems that anorexia related to aging and the associated weight loss play an important role in the pathophysiology of frailty (Fougère and Morley, 2017). Weight loss in elderly people is most often unintentional (Gaulton and Neuman, 2018). According to the phenotypic approach, frailty is determined by unintended weight loss of more than 4.5 kg or ≥5% over the last year (Fried et al., 2001).

Depending on the tool used to assess the nutritional status, the percentage of malnourished patients before cardiac surgery varies between 4.6 and 19.1% (Lomivorotov et al., 2013). In patients qualified for cardiac surgery, abnormal nutrition correlates with increased morbidity, mortality, prolonged hospitalization, abnormal wound healing, and delayed benefits of postoperative cardiac rehabilitation (Arai et al., 2018; Jayaraman et al., 2018). Pre-operative identification of nutritional risk is extremely important for predicting complications and surgical results in cardiac surgery (Ringaitiene et al., 2016). Unfortunately, nutritional risk often remains undiagnosed in cardiac patients, and thus inadequately treated. Studies confirm that patients undergoing cardiac surgery are at a greater risk of iatrogenic malnutrition due to discontinuation of food supply in the early postoperative period (Hill et al., 2018). Most patients are admitted to cardiac surgery from 12–24 h prior to the procedure, which makes it impossible to undertake appropriate nutritional interventions even though the nutritional status has been assessed. Nutritional status assessed before cardiac surgery would provide an early opportunity to implement nutritional interventions and optimize the nutritional status of the patient before surgery. Studies have shown that obese patients have a higher incidence of complications after cardiac surgeries than those with normal body weight or overweight, but have lower short-term mortality rates (Gaulton and Neuman, 2018). Mini Nutritional Assessment-Short (MNA-SF) is a recommended tool for the identification of malnutrition in elderly cardiac patients (Goldfarb et al., 2018).

Sarcopenia

Sarcopenia is the biological basis of the frailty phenotype. The name sarcopenia derives from the Greek language from the words "sarx," meaning body, and "penia" meaning loss. Sarcopenia does not occur in every patient with FS (Morley, 2016). However, the overlap between sarcopenia and frailty ranges from 50 to 70% (Morley et al., 2014). The pathophysiology of sarcopenia is multifactorial and includes, among others, mitochondrial dysfunction, loss of motor neurons, inadequate nutrition, poor absorption, increase in inflammatory cytokines, insulin resistance, growth hormone deficiency, or androgen deficiency. The decrease in physical activity is very important in the pathophysiology of sarcopenia (Morley, 2016).

Sarcopenia is defined as age-related loss of muscle mass and strength. Studies have shown that every year people lose 1–2% of their skeletal muscle mass and the muscle strength is reduced by about 3–4%. This loss is accelerated in patients with FS. If an additional stress factor, i.e., cardiac surgery, is triggered, the patient with sarcopenia has a problem with protein compensation in the amount necessary for proper wound healing or immune system functioning. The demand for protein in such a patient increases even up to 400%. Combination of anabolic insufficiency and stress factors accelerating catabolism is further aggravated by immobilization of the patient in bed or malnutrition, which induce rapid muscle loss and the occurrence of complications. In the case of a patient with FS, even a slight loss of 5% of muscle mass may cause adverse health effects (Afilalo, 2016).

Sarcopenic obesity refers to a subgroup of people with sarcopenia and a high fat content. In addition to low lean body weight or low muscle capacity, the disease is characterized by excessive energy intake, low physical activity, low intensity inflammation, and insulin resistance. This is a subgroup which for some time has been attributed a high risk of complications (Rizzoli et al., 2013). With age, the lean body mass decreases and is replaced by fatty tissue, whose distribution changes. The amount of subcutaneous fat decreases, while that of visceral fat increases. This happens regardless of the classical body mass index (BMI). Therefore, its use may be inadequate among the elderly, in whom an increase in fat mass and a decrease in lean body mass contribute to ill health (Ricci et al., 2014; Badrudin et al., 2016).

The European Working Group on Sarcopenia in older people (EECSOP) recommends administration of the SARC-F questionnaire for screening sarcopenia. To assess muscle strength, one recommends a grip strength or chair stand test (chair rise test). For assessing skeletal muscle mass and quality consensus recommends tests such as dual-energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), computed tomography (CT), or magnetic resonance imaging (MRI). Whereas, in terms of physical performance, the recommended measurements include a walking speed test, short physical performance battery (SPPB), timed-up-and-go test (TUG), 400-m walk, or long-distance corridor walk (400-m walk) (Cruz-Jentoft et al., 2019).

Polypharmacy

Polypharmacy is a common and potentially modifiable risk factor for frailty in elderly people. Polypharmacy, defined as the use of at least five drugs simultaneously, increases the risk of mistakes in drug dosing by the elderly and the occurrence of adverse reactions. Age-related changes in pharmacokinetics and pharmacodynamics of drugs, as well as multi-morbidity, make prescribing drugs for the elderly a clinical challenge (Saum et al., 2017). Polypharmacy is associated with an increased risk of frailty during 8 years of observation, even after taking into account multi-morbidity. The risk of FS increased by 55% in patients treated with four to six drugs and 2.5 times in patients treated with more than seven drugs. Veronese et al. (2017) observed that the inclusion of each additional drug was associated with an 11% increase in the risk of frailty. Another study on polypharmacy showed that it increases 1.5–2 times risk of frailty development within 3 years, regardless of the number of concomitant diseases and their severity (Saum et al., 2017). Polypharmacy may contribute to the development of frailty through negative effects on coexisting diseases and additional factors (e.g., weight loss) stated in the definition of frailty. Polypharmacy-related side effects may further increase the risk of FS as they often lead to the so-called prescribing "cascade," in which new drugs are prescribed to counteract adverse effects of drugs taken so far (Veronese et al., 2017).

In elderly patients, multi-morbidity is common, and this group is particularly susceptible to polypharmacy. Multimorbidity is a factor driving polypharmacy and conducive to the development of FS (Payne, 2016; Yarnall et al., 2017). The overlap of these two concepts is clear and most research investigates this area in parallel, not in cooperation. As noted by Sinnott and Bradley (2015), multi-morbidity and polypharmacy may coexist, hence the recognition of both concepts as FS determinants seems to be present in many studies. Nevertheless, close monitoring for polypharmacy should be advised to assure better clinical outcomes in frail patients (Bonaga et al., 2018). It is necessary to conduct further studies to verify whether the reduction of polypharmacy has a positive effect by modifying, limiting, or delaying FS (Gutiérrez-Valencia et al., 2018).

Depressive Symptoms

Depression is one of the main determinants of frailty in elderly people (Joyce, 2016). It has been found that the prevalence of FS in people with depression is 40.4%. Depression increases the risk of FS four times, and frail individuals are more likely to develop depression. This means that the presence of frailty poses a risk of developing depression and the presence of depression poses a risk of developing frailty (Soysal et al., 2017). These two constructs overlap. Symptoms indicating depression may be difficult to identify clinically due to the coexistence of frailty in old age. Symptoms such as decreased daily life activity may be the result of reduced energy reserves, characteristic of frailty but also of anhedonia depression, or the result of disability, which causes loss of ability in this area. However, a meta-analysis by Vaughan et al. (2015) indicates a stronger relationship between depressive symptomatology and increased risk of frailty. The literature also

describes the relationship between antidepressant treatment and increased incidence of frailty in elderly women.

The coexistence of depression and frailty in the elderly has several pathophysiological mechanisms. One of such overlapping mechanisms is subclinical cerebral vascular disease, which assumes that mood changes and cognitive disorders in the elderly are caused by subclinical cerebral vascular ischemia. More and more evidence also confirm the role of chronic inflammation as a causative mechanism of both depression and frailty in elderly people. Similarly, an "inflammatory hypothesis" has been proposed for geriatric depression, in which inflammatory processes are believed to cause changes in the nervous system, which predispose some patients to the development of geriatric depression. Among pro-inflammatory cytokines, elevated levels of IL-6 were consistently associated with significant depressive symptoms in elderly people. Other possible etiological factors of both depression and FS in the elderly include disorders of hypothalamic-pituitary-suprarenal regulation, age-related testosterone reduction, or daily fluctuations of cortisol (Vaughan et al., 2015).

Anxiety and depressive symptoms are associated with cardiovascular incidents. In cardiac patients, subjective evaluation of patient anxiety was associated with a higher risk of mortality and in-hospital morbidity, taking into account perioperative risk and symptoms of preoperative depression measured with the hospital anxiety and depression scale (HADS-M). Generalized anxiety disorders are associated with perioperative complications in the form of serious cardiovascular incidents (MACCEs) after CABG surgery (Tully et al., 2015).

Since the occurrence of depressive symptoms and the level of anxiety are potentially modifiable, identification of these factors may provide a chance to increase mental comfort and improve clinical outcomes (Williams et al., 2013). Since depression is a psychiatric determinant of FS, one should also mention the other relevant neuropsychiatric symptoms of apathy common in the elderly population. Apathy symptoms more likely result from damage to the fronto-subcortical pathways that manifest in declining cognitive, emotional, and motoric goal-directed behavior (Ayers et al., 2017). Although apathy in displayed symptoms resembles depression, clinically this other pronounced psychiatric condition that can occur in the absence of depression and apathy pose a certain diagnostic challenge. In fact, clinical studies show some correlations between apathy and depression based on the rating scales, although careful quantification of these measures challenges similar symptomatology of both disorders. The findings from neuroimaging support the notion that apathy is not depression as neuropathology specific for both conditions involve different brain regions. In old age, apathy may become a more significant feature of depression, so it is greater in in late-onset depression than in early-onset depression (Ishii et al., 2009). In the study of Ayers et al. people with initial apathy had more than twice the risk of slowing down gait and over three times the risk of disability, which shows the general risk of a decrease in functional efficiency associated with apathy in the elderly. This risk increases with the increase in apathy. This relationship was independent of depressive symptoms even after taking into account demographic factors, health status and cognitive functioning (Ayers et al., 2017).

Cognitive Disorders

Cognitive disorders are considered by some researchers to be one of the predictors of FS (Uchmanowicz et al., 2015a). FS may be treated as an indicator of future cognitive disturbances (Uchmanowicz et al., 2015a). Clinical data suggest a clear relationship between FS and mild cognitive impairments, dementia, cognitive decline in late age, and dementia without Alzheimer's disease in the elderly. A recent systematic review along with the meta-analysis showed a relationship between FS of the elderly and the risk of developing cognitive impairment, especially components of frailty were related to vascular dementia in patients with cardiovascular disease (Borges et al., 2019). In the elderly, frailty is associated with lower global or regional brain volume, a higher number of cerebral microbleeds, and a higher burden of white matter hyperintensities (WMHs) of presumed vascular origin. The study by Kant et al. investigated brain damage in individuals with frailty and found reduced total brain volume and gray matter volume in these patients as opposed to pre-frail and non-frail populations. In addition, individuals with physical frailty and those classified as pre-frail displayed more cerebral infarctions as compared to individuals without frailty. The authors suggested that plausibly the phenotype of physical frailty originated these brain abnormalities (Kant et al., 2018).

Cognitive functions include a range of intellectual processes such as short-term memory, long-term memory, writing, reading, speech, visual and spatial processes, abstract thinking, and the perception of external stimuli. When fully maintained, cognitive abilities enable biopsychosocial functioning on a daily basis. Physiologically, aging processes include age-related memory impairment or age-related cognitive decline (Ishizaki et al., 2006). The International consensus group has identified the coexistence of physical frailty and cognitive deficits in the elderly as cognitive frailty (Uchmanowicz et al., 2018). Patients with cognitive frailty are at a greater risk of disability, limited daily functioning and hospitalization. Pro-inflammatory cytokines play an important role in the pathophysiology of both conditions, and WMH is associated with both cognitive impairment, decreased walking speed, and risk of falls (Morley, 2016). The notion of cognitive frailty describes what is an individual's reduced cognitive reserve which is potentially reversible as opposed to physiological brain aging (Facal et al., 2019).

There are studies on cognitive decline in patients undergoing cardiac surgery, which substantially increases the risk of cognitive decline after surgery and the occurrence of postoperative delirium. Postoperative decline in cognitive function is more frequent in patients with pre-existing cognitive disorders (Neupane et al., 2017). There is a correlation between cognitive impairment and higher dependence regarding basic vital functions within 6 months after cardiac surgery (Lindman and Patel, 2016). There are common tools for identifying cognitive impairment in patients with FS such as the Mini-Mental State Examination (MMSE). This is a short easy-to-use questionnaire, suitable to screen for impairment in cognitive function of orientation in time and place, remembering, attention and

counting, recalling, language functions, repetition, construction praxis (Hao et al., 2018).

Lack of Social Support

According to the English Longitudinal Study of Aging (*ELSA study*), social isolation and loneliness have turned out to be independent factors of FS and have been associated with old age, a lower level of education, a lower economic status, the occurrence of depressive symptoms, a greater number of chronic diseases, and more frailty criteria met. In this study, social isolation has been associated with an increased risk of the pre-frail condition. Loneliness is an important predictor of physical frailty progression, and FS is associated with a greater likelihood of loneliness, which shows a two-way relationship between them. Both social isolation and loneliness are associated with an increase in mortality, an increased risk of cardiovascular incidents, and a decrease in functional performance. Both social isolation and loneliness are associated with a decrease in gait speed (Gale et al., 2018). Recovery after cardiac surgery is largely based on the patient's social structure, and unfavorable health behaviors contribute to increased morbidity and mortality in cardiac surgery patients (Synowiec-Piłat et al., 2014). There are social factors which increase the perioperative risk by making the patient susceptible. These factors include: the lack of social support, loneliness, a remote place of residence, difficult access to healthcare, a low socioeconomic status, and a lower level of education. What is important is that these factors appear to be independent of the biological and physical stress associated with cardiac surgery (Neupane et al., 2017).

The Tilburg frailty indicator is a multidimensional tool for assessing FS and allows to get data on frailty in social domain (Gobbens et al., 2010b). Another tool for assessing social support administered to patients with chronic diseases is a multidimensional scale of perceived social support (MSPSS) (De Maria et al., 2018).

FRAILTY, MULTI-MORBIDITY, DISABILITY

Frailty syndrome, multi-morbidity, and disabilities are closely linked but separate constructs. Multi-morbidity is defined as the presence of two or more diagnosed chronic diseases in a given patient, constituting a measure of their individual state of health. Disability, on the other hand, is defined as functional problems in the performance of everyday activities necessary for independent living and reflects the interaction between the individual and the surrounding environment. Therefore, multi-morbidity should be understood as one of the main causes of FS, and disability as one of its negative consequences. Disability is the final stage, a side effect of FS and human environmental stressors (Afilalo, 2016). FS may precede or coexist with disability (Robinson et al., 2015).

Multi-morbidity occurs in 16% of patients over 65 years of age and 35% of patients over 80 years of age. Multi-morbidity has a key influence on the diagnostic and therapeutic process, because the manifestation of disease symptoms may differ and make their interpretation difficult. Multi-morbidity is associated with a higher risk of death, higher rate of rehabilitation, disability, and reduced quality of life (Pulignano et al., 2017). Optimization of the clinical status of multi-morbidity patients seems to be important in the context of the perioperative risk in cardiac patients.

Disability is most often determined by difficulties in basic daily activities (ADL) and/or complex daily activities (IADL). The Katz scale (ADL) and the Lawton scale (IADL) are the most common tools used in the literature to determine disability. The ADL includes activities such as bathing, dressing and undressing, using the toilet, getting up from bed and moving to a chair, eating, and controlling the excretion of urine and bowel movements. The IADL includes activities such as using the telephone, walking, shopping, preparing meals, do-it-yourself activities, doing laundry, preparing and taking medication, and managing money. Difficulty in performing both basic and complex everyday activities means total disability (Chen, 2015). Disability also occurs in patients qualified for cardiac surgery (Afilalo et al., 2012; Lindman and Patel, 2016). In their study, which concerned the inclusion of disability, among other factors, in the assessment of perioperative risk in cardiac patients, Affilalo et al. observed disability in 5% of patients with respect to basic vital functions and in 32% of patients with respect to complex vital functions. The authors of this study propose a Nagi scale for the evaluation of disability in cardiac surgery, which seems to be more sensitive in its diagnosis and in this case affected 76% of patients (Afilalo et al., 2012). In another study on cardiac patients, Sun et al. (2018) found that disability is more common than mortality 1 year after surgery, and that the risk factors for disability are female gender and heart failure. Given the impact of disability on the quality of life of elderly people, frailty gains in importance. It can represent the intervention-prone condition prior to disability and identify surgical patients with a high probability of developing disability (Graham and Brown, 2017).

DISCUSSION

Our review provides the multidisciplinary approach to understanding measures of FS in cardiological populations. In today's clinical practice in cardiovascular diseases, none of the multivariate measurements of FS is practically available for clinicians. Here, we show that clinician knowledge should take into account several important determinants of frailty that pose risk factors of the negative course of the disease and its adverse health consequences for patients. The frailty determinants in this work are in line with the views presented in the recent literature, emphasizing the combined effect of several determinants on FS in a cardiac patient. For example, the article by Vitale et al. (2018) defines overlapping frailty that includes several domains such as cognitive deficits, functional impairment, physical deficits, mood disorders, undernutrition, or no social support. These accumulating deficits driven by FS determinants contribute to decreasing resources in stress resistance as showed in the recent literature. As indicated by Vitale et al. (2018), although this multidisciplinary approach should be a part of a holistic therapeutic plan to treat frail patients, there are still no relevant

standards in clinical practice. In fact, clinicians based the FS rating for a long time solely on the physical dimension of frailty.

The multifaceted dimension of FS departs from the purely physical definition and emphasizes the possibility of deterioration in many areas of functioning (McDonagh et al., 2018). Uchmanowicz et al. (2015b, 2019) argue that adverse outcomes of frailty are patient rehospitalization, level of self-care, mortality, patient morbidity, and deterioration of patients' quality of life. For instance, van der Vorst et al. (2018) showed that frail older adults from the multidimensional perspective are likely at the greater risk of dependency in ADL. Thus, as Gobbens et al. (2010a) proposed, physical, psychological, social losses in several domains of human functioning are better predicted by the integral, definition of frailty which is "a dynamic state affecting an individual who experiences losses in one or more domains of human functioning ([. . .]) that are caused by the influence of a range of variables and which increases the risk of adverse outcomes." The position paper of Vitale et al. (2019) based on Heart Failure Association experts stress a holistic approach to frailty as more credible than a simplistic, physical approach of FS showing in this fashion that the nature of frailty is dynamic and multidisciplinary, and not influenced by the age factor. Following this account on FS, Vitale et al. (2019) propose Heart Failure Association Frailty Score scale, the rapid and easy-to-use measurement to evaluate four clinical, psycho-cognitive, functional, social in frail patients.

To sum up, understanding frailty and its determinants seems to be crucial for the diagnostic and therapeutic process for cardiology, ultimately leading to targeted interventions with a better potential to reverse the effects of frailty and prevent further complications in cardiac patients. In this review, we attempted to identify the essential determinants of FS based on the multidisciplinary approach. Here, we argue that this way of tackling FS is necessary if one wants to assess frail patients on individual determinants. However, we mainly focus on the significance of individual determinants frailty and therefore other important aspects of FS linked with interventions may be at some point neglected in the presented review. Nevertheless, future research on FS should seek a multidisciplinary definition of frailty embracing wider populations with cardiovascular diseases in order to adopt efficient measurements of FS, building targeted, fragility-reversing therapeutic strategies and guidelines into everyday clinical practice.

SUMMARY

This review attempted to identify the critical determinants of FS embracing this complex medical syndrome from a multidimensional perspective and cardiological conditions. We analyzed individual determinant and added concrete proposals of tools for their FS identification. Undoubtedly, a challenge for modern cardiology both in the stream of future research and in everyday clinical practice is to build a clear definition of frailty. It seems that the adoption of a multidimensional definition is promising, because it ends up with the practical tool in designing strategies and interventions to prevent the development of frailty. Knowledge of individual FS determinants is important for clinicians in identifying individual patient's needs, adapting to them therapeutic strategies, risk stratification, clinical decisions-making, and building programs that would reverse symptoms of FS and reduce the medical, psychological, social, and economic costs incurred for the adverse consequences of FS.

CONCLUSION

Frailty syndrome is a reversible clinical condition. For planning and implementing appropriate measures to prevent the occurrence of FS or minimize its negative health consequences for cardiological patients, important are comprehensive definitions of FS, familiarity with the prevalence of FS in a variety of patient populations, in-depth knowledge of pathophysiology, and additional factors of multi-morbidity and disability in frail patients. The multidimensional approach toward FS adapts individualized interventions for a single patient with cardiovascular disease. Our review shows that insight into FS determinants is the starting point for building both the comprehensive definition of FS and the adoption of the assessment method of FS, and then successful clinical management.

LIMITATIONS

This review mainly refers to frailty determinants in cardiovascular diseases. In this article, we provide neither references on other chronic diseases nor discussion of identifying frailty determinants in individuals without diagnosed chronic diseases. In addition, because of the limited volume, this article scrutinized only tools for identifying individual FS determinants and abandoned their relevant detailed descriptions. The review did not discuss specific strategies for individual determinants to get them clinically reduced for a patient. However, this will be the subject of a future publication, continuing this topic.

AUTHOR CONTRIBUTIONS

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

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Examining Frailty Phenotype Dimensions in the Oldest Old

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Introduction: Frailty has been studied among the old population due to its association with negative outcomes. Presently there is no gold standard for measuring frailty, but several studies have used the frailty phenotype of Fried consisting of five components (weakness, slowness, unintentional weight loss, exhaustion, and low physical activity) that classify individuals as robust, pre-frail, or frail, depending on the number of components affected, respectively, zero, one or two, and three or more. This study aims to explore the specific contribution of each of these components to the frailty phenotype in a sample of oldest old community-dwelling individuals.

Materials and Methods: Individuals aged 80+ years old living in the community (N = 142) participated in this study. Sociodemographic data (age, sex, educational level, and marital status) and Fried's frailty phenotype were collected. Descriptive analysis summarized sociodemographic information and the frailty components. Multiple correspondence analysis (MCA) was performed to detect and explore relationships between frailty's five components.

Results: Participants had a mean age of 88.07 years (SD = 5.30 years) and were mainly women (73.9%). The majority of the sample were considered frail (71.8%) and pre-frail (24.7%), and the most recurrent component for both groups was slowness. From the MCA analysis, a two-dimension solution was considered the most adequate, with 53.47% of variance explained. Dimension 1 (32.21% of variance explained) showed weakness as the most discriminant component; dimension 2 (21.26% of variance explained) showed unintentional weight loss as the most discriminant component.

Discussion: Results revealed a high number of pre-frail and frail participants. MCA proved to add an important understanding in examining the frailty phenotype; it revealed weakness as the most discriminant component for dimension 1, suggesting a high association with the frailty phenotype. MCA also identified two main features of frailty: one related with physical features (motor behavioral and grip strength) including

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weakness, low physical activity, and slowness; and the second related with intrinsic conditions (unintentional weight loss and exhaustion).

Conclusion: This study corroborates the need of a differentiated approach to the frailty phenotype among very old individuals, bringing for consideration the specific influence of its components.

Keywords: physical frailty, Fried phenotype of frailty, phenotype components, oldest old, frailty dimensions

INTRODUCTION

Worldwide trends show an increasing and fast aging population. A longer life expectancy contributes to the increase of individuals aged 80 years and older—the oldest old population. In Portugal, oldest old individuals constitute 5.0% (532,219) of the total population (10,562,178) and 26.5% of the population aged 65+ (2,010,064) (Brandão et al., 2017). Trends show that living longer may lead to a long period of disability and frailty with increasing care demands (Alves et al., 2016).

Frailty has been widely studied among the old population due to its relation with negative outcomes such as falls, institutionalization, hospitalization, and death. Nevertheless, there is not a gold standard to study frailty. Several studies have used Fried's frailty phenotype (Fried et al., 2001), which defines frailty as the presence of five components: weakness, slowness, exhaustion, low physical activity, and unintentional weight loss. According to this perspective, individuals can be classified as robust, pre-frail, or frail depending on the number of components that they score (0 components, 1–2 components, or $\geq$3 components, respectively).

Previous research has shown that there is a significant association between increased age and frailty, revealing that the majority of frail individuals are the oldest ones (e.g., Fried et al., 2001; Duarte and Paúl, 2015; Carey et al., 2018; Lewis et al., 2018). Fried's original study in particular showed that individuals aged 80+ years old represented 34.8% of the frail sample. This number could be higher because there is a large difference between the number of individuals assessed under and above the 80 years old threshold (4,636 versus 681 participants). When analyzing specifically the proportion of frail individuals based on age groups under and above 80 years, Fried's original study revealed that 18.8% of individuals aged 80 and over were frail in contrast with 5.2% of frail individuals below that age (less than one-third of the frail oldest old participants). Along with this discrepancy, the study did not report information on the proportion of pre-frail individuals in groups under and above 80 years, nor the proportion of components impacted based on pre-frail and frail condition.

Recent studies that used the frailty phenotype revealed that the proportion of frailty among oldest old individuals is particularly high (Duarte and Paúl, 2015; Bieniek et al., 2016) in comparison with younger old individuals (e.g., frailty prevalence increased with age from 31.7% in the 60–69 age group to 67.6% in the 90+ age group, and from 22.5% in the 50–65 age group to 60.4% in the 75+ age group, respectively). These results seem to indicate that the frail condition is very frequent among oldest old individuals and suggests that the frailty phenotype provides low variability within the oldest old subgroup once a large proportion of oldest old individuals are frail. Other studies have already analyzed the components of the frailty phenotype and showed some results in relation to characteristics such as age (Hoogendijk et al., 2015), gender (Bieniek et al., 2016), disability (Papachristou et al., 2017), and mortality (Papachristou et al., 2017). Nevertheless, these studies did not inform about the weight/contribution of each component for the frailty phenotype, and it would be important to understand if all components contribute equally (or not) to the frailty condition and how they interrelate with each other.

In the oldest old group, due to the large proportion of individuals classified as frail (low variability), it would be crucial to determine which components of the frailty phenotype contribute the most to establish the frailty condition. Determining such weights would help to make frailty screening more efficient and more targetable, since the success of interventions, considering frailty as a reversible condition, may depend on the specific components to be addressed. This study aims to explore the structure of the frailty phenotype of Fried and the contribution of each of its components in a sample of oldest old community-dwelling individuals by using multiple correspondence analysis (MCA).

MATERIALS AND METHODS

Design

A non-probabilistic sample was recruited from June of 2017 to August of 2018, in the Metropolitan Area of Porto (North of Portugal). Recruitment was based on the referral of individuals by local NGOs—non-governmental organizations (e.g., day centers and home services) and by using a snowball strategy (Biernacki and Waldorf, 1981), which allowed the identification of cases of interest among people who knew others with similar characteristics and therefore within the scope of the research. A two-stage process was used: first, NGOs were invited to participate in the project. Those that agreed to participate identified possible participants according to a set of inclusion criteria (people aged 80+ years old and living in the community in the Metropolitan Area of Porto). The secretary of each organization then contacted each potential participant in order to ask for authorization for sharing personal data with the research team. After this preliminary consent, the research team contacted the subjects and provided a more detailed description of the study, namely, its objectives and conditions. Those willing to

participate were interviewed face-to-face. If the oldest old person had no cognitive ability to respond (e.g., people with dementia), permission to participate was obtained by the legal representative. All participants signed an informed consent form: one for the researcher/interviewer and the other for the participant. The study was approved by the Ethical Committee of the Institute of Biomedical Sciences of Abel Salazar, University of Porto (process no. 188/2017), and authorized by the Portuguese Data Protection Authority (approval no. 1338/2017).

Measures

- Sociodemographic information: age, sex, education level, and marital status.
- Phenotype of frailty: we assessed five components according the definition of physical frailty proposed by Fried et al. (2001): (i) weakness, (ii) slowness, (iii) unintentional weight loss, (iv) exhaustion, and (v) low physical activity. Regarding the frailty phenotype, participants were considered "frail" if they fulfilled three or more criteria, "pre-frail" if they fulfilled one or two, and "robust" if none of the criteria was fulfilled. The metrics were slightly changed following the procedures used in similar studies with very old individuals (e.g., Gonzalez-Pichardo et al., 2013; Nyunt et al., 2017). In particular:

(i) Weakness was measured using handgrip strength [dynamometer (Takei dynamometer, T.K.K. 5401, Japan)]. Grip strength was tested two consecutive times on both the right and left hands. Analysis used the average peak value across both hands, and the third quartile was considered to classify participants according to their weakness; participants with values < 13.6 kg were considered weak and were categorized as 1, and those who obtained values ≥ 13.6 kg were categorized as 0, meaning they were not weak (high strength).

(ii) Slowness was evaluated using gait speed by the Timed "Up and Go" test (Podsiadlo and Richardson, 1991). The patient must stand up from an armchair, walk 3 m, turn around, walk back to the chair, and sit down. If the participants took 16.8 or more seconds [Portuguese cutoff for people 80 years and older (Almeida et al., 2017)] to perform the test they were considered to have low mobility and categorized as 1. Participants who were not able to do the walking test were also categorized as 1 (low mobility). Participants who performed the test in less than 16.8 s were categorized as 0, meaning good mobility.

(iii) Unintentional weight loss was evaluated using step 2 of the Malnutrition Universal Screening Tool (Bapen, 2003). Each participant answered about the total unplanned weight loss in the past 3–6 months considering the total of his or her weight. Initially the question was scored as 0 for weight loss $< 5\%$, 1 for weight loss between 5 and 10%, and 2 for weight loss $> 10\%$ of the total of weight. Answers were then recoded as 0 for weight loss $< 5\%$ and 1 for weight loss $\geq 5\%$.

(iv) Exhaustion was assessed using the question "In this last month, do you feel that you have less energy to do the things you want?," which was categorized as 0 = no exhaustion or 1 = yes exhaustion.

(v) Low physical activity was assessed by the question "How often do you practice any of the following activities (dancing, walking, farmer work, or gardening)?" (Duarte et al., 2014). Answers ranged from one to four, respectively, never/almost never, up to three times a month, once a week, and more than once a week. Answers were then recoded as 0 if answers were "once a week" or "more than once a week," meaning they were active, and 1 for answers "never/almost never" or "up to three times a month," which were considered not active.

Statistical Analysis

The descriptive analysis summarized sample characteristics considering sociodemographic aspects, the components of frailty, and the classification of frailty according to Fried's phenotype (Fried et al., 2001). Results were displayed using absolute and relative frequencies or central location and dispersion measures, according to the type of variable. To detect and explore relationships between the five components of frailty (active variables), age, sex, and education (supplementary variables), a MCA was performed using R software and the packages FactoMineR and factoextra. Supplementary variables are not used for the determination of the principal dimensions. Their coordinates are predicted using only the information provided by the performed MCA on active variables, i.e., the five components of frailty (Lê et al., 2008).

Multiple correspondence analysis is a multivariate technique designed to discover both interrelations and intra-relations of two or more categorical variables by reviewing the closeness and remoteness between the variables, which allows the analysis of patterns of relationships of several categorical dependent variables. MCA facilitates the interpretation of categorical variables in the cross tables providing information about the similarities, divergences, and associations between the row and column variables. In MCA, some discrimination measures are usually analyzed such as inertia, which measures how far the categories are spread out from the origin, and the eigenvalues, which are the percentage of inertia explained. MCA also allows the graphical representation of the associations in a lower-dimensional space, aiding the interpretation of results. Each variable is represented with a dot in a multi-dimensional space. Dots close to the X or Y axes are highly related with the respective dimension, and those close to each other are considered similar to or related to each other, depending on the areas they fall into. Similarly, dots far from each other are considered to be unrelated (Greenacre, 1988; Anderson, 1994). To define the number of dimensions to retain, the following criteria/considerations were employed: (i) inclusion of MCA dimensions with inertia above 0.2 and (ii) scree test (Hair et al., 1998). In interpreting the discrimination measures and the visual outputs from MCA, the aim should be to identify those components that cluster together.

RESULTS

Participants (N = 142) had a mean age of 88.07 years (SD = 5.30 years) and were mainly women (73.9%), and the majority had a low educational level (34.5% were illiterate, and 65.5% had one or more years of school) (**Table 1**). According to the frailty phenotype (**Table 2**), 5 (3.5%) individuals were considered robust, 35 (24.7%) were pre-frail, and 102 (71.8%) frail.

TABLE 1 | Sociodemographic information about participants.

	***N* (%)**
Age years, M (SD)	88.07 (5.30)
Sex	
Male	37 (26.1)
Female	105 (73.9)
Marital status	
Married/unmarried couples	47 (33.1)
Widow(ed)	86 (60.6)
Single/divorced	9 (6.3)
Education level	
Illiterate	49 (34.5)
≥1 year	93 (65.5)

TABLE 2 | Phenotype of frailty assessment.

	Total	**Pre-frail *n* = 35 (24.7%)**	**Frail *n* = 102 (71.8%)**
Handgrip strength			
<13.6 kg	93 (65.5)	7 (20.0)	86 (84.3)
≥13.6 kg	49 (34.5)	28 (80.0)	16 (15.7)
Gait speed			
≥16.8 s	122 (85.9)	23 (65.7)	99 (97.1)
<16.8 s	20 (14.1)	12 (34.3)	3 (2.9)
Exhaustion			
Yes	74 (52.1)	7 (20.0)	67 (65.7)
No	68 (47.9)	28 (80.0)	35 (34.3)
Physical activity			
Never/almost never or up to three times a month	113 (79.6)	19 (54.3)	94 (92.2)
Once a week or more than once a week	29 (20.4)	16 (45.7)	8 (7.8)
Unintentional weight loss			
≥5%	21 (14.8)	1 (2.9)	20 (19.6)
<5%	121 (85.2)	34 (97.1)	82 (80.4)
Number of frailty components			
0	5 (3.5)	–	–
1	13 (9.2)	13 (37.1)	–
2	22 (15.5)	22 (62.9)	–
3	50 (35.2)	–	50 (49.0)
4	44 (31.0)	–	44 (43.2)
5	8 (5.6)	–	8 (7.8)

Considering the phenotype components of the total sample, 93 participants (65.5%) revealed weakness, 122 (85.9%) revealed slowness, 74 (52.1%) reported exhaustion, 113 (79.6%) reported low physical activity, and 21 (14.8%) revealed unintentional weight loss. Specifically, from the pre-frail participants, 13 scored on one component (representing 9.2% of the total of the sample and 37.1% of the pre-frail individuals), and 22 scored on two components (representing 15.5% of the total of the sample and 62.9% of the pre-frail individuals). The most relevant component was gait speed (65.7%), followed by physical activity (54.3%).

Considering the participants labeled as frail, 50 participants scored on three components (35.2% of the total of the sample and 49.0% of the frail individuals), 44 scored on four (31.0% of the total of the sample and 43.2% of the frail individuals), and 8 scored on five components (5.6% of the total of the sample and 7.8% of the frail individuals). Likewise, in participants labeled as pre-frail, the most relevant components were gait speed (97.1%) and physical activity (92.2%).

Our results also showed that of the 62 participants excluded from the analysis, 32 were completely unable to cooperate due to cognitive impairment (e.g., dementia cases, stroke), and 23 due to disability (e.g., stroke consequences, severe hearing impairment) that hampered data collection of some components of frailty. The other seven excluded participants showed tiredness or refusal to perform the some component assessment.

From the MCA analysis, a two-dimension solution was considered the most adequate (**Table 3**). The first and second dimensions showed, respectively, 0.32 and 0.21 of inertia (**Table 3**). The first dimension explained 32.21% of the variance, and dimension two explained 21.26% of the variance (**Figure 1**). Together, both dimensions explained 53.47% of the variance (**Table 3**). **Table 4** describes the MCA dimension discrimination measures. For dimension 1—labeled by us as the functional dimension—the most discriminant variables were weakness, followed by low physical activity and by slowness. Regarding dimension 2—labeled by us as the intrinsic condition dimension—the most discriminant variables were unintentional weight loss and exhaustion (**Table 4**). Considering the sociodemographic variables tested in MCA (age, sex, and education level), we verified a slight relation of each of them with the two dimensions. Age was almost exclusively related with dimension 2, and sex and education level with dimension 1 (**Table 4** and **Figure 1**).

DISCUSSION

In accordance with previous studies (Lewis et al., 2018), our findings revealed a high number of women and widow(ed) participants. The education level among this group is very low (or inexistent), which is why we considered participants who were illiterate versus those who attended school for 1 year or more. This last characteristic is still expressed in the oldest old Portuguese population, as formal education became mandatory only in 1950 for men and in 1960 for women, justifying the high number of participants with low educational level and who were illiterate (Palma et al., 2003).

TABLE 3 | Inertia and eigenvalues on the dimensions of multiple correspondence analysis (MCA).

	Dimension 1	Dimension 2	Dimension 3	Dimension 4	Dimension 5
Inertia	0.32	0.21	0.19	0.15	0.13
% Variance	32.21	21.26	18.74	14.53	13.26
Cumulative% variance	32.21	53.47	72.21	86.74	100.00

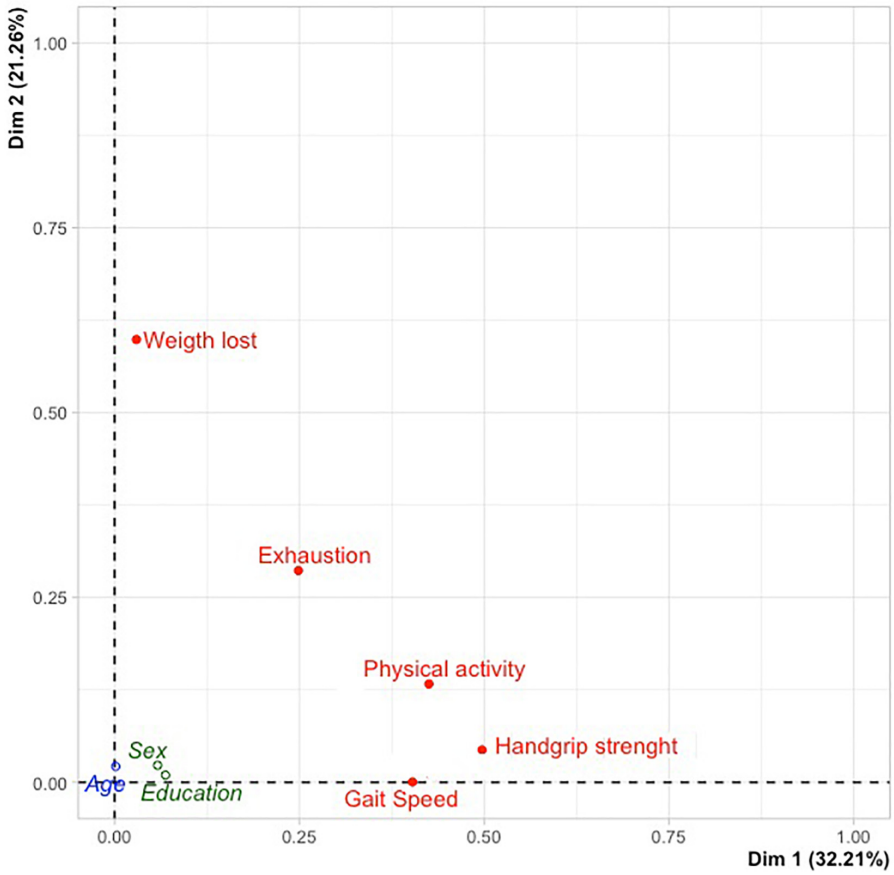

FIGURE 1 | Multiple correspondence analysis (MCA) dimension discrimination measures.

Concerning the frailty condition, five key aspects emerged from our results. First, we observed a great number of pre-frail and frail subjects. Frail individuals represented more than two-thirds of the total sample (71.8 vs. 24.6% of pre-frail). These results are in accordance with other studies (Duarte and Paúl, 2015; Lewis et al., 2018), which also had a great number of frail oldest old individuals in their samples, highlighting the low differentiation (almost all frail persons) provided by the frailty phenotype of Fried among oldest old individuals and emphasizing the need to better understand its components.

Second, the number of frailty components impaired (**Table 2**) provided useful information on the "level" of frailty within both the pre-frail and frail groups. Specifically, in the first group, we observed that participants scored mostly in the upper limit of the pre-frail condition (i.e., two components), whereas in the second group, we found that participants scored mostly in the lower and middle limit of frailty (i.e., three and four components, representing a total of 92.2% of frail participants).

Third, the methodological approach using MCA for the study of frailty components proved to add an important understanding for the study of frailty in the oldest old participants. On one hand, it revealed weakness as the most discriminant component for functional dimension (with higher variance explained, **Figure 1**), evidenced by the fact that among the five components of frailty, weakness was the one with the highest association with the frailty phenotype. On the other hand, MCA identified two main features of frailty: one more related with functionality/physical features (motor behavioral and grip strength) composed of weakness, low physical activity, and slowness; and a second one related with intrinsic conditions (unintentional weight loss and exhaustion). The presence of a functional dimension related with physical

TABLE 4 | MCA dimension discrimination measures.

	MCA dimension 1	MCA dimension 2
Handgrip strength	0.50	0.04
Physical activity	0.43	0.13
Gait speed	0.41	0.00
Weight lost	0.03	0.60
Exhaustion	0.25	0.29
Supplementary variables		
Age[a]	−0.04	−0.15
Sex[a]	0.06	0.02
Education level[a]	0.07	0.01
% of variance	32.21	21.26

[a]*Supplementary variable.*

features might suggest that these components are potentially more modifiable than the two other components from the intrinsic condition dimension (unintentional weight loss and exhaustion). This distinction of the two frailty dimensions may be a key aspect for customized interventions since it would help to better define pathways as well as to understand the effect of interventions on individual components of frailty as well as in the overall condition. The literature has shown a high number of studies analyzing the effect of interventions on improving the frailty condition (Cesari et al., 2015; De Labra et al., 2015; Apostolo et al., 2018), although few have evaluated the effect of individual and combined interventions in components of frailty phenotype and/or in reversing frailty. A recent study (Liao et al., 2019) testing the effect of two exercise interventions in pre-frail and frail older individuals proved that both interventions were effective for weakness, slowness, and physical activity (functional dimension) but not for exhaustion and weight loss (intrinsic condition dimension), corroborating our results. A previous study by Ng et al. (2015) that conducted a randomized controlled trial among older adults to verify the effects of nutritional, physical, cognitive, and combined interventions on frailty reversal found that the components of frailty benefit from targeted interventions such as physical, nutritional, and cognitive, and especially combined ones. A combined intervention seemed to produce the best effects in almost all components of frailty, except for weight lost, which presented some change in the short and middle term depending on the intervention analyzed but without long-lasting effects. Improvements decreased at 12 months, whatever the intervention performed, which may suggest that this component is effectively an intrinsic aspect and more difficult to change. These results may also have two main implications in the interpretation of frailty: (i) its potential of reversibility (Canevelli et al., 2017), since components from functional condition may have higher reversal rates than intrinsic condition components (probably less changeable or urging other types of intervention, including, namely, nutrition, cognition, and social); and (ii) its relation with practical aspects, namely, in terms of individuals' assessment (greater attention to components of frailty rather than to the overall score) and in defining and customizing interventions (suitability and adequacy).

Fourth, the slight association of sociodemographic variables with the two dimensions suggested that this approach of frailty showed very little association with sociodemographic aspects not corroborating previous studies (Bieniek et al., 2016; Nyunt et al., 2017; Papachristou et al., 2017; Lewis et al., 2018), which should be the subject of further research, considering these two dimensions of the frailty phenotype and across different age groups. This study analyzed only the oldest old people with very low variability in education level and health condition, as referred to in the Limitations section.

Fifth, more attention should be given to the great number of individuals excluded from the total sample. Participants were excluded due to their total or partial inability to perform the test of components of frailty (due to auditory deficits, consequences of stroke, and dementia, among others). According to Lewis et al. (2018), the frailty phenotype of Fried requires a certain level of functioning, which is in accordance with what we observed in our study once we had to exclude from our analysis a high number of individuals (55 individuals were considered as not having that "certain level" of functioning). In Fried's original study, that "certain level" of functioning was assured, defining a set of exclusion criteria (e.g., history of Parkinson's disease, stroke, dementia), missing information about the excluded participants in terms of disability level (total or partial), and the components impaired. Probably, at this advanced age, many of the participants were already dependent (with an irreversible condition and not frail). This should be further explored so that the frailty condition becomes more clear and useful to inform interventions. The distinction between the inability to perform a certain task or requirement and a missing value seems crucial to fully understand the frailty condition.

Overall, the results obtained in this study substantiate the need of a discriminant approach to the frailty phenotype, namely, among very old individuals, bringing into consideration the specific relevance of the different components of frailty (functional dimension and intrinsic condition). The subdivision of the frailty phenotype into two dimensions may help professionals to identify if the frail condition is more related with physical features or with intrinsic aspects, leading to the customization of interventions and bearing in mind that functional aspects are potentially more modifiable than intrinsic ones.

Limitations

Some limitations must be mentioned. First, our study might benefit from another reference process for participants. The identification of the target population through NGOs could contribute to higher participants disability levels. Second, this study included very old individuals (mean age of 88 years), who could have a higher incidence of health-related problems. We therefore suggest further studies among other younger age groups to test MCA and to verify if the two-dimension approach to frailty remains useful. Further research should also consider studying frailty in those who cannot be fully assessed by means of Fried's frailty phenotype. In particular,

some studies (Ravindrarajah et al., 2013; Payne et al., 2017) demonstrated that those participants who cannot complete the Fried phenotype requirements should be considered frail or dependent (irreversible condition) and had a higher mortality rate than those who could be assessed. Despite these limitations, our results may represent an improvement to the study and conceptualization of the frailty phenotype as well as to the planning of interventions for pre-frail and frail individuals.

DATA AVAILABILITY STATEMENT

The study was approved by the Ethical Committee of the Institute of Biomedical Sciences of Abel Salazar, University of Porto (process No. 188/2017) and authorized by the Portuguese Data Protection Authority (approval No. 1338/2017), guaranteeing anonymity, privacy, and confidentiality.

ETHICS STATEMENT

The studies involving human participants were reviewed and the study was approved by the Ethical Committee of the Institute of Biomedical Sciences of Abel Salazar, University of Porto (process No. 188/2017) and authorized by the Portuguese Data Protection 396 Authority (approval No. 1338/2017). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SA was responsible for the study design, collecting, analyzing, and interpreting data, and manuscript drafting and revision. LT managed, analyzed, and interpreted the data. OR was responsible for study supervision and manuscript revision. CP was responsible for study supervision and made manuscript revisions.

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ORIGINAL RESEARCH
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Screening for Cognitive Frailty Using Short Cognitive Screening Instruments: Comparison of the Chinese Versions of the MoCA and Q*mci* Screen

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Background: Cognitive frailty describes cognitive impairment associated with physical decline. Few studies have explored whether short cognitive screens identify frailty. We examined the diagnostic accuracy of the Chinese versions of the Quick Mild Cognitive Impairment (Q*mci*-CN) screen and Montreal Cognitive Assessment (MoCA-CN) in identifying cognitive frailty.

Methods: Ninety-five participants with cognitive symptoms [47 with mild cognitive impairment (MCI), 34 with subjective cognitive disorder, and 14 with dementia] were included from two outpatient rehabilitation clinics. Energy (work intensity) and physical activity levels were recorded. Cognitive frailty was diagnosed by an interdisciplinary team using the IANA/IAGG consensus criteria, stratified on the Clinical Frailty Scale (CFS). Instruments were administered sequentially and randomly by trained assessors, blind to the diagnosis.

Results: The mean age of the sample was 62.6 ± 10.2 years; median CFS score was 4 ± 1 and 36 (38%) were cognitively frail. The Q*mci*-CN had similar accuracy in differentiating the non-frail from cognitively frail compared to the MoCA-CN, AUC 0.82 versus 0.74, respectively ($p = 0.19$). At its optimal cut-off (≤55/100), the Q*mci*-CN provided a sensitivity of 83% and specificity of 67% versus 91% and 51%, respectively, for the MoCA-CN (≤23/30). Neither was accurate in separating MCI from cognitive frailty but both accurately separated cognitive frailty from dementia.

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Conclusion: Established short cognitive screens may be useful in identifying cognitive frailty in Chinese adults with cognitive complaints but not in separating MCI from cognitive frailty. The Q*mci*-CN had similar accuracy to the MoCA-CN and a shorter administration time in this small and under-powered study, necessitating the need for adequately powered studies in different healthcare settings.

Keywords: frailty, cognitive frailty, cognitive screen, mild cognition impairment, dementia, China

BACKGROUND

The prevalence of cognitive impairment, both mild cognitive impairment (MCI) (Ward et al., 2012) and dementia (Prince et al., 2013), are increasing worldwide and are associated with the clinical syndrome of frailty (Wallace et al., 2019), particularly its physical phenotype (Ma et al., 2019). While no consensus definition of frailty as yet exists (Rodríguez-Mañas et al., 2013), it is widely regarded as a risk state or vulnerability, predisposing to adverse healthcare outcomes (Clegg et al., 2013). Cognitive frailty is increasingly recognized as a separate clinical subtype of frailty (Sezgin et al., 2019a) closely connected to its prodrome, pre-frailty (Sezgin et al., 2019b). Cognitive impairment and frailty frequently co-exist, interacting in a complex relationship (Robertson et al., 2013; Grande et al., 2019). Frailty can predict cognitive disorders (Borges et al., 2019) and the presence of cognitive impairment improves the predictive validity and operationalization of frailty (Avila-Funes et al., 2009). Building on this, the International Academy on Nutrition and Aging (IANA) and International Association of Gerontology and Geriatrics (IAGG) recently published consensus criteria identifying cognitive frailty as the presence of physical frailty and cognitive impairment [MCI as defined by a Clinical Dementia Rating scale (CDR) score of 0.5], where dementia has been excluded (Kelaiditi et al., 2013).

The World Alzheimer Report (2015 and 2018) estimated that 58% of people with dementia live in low and middle income countries. China, as the worlds most populated country faces many challenges related to aging including high levels of dementia (Chan et al., 2013). At present the estimated prevalence of MCI is 20.8% among those aged over 65 in China (Jia et al., 2014). A recent study shows that the prevalence of cognitive frailty among Chinese community-dwellers (aged $\geq$ 60) is 2.3%, lower than that of frailty, pre-frailty and cognitive impairment overall (Ma et al., 2019). Many countries have suboptimal systems in place to identify the true prevalence of cognitive impairment including cognitive frailty, which confounds estimates and makes public health strategies and resource allocation to address this challenging (Prince, 2015; Patterson, 2018).

Early identification of cognitive frailty is important to facilitate personalized care for older people and the introduction of interventions that may slow onset of physical decline, impairment in activities and dementia (Morris et al., 2001; Kelaiditi et al., 2013). It may also help identify those who could benefit from complex interventions to slow onset of cognitive frailty (Apóstolo et al., 2018). Despite this, few screening instruments are available to screen for MCI and to our knowledge none that specifically identify cognitive frailty (Ruan et al., 2017). Further, it is not known if the co-existence of physical decline with cognitive symptoms may exacerbate cognitive symptoms further such that these are detectable using short cognitive screening instruments and whether this impacts on individual's performance on testing, particularly those without functional impairment, i.e., MCI. At present, the most widely used cognitive screen for MCI is the Montreal Cognitive Assessment (MoCA). However, its specificity is poor in many studies, particularly at its recommended cut-off (Tsai et al., 2016; Breton et al., 2019). Further, it has a relatively long administration time, limiting its use in busy clinical settings in China. The Quick Mild Cognitive Impairment (Q*mci*) screen is a new, short cognitive screen designed to identify MCI (O'Caoimh et al., 2012), which is closely linked with pre-frailty (Amanzio et al., 2017; Sezgin et al., 2019b). It has not yet been translated and validated into Chinese.

Here, we adapted and translated the Chinese version of the Q*mci* screen (Q*mci*-CN) and compared its ability to distinguish cognitive frailty from (a) MCI, (b) non-frail older adults with and without dementia, and (c) other patients presenting with symptomatic memory loss. Finally, we examined its psychometric properties against the established Chinese version of MoCA (MoCA-CN).

MATERIALS AND METHODS

Translation of the Q*mci* Screen

The Q*mci* screen has six subtests: orientation (10 points), 5-word registration (5 points), clock drawing, where a blank template is provided and patients are asked to set the time (15 points), 5-word delayed recall (20 points), verbal fluency (semantic for categories of words, e.g., animals) (20 points) and logical memory (immediate verbal recall of a short story read out loud to the patient) (30 points), giving a total score of 100 points with higher scores and a cut-off of $\geq$62 indicating likely normal cognition (O'Caoimh et al., 2013; O'Caoimh et al., 2017). The Q*mci* screen can be administered in less than 5 min and the test-retest reliability and diagnostic accuracy are good to excellent in different settings, see O'Caoimh and Molloy (2017) (O'Caoimh et al., 2017). It has moderate to high correlation with the Standardized Alzheimer's Disease Assessment Scale-cognitive section (ADAS-cog), CDR and the Lawton-Brody activities of daily living scale (O'Caoimh et al., 2014). The Q*mci* screen

was translated into Chinese (Mandarin) using a forward-backward translation approach using an expert panel of Chinese healthcare professionals, researchers and independent professional translators.

Participants

Consecutive attendees consenting to be included were recruited from adults aged ≥50 years presenting with symptomatic cognitive symptoms attending general rehabilitation outpatient clinics in two hospitals in Guangzhou, China, between July and December 2017. Patients were then divided into three groups; subjective cognitive disorder (SCD), MCI, and dementia. In all, 47 had MCI, 34 had SCD and 14 dementia. Those with cognitive symptoms but found to have normal cognitive testing and no evidence of functional impairment were defined as having SCD consistent with a "medical help–seeking" group under the framework for SCD suggested by Jessen et al. (2014). As this was a convenience study conducted as part of routine care, normal controls were not included. MCI was diagnosed among those with objective memory loss, greater than was expected for their age but without loss of occupational functioning, according to the National Institute on Aging – Alzheimer's Association workgroups diagnostic guidelines for Alzheimer's disease (Albert et al., 2011). A diagnosis of dementia was made using DSM-IV (American Psychiatric Association [APA], 1994) and NINCDS-ADRDA (McKhann et al., 1984) criteria. Cognitive frailty was diagnosed by a consultant physician based on IANA/IAGG consensus criteria (Kelaiditi et al., 2013) in those with physical frailty and cognitive impairment but without dementia. Physical frailty was assessed clinically; self-reported energy levels including patients ability to perform tasks (work intensity) and usual physical activity levels were recorded. Cognitive frailty was stratified on the Clinical Frailty Scale (CFS), score from 1 (very fit) to 9 (terminally ill) (Rockwood et al., 2005). Those aged ≤50 or with clinical depression supported by a Geriatric Depression Scale score >5, or unable to communicate in Chinese were excluded. All participants completed a detailed neuropsychological assessment with the ADAS-cog and Mini-Mental State Examination at baseline. All signed informed consent before participating. This study received ethical approval from The Six Affiliated Hospital of Sun Yat-sen University.

Data Collection

A consultant geriatrician, general rehabilitation physician and a speech and language therapist classified patients into diagnostic groups based on the interview and neuropsychological assessment. The Q*mci*-CN and MoCA-CN were administered by one of four trained assessors (health and social care professionals who were part of the research team) on the same day in random sequence, blind to the final diagnosis, who recorded the final scores and administration times. Alternative versions of the Q*mci*-CN and MoCA-CN were used to reduce learning effects (Cunje et al., 2007). Test administration was alternated and patients were not prompted or informed of the correct answers to the cognitive tests to avoid learning and fatigue effects and subsequent bias. To establish test–retest reliability, the same raters scored the Q*mci*-CN a second time on 59 patients within 2 weeks.

Statistical Analysis

Descriptive statistics for cognitive tests were used to summarize sample data. The Kolmogorov–Smirnov test was used to test normality and found most data were normally distributed. Comparison between three groups was performed using one-way ANOVA with significant differences examined with Tukey's HSD *post hoc* tests. Correlation analyses and reliability were conducted using Pearson correlation coefficients. Finally, receiver operating characteristic (ROC) curve analysis was used to measure diagnostic accuracy based on the area under the curve (AUC). ROC curves were compared using the DeLong method (DeLong et al., 1988). Excellent accuracy is defined by AUC values between 0.90 and 1.0; lower values represent reduced diagnostic accuracy with values between 0.50 and 0.60 regarded as a fail. Optimal cut-off points were identified using Youden's Index. Sensitivity and specificity were reported for the selected cut-off points. All statistical analyses were performed using SPSS version 25, R version 3.5.0 (2018-04-23) – "Joy in Playing" and STATA version 14. A level of statistical significance of 0.05 was used for all inferential analysis. Where appropriate, 95% confidence intervals (CI) are reported.

RESULTS

Of those meeting inclusion criteria, 125 were invited to participate. Of these, 30 declined and one had incomplete data. The final sample included 95 patients. In total, 49% (n = 47) had MCI, 36% (n = 34) symptomatic cognitive symptoms but SCD and 15% (n = 14) dementia. The median CFS score of the sample included was 4 ± 1 and 36 patients (38%) were classified as having cognitive frailty. Descriptive statistics comparing those with cognitive frailty to the other patients are summarized in **Table 1**.

Cognitive Test Scoring and Administration

We found statistically significant differences in total mean scores and standard deviation (SD) between all three diagnostic groups (SCD, MCI and dementia) for both cognitive test scores (p-values < 0.001). The mean scores for each diagnostic group with SD are presented in **Table 2**. Analyses showed that all three diagnostic groups were different from each other, with higher scores associated with higher (better) levels of cognitive ability (normal group). While no significant differences in administration times by diagnostic group were found for either the Q*mci*-CN (p = 0.18) or MoCA-CN p = 0.06), a weak gradient effect was seen with the MoCA-CN (r = 0.2); those with better cognition (higher scores) had non-significantly shorter administration times (see **Figure 1**). This was not seen for the Q*mci*-CN (r = 0.05). Correlation analysis, performed to examine the concurrent validity of the Q*mci*-CN showed that there was a positive, strong, statistically

TABLE 1 | Characteristics of patients included (*n* = 95).

Patient characteristics	Total (*n* = 95) *N* (%) or Mean ± SD [Range]	Cognitive frailty (*n* = 36) *N* (%) or Mean ± SD [Range]	Others (*n* = 59) *N* (%) or Mean ± SD [Range]
Gender			
Female	66 (70%)	23 (64%)	43 (73%)
Male	29 (30%)	13 (36%)	16 (27%)
Clinical Frailty Scale score	3.7 ± 1.0 [1–7]	4.0 ± 0 [4–4]	3.4 ± 1.3 [1–7]
Age (years)	62.6 ± 10.2 [50–89]	64.6 ± 10.1 [50–89]	61.4 ± 10.2 [50–85]
Education (years)	11.4 ± 5.5 [0–25]	9.8 ± 4.5 [0–17]	12.4 ± 5.9 [0–25]
Salary (Yuan)	4664 ± 2953 [0–16000]	4514 ± 2091 [1983–8000]	5016 ± 3240 [300–16000]
Living arrangements			
Living with family	84 (89%)	32 (89%)	52 (88%)
Living with a formal carer	6 (6%)	3 (8%)	3 (5%)
Living alone	5 (5%)	1 (3%)	4 (7%)
Work intensity			
Low	38 (40%)	18 (50%)	20 (34%)
Medium	36 (38%)	12 (33%)	24 (41%)
High	9 (9%)	1 (3%)	8 (13%)
Other (not provided)	12 (13%)	5 (14%)	7 (12%)
Hypertension	19 (20%)	10 (28%)	9 (15%)
Hyperglycemia	12 (13%)	3 (8%)	9 (15%)
Hyperlipemia	14 (15%)	4 (11%)	10 (17%)
Dyssomnia	31 (33%)	16 (44%)	15 (25%)
Q*mci*-CN score	51 ± 13 [6–76]	47 ± 10 [23–48]	53 ± 14 [6–65]
MoCA score	22 ± 4.8 [1–29]	21.5 ± 3 [4–27]	22 ± 5.5 [1–29]

TABLE 2 | Mean test scores and administration times for the Chinese versions of the Quick Mild Cognitive Impairment screen (Q*mci*-CN) and Montreal Cognitive Assessment (MoCA-CN) by diagnostic group, *n* = 95.

Cognitive test	All (*n* = 95)	SCD (*n* = 34)	MCI (*n* = 47)	Dementia (*n* = 14)	One-way ANOVA and *post hoc* tests of significance*
Q*mci*-CN score	51 ± 13	61.4 ± 7.5	48.0 ± 9.3	35.4 ± 13.9	$F(2,91) = 41.5$, $p < 0.001$
(mean ± SD)	[6–76]	[41–76]	[23–60]	[0–48]	All Tukey HSD *post hoc* tests $p < 0.001$
MoCA-CN score	22 ± 4.8	25.4 ± 2.5	21.6 ± 3.0	14.6 ± 5.3	$F(2,91) = 54.2$, $p < 0.001$
(mean ± SD)	[1–29]	[20–29]	[14–27]	[1–21]	All Tukey HSD *post hoc* tests $p < 0.001$
Q*mci*-CN screen time (seconds, mean ± SD)	300 ± 39.6	290 ± 36	306 ± 37	303 ± 53	$F(2,91) = 1.8$, $p = 0.18$
	[141–384]	[206–353]	[221–384]	[141–363]	
MoCA test time (seconds, mean ± SD)	584 ± 124	548 ± 106	595 ± 119	636 ± 159	$F(2,90) = 2.9$, $p = 0.06$
	[350–956]	[361–833]	[355–956]	[350–941]	

*Reported values are Mean ± Standard Deviation (SD) [Range], MCI = Mild Cognitive Impairment; SCD = Subjective Cognitive Disorder. *Comparison between scores for SCD, MCI and dementia.*

significant association between the Q*mci*-CN and MoCA-CN ($r = 0.72$, $p < 0.001$). Comparing test times between the two instruments, the Q*mci*-CN had a statistically significantly shorter administration time (mean 300 s, SD ± 39.6) than the MoCA-CN (mean 584 s, SD ± 124) for all participants (paired $t(92) = 25.67$, $p < 0.001$), for cognitive frailty ($p < 0.001$) and each of the three cognitive groups (all $p < 0.001$). For, cognitive frailty the difference was 272 s. For those classified as having normal cognition, the difference was 258 s; in the MCI group the difference was 289 s; In dementia the difference increased to 333 s. The Q*mci*-CN had excellent test-retest reliability ($r = 0.92$).

Screening for Cognitive Frailty

Examining the accuracy of these instruments in differentiating cognitive frailty from those with MCI but without physical frailty, showed that both the Q*mci*-CN and MoCA-CN were poor at differentiating CF from MCI, AUC's of 0.63 versus 0.51 ($p = 0.38$), respectively. Both instruments were accurate

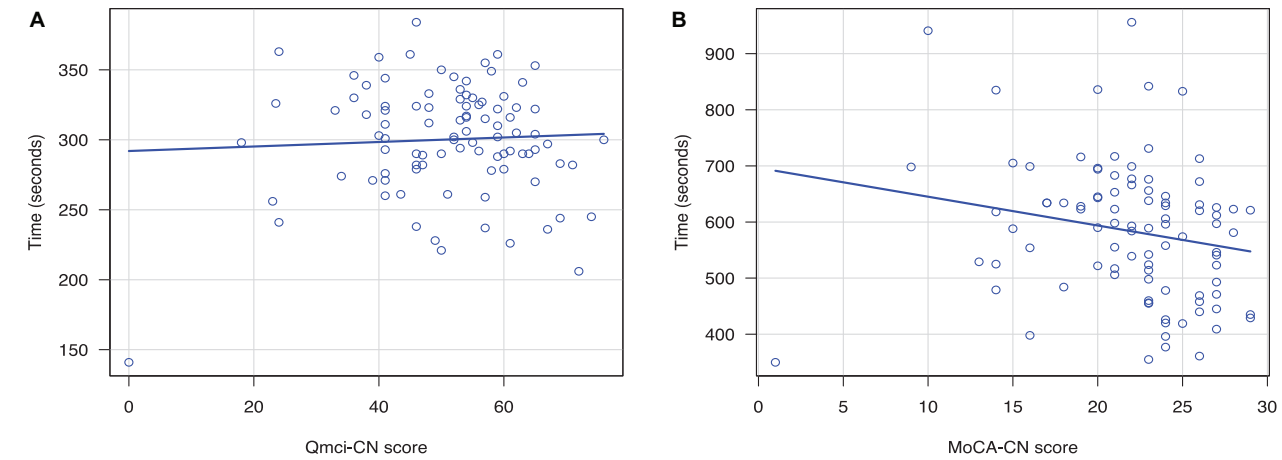

FIGURE 1 | Scatterplots showing the relationship between administration time and scores on the **(A)** Chinese versions of the Quick Mild Cognitive Impairment (Q*mci*-CN) screen and **(B)** Montreal Cognitive Assessment (MoCA-CN).

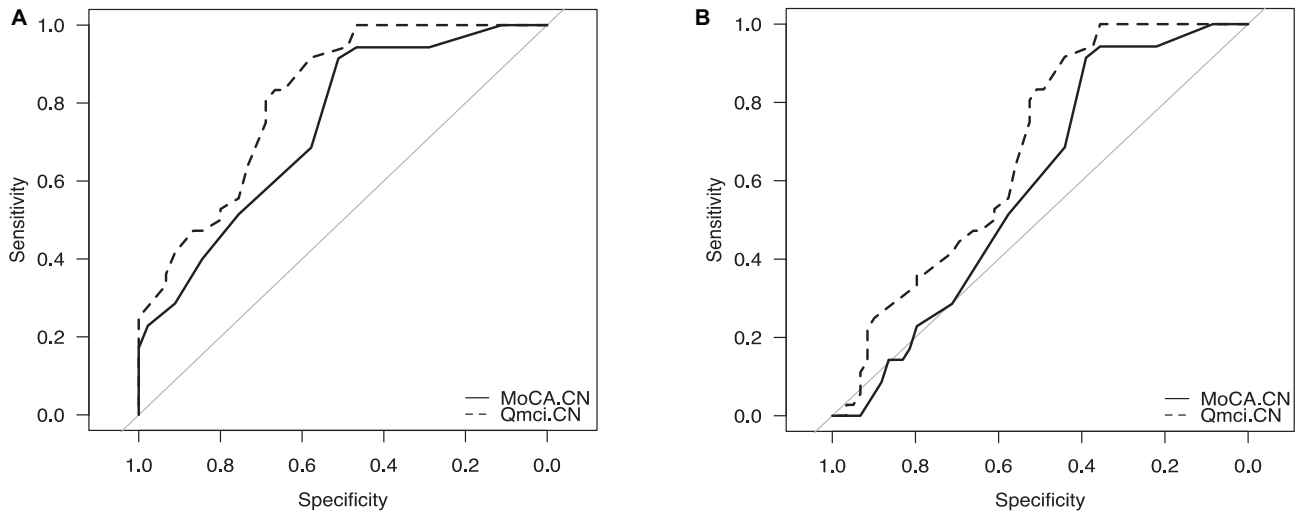

FIGURE 2 | Receiver Operating Characteristic (ROC) curve analysis comparing the Chinese versions of the Quick Mild Cognitive Impairment (Q*mci*-CN) screen and Montreal Cognitive Assessment (MoCA-CN) in identifying **(A)** cognitive frailty from non-frailty and **(B)** cognitive frailty from other patients presenting with symptomatic memory loss.

in separating cognitive frailty from dementia with the MoCA-CN having borderline but not statistically greater accuracy than the Q*mci*-CN, AUC of 0.89 versus 0.76 ($p = 0.05$), respectively. Examining the diagnostic accuracy of both screening instruments in separating those with cognitive frailty from patients who were non-frail (i.e., those with MCI but without physical frailty and SCD who were clinically robust with a CFS score <4), again showed that the Q*mci*-CN and MoCA-CN had similar, AUC 0.81 (95% CI: 0.72–0.90) versus 0.74 (95% CI: 0.63–0.85), respectively, a non-statistically significant difference ($p = 0.19$). Neither instrument was useful in distinguishing cognitive frailty from all of the other patients presenting with symptomatic memory loss (i.e., those with SCD, MCI without frailty and those with dementia); the Q*mci*-CN had an AUC of 0.68 (95% CI: 0.57–0.78) versus 0.59 (95% CI: 0.48–0.70) for the MoCA-CN ($p = 0.10$). At its optimal cut-off (≤55/100), the Q*mci*-CN had a sensitivity of 83% and specificity of 67% for differentiating cognitive frailty from the non-frail. This compared to a sensitivity and specificity of versus 91 and 51%, respectively, for the MoCA-CN at its optimal cut-off in this sample, ≤23/30. These are presented in **Figure 2** and **Table 3**.

Screening for Cognitive Impairment (MCI and Dementia)

Receiver operating characteristic curve analyses were then performed to explore the ability of each cognitive test to differentiate between SCD, MCI, and dementia. This showed that both instruments had similar accuracy in separating

TABLE 3 | Area under the curve (AUC) values and cut-offs for the Chinese versions of the Quick Mild Cognitive Impairment (Q*mci*-CN) screen and Montreal Cognitive Assessment (MoCA-CN).

Diagnostic classification	Cognitive screen	AUC [95% CI]	Comparison of AUC	Optimal cut-off point Sensitivity and Specificity
Cognitive frailty vs. Non-frail	Q*mci*-CN	0.81 [0.72–0.90]	$p = 0.19$	≤55; Sensitivity = 83%, Specificity = 67%
	MoCA-CN	0.74 [0.63–0.85]		≤23; Sensitivity = 91%, Specificity = 51%
Cognitive frailty vs. Other	Q*mci*-CN	0.68 [0.57–0.78]	$p = 0.10$	≤58; Sensitivity = 92%, Specificity = 44%
	MoCA-CN	0.59 [0.48–0.70]		≤ 24; Sensitivity = 91%, Specificity = 39%
Cognitive frailty vs. MCI without frailty	Q*mci*-CN	0.63 [0.43–0.80]	$p = 0.38$	≤58; Sensitivity = 92%, Specificity = 33%
	MoCA-CN	0.51 [0.34–0.67]		≤24; Sensitivity = 31%, Specificity = 83%
Cognitive frailty vs. Dementia	Q*mci*-CN	0.76 [0.63–0.90]	$p = 0.05$	≤50; Sensitivity = 53%, Specificity = 100%
	MoCA-CN	0.89 [0.80–0.98]		≤21; Sensitivity = 71%, Specificity = 93%
MCI/Dementia vs. SCD	Q*mci*-CN	0.91 [0.84–0.97]	$p = 0.42$	≤55; Sensitivity = 83%, Specificity = 82%
	MoCA-CN	0.87 [0.80–0.95]		≤24; Sensitivity = 95%, Specificity = 68%
Dementia vs. MCI/SCD	Q*mci*-CN	0.87 [0.80–0.95]	$p = 0.06$	≤48; Sensitivity = 100%, Specificity = 72%
	MoCA-CN	0.94 [0.89–0.99]		≤21; Sensitivity = 100%, Specificity = 73%
MCI vs. SCD	Q*mci*-CN	0.88 [0.81–0.96]	$p = 0.39$	≤60; Sensitivity = 100%, Specificity = 62%
	MoCA-CN	0.84 [0.75–0.93]		≤25; Sensitivity = 96%, Specificity = 62%
Dementia vs. SCD	Q*mci*-CN	0.99 [0.96–1.00]	$p = 0.74$	≤48; Sensitivity = 100%, Specificity = 97%
	MoCA-CN	0.99 [0.97–1.00]		≤21; Sensitivity = 100%, Specificity = 91%
Dementia vs. MCI	Q*mci*-CN	0.79 [0.67–0.91]	$p = 0.045$	≤46; Sensitivity = 93%, Specificity = 61%
	MoCA-CN	0.91 [0.83–0.98]		≤20; Sensitivity = 93%, Specificity = 74%

cognitive impairment (MCI/Dementia) from normal cognition ($p = 0.42$); the Q*mci*-CN had an AUC 0.91 compared to an AUC 0.87 for the MoCA-CN. The Q*mci*-CN had a better balance in sensitivity and specificity at the optimal cut-off score of ≤55 (Sensitivity = 82%, Specificity = 83%) versus the MoCA-CN, which had a higher sensitivity (95%) but lower specificity (68%) at a cut-off of ≤24. ROC analysis showed that both instruments had similar (non-significantly different) accuracy in identifying people with dementia, AUC of 0.94 compared with AUC of 0.87 for the MoCA-CN and Q*mci*-CN, respectively. The MoCA-CN was more accurate in its predictive ability for dementia versus MCI (AUC 0.91) compared to the Q*mci*-CN (AUC of 0.79), a statistically significant difference, $p = 0.045$. These are presented in **Figure 3** and **Table 2**.

DISCUSSION

Here, we explore the ability of short cognitive screening instruments to identify cognitive frailty as defined by the IANA/IAGG consensus criteria (Kelaiditi et al., 2013), showing that while both the newly translated Q*mci*-CN and established MoCA-CN are able to differentiate cognitive frailty from non-frail individuals and those with dementia, neither instrument was accurate in separating MCI from cognitive frailty in an outpatient rehabilitation setting in China. This suggests that although able to separate cognitive frailty from dementia, where physical symptoms frequently accompany cognitive decline (Tolppanen et al., 2015), the presence of physical frailty in addition to cognitive symptoms in those with normal function (i.e., MCI) does not appear to register on short cognitive screens. The Q*mci*-CN nevertheless compared favorably with the MoCA-CN, with no statistically significant difference in their diagnostic accuracy. We also examined the diagnostic accuracy of the Q*mci*-CN against the MoCA-CN in separating those presenting with cognitive complaints, showing that the Q*mci*-CN's ability to distinguish MCI from SCD or dementia in this sample was good to excellent but that the time taken to complete it was significantly shorter, which is particularly convenient in a rehabilitation clinic setting. The MoCA-CN was significantly better able to separate MCI from dementia. The Q*mci*-CN represents another external validation of the instrument, after the Irish, Dutch, Australian, Turkish, Italian, Taiwanese, Japanese, and Portuguese versions (Bunt et al., 2015; O'Caoimh et al., 2016; Clarnette et al., 2017; Yavuz et al., 2017; dos Santos et al., 2019; Iavarone et al., 2019; Lee et al., 2018; Morita et al., 2019). This study adds more evidence to support its use in patients with MCI in busy clinical setting.

Although, the results did not show that the Q*mci*-CN is superior at differentiating cognitive frailty, it is likely that it would have been underpowered to show this; based on previous studies comparing the Q*mci* screen to the MoCA a sample of 300 patients with MCI and 300 controls would be required (O'Caoimh et al., 2016). Due to time and resource constraints recruitment was discontinued after 6 months. Further, because of this additional research is needed to come to any confident conclusions regarding diagnostic accuracy. Nevertheless, its administration took significantly less time than the MoCA-CN ($p < 0.001$) and no marked gradient effect was evident compared to that seen for the MoCA-CN, where people with dementia took much longer to complete the test. The Q*mci*-CN took on average 300s (5 min) to complete, while the MoCA-CN took on average 584s (9.7 min), almost double the time. Given this, the Q*mci*-CN appears to be more

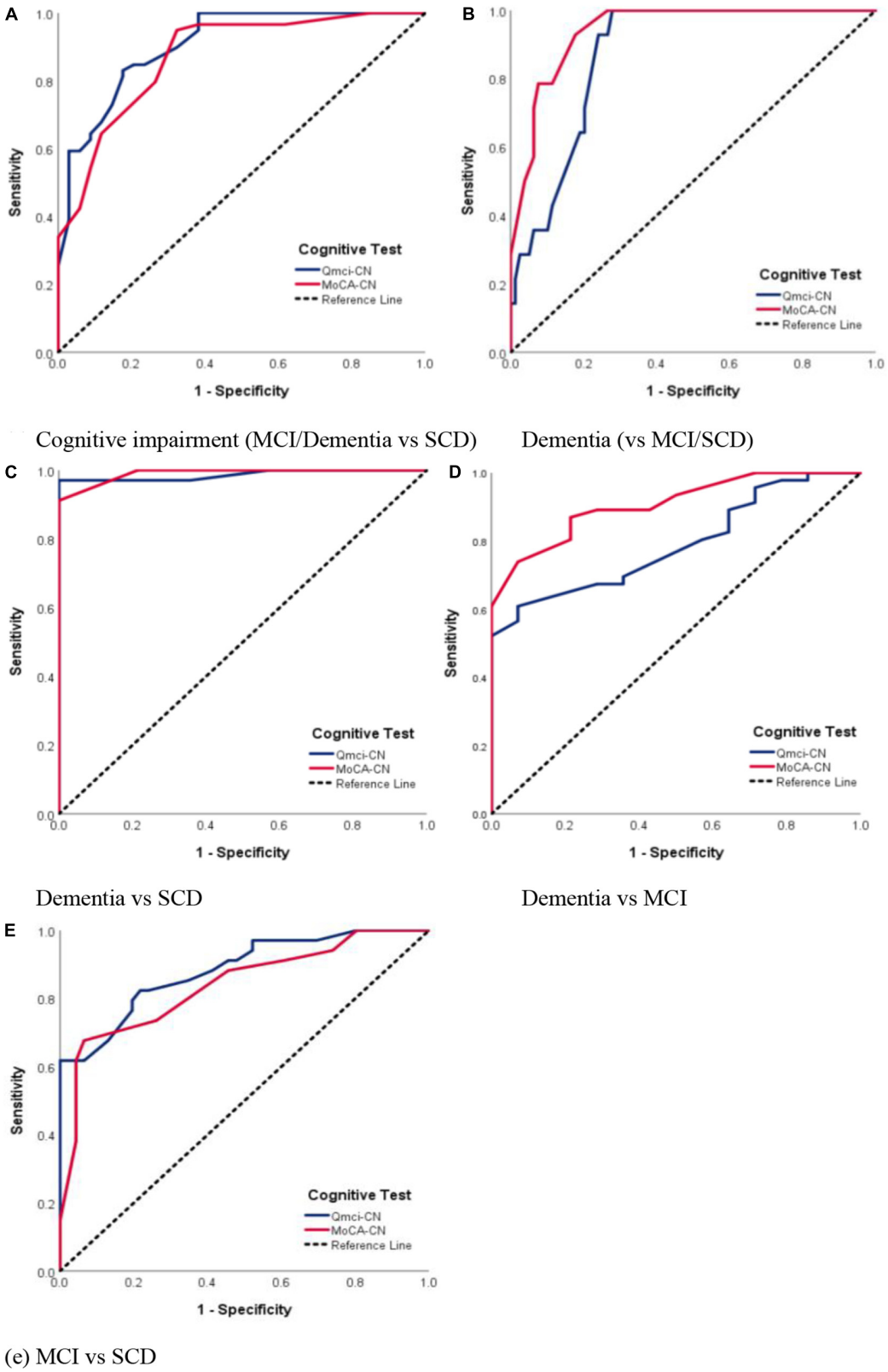

FIGURE 3 | Receiver Operating Characteristic (ROC) curve analysis comparing the Chinese versions of the Quick Mild Cognitive Impairment (Q*mci*-CN) screen and Montreal Cognitive Assessment (MoCA-CN) in separating subjective cognitive disorder (SCD), mild cognitive impairment (MCI) and dementia. **(A)** Cognitive impairment (MCI/Dementia vs. SCD). **(B)** Dementia (vs. MCI/SCD). **(C)** Dementia vs. SCD. **(D)** Dementia vs. MCI. **(E)** MCI vs. SCD.

convenient to use in clinical settings where time is limited or numbers attending high, which is especially relevant in China. Additional research is also required to examine if this time saving could improve efficiency (e.g., more patients seen per clinic) or if there are cost savings associated with the reduced administration time of the Q*mci*-CN versus the MoCA-CN.

This paper also provides the optimal cut-off scores for both instruments to identify cognitive frailty, which are similar to those for identifying cognitive impairment in this sample, particularly MCI suggesting that there is likely to be significant overlap between these patients (Won et al., 2018). This is reinforced by the fact that both instruments were poor at separating MCI from cognitive frailty. Their diagnostic accuracy was better at distinguishing cognitive frailty from dementia, i.e., those with cognitive impairment with physical impairment and functional impairment, respectively. For example, the optimal cut-off for the Q*mci*-CN in separating MCI from normal was $\leq$60, similar to that found in an Irish cohort (O'Caoimh et al., 2016). Cut-off scores for dementia were however, lower than those found in other countries. Possible reasons for this discrepancy include the lower level of education of participants, a mean/median of 11 versus 12 years in the studies in Ireland and Canada, and the setting as all participants were recruited from rehabilitation clinics. At the same time, the MoCA-CN's optimal cutoff score for cognitive impairment was $\leq$24 (Sensitivity = 95%, Specificity = 68%), which is also lower than the recommended MoCA cutoff score ($<$ 26) (Nasreddine et al., 2005).

Limitations

First, we cannot be certain that all patients were classified appropriately, as differentiating cognitive frailty from MCI and from dementia with frailty was based on clinical criteria, which are inherently subjective. Nevertheless, within the confines of these criteria, patients were correctly classified. Further, the neuropsychological testing used here is different to that applied in IANA/IAGG criteria for cognitive frailty (i.e., the CDR). This said there is still no gold standard to diagnose cognitive frailty and detailed neuropsychological testing (i.e., ADAS-cog), which are routine in our clinics was conducted. Further, IANA/IAGG have been criticized for being impractical in busy clinical practice (Won et al., 2018). Second, the sample size was small, especially the number of people with cognitive frailty (n = 36) such that the sample was not powered adequately to detect significant differences in the diagnostic accuracy of the instruments. This is particularly evident in the analysis examining the performance of the screening instruments in separating MCI from cognitive frailty with only 12 patients with MCI without physical frailty available. The low accuracy for this comparison raises the concern that the instruments are not diagnosing cognitive frailty specifically, but just performing as would be expected in separating people with normal and abnormal cognition regardless of physical ability. This requires a larger sample to evaluate. Third, this was a highly selected sample with those found to have clinical depression and those with atypical presentations excluded as they often present with exaggerated functional and cognitive impairments. Fourth, given the relatively homogenous sample, spectrum bias may have occurred further limiting the results (Chopard et al., 2015). Finally, cognitively healthy (asymptomatic age-matched with normal neuropsychological testing) controls were not included in this analysis. To correctly interpret the tests, particularly the psychometric evaluation of these CSIs, a control group without subjective memory problems is needed as a comparison group. This is also important as those with SCD have a higher risk for conversion to subsequent MCI and dementia, though the majority do not develop progressive cognitive decline (Jessen et al., 2020). As many studies include both groups this is needed to improve comparability with other studies.

CONCLUSION

In conclusion, screening for cognitive frailty was possible using short cognitive screening instruments in this sample of middle-aged and older Chinese adults. The Q*mci*-CN screen, which is validated here for the first time in Chinese among those presenting with cognitive symptoms, appears to be a short, and reliable instrument that can be used to differentiate SCD from MCI and dementia. Here it shows similar accuracy to the MoCA-CN with a shorter administration time and can be applied in busy rehabilitation settings. While both screens separated cognitive frailty from physically robust patients and those with dementia, neither accurately separated MCI from cognitive frailty. This suggests that in this sample, as might be expected, cognitive screening instruments are better able to detect the cognitive rather physical aspects of frailty in those with cognitive decline. Further research is required to examine this and to recruit more patients to adequately power a study to investigate if short cognitive screens can accurately identify cognitive frailty in a range of different settings, such as community, memory clinics and acute hospitals in comparison with non-frail and asymptomatic normal controls. Similarly, there is a need to examine the psychometric properties of the Q*mci*-CN in more detail and compare its diagnostic accuracy to the MoCA-CN in older Chinese adults presenting with cognitive symptoms.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

All signed informed consent before participating in our research. This study received ethical approval from The Six Affiliated Hospital of Sun Yat-sen University.

AUTHOR CONTRIBUTIONS

YX: design, concept, data collection, analysis, writing and revising manuscript. YW: design, concept and supervision. YL, LY, ZL, XL, YY, YG, HJ, and ZC: concept and data collection. AS: statistical analysis and supervision of statistics. YG: design. DM: design, concept. RO'C: design, concept, analysis, writing, and revising manuscript.

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Assessment of Major Neurocognitive Disorders in Primary Health Care: Predictors of Individual Risk Factors

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Major Neurocognitive Disorders describe the symptoms of a large group of diseases causing a progressive decline in individual's functioning. It is an umbrella term describing a decline in memory, intellectual ability, reasoning, and social skills, as well as changes in normal emotional reactions. The general practitioner is instrumental in the early diagnosis of Major Neurocognitive Disorder. Individual risk factors act as contributing variables affecting the probability of someone developing a Major Neurocognitive Disorder and may be considered predictive factors. This study aimed (i) to show the utility of using the Global Deterioration Scale in primary health care settings as a measure to assess the stage of cognitive function for individuals identified with Major Neurocognitive Disorders and (ii) to identify predictors of severe Major Neurocognitive Disorders. Potential predictors of Major Neurocognitive Disorders considered in this study were: sex, age, years of education, social isolation, hearing impairment, cardiovascular disease, hypertension, diabetes, smoking habits, alcohol consumption, physical activity, hand strength, and nutritional status. The sample comprised 250 adults, 30.4% were classified as having probable Major Neurocognitive Disorder. The variables significantly associated with probable Major Neurocognitive Disorder were age, years of education, hearing impairment, cardiovascular disease, hand strength, nutritional status, and physical activity. In the multivariable model, only age, education, physical activity and hand strength remained significant predictors of probable Major Neurocognitive Disorder. The Global Deterioration Scale seems to be a usefull instrument in primary healthcare settings, as it guides the general practitioner in observing the patients' cognitive functioning. Advanced age, lower education, lower hand strength and absence of physical activities should be taken into account as they increase the chance of severe Major Neurocognitive Disorders. Primary health care providers, including general practitioners are very important in the diagnosis and follow up of Major Neurocognitive Disorder. The general practitioner is in most cases the patients' first and for many patients the only contact, thus having a critical role in evaluating with caution what is part of normal or pathological aging, and the individual factors that can increase the likelihood of developing Major Neurocognitive Disorder to further support patients in the course of the disease.

Keywords: major neurocognitive disorders, predictors, primary health care, older people, health

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INTRODUCTION

Major Neurocognitive Disorder (MND) – previously called dementia – is a syndrome that progresses with significant deterioration of cognitive domains as compared to previous levels of cognitive performance in memory, speech, reasoning, intellectual function, and/or spatiotemporal perception, and may also be associated with changes in emotional behavior and difficulties at the functional level. The decline is initially noticed by the individual, the family, or the General Practitioner (GP) who is usually responsible for the early diagnosis (American Psychiatric Association [APA], 2014).

MND may result from brain disorders, classified as primary (degenerative), or consequence of other conditions (secondary) (Emre, 2009). The most common types of MND are: Alzheimer's disease, Vascular dementia, Lewy body dementia and Frontotemporal dementia. In secondary MND (e.g., alcoholic dementia, infectious diseases) the symptoms may be treated and/or prevented. Therefore, a correct diagnosis is crucial. This is supported by a detailed collection of the person's clinical history, neurological and neuropsychological examination and the comprehensive use of laboratory and imaging tests. In primary MND, early diagnosis is equally crucial either to delay the progression of cognitive symptoms and to control/stabilize psychiatric manifestations (Ribeira et al., 2004).

Some symptoms of MND might be confused with typical changes occurring in healthy aging. The first signs of MND are very subtle and vague, and can be difficult to detect. Those signs are also very diverse and, as such, we must do a staging of Dementia, which is not only centered on aspects of the cognitive forum (Fernández-Ballesteros et al., 2012).

The GP is instrumental in the detection of the first signals of MND. Additionally, the GP supports the persons with MND and their caregivers in organizing and planning interventions at an early stage of the disease and care provision as the disease progresses (Sequeira, 2010). To confirm any suspicion on the decline in cognitive functioning of a patient, the GP needs to use a screening instrument that should be easy and quick to apply. The most common practice is the use of the Mini Mental State Examination (MMSE) (Folstein et al., 1975) that has been used to detect and monitor the evolution of cognitive impairment (Valle et al., 2009). The disadvantage of using MMSE, however, is the fact that it does not allow to establish stages of cognitive function or detect early stages of cognitive decline.

The Global Deterioration Scale (GDS), developed by Barry Reisberg (1988), provides an overview of the stages of cognitive function for those living with a primary degenerative dementia. This instrument is easy to use and facilitate the assessment of subjective cognitive complaints (Custodio et al., 2017). GDS stages are associated with cognitive function but also with basic and instrumental activities of daily living (ADL; e.g., dressing, eating, and bathing) and instrumental activities of daily living (IADL; e.g., handling finances, medication management (Paul et al., 2002). GDS is not a diagnostic scale and was developed as a qualitative severity rating only (Hartmaier et al., 1994; Brooke and Bullock, 1999; Petersen et al., 1999). According to Custodio et al. some studies validate the GDS as an assessment tool to detect mild cognitive impairment.

The GDS includes seven stages: Stage 1 (no cognitive decline) – No subjective or objective memory deficits. Stage 2 (Very Mild Cognitive Decline) – Subjective complaints of memory deficit, but no objective measurements of memory deficit. Stage 3 (Mild Cognitive Decline) – The individual now meets criteria for mild cognitive impairment. Stage 4 (Moderate Cognitive Decline) – The individual is now classified as being mildly demented. This could manifest as a clear deficit on concentration, handling finances, orientation, and recognition of time and place. Symptoms such as flattening of affect and anxiety start to occur. Stage 5 (Moderately Severe Cognitive Decline) – The individual now meets criteria for moderate dementia and can no longer function without some assistance but can toilet and eat on their own. Stage 6 (Severe Cognitive Decline) – The individual meets criteria for moderately severe dementia. The individual is entirely dependent on someone else for survival and are generally unaware of their surroundings, year, season, etc. Personality and emotional changes occur. Stage 7 (Very Severe Cognitive Decline) – The individual is now severely demented. The individual has lost all verbal abilities and is incontinent, as well as basic psychomotor skills (Hardcastle et al., 2019).

Predictive Factors of MND

MND is likely to develop in a continuous process (Brooks and Loewenstein, 2010). Individual factors affect the likelihood of developing MND. Those factors predicting the development of the disease should be known, and preventive interventions must build on this knowledge.

Previous studies have identified predictive factors of MND, which can be grouped into sociodemographic (e.g., sex, age, and years spent in education and social isolation), health factors (e.g., hearing loss, cardiovascular diseases, hypertension, diabetes, handgrip strength, and nutritional status) and bio-behavioral factors (e.g., smoke, alcohol, and physical activity) (Helzner et al., 2009; Nagai et al., 2010; Polidori et al., 2012; Baumgart et al., 2015; Santana et al., 2015; Schwarzinger et al., 2018). Given that most of these factors are potentially modifiable (e.g., diabetes, cholesterol, depression, or malnutrition; Chen et al., 2017), the individual can play an active role in the development of the disease, allowing for more efficient intervention. Primary prevention in the primary health care context is very important for the course of MND, and should focus on the identification of situations that increase the likelihood of occurrence or worsening of symptoms. However, few studies identify predictive factors associated with severe stage of MND (Eshkoor et al., 2016).

The objectives of this paper are: (i) to show the utility of using the GDS in primary health care settings as a measure to assess the stage of cognitive function for individuals identified with MND (ii) to identify predictors of severe MND.

MATERIALS AND METHODS

Participants

This study is an observational cross-sectional study that is part of a larger project aiming at "Needs of Care for People with Dementia."

The inclusion criteria defined in the largest project, also used in this study, are: (i) to be a user of a primary care unit in the area of Portuguese North Regional Health Authority (ARS Norte); (ii) age 65 years or plus; (iii) living in the community; (iv) presence of mental health concerns. The exclusion criteria were as follows: (i) patient not using a primary health-care unit covered by the ARS North; (ii) age less than 65 years old; (iii) living in nursing home, hospital or psychiatric institution; and (iv) absence of memory concerns (patients classified in stage 1 of the GDS).

Instruments

The study protocol was based on the "Community Assessment of Risk and Treatment Strategies (CARTS) Program" developed in the University College Cork, Ireland (Caoimh et al., 2012). The protocol is divided in three different sections: The purpose of the first part (Part A) was to assess the patient with probable dementia referred by the health professional (GP or nurse); the second part (Part B) was used to assess the patient with probable dementia by the GP; the final part (Part C) focus the evaluation of the informal caregiver of the patient with probable dementia (if available).

In this study, information provided in Part A and B of the assessment protocol was used. Data were collected by resorting to the following instruments:

Sociodemographic questionnaire: It allows to collect data about the patient with probable dementia, including sex (M/F), age, years spent in education, and social isolation (living with someone/living alone).

Cognition: Global Deterioration Scale (GDS) (Reisberg et al., 1982, portuguese version; Leitão et al., 2007).This instrument allows to qualitatively classify the individuals according to the stage of primary degenerative dementia. This scale has been validated with behavioral, neuroanatomic, and neurophysiological measures in patients with primary degenerative dementia. GDS includes seven different stages of patient classification (see section "Introduction"). An overall description of the symptoms and clinical characteristics expected for each stage of dementia is provided in the instrument, and such descriptions are considered for deciding on the most appropriate global level (stage) of cognition and function.

Health: Older Americans Resources and Services (OARS) (Fillenbaum and Smyer, 1981, portuguese version; Rodrigues, 2008) is a program of resources and services for old people. The OARS methodology was developed to assess functional capacity in five key areas for older adults' quality of life: social resources, economic resources, mental health, physical health, and activities of daily living. It also measures the use and perceived need for various types of services, enabling the evaluation of intervention programs and informed decision-making on the impact of resources and services. This instrument contains a list of the most common problems in older people and this study considered cardiovascular problems, hypertension, diabetes, hearing loss, and dementia; Handgrip strength was assessed using a dynamometer considering four attempts, two on each hand. The final score corresponds to the average of the highest values for each hand (Wearing et al., 2018; Zammit et al., 2019).

Bio-behavioral aspects: Frequency of physical activity [(1) more than once a week; (2) once a week; (3) 1–3 times per month; (4) almost never or never]; Alcohol and tobacco consumption [(1) no; (2) yes, but stopped; (3) yes]; Short-Term Nutritional Assessment (MNA-SF) (Rubenstein et al., 2001) is a nutritional screening and assessment tool aimed at identifying malnourished patients. It consists in six questions and the total score ranges from 0 to 14. A score of 11 or above indicates possible malnutrition.

Procedures

The Risk Instrument for Screening in the Community (Caoimh et al., 2012) was first used as a screening tool to identify potential participants, i.e., patients with mental health concerns. Based on these results, and considering strata by age group, sex, and region, 572 participants with mental health concerns were randomly selected. Of these, 504 agreed to participate and 436 were eligible to participate. The final sample of this study included 250 individuals with mental health concerns and with the evaluation provided by the GP (Part B of the study protocol).

The data collection lasted 27 months (from January 2014 to April 2016). The Part A of the study protocol was administered to potential participants by trained interviewers and took on average 45 min to complete. Most interviews were carried in health-care centers, and, when participants were not able to meet the interviewers at the health centers, interviews were completed at patients' home.

After the first interview, the GP completed the Part B of the evaluation protocol using mainly the existing clinical registries of the patient. To complete the checklist of diagnoses (OARS), the GP used the International Classification of Diseases 9th Revision Clinical Modification (ICD-9-CM). This classification was adopted in Portugal in 1989 for the purposes of clinical coding. In the specific case of the diagnosis of dementia, the coding F03-dementias (not specified) was considered.

The study was submitted to the Ethics Committee of the ARS-Norte and was approved unanimously on January 7, 2014 (Reference No. 6/2014). All participants signed the informed consent form complying with the Declaration of Helsinki.

The detailed methodological aspects are reported and can be consulted elsewhere (Teixeira et al., 2017).

Statistical Analysis

First, a receiver operating characteristic (ROC) analysis was performed to determine the optimal GDS cutoff point to identify stages of MND, considering the GP diagnosis as gold standard [coding F03-dementias (not specified) in the diagnosis' checklist]. The area under the curve (AUC) was calculated as well as the sensitivity and specificity values. The Youden Index (Sensitivity + Specificity-1) was used to obtain the optimal cutoff point.

Then, based on the optimal cutoff point obtained, two groups were considered: patients with non-severe MND vs. patients with severe MND.

Descriptive analysis of the data was performed in order to describe the sociodemographic and health profile of the study sample. Differences between groups with and without

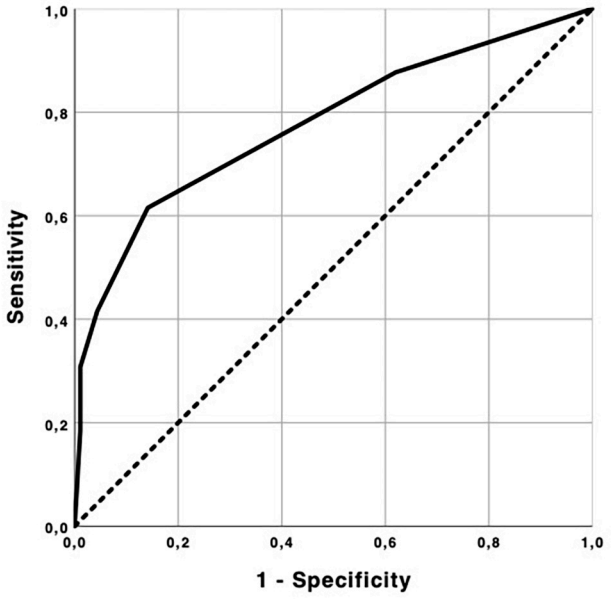

FIGURE 1 | ROC curve.

non-severe MND across sociodemographic, health, and bio-behavioral variables were assessed using the Student *t*-test (for continuous variables) and the Chi-Square test (for categorical variables). To identify potential predictors of severe MND, a multivariable binary logistic regression model was used.

All analyses were performed using IBM SPSS Statistics 24. A significance level of 0.05 was considered.

RESULTS

In order to identify stages of MND through the optimal GDS cutoff point, we use a ROC curve analysis. The area under the ROC curve [AUC = 0.777, 95% CI = (0.700; 0.854)] shows that GDS can predict about 77.7% of the events (severe MND). Given the estimates for sensitivity and specificity (0.615 and 0.860, respectively) and based on the Youden index, the optimal cutoff was 3.5, i.e., individuals with a score equal or greater than four were classified as severe MND (**Figure 1**).

With this cutoff point we classified and grouped the individuals in the sample as "with non-severe MND" or "with severe MND."

More than half of the sample (N = 250) is female, and the average age 76 years old. The participants spent, on average, 2.5 years in formal education and only a small percentage live alone. About 1/3 of the participants have hearing impairment and more than 40% have diabetes, cardiovascular problems or hypertension. The average handgrip strength and nutritional status score is below 20%. Regarding the bio-behavioral aspects, more than 50% of the sample do not smoke, report to exercise more than once a week and less than 50% do not drink alcohol (**Table 1**).

The potential predictors of severe MND considered in this study were: gender, age, years of education, social isolation, hearing loss, cardiovascular disorders, hypertension, diabetes, smoking, alcohol consumption, physical activity, hand strength, and nutritional status.

Of the referred factors, there was a significant association with severe MND for age ($p < 0.001$), years of education ($p = 0.006$), hearing loss ($p = 0.002$), cardiovascular disorders ($p < 0.001$), hand strength ($p < 0.001$), nutritional status ($p < 0.001$), and physical activity ($p < 0.001$).

Individuals with severe MND had a higher mean age and lower years of education compared to individuals with non-severe MND. Additionally, the percentage of individuals with severe MND was higher in individuals with hearing and cardiovascular problems. Individuals with severe MND had a lower mean of Hand Strength and a lower mean of MNA score. Finally, individuals who exercise more than once a week have a lower percentage of severe MND than individuals who never exercise.

In order to identify independent predictors of severe MND, we used a multivariable binary logistic regression model, considering results obtained from the bivariate analysis (**Table 1**). Only age, years of education, physical activity and hand strength have shown to be significant predictors of severe MND (see **Table 2**).

Older patients had more chances to had severe MND (*OR* = 1.090; 95% CI 1.017–1.167). Additionally, the more years of education the participants had, the lower the chance of having been classified with severe MND (*OR* = 0.696; 95% CI 0.550–0.882). Similar results were found for hand strength, with higher hand strength related with a decreased risk of severe MND (*OR* = 0.919; 95% CI 0.856–0.986). Finally, regarding physical activity, those who almost never or never practice physical exercise had a higher chance of being classified as having severe MND than those who never practice physical exercise (*OR* = 4.121; 95% CI 1.635–10.390).

DISCUSSION

The first objective of this study related to the need of identification of MND stages of MND by GPs, to facilitate an early referral of patients to specific and beneficial interventions. This would enable to timely implement appropriate interventions targeted at these patients and their caregivers and aimed at monitored more effectively the disease from its outset and during its course. There is no specific protocol to make the diagnosis of MND in Primary Health Care settings. GPs tend to use various tests and complementary exams, whenever available, to determine whether symptoms meet diagnosis criteria of MND and to exclude other possible causes for observed symptoms.

Although there are other scales widely used, such as the "Clinical Dementia Rating scale (CDR)" and the "Clinical Dementia Score" (Morris, 1991) we have selected the GDS accounting for the fact that this is a friendly tool that allows the GP to go further with the diagnosis and classify the state of the MND, through observational interviewing and recording

TABLE 1 | Characteristics of the total sample and according groups.

		Total	Non-severe MND	Severe MND	*p*	OR
		n (%) or mean (*SD*)	*n* (%) or mean (*SD*)	*n* (%) or mean (*SD*)		
Sex	Male	111 (44.4)	80 (72.1)	31 (27.9)	0.448	Ref
	Female	139 (55.6)	94 (67.6)	45 (32.4)		1.235
Age		76.14 (7.3)	74.39 (6.5)	80.17 (7.2)	<0.001	1.125
Years education		2.85 (2.0)	3.31 (1.9)	1.79 (1.8)	0.006	0.631
Social isolation	Living with someone	212 (85.5)	147 (69.3)	75 (30.2)	0.728	1.150
	Living alone	36 (14.5)	26 (72.2)	10 (27.8)		Ref
Hearing loss	With problems	53 (23.2)	28 (52.8)	25 (47.2)	0.002	2.658
	Without problems	175 (76.8)	131 (74.9)	44 (25.1)		Ref
Cardiovascular diseases	Yes	102 (45.9)	58 (56.9)	44 (43.1)	<0.001	2.883
	No	120 (54.1)	95 (79.2)	25 (20.8)		Ref
Hypertension	Yes	188 (78)	128 (68.1)	60 (31.9)	0.616	1.187
	No	53 (22)	38 (71.7)	15 (28.3)		Ref
Diabetes	Yes	98 (42.1)	69 (70.4)	29 (29.6)	0.712	0.899
	No	135 (57.9)	92 (68.1)	43 (31.9)		Ref
Hand strength		19.6 (8.9)	21.2 (9.1)	15.5 (7.1)	<0.001	0.914
Nutritional status		10.7 (2.6)	11.41 (2.2)	9.11 (2.9)	<0.001	0.713
Smoke	No	131 (79.4)	89 (67.9)	42 (32.1)	0.255	Ref
	Yes, but I stopped	29 (17.6)	24 (82.8)	5 (17.2)		0.441
	Yes	5 (3)	4 (80)	1 (20)		0.530
Alcohol consumption	No	68 (41.7)	41 (60.3)	27 (39.7)	0.108	Ref
	Only on very special occasions	14 (8.6)	11 (78.6)	3 (21.4)		0.414
	Occasionally	26 (16)	21 (80.8)	5 (19.2)		0.362
	Yes	55 (33.7)	42 (76.4)	13 (23.6)		0.470
Physical activity	More than 1x/week	146 (59.1)	123 (84.2)	23 (15.8)	<0.001	Ref
	1x/week	17 (6.9)	13 (76.5)	4 (23.5)		1.645
	1–3x/month	8 (3.2)	7 (87.5)	1 (12.5)		0.764
	Almost never or never	76 (30.8)	30 (39.5)	46 (60.5)		8.200

of the patients' symptoms. In addition to the usefulness of this instrument to appraise the stage of MND, thus focusing mainly on cognition, it is one of the simplest scales, helping to understand the patients' actual and future condition, and proved to be very suitable. We determined the optimal cutoff point for the GDS in the early diagnosis of probable MND, considering the medical diagnosis as gold standard. We have determined that individuals with a GDS score equal or greater than four are considered as having severe MND.

Having as a health priority the early diagnosis of MND and the classification of the stage of the disease in primary health care settings, the second aim of this study was to investigate the predictors of MND, with the ultimate goal of preventing/intervening in some risks that may be circumventable. It was possible to identify four predictors of MND: age, years spent in education, physical activity and hand strength. Physical activity, hand strength and education play a protective role ("the more the better"). On the other hand and as expected, while age increases, the risk of MND also increases.

The findings from this study on the risk factors for MND are in line with available literature on the topic. Regarding physical activity, other studies have suggested Weuve et al. (2004) that regular physical activity reduces vascular risk factors and may directly increase the production of neurotrophic factors in the brain physical exercise as a protective function of neurons. Regarding the role of education, some studies (Amieva et al., 2014) report that the mechanism through which more educated individuals are at lower risk of developing MND is the greater ability of more educated individuals to cope with symptoms.

The older the person, the greater the risk of having MND. Age is the main risk factor for MND. After the age of 65, the risk of MND increases every 5 years. The same is true for hand strength: the lower the strength, the higher the risk of MND. Among older adults, this association is often cited for its relation to the concept of frailty and implications on the person's functional status (Abizanda et al., 2012). Several studies (Jang and Kim, 2015) have found a significant association of cognitive decline with worse hand strength among older adults values in the elderly. Hand strength may represent an age-related change in physical function and frailty, contributing to cognitive decline and increasing the risk of MND. Thus, we can formulate the hypothesis that cognitive changes may influence the motor skills of older adults, which would justify the worse performance in the hand strength test in older persons with cognitive deficit. Another justification would be that that low hand strength is

TABLE 2 | Multivariable logistic regression model.

Predictors		OR	95% CI	*p*
Sex	Male	1	–	–
	Female	1.282	0.430–3.829	0.656
Age		1.090	1.018–1.168	0.014
Years of education		0.696	0.550–0.882	0.003
Physical activity	More than once a week	1	–	–
	About once a month	0.917	0.234–3.590	0.901
	Almost never or never	4.121	1.635–10.39	0.003
Hand strength		0.919	0.856–0.987	0.020
Nutritional status		0.954	0.794–1.146	0.613
Cardiovascular diseases	No	1	–	–
	Yes	2.164	0.892–5.246	0.088
Hearing loss	No	1	–	–
	Yes	0.745	0.268–2.072	0.573

a consequence of inactivity, which can contribute to cognitive decline. In any case, hand strength losses arean alert sign to the development of MND.

Although significant contribution of sex was not found in this study, the literature has been suggesting that female are at greater risk of developing MND than male. Worldwide, most people with MND or at risk of developing MND are women, according to Alzheimer's Disease International (2015). However, other studies suggest that, up to the age of 90, there is no sex differences in the incidence of MND, above this age men appear to be at lower risk than women (Ruitenberg et al., 2001).

In future studies, other variables should be taken into account and investigated about their association with the development of MND. Sleep hygiene, for instance, is an important variable. Some studies suggest that sleep changes often occur in people with MND, and can aggravate with the progression of MND. In addition to normal sleep changes as a result of aging, changes that occur in the brain increase sleep disorders in older adults with MND (Rose and Lorenz, 2012). Changes in the pattern of sleep modify the homeostatic balance, with repercussions on psychological function, immune system, performance, behavioral response, mood and ability to adapt (Ebersole and Hess, 2001).

The main limitations of this study are related to its cross-sectional design, not allowing the observation of the disease progression as classified by GDS. Moreover, the GDS may not be very sensitive to cognitive changes over time. Also, while the coding system for the diagnosis of dementia is unique both at national and international levels, the GPs follow different protocols to assess patients and stablish the diagnosis that was used as a golden standard in this study. Other concerns are the dimension of the sample and the heterogeneity of this population (in terms of age, education, access to health services and even life style) making it difficult to generalize the results. However, this study is innovative because it is based in a Portuguese representative sample of users of the health care centers in the north of the country, and reports on current MND diagnosis by GPs. These findings have clinical relevance and implications for case management in dementia in the context of primary health care.

CONCLUSION

Primary health care settings are very important in the identification of MND. The GP is in most cases the patients' first and only contact and for this professional the differentiation between normal or pathological aging should be clear and the individual factors that can contribute to MND must be known. The recognition of the stage of MND supports a more accurate understanding of the patient, family conditions and needs during the progression of the disease and should lead to an adequate customization of available health and social support services. An early diagnosis of MND, together with the use of GDS to acknowledge the stage of the disease in which the patient is, and the identification of predictors of probable MND will consubstantiate very relevant aspects of clinical practice. These aspects are the foundation of the design of more targeted interventions for each individual, which at should emphasize physical and lifelong learning throughout life.

DATA AVAILABILITY STATEMENT

The datasets for this article are not publicly available because: this study is part of a larger study. Requests to access the datasets should be directed to CP, paul@icbas.up.pt.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the ARS-Norte on January 7, 2014 (Reference No. 6/2014). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SS wrote the manuscript and conducted the data analysis. LT and CP reviewed the manuscript. All authors contributed to the manuscript and approved the submitted version.

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ORIGINAL RESEARCH
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Emotional Well-Being and Cognitive Function Have Robust Relationship With Physical Frailty in Institutionalized Older Women

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Introduction: Frailty associated to core dimensions of psychological well-being (PwB) has appeared as a possible new frailty phenotype named psychological frailty, implying a parallel to physical frailty (PF). Very little is known about the associations between mental well-being, especially emotional, mood, and self-perception dimensions, and the frailty syndrome in institutionalized older populations. The present study aims to examine the interlink between the PF phenotype and the core dimensions of PwB in Portuguese institution-dwelling older women.

Methods: Cross-sectional data were collected. A total of 358 older women, aged 75 years or more, were recruited from four nursing homes within the city of Coimbra and asked to complete a sociodemographic and a general health assessment survey. The main PwB dimensions were assessed in all participants: (i) global cognitive status was assessed using The Montreal Cognitive Assessment (MoCA) Neuropsychology Test, (ii) self-perception was screened using the General Self-Efficacy Scale (GSES) and Global Self-Esteem Scale, (iii) CES-D of depression and Perceived Stress Scale (PSS) were used to screen mood states, and (iv) subjective happiness, satisfaction with life, and attitudes to aging psychometric rating scales were used to screen for emotional well-being. The syndrome of PF was assessed using Fried's PF phenotype that includes weight loss, weakness, slowness, exhaustion, and low physical activity (PA) level assessments.

Results: Frail older women had a poor score in all PwB outcomes, except for global self-esteem and satisfaction with life. A hierarchical regression model analysis showed that global cognitive status and emotional well-being of subjective happiness and attitude to aging showed a significant negative relationship with PF in both unadjusted and adjusted models (explaining 34 and 40% of variance, respectively).

Conclusion: Emotional well-being and global cognitive performance are strongly associated with PF. Implementing active lifestyle interventions to improve positive psychological outcomes using geriatric assessments could assist in the older institutionalized patients' physical and mental health care.

Keywords: frail older adults, subjective well-being, mental health, mild cognitive impairment, psychological frailty, depression, happiness

INTRODUCTION

Frail populations are at an increased risk for adverse negative health consequences (Middleton et al., 2008). Disability, morbidity, institutionalization, and hospitalization are likely outcomes of this clinical time-progressive form of unsuccessful aging (Clegg et al., 2013). In the frail person, the order of adverse events occurs earlier and faster, significantly affecting their psychological adjustment and quality of life (Gobbens et al., 2013; Kanwar et al., 2013). A contemporary approach to the concept of physical frailty (PF) made by specialists recognizes it as a syndrome associated with aging that causes increased vulnerability to stressors due to deficiencies between various interrelated physiological systems, leading to a decline in homeostasis (Morley et al., 2013). The concept of PF established by Fried et al. (2001) is understood as a robust construct and has five components that comprised perceived exhaustion, weight loss, and also low levels of hand grip strength, gait speed, and physical activity (PA). It is assumed to be very helpful for health professionals and researchers and to comprehend the heterogeneity of health trajectories linked to frailty (Morley et al., 2013).

Despite the considerable evolution of the concept of frailty carried out to date, which culminated in the development of other models and frailty indexes, recent observational studies have presented other health-related dimensions that can better explain this syndrome (Kelaiditi et al., 2013). The recently coined concept of cognitive frailty (CF) has been described to mediate the probability of numerous types of neuropsychological impairments (Buchman and Bennett, 2013). The concept of CF proposes a communality to frailty syndrome, with loss of adaptability in the domain of cognitive skills and decreasing resilience to internal and external factors, and also denotes a linkage to PF (Canevelli et al., 2015). Several research on expanded PF have concerned cognition domain as a prospective factor strongly affecting health-related geriatric outcomes (Panza et al., 2015).

As with the concept of CF, the term "psychological frailty" appears as a new frailty sub-phenotype and implies a parallel to PF but in the brain activities dimension and suggesting a relationship between the two (Fitten, 2015). Recently, the conceptual origins of psychological well-being (PwB) dimensions were revisited, which gave rise to an update of the concept focusing on six emerging areas of contemporary psychology: (i) perception of well-being changes throughout human development, (ii) personality correlates of well-being, (iii) well-being linked to experiences in family life, (iv) well-being associated to employment activities and other work occupations, (v) interconnections between physical and mental health, including biological aspects, and (vi) clinical and intervention research involving well-being in different segments of society (Ryff, 2014).

The phenotype of PF has been characterized by factors linked with several negative psychosocial facets that manifest throughout the aging progression and have already been studied, but the difference is that the PF condition seems to worsen some psychological aspects (Freitag and Schmidt, 2016). In addition to cognitive status, studies aimed to analyze the multifaceted interactions between different PwB markers and frailty revealed that motivation (i.e., self-efficacy and attitudes), negative and positive feelings of mood (i.e., depression and stress), and emotional well-being were identified as the core dimensions of PwB t in older populations (McAuley et al., 2006; Dent and Hoogendijk, 2014; Gale et al., 2014; Freitag and Schmidt, 2016).

Each individual has a single genotype and a set of lifespan involvements that will fare in terms of general health and chance of disease (McEwen, 2015). Thus, distinct mood states are the most important contributors to PwB and reflect in the self-perception of physical health (Thoits, 2011). Psychosocial stress, for example, is associated with the onset and the progression of many and costly comorbidities, including chronic pain conditions linked to functional disabilities (Muscatell et al., 2015). Positive self-esteem, on the other hand, is seen as a protective factor that contributes to a highly positive physical self-perception in frail subjects (McAuley et al., 2005). High perceptions of self-efficacy appear to be associated with good levels of motor skills in frail people (Chou et al., 2012). Adverse negative conditions of physical health can influence older people's subjective perception of positive feelings, mostly when they determine a reduction in their levels of subjective well-being and their individual perception of their general health (Cho et al., 2011; Wu et al., 2013).

In spite of the critical contribution of core PwB s to explain PF, not many studies used different measurements to describe how frail populations evaluate their levels of subjective well-being, self-perceptions, mood states, and how these are related to PF. A previous research looking at these associations was done in community and in hospital-based populations (Dent and Hoogendijk, 2014). Other recent findings show that some domains of subjective well-being perception decreased by a PF identity crisis may mediate a self-reported health status in older populations (Andrew et al., 2012). However, very little is known about this relationship in specific populations, e.g., those living in nursing homes. Another important question is the fact that most studies used the Mini-Mental State Exam to assess the general cognitive profile (Furtado et al., 2018). However, in this research,

we opted for the Montreal Cognitive Assessment (MoCA) due to its efficiency in screening older individuals with mild cognitive impairment and the careful manner in which the validation for the Portuguese population has been carried out (Duro et al., 2010; Freitas et al., 2014).

The context of nursing homes provides a crucial location for the study of these connections due to the patients' heterogenic condition in terms of physical status, comorbidities, and psychological outcomes. Thus, this study aimed to analyze the association of PF with core PwB dimensions, specifically, to explore the relationship between PF and subjective and mental well-being in institutionalized older women.

MATERIALS AND METHODS

Data collection of all outcome measures was organized by the principal investigator and performed by independent specialists who had been extensively trained by the research team. The same evaluators for each study domain performed the data collection in all study participants using a face-to-face approach. Individual attention was provided to the participants with interpretation queries, and questions were read from a standard sheet to avoid response bias.

Initial Procedures and Study Design

A cross-sectional design using a survey on frailty incidence in institution-dwelling older individuals living in the region of Coimbra City (Portugal) was followed. The participants consisted of a subgroup within a previously published study (Furtado et al., 2019). A total of 10 centers for social and health care (CSH) were selected as eligible to participate in the first study phase. After the visits to the homes to communicate the purpose of the study and to verify the eligibility selection criteria, five CSH were selected to participate in this study.

Eligibility Criteria

All eligible participants that took part in the study voluntarily signed a written informed consent form. In the first phase, all female participants aged 75 years and above agreed to take part on this research and, with their prescribed medications controlled, were admitted to the study. The specific exclusion criteria were: (i) the existence of some type of illness disorder that could hinder the assessment of autonomy, such as musculoskeletal impairment (i.e., advanced attrite or arthrosis), cardiomyopathy, cardiorespiratory illness, and other clinical settings that might prevent functioning (i.e., recent fractures); (ii) mental disorders (i.e., psychosis, depression, anxiety, and dementia), low visual acuity and hearing ability, and classified as morbidly obese; (iii) identification of any drug therapy in the process of adaptation or deregulation that may cause deficit of attention and/or substantial changes in motor activities (i.e., anti-depressants, betablockers, and anxiolytics).

Sample Selection Statement

The first eligible participants included in the study were 486 (100%) institution-dwelling old adults aged over 75 years. After applying the sample selection criteria, 128 participants (25%) were excluded or dropped out due to (i) physical impairment associated with musculoskeletal disorders and joint or muscle pain in the performance of specific movements or tests (n = 44), (ii) closed diagnosis of early stage dementia or other mental disorders (n = 29), (iii) severe uncorrected impairment of hearing or visual functions that made it impossible to perform all tests (n = 17), (iv) need of palliative health care or special nutritional support, with medical indications not to participate in the study (n = 19); (v) participants who dropped out when applying the tests (n = 20); and (vi) inconsistent data (n = 08). The final number of participants was 358.

Ethical Report

This study respected the Health Sciences Portuguese Resolution (Article 4th; Law number 12/2005, 1st series) on ethics in research and complied with the guidelines for research with human beings in the Helsinki Declaration (Petrini, 2014). First, the study protocol was approved by the Multidisciplinary Ethical Committee of the Faculty of Sport Science and Physical Education (reference code number CE/FCDEF-UC/000202013). All CSH directors and participants signed the informed consent form in the first study approach. This document explains in detail the phases of the study, how to collect, treat, and analyze the obtained data, and the criteria used for identity privacy.

OUTCOME MEASURES

The PF phenotype and its five components were the primary outcomes and the domains of PwB were the secondary outcomes. Sociodemographic, general health status, and anthropometric measures that showed significant statistical differences in comparison to PF subgroups were understood as possible confounders and were entered as covariates in a subsequent analysis.

Physical Frailty Screen

A negative evaluation in one or two criteria classified the participants as pre-frail, in three or more as frail, and as non-frail when the subject had a void in any of the five criteria, forming a dichotomic categorical classification. Fried's PF protocol was used (Fried et al., 2001):

(i) Weight loss: the medical record was consulted to check if the participant had unintentionally lost 4 kg of weight or more in the last 6 months.
(ii) Exhaustion: consisted in a self-report measure that was evaluated through the agreement of questions 7 (*I felt that everything I did was an effort)* and 20 (*I could not get going*) of the CES-D questionnaire (Gonçalves et al., 2014).
(iii) Muscle weakness: analyzed using the handgrip strength test. This test uses a portable dynamometer device (Lafayette, model 78010, United States). The participant grabs the device in one hand, with the arms extended next to the trunk. At the signal, the participant squeezes the device with maximum effort, using an isometric

contraction force, for 5 s to acquire stability in the measure. The best result of two attempts was taken as an official measure for scoring purposes (Syddall et al., 2003). The participants who did not achieve proficiency in the test and those who classified themselves below 20% [adjustment by body mass index (BMI) and sex] were categorized as individuals who have muscle weakness (Fried et al., 2001).

(iv) Slowness of gait: measured by using the "4.6 m test" where the participant had to walk the distance of 4.6 m, without assistance, in a straight line. The time in seconds characterizes the registration measure for this test, adjusted by the participants' gender and height. The participants had two attempts to perform the test, and the cutoff values used were the ones suggested by the original PF protocol (Fried et al., 2001).

(v) Low levels of PA were assessed using the International PA Short Form assessment (IPAQ-sf). The participants were categorized as "inactive" and "minimally" active according to the IPAQ-sf criteria if they had a positive score for the PF status.

In addition, the prevalence of each of the five components was calculated to generate the continuous variable of PF composed score with a range from 0 to 5 points, where the higher values represent a higher frailty status.

Screen of PwB Dimensions

The psychometric tests described below were chosen because they had been validated in the Portuguese population and characterize the core PwB dimensions described in the concept of psychology of frailty as previously defined (Fitten, 2015):

(i) Cognitive status: The Montreal Cognitive Assessment was used to evaluate global cognitive performance. The MoCA assesses different areas of cognitive function: language, working memory and task concentration, spatial orientation, executive functions, and visuospatial abilities. The maximum score to be achieved in the MoCA is 30 points, and according to the validation values presented for the Portuguese population, if the participant obtains a score below 22 points, he/she can be screened as having mild cognitive impairment or dementia (Freitas et al., 2013).

(ii) Mood states: CES-D scale was used to assess the depression state. Each one of the 20 questions has four answer options in a Likert-type scale, with global scores between 0 and 60 points. The highest scores correlate with more depressive sign in the last week (Gonçalves et al., 2014). The Perceived Stress Scale (PSS) assesses the perception of stressful experiences. This scale has 14 items; seven have a positive connotation and the other seven a negative direction. The scores can vary between 14 and 70 points, and the higher scores attained by the participants reveal greater symptoms of stress (Taylor, 2015).

(iii) Self-perception: The Rosenberg Self-Esteem Scale (RSES) analyzes the evaluative dimension of self-concept. The RSES has 10 questions with a Likert-type scale and four answer options, with global scores between 10 and 40 points. The higher scores reveal greater self-esteem levels (McKay et al., 2014). The General Self-Efficacy Scale (GSES) was used to evaluate resilience and optimism to deal with situations and the ability to solve everyday life problems effectively. When answering the questions, the participants can achieve a score ranging from 10 to 40 points. The higher scores reveal greater GSES levels (McAuley et al., 2005).

(iv) Emotional well-being: The Satisfaction With Life Scale (SWLS) assesses general and personal judgments of satisfaction with one's own life. The five-item scale results are scored between one and 35 points. A high score achieved by the respondents represents greater personal satisfaction with one's own life at the present moment (McKay et al., 2014). The Happiness Face Scale (HFS) consisted of a graphical scheme where for each face one letter is assigned, in which letter A (seven points) is considered as the maximum and letter G as the minimum (one point). The participant has to identify with one of the faces, depending on his/her state of happiness (Andrews and Withey, 1976). The Attitudes to Aging Questionnaire (AAQ) assesses specific feelings toward the aging process as an intrapersonal experience from the older point of view, taking into account their expectations, worries, emotions, and behavior. The AAQ contains 24 items and total scores range from 8 to 40 points. The higher scores express a more positive attitude toward our own aging process across the life (Low et al., 2013).

Anthropometric and Sociodemographic Measures

Chronological age was treated as a continuous variable. Marital state was assessed as a four-category variable: single, married, widowed, and divorced. The level of education was collected for each participant, classified in number of years, and analyzed as a continuous variable. Standardized and validated techniques were respected, and anthropometric data collection procedures were as previously described (Chumlea and Baumgartner, 1989) and included the following measures: (i) weight or body mass was measured by a portable scale with a precision of 0.1 kg and (ii) stature was determined using a portable stadiometer with a precision of 0.1 cm (Seca Portable Anthropometric Body meter® model 208, Germany). BMI was calculated according to the formula BMI = weight/height^2.

General Health Profile

Levels of comorbidity were assessed by the Charlson Comorbidity Index (CCI). The CCI evaluated the weight of several diseases. Each disease has a specific score, varying from 1 to 3 points, and the sum of the total values related to the diseases recorded in the participants' medical record forms a single score, treated as a continuous variable. One point for each additional 10 years is added to the initial score that has been shown to predict 1- and 10-year mortality. A recent study carried out a successful update of the index to 12 comorbidities (Quan et al., 2011).

The use of chronic or acute medication of each participant was systematically checked with the medical staff, and polypharmacy was considered according to the Classification System of Human Medicine in Portugal when the participant uses more than three drugs in a chronic treatment.

Statistical Analysis

The initial assumptions of data were verified by visual inspection of the normality plots and the Shapiro–Wilk statistical test. Continuous variables were reported by their medians and 25th and 75th percentiles, whereas categorical variables were reported by relative and absolute frequencies. A comparison of quantitative variables between the frail subgroups was performed using ANOVA or Kruskal–Wallis, depending on whether the variables were found to be normally distributed, which was ascertained by employing the Shapiro–Wilk tests. Bonferroni correction test was performed to adjust the comparisons analysis. In this study, the PF composed score was assumed as a dependent variable, following previous publications (Ávila-Funes et al., 2011). The association between the groups of qualitative variables was assessed using chi-square tests. Partial correlations between the PF and the PwB were computed together with partial correlations controlling for the assumed covariates (cognitive status, comorbidities, marital status, and height). The PwB variables that showed stability in significance after controlling for covariates in the partial correlation model were taken from the regression analysis, respecting the statistical assumption (Jeong and Jung, 2016). The relationships between PF and PwB were analyzed using a hierarchical stepwise regression model. In this model of analysis, the PwB outcomes were assumed as independent variables. A total of three independent linear regressions were selected over a hierarchical stepwise and multiple-regression analysis, considering the previous hypothetical and theoretical assumption that CES-D and MoCA showed a strong statistical significance with PF (Jeong and Jung, 2016). In these, cognitive status was introduced as a first block in the model. Secondly, the depression state of CES-D was entered together with cognitive status. Lastly, all other PwB indicators were entered in the statistical models to possibly explain the assumption of regression model maximal variance. The unadjusted bivariate model 1 simply included the dependent variable of PF composed score and the independent variable of PwB outcomes. Model 2 was further adjusted for variables of height, marital status, and comorbidity. The degree of the associations was discussed according to the magnitude of the correlations, which are understood as robust ($r = 0.7$–0.8), strong ($r = 0.5$–0.7), moderate (r from 0.3 to 0.4), small (0.1–0.2), and trivial ($r < 0.1$) (Hopkins et al., 2009). The software R 3.3.1 and IBM SPSS 22.0 were used for all statistical treatments. The statistical significance level adopted in this study was $p < 0.05$.

RESULTS

The descriptive characteristics of the participants for all variables by frail subgroups are presented in **Table 1**. According to preliminary checks, the variables that did not show normality were marital state, MNA, weight, BMI, and medication use. For those, comparative analysis was performed using Kruskal–Wallis test ($p < 0.05$). For all the others, ANOVA test was used. A total of 78 participants were categorized as non-frail (16%), 136 as pre-frail (38%), and 144 as frail (46%). Sociodemographic data showed that the participants have a median age of 83.0 (76.0–88.0) years, low median (3rd grade) academic achievement levels according Portuguese classification, and also mostly without a husband (94%). There were significant statistical differences between frail subgroups in marital status ($p = 0.028$) and anthropometric measure of height ($p = 0.008$), but not weight. Regarding to general health status, the mean scores of the total sample reflected a high prevalence of comorbidities and mortality with a median of 7 (6–9), with significant statistical differences between frail subgroups ($p = 0.013$). A high incidence of polypharmacy and a clear trend for increased polypharmacy in the frail subgroup were revealed. Taking into account the assumptions initially established for this study, marital state, height, and CCI variables were classified as covariates in the analysis of the correlation models. In addition, a preliminary comparison analysis performed by "nursing homes" subgroups for all variables showed that no significant statistical differences were found, which means that it did not enter as a covariate in the adjustment models ($p < 0.05$).

Table 2 shows the characteristics of the study sample and the comparison analysis by frail subgroups according to the PwB indicators. According to the initial normality verification, variables such as AAQ, CES-D, and MoCA did not fulfill the normality assumptions, and a comparison analysis was performed using Kruskal–Wallis test ($p < 0.05$). For all the other PWB variables, ANOVA test was used for comparison. The results showed significant statistical differences for cognitive profile of MoCA ($p < 0.001$), mood states of CES-D scale ($p = 0.001$), and stress scale of PSS ($p = 0.003$) as well as lower scores for self-perception of GSES ($p = 0.017$), attitudes to aging as assessed with the AAQ ($p = 0.005$), and subjective well-being of HFS ($p = 0.037$). No significant statistical differences were found for SWLS and RSES. Independent of directions of the scale's quotation, the statistically significant results indicated worse values for the frail subgroup.

Table 3 shows the Spearman's rank and partial correlations, controlling for potential confounders (marital status, height, and CCI). The data were analyzed by the five nursing homes (categorical variables) that were part of the study and did not present significant differences for all biosocial and general health status variables, so it did not enter as a covariate in the adjustment models ($p < 0.05$). A significant and stable correlation emerged between PF and all PwB indicators, except with SWLS and RSES. After applying a statistical adjustment, the correlations were moderately attenuated or increased, but several important associations persisted. In the correlations between the PwB variables, it was verified that all values were lower than $r = 0.70$, indicating that the assumption of non-multicollinearity among factors (taking into account the introduction of these variables in the regression model) was not violated.

Supported by the evidence presented in the correlational analyses, multiple linear regression analyses were used to

TABLE 1 | Characterization of the total sample and comparison by physical frailty subgroups for sociodemographic, anthropometric, and general health status.

Variable	Total sample (*n* = 358, 100%)	Non-frail (*n* = 78, 21%)	Pre-frail (*n* = 136, 38%)	Frail (*n* = 144, 40%)	*p* value
Sociodemographic (M1:3)					
Chronological age (years)	83.0 (76.0; 88.0)	82.0 (77.0; 88.0)	83.0 (76.0; 89.0)	83.0 (76.0; 87.0)	0.954
Level of education (degree)	3.0 (3.0; 4.0)	4.0 (3.0; 6.0)	3.0 (3.0; 4.0)	3.0 (2.0; 4.0)	0.060
Marital state (*n*,%)					
Single	30 (25.4)	6 (31.6)[b,c]	11 (24.4)	13 (24.1)	0.028
Married	7 (5.9)	4 (21.1)[b,c]	1 (2.2)[a]	2 (3.7)	
Widowed or divorced	81 (68.6)	9 (47.4)[b,c]	33 (73.3)[a,c]	39 (72.2)[a,b]	
Anthropometric (M1:3)					
Weight (kg)	66.1 (57.2; 71.4)	65.7 (58.6; 77.9)	65.7 (56.8; 71.4)	66.5 (53.1; 70.5)	0.951
Height (m)	1.5 (1.5; 1.6)	1.6 (1.5; 1.6)	1.5 (1.5; 1.6)	1.5 (1.5; 1.5)	0.008
Body mass index (M1:3)	29.0 (24.6; 31.5)	27.0 (24.6; 30.1)	29.2 (24.4; 31.6)	30.2 (25.3; 32.3)	0.207
General health state					
Charlson Comorbidity Index (0–10 pts, M1:3)	7.0 (6.0; 9.0)	8.4 (6.0; 10.0)[b]	7.0 (6.0; 8.0)[a,c]	8.3 (7.0; 9.0)[b]	0.013
Mini-Nutritional Assessment (0–10 pts, M1:3)	24 (19, 25)	23 (17, 21)	24 (18, 24)	23 (22, 25)	0.918
Medication use, per day (*n*,%)					
I use more than three	108 (91.5)	17 (89.5)	43 (95.6%)	48 (88.9)	0.434
I use three or less	10 (8.5)	2 (10.5)	2 (4.4)	6 (11.1)	

M1:3, median, first, and third quartile; n,%, number and percentage of participants; pts, points. [a]Significant differences compared to non-frail. [b]Significant differences compared to prefrail. [c]Significant differences compared to frail. ANOVA or Kruskal–Wallis test was computed depending on assumption of data.

TABLE 2 | Comparison scores of psychological well-being outcomes by physical frailty subgroups.

Psychological well-being status	Total sample (*n* = 358, 100%)	Non-frail (*n* = 78, 21%)	Pre-frail (*n* = 136, 38%)	Frail (*n* = 144, 40%)	*P* value
Montreal Cognitive Assessment (0–30 pts)	17.0 (13; 21)	22.0 (21; 27)[b,c]	19.0 (14; 22)[c]	14.0 (10; 19)[a,b]	<0.001
CES-D Depression Scale (0–60 pts)	22 (16; 28)	17 (12; 27)[c]	18 (14; 24)[c]	24 (20; 30)[b]	0.001
Perceived Stress Scale (0–60 pts)	27 (22; 31)	22 (14; 27)[b,c]	26 (22; 32)[a]	27 (26; 32)[a]	0.003
Global Self-Esteem Scale (10–40 pts)	22 (19; 25)	22 (17; 26)	23 (19; 25)	22 (20; 25)	0.928
General Self-Efficacy Scale (10–40 pts)	30 (25; 34)	33 (29; 36)[b,c]	30 (25; 34)[a]	30 (25; 31)[a]	0.017
Attitudes to Aging Questionnaire (8–40 pts)	73 (64; 88)	81 (73; 102)[b,c]	76 (67; 89)[a,c]	68 (59; 80)[a,b]	0.005
Satisfaction With Life Scale (1–35 pts)	23 (20; 28)	24 (19; 27)	24 (22; 29)	22 (20; 27)	0.171
Subjective Happiness Face Scale (1–7 pts)	3 (2; 5)	4 (3; 7)[c]	4 (3; 5)[c]	3 (2; 4)[a,b]	0.037

CES-D, Center of Epidemiology Studies for Depression; pts, points. ANOVA or Kruskal–Wallis test was computed depending on assumption of data. [a]Significant differences compared to non-frail. [b]Significant differences compared to prefrail. [c]Significant differences compared to frail.

explore the relationships between the dependent variable of PF composed score and the independent variables of PwB indicators as shown in **Table 4**. The dimensions of RSES and GSES were not introduced in this analysis as these were not correlated with PF. A hierarchical stepwise model was used, considering the theoretical assumption that cognitive profile and depression state presented a close relationship with frailty (Buchman and Bennett, 2013; Lohman et al., 2016). The results in **Table 3** showed that, as expected, the cognitive profile of MoCA explained 22% of the variance by itself (model block 1). Both unadjusted [$F(6.100) = 11.613$; $p < 0.001$; $R^2 = 0.340$)] and adjusted [$F(9.97) = 6.789$; $p < 0.001$; $R^2 = 0.401$)] regression analysis (model block 3) models were statistically significant. Observing model (block) 2, the entry of the depression state of CES-D variable did not change the significance values of the MoCA. In model 3, cognitive status (using the MoCA), the HFS score, and the score of the AAQ showed a significant independent relationship with PF in both the unadjusted and the adjusted models (explaining 34 and 40% of variance, respectively). Stress, satisfaction with life, negative mood of depression, and self-efficacy did not significantly contribute to the model. The results indicated that decreased cognition, self-efficacy, and happiness were accompanied by an increased likelihood for being frail. In regression model 3, the strengths of the associations found were attenuated in the adjustment models after the entry of possible bias factors; even so, they were preserved.

DISCUSSION

The purpose of this paper was to examine the relationship between indicators of PF and PwB. Firstly, we verified the PF differences in PwB indicators, and the results indicated

TABLE 3 | Spearman and equivalent partial correlations between physical frailty composed score and psychological well-being outcomes (n = 358).

Variables	1	2	3	4	5	6	7	8
1. Physical Frailty Composed Score								
2. Montreal Cognitive Assessment	−0.401**							
	−0.438							
3. CES-D Depression Scale	0.317**	−0.152						
	0.248**	−0.201*						
4. Perceived Stress Scale	0.294**	−0.162	0.416**					
	0.238*	−0.187	0.375**					
5. Global Self-Esteem Scale	0.085	−0.085	0.093	0.398**				
	0.036	−0.114	0.060	0.375				
6. General Self-Efficacy Scale	−0.274**	−0.322**	−0.278**	−0.453**	−0.251**			
	−0.161	−0.252*	−0.258**	−0.439**	−0.256**			
7. Attitudes to Aging Questionnaire	−0.332**	0.205*	−0.321**	−0.385**	−0.315**	0.302**		
	−0.221	0.285**	−0.271**	−0.337**	−0.269**	0.254**		
8. Satisfaction With Life Scale	−0.204**	−0.008	−0.315**	−0.307**	−0.238*	0.223*	0.381**	
	−0.212*	−0.266**	−0.330**	−0.294**	−0.212*	0.221*	0.379**	
9. Subjective Face Happiness Scale	−0.182	−0.034	−0.237*	−0.024	0.266**	0.027	−0.180	0.072
	−0.240*	−0.249*	−0.280**	−0.045	0.243*	0.055	−0.144	0.113

*Significant at *p ≤ 0.01; *p ≤ 0.05. Partial correlation values are expressed in underline of each variable, controlling for marital status, height, and comorbidity. CES-D, Depression Scale.*

TABLE 4 | The association of psychological well-being indicators and physical frailty composed score (n = 358).

Regression models	Physical frailty composed score[a]					
	Unadjusted			Adjusted		
	R^2	B coefficient	p value	R^2	B coefficient	p value
Model (block) 1	0.22			0.29		
Montreal Cognitive Assessment		−0.467	0.000		−0.452	0.000
Model (block) 2						
Montreal Cognitive Assessment	0.30	−0.440	0.000		−0.420	0.000
CES-D Depression Scale		0.169	0.052	0.32	0.169	0.163
Model (block) 3						
Montreal Cognitive Assessment		−0.378	0.000		−0.369	0.000
CES-D Depression Scale		0.011	0.909		0.028	0.771
Perceived Stress Scale	0.34	0.143	0.157	0.40	0.112	0.264
Satisfaction With Life Scale		−0.024	0.809		−0.024	0.798
Happiness Face Scale		−0.188	0.032		−0.198	0.022
Attitudes to Aging Questionnaire		−0.212	0.034		−0.209	0.038

Hierarchical stepwise regression model was used and unadjusted bivariate model 1 included PF total score and PwB indicators. Model 2 was further adjusted for variables of height, marital status, and comorbidity. [a]Varies from zero to five points.

that frail individuals had a poor satisfaction with life, poor attitudes to aging, poor general self-efficacy, and a heightened state of depression and perceived stress. Based on the relationship of depressive and mood states and cognitive status symptoms, additional PwB variables were investigated to explain the incremental variance in PF scores. Besides the expected effect of the cognitive profile, the results showed that not depressive mood states but a negative attitude to aging and low feelings of happiness proved to independently contribute to the variance in PF status. As far as our knowledge allows, this is the first scientific evidence for the association of PwB health-related domains with PF status in a Portuguese institutionalized female population over 75 years old.

Comparison by Frailty Subgroups

In agreement with other studies using samples with similar attributes, PF had a similar prevalence (46%) when compared with other European countries who studied population samples living in nursing homes (González-Vaca et al., 2014). The general health was poor and the comorbidities presented with high scores in the frail subgroups, showing that a possible overlap between morbidity and frailty exists (Wong et al., 2010). Interestingly, the sociodemographic of height (but not weight)

and marital status (more widowed or divorced) presented with worse results in the frail subgroup. The trend for a reduction in height values in the group of frail elderly could be related to osteopenia/osteoporosis, leading to loss of height (Johansen et al., 2007). This relationship was independent of age in the statistical model and needs to be further explored. Marital status has also been shown in several longitudinal studies to be a powerful predictor of a number of chronic diseases (Lunenfeld and Stratton, 2013) and seems to follow the same trend toward the PF condition.

An analysis of PwB indicators showed that higher scores were found with an increased incidence of PF. This was similar in the Canadian Aging Study (CAS), the results of which revealed that the phenotype of frailty was in an intrinsic relationship with low levels of subjective well-being. The authors of CAS suggested that the low levels of PwB impaired by a frailty syndrome may play an important role in describing the subjective perception of health in older individuals (Andrew et al., 2012). A more recent longitudinal study carried out in a United Kingdom population also found that a higher feeling of PwB was associated with a sense of control, self-realization, and autonomy and may exert a protective effect against PF (Gale et al., 2014). Despite the differences in populations and the different protocols for the evaluation of frailty, these studies were unanimous in confirming the link between frailty status and low general PwB.

Looking at the results of the Bonferroni test after the comparison analysis, it seems that the transition from the non-frailty to the pre-frailty condition is the most critical period for the development of negative outcomes in several PwB dimensions. Some studies indicate that this may also be the most critical stage for the appearance of cognitive decline (Furtado et al., 2018). Apparently, the period of critical intervention for the manifestation of some negative outcomes would be the period attending the transition between frailty and pre-frailty status. The identification of this period would be a primary preventive measure against the arrival of early CF (Ruan et al., 2015), which is currently characterized as one of the outcomes entailing more expenditure for public health.

Relationships Among PF and PwB

Several PwB indicators were found to be directly associated with the PF composed score. A recent study showed a clear interconnection between PF status and a set of PwB outcomes, highlighting self-efficacy, anxiety, depression, and resilience (Freitag and Schmidt, 2016), but unlike our results, in this study, depression emerged as an important psychological domain that explained the variance in PF scores. In the regression analysis of the present study, a satisfactory relationship explained the PwB variance of PF, and the covariates only had a slight attenuating effect on these relationships. It may be that cognitive status (and an ability to explore and analyze negative feelings) explained the association of depression, self-efficacy, and stress with frailty in our sample. Similar to Campbell and Bucher's findings 20 years ago, this study and others found that the MoCA independently predicted PF (Lerner et al., 2015). CF is already a widely accepted concept, as is the temporal similarity between the onset of cognitive decline and subsequent deficit in physical function (Kelaiditi et al., 2013). Other factors associated with PF, such as perceived stress and self-efficacy, did not contribute to the regression models in this sample. However, these indicators play an important role in the establishment of the indirect relationships with PF.

The interconnections between stress and physical health remain the most widely studied under a biological approach (Corazza et al., 2013). However, it is possible that several psychosocial events exist, activating emotional stressors with aging. Also, the ability to cognitively adjust to these events and reduce stress and improve self-efficacy to deal with stressors could mediate the relationships found. Attitudes to aging, subjective feelings of happiness, and their association with PF appeared as surprising findings. The attitudes toward aging played an important role in the regression model. A robust cross-sectional survey that collected data in 20 countries and was carried out by a WHO quality-of-life research group showed that attitudes to aging mediated the associations between satisfaction with ones' health including quality of life, psychosocial, physical, and environmental health (Low et al., 2013). These associations represent robust evidence since the AAQ is a multidimensional construct, which includes three sub-dimensions of psychosocial loss that reflect a high perception of negative feelings; PwB growth is related to the increase of positive feelings regarding life events and physical change, accentuating on items largely associated to health and to the experience of aging itself and consequently resulting in an individualized PwB perception viewpoint that affects physical health (Laidlaw et al., 2007).

In this study, happiness was shown to be an additional factor to explain PF. Positive psychology in recent years has advocated for the assessment of happiness rather than only assessing negative mood and its associations with general health status (Jones et al., 2003). Our data suggest that positive mood may have a more satisfactory contribution to PF rather than a negative mood which may have been explained by other factors present in the model. Interestingly, satisfaction with life and self-esteem were not associated with frailty. Experimental studies including those which can improve mood, such as regular exercise, will show whether our findings may reflect causality. If this is the case, it may be that, through exercise or other activities that improve mood and perceived coping styles (reducing stress and possibly a related increase in self-efficacy and self-esteem), improved attitudes to aging (and possibly the related life satisfaction) will also improve and mediate improvement in PF symptoms.

The take-home significant message of this study is that increasing evidence supports the protective features of the maintenance of a stronger sense of PwB, which may help to reduce the risk for PF and support a reasonable end-of-life-course. Carol Ryff, who has substantial expertise of PwB domains, makes clear the importance of introducing new concepts to help understand the links between the aging process and PwB, highlighting attitude and resilience (Ryff, 2014). Currently, these are key psychological skills for the development of the capacity to maintain or recover good feelings of PwB when facing everyday challenges and difficulties.

Study Limitations

Despite a construct of satisfactory evidence, this study had some limitations. Firstly, these lie within the sample characteristics, which included more fit individuals than frail people and thus could have caused biased results. Our study is limited to the female sample. In the pilot study, we recorded a small participation of older men. In addition, the percentage of women living in institutions and homes in Portugal is much higher than men, 78 and 22%, respectively. These values made us focus our study on older women. Furthermore, this study has a cross-sectional design and the associations may be bidirectional, and causal reasoning is difficult here as those with PF, because of their limitations, may be more likely to feel less in control, more stressed, and have a more negative attitude and lower feelings of happiness in life. However, the results of the present study showed a similar trend to the other studies with larger samples and those that had a longitudinal follow-up.

Practical Applications

A meaningful interconnection with important markers of PwB dimensions and PF phenotype was demonstrated in this study. Apparently, PF shows a strong relationship with cognitive aspects, but it also showed a consistent relationship with some emotional dimensions. The transition from frailty to pre-frailty appears to be the most critical period of PwB decline. In this sense, implementing active lifestyle interventions that take into consideration markers of positive feelings in geriatric assessments will assist in the patients physical and mental health care planning as well as prevent the early CF. In this context, it seems that physical–motor activity programs, for example, can help elderly people living in health care and social welfare centers to assist in a possible psychological readjustment in the face of a more secluded lifestyle.

CONCLUSION

Overall, the results show that PF was related to poor scores of PwB indicators in institutionalized older women. However, the novelty in this research is the fact that self-perception (attitude toward aging) and emotional well-being (feelings of subjective happiness) were revealed as independent negative predictors of PF since the global cognition performance had already demonstrated strong associations with PF in other studies. It will be necessary in the nearby future to investigate gender differences between these or similar variables and, in addition, to introduce some biological variables in the statistical model in order to test the possible mediators of these relationships.

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 CE/FCDEF-UC/000202013. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GF organizing and drafted the manuscript and worked in the acquisition of data. RL, AV-P, and AC helped in the discussion. EH assisted in the interpretation of data, made additional statistical analysis, and contributed to the critical revision of the content. JF and AT coordinated the research, revised the final version of the manuscript, and added some considerations.

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frontiers in Psychology

MINI REVIEW
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A Possible Association Between Executive Dysfunction and Frailty in Patients With Neurocognitive Disorders

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Frailty is an age-related dynamic status, characterized by a reduced resistance to stressors due to the cumulative decline of multiple physiological systems. Several researches have highlighted a relationship between physical frailty and cognitive decline; however, the role of specific cognitive domains has not been deeply clarified yet. Current studies have hypothesized that physical frailty and neuropsychological deficits may share systemic inflammation and increased oxidative stress in different neurodegenerative disorders, such as Alzheimer's and Parkinson's disease. However, the role of the executive dysfunction should be investigated in a more detailed way using a multidimensional approach. With this aim, we conducted a review of the literature on the few experimental articles published to discuss the existence of a relationship between frailty and cognitive impairment in neurocognitive disorders, particularly focusing on the domain of executive dysfunction. The data suggest that physical frailty and cognitive decline, especially executive dysfunction, are two aspects strongly linked in mild and major neurocognitive disorders due to Alzheimer's and Parkinson's disease. In light of this, a new framework linking aging, cognitive decline, and neurodegenerative diseases is needed. In order to analyze the effects that aging processes have on neural decline and neurocognitive disease, and to identify relevant groups of users and patients, future longitudinal studies should adopt a multidimensional approach, in the field of primary prevention and in the continuum from mild to major neurocognitive disorder.

Keywords: frailty, mild cognitive impairment, neurocognitive disorders, Alzheimer's disease, Parkinson's disease, executive functions, mini-review

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INTRODUCTION

Frailty is a complex and heterogeneous clinical status described as the loss of harmonic interactions among various dimensions, such as biological, genetic, functional, psychological, cognitive, and social domains (Pilotto et al., 2020), that lead to homeostatic instability. Although the relationship between this issue and poor outcomes has been highlighted, currently there is no gold standard on how to define measure and diagnose frailty (Richards et al., 2018).

Nowadays, there are at least three main models to study frailty in aging subjects (**Figure 1**): the phenotypic model (Fried et al., 2001), the deficit accumulation model (Rockwood et al., 2005; Rockwood and Mitnitski, 2007b), and the bio-psycho-social model (Gobbens et al., 2010); the first two characterize the biomedical approach.

The biomedical approach highlights how a reduction in the ability to preserve homeostasis from a physiological point of view, and to respond to environmental changes appropriately, implies a loss of functional autonomy (Xue, 2011).

The phenotypic model (Fried et al., 2001) considers frailty in terms of a physiopathological syndrome composed of five physical determinants: slowness in walking, a decrease in hand-grip-strength, unintentional weight loss, low physical activity, and asthenia. The presence of one or two criteria identifies a pre-frailty status; instead, the presence of three or more, a frailty condition (see **Figure 1A**).

The deficit accumulation model (Rockwood et al., 2005; Rockwood and Mitnitski, 2007b), may be interpreted in line with a Frailty Index (FI) characterized by age-related deficits, which configure an augmented vulnerability resulting from age-related decline across several body organs and physiological systems. Considering this model of clinical frailty syndrome, the higher the FI, the frailer the individual (see **Figure 1B**).

Although Rockwood's model allows for a more extensive evaluation compared to Fried's one, also demonstrating greater sensitivity in predicting poor outcomes (Rockwood et al., 2007a), it did not fully take into account the psycho-social aspects that may affect the development of frailty.

Over time, the biomedical approach has been criticized (Canevelli et al., 2015) for different reasons: (1) frailty assessment was carried out above all by adopting Fried's criteria (Fried et al., 2001), as they focused mainly on physical frailty; (2) the majority of these studies evaluated the global cognitive functioning only through the Mini Mental State Examination (MMSE: Folstein et al., 1975), lacking of a full neuropsychological screening; (3) most of the participants were community-dwelling elderly people, compromising the applicability of the results to different types of patients, such as those with neurodegenerative disorders. Therefore, a new concept of frailty has emerged in relation to its applicability in clinical practice. According to this view, frailty can be interpreted as an integrated and multidimensional condition in which multiples domains (such as biological, functional, psychological, and social dimension) interact together, determining and characterizing a frailty status. The above led to the development of the third model, represented by the bio-psycho-social paradigm (Gobbens et al., 2010). Since the interaction of the different "dimensions" is likely to be the basis of the bio-psycho-social and clinical complexity of the frail elderly, multidimensional evaluation is the most suitable choice for frailty detection; it allows to explore not only the physical/medical symptoms but also other important variables that must complete this complex picture (see **Figure 1C**).

Lately, the importance of a multidimensional approach has been emphasized to better comprehend frailty, not only as a physiopathological syndrome (Amanzio et al., 2017). According to this approach, the multidimensional prognostic index (MPI) could be considered a more comprehensive evaluation tool (Pilotto et al., 2013, 2020; Angleman et al., 2015), useful for the assessment of subjects with neurodegenerative disorders, from minor to major neurocognitive decline, with different frailty status (Amanzio et al., 2017).

Frailty and Cognitive Functions: What Kind of Association?

Originally, the concept of frailty referred only to a physical condition; recently, it includes also a cognitive status, which could be related to a reduction of neurophysiological reserves. At present, cognition is considered a relevant domain for frailty comprehension and a novel target for the prevention of elderly dependency (Ruan et al., 2015). Indeed, cognitive frailty seems to be both an effect and a cause of physical frailty.

Physical frailty is considered a risk factor for Mild Cognitive Impairment (Boyle et al., 2010). In a 10-year longitudinal study, Raji et al. (2010) explored whether cognitive impairment could predict frailty risk in robust elderly. The authors suggested that robust older people with cognitive dysfunctions had a 9% higher chance to become frail per year, compared to the individuals with preserved cognition. 30.9% of the elderly with cognitive impairment fulfilled the criteria for weight loss from the first to the second follow-up, while the 25% fulfilled the criteria for slowness from the second to the last follow-up (Raji et al., 2010).

More recently, data from the Italian Longitudinal Study on Aging (ILSA) suggested that cognitive frailty increased risk of all common cause of mortality in older people, over a 3.5-year and 7-year follow-up (Solfrizzi et al., 2017). Cognitive impairment was found to be associated in a higher risk of adverse health outcomes also in The Singapore Longitudinal Aging Studies (SLAS), for which cognitive impairment resulted implicated in the increased prevalence and incidence of functional disability, poor quality of life, and mortality (Feng et al., 2017).

Cognitive impairment can be easily detected by administering neuropsychological cognitive tests, such as the MMSE. Exceeding the limit of the exclusive use of the MMSE, a small number of studies examined the association between specific cognitive functions and physical frailty (Canevelli et al., 2015), pointing out a relationship between a reduction in gait speed or grip strength and an impairment of attention and executive functions (Woollacott and Shumway-Cook, 2002; O'Halloran et al., 2014; Canevelli et al., 2015). These findings were supported by the results of a 9-year longitudinal study of 331 healthy women, which showed the association of executive functioning with frailty progression, suggesting that both impairments and declines in executive functioning were associated with risk of frailty onset (Gross et al., 2016). More recently, data from The Toledo Study for Healthy Aging (TSHA) demonstrated that deficit in executive functioning is a powerful predictor of frailty (increased risk of 13%), disability (increased risk of 11%), and mortality (increased risk of 7%) (Rosado-Artalejo et al., 2017).

Executive Functions (EFs) are a set of abilities that control thoughts and behaviors (Miyake and Friedman, 2012). They can be categorized into "cool" EFs, which involve conscious control of thoughts and actions in non-emotional

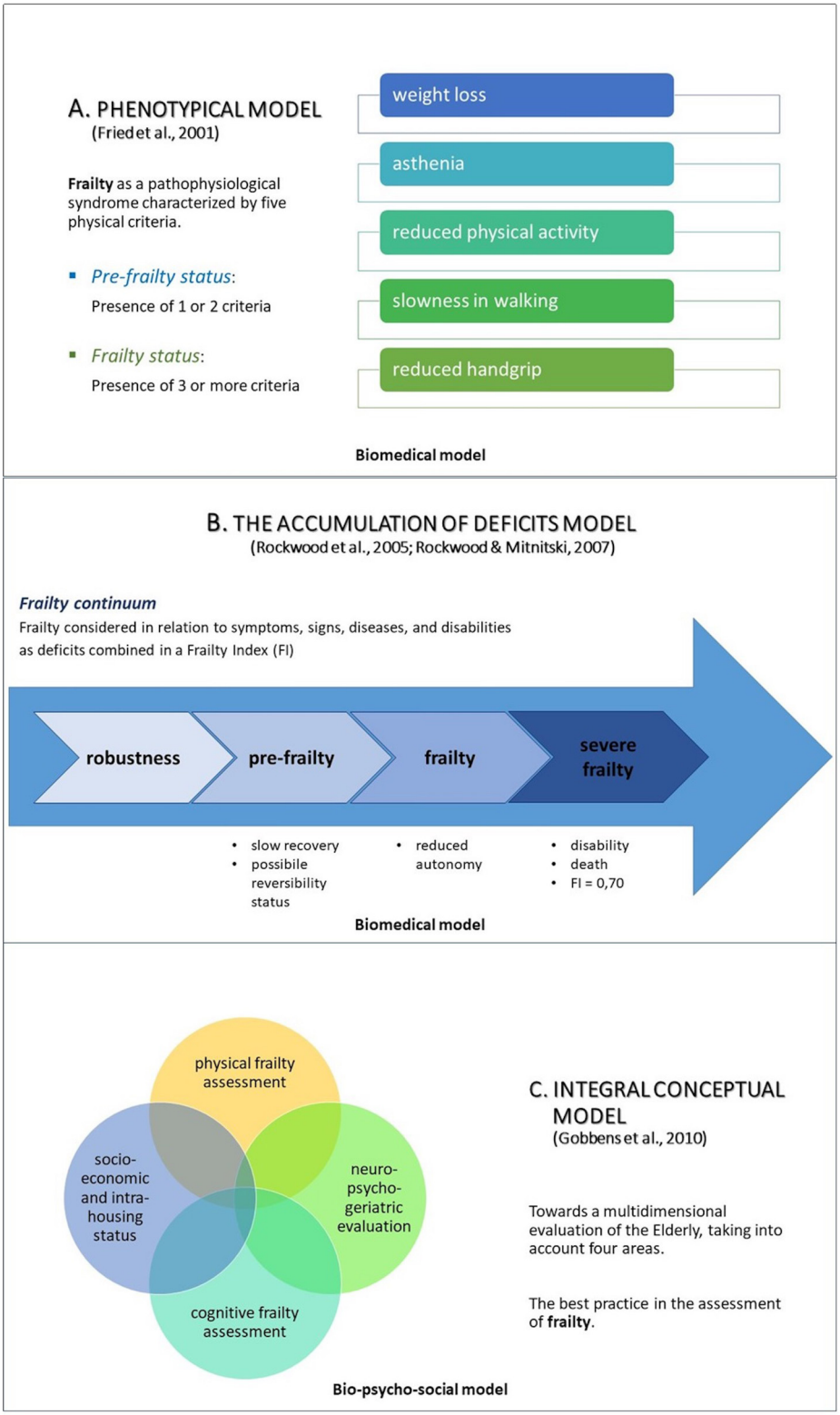

FIGURE 1 | The three main approaches to study frailty: the phenotypical model (Fried et al., 2001; **A**), the accumulation of deficits model (Rockwood et al., 2005; Rockwood and Mitnitski, 2007b; **B**), and the integral conceptual model, based on a bio-psycho-social approach (Gobbens et al., 2010; **C**).

conditions, and "hot" EFs, concerning goal-directed and future-oriented cognitive processes in contexts that elicit emotions, motivation, and tension (Poon, 2018). Although there is still no consensus regarding which are the cognitive functions that may or may not be included in the EFs (Poon, 2018), there is a general agreement that shifting, updating/monitoring, and inhibition are the core EFs (Diamond, 2013), which play a different and complementary role in performing complex executive tasks (Miyake et al., 2000). In order to comprehend the unity but also the heterogeneity of EFs, Miyake et al. (2000) proposed a structural model characterized by mental shifting, information monitoring and updating, and inhibition of preponderant responses. From these, higher-order EFs arise such as problem solving and planning (Lunt et al., 2012).

On the other hand, the term "executive dysfunction" refers to the inability to formulate, organize, and plan goal-directed behaviors and novel cognitive tasks (Parker et al., 2013).

Executive deficits are related to frontal network disruption and can occur in various diseases, including neurodegenerative disorders (Elliott, 2003). Several executive dysfunctions, evaluated by different methodologies and tools, have been reported in literature. The most common concern deficits in inhibitory control (inability to initiate an action or inhibit a predominant response and maintain attention), cognitive flexibility (shifting from a cognitive task to another), and monitoring (maintaining, organizing information and planning behavior) (Diamond, 2013).

Prefrontally mediated attentional-executive functions have been previously related to motor and other important features of physical frailty (Rosano et al., 2008; Amboni et al., 2013). Specific executive functions (EFs) associated with the medial prefrontal cortex - such as "action monitoring"—have been also considered in pre-frailty status in neurocognitive disorders due to Alzheimer's disease (Amanzio et al., 2017).

Frailty and Cognitive Impairment: The Need to Study the Case of Neurodegenerative Disorders

The first studies on frailty analyzed the association with cognitive impairment through the biomedical model (see **Figures 1A,B**). They emphasized how physical frailty, combined with cognitive impairment, is predictive of an increased risk of a poor prognosis. One of the first studies analyzed the association between physical frailty and a progressive cognitive decline (Samper-Ternent et al., 2008). In particular, 1370 subjects were studied and baseline values for physical frailty (according to Fried's paradigm) and MMSE were observed after 3, 5, and 10 years. The results showed a substantial reduction of the mean of MMSE among frail individuals compared to pre-frail and robust ones.

Subsequent studies, while analyzing the presence of frailty with Fried's paradigm, began to investigate different cognitive sub-domains, widening the focus of observation. This new approach, characterized by the assessment of the cognitive dimension of frailty, enabled to outline the neuropsychological profile of the elderly people analyzed. Some studies tried to investigate more deeply the relationship between cognitive domains and physical frailty (Canevelli et al., 2015). The authors pointed out that the best neuropsychological model to study the presence of frailty associated with cognitive impairment was the paradigms of attentional and executive functions (Canevelli et al., 2015). Interestingly, attention domain and executive functions seemed to be associated with frailty; on physical side, gait speed and grip strength were mainly related to cognitive impairment, with a particular role played by executive dysfunction (Lundin-Olsson et al., 1998; Patrick et al., 2002; Woollacott and Shumway-Cook, 2002; Harley et al., 2009; Kang et al., 2009; O'Halloran et al., 2011, 2014; Langlois et al., 2012; McGough et al., 2013; Shimada et al., 2013; Delrieu et al., 2016; Hooghiemstra et al., 2017; Sargent and Brown, 2017). In this direction, subjects in a pre-frail and frail status were less able to perform the "Sustained Attention to Response Task" (SART), compared to robust ones. Frailty patients made more commission errors and omissions, suggesting that their response monitoring ability could be impaired (Langner and Eickhoff, 2013; O'Halloran et al., 2014; Robertson et al., 2014).

Robertson et al. (2014), carried out a study on a community population of 50 years and older to analyze the association between frailty and different cognitive domains. The authors investigated the effect of each frailty indicator (according to the phenotypic model) on each cognitive domain analyzed (i.e., global cognition, memory, attention, executive functions, processing speed, and self-rated memory) through a multivariate linear regression. Results showed that asthenia was associated with global cognitive functioning, as was the decrease in handgrip strength. The latter was also associated with executive functioning, assessed by neuropsychological tests concerning reasoning, verbal fluency (phonemic) and response inhibition. Finally, walking speed was associated with different cognitive domains, such as attention, processing speed and executive functions.

Some other studies investigated the role played by mood changes on frailty (Mezuk et al., 2012; Espinoza et al., 2013; Paulson and Lichtenberg, 2013). Their results showed a possible association between depressive symptoms and frailty. In particular, depression could be both a cause and an effect of frailty (Robertson et al., 2013).

Even if these studies represent a first important attempt to describe the association between cognitive functions and physical frailty, there is still a need to assess frailty with a multidimensional approach (Pilotto and Ferrucci, 2011; Avelino-Silva et al., 2014; Sternberg and Bentur, 2014) (see **Figure 1**, C). Indeed, as underlined by the bio-psycho-social model, frailty is composed not only of physical aspects but also by cognitive and social components, which interact and influence each other (Mantovani et al., 2020).

Future studies should clarify the type of association between cognitive impairment and frailty, in order to implement effective treatments. It also remains to be determined whether this association is causal or shares aging-related mechanisms, such as neurodegeneration. To understand which one is predominant on the other, longitudinal studies should be set up in the field of primary prevention and in the continuum from MCI to major

neurocognitive disorder. As well highlighted by Lyreskog (2018), a new framework that connects aging, cognitive decline, and neurodegenerative disease is needed. This new paradigm would be useful for "(a) adequately account for the effects that the processes of aging have on neural decline and disease, and (b) be helpful in identifying relevant groups of users and patients" (Lyreskog, 2018; page 57).

The progression of cognitive frailty towards neurodegenerative disorders is not currently clear. However, several longitudinal studies have investigated the possible association (Gómez-Gómez and Zapico, 2019). It has been suggested that classic aging mechanisms, such as oxidative stress, mitochondrial malfunction, and systemic inflammation could play a role in the pathogenesis of cognitive frailty and other associated neurodegenerative diseases (such as Alzheimer's and Parkinson' diseases) (Buchman et al., 2007; Ahmed et al., 2008; Robertson et al., 2013; Gómez-Gómez and Zapico, 2019). Frailty prevalence in neurodegenerative disorders was explored by The Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) Study (Burt et al., 2019), which verified a prevalence rate equal to 11% and 14% according to the Frailty Index and the frailty phenotype, respectively. The prevalence of frailty in Alzheimer's disease varied with a wide range from 11.1% to 50.0% (with a pooled prevalence of 31.9% in mild-moderate stages) (Kojima et al., 2017). A similar prevalence was found by Borda et al. (2019), who also observed a rate of 37.14% in a sample of patients with Lewy body dementia.

In Parkinson's disease (PD) many motor and non-motor symptoms are difficult to explain in terms of a purely ascending degeneration process (Diederich and Parent, 2012), suggesting the need to consolidate the multidimensional elements of PD. In this perspective, the frailty model can be applied to motor disorders albeit with some caution. Frailty and PD may clinically overlap and screening PD patients for frailty may be warranted. Roland et al. (2012) found that correlation coefficients described relationships between PD-related characteristics and physical frailty according to the phenotype criteria. Indeed, frailty is common in PD (prevalence rate = 22.2%) and is associated with a more adverse clinical outcome (Peball et al., 2019). A review by Smith et al. (2019) also provided data in this direction: authors found a prevalence of frailty, which ranged from 29% to 67%.

All together, these findings suggest that the influence of underlying frailty should be considered when managing neurological conditions.

Therefore, a better understanding of cognitive factors, associated with multidisciplinary caring, will form the basis of assistance to frail elderly, with the following possible clinical relapses: slowing of functional decline, reduction of mortality/morbidity, improvement of the quality of life, and reduction of re-hospitalizations. Despite this, very few studies investigated the impact of cognitive functions (more specifically on executive functions) as a precipitating and perpetuating factor of frailty in subjects suffering from neurodegenerative disorders. The proposed mini-review focuses on common points characterizing executive dysfunction, neurocognitive and neurobiological factors potentially involved in frailty in such patients. In particular, the present study aims to investigate and address the following issues:

1. Since physical frailty and cognitive decline (in particular executive dysfunction) are two aspects strongly connected within neurodegenerative disorders (i.e., Alzheimer's disease and Parkinson's disease), are the latter duly taken into consideration in the literature?
2. Which of the frailty models are referred to in these studies (biomedical, bio-psycho-social)?
3. What kind of executive dysfunction are considered and with what neuropsychological tools are they detected?

Selection of Studies

A systematic search strategy was implemented to identify studies on frailty, published until 31st March 2020, across the online database most frequently used in the international literature (Medline database with PubMed literature search[1]). We used a single set of query terms: *Frailty* AND *Executive Functions* [ALL].

We adopted the "PRISMA Statement" in order to make the selection and data collection process clear (Liberati et al., 2009).

With this aim, we reviewed the relevant literature in order to ensure to select only papers regarding patients with mild or major neurocognitive disorders (DSM 5; American Psychiatric Association [APA], 2013) due to neurodegenerative disorders. We only selected original studies. Moreover, descriptive reviews, systematic reviews or meta-analyses were excluded.

During the selection phase, we found 69 studies analyzing frailty in the above-mentioned pathologies. 64 studies were excluded because not consistent with the purpose of the review, while 5 were selected (see the flow chart in **Figure 2** and the **Supplementary Material** for the selection of the articles and the reason for the exclusion).

Description of the Selected Studies

The selected studies mainly concerned subjects with AD and PD, focusing in particular on the two most common neurodegenerative disorders (Xie et al., 2014). Four out of the five selected studies assessed frailty through the biomedical paradigm. In particular, three of those (Shimada et al., 2013; Chen et al., 2019; Lin et al., 2019) adopted Fried's criteria, while one (Dutzi et al., 2017) used the model proposed by Rockwood et al. (2005) and Rockwood and Mitnitski (2007b).

Shimada et al. (2013) analyzed the relationship between physical frailty and Mild Cognitive Impairment (MCI) in 5104 community-dwelling persons aged 65 years and older (mean age 71 years).

The criteria used to define mild cognitive impairment are those reported by Petersen et al. (1999, 2001) for the "MCI-amnestic" type, which presents a high risk of conversion into a major neurocognitive disorder due to Alzheimer's disease (Petersen et al., 1999; Grundman et al., 2004; Petersen and Negash, 2008);.

By adopting the phenotype model, Shimada et al. (2013) subdivided participants in respect of frailty status and level of

[1]http://www.ncbi.nlm.nih.gov/pubmed

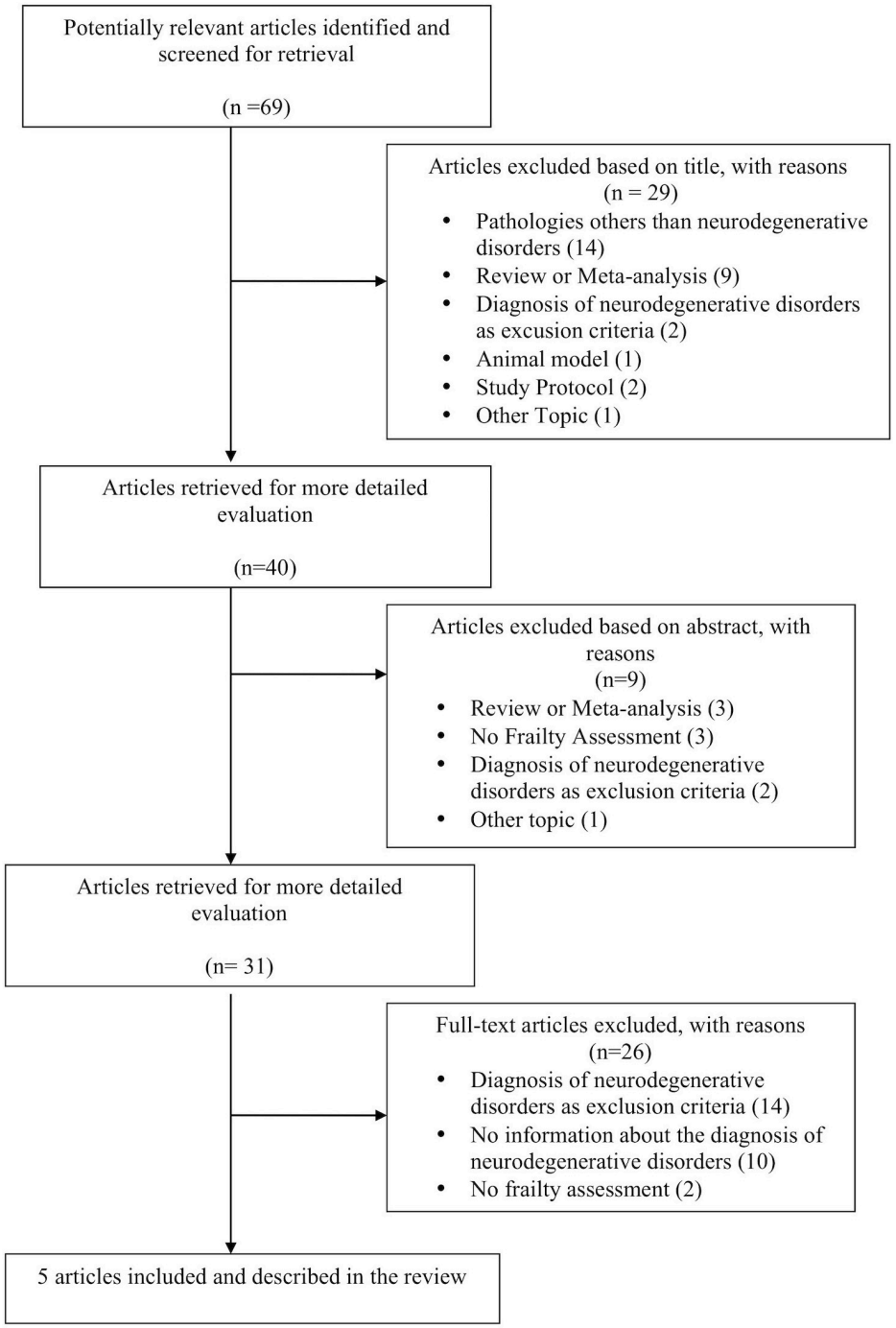

FIGURE 2 | Article selection flow chart according to the PRISMA statement.

cognitive impairment using the MMSE and 8 cognitive tests on memory, attention and executive functions, processing speed, and visuospatial skills. Particularly, the executive functioning – in terms of cognitive flexibility – was assessed through the trail making test (part A and B; Reitan and Wolfson, 1994).

The authors reported the presence of a frailty status in about 11% of the subjects and a MCI in about 19% of the participants. Considering the two aspects together, about 3% of subjects had both, frailty status and MCI, i.e., a cognitive frailty status (Kelaiditi et al., 2013).

Moreover, authors found that the subjects at higher risk for frailty were 80 years and older, with 9 years or less of education. As for cognitive impairment, the subjects with a higher probability of developing MCI were men, with 9 years

or less of education. Finally, the co-occurrence of frailty and MCI (cognitive frailty) increased in relation with age and lower level of education.

The other two selected studies adopting the phenotypic model analyzed the relationship between physical frailty and cognitive impairment in patients with PD (Chen et al., 2019; Lin et al., 2019).

Chen et al. (2019) investigated structural brain changes in relation to physical frailty and cognitive decline in sixty-one PD patients (mean age 62.61 ± 8.59 years), by using MRI. Voxel-wise multiple linear regression analyses were carried out in order to identify the overlapping areas of gray matter volume decrease concerning such aspects.

Frailty was assessed by adopting Fried's criteria. Several cognitive domains, such as attention, memory, language, visuospatial skills, and executive functions, were neuropsychologically evaluated. In particular, EFs were investigated, as indicated by the authors, by using some Wechsler Adult Intelligence Scale-III subtests (picture arrangement, arithmetic, digit symbol coding, and matrix reasoning) (Wechsler et al., 2002), and by the abstract thinking scores from the Cognitive Ability Screening Instrument (Lin et al., 2012).

The authors identified the lateral occipital cortex as an overlapping region of physical frailty and cognitive impairment. Specifically, an overlapping region was observed in the left lateral occipital cortex for every cognitive domain in relation to frailty. This cerebral region is part of the ventral object-based visual pathway (Mishkin et al., 1983), whose decrease in thickness had previously been identified in PD patients in relation to impaired cognitive functioning, in particular visuospatial skills, memory, and executive functions (Pereira et al., 2014).

Moreover, an additional overlapping region relating to the superior frontal gyrus had been identified in connection with executive functioning and frailty. These findings highlighted how frailty and cognitive decline are connected in the brain (Chen et al., 2019).

As a precaution, considering the elements of difficult disambiguation between frailty and PD, it is appropriate to consider the correlations between frailty and cognitive impairments observed in the study by Chen and collaborators related to the pathophysiology (e.g., alpha synuclein in the brain) rather than a sign of frailty.

Finally, by adopting Fried's criteria, Lin et al. (2019) divided their sample of 76 PD patients (mean age 62.64 ± 9.23 years) into two groups: "with physical frailty" (38.2%) and "without physical frailty" (61.8%). PD patients with frailty were significantly older, showed worse disease severity, and poorer cognitive functions compared to robust ones. The neuropsychological assessment was the same carried out in Chen et al.'s study (2019).

A stepwise logistic regression analysis indicated how impaired executive functions increased considerably the risk of physical frailty.

In light of these results, the authors suggested that assessing cognitive functions in PD patients might be a useful approach to identify the subjects at greatest risk of developing frailty and to prevent negative outcomes through targeted strategies of intervention (Lin et al., 2019).

Dutzi et al. (2017) assessed frailty by using the model proposed by Rockwood et al. (2005). The authors investigated cognitive changes following hospital rehabilitation in 154 patients (mean age 83.7 ± 5.9) with mild and major neurocognitive disorder, with different etiopathogenesis [Alzheimer's disease (AD) prevalently]. They considered several aspects that could affect rehabilitation, including cognitive functioning, independence in basic activities of daily living (bADL), and frailty status. Particularly, frailty was evaluated using the Clinical Frailty Scale (CFS) (Rockwood et al., 2005), which allows the clinician to assess the patient's degree of frailty through clinical data. This tool correlates strongly with FI but is faster and easier to administer (Rockwood et al., 2005). The executive functioning was evaluated by the verbal fluency and the modified version of the trail making test, from Nuremberg Gerontopsychological Inventory (Oswald and Fleischmann, 1985). The verbal fluency test is considered a task for the assessment of cognitive flexibility (Diamond, 2013), as well as the trail making test (Lezak et al., 2004).

The authors found that patients presenting a worse frailty status and lower functional independence during the admission were those who did not benefit from cognitive rehabilitation.

They suggested that frailty and deficit in the bADL may have played an important role in the worsening of cognitive decline and in the ineffectiveness of the rehabilitation intervention (Dutzi et al., 2017).

As previously mentioned, 4 out of the 5 selected studies analyzed frailty by adopting the biomedical models. Only one study (Amanzio et al., 2017) provided for the assessment of frailty through the bio-psycho-social model, highlighting its multidimensionality (Pilotto et al., 2020). Amanzio et al. (2017) investigated the association among a multidimensional assessment of frailty, executive dysfunction, and specific cognitive and behavioral changes, using an overall neuropsychological battery in sixty patients with mild and major neurocognitive disorders due to AD (mean age 66.62 ± 6.80).

The authors used the MPI for a comprehensive assessment of frailty (EIP-AHA–European Innovation Partnership on Active and Healthy Ageing, 2013; Pilotto et al., 2013, 2020; Angleman et al., 2015). This tool not only takes into consideration the clinical, functional, neuropsychological, and nutritional status, but also gives information on the associated pathologies and pharmacological therapies, and on the social support network (Pilotto and Ferrucci, 2011, Pilotto et al., 2013, 2020). Executive functions, in terms of self-monitoring, were assessed through the metacognitive version of the Wisconsin Card Sorting test (m-WCST: Koren et al., 2006). This version differs from the original one as the subject is asked to answer two questions: to assess his or her online self-monitoring ("What is your degree of confidence in this answer?") and to control abilities ("Do you want to take this response into account in your total score?") (see Amanzio et al., 2017).

These findings suggested that also a pre-frailty status was associated with metacognitive-executive dysfunction, in terms of action monitoring in MCI-likely due to AD and AD patients. Specifically, it was observed a significant association between the MPI and monitoring resolution at the m-WCST, where patients failed to distinguish between correct

and incorrect sorts. These results were specific and not influenced by other cognitive functions such as global cognition, memory, language comprehension, and non-verbal reasoning, with the exception of the selective attention task that reached a near significance level. Moreover, taking into account the MPI scores, this study demonstrated an involvement of mood depression changes, apathy, disinhibition, and a reduced awareness of IADL, associated with a higher frailty status (Amanzio et al., 2017).

Since apathy, disinhibition, and executive dysfunction seemed to be attributable to the malfunction of the same brain network (Masterman and Cummings, 1997; Bonelli and Cummings, 2007), the authors hypothesized that pre-frailty might also be due to a dysfunction of the medial prefrontal-ventral striatal network (Amanzio et al., 2017).

CONCLUSION

The studies analyzed in this mini-review highlighted how physical frailty and cognitive decline, particularly executive dysfunction, are two aspects heavily connected within neurodegenerative disorders (i.e., AD and PD).

Several cognitive domains have been taken into account in the selected studies due to the lack of a univocal definition of EFs, assessed by different neuropsychological instruments.

The analyzed studies showed that frailty is related to executive dysfunction, in terms of cognitive flexibility (Shimada et al., 2013; Dutzi et al., 2017) and self-monitoring (Amanzio et al., 2017) in neurocognitive disorders.

In our opinion, the Wechsler Adult Intelligence Scale-III (WAIS-III) subtests, used by Chen et al. (2019) and Lin et al. (2019), are not the gold-standard instruments to assess EFs, as WAIS-III was created for the evaluation of reasoning and intellectual abilities (Wechsler, 1997).

However, as reported by Robertson et al. (2014), several cognitive functions such as global cognition, attention, executive functions—including reasoning—and memory are associated with frailty status. These results confirm the hypothesis that there is a relation between frailty and cognitive decline in different domains, even within neurodegenerative disorders (such as PD).

Previous researches had shown a strong association between physical frailty and the incident of neurocognitive disorders, such as AD, MCI (Panza et al., 2015; Xu et al., 2015; Kojima et al., 2016), and cerebral vascular diseases (Avila-Funes et al., 2012). Frailty and cognitive impairment share several risk factors such as age-related chronic diseases, inflammation or cardiovascular problems (Robertson et al., 2013).

In a recent work of systematic review and meta-analysis, Borges et al. (2019) investigated the relationship between physical frailty and cognitive impairment, highlighting how frailty seemed to be one of the greatest risk factors for the development of major neurocognitive disorders.

However, it is important to underline how, to date, the studies have not clarified the direction of the association between frailty and the presence of a cognitive impairment yet. In particular, it is the presence of frailty that determines cognitive impairment or vice versa?

In our opinion, given the multidimensional nature of frailty, the bio-psycho-social model is the most appropriate paradigm for the evaluation and management of frail older people with cognitive decline.

Longitudinal studies may be the most correct approach to assess the presence of cognitive disorders many years before the development of frailty itself. Further studies will be important to better characterized this association over time and replicate these findings in a larger group of patients. Analyzing the association between frailty and cognitive dysfunction in this at-risk population, would allow to develop specific physical and/or cognitive empowerment and rehabilitation measures.

AUTHOR CONTRIBUTIONS

MB wrote the manuscript, developed the search strategy, revised the images and figures, and took part in the review and critique processes. SP wrote the manuscript and took part in the review and critique processes. GEC wrote and edited the manuscript, revised the images and figures. MA conceived the content of the review, developed the search strategy, wrote the first draft of the manuscript, proceeded to extend the theoretical models of frailty associated with executive functions, supervised subsequent changes and took part in the critique processes. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.554307/full#supplementary-material

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Grip Strength, Neurocognition, and Social Functioning in People WithType-2 Diabetes Mellitus, Major Depressive Disorder, Bipolar Disorder, and Schizophrenia

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Background: Frailty is a common syndrome among older adults and patients with several comorbidities. Grip strength (GS) is a representative parameter of frailty because it is a valid indicator of current and long-term physical conditions in the general population and patients with severe mental illnesses (SMIs). Physical and cognitive capacities of people with SMIs are usually impaired; however, their relationship with frailty or social functioning have not been studied to date. The current study aimed to determine if GS is a valid predictor of changes in cognitive performance and social functioning in patients with type-2 diabetes mellitus and SMIs. Methods: Assessments of social functioning, cognitive performance, and GS (measured with an electronic dynamometer) were conducted in 30 outpatients with type 2 diabetes mellitus, 35 with major depressive disorder, 42 with bipolar disorder, 30 with schizophrenia, and 28 healthy controls, twice during 1-year, follow-up period. Descriptive analyses were conducted using a one-way analysis of variance for continuous variables and the chi-squared test for categorical variables. Differences between groups for the motor, cognitive, and social variables at T1 and T2 were assessed using a one-way analysis of covariance, with sex and age as co-variates ($p < 0.01$). To test the predictive capacity of GS at baseline to explain the variance in cognitive performance and social functioning at T2, a linear regression analysis was performed ($p < 0.05$). Results: Predictive relationships were found among GS when implicated with clinical, cognitive, and social variables. These relationships explained changes in cognitive performance

after one year of follow-up; the variability percentage was 67.7%, in patients with type-2 diabetes mellitus and 89.1% in patients with schizophrenia. Baseline GS along with other variables, also predicted changes in social functioning in major depressive disorder, bipolar disorder, and schizophrenia, with variability percentages of 67.3, 36, and 59%, respectively. Conclusion: GS combined with other variables significantly predicted changes in cognitive performance and social functioning in people with SMIs or type-2 diabetes mellitus. Interventions aimed to improve the overall physical conditions of patients who have poor GS could be a therapeutic option that confers positive effects on cognitive performance and social functioning.

Keywords: frailty, grip strength, cognitive performance, social functioning, severe mental illness, type-2 diabetes mellitus

INTRODUCTION

Physical fitness, cognitive ability, and social functioning are critical for living a healthy and happy life. Although connections between these three health components have been suggested, the causality and directionality of these relationships have not yet been fully elucidated (Firth et al., 2018a). These components are impaired in elderly patients and in those who, regardless of age, have chronic diseases such as type-2 diabetes mellitus (T2DM), major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SZ) (Guerra and Amaral, 2009; Catalá-López et al., 2013). Additionally, physical fitness, cognitive ability, and social functioning contribute to frailty. Traditionally, frailty has been defined as "a state of greater vulnerability to stressors, which is a consequence of the decrease in the physiological reserve in multiple organ systems, assuming a limited ability to maintain homeostasis" (Fried et al., 2001). Thus, understanding the relationships between these three components of frailty and the clinical implications of these relationships for people with chronic diseases, such as severe mental illnesses (SMIs) or T2DM, is critical.

In the pathology of SMIs or T2DM, frailty becomes evident with the progression of the disease. From the time of onset of these diseases, there are notable negative impacts in the work life, interpersonal relationships, or self-care of patients, compared to the premorbid phase of the disease. In this regard, understanding the progression of frailty is essential for assessing the deterioration in the quality of life. The causal relationship between the progression of mental pathologies/T2DM and frailty status is not clear, but previous research has suggested that they may have parallels (Rosas-Carrasco et al., 2011; Bartley et al., 2016). These diseases have been associated with reduced autonomy of patients and a potential decrease in physiological capacity and social functioning (Robertson et al., 2013; Rahman, 2018). Therefore, frailty contributes to the pathology of these comorbidities and could trigger a quicker, more progressive deterioration in the quality of life.

Physical capacity is a key component of frailty. Certain physical parameters, such as grip strength (GS), gait speed, and weight loss, may be measured to assess the frailty status of patients. Additionally, previous research has indicated that non-physical aspects, such as nutritional status, mental health, and changes in cognitive ability, could also contribute to frailty (Robertson et al., 2013). GS is a good indicator of frailty and could be useful as an indicator of pre-frailty status in patients with impaired GS (Alfaro-Acha et al., 2006; Boyle et al., 2009). Moreover, an increased GS is related to better performance of functional tasks, such as walking and getting up from a seated position. Additionally, GS affects the ability to perform self-care tasks (Goins et al., 2011; Robertson et al., 2013). In fact, GS has been suggested as a better marker of frailty than chronological age (Syddall et al., 2003; Guerra and Amaral, 2009; Ortega et al., 2012). During a 4-year follow-up, Leong et al. (2015) determined that reduced GS was related to an increase in all-cause mortality and, cardiovascular and non-cardiovascular mortality. The results indicated that GS was the best predictor of mortality, surpassing systolic blood pressure.

Cognitive frailty, which is defined as the deterioration of cognitive abilities that is associated with a state of frailty, is being recognized as a fundamental part of individual vulnerability and resilience to stressors (Panza et al., 2015). In addition, there is evidence of a pathophysiological relationship between the state of physical and cognitive frailty (Fritz et al., 2017). Previous research suggests that there is an association between physical frailty and decreased cognitive abilities; therefore, these two conditions may have similar mechanisms (Rockwood and Mitnitski, 2007; Robertson et al., 2013; Suo et al., 2016). However, the causal relationship between them is not clear (Debette and Markus, 2010). Therefore, it is necessary to elucidate the potential relationship between cognitive and physical frailty.

Furthermore, decreased GS has been associated with lower executive function, focus, working memory, language, semantic categorization, and general cognition in non-demented older people (Fritz et al., 2017). Recent research demonstrates that the decrease in GS at baseline is more strongly associated with the development of mild cognitive impairment and that higher GS at baseline protects cognitive function, functional status, mobility and mortality in people aged 60 years and older (Bohannon, 2008; Boyle et al., 2009; Rijk et al., 2016; Veronese et al., 2016). GS measured with a dynamometer is a reliable measure for estimating the frailty status of patients. Although other relevant components of frailty have been studied, muscle

strength is a very simple non-invasive measure, and has been shown to be of remarkable importance as a marker of physical and cognitive deterioration.

Frailty can lead to the development of numerous chronic diseases, but can also be caused by multiple comorbidities (Vancampfort et al., 2019). Reportedly, SMIs are included as chronic diseases that are bi-directionally associated with frailty (Vetrano et al., 2018). For example, patients with SZ suffer from different comorbidities, some of which are related to reduced physical activity; these conditions include, reduced bone mass. On the other hand, these patients are treated with antipsychotics and other medications (Firth et al., 2018b). These factors contribute to an increased risk of adverse events and worsened overall health. In SMIs, GS and cognitive impairment have been found to be associated and cognitive performance is significantly correlated with physical health (Bohannon, 2015; Firth et al., 2018b; Hidese et al., 2018; Laredo-Aguilera et al., 2019; McGrath et al., 2019). Therefore, measuring GS could be a valid indicator of future cognitive performance and social functioning impairment in patients with SMIs.

To the best of our knowledge, no study has evaluated the association between GS, as a measure of frailty, and cognitive performance and its implications for social functioning in patients with SMIs and T2DM. Furthermore, no known studies have included patients with mental illnesses or T2DM. The present study aimed to investigate if GS is a significant predictor of changes in cognitive performance and social functioning after 1 year of follow-up and determine, if the relationships between GS, cognitive performance, and social functioning measures were different among the groups. Thus, we formulated the following objectives: a) To elucidate the relationship between the decrease in GS and cognitive performance and its implications on social functioning, b) To analyze the differences between motor, cognitive, and social variables in the different groups, and c) To examine whether there are predictive relations between a decrease in GS and impairment in cognitive performance or social functioning.

MATERIALS AND METHODS

Study Design and Ethical Considerations

This article shows partial results of a more extensive study that seeks the identification and validation of peripheral biomarkers for a neurocognitive deficit in depression, BD, SZ, and T2DM. Only those variables that could provide clarity to the study of the GS as a measure of frailty were included in the analyses. Statistical data that did not represent significant differences were excluded. This prospective, comparative cohort study was conducted between April 2015 and January 2018. During this 1-year, follow-up study, several biomarkers, frailty components, and clinical, sociodemographic, and neurocognitive functioning data were collected at baseline (T1) and after 1 year (T2). The patient sample was recruited from mental health units (MHU) at several towns in the province of Valencia (Spain) (Foios, Catarroja, Paterna, and Sagunto), the psychiatry outpatient clinic and endocrinology department of the University Hospital Dr. Peset and in the MHU of the Health Center of Miguel Servet, in Valencia City. Healthy controls (HC) were residents of the same areas of the patients. We compared them in terms of sex, age, and years of education to the extent possible. Study procedures were explained to the participants and all participants provided informed consent. The ethical committees or an institutional review board at each participating center approved the study protocol, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Participants

At baseline (T1), the sample consisted of 165 subjects, including 30 patients with SZ, 42 patients with BD, 34 patients with MDD, 30 patients with T2DM, and 29 genetically unrelated HC. At T2, there were 125 subjects, including 27 patients with SZ, 29 patients with BD, 24 patients with MDD, 25 patients with T2DM, and 20 HC. SZ, BD, and MDD, were diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders – DSM-5 (American Psychiatric Association APA, 2014). T2DM was diagnosed based on the Standards of Care criteria of the American Diabetes Association (American Diabetes Association ADA, 2015). For recruitment as HC, the absence of physical illness, pharmacological treatments, and family history of SMI in first-degree relatives was required. In addition to being diagnosed with one of the above-mentioned conditions, the other inclusion criterion was the ability to understand and give written consent. For BD and MDD, it was necessary to meet the remission criteria of an acute affective episode, and patients with SZ had to be clinically stable. Patients with T2DM had to be free of severe diabetic neuropathy and kidney disease (serum creatinine $<$1.5 mg/dl). General exclusion criteria for all groups included: clinical conditions that hindered the study design, current hospitalization, documented cognitive impairment (intellectual disability or dementia), disability or inability that prevented understanding of the protocol, current substance abuse disorder, pregnancy, intake of steroids, corticosteroids, antioxidants, antibiotics, and immunologic therapies, fever over 38°C, and history of vaccination within 4 weeks of the evaluation. The same inclusion and exclusion criteria were used at T1 and T2. Patients with reduced mobility or motor deficits that made it difficult to perform or prevented them from performing the GS test were excluded from this study.

Assessments

The assessments were conducted by the same experienced psychologists and psychiatrists of the research group. Sociodemographic data, including sex, age, years of education, and motor laterality, were collected at T1. For patients, the age of disease onset and illness duration were obtained and the body mass index (BMI; kg/m^2) was measured for all the participants. The evaluations of each patient were carried out in the morning at their referral health centers, and were one or two hours in length with an intermediate break when necessary. Manual force was evaluated initially, followed by the remainder of the tests. The pharmacological treatment of each patient was recorded in detail and was taken into account as a covariate within the statistical analysis. All of the tests and scales were applied

and scored according to the methodologies described in their respective manuals (see cited references below). To transform the direct scores into *Z* scores, a HC group, not genetically related to the patients, was used.

Clinical evaluations were conducted using the following scales: (i) the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960; Ramos-Brieva and Cordero-Villafáfila, 1986), (ii) the Young Mania Rating Scale (YMRS) (Young et al., 1978; Colom et al., 2002), (iii) the Positive and Negative Symptoms Scale (PANSS) (Peralta and Cuesta, 1994), which is also used to assess the severity of illness in psychiatric patients, and (iv) the Clinical Global Impression (CGI) scale (Vieta et al., 2002). The HDRS and YMRS are used for cases of BD and MDD that meet the remission criteria (Euthymia = HDRS < 9 and YMRS < 7).

Social functioning was evaluated using: (i) the Functional Assessment Short Test (FAST) (Rosa et al., 2007), (ii) the Short Form-36 Health Survey questionnaire (SF-36) (Alonso et al., 1995), and (iii) the Quality of Life of the World Health Organization assessment instrument (WHO-QoL-Bref) (Bobes et al., 2004).

Cognitive performance was evaluated using a battery of neurocognitive tests and subtests previously used by our group (Balanzá-Martínez et al., 2005; Tabarés-Seisdedos et al., 2008; Salazar-Fraile et al., 2009; Selva-Vera et al., 2010; Correa-Ghisays et al., 2017). Evaluation of cognitive performance was divided into (i) the premorbid Intelligence Quotient (IQ), which was calculated using the Wechsler Adult Intelligence Scale (WAIS-III) vocabulary subtest (Weschler, 1999), (ii) the Cognitive Reserve (CR), which was estimated based on the results of the WAIS-III Vocabulary subtest (Lyman, 1971; Weschler, 1999), considered a classical measure of the level of intelligence before the onset of a mental disorder, and calculated based on the number of years of formal education, and (iii) the Global Cognitive Score (GCS), which was calculated by averaging seven cognitive domain scores, including learning and verbal memory, cognitive flexibility, verbal fluency, working memory, short-term memory, visual memory and processing speed scores.

GS was measured using an electronic dynamometer (NedVEP/IBV), with a built-in extensometric transducer and NedDiscapacidad/IBV software V4.1.1 from the Valencia Institute of Biomechanics (Lorenzo-Agudo et al., 2007; Hervás et al., 2011; Montero-Vilela et al., 2012). Each dynamometer was calibrated before every test for each participant. The test was performed with the participant sitting in an upright position in a chair with a backrest and without armrests. The feet had to be supported on the floor with 90° of knee flexion. The arm was positioned with 90° of elbow flexion and neutral pronosupination of the forearm (Su et al., 1994). The hand strength was recorded for three functional positions: (A) handgrip, (B) lateral/key pinch (thumb pad and lateral aspect of index finger), (C) tip pinch (thumb opposed by the index and long fingers), as previously described (Montero-Vilela et al., 2012; McQuillan et al., 2016) (**Figure 1**). For each functional position, three maximum strength scores (in N or kg) were obtained for both hands. The repetitions in each hand did not differ by more than 10% and the average was calculated for each side (Mathiowetz et al., 1984). To simplify the GS measures and inspect if only a frailty marker could be obtained to predict changes at T2, two global measures were created, such as the means of the following measures: (i) the Global Handgrip Score (GHGS) from the right and left handgrip (RHG and LHG, respectively), and (ii) the Global Pinch Score (GPS) from the right lateral/key pinch (RLP), left lateral/key pinch (LLP), right tip pinch (RTP), and left tip pinch (LTP).

Figure 2 illustrates the research methodology adopted in this study.

Statistical Analyses

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 24 for Windows (SPSS Inc., Chicago, IL, United States). Descriptive analyses were conducted using a one-way analysis of variance for continuous variables and the chi-squared test for categorical variables. Normality was assumed for all continuous variables because the sample is sufficiently representative of the target population, which was statistically verified. This fact guarantees that the variables

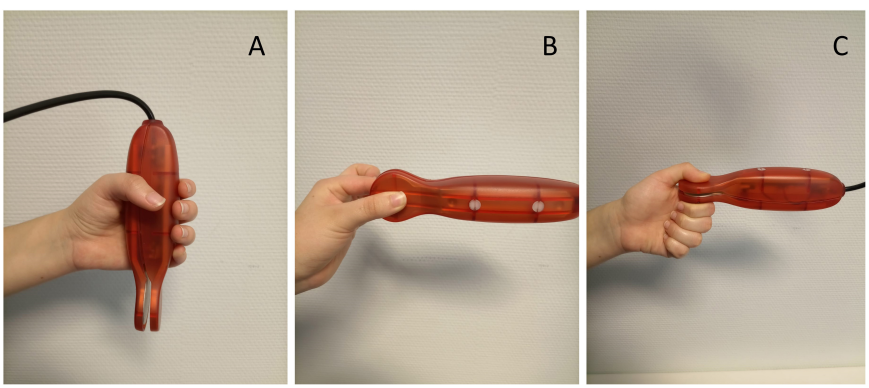

FIGURE 1 | Electronic dynamometer (NedVEP/IBV) functional positions: **(A)** handgrip, **(B)** lateral/key pinch (thumb pad and lateral aspect of index finger), **(C)** tip pinch (thumb opposed by the index and long fingers).

are distributed in a normalized way. The differences between groups for the motor, cognitive, and social variables at T1 and T2 were assessed using a one-way analysis of covariance, with sex and age as co-variates. A *post hoc* analysis with Bonferroni corrected pairwise t-test and Mann–Whitney *U* tests were performed to examine the differences between groups. To test the predictive capacity of GS at baseline to explain the variance in cognitive performance and social functioning at T2, a linear regression analysis was performed using a predictive model that included only sociodemographic, clinical, social, and cognitive variables that were significant for each group. For all analyses, $p < 0.05$ was considered statistically significant. The procedure to create the predictive models was the following: first, a predictive analysis was performed only with the motor functioning variables; however, since they were not optimal by themselves, they were associated, one by one, to the sociodemographic, clinical, cognitive, and social variables. Then, the predictive models were generated including and combining the statistically more powerful variables; therefore, we obtained the optimal predictive combination. No more than five variables were included in each model, thus guaranteeing the correct performance of the analysis.

RESULTS

Sample Description

The sociodemographic and clinical data of the five sample groups at T1 are shown in **Table 1**.

Sociodemographic Variables

The average age of the HC group was significantly lower than the rest of the groups. SZ patients had the lowest mean age, while T2DM patients had the highest mean age; there were significant differences between the groups. The years of education was significantly different, with participants in the HC group having the most. The years of education were similar among the clinical groups. No significant differences were found in motor laterality.

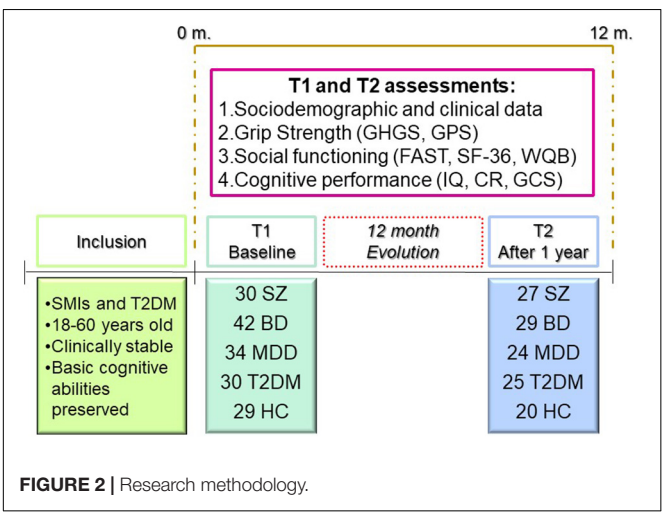

FIGURE 2 | Research methodology.

Clinical Variables

There were significant differences in the scores of the PANSS tests (negative, positive, general, and total), with SZ patients having the highest scores, compared to the other groups. Patients with BD had higher scores in the total and general PANSS compared to the HC group. Scores on the HDRS were higher in patients with MDD, BD, and SZ compared to HC. Among them, patients with MDD showed higher scores than those with SZ, T2DM, and BD. Significant differences were also found for SZ, BD, MDD, and T2DM patients in terms of the CGI; patients with SZ had the worst scores. In addition, BMI was significantly higher in the SZ, BD and T2DM groups compared to the HC group.

Between-Group Comparison of GS, Cognitive Performance, and Social Functioning

Grip strength measures, cognitive, and social variables of the five groups from the sample at T1 and T2 are shown in **Table 2**. Regarding the results obtained when comparing the motor variables between the clinical groups and HC, all of them showed significant differences at both T1 and T2. Notably, the GHGS and GPS indicated that the five groups had significantly different global GS measures. We observed significant differences in the GS, global GHGS, and GPS scores, for both hands. At T1, the MDD group performed significantly lower on the GHGS than the other three clinical groups. This difference remained at T2, but was only significant when compared to patients with T2DM. The GPS was also lower for MDD patients compared to T2DM and SZ patients at T1 and T2. For both time points, patients with SZ achieved significantly higher GPS scores than HC.

Regarding social functioning, patients with SZ had significantly lower FAST total scores than the rest of the groups at T1. Moreover, the BD and MDD groups had worse results than the T2DM and HC groups. At T2, the SZ, BD, and MDD groups showed significantly lower FAST total scores compared to the T2DM and HC groups. The SF-36 test revealed that patients with MDD had the lowest scores, at T1 and T2. In addition, the SZ and BD groups obtained lower scores than the HC at T1; a similar outcome was observed with the WHO-QoL-Bref. The rest of the results for WHO-QoL-Bref were similar to those of the SF-36 for all groups, except the BD group, with worse results in the MDD group at T1 and T2.

For the analysis of cognitive performance, different variables were analyzed; among them, we highlight the GCS. The IQ, CR, and GCS were significantly different among the five groups ($p < 0.001$). *Post hoc* analyses revealed that the GCS was significantly more affected in the SZ group, with the worst scores at both time points. Likewise, the BD group had lower scores at T1 compared to the HC and T2DM groups. Similarly, this occurred at T2 in patients with BD and MDD, but only when compared to the HC group. The differences in performance between the time points within each group were not significant.

Results of the Predictive Model

Table 3 shows the results of the statistical analysis from the relative contributions of the factors studied at baseline (T1), to

TABLE 1 | Sociodemographic and clinical characteristics of the sample at T1.

Variables[a]	HC	T2DM	MDD	BD	SZ	Statistical analyses	
	(*n* = 28)	(*n* = 30)	(*n* = 35)	(*n* = 42)	(*n* = 30)	F(*p*)[e]	*Post hoc* test[g]
Sociodemographic variables							
Sex[b,f,h]	18(64%)	9(30%)	24(68%)	21(50%)	7(23%)	20.1****	SZ, T2DM < HC; SZ < BD SZ, T2DM < MDD
Age (years)	36.6(14.5)	57.3(9.3)	47.3(11.8)	50(9.5)	40.8(10.7)	15.3****	HC < SZ, MDD, BD, T2DM SZ < BD, T2DM MDD < T2DM
Years of Education	16.1(3.3)	12.5(5.8)	11.9(4.3)	11.6(4.4)	10.4(3.3)	7.1****	SZ, BD, MDD, T2DM < HC
Motor Laterality[c]	23(82%)	27(90%)	34(97%)	38(90%)	28(93%)	NS	
Clinical variables							
HDRS[d]	2.0(1.8)	3.9(3.9)	11.6(8.3)	6.4(4.4)	7.0(5.8)	14.2****	HC < BD, SZ, MDD T2DM, BD, SZ < MDD
YMRS[d]	0.8(1.6)	1.5(2.2)	1.9(2.6)	3.5(4.5)	3.2(4.9)	3.4**	HC < BD
PANSS positive[d]	7.0(0.0)	7.0(0.0)	7.0(0.3)	8.5(3.8)	10.6(4.3)	10.6****	HC, T2DM, MDD, BD < SZ
PANSS negative[d]	7.0(0.0)	7.1(0.7)	8.4(4.9)	10.3(6.5)	18.6(10.1)	20.1****	HC, T2DM, MDD, BD < SZ
PANSS general[d]	16.0(0.0)	17.0(2.3)	19.8(8.6)	22.7(9.9)	31.8(12.7)	16.9****	HC < BD, SZ T2DM, MDD, BD < SZ
PANSS total[d]	30.0(0.0)	31.2(2.8)	35.4(13.4)	41.6(18.9)	61.1(24.4)	20.2****	HC < BD, SZ T2DM, MDD, BD < SZ
CGI[d]	1.0(0.0)	1.9(1.0)	3.3(1.2)	3.5(0.7)	4.5(1.0)	63.8****	HC < T2DM, MDD, BD, SZ T2DM < MDD, BD, SZ MDD, BD < SZ
Age of onset (years)	-	44.3(9.8)	35.3(12.1)	26.5(8.6)	25.6(8.0)	16.8****	SZ < MDD, T2DM BD < MDD, T2DM MDD < T2DM
Illness duration (years)	-	13.0(9.0)	12.0(11.6)	23.4(11.5)	15.2(8.4)	25.9****	MDD, T2DM, SZ < BD
BMI (kg/m^2)	24.9(5.1)	30.4(4.3)	28.6(5.8)	29.7(5.6)	31.9(5.4)	7.0****	HC < BD,T2DM,SZ

[a] *Expressed as mean(standard deviation) except when indicated,* [b] *female n(%),* [c] *right-handed n(%).* [d] *Lower scores represent a better outcome.* [e] *ANOVA.* [f] *Chi-squared test.* [g] *Bonferroni test.* [h] *Mann–Whitney U test. Abbreviations: HC = Healthy control, T2DM = Type-2 Diabetes Mellitus, MDD = Major Depressive Disorder, BD = Bipolar Disorder, SZ = Schizophrenia, HDRS = Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale, PANSS = Positive and Negative Syndrome Scale, CGI = Clinical global impression, BMI = Body Mass Index, ANOVA = Analysis of variance, NS = not significant. (NS = $p > 0.05$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; ****$p \leq 0.0001$).*

explain the variation of the results after 1 year of follow-up (T2). In each of the groups, different variables have been included that could explain the endpoint performance at T2. We have observed that the GHGS and/or the GPS alone did not give significant results, in terms of their ability to predict cognitive or social functioning. In contrast, with other combinations that considered more specific motor domains (not just the global one), and other cognitive domains, we found that they were predictive of the results at T2. Therefore, for each of the groups included in the study, combinations of different variables were analyzed together with motor variables to determine if any of them had predictive value, in terms of changes in cognitive performance and social functioning. The results of each of the groups were as follows:

In the SZ group, 89% of the variance of the GCS can be explained after 1 year, when considering the changes that have been produced in the RHG, the motor laterality, and the GCS from T1. In this group, with these combinations, the highest percentage of variability has been explained in terms of changes in cognition. Regarding the changes in the social functioning, as evaluated with SF-36, the FAST with the RHG explained up to 59% of the changes in the results. This indicates that, in patients with SZ, RHG may have a predictive component, in terms of cognitive performance and social functioning. In contrast, patients with BD obtained the lowest percentages of variance. In this case, social functioning, which was evaluated with FAST and WHO-QoL-Bref, was explained by approximately 36% due to changes in PANSS and GS, measured in one case with RHG (for FAST) and in another with RTP (for the WHO-QoL-Bref). Those with MDD are affected by their social functioning capacity, which was measured with the SF-36, at a level of 67.3%, when considering BMI, CGI, and LHG. We have highlighted that LHG has influenced the predictive results at T2 in these patients; however, 97% of the patients in the MDD group were right-handed, so the strength of the left hand cannot be explained, in the case that has intervened in the variability of the results after one year. We conclude that changes in GS, BMI and overall clinical impression affect the functional ability of patients with MDD. Patients with T2DM are affected by their cognitive functioning through the GCS; if we combine the variables of CR, illness duration, and RHG, cognitive functioning was explained by up to 67.7%. These results indicate that in our group, changes in GS, along with years of illness and CR, could act by predicting deterioration in global cognition over a 1 year period.

TABLE 2 | Outcomes variables at Time 1 and Time 2 (*Z*-scores).

	HC		T2DM		MDD		BD		SZ		Statistical analyses			
	T1 (*n* = 28)	T2 (*n* = 19)	T1 (*n* = 30)	T2 (*n* = 25)	T1 (*n* = 35)	T2 (*n* = 25)	T1 (*n* = 42)	T2 (*n* = 29)	T1 (*n* = 30)	T2 (*n* = 27)	T1 F(*p*)[b]	*Post hoc* test[d]	T2 F(*p*)[b]	*Post hoc* test[d]
GS measures														
RHG	0.0(1.0)	−0.1(0.8)	0.2(1.0)	0.1(1.1)	−0.5(0.9)	−0.7(0.7)	−0.2(1.0)	−0.5(0.9)	0.0(0.9)	−0.2(0.8)	4.0**	MDD < SZ, T2DM	3.8**	MDD < T2DM
LHG	0.0(1.0)	−0.2(0.9)	0.2(1.1)	0.2(1.1)	−0.5(1.0)	−0.8(0.9)	−0.1(1.1)	−0.3(1.0)	0.0(1.0)	−0.2(0.9)	4.1**	MDD < BD, T2DM	4.7***	MDD < BD, T2DM
GHGS	0.0(1.0)	−0.2(0.8)	0.2(1.1)	0.2(1.1)	−0.6(1.0)	−0.8(0.8)	−0.1(1.1)	−0.4(0.9)	0.0(1.0)	−0.2(0.9)	4.2**	MDD < BD, SZ, T2DM	4.3**	MDD < T2DM
RLP	0.0(1.0)	0.3(0.8)	0.4(0.9)	0.7(0.7)	−0.1(0.8)	0.2(0.7)	0.1(0.9)	0.2(0.7)	0.7(0.6)	0.8(0.6)	5.7****	MDD < T2DM, SZ; HC < SZ	4.8***	MDD, HC < SZ
LLP	0.0(1.0)	0.3(0.8)	0.6(1.1)	0.9(0.9)	−0.1(0.9)	0.3(0.8)	0.3(1.0)	0.5(0.9)	0.9(0.7)	0.9(0.7)	6.3****	HC, MDD < T2DM, SZ	4.2**	MDD, HC < SZ
RTP	0.0(1.0)	0.2(0.6)	0.4(1.1)	0.8(0.9)	−0.3(0.9)	0.0(0.8)	0.1(1.1)	0.3(1.0)	0.6(0.6)	0.5(0.7)	5.0***	MDD < T2DM, SZ	3.6**	MDD < T2DM
LTP	0.0(1.0)	0.2(0.8)	0.6(1.2)	1.0(1.0)	−0.2(1.0)	0.0(0.8)	0.2(1.2)	0.3(1.2)	0.8(0.8)	0.7(0.9)	6.2****	HC, MDD < T2DM, SZ	4.9***	MDD, HC < T2DM
GPS	0.0(1.0)	0.3(0.7)	0.5(1.1)	0.9(0.9)	−0.2(0.9)	0.1(0.7)	0.2(1.1)	0.4(0.9)	0.8(0.7)	0.8(0.7)	6.3****	MDD < T2DM, SZ; HC < SZ	4.9***	MDD < SZ, T2DM; HC < SZ
Social functioning														
FAST	0.0(1.0)	0.0(0.8)	−1.2(1.8)	−1.0(1.5)	−3.7(2.6)	−3.5(2.5)	−4.3(1.9)	−3.9(1.9)	−5.6(2.4)	−4.7(2.5)	22.3****	SZ < BD, MDD, T2DM, HC BD, MDD < T2DM, HC	9.7****	SZ, BD, MDD < T2DM SZ, BD, MDD < HC
SF-36	0.0(1.0)	0.2(0.5)	−1.2(1.8)	−1.0(1.7)	−3.9(2.1)	−3.8(2.7)	−2.6(1.9)	−2.6(1.8)	−1.9(1.9)	−2.3(1.9)	14.4****	MDD < BD, SZ, T2DM, HC BD, SZ < HC	9.1****	MDD < BD, SZ, T2DM, HC
WQB	0.0(1.0)	0.3(1.1)	−0.6(1.2)	−0.5(1.4)	−2.2(1.2)	−2.2(1.8)	−1.6(1.2)	−1.9(1.1)	−1.3(1.0)	−1.2(1.2)	13.7****	MDD < SZ, T2DM, HC BD, SZ < HC	7.8****	MDD < SZ, T2DM, HC
Cognitive performance														
IQ	0.0(1.0)	1.5(1.0)	−0.2(1.2)	0.7(1.2)	0.0(1.3)	1.0(1.1)	0.0(1.3)	0.1(1.4)	−1.0(1.5)	0.1(1.1)	3.4**	SZ < T2DM, MDD, BD	4.7***	BD,SZ < HC
CR[a,c,e]	6(21%)	2(10%)	16(53%)	11(44%)	16(46%)	12(48%)	23(55%)	18(62%)	22(73%)	20(74%)	16.4**	HC < T2DM, MDD, BD, SZ MDD < SZ	20.1****	HC < T2DM,MDD, BD,SZ MDD,T2DM < SZ
GCS	0.0(0.5)	0.3(0.6)	−0.9(0.8)	−0.8(0.9)	−0.8(0.8)	−0.7(0.9)	−1.3(1.0)	−1.1(0.9)	−1.7(1.0)	−1.5(0.9)	16.6****	SZ < BD, T2DM, MDD, HC BD < T2DM, HC	14.6****	SZ < BD,T2DM,MDD,HC BD,MDD < HC

*Expressed as mean (standard deviation) except when indicated.[a]Low n(%).[b]ANCOVA.[c]Chi-squared test.[d]Bonferroni test.[e]Mann–Whitney U test.HC, healthy control; T2DM, type-2 diabetes mellitus; MDD, major depressive disorder; BD, bipolar disorder; SZ, schizophrenia; T1, Time 1; T2, Time 2; RHG, right handgrip; LHG , left handgrip; GHGS, Global Handgrip Score; RLP, right lateral/key pinch; LLP, left lateral/key pinch; RTP, right tip pinch; LTP, left tip pinch; GPS, Global Pinch Score; WQB, WHO-QoL-BREF; IQ, Intelligence Quotient; CR, cognitive reserve; GCS, Global Cognitive Score; ANCOVA, analysis of covariance; SF-36, Short-form 36; FAST, Functional Assessment Short Test; NS, not significant.[NS]$p > 0.05$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; and ****$p \leq 0.0001$.*

TABLE 3 | Predictive model.

Dependent variables at T2	Predictors at T1 associated	β	95% CI	*t*	Percent of variance explained (adjusted R^2)
Group: T2DM					
GCS	CR	−0.557	−1.46 to −0.53	−4.43****	67.7
	Illness duration	−0.293	−0.05 to 0.00	−2.01*	
	RHG	0.309	0.00 to 0.05	2.11*	
Group: MDD					
SF-36	CGI	−0.567	−1.65 to −0.59	−4.38****	67.3
	BMI	−0.324	−0.27 to −0.02	−2.48*	
	LHG	0.301	0.01 to 0.16	2.37*	
Group: BD					
FAST	PANSS-T	−0.430	−0.06 to −0.01	−2.73**	35.9
	RHG	0.410	0.01 to 0.13	2.60**	
WQB	PANSS-N	−0.436	−0.11 to −0.01	−2.79**	36.7
	RTP	0.413	0.03 to 0.30	2.64**	
Group: SZ					
GCS	GCS	0.837	0.66 to 0.95	11.55****	89.1
	Motor laterality	−0.235	−1.97 to -0.43	−3.23***	
	RHG	0.086	−0.00 to 0.02	1.24*	
SF-36	FAST	0.595	0.26 to 0.71	4.40****	59.0
	RHG	0.357	0.16 to 1.33	2.64**	

T1, Time 1; T2, Time 2; CI, confidence interval; T2DM, type-2 diabetes mellitus; MDD, major depressive disorder; BD, bipolar disorder; SZ, schizophrenia; RHG, right handgrip; LHG, left handgrip; RTP, right tip pinch; WQB, WHO-QoL-BREF; PANSS, Positive and Negative Syndrome Scale; CGI, clinical global impression; BMI, body mass index; CR, cognitive reserve; GCS, Global Cognitive Score; SF-36, Short-form 36; FAST, Functional Assessment Short Test; NS, not significant.$^{NS}p > 0.05$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; and ****$p \leq 0.0001$.

DISCUSSION

The purpose of this study was to determine the clinical implications of GS, in regard to cognitive performance and social functioning, in patients with SZ, BD, MDD and T2DM, and confirm if GS can provide valuable information about physical function, which may be considered a frailty marker. Our findings indicate that GS can, in part, account for variabilities in cognitive and social functioning after one year of follow-up. However, it is clear that along with other variables, changes in physical performance influence long-term and predict cognitive and social functioning impairment in patients with MDD, BD, SZ, and T2DM, when compared to HC. In our study, changes in GS significantly influenced the GCS and we emphasized that the RHG is the most powerful motor variable, as it contributed to the most changes after 1 year. These findings are consistent with the literature, which indicates that the best results are obtained when the task is performed in the most comfortable position and with the right hand (Sternäng et al., 2014; Soysal et al., 2017; Firth et al., 2018a; Smith et al., 2018). Furthermore, we observed that the relationships between GS and, cognitive and social functioning measures were different for people with T2DM, MDD, BD and SZ. Each of the combinations of variables, which are different for each group, can explain the variability in the results after one year of follow-up. In the case of patients with T2DM, CR and illness duration together with RHG are fundamental for the cognitive impairment, accounting for almost 70% of the variability at T2. In this regard, another study found that diabetic microangiopathy and/or chronic inflammation in these patients, which is closely related to T2DM pathology, could be related to a deterioration of physical abilities, as evidenced by a decrease in GS (Zilliox et al., 2016). Similarly, previous research asserts that a worsened clinical status of MDD patients is associated with a decrease in physical activity (Montero-Vilela et al., 2012). In addition, changes in diet, weight, or BMI of MDD patients, can result in lower GS (Vancampfort et al., 2011). In this study, those changes have been shown to have a long-term impact on the social functioning of the MDD patients. Smith et al. (2018) reached the same conclusion after analyzing GS in patients with depression and overweightness. The findings of our study demonstrate, according to previous literature, that a weaker GS is associated with a lower quality of life; in turn, a low quality of life has a detrimental impact on mental health (Whiteford et al., 2015). These changes may explain the 67.3% variability in the social functioning for patients with MDD; despite the inclusion of BMI for the different groups, all clinical groups are equal and only the HC group has significant differences in BMI compared to the other groups.

However, studies regarding GS in BD patients are scarce. Firth et al. (2018b) demonstrated that GS predicted cognitive impairment in these patients. In our study, changes in the total and negative PANSS together with GS (RHG and RTP) predicted changes in social functioning. Symptom worsering, such as changes in appetite, smoking and/or drinking alcohol, sleep disorders, reductions in physical activity, and changes

in body composition and metabolism, influenced the risk of decreased physical functions, which determine a greater degree of difficulty of the patient in terms of autonomy, work performance, and social functioning (up to 36% in our study) (Fried et al., 2001). However, more variability was observed in the SZ group. Almost 90% of the changes in the GCS at T2 are explained by the RHG, along with the motor laterality and the GCS at T1. It is noteworthy that, in this group, the GCS was significantly lower than that of the rest of the groups, and this was maintained at both time points. Similarly, patients with SZ showed lower scores in the social functioning at T1 compared to the other groups; the scores were worse than those of the HC and T2DM groups at T2. RHG, motor laterality, and GCS were the best predictors of changes in cognitive performance after 1 year in SZ patients (89.1%); this was similar to the ability of RHG and FAST to predict impairment in social functioning, when measured with the SF-36 (59%).

Therefore, the measurement of GS (and other variables) in the psychiatric population and in patients with T2DM could be a valid indicator to predict cognitive and social impairment in the future. Thus, GS does not only influence cognitive and social changes since the physical condition in these patients is closely associated with the state of their disease. These findings suggest that people who are physically weaker or those whose physical abilities are diminished may be more vulnerable to a worsened pathology, that is, they may be in a state of physical and/or cognitive frailty. It is difficult to biologically explain this situation, but the reverse causality could partially explain it and, some of the results of the study: people with SMI may be less likely to participate in any social activity, including physical activities, which would result in a lower physical condition and lower GS due to inactivity. On the other hand, psychiatric disorders are highly related to maladjustment of those who suffer from it; therefore, their social functioning is affected as soon as their disease worsens. As previously suggested, this could be explained because there is bidirectionality and/or causality of a third factor or factors in this relationship. The relationship between frailty (GS), cognitive performance, and social functioning is depicted in **Figure 3**.

Considering the GS as a marker of cognitive and social functioning, we could conclude that the increase of the GS as a measure of frailty combined with other variables such as the BMI, cognitive reserve, or disease duration could become both a new study objective and a therapeutic target to improve the cognitive and social functioning of people with SMI and DMT2. We propose that future research on the treatment of these diseases could explore the potential benefits of including strength training along with traditional psychotherapeutic and pharmacological interventions.

Limitations

This study has some limitations that should be addressed. First, this study includes a small sample size (n = 165). Therefore, studies with larger sample sizes could provide more generalizable results. Additionally, after one year of follow-up, 40 patients were lost for different reasons, which resulted in a smaller sample at T2. Furthermore, a longer follow-up period should be included in future studies in order to detect stronger differences in the neurocognitive decline. Another limitation of the study is the average age of the participants (45 years). Because of this limitation, the results cannot be extrapolated to younger patients. Despite these limitations, this study is the first known study to investigate the association between GS and, cognitive and social functioning in patients with SZ, BD, MDD, and T2DM.

Conclusions and Future Directions

Grip strength, especially RHG, plays a significant role in predicting changes in cognitive performance and social functioning in people with SZ, BD, MDD, and T2DM. There are differences between the studied groups in terms of variability of results and the variables included in the regression models, with GS included at T1 to explain changes over time (T2). RHG combined with other variables, which are different for each group, shows significant differences that may predict cognitive performance and social functioning during an 1-year follow-up. Therefore, it is clear that there is a common denominator (physical status), which is evidenced by the influence of GS on cognition and social functioning.

The results of this study are supported by the review of the medical literature where GS, when used as a representative parameter of frailty, is considered as a good biomarker of future neurocognitive and social changes. The variables taken into account in this study, and their functional implications within the state of frailty and cognitive deterioration in SMIs and T2DM have not been found in previous work. In our study, we found that, together with GS, some of these variables may have strong predictive values. Nonetheless, more studies should be conducted to further explore how and why these variables predict patient alterations over time.

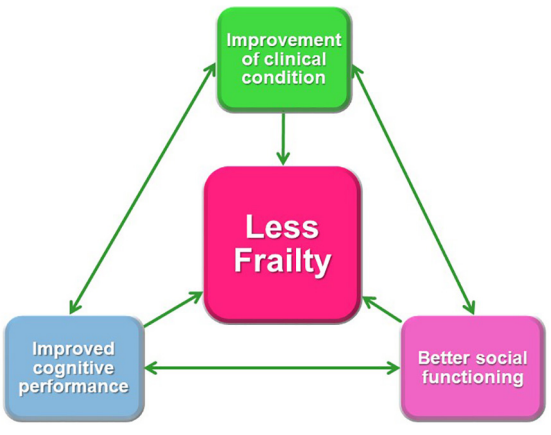

FIGURE 3 | Relationship between frailty (grip strength), cognitive performance, and social functioning.

Therefore, GS could be used for monitoring these patients, detecting changes in their physical condition that serve to intervene clinically, and preventing future adverse events. Future research should focus on establishing interventions that can be used to improve GS, cognitive status, and long term social functioning in patients who are in a state of frailty or pre-frailty. Interventions aimed to improve the overall physical conditions of patients who have poor GS could be a therapeutic option that confers positive effects on cognitive performance and social functioning.

Finally, we recommend carrying out additional studies, similar to this study, which include young people with chronic diseases such as severe early onset mental disorders and type 2 diabetes mellitus. This could expand the minimum and maximum reference values of GS as a marker of frailty. In addition, longitudinal studies at 5, 10, 15, 20, or more years of follow-up would be beneficial.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité Ético de Investigación Clínica del Hospital Clínico Universitario de Valencia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MA-D: interpretation of the data and drafting the manuscript. JS-O: statistical analysis, drafting the manuscript, and critical review of the manuscript. PC-G: study supervision, patient inclusion, acquisition and interpretation of data, drafting the manuscript, and critical review of the manuscript. JV-F: statistical analysis. VB-M: patient inclusion and critical review of the manuscript. GS-V: patient inclusion. PC-E, JF-M, CS-MV, MM-P, RA-A, MR-V, and BC-F: critical review of the manuscript. RT-S: study concept and design, study supervision, and critical review of the manuscript. All authors approved the final version of the manuscript.

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REVIEW
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Comprehensive Model for Physical and Cognitive Frailty: Current Organization and Unmet Needs

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Aging is characterized by the decline and deterioration of functional cells and results in a wide variety of molecular damages and reduced physical and mental capacity. The knowledge on aging process is important because life expectancy is expected to rise until 2050. Aging cannot be considered a homogeneous process and includes different trajectories characterized by states of fitness, frailty, and disability. Frailty is a dynamic condition put between a normal functional state and disability, with reduced capacity to cope with stressors. This geriatric syndrome affects physical, neuropsychological, and social domains and is driven by emotional and spiritual components. Sarcopenia is considered one of the determinants and the biological substrates of physical frailty. Physical and cognitive frailty are separately approached during daily clinical practice. The concept of motoric cognitive syndrome has partially changed this scenario, opening interesting windows toward future approaches. Thus, the purpose of this manuscript is to provide an excursus on current clinical practice, enforced by aneddoctical cases. The analysis of the current state of the art seems to support the urgent need of comprehensive organizational model incorporating physical and cognitive spheres in the same umbrella.

Keywords: aging, frailty, motoric cognitive syndrome, mild cognitive impairment, organizational models

INTRODUCTION

The term *aging* defines the changes occurring during an organisms' life (da Costa et al., 2016). From a biological perspective, *aging* is associated with functional decline and cellular impairments resulting in a wide variety of molecular damage over time. All these changes affect physical and mental capacity (World Health Organization [WHO], 2018).

Aging population is the result of low immigration and reduced fertility (Christensen et al., 2009) with constant increased life expectancy (Ferrucci et al., 2008).

The rate of aging of the world population is increasing from 900 million in 2015, and the population older than 60 years is expected to reach 2 billion by 2050, mostly in low–middle socioeconomic level countries (World Health Organization [WHO], 2018). Nowadays, the number of people aged 80 and over is 125 million.

In the United States, the entire population will grow to 400 million people in the next 40 years. The 65-year age group and older will increase by almost two times, reaching 95 million people, 25% of the entire country population (Vespa et al., 2020).

Italy and Germany are the oldest European and World Countries. By 2030, almost 25% of the European population will be represented by seniors (Ferrucci et al., 2008).

The relationship between the older adults and the working age population, defined age dependency ratio, is used to define the level of support provided to the older population by the 15–64-year-old population (EUROSTAT, 2019).

In the next 5–10 years, the Italian population is expected to decrease, from 60.6 million in January 2017 to 54.1 million in 2065 (Istituto Nazionale di Statistica [ISTAT], 2018).

Furthermore, the geographic areas of longevity have been extensively studied. Many centenarians living in these "zones" are free of chronic diseases, completely independent in activities of daily living (ADL), and do no develop any condition of disability up to the age of 90 (Deiana et al., 1999; Ferrucci et al., 2008).

Aging cannot be considered a homogeneous process. When the intrinsic capacity, which is the sum of physical and mental capacities, is reduced or lost, a condition of frailty occurs (Cesari et al., 2006; Longobucco et al., 2019). Frailty, defined as a state of increased susceptibility to stressors (high or low temperature, acute illnesses, or injuries), implies the homeostatic dysregulation of many physiological systems (Fried et al., 2004). It may be characterized by low physical function, cognitive performance, or both, with increased difficulty or dependence in basic activities of daily life.

Frailty is a highly prevalent condition worldwide. For example, in a Malaysian over 60 institutionalized population, the prevalence of physical frailty and prefrailty was 56.6 and 40.7%, respectively (Murukesu et al., 2019). In the same country, in a community setting, the prevalence of cognitive frailty was 2.2%, while the prefrail persons were the 37.4% (Malek Rivan et al., 2019). The incidence of cognitive impairment was estimated in 7.1/100 persons per year (Rivan et al., 2020). A recent meta-analysis showed that the hazard ratio for the co-occurrence of both physical and cognitive frailty was 5.36 (Grande et al., 2019).

FRAILTY AS A DYNAMIC PROCESS

In this manuscript, we underline the close relationship between the motor and cognitive components and their contribution to a predisability condition. We bridge the concepts of frailty and motoric cognitive risk syndrome, providing an operational interpretation (Verghese et al., 2019).

The progression of physical and cognitive frailty leads to physical disability and dementia. As suggested by some authors (Rossini et al., 2019), the evolution of mild cognitive impairment toward Alzheimer's disease occurs in 50% of the patients.

At the same time, sarcopenia becomes a leading determinant of physical frailty and represents a reversible precursor of hypomobility or bed rest. These issues have been conceptualized in the operative definition of the Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies (SPRINTT) project, the most important randomized controlled trial on physical frailty (Marzetti et al., 2018).

If screening tests are combined to assess the physical and cognitive components of frailty (for instance, sarcopenia and mild cognitive impairment), the diagnostic accuracy of the prodromal of dementia is increased. In fact, the combined use of physical and cognitive frailty allows to detect the highest risk of developing dementia and disability (Grande et al., 2019).

Moreover, the widespread deposition of amyloid in the central nervous system of patients suffering from mild cognitive impairment and Alzheimer's disease can contribute to the decline in physical and cognitive performances (Lauretani et al., 2020).

Therefore, our discussion regarding the pathophysiological mechanisms of frailty will be restricted to sarcopenia and cognitive frailty as determinants of frailty. We will also address the possible synthesis of these two conditions by discussing the motoric cognitive risk syndrome.

History and Models

The term *frail older persons* was used for the first time by Bertha Adkins, past president of the Federal Council on the Aging, during a radio interview to describe "those people needing continuous social support due to accumulation of disabilities associated with aging." Despite the increase in geriatric medicine over the last decades, a univocal definition of frailty is still missing (Pilotto et al., 2020).

Fried et al. (2004) identified frailty as a clinical syndrome of vulnerability with low functional supply and compromised capacity to face stressful conditions, resulting in multiple organ failure and adverse outcomes.

Rockwood and Mitnitski (2007) gave an alternative definition operationalizing frailty as a state of dysregulation of physiological systems estimated by functional state, multimorbidity, motoric and cognitive deficits, and social predisposing conditions, for outlining the risk of unfavorable events. All these predisposing conditions were enumerated into a preformed list called "Frailty Index" (Rockwood and Mitnitski, 2007).

Gobbens et al. (2010) moved toward a biopsychosocial model of frailty, a dynamic, multifactorial condition characterized by changes in one or more than psychological, social, and physical domains, and determining an increased risk of unfavorable outcomes.

Definition

Despite the different approaches, most of the authors agree that *frailty* is a dynamic intermediate condition between a normal functional state and disability determining the decline of functional abilities (Walston et al., 2006).

Frailty has been also assimilated to a multidimensional geriatric syndrome featured by the decreased ability to recover homeostasis when a stressor event and the loss of functional reserves occur. Frailty affects physical, psychological, and social domains involving cognitive, emotional, and spiritual aspects (Longobucco et al., 2019).

Seventeen of the European elders show frailty. The increasing prevalence across European countries suggested the need of

crossing the geriatric field and improving an appropriate diagnosis (Wleklik et al., 2020).

Pathophysiology

The pathogenesis of frailty is multifactorial and includes age, acute and chronic diseases (multimorbidity), genetic heritage, loss of loved ones, and polypharmacy as risk factors (Gutiérrez-Valencia et al., 2018). Physical (inflammatory status, hormonal imbalance), psychological (stress and depression), and social factors are core determinants and components.

In a small frail cohort of elder patients, Leng et al. (2002, 2004a) found that lower hemoglobin and hematocrit levels inversely related with interleukin 6 levels and proxy of inflammatory status.

An increased activation of monocytes and macrophages has also been documented in frail patients (Leng et al., 2011; Ramanathan et al., 2013). Frailty was also linked to changes in hormonal milieu, namely low serum levels of insulin like growth factor-1 (IGF-1) and dehydroepiandrosterone sulfate (DHEAS) well-known anabolic hormones (Leng et al., 2004b; Puts et al., 2005; Shardell et al., 2009; Maggio et al., 2012, 2014).

Stress, depression, low activity levels, lower dietary protein, and micronutrient intake can accelerate the process of frailty (Fried et al., 1999). Other contributing causes of frailty (Strawbridge et al., 1998) include social isolation, alcohol abuse, smoking, chronic diseases, and polypharmacy.

A special contribution to physical frailty comes from sarcopenia and the decay of muscle quantity and quality, which can be considered its biological substrate (Xue, 2011; Clegg et al., 2013; Coelho et al., 2015; Morley, 2016).

According to the presence of multimorbidity, polypharmacy, sensory deficits, and loss of social support, we can distinguish prefrailty and frailty. Both forms are associated with increased risk of hospitalization and death (Newman et al., 2001).

Earlier recognition (catching signs and symptoms of physical and cognitive domains), diagnosis, and multimodal treatment are needed to prevent the progression of prefrailty into functional decline. This approach is also fundamental to attenuate the risk of morbidity, dependence, falls, mortality, social isolation, admission to care facility, and reduced quality of life (Longobucco et al., 2019).

Actually, there is no global evaluating scale available to address all the clinical aspects of this syndrome including sarcopenia, which is closely connected to physical frailty and requires a parallel evaluation (Cruz-Jentoft et al., 2019). We are still using many different physical, psychological, and social tools to explore different spheres of frailty in the context of comprehensive geriatric assessment.

Sarcopenia

Sarcopenia is a skeletal muscle disorder characterized by low muscle mass and quality. Nowadays, the most influential definition is presented by the "European Working Group on Sarcopenia in Older People" (EWGSOP), supported by the "Asian Working Group on Sarcopenia," and updated as "EWGSOP2" in January 2019 (Cruz-Jentoft et al., 2019).

Sarcopenia is an age-related physical condition with a multifactorial etiology, including genetic and lifestyle factors and multimorbidity. The most important causes of sarcopenia are inactivity, eating habits, diseases, and medications.

Therefore, sarcopenic persons have a peculiar physical condition characterized by loss of muscle strength (quality) and mass (quantity). We can identify an acute (usually after surgery, during hospital admission, or in other conditions of immobility) and chronic sarcopenia especially due to prolonged inactivity and immobilization (Cruz-Jentoft et al., 2019).

Muscle aging is characterized by an imbalance between anabolic and catabolic pathways with reduced muscle proteins and myofibers (in particular type II fibers) frequently replaced by adipose tissue.

It is possible to diagnose sarcopenia combining different data, including motoric performance tests and measures of muscle mass and strength.

Given the related risks of functional decline, falls, frailty, and death, several studies are now focusing on easier and more accurate techniques to measure muscle mass.

In particular, the daily application of well-known techniques such as dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), and bioimpedance analysis (BIA) is limited by the costs and complex analyses. In this scenario, B-mode muscle ultrasound is a promising technique for screening muscle mass and structure and in the future for diagnosing sarcopenia (Ticinesi et al., 2017).

Handgrip strength has been commonly used to measure muscle strength. EWGSOP2 suggests to identify cutoff gender dependent and explained by the different hormonal milieu (Maggio et al., 2013; Cruz-Jentoft et al., 2019).

Short Physical Performance Battery test (Guralnik et al., 2000), "Timed Up and Go," and "Walking Speed Test" are the tests commonly used to assess the motoric performance and sarcopenia severity (Cruz-Jentoft et al., 2019).

Additional and useful information comes from SPRINTT Study. This trial was conducted with the double goal of finding a consensus on the identification of older adults with physical frailty and sarcopenia and to test the effectiveness of a multifactorial intervention in this specific population living in the community. A specific program of physical activity, dietary, and technological intervention was compared to a successful Aging Lifestyle Education program having as primary outcome changes in 400 m walking. The results of this trial are close to be published (Landi et al., 2017).

Cognitive Frailty

Cognitive frailty is an emerging concept and condition of reduced neuropsychological reserve where physical frailty and mild cognitive impairment (MCI) coexist. We are facing a heterogeneous geriatric condition where cognitive capacities are preserved or slightly reduced with preserved activities of daily living. Two MCI subtypes are potentially reversible cognitive frailty (physical frailty/MCI) and reversible cognitive frailty (physical frailty/pre-MCI subjective cognitive decline) (Panza et al., 2018).

Cognitive impairment is more frequently detected in physically frail patients. In this specific category, we can observe adverse clinical outcomes linked to physical (functional independence, hospitalization, and risk of death) and cognitive

components of frailty [dementia, in particular Alzheimer's disease (AD)]. Several studies are revealing the role of brain as the core not only for dementia but also for frailty syndrome. Physical activity has beneficial effects on the brain and muscle, suggesting that neuroprotection is a potential way to increase muscle function.

The research is also focusing on disease-modifying therapies targeting various forms of dementia and in particular Alzheimer's type. Ongoing clinical trials (Murukesu et al., 2020) are testing feasible and promising treatments capable to slow down the natural course of the disease.

This is why growing attention should be payed to scenarios frequently occurring in clinical practice.

Scenario 1

Asymptomatic patients at high risk of dementia. This definition is presently applicable to overall healthy patients carrying genetic mutations that are pathogenic for AD or frontotemporal dementia (FTD) (guidelines for the detailed description of high-risk patients are fully described in SINDEM consensus paper by Bocchetta et al., 2016). The asymptomatic stage must be verified by the administration of questionnaires for cognitive symptoms followed by accurate neuropsychological and neurological examinations. The Clinical Dementia Rating (CDR) scale must be 0. In the case of familiar history of dementia, a genetic counseling and testing shall be performed together with an accurate analysis of the age of onset of symptoms and the timing for starting therapy. If the family carries pathogenic mutations, the use of biomarkers is considered useful just for follow-up but not for diagnostic purposes. If we consider this status, an early onset Alzheimer's disease (EOAD) case (Stevens et al., 2011), in Italy, there are (2016) about 6,000 cases, 50% of which carry mutations of pathogenic genes.

Scenario 2

Patients with a prodromal stage of AD (IWG2) or mild cognitive impairment (MCI) prodromal to AD (NIA-AA). MCI is an intermediate stage between normal cognition and dementia, considered a clinical and neuropsychological condition typical of older persons' brain.

The neuropsychological evidence of memory impairment is the main characteristic of this condition that does not fully meet the criteria of dementia.

Recent studies indicate that mnesic MCI (aMCI) precedes Alzheimer's disease, with 50–60% of patients developing dementia and the remaining 50–40% stable in this condition or get back to normality.

Thus, it is fundamental to diagnose aMCI and to evaluate possibilities and timing of progression to dementia. The appropriate diagnosis will allow to plan organizational and rehabilitative interventions and to start therapies. The following criteria used to define MCI are based on cognitive questionnaires and screening tests [Mini-Mental State Exam (MMSE)], neuropsychological evaluation (including two tests for episodic memory, tests for language, visuospatial abilities, and behavioral scales with appropriate normative thresholds, functional scales, neurological examination, and CDR score of 0.5) (Cerami et al., 2017; Costa et al., 2017).

The capacity of identifying and diagnosing this condition in the first stages increases the probability of reducing health and social costs related to dementia.

Moreover, the ability to detect MCI can be harnessed in new clinical trials with potential disease-modifying experimental drugs. The combination of specific tests [i.e., hippocampal volumetric MRI, 18F-fluorodeoxyglucose (18F-FDG)-PET and lumbar puncture for cerebrospinal fluid (CSF) examination] is already helpful to identify MCI and predict its evolution into AD.

However, their widespread use in a large population is difficult given the high costs, low availability, and invasiveness. A meta-analysis conducted by an international consortium (Sachdev et al., 2013) has clarified the epidemiological features of MCI condition. Its prevalence in a population with 60 years and older is 5.9% and increases over time ranging from 4.5 to 7.1% in individuals of sixth and eighth decade, respectively. Based on such values, in 2016, around 735,000 Italians were estimated to be MCI clients. Another reason to target this type of patients (scenario 2) relies on the growing evidence that the prodromal stage seems the most responsive to experimental disease-modifying drugs (including those recently failed in the early/moderate AD stage).

Scenario 3

Patients with early AD condition defined by MMSE adjusted for age and education, score between 21 and 25/30, neuropsychological evaluation (including two tests for episodic memory, tests for language, visual–spatial abilities, and behavioral scales with appropriate normative thresholds, functional scales, neurological examination) and a CDR score of 1 (Cerami et al., 2017; Costa et al., 2017). In Italy, there are about 500,000 AD cases. Although it is not easy to count the participants in the early stage, using the CRONOS project, we can estimate that 60% of them—nearly 300,000 patients are in this stage (Vanacore et al., 2002).

Mild cognitive impairment and frailty require a multidomain approach including physical, nutritional, cognitive, and psychological one. It would be also important to start pharmacological and non-pharmacological treatments during the initial stages of cognitive frailty.

However, the need of standardized treatments is not supported by robust clinical trials.

Interaction Between Physical and Cognitive Frailty: Motoric Cognitive Risk Syndrome

Cognitive impairment should be considered as an intermediate stage between "normal" aging and advanced dementia. It is also known that cognitive decline, known as cognitive frailty, coexists or even is preceded by conditions of physical frailty such as low mobility and gait impairment. Therefore, these preclinical conditions should be considered as a unicum (Montero-Odasso et al., 2012).

Verghese et al. (2012) validated the motoric cognitive risk (MCR) syndrome, the combination of initial cognitive decline (but without a diagnosis of dementia) and relevant functional impairment in older persons. The authors considered four diagnostic criteria: cognitive complaints assessed with the

Consortium to Establish a Registry for Alzheimer's (CERAD) questionnaire (Rossetti et al., 2010), slow gait speed, preserved activities of daily living, and absence of dementia. In this study, older participants meeting the MCR criteria had a global risk of developing dementia about three times higher, and risk of developing vascular dementia increased by about 12 times (Verghese et al., 2013).

Clinical extrapyramidal and other neurological signs such as tone or strength alone do not predict dementia (Waite et al., 2001).

None of the patients with only slow gait, and then without cognitive disorders, developed vascular dementia. These data support the need of a global patient evaluation including cognitive and physical dimensions (Verghese et al., 2013).

Furthermore, these authors investigated cognitive and risk factors profiles of five different subtypes of MCR and their respective risk of incident cognitive impairment: slow gait velocity MCR (MCRv), short stride length MCR (MCRsl), slow swing time MCR (MCRsw), high stride length variability MCR (MCRslv), and high swing time variability MCR (MCRswv). The MCRswv was associated with incident memory impairment, strengthening the role of MCRswv as preclinical marker of Alzheimer's. One possible explanation is that oscillation time variability represents a higher level of gait control and proxy of cognitive function (Allali et al., 2016). Hippocampal regions, which oversee walking control, are damaged during early stages of Alzheimer's disease (Fox and Schott, 2004). MCRsl was a predictor not only of cognitive decline but also of visual–spatial impairment, which is a typical clinical picture of Parkinson's disease. These data are consistent with the notion that decreased stride length is the hallmark of synucleinopathies (Calabresi et al., 2006; Grabli et al., 2012; Allali et al., 2016).

Epidemiological population studies suggest that about 10% of the older persons are affected by MCR, and the presence of this syndrome represents a risk factor for disability (Verghese et al., 2014). Nowadays, MCR is detected with different tools and outcomes (**Table 1**) (Ferrucci et al., 2000; Jhoo et al., 2008; Callisaya et al., 2010; Herman et al., 2010; Montero-Odasso et al., 2011, 2018; Kowal et al., 2012; Meguro et al., 2012; Verghese et al., 2012; Bridenbaugh et al., 2013; Lord et al., 2013; Vannier-Nitenberg et al., 2013; Holtzer et al., 2014; Cruz-Jentoft and Sayer, 2019; Grande et al., 2020). Prevalence of MCR in Europe is around 8.0%, reaching 7.0% in the United States and 6.3% in Japan. It is estimated that the incidence is 65.2/1,000 inhabitants/year in people aged 60 or over (Maggio and Lauretani, 2019).

Figure 1 underlines the need of a comprehensive evaluation in older persons and the parallel detection of physical and cognitive frailty.

On the one side, low muscle strength could represent the *primum movens* of physical frailty given its role as determinant of slow gait speed, mobility decline, and increased risk of death (Lauretani et al., 2017).

Therefore, hand-grip strength and gait under dual tasking are measurements that should be part of global assessment of MCR syndrome, given their sensitivity to changes in brain function during early stages of the cognitive decline.

From the other side, Osawa et al. (2020) recently published the first longitudinal study in older people testing the correlation between brain volume modifications and changes in muscular strength. These authors found that areas of regional atrophy are related to knee extension isokinetic strength decline, supporting the potential contribution of regional brain atrophy in affecting age-related changes in muscle strength. These results could also imply that a greater rate of strength decline might indicate accelerated shrinkage in brain regions related to motor control (Osawa et al., 2020).

By considering together these findings and bearing in mind that preventing disability is the first goal of geriatric medicine, we should rapidly change our current approach in non-hospitalized patients with comprehensive evaluations and tailored pathways.

There are several European studies focusing on the identification and treatment of the frailty of the older adults and based on an integrated model of care.

In particular, the SUNFRAIL study developed a model and a tool to improve prevention, detection, and treatment of frailty and the management of multimorbidity (Maggio et al., 2020).

Cross-Talk Between Brain and Skeletal Muscle: The Unifying Role of Exercise and Growth-Neurotrophic Factors

Physical inactivity and sedentary behavior are among the most important risk factors for disability and dementia. Several chronic diseases such as type 2 diabetes and hypertension accelerate the onset and progression of motoric disability and cognitive impairment. All this information implies that physical exercise can exert a protective action against muscle loss and dementia acting on modulation of endothelial function and cross-talk molecules of the so-called "brain–muscle axis" (Yan et al., 2020) (**Figure 2**).

Physical activity stimulates brain-derived neurotrophic factor (BDNF) either at central and peripheral level (Delezie and Handschin, 2018).

Central BDNF can use TrkB and p75NRT receptors to improve learning and memory (Yang et al., 2009). Muscle BDNF is produced and secreted by human skeletal muscle in response to exercise. It enhances fat oxidation within the muscle and development of the muscle itself. Moreover, physical exercise directly or indirectly via molecular messengers (the PGC-1 alfa or the AMPK) induce the production of several proteins such as irisin, cathepsin-B, Kina, and β-hydroxybutyrate, all triggers of BDNF production (Boström et al., 2012; Chavan et al., 2016; Moon et al., 2016). The lactates produced in response to physical exercise enhance the production of vascular endothelial growth factor (VEGF) that, together with BDNF and insulin-like growth factor-1 (IGF-1), can increase cell growth and neuronal plasticity (Bibel and Barde, 2000).

Type of Exercise

Some studies showed that several weeks of resistance exercise in community older persons improve gait and decrease the fall risk (Cadore et al., 2013). In institutionalized older adults with dementia and cognitive impairment, multicomponent

TABLE 1 | Tests used in the main studies for the diagnosis of motoric cognitive risk syndrome and related clinical outcomes (modified from Verghese et al., 2014).

	Study	Assessment Method		Outcomes
		Physical function	Cognitive complaint	
Cognitive Frailty				
79	Italy (INTERCEPTOR Project), 2020		CDR = 0.5 (presence of mild cognitive impairment)	Conversion to Alzheimer's disease: CDR = 1
Motoric Frailty				
58	Europe (SPRINTT Project), 2018	SPPB (score between 9 and 3) and ability to walk for 400 m in <15 min		Occurrence of motoric disability: inability to walk for 400 m in <15 min and/or loss of one or more points of SPPB score
Cognitive and Motoric Frailty				
10	Australia (TASCOG), 2005	Instrumented walkway (GAITRite)	GDS	Clinical diagnosis of dementia
60	Canada, 2007	Instrumented walkway (GAITRite)	Self-report cognitive questionnaire	DSM-IV diagnosis of dementia
61	Canada, 2018	Instrumented walkway (GAITRite)	Mini-mental state examination and the montreal cognitive assessment	Onset of motoric cognitive risk syndrome
42	China (SAGE), 2007	4-m timed walk	Self-report cognitive questionnaire	Clinical diagnosis of dementia
86	France (GAIT), 2009	Instrumented walkway (GAITRite)	Self-report cognitive questionnaire	DSM-IV diagnosis of dementia
42	Ghana (SAGE), 2007	4-m timed walk	Self-report cognitive questionnaire	Clinical diagnosis of dementia
88	India (KES), 2011	10-ft timed walk	GDS	DSM-IV diagnosis of dementia
42	India (SAGE), 2007	4-m timed walk	Self-report cognitive questionnaire	Clinical diagnosis of dementia
38	Israel (2 cohorts), 2003	10-m timed walk	GDS	DSM-IV diagnosis of dementia
		Instrumented walkway (GAITRite)	GDS	DSM-IV diagnosis of dementia
27	Italy (InCHIANTI), 1998	4-m timed walk	WHO Disability Scale	DSM-IV diagnosis of dementia
59	Japan, 2008	6-m timed walk	Self-report cognitive questionnaire	DSM-IV diagnosis of dementia
41	Korea (KLOSHA), 2005	4-m timed walk	Self-report cognitive questionnaire	DSM-IV diagnosis of dementia
42	Mexico (SAGE), 2007	4-m timed walk	Self-report cognitive questionnaire	Clinical diagnosis of dementia
42	Russia (SAGE), 2007	4-m timed walk	Self-report cognitive questionnaire	Clinical diagnosis of dementia
42	South Africa (SAGE), 2007	4-m timed walk	Self-report cognitive questionnaire	Clinical diagnosis of dementia
35	Sweden (SNAC-K), 2020	4-m timed walk	Free recall, trail making test part B, category and letter fluency, mental rotation, digit cancelation, and pattern comparison	Diagnosis performed if the score is 1.5 standard deviation below age-specific means on ≥ 1 cognitive domains
6	Switzerland, 2007	Instrumented walkway (GAITRite)	GDS	DSM-IV diagnosis of dementia
51	United Kingdom, 2007	Instrumented walkway (GAITRite)	GDS	DSM-IV diagnosis of dementia
39	USA (CCMA), 2011	Instrumented walkway (GAITRite)	GDS and AD8	DSM-IV diagnosis of dementia

exercise has been shown to increase functional capacity and executive functions by decreasing the risk of falling also (Cadore et al., 2014).

Therefore, in patients with dementia, multicomponent exercise program is able to parallel improve cognitive and functional status (Casas-Herrero et al., 2019).

Future Prospective

Severe forms of global inability are usually triggered by the development of mobility disability. Thus, preventing mobility disability is an important target to prevent advanced disability.

For this reason, a project consisting in a randomized controlled trial (RCT) and named SPRINTT tested the effectiveness of a multicomponent intervention (MCI) in older persons with physical frailty and sarcopenia (Landi et al., 2017).

DISCUSSION

Organizational Response Path and Professionals Involved: The Response of Parma Health Trust

All presented data show that the more delayed are the interception and treatment of frailty, the lower are the therapeutic margin and the probability of preventing the

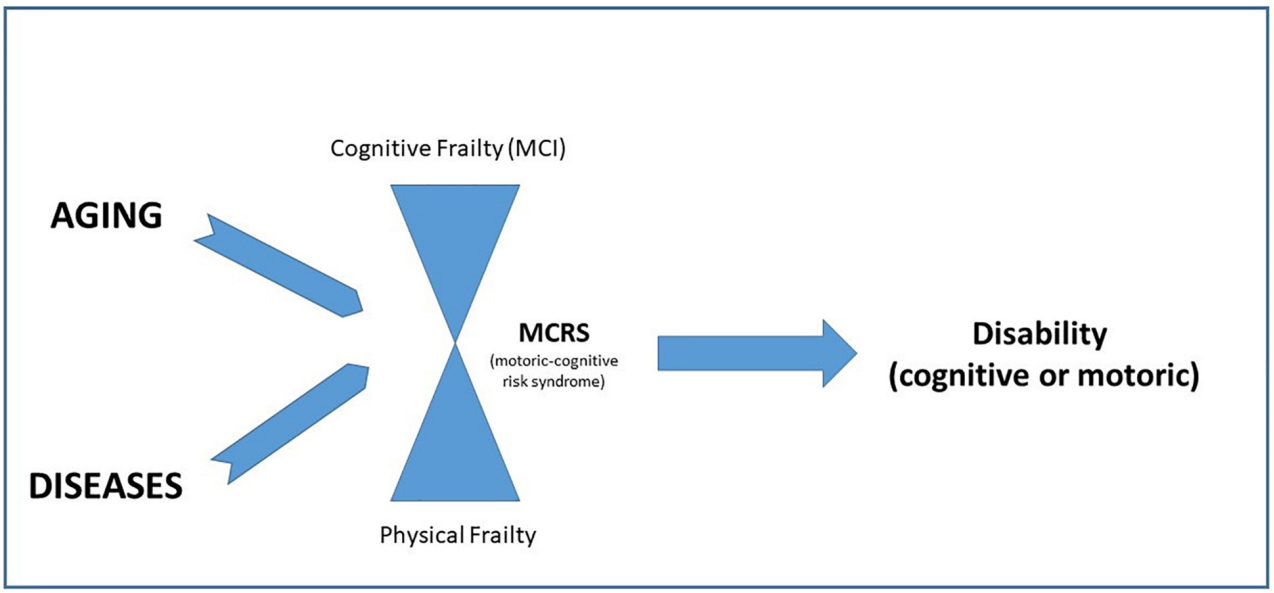

FIGURE 1 | The interaction between cognitive and physical frailty in the evolution toward disability.

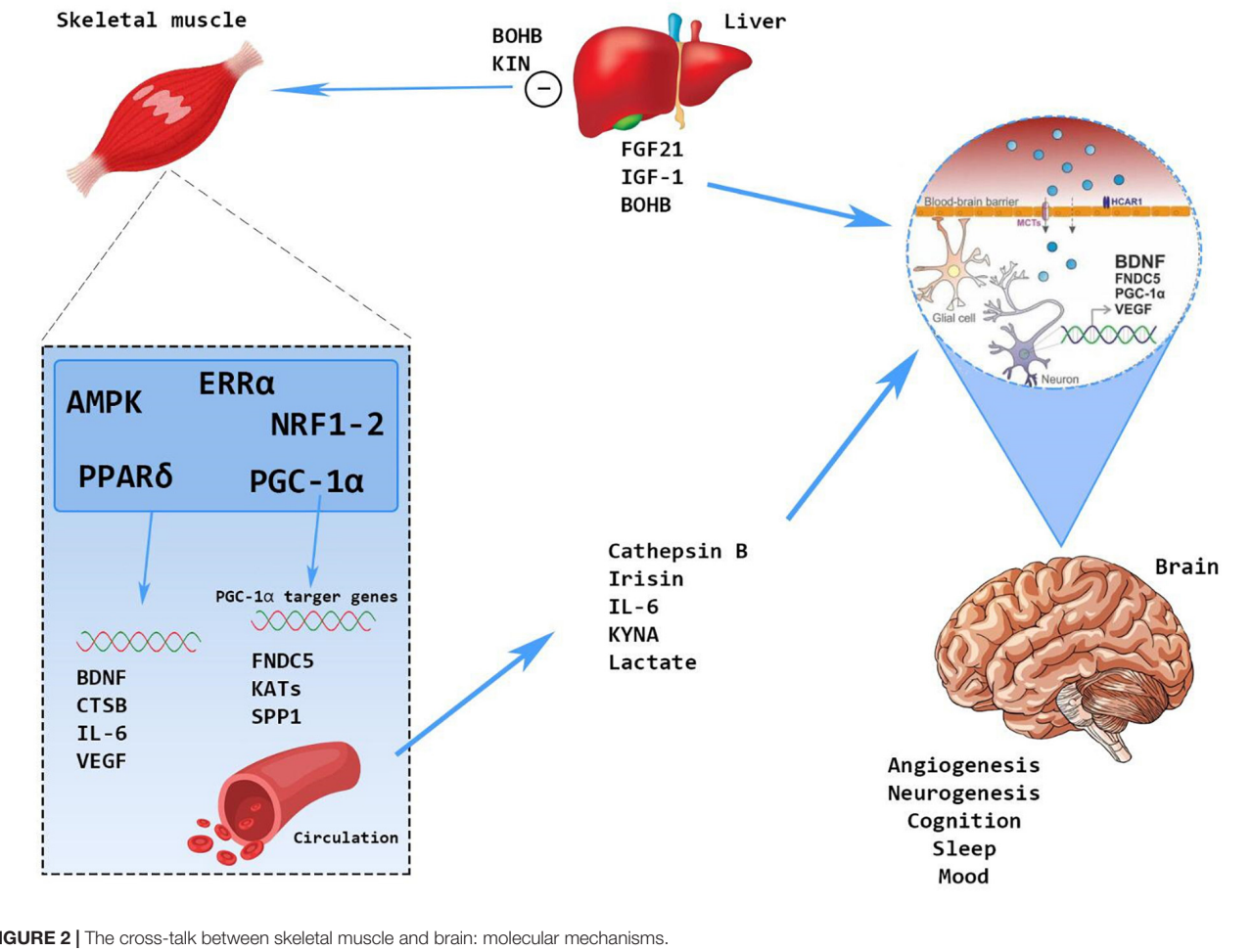

FIGURE 2 | The cross-talk between skeletal muscle and brain: molecular mechanisms.

commonest frailty adverse events (disability, dementia, and hospitalization).

However, today, the health response to frailty is mainly reactive and is targeting acute late events of frailty. This obviously represents an episodic service completely unable to meet the care needs of these citizens.

A paradigm shift is needed to address the phenomenon of frailty, moving from a "reactive" to a "proactive" model.

Prevention programs and early intervention strategies devoted to face frailty should be implemented in primary care in order to increase the therapeutic margin of these patients and even the appropriateness of hospital admissions (Di Bari et al., 2014).

Nowadays, there are only fragmented care pathways for frailty in the primary care setting, and the existing organizing models consider physical and cognitive domains separately (with Frailty and Motoric Lab devoted to mobility limitation and disability and Cognitive Lab for the rapid assessment and care of Dementia) (Lauretani et al., 2017). These approaches also divide primary care physicians and specialists in Internal and Geriatric Medicine and do not account for the crucial close interaction between domains and disciplines (Lauretani et al., 2017; Grande et al., 2019).

In this perspective, proactive and cost-effective screening programs of both cognitive and physical frailty in older persons would allow the early detection of those who need measures of disability prevention.

For these reasons, the Parma Health Trust of Emilia Romagna Region aims to implement an organizational path that considers both cognitive and physical frailty as a whole, where the community and hospital should fully cooperate in all phases of detection and treatment of frailty by integrating competences and adopting easy to use approaches and methodology.

First Phase: Identification of Frailty

The first phase can only start in the context of primary care, the closest context to living environment of the older persons.

Recent studies have shown the efficacy of the SUNFRAIL Screening Tool in appropriately detecting the citizens needing a more in-depth evaluation, thanks to its negative predictive value of 84.6% (Maggio et al., 2020).

This assessment of frailty in the primary care should be conducted by the general practitioner or, when present, a community nurse (Obbia et al., 2020). After the administration of the SUNFRAIL Tool, the suspect of frailty condition should induce these professionals to move into a second-level comprehensive geriatric assessment (Cesari et al., 2016).

This type of assessment, which can be carried out both in the community and in the hospital, should be performed by a multidisciplinary team in order to ensure a combined and in-depth evaluation of motoric and cognitive functions (Pilotto et al., 2017).

During the visit, the following domains should be assessed:

- Physical function: conducted mainly by the geriatrician and the nurse, this type of evaluation must at least investigate the balance, the strength of the lower and upper limbs, and the characteristics of the gait. Crucial is also the pharmacological recognition and reconciliation operated by the geriatrician. This professional figure, when suspects sarcopenia, could prescribe BIA or DEXA examination to confirm the presence of low muscle mass.
- Cognitive function: the neuropsychologist and, where present, the neurologist should perform a complete cognitive, depression, and IADL assessment in order to identify mild cognitive impairment. Brain CT should be included in the diagnostic process together with the assessment of quality of life.

Second Phase: Treatment of Frailty

Similarly to diagnostic evaluation, the treatment of frailty requires a multidisciplinary approach, starting from the community that is the ideal setting in this regard.

Physical activity is the most effective treatment for physical frailty. Regular adherence to physical activity programs improves balance, functional autonomy, mood, and cognitive performance (Landi et al., 2017; Alhambra-Borrás et al., 2019; Casas-Herrero et al., 2019).

Depending on the conditions of the patient, physical activity can be administered by motor scientists or physiotherapists, with the potential advice of a physiatrist, and requires the supervision of geriatricians and multiprofessional team for ensuring the safety and the effectiveness of the intervention.

In cases of sarcopenia, physical activity needs to be accompanied by nutritional intervention, held by a nutritionist or a dietician, in order to guarantee the correct intake of protein, essential amino acids, vitamin D, and micronutrients (Landi et al., 2017).

Finally, an intervention conducted in patients at risk of dementia should be based on memory training and managed by a neuropsychologist. Also in these cases, nutritional intervention produces a good response in terms of cognitive performance (Ng et al., 2015).

Three different case scenarios can better explain why the current approach considering physical and cognitive domain separately should be changed in the next future.

Case Scenarios and Current and Hypothetical Organization Models and Contexts

Outpatient Evaluation in the Context of a Clinical Study on Physical Frailty

Male patient, in the age range of 70–80 years old, independent in daily activities with history of falls. This patient was admitted to the Frailty and Morbidity Laboratory of the University-Hospital of Parma, where clinical evaluation was performed (**Table 2**).

The multidisciplinary team was composed of a geriatrician, a nurse, and nutritionist; the routine biochemical tests were normal. The patient also underwent DEXA scan that was suggestive of sarcopenia according to the Foundation for the National Institutes of Health (FNIH) criteria. The team agreed on the diagnosis of sarcopenia and physical frailty with lower limbs strength as potential factor explaining the history of falls.

TABLE 2 | Most relevant parameters of the clinical evaluation performed in Frailty and Multimorbidity Laboratory of Hospital of Parma—first case.

Vital Signs	Blood pressure: 140/90 mmHg; heart rate: 73 bpm; ambient air oxygen saturation: 98%
Physical examination	Normal
BMI	41.54—class 3 obesity
Pharmacological therapy	Atenolol, Doxazosin, Simvastatin
MMSE	30/30
SPPB score	Balance: 4/4; gait speed: 4/4; Chair test: 1/4; Total: 9/12 expressive of physical frailty
ADL	6/6
IADL	8/8
MNA-SF	14/14—no risk of malnutrition

BMI, body mass index; MMSE, mini-mental state examination; SPPB, short physical performance battery; ADL, activities of daily living; IADL, instrumental activities of daily living; MNA-SF, mini nutritional assessment short form.

A cardiologist visited the patient in order to evaluate the safety of a physical-exercise-based intervention. The ambulatory blood pressure monitoring (ABPM) showed normal blood pressure (126/75 mmHg). The cardiologist also diagnosed a left ventricular hypertrophy not precluding the physical activity intervention.

The patient also underwent a complete nutritional visit in order to adhere to a personalized diet based on caloric restriction but with and adequate protein intake.

Finally, a motor scientist prepared a specific exercise program, composed of aerobic and resistance exercises, with sessions regularly performed in the clinic's gym and at home.

Outpatient Evaluation in a Cognitive Frailty Clinic: Diagnosis and Treatment

Female patient, in the age range of 80–90 years old, living alone, and independent in daily activities.

The patient had history of falls and fractures in the previous 2 years, subjective cognitive decline in the focusing and capacity.

This patient was admitted to the Cognitive Frailty Clinic Hospital of Parma, where a clinical evaluation was performed (**Table 3**).

The patient underwent second-level neuropsychological assessment, which revealed the presence of multiple cognitive deficits (linguistic, praxic, attentional, and executive) and, together with preserved functionality, allowed the suspicion of extra-mnestic MCI, minor neurocognitive damage.

The multidisciplinary team, composed of a geriatrician, a nurse, and a neuropsychologist, agreed to suggest a cognitive stimulation-training-based intervention and a close follow-up as also suggested by the Interceptor project having Parma as participating sites (Rossini et al., 2019).

Integrated evaluation of Physical and Cognitive Frailty: A Future Model

Female patient, in the age–range of 80–90 years old, independent in daily activities.

The patient has history of falls and fractures in the previous 2 years, subjective cognitive decline in the mnestic domain.

TABLE 3 | Most relevant parameters of the clinical evaluation—second case.

Vital Signs	Blood pressure: 145/80 mmHg; heart rate: 60; oxygen saturation: 97%
Neurological examination	Romberg+
Pharmacological therapy	Folic acid, Propranolol, Lansoprazole, Atorvastatin, Timolol, Mesalazine, Rifaximin, Levothyroxine sodium
MMSE	28/30–27.1/30 adjusted, suggestive of normal cognitive functions
CDT	1/3, suggestive of a cognitive impairment

MMSE, mini-mental state examination; CDT, clock drawing test.

TABLE 4 | Most relevant parameters of the clinical and biochemical evaluation—third case.

Vital Signs	Blood pressure: 150/80 mmHg; heart rate, 70; ambient air oxygen saturation: 97%
Physical examination	Normal
Biochemistry analysis	Total cholesterol, 203 mg/dl; triglycerides, 168 mg/dl; Mg^{2+}, 3.5 mg/dl; vitamin D, 23 ng/ml
Pharmacological therapy	Alendronate and cholecalciferol (for 10 years), SSRI, benzodiazepine as needed, statin and acetylsalicylic acid
MOCA	16.5, suggesting a scarce performance in visual–spatial, mnestic and temporal orientation domains.
SPPB score	Balance: 4/4; gait speed: 4/4; chair test: 3/4; total: 11/12 expressive of absence of physical frailty
ADL	6/6
IADL	6/8

SSRI, selective serotonin reuptake inhibitors; BP, blood pressure; HR, heart rate; SPPB, short physical performance battery; Mg, magnesium; MOCA, Montreal Cognitive Assessment; ADL, activities of daily living; IADL, instrumental activities of daily living.

TABLE 5 | Second-level cognitive–physical assessment.

Brain CT scan	**No signs of cerebrovascular disease.**
Nutritional status assessment and anthropometry	BMI, 25.6; MNA-SF: 13/14; analysis of 3-day dietary records revealed a total kcal/day: 1,340 (25–30 kcal/kg with a daily protein intake was 0.88 g/kg body weight).
Body composition and sarcopenia assessment	SMI, 6.78 kg/m^2 obtained by BIA; handgrip test, 11 kg
Neuropsychological evaluation	Multiple cognitive impairments mnestic and extramnestic (executive and praxic), with a reduction in the instrumental activities of daily living
NPI	26/144, moderate anxiety, disinhibition, irritability associated with moderate aberrant motor activity

CT, computed tomography; MNA, mini nutritional assessment; SMI, skeletal mass index; BIA, bioelectrical impedance; NPI, neuropsychiatric inventory.

In this patient, a first clinical evaluation was performed in the context of primary care setting. Then, she was admitted to the Frailty and Morbidity Laboratory of Hospital of Parma, with blood chemistry evaluation (**Table 4**).

Alendronate was deprescribed given the 7-year treatment in the history and low vitamin D levels, and the patient underwent second-step analysis as reported in **Table 5**.

The multidisciplinary team was composed of a geriatrician, a neuropsychologist, a nutritionist, and a physical therapist. The multidisciplinary team agreed on the diagnosis of major cognitive

disorder associated with behavioral and psychological symptoms of dementia and muscle dysfunction with lower handgrip strength. This pathological condition could have explained the history of falls and allowed the diagnosis of possible/probable Alzheimer's disease.

The correct treatment of major neurocognitive disorder (pharmacological and non-pharmacological) and psychological symptoms of dementia was started by the multidisciplinary team.

The pharmacological therapy can be summarized as follows:

(1) Evaluation of the current pharmacological treatment with deprescription of alendronate and beginning of 25-hydroxycholecalciferol vitamin D supplementation to reduce the risk of osteoporotic fractures and falls;
(2) Specific treatment with acetylcholinesterase inhibitors, after a cardiac examination.

Non-pharmacological intervention consisted of motoric exercises for improving balance, motor coordination, and ability on ideation of motoric programs.

CONCLUSIVE REMARKS

This paper aims to show a possible treatment model based on integrated motoric cognitive approach in order to stimulate this new vision and to proactively manage community-dwelling older persons with suspected frailty.

AUTHOR CONTRIBUTIONS

FL and MM contributed to the conception and design of the work, the acquisition, analysis, and interpretation of data for the work, drafting the work or revising the work critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved. YL, FFP, AD, CF, RF, EG, UL, GR, MR, MS, IZ, and GP contributed to the acquisition, analysis of data for the work, revising the work critically for important intellectual content, and final approval of the version to be published. All the authors have read and agreed to the published version of the manuscript.

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The Mediating Effect of Physical Function Decline on the Association Between Social Activity and Cognitive Function in Middle and Older Korean Adults: Analyzing Ten Years of Data Through Multivariate Latent Growth Modeling

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Purpose: This study aimed to examine the long-term association between social activity, physical function decline and cognitive function, as well as verify the long-term mediating effect of physical function decline on the relationship between social activity and cognitive function.

Methods: Data from the Korean Longitudinal Study of Aging (KLoSA) that was collected over 10 years was analyzed. The sample included 10,240 adults aged 45–93 years (Mean age = 61.66 [SD = 11.061]). Multivariate latent growth modeling (LGM) was applied to verify the long-term effect of social activity and physical function on cognitive function.

Results: The results revealed that social activity had a positive impact on cognitive function and negative impact on physical function decline after controlling for age and education level. Additionally, physical function decline negatively influenced cognitive function. Finally, social activity indirectly affected cognitive function through physical function decline.

Conclusion: The contribution of this study was to test the long-term effect social activity on physical and cognitive function.

Keywords: social activity, physical function, cognitive function, latent growth modeling, elderly

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INTRODUCTION

Decreased physical and cognitive function are major issues associated with aging (Clouston et al., 2013; Kim, 2016). Therefore, researchers have explored modifiable variables that prevent physical and cognitive decline. Previous research has examined the relationship of social activity with physical and cognitive function (Glei et al., 2005; Bidzan et al., 2016; Frith and Loprinzi, 2017;

Abbreviations: IADL, Instrumental activities of daily living; KLoSA, The Korean Longitudinal Study of Aging.

Bidzan-Bluma and Lipowska, 2018; Dugan et al., 2018) and social activity may be a key factor mitigating physical and cognitive decline.

Social activity refers to various activities in social situations, such as participation in social organizations (e.g., civic organization), interactions with friends, and leisure and hobby activities (Glei et al., 2005; Bidzan et al., 2016; Su et al., 2018). Past studies have verified the effect of social activity on cognitive function and impairment (Hsu, 2007; Fu et al., 2018). In particular, the 3-year Monongahela-Youghiogheny Healthy Aging Team (MYHAT) study revealed that the frequency of engagement in social activities was negatively related to the risk of cognitive impairment (Hughes et al., 2013). In addition, a longitudinal and population-based study by Glei et al. (2005) revealed that social activities such as socializing with friends, performing volunteer work, and participating in religious, political, and elderly organizations helps preserve cognitive function in older adults.

Social activity could also mitigate decline in physical function. Social activities provide opportunities for maintaining physical function, and, as a result, they help preserve physical function (Tomioka et al., 2017). In other words, social activities may prevent motor function decline and loss of the ability to perform activities of daily living (Tomioka et al., 2016). Indeed, previous research has found that social activities (or social participation) are negatively associated with physical function decline (James et al., 2011; Fujihara et al., 2018; Tomioka et al., 2018).

Physical function is well known as a key predictor of cognitive function. Physical function is basic physical ability for activity and includes basic activities of daily living and instrumental activities of daily living (IADL) such as shopping, handling money, and transportation utilization (Bidzan et al., 2016; Bae et al., 2019). Actually, past studies verified the relevance between physical function and cognitive function (Grande et al., 2014; Vancampfort et al., 2017, 2018). Inversely, decreased physical function was positively related to cognitive impairment.

Based on previous research, social activity can directly influence cognitive function and may have an indirect impact on cognitive function through physical function (Glei et al., 2005; Fujihara et al., 2018; Su et al., 2018). However, there is a lack of understanding of the specific relationship between the three variables. In particular, the long-term mediating effect of physical function on the relationship between social activity and cognitive function has not been confirmed.

In order to accurately test the association between social activity, physical function, and cognitive function, confounding variables should be controlled. In particular, age and education are related to cognitive function. Previous studies have verified that age is positively related to cognitive impairment and education are negatively associated with cognitive decline (Grande et al., 2014; Xiang and An, 2015; Chen and Chang, 2016).

The object of this study was to verify the mechanism whereby social activity affects cognitive function. In other words, this study examined the long-term mediating effect of physical function decline on the relationship between social activity and cognitive function using multivariate latent growth modeling (LGM). LGM is a powerful method for analyzing the relationship between changes in latent factors over time.

MATERIALS AND METHODS

Participants and Survey

Data from the Korean Longitudinal Study of Aging (KLoSA) (Shin et al., 2016) conducted by the Korea Employment Information Service, were used in this study. The KLoSA was performed biennially from 2006 to 2016 and included adults nationwide aged 45 and older. The KLoSA measured the social, economic, psychological demographic characteristics and health status of the elderly. The sample was extracted from 1,000 survey sites based on population proportions from the 2005 Population and Housing Census. Trained professional interviewers visited the household and explained the purpose of the survey. The survey was conducted using a computer assisted personal interviewing (CAPI) using a notebook computer. Participants signed consent forms and the interviewer confirmed that the subject completed the survey. Data from adults aged 45 to 93 were utilized in final analysis. A total of 10,240 people (Mean age = 61.66 years [SD = 11.06]; 4463 men, 5777 women) participated in 2006, and the response rate was 84.78% (Mean age = 63.62 years [SD = 10.88]; 8681 people; 3766 male, 4915 female) in 2008, 77.29% (Mean age = 65.25 years [SD = 10.52]; 7915 people; 3411 male, 4504 female) in 2010, 73.08% (Mean age = 66.79 years [SD = 10.20]; 7484 people; 3215 male, 4269 female) in 2012, 68.63% (Mean age = 68.29 years [SD = 9.90]; 7028 people; 2987 male, 4041 female) in 2014, and 64.62% (Mean age = 70.80 years [SD = 9.60]; 6617 people; 2781 male, 3836 female) in 2016. Reasons for dropouts included death, disease, and loss of contact, and the number of deaths in each wave were as follows: 187 people in the 2nd wave, 309 in the 3rd, 327 in the 4th, 438 in the 5th, and 403 in the 6th.

Measures

Physical Function Decline

The Korean IADL was used to measure decline in physical function (Shin et al., 2016); this list is a revision of the original IADL by Lawton and Brody (1969). The inventory consists of ten items on a 3-point scale, ranging from 1 (can do without help) to 3 (need full help). The items address housework, cooking, shopping, washing clothes, utilization of public transportation, and handling money. Higher total scores indicate greater physical function decline.

Social Activity

The five items was used to measure the frequency of participation in social activities. This measure consists of seven items on a 10-point scale (1 = no activity, 6 = once a month, 10 = almost every day). The questionnaire assesses social activities including religious activity, volunteer work, political/civic organization activities, meeting with friends and acquaintances, and leisure/culture/sports organization activities (Lin, 2017). Higher total scores indicate more frequent participation in social activities.

Cognitive Function

In order to measure the degree of cognitive impairment, the Korean version of the Mini-Mental Status Exam was used (Kang et al., 1997). The measure consists of the following subscales: orientation, verbal memory, concentration and calculation, language, praxis, and visuospatial construction. Total scores range from 0 to 30, and a higher total score indicates higher cognitive function.

Control Variables

Age was measured as continuous variable ranging from 45 to 93 years. Education was coded as a nominal variable (1 = below middle school graduation, 2 = high school graduation or above). Sex was coded as a dummy variable (male = 0, female = 1).

Analysis

Independent-sample *t*-tests and ANOVA were conducted to test the differences in cognitive function by age, gender, education, marital status, and religion in baseline (2006 year). LGM by the AMOS 20.0 program was used to verify the trajectories (change trend) in a variable and the associations between changes in the parameters of variables. Parameters comprise an intercept and slope. LGM can verify the direct effect of intercept of one latent factor on the intercept and slope of another latent factor. LGM also can test the direct effect of slope of one latent factor on the slope of another latent factor. In the first step, univariate LGM was performed to test the change trajectories in social activity, physical function decline, and cognitive function, and compared the fit of a no growth and a linear growth model. In the second step, multivariate LGM was conducted to test the relevance between latent factors. Full-information maximum likelihood, which is an efficient and unbiased method, was used to estimate parameters. The fit of the research model (**Figure 1**) was verified based on the chi-square value, the Tucker-Lewis index (TLI), comparative fit index (CFI), and root mean square error of approximation indices (RMSEA). TLI and CFI are deemed acceptable (good or excellent) if they have values higher than 0.95, and RMSEA is acceptable (good or excellent) if it is lower than 0.05 (Hong, 2000). Finally, A Bootstrapping test was conducted to examine the indirect effects of physical function decline on the relationship between social activity and cognitive function. The direct effect is significant when a zero value is not included in the confidence interval.

RESULTS

t-Tests and ANOVA

Descriptive statistics such as minimum and maximum values, mean, and standard deviation are presented in **Table 1**. *T*-test

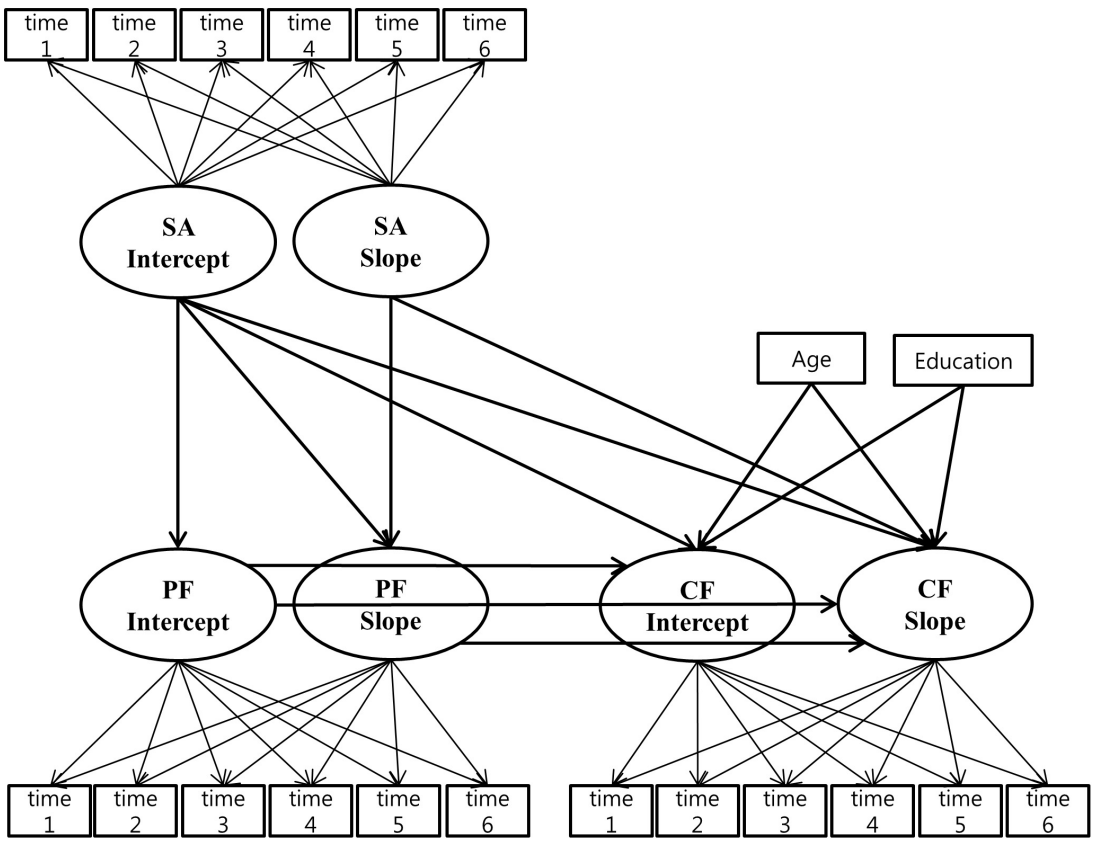

FIGURE 1 | Multivariate latent growth model. PF, physical dysfunction; SA, social activity; CF, cognitive function.

TABLE 1 | Descriptive statistics of the variables.

	Min	Max	Mean	SD	*N*
PF1(2006)	10	50	11.63	5.801	10240
PF2(2008)	10	50	11.66	5.979	8681
PF3(2010)	10	50	11.84	6.602	7915
PF4(2012)	10	50	11.79	6.448	7483
PF5(2014)	10	50	11.92	6.671	7028
PF6(2016)	10	50	11.99	6.654	6617
SA1(2006)	0	32	4.30	4.463	10240
SA2(2008)	0	27	4.22	4.018	8681
SA3(2010)	0	28	3.82	3.748	7915
SA4(2012)	0	37	3.87	3.750	7483
SA5(2014)	0	31	3.96	3.646	7028
SA6(2016)	0	24	3.80	3.671	6617
CF1(2006)	0	30	25.43	5.324	10033
CF2(2008)	0	30	25.20	5.303	8370
CF3(2010)	0	30	25.12	5.514	7484
CF4(2012)	0	30	25.30	5.516	7112
CF5(2014)	0	30	25.09	5.605	6657
CF6(2016)	0	30	25.09	5.521	6278

PF, Physical dysfunction; SA, Social activity; CF, Cognitive function.

results indicated that that cognitive function was higher in men than in women ($p < 0.0001$), higher in married people than those living alone ($p < 0.0001$), and higher in people with higher education than high school graduates ($p < 0.0001$), while people with religion had higher cognitive function than those without ($p < 0.0001$). As a result of ANOVA, there was no difference in cognitive function according to age (**Table 2**).

The Changing Patterns of the Variables

A univariate LGM was performed to identify the trajectories of the variables, and the results are described in **Table 3**. Based on past studies and the mean trend in each variable, we compared the linear growth model and no growth model. First, the fitness of linear growth model of physical function decline was better than no growth model, which means that physical function decline increased linearly over time. Second, the fit of linear growth model of social activity was better than no growth model. In other words, social activity decreased linearly from wave 1 to 6. Third, the fitness of linear growth model of cognitive function was better than no growth model. That is, cognitive function decreased linearly over time.

Verification of the Mediation Effects by a Multivariate LGM

Fitness of the Mediation Model

The chi-square value for the research model was 611.208 ($df = 87$), and the alternative hypothesis was rejected. However, the TLI and CFI were 0.984 and 0.993, and the RMSEA was 0.024 (LO = 0.022, HI = 0.026). Based on these indexes, the fitness of the research model was acceptable (**Figure 1**).

Direct Effect Between Variables

Figure 1 shows pathways for direct effects between intercepts and slopes of latent factors. The direct effects are indicated in **Table 4**. First, the intercept of social activity had a negative impact on the intercept of physical function decline ($\beta = -0.401$, $t = -18.193$, $p < 0.001$). The rate of change of social activity had a negative impact on the rate of change of physical function decline ($\beta = -0.397$, $t = -10.827$, $p < 0.001$). This indicates that social activity was negatively related to physical function decline in baseline and greater increase in social activity was related to a greater decrease in physical function decline over time.

Second, the intercept of social activity had a positive impact on the intercept of cognitive function ($\beta = 0.077$, $t = 4.466$, $p < 0.001$). The rate of change of social activity positively impacted the rate of change of cognitive function ($\beta = 0.524$, $t = 19.403$, $p < 0.001$). This indicates that social activity was positively associated with cognitive function in baseline and a greater increase in social activity was related to a greater increase in cognitive function.

TABLE 2 | *T* tests and ANOVA in MMSE for socio-demographic variables.

			MMSE		*p*-value
	N	%	Mean	SD	
Age					<0.0001
45–54	3249	32.1	28.03	2.61	
55–64	2748	27.2	26.56	3.85	
65–74	2646	26.2	24.21	5.16	
≥75	1398	14.4	19.41	7.24	
Gender					<0.0001
Male	4463	43.5	26.64	4.36	
Female	5791	56.5	24.48	5.82	
Education					<0.0001
≤Elementary	4832	47.1	22.77	6.12	
Middle school	1657	16.2	27.06	3.29	
High school	2708	26.4	27.91	2.96	
≥College	1057	10.3	28.49	2.37	
Marital status					<0.0001
Married	7971	77.7	26.34	4.43	
Single (including separated, divorced)	2283	22.3	21.97	6.83	
Religion					
Yes	5680	55.4	25.71	4.97	<0.0001
No	4574	44.6	25.06	5.75	
Total	10254	100.0	25.42	5.34	

TABLE 3 | Comparisons of fitted growth curve models for the variables.

Variable	Model	χ^2 (df)	df	TLI	CFI	RMSEA
Physical dysfunction	No growth	1764.505	12	0.857	0.886	0.119
	Linear growth	494.734	10	0.953	0.968	0.069
Social activity	No growth	733.015	12	0.944	0.955	0.077
	Linear growth	155.322	10	0.987	0.991	0.038
Cognitive function	No growth	1043.296	12	0.950	0.960	0.092
	Linear growth	279.220	10	0.984	0.990	0.051

TABLE 4 | Path coefficients of multivariate latent growth modeling.

Path	β	B	S.E.	C.R.
SA intercept → PF intercept	−0.401	−0.263	0.022	−18.193***
SA intercept → PF slope	0.034	−0.093	0.007	−4.717***
SA slope → PF slope	−0.397	−0.219	0.037	−10.827***
SA intercept → CF intercept	0.077	0.055	0.017	4.466***
SA intercept → CF slope	0.076	0.268	0.006	13.661***
SA slope → CF slope	0.524	0.375	0.027	19.403***
PF intercept → CF intercept	−0.407	−0.446	0.015	−26.658***
PF intercept → CF slope	0.046	0.249	0.005	10.151***
PF slope → CF slope	−0.352	−0.457	0.018	−19.618***
Age intercept → CF intercept	−0.201	−0.556	0.005	−44.487***
Age intercept → CF slope	0.018	0.239	0.001	15.100***
Education intercept → CF intercept	1.125	0.134	0.108	10.428***
Education intercept → CF slope	−0.002	−0.001	0.028	−0.057
Sex intercept → CF intercept	−1.462	−0.182	0.072	−20.174***
Sex intercept → CF slope	0.207	0.126	0.019	10.792***

$^{***}p < 0.001$; PF, physical dysfunction; SA, social activity; CF, cognitive function.

Third, the intercept of physical function decline had a negative impact on the intercept of cognitive function (β = −0.407, t = −0.26.658, $p < 0.001$). The rate of change of physical function decline negatively influenced the rate of change of cognitive function (β = −0.352, t = −19.618, $p < 0.001$). This indicates that physical function decline was negatively related to cognitive function in baseline and greater increase in physical function decline was associated with a greater decrease in cognitive function.

Finally, the intercept of age had a negative impact on the intercept of cognitive function (β = −0.201, t = −44.487, $p < 0.001$). The intercept of age positively impacted the rate of change of cognitive function (β = 0.018, t = 15.100, $p < 0.001$). This indicates that higher age in the first wave was related to a greater decrease in cognitive function over time. In addition, the intercept of education level had a positive impact on the intercept of cognitive function (β = 1.125, t = 10.428, $p < 0.001$). The intercept of education level had no effect on the rate of change of cognitive function (β = −0.002, t = −0.057, $p > 0.05$). This indicates that a higher level of education was positively associated with cognitive function in the first wave. The intercept of sex had a negative influence on the intercept of cognitive function (β = −1.462, t = −20.174, $p < 0.001$) and positively affected the rate of change of cognitive function (β = 0.207, t = 10.792, $p < 0.001$). The results indicate that cognitive function was lower in female participants than male ones.

Indirect Effect of Physical Function Decline

A bias-corrected bootstrap test was performed to examine the mediating effect of physical function decline on the association between social activity and cognitive function. The indirect effect of the initial value of social activity had a positive impact on the initial value of cognitive function through the initial value of physical function decline (β = 0.117, $p < 0.01$, CI = LO.105, UP.135). Also, the direct effect of the initial value of social activity influenced the initial value of cognitive function (β = 0.077, t = 4.466, $p < 0.001$). These results indicated that the initial value of physical function decline had a partial mediating effect between initial value of social activity and cognitive function.

Additionally, the indirect effect of the rate of change of social activity positively affected the rate of change of cognitive function through the rate of change of physical function decline (β = 0.100, $p < 0.01$, CI = LO.081, UP.119). The rate of change of social activity had a direct effect on the rate of cognitive function (β = 0.524, t = 19.404, $p < 0.001$). The results indicated that the rate of change of physical function decline had a partial mediating impact between the rate of change of social activity and cognitive function.

Change Trends in Cognitive Function by Level of Social Activity

Figure 2 shows the change trends in cognitive function by the level of social activity. Cognitive function in the group with low social activity (bottom 30 percent) tended to decrease over time, while it decreased slightly in the group with moderate social activity and showed a slight increase over time in the group with high social activity (top 10 percent).

Figure 3 indicate the change trends in cognitive function by the level of physical function decline. Cognitive function in the group with bad physical function (bottom 10 percent) decreased to the level of mild dementia over time. However, cognitive function in the group with good physical function (people who report that there are no problem with their IADL) was maintained in the normal range.

DISCUSSION

The purpose of this study was to examine the mediating effect of physical function decline on the association between social activity and cognitive function. The main result of this study was that social activities in middle-aged and elderly people had a positive effect on cognitive function over time. In addition, this study determined that social activity indirectly affected cognitive function by alleviating physical function decline. A discussion of the results, along with several suggestions for this study, is as follows.

First, this study revealed that an increase in social activity was associated with an increase in cognitive function. Recently, a cross-sectional study by Fu et al. (2018) among the elderly in China verified the effect of social activity on cognitive function, while adjusting for control variables such as age, smoking, drinking, hypertension, diabetes, and depression. In addition, a longitudinal study by Choi et al. (2016) indicated that a change in social activity impacted cognitive function in middle and older Korean adults. In particular, the results outlined in **Figure 2** indicate a clear association between social activity and cognitive decline, and hence may serve to maintain or even improve cognitive function. Various social activities such as social gatherings, cultural activities, and volunteering can promote such cognitive activities as forming perceptions, reasoning, considering, evaluating, and

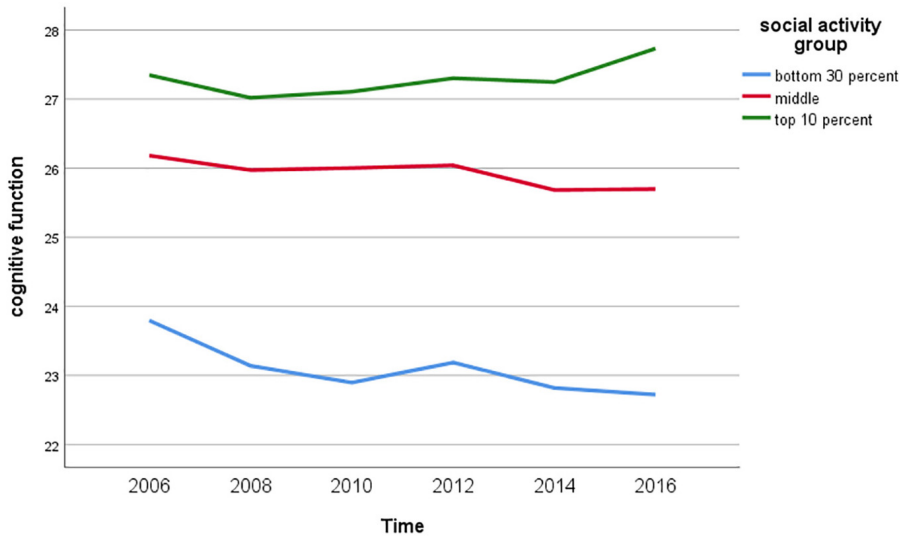

FIGURE 2 | Cognitive function according to the level of social activity.

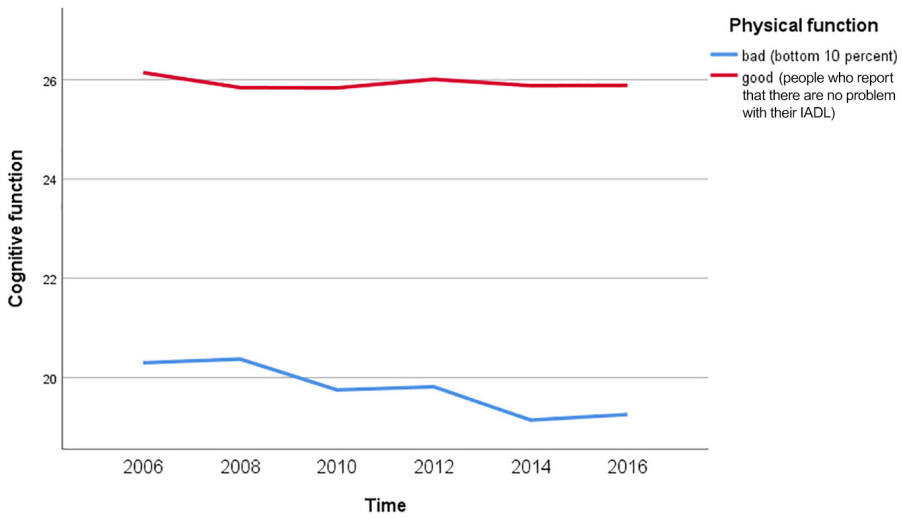

FIGURE 3 | Cognitive function according to the level of physical function decline.

contemplating that can contribute to the maintenance of cognitive function.

A number of studies did not measure various types of social activity (Lee and Kim, 2016). Our study, however, examined the long-term effect of social activity on cognitive function by measuring various types of social activities. In addition, the majority of previous research on this was conducted for western populations (Zunzunegui et al., 2003); this study, however, indicates which results can be generalized to a non-western sample.

Second, the present study found that social activity negatively affected physical function decline. Specifically, social activities can promote the performance of basic and IADL, such as community mobility, dressing, driving, and health management, which in turn can contribute to maintaining physical functioning. Most past cross-sectional studies have argued that social activities can prevent decline in physical function. By analyzing data over 10 years, the present study confirmed that social activity could alleviate physical function decline.

Third, the present study revealed physical function decline had a negative effect on cognitive function. This result is in line with those reported by past studies, which suggested greater physical function can buffer cognitive impairment (Grande et al., 2014; Vancampfort et al., 2017, 2018). Changes in physical and cognitive function are common among older individuals, and the causal mechanism between the two variables is debated widely. Specifically, a meta-analysis that utilized longitudinal

data indicated that physical functioning assessed using objective measures, such as walking speed, grip strength, and chair rise time was strongly associated with cognitive function (Clouston et al., 2013).

Fourth, social activity indirectly affected cognitive function through alleviating physical function decline. This study verified the mechanism that social activity affects cognitive function. That is, social activity increase opportunity improving physical function such as activities of daily lives, which can lead to increase in cognitive function. This study provides information useful for planning strategies to maintain cognitive function in old age by identifying the longitudinal effects of social activity and physical function on cognitive function.

The contribution of this study is to verify the longitudinal effect of social activity on cognitive function through an analysis of national sample data of middle-aged adults and the elderly. It also revealed the mechanism whereby social activities affect cognitive function. The results of this study hold implications for clinical intervention. First, our findings suggest that it is necessary to establish and implement policies to support a variety of social activities as preventive efforts to reduce the social burden due to treatment of cognitive impairment (or dementia) (Kuiper et al., 2016; Aw et al., 2017). In addition, individual efforts to preserve physical function is needed to maintain cognitive function throughout advanced aging. The limitations of this study and suggestions for future analysis are as follows. This study included control variables such as age and education, but other variables such as alcohol abuse, high blood pressure, obesity, and smoking may be associated with cognitive decline. Therefore, in future studies, researchers should consider these variables to retest the fitness of the research model in this study. This study did not verify the effects of specific types of social activities on cognitive function. However, past studies suggest that the influence of social activity on cognitive function may vary depending on the type of social activity. Future studies are needed to verify this in detail.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: "T" the Korean Longitudinal Study of Aging (KLoSA), conducted by the Korea Employment Information Service, available at https://survey.keis.or.kr/klosa/klosa01.jsp.

ETHICS STATEMENT

Ethical approval was not provided for this study on human participants because since this study used data freely available to the public, it did not require ethical approval. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SB performed the study design, data analysis, and writing.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.02008/full#supplementary-material

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Heterogeneous Influence of Frailty Phenotypes in Age-Related Hearing Loss and Tinnitus in Chinese Older Adults: An Explorative Study

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Background: Fried physical frailty, with mobility frailty and non-motor frailty phenotypes, is a heterogeneous syndrome. The coexistence of the two phenotypes and cognitive impairment is referred to as cognitive frailty (CF). It remains unknown whether frailty phenotype has a different association with hearing loss (HL) and tinnitus.

Methods: Of the 5,328 community-dwelling older adults, 429 participants aged ≥58 years were enrolled in the study. The participants were divided into robust, mobility, and non-mobility frailty, mobility and non-mobility CF (subdivided into reversible and potentially reversible CF, RCF, and PRCF), and cognitive decline [subdivided into mild cognitive impairment (MCI) and pre-MCI] groups. The severity and presentations of HL and/or tinnitus were used as dependent variables in the multivariate logistic or nominal regression analyses with forward elimination adjusted for frailty phenotype stratifications and other covariates.

Results: Patients with physical frailty (mobility frailty) or who are robust were found to have lower probability of developing severe HL and tinnitus, and presented HL and/or tinnitus than those with only cognitive decline, or CF. Patients with RCF and non-mobility RCF had higher probability with less HL and tinnitus, and the presentation of HL and/or tinnitus than those with PRCF and mobility RCF. Other confounders, age, cognitive and social function, cardiovascular disease, depression, and body mass index, independently mediated the severity of HL and tinnitus, and presented HL and/or tinnitus.

Conclusion: Frailty phenotypes have divergent association with HL and tinnitus. Further research is required to understand the differential mechanisms and the personalized intervention of HL and tinnitus.

Clinical Trial Registration: ClinicalTrials.gov identifier, NCT2017K020.

Keywords: age-related hearing loss, subjective tinnitus, mobility frailty, non-mobility frailty, mobility cognitive frailty, non-mobility cognitive frailty, social dysfunction

INTRODUCTION

Frailty is a heterogeneous clinical syndrome with a decline in the functioning of multiple physiological systems, including physical, cognitive, social, or psychosocial frailty phenotypes. It could result in adverse outcomes, such as dependency, falls, disability, and death (Andrew et al., 2008; Ruan et al., 2015; Bunt et al., 2017; Hoogendijk et al., 2019). The coexistence of physical frailty and cognitive impairment in older adults is defined as cognitive frailty (CF) (Kelaiditi et al., 2013), including reversible cognitive frailty (RCF) and potential reversible cognitive frailty (PRCF) based on the severity of cognitive impairment (Ruan et al., 2015). Physical frailty could be divided into mobility and non-mobility frailty phenotypes (Liu et al., 2017). Motor dysfunctions, such as slowness and/or weakness, are the important components of physical frailty and CF (Fried et al., 2001; Kelaiditi et al., 2013; Ruan et al., 2015). Individuals with pre-frailty phenotype (one or two of weakness, slowness, and low physical activity) had a faster development trajectory of adverse outcomes than those with exhaustion and/or unexplained weight loss (Romero-Ortuno et al., 2019). Slowness and/or weakness were defined as the core of mobility frailty phenotype (Liu et al., 2017) and are closely associated with cognitive impairment (Boyle et al., 2009; Mielke et al., 2013). The coexistence of mobility or non-mobility frailty with cognitive decline may be referred to as mobility or non-mobility CF. The simultaneous presence of gait disturbances and cognitive decline, as a phenotype of mobility CF, was also defined as motoric cognitive risk syndrome, which has been proposed as a new powerful predictor of dementia and age-related adverse outcomes (Chhetri et al., 2017). Social frailty, social vulnerability, or social dysfunction also increased the risk of adverse outcomes such as fitness and mortality (Andrew et al., 2008), age-related hearing loss (HL), cognitive deficits, depression, and tinnitus in older adults (Li et al., 2015; Panza et al., 2015; Lozupone et al., 2018; Ma et al., 2018; Yoo et al., 2019; Loughrey et al., 2020).

Hearing loss, or presbycusis, which is the most common sensory dysfunction, is an important component of frailty index, and both presbycusis and the degree of frailty index are associated with a higher risk of developing cognitive impairment and dementia (Panza et al., 2015; Deal et al., 2017; Wallace et al., 2019). The coexistence of physical frailty and HL in older adults was related to a worse cognitive performance compared with HL alone (Bonfiglio et al., 2020). Furthermore, cognitive impairment and depressive symptoms may be present during subclinical HL (Golub et al., 2019, 2020). The occurrence of HL on at least one side in older adults can significantly affect the motor functions and increase the risk of postural instability and falls (Bang et al., 2020); it is independently associated with mobility frailty (Kamil et al., 2016), greater disability, and limitations in multiple self-reported difficulties in physical functioning (Chen et al., 2014). HL could result in loneliness and social isolation due to communication difficulty. Social factors might mediate the association between HL and episodic memory (Loughrey et al., 2020). HL in combination with low social activity was an independent risk factor of the development of a disability (Bae et al., 2018). Improving the social networks of older adults with HL by intervention could decrease HL-associated episodic memory impairment (Maharani et al., 2019).

Subjective tinnitus is another common comorbid disorder of the auditory system in older adults. Apart from an aberrant auditory sensory perception, chronic tinnitus is closely associated with cognitive deficits and emotional, psychological, and mental health disorders, such as depression, anxiety, and sleep disturbance or insomnia (Langguth et al., 2013; Ruan et al., 2018; Jafari et al., 2019). Chronic tinnitus-related cognitive impairment includes working memory, executive control of attention, and processing speeds. Higher physical activity in individuals with tinnitus had lower levels of tinnitus severity (Carpenter-Thompson et al., 2015). However, studies on the association between chronic tinnitus and other components of physical frailty are extremely scarce. The contribution of tinnitus and/or HL to the development of cognitive decline and CF subtypes in older adults is not well understood. As sensory and motor regions of the central nervous system are affected by Alzheimer's disease (AD) pathology (Albers et al., 2015; Maharani et al., 2019; Loughrey et al., 2020), we hypothesized that patients with a frailty phenotype that involves cognitive or mobility decline had higher risks of severe HL and tinnitus, and presented HL and/or tinnitus.

Hence, the present study aimed to investigate the association between the severity of age-related HL or chronic tinnitus and frailty phenotypes, including CF subtypes, as well as the association between the presentation of HL and/or tinnitus with frailty phenotype stratifications.

METHODS

Design and Setting

The participants of the Shanghai study of health promotion for elderly individuals with frailty, which is a population-based cross-sectional study, were enrolled in the present study (Ruan et al., 2020c). We analyzed the demographic, health, social, and neuropsychological data of individuals aged 58 years and above.

Participants

After excluding individuals with severe disability, complete loss of hearing and vision, and dementia based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 1994), 429 qualified volunteers were recruited from the previous cohort (Ruan et al., 2020c). The individuals were divided into robust, mobility and non-mobility frailty, mobility and non-mobility CF (including RCF and PRCF), and cognitive decline (including pre-MCI and MCI) (**Table 1**).

Ethical Approval

The study was approved by the Ethics Committee of Huadong Hospital (Approval No. Ref 2018K055), and written

TABLE 1 | Sample characteristic (medians and interquartile ranges [Q25–Q75] for continuous variables, and absolute numbers or percentages for categorical variables) of 429.

Variable	Full sample (*n* = 429)	The status of frailty phenotypes									*P*-value
		Robust (*n* = 105; 24.5%)	Mobility frailty (*n* = 68; 15.9%)	Non-mobility frailty (*n* = 40; 9.30%)	Mobility CF (*n* = 107, 24.94%)		Non-mobility CF (*n* = 31, 7.23%)		Only cognitive impairment (*n* = 78, 18.18%)		
					Mobility RCF (*n* = 51; 11.90%)	Mobility PRCF (*n* = 56; 13.10%)	Non-mobility RCF (*n* = 19; 4.40%)	Non-mobility PRCF (*n* = 12; 2.80%)	Only pre-MCI (*n* = 43; 10.00%)	Only MCI (*n* = 35; 8.20%)	
Demographics											
Age (mean ± SD)	72.00 (67.00, 78.00)	70.00 (65.00, 75.50)	76.00 (70.25, 81.75)	68.00 (64.25, 73.00)	75.00 (69.00, 79.00)	76.50 (72.00, 81.00)	76.00 (68.00, 80.00)	73.00 (67.50, 77.50)	70.00 (65.00, 75.00)	72.00 (67.00, 76.00)	0.000
Female (n;%)	246 (57.30)	55(52.40)	32 (47.10)	24 (60.00)	34 (66.70)	32 (57.10)	14 (73.70)	6 (50.00)	26 (60.50)	23 (65.70)	0.307
Education	12.00 (9.00, 15.00)	12.00 (9.00, 15.00)	14.00 (10.00, 16.00)	12.00 (9.00, 15.00)	9.00 (9.00, 15.00)	9.00 (8.00, 12.00)	11.00 (9.00, 12.00)	11.50 (9.00, 16.00)	12.00 (9.00, 15.00)	9.00 (9.00, 12.00)	0.000
HL category	425	104 (24.47)	68 (16.00)	40 (9.41)	51 (12.00)	56 (13.18)	19 (4.47)	10 (2.35)	42 (9.88)	35 (8.24)	0.000
0	184 (43.30)	60 (57.69)	39 (57.35)	21 (52.50)	15 (29.41)	7 (12.50)	10 (52.63)	2 (20.00)	23 (54.76)	7 (20.00)	
1	129 (30.40)	30 (28.85)	13 (19.12)	12 (30.00)	20 (39.22)	20 (35.71)	8 (42.11)	1 (10.00)	10 (23.81)	15 (42.86)	
2	112 (26.40)	14 (13.46)	16 (23.53)	7 (17.50)	16 (31.37)	29 (51.79)	1 (5.26)	7 (70.00)	9 (21.43)	13 (37.14)	
THI score	427	105 (24.59)	67 (15.69)	40 (9.37)	50 (11.71)	56 (13.11)	19 (4.45)	12 (2.81)	43 (10.07)	35 (8.20)	0.177
0	279 (65.30)	77 (73.33)	48 (71.64)	24 (60.00)	32 (64.00)	30 (53.57)	13 (68.42)	7 (58.33)	26 (60.47)	22 (62.86)	
1	61 (14.30)	21 (20.00)	16 (23.88)	9 (22.50)	13 (26.00)	15 (26.79)	5 (26.32)	5 (41.67)	13 (30.23)	11 (31.43)	
2	24 (5.60)	7 (6.67)	3 (4.48)	7 (17.50)	5 (10.00)	11 (19.64)	1 (5.26)	0 (0.00)	4 (9.30)	2 (5.71)	
HL and tinnitus	424	104 (24.53)	67 (15.80)	40 (9.43)	51 (12.03)	56 (13.21)	19 (4.48)	10 (2.36)	42 (9.91)	35 (8.25)	0.003
0	113 (26.70)	36 (34.62)	24 (35.82)	13 (32.50)	7 (13.73)	6 (10.71)	7 (36.84)	2 (20.00)	14 (33.33)	4 (11.43)	
1	105 (24.80)	23 (22.12)	15 (22.39)	8 (20.00)	15 (29.41)	20 (35.71)	2 (10.53)	4 (40.00)	7 (16.67)	11 (31.43)	
2	68 (16.00)	22 (21.15)	14 (20.90)	8 (20.00)	8 (15.69)	1 (1.79)	3 (15.79)	0 (0.00)	9 (21.43)	3 (8.57)	
3	138 (32.50)	23 (22.12)	14 (20.90)	11 (27.50)	21 (41.18)	29 (51.79)	7 (36.84)	4 (40.00)	12 (28.57)	17 (48.57)	
Covariates											
BMI (*n* = 421)	24.40 (22.00, 26.20)	24.10 (21.95, 26.40)	24.60 (21.60, 26.00)	24.90 (22.43, 25.78)	24.90 (22.00, 26.40)	25.05 (23.08, 27.30)	23.80 (20.80, 25.80)	22.60 (19.98, 25.60)	24.40 (22.60, 25.90)	24.30 (21.35, 26.00)	0.334
Chronic comorbility	398	95	66	35	48	55	18	11	38	32	0.003
0	49 (12.30)	18 (18.90)	10 (15.20)	3 (8.60)	3 (6.30)	3 (5.50)	1 (5.60)	2 (18.20)	4 (10.50)	5 (15.60)	
1	127 (31.90)	39 (41.10)	15 (22.70)	10 (28.60)	12 (25.00)	14 (25.50)	4 (22.20)	0 (0.0.00	17 (44.70)	16 (50.00)	
2	124 (31.20)	26 (27.40)	23 (34.80)	11 (31.40)	19 (39.60)	15 (27.30)	7 (38.90)	6 (54.50)	12 (31.60)	5 (15.60)	
≥ 3	98 (24.60)	12 (12.60)	18 (27.30)	11 (31.40)	14 (29.20)	23 (41.80)	6 (33.30)	3 (27.30)	5 (13.20)	6 (18.80)	
CVD	254/428 (59.30)	53 (50.50)	39 (58.20)	18 (45.00)	37 (72.50)	38 (67.90)	13 (68.40)	8 (66.70)	27 (62.80)	21 (60.00)	0.100

(Continued)

TABLE 1 | Continued

Variable	Full sample (*n* = 429)	The status of frailty phenotypes									*P*-value
		Robust (*n* = 105; 24.5%)	Mobility frailty (*n* = 68; 15.9%)	Non-mobility frailty (*n* = 40; 9.30%)	Mobility CF (*n* = 107, 24.94%)		Non-mobility CF (*n* = 31, 7.23%)		Only cognitive impairment (*n* = 78, 18.18%)		
					Mobility RCF (*n* = 51; 11.90%)	Mobility PRCF (*n* = 56; 13.10%)	Non-mobility RCF (*n* = 19; 4.40%)	Non-mobility PRCF (*n* = 12; 2.80%)	Only pre-MCI (*n* = 43; 10.00%)	Only MCI (*n* = 35; 8.20%)	
diabetes mellitus	76/428 (17.80)	6 (5.70)	12 (17.90)	5 (12.50)	14 (27.50)	19 (33.90)	2 (10.50)	9 (25.00)	9 (20.90)	6 (17.10)	0.001
Stroke	42/428 (9.80)	5 (4.80)	6 (9.00)	6 (15.00)	6 (11.80)	15 (26.80)	0 (0.00)	2 (16.70)	2 (4.70)	0 (0.00)	0.000
non-skin malignancy	31/428 (7.20)	6 (5.70)	7 (10.40)	3 (7.50)	2 (3.90)	5 (8.90)	1 (5.30)	1 (8.30)	1 (2.30)	5 (14.30)	0.566
Social dysfunction	28.00 (24.00, 26.20)	26.00 (23.00, 29.75)	27.00 (25.00, 33.50)	29.00 (27.00, 42.75)	29.00 (24.00, 38.25)	31.00 (25.00, 38.50)	33.00 (26.00, 34.50)	35.00 (28.00, 42.00)	25.50 (22.00, 32.00)	27.50 (23.25, 33.00)	0.001
MMSE	419 (26.00, 29.00)	99 (27.00, 29.00)	67 (27.00, 29.00)	39 (27.00, 29.00)	51 (26.00, 28.00)	55 (25.00, 28.00)	19 (25.00, 28.00)	12 (27.00, 29.00)	42 (27.00, 29.00)	35 (25.00, 28.00)	0.000
GDS 15	420	104	65	40	50	55	19	10	42	35	0.328
<6	317 (75.48)	84 (80.80)	49 (75.40)	25 (62.50)	34 (68.00)	40 (72.70)	15 (78.90)	8 (80.00)	32 (76.20)	30 (75.50)	
≥6	103 (24.52)	20 (19.20)	16 (24.60)	15 (37.50)	16 (32.00)	15 (27.30)	4 (21.10)	2 (20.00)	10 (23.80)	5 (14.30)	
Smoking status	422	103	68	38	51	56	19	11	42	34	0.317
Never	353 (83.60)	83 (80.60)	60 (88.20)	26 (68.40)	46 (90.20)	48 (85.70)	16 (84.00)	10 (90.90)	38 (90.50)	26 (76.50)	
Previous	38 (9.00)	11 (10.70)	6 (8.80)	6 (15.80)	3 (5.90)	6 (10.70)	1 (5.30)	0 (0.00	2 (4.80)	3 (8.80)	
Current	31 (7.30)	9 (8.70)	2 (2.90)	6 (15.80)	2 (3.90)	2 (3.60)	2 (10.50)	1 (9.10)	2 (4.80)	5 (14.70)	
Alcohol intake	422	104	68	37	51	56	19	11	42	34	0.561
Never	378 (89.60)	90 (86.50)	62 (91.20)	31 (83.80)	46 (90.20)	52 (92.90)	17 (89.50)	10 (90.90)	40 (95.20)	30 (88.20)	
Previous	14 (3.30)	7 (6.70)	0 (0.00)	1 (2.70)	1 (2.00)	1 (1.80)	1 (5.30)	1 (9.10)	0 (0.00)	2 (5.90)	
Current	30 (7.10)	7 (6.70)	6 (8.80)	5 (13.50)	4 (7.80)	3 (5.40)	1 (5.30)	0 (0.00)	2 (4.80)	2 (5.90)	
TFI (*n* = 426)	3.00 (0.00, 33.30)	0.00 (0.00, 26.60)	0.00 (0.00, 22.80)	0.00 (0.00, 49.90)	17.20 (0.00, 39.10)	18.40 (0.00, 40.80)	8.00 (0.00, 41.00)	0.00 (0.00, 31.00)	2.80 (0.00, 26.80)	14.00 (0.00, 40.00)	0.385
Neuropsychological test Z-scores											
TMT A (*n* = 416)	−0.13 (−0.56, 0.71)	−0.38 (−0.73, −0.06)	−0.38 (−0.66, 0.10)	−0.20 (−0.59, 0.05)	−0.05 (−0.33, 1.02)	0.78 (−0.10, 2.49)	0.72 (−0.56, 1.55)	0.85 (−0.09, 3.59)	0.01 (−0.47, 0.71)	1.24 (0.49, 1.99)	0.000
TMT B (*n* = 415)	−0.09 (−0.56, 0.46)	−0.37 (−0.65, −0.02)	−0.18 (−0.70, 0.19)	−0.18 (−0.69, 0.03)	−0.10 (−0.56, 0.45)	0.61 (−0.28, 1.77)	0.002 (−0.61, 0.40)	1.29 (−0.01, 1.81)	−0.06 (−0.48, 0.17)	0.96 (−0.11, 1.77)	0.000
Delay recall (*n* = 420)	−0.30 (−0.97, 0.44)	0.29 (−0.30, 0.89)	0.03 (−0.32, 0.70)	−0.22 (−0.51, 0.46)	−0.52 (−1.08, 0.20)	−1.10 (−1.47, −0.25)	−0.82 (−1.32, −0.23)	−0.90 (−1.49, −0.46)	−0.79 (−1.51, −0.47)	−0.90 (−1.61, −0.29)	0.000

(Continued)

TABLE 1 | Continued

Variable	Full sample (*n* = 429)	The status of frailty phenotypes									*P*-value
		Robust (*n* = 105; 24.5%)	Mobility frailty (*n* = 68; 15.9%)	Non-mobility frailty (*n* = 40; 9.30%)	Mobility CF (*n* = 107, 24.94%)		Non-mobility CF (*n* = 31, 7.23%)		Only cognitive impairment (*n* = 78, 18.18%)		
					Mobility RCF (*n* = 51; 11.90%)	Mobility PRCF (*n* = 56; 13.10%)	Non-mobility RCF (*n* = 19; 4.40%)	Non-mobility PRCF (*n* = 12; 2.80%)	Only pre-MCI (*n* = 43; 10.00%)	Only MCI (*n* = 35; 8.20%)	
Recognition (*n* = 421)	0.06 (−0.65, 0.53)	0.29 (−0.27, 0.71)	0.50 (−0.04, 0.87)	0.11 (−0.57, 0.69)	−0.15 (−0.64, 0.42)	−0.51 (−1.74, 0.18)	0.06 (−0.47, 0.40)	−0.89 (−1.75, 0.55)	−0.51 (−1.14, 0.32)	−0.46 (−1.01, 0.11)	0.000
Learning slope (*n* = 421)	−0.03 (−0.59, 0.51)	0.23 (−0.28, 0.79)	0.21 (−0.26, 0.75)	0.25 (−0.25, 0.80)	−0.24 (−1.34, 0.46)	−0.23 (−0.70, 0.46)	−0.51 (−0.94, 0.49)	−0.75 (−1.07, 0.11)	−0.46 (−1.20, 0.03)	−0.28 (−1.02, 0.45)	0.000
Intrusion errors (*n* = 421)	−0.24 (−0.77, 0.49)	−0.34 (−0.65, 0.40)	−0.28 (−0.78, 0.18)	−0.48 (−1.04, −0.11)	0.16 (−0.75, 0.99)	−0.46 (−1.03, 0.65)	0.12 (−0.55, 0.92)	−0.09 (−0.38, 0.50)	0.17 (−0.77, 1.31)	−0.28 (−0.77, 0.49)	0.045
Retroactive interference (*n* = 421)	−0.11 (−0.61, 0.39)	0.07 (−0.28, 0.55)	0.12 (−0.55, 0.62)	0.14 (−0.28, 0.53)	−0.23 (−0.90, 0.14)	−0.22 (−1.18, 0.30)	−0.47 (−1.20, −0.27)	−0.15 (−0.89, 0.25)	−0.19 (−0.98, 0.47)	−0.24 (−1.04, 0.12)	0.000
BNT (*n* = 422)	−0.12 (−0.78, 0.37)	0.26 (−0.29, 0.68)	0.10 (−0.29, 0.46)	0.06 (−0.29, 0.50)	−0.26 (−0.98, 0.33)	−1.20 (−1.63, −0.49)	−0.28 (−1.43, 0.16)	−0.12 (−0.95, 0.05)	−0.07 (−0.74, 0.16)	−0.88 (−1.22, −0.02)	0.000
Animal fluency (*n* = 422)	−0.33 (−0.87, 0.35)	0.10 (−0.36, 0.88)	−0.09 (−0.67, 0.60)	0.13 (−0.44, 0.52)	−0.77 (−1.19, −0.17)	−1.04 (−1.45, −0.42)	−0.46 (−0.80, 0.22)	−0.46 (−1.26, −0.13)	−0.42 (−0.84, 0.32)	−0.63 (−1.26, −0.35)	0.000

HL, hearing loss; BMI, body mass index; CVD, cardiovascular disease; GDS, the Geriatric Depression Scale; THI, handicap inventory; TFI, tinnitus functional index; TMT A and B, Trail Making Test A and B; BNT, Boston naming; CF, cognitive frailty; RCF, reversible cognitive frailty; PRCF, potential reversible cognitive frailty; MCI, mild cognitive impairment. HL 0 = Normal hearing; HL 1 = mild HL; and HL 3 = moderate or severe HL. Tinnitus 0 = no tinnitus; tinnitus 1 = mild or moderate tinnitus; tinnitus 2 = severe or disastrous tinnitus. HL and tinnitus 0 = without HL and tinnitus; HL and tinnitus 1 = only HL; HL and tinnitus 0 = only tinnitus; HL and tinnitus 3 = with HL and tinnitus.

informed consent was obtained from each volunteer or authorized representative.

Measurements

Hearing was objectively measured using a pure-tone audiometry in a sound-attenuating booth according to the American National Standards Institute standards. The air conduction thresholds in each ear [in decibel (dB) hearing level] were measured from 500 to 8,000 Hz. The pure-tone average (PTA) in the better hearing ear was calculated using the 0.5-, 1-, 2-, and 4-kHz thresholds (World Health Organization, 2015). The participants were divided into groups based on the hearing levels: normal hearing (PTA $\leq$ 25 dB), mild loss (>25 and $\leq$40 dB), moderate loss (>40 and $\leq$70 dB), and severe loss (>70 dB) (Lin et al., 2013).

The Tinnitus Handicap Inventory (THI) is validated in Chinese people with a 25-item self-rating instrument and can yield a score (0, 2, or 4, which correspond to "not affected," "sometimes affected," and "always affected," respectively) from 0 to 100. THI includes items concerning general tinnitus severity, quality of life, and psychological aspects of tinnitus (Newman et al., 1996). Tinnitus severity is divided into three levels, including the mild (1–16 and 18–36), the moderate (38–56 and 58–76), and the disaster (78–100) level according to the THI scores (1–100). The Tinnitus Functional Index (TFI) is a standardized tinnitus severity assessment tool, and its score is the total scores of eight domains including intrusive, sense of control, cognitive, sleep, auditory, relaxation, emotional, and quality of life (Carpenter-Thompson et al., 2015). All individuals with self-reported chronic subjective tinnitus (more than 3 months) were required to complete the THI and TFI.

The objective assessment of cognitive performance had been reported in the literature (Thomas et al., 2018, 2020). In the present study, the MCI and pre-MCI evaluation were conducted using normative z-scores of neuropsychological test battery, including Trail Making Test A and B (TMT A and B) for executive or attention domain; Boston Naming Test (BNT) and Animal List generation for language domain; the Hopkins Verbal Learning Test-Revised (HVLT-R) for memory domain, including delayed free correct responses and HVLT-R recognition; and three process scores from the HVLT-R (Ruan et al., 2020b). Two impaired process scores, one impaired process score and one impaired total score, impaired total score on two measures across different cognitive domains or a Functional Assessment Questionnaire (FAQ) score of 6–8 was classified as pre-MCI. Impaired total score on two measures in the same domain, one impaired score in each of the three cognitive domains or a FAQ score of $\geq$9 was classified as MCI (Thomas et al., 2018, 2020).

The mobility and non-mobility frailty phenotypes were evaluated using the five-item Fried scale with Chinese reference values (Hao et al., 2017). Mobility frailty was marked by weakness and/or slowness, whereas non-mobility frailty was indicated by the existence of at least one of the following criteria: unexplained weight loss, fatigue, and low physical activity after excluding mobility frailty (Liu et al., 2017). The CF groups were further divided into mobility or non-mobility RCF if the individuals had both mobility or non-mobility frailty and pre-MCI and mobility or non-mobility PRCF if the individuals had both mobility or non-mobility frailty and MCI.

Demographic information (including age, sex, and education level), self-reported smoking, alcohol intake, and chronic comorbidity, which were validated by conducting a medical chart review were obtained by trained medical staff in 2018–2019. Chronic comorbidity was evaluated according to our previous study (Ruan et al., 2020a). A total of 13 chronic disorders were included: diabetes mellitus, cardiovascular disease, osteoporosis, stroke, arthritis, chronic obstructive lung disease, anemia, peripheral vascular disease, Alzheimer's disease, Parkinson's disease, mental or psychiatric disorders, chronic renal disease, and non-skin malignancy. Cardiovascular disease (CVD) includes coronary problems (myocardial infarction/heart attack or angina pectoris), hypertension, congestive heart failure, or cardiac arrhythmia. Global cognitive status was evaluated by using a Mini Mental Status Examination (MMSE). Depression was assessed by using the 15-item short form of the Geriatric Depression Scale (GDS) (Chau et al., 2006). Social dysfunction was assessed by using the 21-item Social Dysfunction Rating Scale (Linn et al., 1969). Body mass index (BMI) was calculated as weight in kilograms divided by height in meter squared.

Statistical Analysis

The distribution of continuous variables of frailty phenotype stratifications was tested for normality using the Kolmogorov–Smirnov Test. The difference between the groups was analyzed using a bivariate correlation (Pearson's test for normally distributed variables or Spearman's test for variables with non-normal distribution). The difference in categorical variables among groups was tested *via* one-way analysis of variance. If the test of homogeneity of variances was inappropriate, the Mann–Whitney *U*-test was employed to analyze the univariate correlation. Some categorical data were expressed as a proportion and compared using the χ^2 test. All significant categorical and continuous variables associated with HL and/or tinnitus were further analyzed using multivariate logistic regression or nominal regression with forward elimination. The *p*-value for multiple comparisons was corrected, and a p-value < 0.05 was considered significant. All analyses were conducted using the SPSS 18.0 software.

RESULTS

Table 1 presents the characteristics of robust; mobility frailty; non-mobility frailty; mobility CF, including mobility RCF and mobility PRCF; non-mobility CF, including non-mobility RCF and non-mobility PRCF; and cognitive decline, including pre-MCI and MCI patients. The distribution of HL ($p < 0.001$) and the presentation of HL and/or tinnitus ($p = 0.003$) were significantly different among frailty phenotype stratifications. Tinnitus severity based on THI score ($p = 0.177$) and TFI score ($p = 0.385$) was not significantly different among frailty phenotype stratifications (**Table 1**).

After the adjustment for confounders, the robust and mobility frailty phenotypes were associated with significantly higher odds of normal hearing [odds ratio (OR), 5.99 and 6.82, respectively] than that of moderate and severe HL when compared with the cognitive decline phenotype (model 3, **Table 2**). When compared with the MCI group, the mobility frailty was associated with significantly higher odds (OR, 12.69) of normal hearing than that of the moderate and severe HL (model 4, **Table 2**). After dividing CF into RCF and PRCF, and cognitive decline being divided into pre-MCI and MCI, the mobility RCF (OR, 3.28; $p = 0.076$), non-mobility RCF (OR, 27.43), and pre-MCI (OR, 4.06) phenotypes were associated with higher odds of normal hearing, and the non-mobility RCF group with higher odds of mild HL (OR, 8.33, $p = 0.065$) than of the moderate and severe HL (model 5, **Table 2**) when compared with the MCI phenotype. After excluding non-mobility frailty phenotypes in model 6 of **Table 2**, including non-mobility frailty, non-mobility RCF, and PRCF, the robust (OR, 9.11) and mobility frailty (OR, 11.32) phenotypes were associated with significantly higher odds of normal hearing. After the adjustment for covariates, age was an independent risk factor of the severity of HL among different frailty stratifications in all six models (**Table 2**). TMT B and animal fluency scores (OR, 0.62, $p = 0.06$) in model 3 and TMT B in model 4 were also independent risk factors of the severity of HL.

Compared with the cognitive decline or MCI group, other frailty stratifications were not associated with odds of without tinnitus or with severe and disastrous tinnitus (models 1–6, **Table 3**); however, the mobility CF (OR, 0.36, 0.24, 0.26, and 0.20; $p = 0.066$, 0.086, 0.075, and 0.07 in models 1–4) or mobility RCF phenotype (OR, 0.21; $p = 0.074$ in model 5) was associated with marginally lower odds of mild and moderate tinnitus than that of severe and disastrous tinnitus. BMI was an independent factor associated with the tinnitus severity in all three groups in model 1 of **Table 3**. Among the four stratifications in model 2 of **Table 3**, patients experiencing depression were associated with higher odds of severe and disastrous tinnitus than those without tinnitus (OR, 0.83). Patients with social dysfunction were associated with higher odds of severe and disastrous tinnitus than those without tinnitus (model 3, **Table 3**). Other confounders, CVD (OR, 0.19; model 3), the z-scores of TMT A (OR, 0.75, 0.75, and 0.80; models 3–5), recognition (OR, 3.74), and Boston naming scores (OR, 2.88; $p = 0.054$; model 6) were independently associated with the severity of tinnitus.

Among the six frailty stratifications in model 3 of **Table 4**, robust (OR, 4.23) and mobility frailty (OR, 11.43) phenotypes were associated with significantly higher odds of without HL and tinnitus, or with tinnitus (OR, 9.81) than those of HL and tinnitus when compared with the cognitive decline group. The mobility frailty phenotype was associated with significantly higher odds of without HL and tinnitus (OR, 36.41) and only tinnitus (OR, 7.92) than those of HL and tinnitus when compared with the MCI group (model 4, **Table 4**). The non-mobility RCF (OR, 5.29; $p = 0.055$) and pre-MCI (OR, 3.97; $p = 0.067$) stratifications were associated with marginally higher odds of without HL and tinnitus than those of HL and tinnitus when compared with the MCI stratification (model 5, **Table 4**). After excluding the non-mobility frailty phenotypes, the robust (OR, 8.73; $p = 0.092$) and mobility frailty (OR, 25.31) phenotypes were associated with higher odds of without HL and tinnitus than those of HL and tinnitus (model 6, **Table 4**). Age was an independent confounder associated with the presentation of HL and/or tinnitus ($p = 0.054$ in model 2; $p = 0.065$ in model 3; $p = 0.078$ in model 6; and $p < 0.05$ in other models; **Table 4**). Social dysfunction (model 1, **Table 4**), BNT score (models 2 and 3), and CVD (model 3, **Table 4**) were also independent confounders associated with the presentation of HL and/or tinnitus.

DISCUSSION

From the cross-sectional study, we found that frailty phenotypes and CF subtypes had a different association with the severity of HL and tinnitus and presented HL and/or tinnitus. Patients with physical frailty, such as mobility frailty or who are robust had lower probability with severe HL, tinnitus, and presented HL and/or tinnitus than those with cognitive decline, CF, and mobility RCF and PRCF. Patients with RCF and non-mobility RCF had higher probability with less HL, tinnitus, and presented HL and/or tinnitus than those with PRCF and mobility RCF. Our findings provided additional evidence supporting the results of a previous longitudinal study, which indicated that the frailty phenotypes are heterogeneous with different longitudinal trajectories of mortality and disability (Romero-Ortuno et al., 2019).

Although many epidemiological studies indicated that physical frailty increases the risk of future cognitive decline (Robertson et al., 2013), the addition of cognitive impairment to the assessment of physical frailty may improve the prediction of adverse outcomes of physical frailty during the later stages of life (Lee et al., 2018), including death from heart transplantation (Jha et al., 2016), death among oldest-old individuals (Brigola et al., 2020), functional decline, falls, and hospitalization (Hao et al., 2018). The overall or individual domain score for cognitive decline in the Chinese version of the mini-mental state examination may improve the pre-frailty predictive power for poor quality of life, incident physical limitation, increased cumulative hospital stay, and mortality (Yu et al., 2018). Our study indicated that individuals with cognitive decline or CF had higher risks of severe HL and tinnitus and presented with HL and/or tinnitus. Moreover, individuals with RCF had lower risks of severe HL and tinnitus and presented with HL and/or tinnitus. Similarly, individuals with non-mobility RCF had lower risks of severe HL and tinnitus than those with mobility RCF. Slowness has been reported as the most related physical component to cognitive impairment (Mielke et al., 2013; Chhetri et al., 2017) and health-related quality of life (Henchoz et al., 2017). Indeed, motor cognitive risk syndrome has been considered as an important disease (Cohen et al., 2016; Chhetri et al., 2017). Our results extend the significant association between physical frailty, CF, CF subtype, and RCF phenotype and adverse health outcomes of older adults. These results support the evidence that CF may be an important clinical syndrome with physical and cognitive heterogeneities. Motor cognitive risk syndrome may be defined as a phenotype of CF.

TABLE 2 | Association between frailty phenotype and the severity of hearing loss by using multivariate logistic regression or nominal regression.

	HL (0, ref: 2)					
	Model 1 OR (95%CI)	**Model 2 OR (95%CI)**	**Model 3 OR (95%CI)**	**Model 4 OR (95%CI)**	**Model 5 OR (95%CI)**	**Model 6 OR (95%CI)**
Frailty phenotypes						
Robust	NA	**4.04 (0.87, 18.76)**	5.99 (1.38, 25.95)*	NA	NA	9.11 (1.40, 59.18)*
Mobility frailty	NA	NA	6.82 (1.48, 31.50)*	12.69 (1.95, 82.55)**	NA	11.32 (1.61, 79.51)*
Non-mobility frailty	NA	NA	2.88 (0.41, 20.34)	5.45 (0.60, 49.65)	NA	NA
Mobility CF	0.53 (0.21, 1.32)	0.90 (0.24, 3.35)	0.95 (0.31, 2.95)	1.79 (0.39, 8.27)	NA	NA
Mobility RCF	NA	NA	NA	NA	**3.28 (0.88, 12.19)**	2.60 (0.43, 15.72)
Mobility PRCF	NA	NA	NA	NA	0.66 (0.17, 2.56)	0.47 (0.06, 3.52)
Non-mobility CF	3.13 (0.73, 13.38)	4.40 (0.33, 59.10)	2.57 (0.44, 15.21)	4.77 (0.61, 37.17)	NA	NA
Non-mobility RCF	NA	NA	NA	NA	27.43 (2.50, 301.48)**	NA
Non-mobility PRCF	NA	NA	NA	NA	0.93 (0.13, 6.88)	NA
Cognitive decline	0[a]	0[a]	0[a]	–	–	–
Pre-MCI	NA	NA	NA	3.43 (0.51, 23.23)	4.06 (1.04, 15.90)*	2.38 (0.32, 17.65)
MCI	–	–	–	0[a]	0[a]	0[a]
Age	0.85 (0.79, 0.91)***	0.84 (0.76, 0.92)***	0.87 (0.81, 0.93)***	0.87 (0.81, 0.94)***	0.85 (0.80, 0.91)***	0.84 (0.77, 0.92)***
GDS15	–	0.79 (0.65, 0.96)*	–	–	–	–
TMT B	–	–	0.784 (0.53, 1.15)	0.79 (0.52, 1.17)	–	–
Animal fluency	–	–	1.05 (0.64, 1.72)	–	–	–
	HL (1, ref: 2)					
Frailty phenotypes						
Robust	NA	2.55 (0.58, 11.17)	2.42 (0.61, 9.65)	NA	NA	**4.65 (0.82, 26.29)**
Mobility frailty	NA	NA	0.61 (0.12, 3.12)	0.49 (0.08, 2.80)	NA	1.55 (0.22, 10.91)
Non-mobility frailty	NA	NA	1.06 (0.14, 7.84)	0.81 (0.10, 6.49)	NA	NA
Mobility CF	0.88 (0.38,2.01)	0.66 (0.21, 2.11)	**0.39 (0.14, 1.04)**	0.43 (0.14, 1.32)	NA	NA
Mobility RCF	NA	NA	NA	NA	1.36 (0.45, 4.09)	1.35 (0.27, 6.90)
Mobility PRCF	NA	NA	NA	NA	0.65 (0.23, 1.82)	0.62 (0.12, 3.23)
Non-mobility CF	2.43(0.61, 9.62)	2.76 (0.23, 32.63)	0.81 (0.14, 4.60)	0.85 (0.14, 5.15)	NA	NA
Non-mobility RCF	NA	NA	NA	NA	**8.33 (0.88, 79.18)**	NA
Non-mobility PRCF	NA	NA	NA	NA	0.18 (0.02, 1.80)	NA
Cognitive decline	0[a]	0[a]	0[a]	–	–	–
Pre-MCI	NA	NA	NA	0.76 (0.15, 3.82)	1.06 (0.29, 3.81)	1.88 (0.30, 11.77)
MCI	–	–	–	0[a]	0[a]	0[a]
Age	0.96 (0.90, 1.01)	0.96 (0.89, 1.05)	0.98 (0.92, 1.04)	0.97 (0.91, 1.03)	0.96 (0.91, 1.02)	0.95 (0.88, 1.03)
GDS15	–	0.87(0.73, 1.04)	–	–	–	–
TMT B	–	–	0.60 (0.42, 0.86)**	0.61 (0.42, 0.89)**	–	–
Animal fluency	–	–	0.62 (0.38, 1.02)	–	–	–

*[a]means reference category; OR = odds ratios; CI = confidence intervals; NA, not applicable; CF = cognitive frailty; RCF = reversible cognitive frailty; PRCF = potential reversible cognitive frailty; MCI, mild cognitive impairment; BMI, body mass index; HL, hearing loss; TMT B, Trail Making Test B; GDS, the Geriatric Depression Scale. Model 1 is adjusted for mobility CF, non-mobility CF, cognitive decline, and age. Model 2 is adjusted for robust, mobility CF, non-mobility CF, cognitive decline, age, and GDS15. Model 3 is adjusted for robust, mobility frailty; non-mobility frailty; mobility CF, non-mobility CF, cognitive decline, age, TMT B, and animal fluency. Model 4 is adjusted for mobility frailty; non-mobility frailty; mobility CF, non-mobility CF, pre-MCI, MCI, age, and TMT B. Model 5 is adjusted for mobility RCF, mobility PRCF, non-mobility RCF, non-mobility PRCF, pre-MCI, MCI, and age. Model 6 is adjusted for robust, mobility frailty; mobility RCF, mobility PRCF, pre-MCI, MCI, and age. HL 0 = Normal hearing; HL 1 = mild HL; and HL 3 = moderate or severe HL. Chinese adults aged 58 years and older and stratified by frailty phenotypes. *$p < 0.05$; **$p \leq 0.01$; and ***$p < 0.001$; bold values denote marginally statistical significance.*

Apart from frailty phenotypes, age was the most significant independent risk factor for HL severity and HL with tinnitus. Previous epidemiological studies revealed that the prevalence of sensory and motor dysfunction and cognition deficit, frailty, and tinnitus increases with age (Shargorodsky et al., 2010; Panza et al., 2015; Ruan et al., 2018; Jafari et al., 2019). Although HL is associated with cognitive impairment, frailty, and motor dysfunction (Chen et al., 2014; Panza et al., 2015; Kamil et al., 2016; Deal et al., 2017; Bang et al., 2020; Bonfiglio et al., 2020), identifying the causal relationship between HL and frailty phenotype and cognition decline is difficult because HL is similar to pre-MCI, with long subclinical period (Golub et al., 2019, 2020). Our results revealed that aging does not increase the severity of tinnitus and confirmed the reports of previous studies,

TABLE 3 | Association between frailty phenotype and the severity of tinnitus by using multivariate logistic regression or nominal regression.

	Tinnitus (0, ref: 2)					
	Model 1 OR (95%CI)	**Model 2 OR (95%CI)**	**Model 3 OR (95%CI)**	**Model 4 OR (95%CI)**	**Model 5 OR (95%CI)**	**Model 6 OR (95%CI)**
Frailty phenotypes						
Robust	NA	0.58 (0.16, 2.10)	0.80 (0.24, 2.66)	NA	NA	0.84 (0.14, 5.01)
Mobility frailty	NA	NA	1.72 (0.38, 7.90)	1.71 (0.32, 9.08)	NA	1.65 (0.21, 13.09)
Non-mobility frailty	NA	NA	1.21 (0.17, 8.57)	0.84 (0.12, 6.01)	NA	NA
Mobility CF	0.52 (0.23, 1.20)	0.42 (0.13, 1.37)	0.53 (0.19, 1.45)	0.48 (0.14, 1.62)	NA	NA
Mobility RCF	NA	NA	NA	NA	0.52 (0.16, 1.71)	0.39 (0.07, 2.33)
Mobility PRCF	NA	NA	NA	NA	0.39 (0.13, 1.24)	0.21 (0.03, 1.45)
Non-mobility CF	1.25 (0.34, 4.61)	0.61 (0.09, 4.25)	0.73 (0.14, 3.75)	0.57 (0.10, 3.28)	NA	NA
Non-mobility RCF	NA	NA	NA	NA	0.96 (0.19, 4.76)	NA
Non-mobility PRCF	NA	NA	NA	NA	0.72 (0.11, 4.67)	NA
Cognitive decline	0[a]	0[a]	0[a]	–	–	–
Pre-MCI	NA	NA	NA	1.01 (0.19, 5.55)	0.66 (0.18, 2.40)	0.91 (0.12, 7.07)
MCI	–	–	–	0[a]	0[a]	0[a]
BMI	1.13 (1.01, 1.25)*	–	–	–	–	–
CVD (ref: yes)	–	–	0.54 (0.26, 1.14)	–	–	–
Social dysfunction	–	–	0.95 (0.92, 0.98)**	–	–	–
GDS15	–	0.83(0.70, 0.97)*	–	–	–	–
Recognition	–	–	–	–	–	0.97 (0.62, 1.54)
Boston naming	–	–	–	–	–	0.83 (0.49, 1.41)
TMT A	–	–	1.02 (0.90, 1.15)	1.05 (0.93, 1.20)	1.01 (0.92, 1.10)	–
	Tinnitus (1, ref: 2)					
Frailty phenotypes						
Robust	NA	0.20 (0.03, 1.54)	0.16 (0.02, 1.12)			0.10 (0.01, 1.48)
Mobility frailty	NA		0.53 (0.06, 4.54)	0.40 (0.04, 3.99)		0.19 (0.01, 3.46)
Non-mobility frailty	NA		0.42 (0.03, 6.92)	0.28 (0.02, 4.78)		
Mobility CF	0.36 (0.12, 1.07)	0.24 (0.05, 1.23)	0.26 (0.06, 1.14)	0.20 (0.04, 1.14)		
Mobility RCF	NA	NA	NA	NA	0.21 (0.04, 1.16)	0.15 (0.01, 2.15)
Mobility PRCF	NA	NA	NA	NA	0.35 (0.07, 1.65)	1.26 (0.07, 21.83)
Non-mobility CF	1.09 (0.21, 5.60)	0.48 (0.03, 7.22)	1.31 (0.17, 9.89)	0.92 (0.11, 7.94)	NA	NA
Non-mobility RCF	NA	NA	NA	NA	0.47 (0.05, 4.33)	NA
Non-mobility PRCF	NA	NA	NA	NA	1.01 (0.10, 10.46)	NA
Cognitive decline	0[a]	0[a]	0[a]	–	–	–
Only pre-MCI	NA	NA	NA	0.70 (0.08, 5.96)	0.54 (0.10, 2.83)	2.58 (0.15, 45.30)
MCI	–	–	–	0[a]	0[a]	0[a]
BMI	1.17 (1.01, 1.35)*	–	–	–	–	–
CVD (ref: yes)	–	–	0.19 (0.46, 0.75)*	–	–	–
Social dysfunction	–	–	0.96 (0.91, 1.02)	–	–	–
GDS15	–	0.95 (0.74, 1.22)	–	–	–	–
Recognition	–	–	–	–	–	3.74 (1.15, 12.18)*
Boston naming	–	–	–	–	–	2.88 (0.99, 8.38)
TMT A	–	–	0.75 (0.60, 0.93)**	0.75 (0.59, 0.94)*	0.80 (0.67, 0.96)*	–

*$p < 0.05$ and **$p \leq 0.01$. [a]means reference category; OR = odds ratios; CI = confidence intervals; NA, not applicable; CF = cognitive frailty; CVD, cardiovascular disease; RCF = reversible cognitive frailty; PRCF = potential reversible cognitive frailty; MCI, mild cognitive impairment; BMI, body mass index; TMT A, Trail Making Test A; GDS, the Geriatric Depression Scale; BNT, Boston naming. Model 1: adjusted for mobility CF, non-mobility CF, cognitive decline, and BMI; Model 2: adjusted for robust, mobility CF, non-mobility CF, cognitive decline, and GDS15; Model 3: adjusted for robust, mobility frailty; non-mobility frailty; mobility CF, non-mobility CF, cognitive decline, CVD, social dysfunction, and TMT A. Model 4: adjusted for mobility frailty; non-mobility frailty; mobility CF, non-mobility CF, pre-MCI, MCI, and TMT A; Model 5: adjusted for mobility frailty; mobility RCF, mobility PRCF, non-mobility RCF, non-mobility PRCF, pre-MCI, MCI, and TMT A. Model 6 is adjusted for robust, mobility frailty; mobility RCF, mobility PRCF, non-mobility RCF, non-mobility PRCF, pre-MCI, MCI, recognition, and BNT. Tinnitus 0 = no tinnitus; tinnitus 1 = mild or moderate tinnitus; tinnitus 2 = severe or disastrous tinnitus.*

which indicated that depression increases the risk for severe HL or tinnitus (Shargorodsky et al., 2010; Langguth et al., 2013; House et al., 2018; Ruan et al., 2018; Jafari et al., 2019; Golub et al., 2020). Hypertension was a risk factor for tinnitus (Shargorodsky et al., 2010). The present study demonstrated that patients with CVD have a higher risk for severe and disastrous

TABLE 4 | Association between frailty phenotype and comorbid hearing loss and tinnitus by using multivariate logistic regression or nominal regression.

	HL and tinnitus (0, ref: 3)					
	Model 1 OR (95%CI)	**Model 2 OR (95%CI)**	**Model 3 OR (95%CI)**	**Model 4 OR (95%CI)**	**Model 5 OR (95%CI)**	**Model 6 OR (95%CI)**
Frailty phenotypes						
Robust	NA	3.23 (0.72, 14.59)	4.23 (1.06, 16.97)*	NA	NA	**8.73 (0.71, 108.25)**
Mobility frailty	NA	NA	11.43 (2.14, 61.11)**	36.41 (3.10, 428.33)**	NA	25.31 (1.68, 380.46)*
Non-mobility frailty	NA	NA	2.19 (0.26, 18.32)	7.27 (0.44, 119.28)	NA	NA
Mobility CF	0.56 (0.20, 1.62)	0.86 (0.19, 3.79)	1.14 (0.31, 4.19)	4.34 (0.46, 41.14)	NA	NA
Mobility RCF	NA	NA	NA	NA	1.89 (0.43, 8.40)	2.60 (0.19, 34.95)
Mobility PRCF	NA	NA	NA	NA	1.14 (0.25, 5.12)	1.25 (0.08, 18.99)
Non-mobility CF	2.10 (0.54, 8.14)	1.11 (0.10, 11.76)	1.91 (0.29, 12.43)	6.21 (0.45, 85.46)	NA	NA
Non-mobility RCF	NA	NA	NA	NA	**5.29 (0.97, 28.99)**	NA
Non-mobility PRCF	NA	NA	NA	NA	3.23 (0.36, 29.00)	NA
Cognitive decline	0[a]	0[a]	0[a]	–	–	–
Pre-MCI	NA	NA	NA	7.88 (0.66, 94.19)	**3.97(0.91, 17.32)**	3.75 (0.26, 54.09)
MCI	–	–	–	0[a]	0[a]	0[a]
Age	0.86 (0.80, 0.93)***	0.82 (0.74, 0.91)***	0.86 (0.80, 0.93)***	0.85 (0.78, 0.93)***	0.87 (0.81, 0.94)***	0.83 (0.76, 0.91)***
CVD (ref: yes)	–	–	1.13 (0.46, 2.79)	–	–	–
Social dysfunction	0.97 (0.92, 1.02)	–	–	–	–	–
BNT	–	0.66 (0.32, 1.35)	0.82 (0.48, 1.38)	–	–	0.55 (0.26, 1.17)
	HL and tinnitus (1, ref: 3)					
Frailty phenotypes						
Robust	NA	1.41 (0.37, 5.45)	1.39 (0.42, 4.59)	NA	NA	1.56 (0.27, 8.82)
Mobility frailty	NA	NA	1.99 (0.42, 9.46)	1.20 (0.25, 5.84)	NA	2.48 (0.32, 19.05)
Non-mobility frailty	NA	NA	0.74 (0.11, 5.25)	0.60 (0.08, 4.36)	NA	NA
Mobility CF	0.93 (0.40, 2.19)	0.55 (0.17, 1.85)	0.56 (0.22, 1.46)	0.65 (0.23, 1.82)	NA	NA
Mobility RCF	NA	NA	NA	NA	0.65 (0.22, 1.97)	0.53 (0.09, 3.15)
Mobility PRCF	NA	NA	NA	NA	0.83 (0.30, 2.32)	0.56 (0.10, 3.23)
Non-mobility CF	0.58 (0.14, 2.34)	0.42 (0.04, 5.00)	0.46 (0.8, 2.83)	0.37 (0.06, 2.36)	NA	NA
Non-mobility RCF	NA	NA	NA	NA	0.34 (0.06, 2.02)	NA
Non-mobility PRCF	NA	NA	NA	NA	1.18 (0.20, 7.11)	NA
Cognitive decline	0[a]	0[a]	0[a]	–	–	–
Only pre-MCI	NA	NA	NA	0.89 (0.20, 4.02)	0.92 (0.26, 3.28)	1.08 (0.16, 7.24)
MCI	–	–	–	0[a]	0[a]	0[a]
Age	0.99 (0.93, 1.06)	0.95 (0.88, 1.03)	0.97 (0.92, 1.03)	0.98 (0.92, 1.04)	1.00 (0.95, 1.06)	0.95 (0.88, 1.03)
CVD (ref: yes)	–	–	0.59 (0.26, 1.36)	–	–	–
Social dysfunction	0.94 (0.90, 0.98)**	–	–	–	–	–
BNT	–	0.46 (0.26, 0.83)**	0.57 (0.38, 0.87)**	–	–	0.43 (0.22, 0.82)*
	HL and tinnitus (2, ref: 3)					
Frailty phenotypes						
Robust	NA	1.91 (0.37, 9.91)	3.75 (0.77, 18.36)	NA	NA	2.07 (0.25, 17.16)
Mobility frailty	NA	NA	9.81 (1.54, 62.34)*	7.92 (1.02, 61.77)*	NA	5.57 (0.53, 58.21)
Non-mobility frailty	NA	NA	2.80 (0.32, 24.67)	3.30 (0.31, 35.32)	NA	NA
Mobility CF	0.65 (0.20, 2.10)	0.66 (0.14, 3.27)	0.92 (0.21, 4.08)	1.17 (0.20, 6.99)	NA	NA
Mobility RCF	NA	NA	NA	NA	2.82 (0.58, 13.73)	1.29 (0.16, 10.53)
Mobility PRCF	NA	NA	NA	NA	0.25 (0.02, 2.76)	NS
Non-mobility CF	0.89 (0.14, 5.52)	1.81 (0.19, 16.99)	1.74 (0.22, 13.53)	2.11 (0.22, 20.39)	NA	NA
Non-mobility RCF	NA	NA	NA	NA	2.30 (0.28, 19.04)	NA
Non-mobility PRCF	NA	NA	NA	NA	NS	NA
Cognitive decline	0[a]	0[a]	0[a]	–	–	–
Only pre-MCI	NA	NA	NA	1.78 (0.19, 17.13)	3.54 (0.70, 17.95)	0.93 (0.08, 10.67)

(Continued)

TABLE 4 | Continued

	HL and tinnitus (0, ref: 3)					
	Model 1 OR (95%CI)	**Model 2 OR (95%CI)**	**Model 3 OR (95%CI)**	**Model 4 OR (95%CI)**	**Model 5 OR (95%CI)**	**Model 6 OR (95%CI)**
MCI	–	–	–	0[a]	0[a]	0[a]
Age	0.87 (0.80, 0.95)**	**0.90 (0.82, 1.00)**	0.90 (0.83, 0.98)*	**0.92 (0.84, 1.01)**	0.88 (0.80, 0.96)**	**0.91 (0.83, 1.01)**
CVD (ref: yes)	–	–	0.25 (0.07, 0.87)*	–	–	–
Social dysfunction	0.92 (0.86, 0.99)*	–	–	–	–	–
BNT	–	0.70 (0.33, 1.50)	0.67 (0.39, 1.15)	–	–	0.55 (0.24, 1.22)

**p < 0.05; **p ≤ 0.01; ***p < 0.001; bold values denote marginally statistical significance. a means reference category; OR = odds ratios; CI = confidence intervals; CVD, cardiovascular disease; NA, not applicable; NS, no significance; RCF = reversible cognitive frailty; PRCF = potential reversible cognitive frailty; MCI, mild cognitive impairment; HL, hearing loss; BNT, Boston naming. Model 1 is adjusted for mobility CF, non-mobility CF, cognitive decline, age, and social dysfunction. Model 2 is adjusted for robust, mobility CF, non-mobility CF, cognitive decline, age, and BNT. Model 3 is adjusted for robust, mobility frailty; non-mobility frailty; mobility CF, non-mobility CF, cognitive decline, age, CVD, and BNT. Model 4 is adjusted for mobility frailty; non-mobility frailty; mobility CF, non-mobility CF, pre-MCI, MCI, and age. Model 5 is adjusted for mobility RCF, mobility PRCF, non-mobility RCF, non-mobility PRCF, pre-MCI, MCI, and age. Model 6 is adjusted for robust, mobility frailty; mobility RCF, mobility PRCF, pre-MCI, MCI, age, and BNT. HL and tinnitus 0 = without HL and tinnitus; HL and tinnitus 1 = only HL; HL and tinnitus 0 = only tinnitus; HL and tinnitus 3 = with HL and tinnitus.*

tinnitus and HL with tinnitus than tinnitus only. Among patients with cognitive decline, BMI was independently associated with the severity of tinnitus. This finding indicates that obesity and metabolic diseases can affect the severity of tinnitus. In fact, the cardiometabolic risk factors, such as hypertension and waist circumference, had a weak correlation with tinnitus and THI level (Langguth et al., 2013; House et al., 2018). Although sex is an important risk factor for cognitive decline, and female older people have high risk for cognitive impairment and frailty (Ruan et al., 2017), our results did not show sexual difference in frailty phenotypes, HL, tinnitus, motor dysfunction, and cognitive decline.

Cognitive function is associated with HL and tinnitus. Individuals with HL had memory (Deal et al., 2017) and executive dysfunctions (Lin et al., 2013). The cognitive deficits of patients with tinnitus included executive domain, working memory, processing speeds, and attention (Ruan et al., 2018; Jafari et al., 2019). Our study further confirmed that the differences in HL and tinnitus severity and the presentation of HL and/or tinnitus are independently associated with the z-scores of memory (recognition), attention, and executive function (TMT A and TMT B), as well as language (BNT and animal fluency). Patients with attention and executive (TMT A and/or B) dysfunctions had a higher risk for more severe HL and tinnitus among the frailty phenotype and CF subtype stratifications. Patients with language domain (BNT) dysfunction had a higher risk for the presentation of HL with tinnitus rather than HL alone. Although cognition was another independent risk factor for the severity of HL, severity of tinnitus and the presentation of HL and/or tinnitus, the causal relationship between HL or tinnitus and cognition remains elusive.

The total amount of social dysfunction might be detected with the Social Dysfunction Rating Scale optimal cut-off value ≥ 26 (Lozupone et al., 2018). The cut-off value could be used to detect social vulnerabilities, including social frailty. Social dysfunction or social frailty has been validated to be associated with cognitive, depression and HL (Lozupone et al., 2018; Ma et al., 2018; Yoo et al., 2019), and the relationship between cognition and hearing loss (Loughrey et al., 2020). In this study, social dysfunction was also an independent risk factor for the differences in the severity of HL, tinnitus, and presented HL and/or tinnitus. Individuals with severe social dysfunction had a higher risk for severe tinnitus and presented HL and tinnitus rather than HL alone or tinnitus alone. Social dysfunction or isolation and loneliness due to communication impairment had been linked to HL and cognitive deficits (Panza et al., 2015). Social factors may influence tinnitus perception, interpretation, and mental representation and were considered in patients with tinnitus (Li et al., 2015). The potential link mechanism of social dysfunction and tinnitus and presentation of HL with tinnitus need further investigation.

Multidisciplinary studies showed that peripheral and central HL, and motor dysfunction are observed in the preclinical AD stage. The major AD pathological changes, including amyloid plaques and neurofibrillary tangles, were observed in the central auditory neural pathway, primary motor cortex, and supplementary motor areas in AD patients. Interventions targeting the amelioration of sensory-motor deficits in AD may enhance patient function as AD progresses (Albers et al., 2015). The common-cause hypothesis that systematic age-related nervous system pathologies such as AD pathology, brain atrophy, and reduced dendritic spine densities in widespread brain regions are linked to HL, tinnitus, and dementia risks had been supported by many studies (Panza et al., 2015; Jafari et al., 2019). The common etiological pathways, including microvascular disease, inflammation, metabolic dysfunction, and nutritional and hormonal factors, lead to HL, tinnitus, motor impairment, and cognitive decline. Social dysfunction or frailty is the immediate stage between HL and/or tinnitus and cognitive decline (Panza et al., 2015). Our results show that patients with a frailty phenotype that involves cognitive or mobility decline had higher risks of severe HL and tinnitus, and presented with HL and/or tinnitus. These results also provide additional evidence to the common-cause hypothesis.

A major strength of this study is the objective cognitive measures. Cognitive status was measured on the basis of the normative *z*-scores of six neuropsychological tests and process *z*-scores of HVLT-R (Ruan et al., 2020b), which decrease the diagnostic errors resulting from the clinical evaluation for MCI or subjective questionnaire for pre-MCI. The present study shows that implementation of integrated care based on intrinsic capacity (World Health Organization, 2017), including sensory, motor, cognitive performance, and frailty status of older people, is necessary in clinical practice. Although this cohort includes a sample representing community-dwelling older adults and has a substantial number of potential confounders, one main limitation in this study is the sample size. The number of patients in the non-mobility CF stratification, especially the non-mobility CF subtypes, RCF and PRCF stratifications, are small, which limits the representativeness of the population, and the conclusion about the differences in their association with HL, tinnitus, and HL with tinnitus. In addition, the cross-sectional study cannot determine the causal relationship between independent risk factors and HL, tinnitus, and HL with tinnitus. Finally, although social dysfunction and depression were validated to be independent confounders of the severity of HL and tinnitus, this study focused on mobility and non-mobility frailty, mobility and non-mobility CF and their subtypes, and other dimensions such as social and psychological frailty phenotypes (Lozupone et al., 2018; Ma et al., 2018; Solfrizzi et al., 2019; Yoo et al., 2019), and loneliness as a study variable assessed by using a validated scale, which are related to the severity of HL and tinnitus, and presentations of HL and tinnitus. These require further investigation in a future study. Future research should further explore the relationship between multi-sensory dysfunction, cognitive decline, and frailty phenotypes to develop person-centered assessment, and integrated care in clinical practice.

Frailty phenotypes had different associations with the severity of HL and tinnitus, and the presentation of HL with tinnitus. Patients with cognitive decline or CF had higher risk for severe HL and tinnitus, and presented HL with tinnitus than robust and those with physical frailty. Patients with RCF or non-mobility RCF had lower risk for severe HL and tinnitus, and presented HL with tinnitus than those with PRCF or mobility RCF.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study was approved by the Ethics Committee of Huadong hospital and written informed consent was obtained from each volunteer or authorized representative. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QR and ZY designed the study and drafted the initial version of the manuscript. QR, JC, WZ, JR, and ZY collected the data, performed clinical and neuropsychological test measures, and data analysis. MZ, RZ, and CH performed hearing and tinnitus assessment. All authors contributed to the final version of the manuscript.

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Combined Chair-Based Exercises Improve Functional Fitness, Mental Well-Being, Salivary Steroid Balance, and Anti-microbial Activity in Pre-frail Older Women

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Introduction: Regular exercise has long been shown to positively impact the immune system responsiveness and improve mental well-being (MWB). However, the putative links between biomarkers of mental health and immune efficiency in exercising subjects have been scarcely investigated. The aim of this study was to verify the effect of a 14-week combined chair-based exercise program (CEP) on salivary steroid hormones and anti-microbial proteins, functional fitness, and MWB indexes in pre-frail older women.

Methods: The participant women (82.8 4.6 years old; n = 32) were randomly divided into the exercising group (CEP, n = 17) and the non-exercising control group (CG, n = 15). The pre/post assessment included: (1) salivary anti-microbial proteins lysozyme; (Lys) and immunoglobulin-A (IgA); (2) salivary steroid hormones of testosterone (TT) and cortisol (COR); (3) functional fitness (gait speed, hand grip strength, and static balance); (4) MWB questionnaires (happiness, depression state, satisfaction with life, and stress).

Results: Significant differences with large Cohen's *(d)* effect sizes were found on increased salivary TT ($p < 0.05$; $d = 0.60$) after exercise intervention. The results revealed a decrease in IgA levels after CEP ($p < 0.01$, $d = 0.30$). The increase in subjective happiness levels ($p < 0.05$, $d = 0.30$) and decrease of stress perception ($p < 0.01$, $d = 2.60$) and depressive state ($p < 0.05$, $d = 0.30$) were found after intervention in the CEP group. Robust statistical differences in gait speed ($p < 0.05$; $d = 0.60$) and balance

tests ($p < 0.05$; $d = 0.80$) were also found in the CEP group. In control, COR increased moderately ($p < 0.05$; $d = 0.65$) while no changes were found for the other indicators. Correlation analyses showed inter-dependence between pre–post variations of MWB, biochemical indexes, and fitness function (e.g., COR inverse correlation with hand grip strength and balance tests).

Conclusion: The CEP program was able to improve functional-fitness performance, decrease feelings of stress, and increase happiness. The CEP also induced clinically relevant hormonal and immune responses, which suggests that chair exercises that combine muscular strength, balance, and gait speed training are promising interventions to improve physical and mental health of older pre-frail adults.

Keywords: frailty, subjective well-being, aging, health, cortisol, testosterone, immune system

INTRODUCTION

Aging is a natural progressive process of morphologic and physiologic alterations that innately predisposes older populations to a gradual poor health regression (Clegg et al., 2013). Despite the natural decline of some cognitive and physiological functions with aging (Gruver et al., 2007), concomitant harmful factors, such as malnutrition, lack of physical activity, social isolation, depression, etc., could exacerbate these dysfunctions, aggravating the mental and physical adverse health conditions of older adults (Artaza-Artabe et al., 2016). This dysfunctional cognitive-physical state is called cognitive frailty, which is also recognized by the general vulnerability in offering a prompt homoeostatic response after a stressor episode, and are thought to be the result of cumulative weakening of many cognitive and psychophysiological functions throughout a lifecycle (Ruan et al., 2015).

Regarding the mechanisms of physiological responses to stress, it is well known that the hypothalamic–pituitary–adrenal (HPA) axis is highly responsive to emotional and environmental stress, displaying cortisol (COR) and testosterone (TT) as main protagonists of the psychosomatic effects of stress, especially via the autonomic nervous system (Hek et al., 2013). The exposure to chronic stressors, and consequently the hyperactivation of physiological stress systems, will increase heart rate and basal oxygen uptake, elevate COR, TT, and other steroid hormone levels (to induce endocrine imbalances) (Rhebergen et al., 2015), interfere in energy metabolism (with putative induction of metabolic disorders, such as obesity and related diabetes), hinder immune responses, and inhibit organism defensive systems (Baylis et al., 2013). Altogether, these factors will contribute to accelerate biological aging, often associated with severe comorbidities and frailty (Révész et al., 2014).

Among several non-pharmacological strategies to treat frailty, combined muscle strength and aerobic exercises–although still dependent on an adequate nutrition (Artaza-Artabe et al., 2016)–have been shown as the easiest and most cost-effective intervention to delay or reverse frailty to implement in primary care (Travers et al., 2019). Timely diagnosis and interventions to address frailty is essential for older individuals to build resilience and live independently, but also help health systems use resources more efficiently in the context of growing life expectancy worldwide (Park and Lee, 2010; Clegg et al., 2012; Jadczak et al., 2018).

The positive effects of regular exercise are extended throughout many biological levels in the practitioners, including metabolic adaptations (Barbosa et al., 2009), such as e.g., induction of muscle lactate dehydrogenase and tricarboxylic acid cycle enzymes, hepatic gluconeogenesis, more efficient protein turnover, etc., physiological gains (especially skeletal-contractile, cardiovascular, and respiratory capacities), adjustment of hormonal balance (glycemic glucagon/insulin ratio, TT and COR levels, etc.), and cognitive-psychological benefits, such as good mood, higher well-being perception, anxiolytic and anti-depressive effects, and others (Travers et al., 2019). Regarding older adults, all these benefits are strongly recommended to promote a safe, independent and physically–mentally healthy life (Walsh et al., 2011; Hogervorst and Clifford, 2012; Hatta et al., 2013).

Taking the physical limitations of frail (and pre-frail) older individuals, exercise adaptations and special training protocols have been suggested (Doody et al., 2019; Grimmer et al., 2019). Among many adapted protocols, chair-seated exercises have gained much interest nowadays since it imposes an autonomous resistance effort concomitantly avoiding risks of injuries and high impact on the articulations of practitioners (Rathleff et al., 2017; Furtado et al., 2020). Thus, the aim of this study is to verify the effect of a chair-based combined exercise program (CEP) on salivary COR, TT, and biomarkers of anti-microbial activity [immunoglobulin-A (IgA) and lysozyme (Lys), respectively], their link to functional status, and positive and negative mental well-being (MWB) in pre-frail older women.

MATERIALS AND METHODS

Initial Procedures

Older adult women (≥65 years) were recruited to participate in this study. The participants were residents of social and health care support centers from Coimbra, Portugal, and were part of a more comprehensive study protocol recently carried out by our group (Teixeira et al., 2016). Participants and their

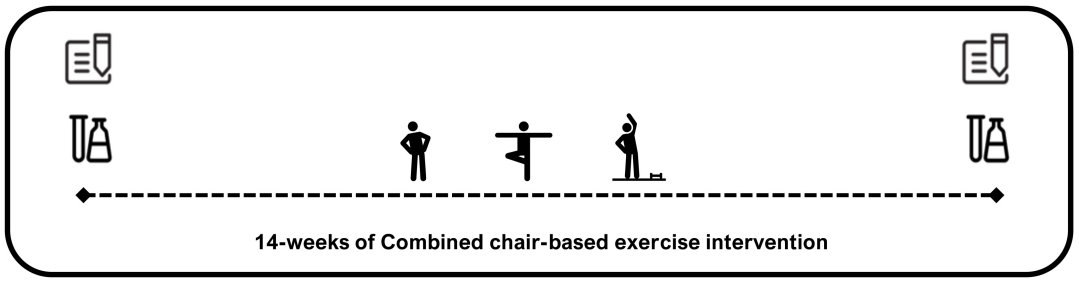

FIGURE 1 | Graphical scheme of intervention study design.

guardians were required to give a full informed written consent before beginning the research. This study was approved by the Faculty of Sport Sciences and Physical Education Ethical Committee–University of Coimbra reference code CE/FCDEF-UC/000202013; it respects the Portuguese Resolution (Art.° 4st; Law n. 12/2005, 1st series) on ethics in research with humans (Braga, 2013), follows the guidelines for ethics in scientific experiments in exercise science research (Shephard, 2002), and complies with the guidelines for research with human beings of the Helsinki Declaration (Petrini, 2014). This clinical trial is officially registered at ClinicalTrials.gov with the registration ID: NCT04435899.

Study Design

This is an interventional pre–post randomized (controlled) trial study that investigated the effects of a 14-week combined chair-based exercise program (CEP) on salivary immune biomarkers, functional fitness, and happiness–well-being perception in institutionalized pre-frail older women. Our hypothesis is that combined chair-based exercises will result in both physical (immunological and functional fitness) and mental improvements in pre-frail women, to bring them more autonomy and increase their quality of life. The physical and psychological tests were applied to all groups before and after (pre/post) the exercise intervention (**Figure 1**).

Sample Selection Criteria

Inclusion criteria were as follows: (i) women should be aged over 65 years; (ii) if dependent of drug therapy, it should be controlled and updated; (iii) if the participant presented a clinical condition or comorbidity, it must be stable and medicated (as shown in item ii); and (iv) they should be physically able to participate in exercise classes, based on local medical diagnosis. The Exclusion Criteria were (i) participating in other structured exercise programs; (ii) presenting severe cardiomyopathy, asthmatic bronchitis or uncontrolled hypertension, musculoskeletal disorders that limit physical tests (i.e., osteoarthritis, recent fractures), psychiatric disorder or dementia (e.g., diagnosed severe cognitive impairment or Alzheimer), hearing and vision impairment, morbid obesity or the use of medications that significantly affect attention; and (iii) adherence to the exercise program $\leq$60%. In addition, biosocial, social interactive behavior, and overall health status, evidenced by the local clinical staff reports, were also included as a post-inclusion criteria to finalize the selected group of participants.

Participants

The initial sample was composed of 60 institutionalized women, who were mainly sedentary from two social and health care institutions. We also recruited 18 additional participants to avoid an estimated loss of 30% of the participants during the study, based on previous studies from our group (Rieping et al., 2019). Accordingly, we counted 47 participants at the end of the intervention (age = 82.8 $\pm$ 4.6 years) who were randomly assigned to one of two groups using software (Randomizer App, V-team ESRB): the combined CEP (n = 17) and the non-exercising control group (CG) (n = 15) who received care as usual. The sample size was calculated using G*Power (version 3.1.9.2). Alpha was adjusted at 0.05 and power at 0.85 to allow for repeated measures ANOVA. A 14-week period was applied for the CEP intervention. The CG group did not participate in any type of supervised exercise intervention, but was encouraged to engage in complementary activities provided by the institutions, like outside tours, art education, and cultural activities, as well as maintaining their regular daily activities during the 14-week period (see **Figure 1**).

Comorbidities

The Charlson Comorbidity index (CCI) was used to identify possible comorbidities. This method predicts the levels of comorbidities and mortality by classifying (or weighting) comorbid conditions. This instrument has been widely used by health researchers to evaluate burden of disease and has a weighted index based on 17 comorbid conditions, which has been shown to predict 1- and 10-year mortality (Quan et al., 2011).

Combined Chair-Based Exercises

To create a progressive CEP to improve the walking capability, balance, and muscle strength and resistance, specific numbers of exercises (7–10) were performed with a determined number of repetitions (6–10), sets (2–3), cadence of execution (1:2), and rest between sets (45–60 s), following a circuit training protocol (Giné-Garriga et al., 2014). In addition, the CEB method was integrated in this program. The CEB consists of systematized and gradual exercises performed with a chair for support that guarantees the individual's stability during the session, respecting

individual limitations without discouraging individuals to reach beyond their limits (Kevin et al., 2011). However, the goal is to decrease the time of using the chair support, aiming to increase the standing position during the sessions. Intensity was indirectly calculated using Karvonen's formula to predict target heart rate (HR). The maximum HR (HR_{max}) was calculated using a specific formula for older population (Tanaka et al., 2001): [Target Heart Rate = [(HR_{max} – resting HR) × %Intensity] + resting HR]. The HR_{max} was monitored using heart rate monitors (Polar, RCX5) randomly distributed among participants. A low to moderate intensity effort, around 50–75% of maximum heart rate zone (HRz_{max}), was attained as recommended by the ACSM (Nelson et al., 2007). In addition, intensity was measured by the modified BORG scale of perceived exertion (PSE), that consists of an arbitrary scale ranging from 0 to 10 points (pts), with identical intervals and with reference to the quality of effort: (0) nothing at all; (1) very weak; (2) weak; (3) moderate; (4) somewhat strong; (5–6) strong; (7–9) very strong; (10) very, very strong (almost maximal). Each session was divided into five parts: 7 min of warm-up and body mobilization (PSE = 1–3, HRz_{max} = 50–55%); 15 min of low/upper body elastic-band exercises, 15 min of static and dynamic balance exercises, 15 min of sequential exercises improving gait speed (PSE 3–4, HRz_{max} = 56–70%) and finally, 7 min of stretching exercises as a "cool down" strategy (PSE 1–2, HRz_{max} = 45–50%). The frequency of classes was 2–3 times/week, for 14 weeks, to totalize 32 sessions and attendance was documented daily.

Assessments

The experimental approach collected information on the global health and biosocial status of the participants, applied the validated Portuguese version of psychometric rate scales for screening MWB, assessed the functional fitness of participants, measured the anthropometric indexes, and determined the salivary steroid hormones and anti-microbial protein levels. All data were collected and processed by expert technicians and trained researchers.

Frailty Status

Physical frailty (PF) was assessed using the hand grip strength test (HGT), following the criteria of the Fried protocol (Fried et al., 2001). Recent findings demonstrate that HGT is a useful single marker for frailty status screen (Syddall et al., 2003). The HGT test uses a hand-held dynamometer (HD), and strength kilograms is a unit of measure (Lafayette Dynamometer, model 78010, United States). The participants hold the HD in the dominant hand to be tested, with their elbow by the side of the body. When ready, the participant squeezes the HD with the highest isometric effort, which is sustained for 5 s. The best score of three trials was used for scoring purposes. The selected score was adjusted by gender and body mass index. In the case of this study, the cut-off value of BMI 23–28 (HGT scores 15–18 kg) was used for screen pre-frail individuals.

Salivary Biomarkers

Saliva collection was carried out in the morning (between 9:00 and 11:30 a.m.), at least 30 min after the first diurnal food intake. The participants remained seated, with their head slightly tilted down, eyes open, and oriented to perform a minimum of orofacial movements. Saliva samples were collected in polypropylene tubes, then sealed, and immediately refrigerated at −20°C. The levels of COR and TT in saliva were measured by competitive ELISA (kit #1-3002 and #1-2402, respectively; Salimetrics, United Kingdom). The concentrations of Lys and IgA in saliva were also determined by ELISA (respectively, kit ab108880, Abcam, United Kingdom; and #1-1602, Salimetrics, United Kingdom). The determination of salivary markers followed the manufacturer instructions and were described in a previous study (Allgrove et al., 2008). The sensitivity and range of detection limits for COR (<0.007 and 0.012–3.000 μg/dl), TT (1.0 and 6.1–300 pg/ml), Lys (0.1 and 0–300 μg/dl), and IgA (2.5 and 2.5–100 μg/dl) were reported by the manufacturer (Miller et al., 2013).

Global Health and Biosocial Status

Clinical and sociodemographic information was also collected: age, sex, marital status, and education. In addition, the comorbidity index was applied to screen the clinical history related to chronic diseases and cognition profile of the participants with the help of the institutional medical staff.

Anthropometric Measurements

The anthropometric measurements were performed following standardized procedures (Baumgartner et al., 1989). Body mass was measured (kg) using a portable scale (Seca, model 770, Germany) with a precision of 0.1 kg. Waist circumference was measured using a retractable glass fiber tape measure (Hoechstmass-Rollfix, Germany) with a precision of 0.1 cm. Stature was determined using a portable stadiometer (Seca Bodymeter, model 208, Germany) with a precision of 0.1 cm.

Nutritional Status

The nutritional status of participants was assessed using the Mini-Nutritional Assessment questionnaire (MNA). This is an 18-item questionnaire that includes four domains, namely, anthropometric, general health, dietary, and self-assessment of health and nutritional status. The maximum score of MNA is 30 pts, and classifies subjects as well-nourished (24–30 pts), having risk of malnutrition (17–23.5 pts), or as malnourished, score ≤17 pts (Guigoz, 2006).

Mental Well-Being

The Satisfaction with Life Scale (SWLS) was used to assess the subjective well-being perspective of the participants. SWLS measures global cognitive judgments of satisfaction with one's life. This scale is recommended as a complement to other instruments that focus on psychopathology or emotional well-being because it assesses an individual's conscious evaluative judgment of his or her life by using the person's own criteria. The five-item scale results in scores between 1 and 35 pts, with higher values representing higher levels of life's satisfaction (Laranjeira, 2009). The Happiness Face Scale (HFS) is a pictorial scale used for measuring global subjective happiness related to well-being.

The HFS consists of a graphical scheme containing seven faces with different expressions, using a progression of faces from "very happy" to "very sad," to address the question "How happy are you most of the time?" For each face is assigned one letter (A–G), in which letter A is considered the maximum happiness quotation (with 7 pts) and letter G the minimum value (with 1 pts). The participant will have to identify with one of the faces, depending on their state of happiness (Andrews and Withey, 1976). The Perceived Stress Scale (PSS) is the most widely used instrument for assessing the perception of stress. It is a measure of the level to which situations in one's life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. The scale also includes a number of direct queries about current levels of experienced stress. Seven out of the 14 items are considered negative and seven as positive. Final scores can vary from 14 to 70 pts, a higher score indicating greater feelings of stress (Trigo et al., 2010). The Centre of Epidemiologic Studies for Depression scale, called CES-D, was also applied. CES-D includes 20 items comprising six sub-scales reflecting major facets of depression: depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance (Gonçalves et al., 2014). Responses to each item are given on a four-point Likert scale (0–3) corresponding to the frequency with each symptom was experienced in the past week. Every answer is assigned a score from 0 to 3, respectively. The 20 items total an overall score between 0 and 60, in which the highest scores correlate with more depressive symptoms due to the occurrence frequency of the last week (Ros et al., 2011).

Functional Fitness

Muscle strength (kg) was measured by HGT using a HD, following the criteria described previously. Gait speed was determined using the 4.6 meters test (GST), which is expressed in seconds. This test consists of the participant walking this distance as quickly as possible. Two trials were performed and the lowest time was used for final scoring (Fried et al., 2001). To assess static balance, the Tandem Stance Balance Test (TSBT) was applied. The TSBT consists of the participant maintaining the standing position with open eyes and one foot in front of the opposite foot for a maximum of 30 s (Cho et al., 2004).

Exercise Engagement

The exercise adherence was calculated individually (as %) through the total sum of participation. After two consecutive absences, the participant was directly contacted by nursing home to return to the group classes. The minimum adherence accepted for the participant to take part in the study was 60% (exclusion criterion) to minimize bias evidence and in accordance with previous studies (Picorelli et al., 2014). To reduce disparity in data collection, the same evaluators performed the data collection both at baseline and follow-up assessments. The instructor of the sessions did not take part in the data collection processes.

Data Analysis

The Kolmogorov–Smirnov and visual inspection was done to check the distribution of data. For an older adult population, it should be noted that the intra-individual variability of the data becomes a major research challenge, with regard to homogeneity (Callisaya et al., 2010). Descriptive statistics were summarized as median and standard deviation (M ± SD). Comparisons between groups were performed using *t*-tests for two independent samples. The paired *t*-test accessed differences between variables pre- and post-exercise and percentage-based changes were calculated (Δ%). Linear correlations between all indexes were tested by calculating Spearman's rho factor. The between-subject mean and SD for each dependent variable was used to convert the changes of all indicators into standardized Cohen effect size (ES). The magnitude of ES was classified following the standards: trivial [$r \leq 0.3$]; moderate [$0.3 < r \leq 0.5$]; strong [$0.5 < r \leq 0.7$], and robust [$r \geq 0.7$] (Hopkins et al., 2009). The statistical analysis was made with SPSS 20.0 (Statistical Package for Social Sciences, IBM) and $p \leq 0.05$ used as the level of significance.

RESULTS

A total of 60 potential participants were initially screened for study admissibility (see flowchart; **Figure 2**). First, 13 participants were excluded by low interest in taking part of the study (personal decision after the study intervention was explained). Then, 47 older women who matched the inclusion criteria were assigned to the experimental group random division. In total, 13 participants withdrew for several reasons in the follow-up phase and two participants were excluded by low exercise engagement (exclusion criterium 60% adherence). A total of 32 participants (CEP, $n = 17$ and CG, $n = 15$) completed the 14-week study (see **Figure 1**). No adverse effects were detected as a result of participating in the intervention program. **Table 1** shows the baseline characterization of the sample. No statistically significant differences between groups were found. In other words, they were homogeneous for all variables at the beginning of the study.

Table 2 shows the pre- and post-exercise values of the salivary levels of steroid hormones and anti-microbial proteins, MWB, functional fitness, and health status of CEP and CG groups. Significant differences with strong ES were found for levels of salivary TT ($p < 0.05$; $d = 0.56$). The levels of COR showed a statistical tendency to increase in both CEP ($p = 0.06$; $d = 0.54$) and GC groups ($p = 0.07$; $d = 0.65$), with moderate ES. The levels of IgA decreased in the CEP group ($p < 0.01$, $d = 0.68$) with no changes in the CG. No changes were observed for Lys levels in both groups. In the MWB psychometric test of the HFS, significant differences with moderate ES were found for CEP ($p < 0.05$; $d = 0.30$), together with statistical significance with robust ES for the PSS ($p < 0.01$; $d = 2.60$). Significant differences with moderate ES were found for levels of depressive state ($p < 0.05$; $d = 0.45$). Regarding physical fitness tests, statistical differences with robust ES on GST ($p < 0.05$; $d = 0.60$) and TSBT ($p < 0.05$; $d = 0.80$) were observed in the CEP group, whereas no significant alterations were observed in all markers for the GC, except for COR ($p < 0.05$; $d = 0.65$), which showed a significant and moderate increase.

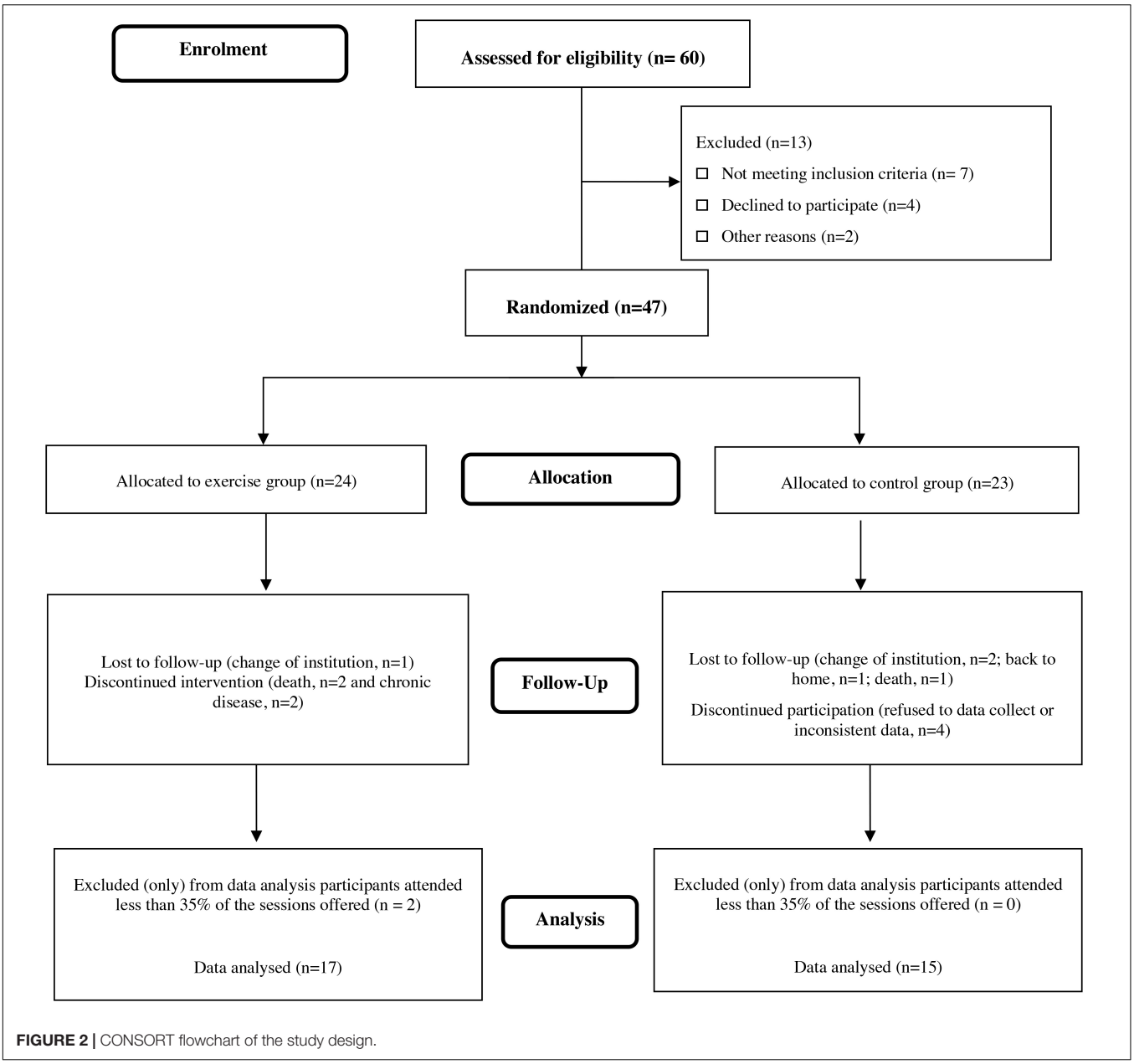

FIGURE 2 | CONSORT flowchart of the study design.

Results were also expressed as %pre–post variation (Δ%) for all variables after 14 weeks of exercise intervention for CEP group (**Figure 3**). The TT values decreased 14.6% in the CG, while an increase of 26.8% was observed in the CEP group. On the other hand, higher COR levels were both observed in CEP (+28.6%) and CG groups (+55%). Values of IgA decreased 26% in the CEP and 11% in the CG. Regarding Lys, the values also decreased 46% in the CEP group and 11% in the CG. MWB scores (PSS) presented a slight reduction in the CEP group PSS (−8.6%). Increases of HFS scores were also shown in CEP group (+35.2%), in contrast with the observed decrease of 16.2% in the CG group. Finally, lower GST times (−20.5%) and higher performance from the TSBT test (+123.8%) were found in the CEP group in this pre–post analysis.

Table 3 shows the correlation indexes between the Δ% of all variables analyzed in this study. Salivary COR showed (i) significant (but negative) and moderate correlation with HGT ($r = -0.48$; $p = 0.00$), (ii) a moderate and negative association with TSB ($r = -0.36$; $p = 0.04$), and (iii) a moderately positive association with IgA ($r = 0.49$; $p = 0.01$). The CES-D scale showed a negative and moderate correlation with HFS ($r = -0.36$; $p = 0.05$) and Lys ($r = -0.42$; $p = 0.02$) on the application of the exercise intervention. A negative and moderate association between SWLS and PSS was also found ($r = -0.35$; $p = 0.05$). Moderate and positive correlations between the GST score and HGT ($r = 0.35$; $p = 0.05$), and salivary Lys ($r = 0.39$; $p = 0.03$) scores were observed. In CG, no correlations were significantly observed between any of the Δ% values tested here.

TABLE 1 | Anthropometric, nutritional, and clinical characteristics of exercised (CEP) and control (CG) groups at the baseline of a 14-week program of chair-based exercises.

Variables	CEP (n = 17) M ± SD	CG (n = 15) M ± SD	f value	p value
Chronological age (years)	81.1 ± 7.5	83.3 ± 8.2	0.63	0.43
Height (m)	1.52 ± 0.06	1.51 ± 0.08	1.18	0.29
Weight (kg)	63.2 ± 10.7	68.7 ± 17.3	0.16	0.69
Body mass index (kg/m^2)	27.3 ± 4.5	30.2 ± 7.3	1.80	0.19
Charlson Comorbidity Index (score 0–20 points)	7.7 ± 1.9	8.7 ± 2.3	1.90	0.18
Mini Nutritional Assessment (score, 0–30 points)	23.7 ± 2.8	23.8 ± 2.9	0.00	0.92
Mini-Mental State Examination (score, 0–30 points)	19.2 ± 4.3	19.3 ± 5.0	0.00	0.98
Polypharmacy use	6.1 ± 1.2	5.1 ± 2.0	0.12	0.76

Comparison using t-test for independent samples.
M, mean; SD, Standard deviation; CEP, combined chair-based exercise program; CG, control group non-exercising.

DISCUSSION

The goals of this study were to verify the effects of CEP in the aging-related health dimensions of functional fitness, subjective well-being, and immune/anti-microbial activity of pre-frail older women. Our main findings indicate that the CEP was capable of improving performance in static balance and gait speed, decreasing feelings of stress, and increasing the state of happiness. The CEP program also showed a clinically relevant immune and anti-microbial response by changing levels of salivary TT, COR, IgA, and Lys. Although the older women participating in this study were properly characterized as pre-frail, it is tempting to suggest that the applied CEP described here, based on salivary biomarkers and well-being/happiness indexes, could also ameliorate physical and mental health of frail older individuals. However, more studies are necessary to address the efficiency of CEP related to the frail stage, when it should be applied, and the physically and mentally progression of the frailty status.

Salivary-Based Markers

Salivary COR levels are related to psychophysiological systems and they respond to stress stimuli, although the relationship established between COR levels, stress, and well-being is notoriously complex (Kudielka et al., 2009). Therefore, a decrease in salivary levels of COR could reflect a decrease in feelings of stress and, thereby, increased feelings of happiness. However, our results did not show significant correlations between the differences in cortisol levels and the scores from mental health questionnaires. In fact, COR levels increased after the 14-week CEP and this can probably be due to the effect of chronic exercise on the activation of the adrenal glands and stimulation of COR production (Furtado et al., 2016; Ahn and Kim, 2018). Interestingly, CEP participants did show a clear decrease in the stress scale levels together with an increase in the SWLS (see **Table 2**). COR is also known to stimulate degradation and inhibit synthesis of muscle proteins, contributing to reduced muscle strength, which is therefore associated with loss of physical function (van Schoor et al., 2007). As shown in **Table 2**, the performance in CEP group was improved in terms of static balance and gait speed. Also, negative correlations between changes (Δ%) in COR and both hand grip strength and static balance were indeed found, which reinforces the conclusion that COR increased levels in CEP are not due to increased stress levels, but represent an adaptation to physical exercise (Hatta et al., 2013). On the other hand, the moderate effect seen on cortisol levels in the CG could point to a poor mental health state because no improvements in those variables were seen.

It is known that a decrease in the concentration of circulating TT in older men is a natural process and possibly serves as a contributing factor to health problems (Harman et al.,

TABLE 2 | Statistical and effect size scores of pre- and post-intervention comparison of salivary hormones and anti-microbial proteins, mental well-being, functional fitness, and health status of older women.

	CEP (n = 17)			Cohen's d effect size	CG (n = 15)			Cohen's d effect size
	Pre M ± SD	Post M ± SD	Δ%		Pre M ± SD	Post M ± SD	Δ%	
Testosterone (μg/ml)	52.4 ± 26.3	66.5 ± 23.6*	+26.8	0.56	61.2 ± 28.1	52.2 ± 26.3	−14.7	0.33
Cortisol (μg/ml)	0.20 ± 0.11	0.26 ± 0.09	+28.6	0.54	0.20 ± 0.13	0.31 ± 0.20*	+55	0.65
Immunoglobulin-A (μg/ml)	262.1 ± 98.2	151.1 ± 93.1*	−42.3	0.68	365.2 ± 92.6	369.1 ± 85.6	+1	−0.01
Lysozyme (μg/ml)	2.57 ± 3.98	1.38 ± 1.60	−46.3	0.39	4.19 ± 3.44	4.07 ± 4.77	−2.8	0.01
State of Depression Scale	44.4 ± 9.1	40.4 ± 8.3	−9	0.45	37.2 ± 10.7	35.6 ± 7.8	−4.3	0.17
Perceived Stress Scale	27.9 ± 8.0	25.5 ± 7.7*	−8.6	0.30	28.4 ± 6.5	28.6 ± 4.9	+0.7	0.12
Happiness Face Scale	2.5 ± 1.0	3.4 ± 0.8**	+36	2.60	3.5 ± 1.8	2.9 ± 1.2	−17.1	0.17
Satisfaction with Life Scale	24.9 ± 5.8	25.5 ± 6.2	+2.5	0.10	21.7 ± 7.0	21.1 ± 6.2	−2.7	0.10
Hand grip strength test	19.6 ± 11.6	20.4 ± 10.0	+4	0.07	14.6 ± 4.4	14.5 ± 5.0	−0.6	0.01
4.6 meters gait speed test	12.8 ± 5.2	10.2 ± 3.2*	−20.3	0.60	18.7 ± 7.6	17.4 ± 6.4	−6.9	0.10
Tandem Stance Balance Test	2.6 ± 7.1	5.9 ± 9.0*	+123.8	0.80	2.8 ± 4.9	2.1 ± 2.0	−25	0.16

***$p < 0.01$; *$p < 0.05$.*
M, mean; CEP, combined chair-based exercise program; CG, control group non-exercising; Δ%, percent of variations.

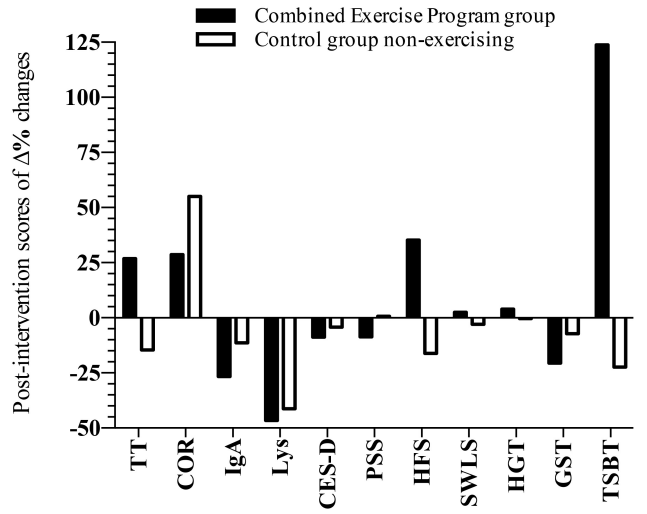

FIGURE 3 | Graphical representation of the pre–post variations (Δ%) of salivary hormones and anti-microbial proteins, MWB, functional fitness, and health status scores of older women after 14 weeks of CEP and non-exercising control group (n = 32). COR, cortisol; TT, testosterone; IgA, immunoglobulin-A; Lys, lysozyme; CES-D, Center of Epidemiology Studies for Depression scale; HFS, Happiness Face Scale; PSS, Perceived Stress Scale; SWLS, Satisfaction with Life Scale; TSBT, Tandem Stance Balance Test; HGT, Hand Grip Strength Test; delta percentage scores = [post-value/pre-value]–1.

2001). Low circulating TT concentration has been associated with cardiovascular disease, reduced cognition, fracture risk, and anemia (Yeap et al., 2018). However, the regular practice of physical exercise can attenuate this process by stimulating TT production and secretion in men and women (Kraemer et al., 2016). In our study, an increase in salivary TT levels was observed in the exercising CEP group ($p < 0.05$; $d = 0.56$), while a trend to decreasing levels was seen in the CG (**Table 2**). TT can be converted to estradiol and this can benefit many organ systems in female participants, but also directly beneficial effects of TT on female physiology and MWB has been found.

When it comes to the increase of TT after a training period, it is known that an acute hormonal effect (hormone increase) occurs when strength training is performed. However, it appears that the acute response is more pronounced for tissue remodeling than chronic changes, with several studies failing to show a significant variation during muscle strength (hypertrophy) training in the older adults (Kraemer and Ratamess, 2005; Kraemer et al., 2016). Regarding CEP, there are few studies that have evaluated the chronic and acute responses of this type of exercise to TT levels in physically frail elderly (Cadore et al., 2014). Previous studies from our group have shown that both aerobic-like and strength chair-based exercises, applied separately, also brought physical benefits to pre-frail older women, such as agility-dynamic balance, autonomy, lower fear of falling, etc. (Marques et al., 2017). Although not included in that experimental design, we suggest that similar hormonal adjustments to those observed here (TT and COR, **Table 2**) could have mediated the physical gains observed in a similar study (Rieping et al., 2019).

In addition to the known benefits of increased TT concentration for muscle strength and mass (Paunksnis et al., 2018), a neuroprotective effect is also believed to occur that may affect cognition via androgen and estrogen receptors in the hippocampus, decreasing the neuronal damage caused by oxidative stress and neuronal apoptosis (Yalamanchi and Dobs, 2017). However, the relationship found between endogenous TT and cognitive domains of the main global function such as memory, visuospatial performance, visuo-perceptual, attention, and executive function in healthy older men and women is still conflicting and more studies within this area need to be performed (Hogervorst and Clifford, 2012).

In the last years, few exercise intervention studies have examined salivary antimicrobial proteins, such as IgA and Lys (Allgrove et al., 2008; da Silva et al., 2009; Shibuya et al., 2015). In the study of Akimoto et al. (2003), 12 weeks of regular, moderate, and combined exercises apparently enhanced IgA in older individuals. However, his sample had a much younger average age (almost 20 years younger) and, for this reason, the authors may have observed different results. In another recent long-term intervention study, no changes but a trend toward a moderate increase in IgA secretion was observed after 28 weeks of low-intensity yoga exercises, whereas a trend toward a decrease of IgA secretion was found in the CG (Marques et al., 2017). Intensity of exercise does seem to be an important factor when IgA levels are concerned (Papacosta and Nassis, 2011).

Despite the lack of information regarding the chronic effects of exercise on Lys, some studies showed that Lys, IgA, and other salivary markers, such as alpha-amylase, seem to respond in a similar way during and after physical exercise (Allgrove et al., 2008). These markers share the same control and activation that are regulated by the autonomic nervous system, and are influenced by psychosocial stress (Nater et al., 2006). A negative correlation between the changes in Lys concentration and the CES-D scale did emerge in our study. There are, however, little data available regarding the changes in Lys levels with long-term exercise programs in older frail individuals. A recent study described that Lys secretion increased after moderate-intensity exercise and increased further after high-intensity exercise, which implies that Lys levels may be also related with exercise intensity (Papacosta and Nassis, 2011), and shows the same effects as found for IgA.

Mental Well-Being

The hypothetical premise that exercise behavior has benefits for subjective psychological well-being still takes place in current scientific discussions (Biedenweg et al., 2014). Many studies have defined subjective well-being as the absence of depressive and anxious symptoms. However, some authors added to this by using subjective perception of happiness and satisfaction with life as a marker of positive well-being (Stubbe et al., 2007).

The results of our study corroborate the recent meta-analysis that indicated that exercise was effective in improving the MWB of older people and that MWB in later life is modifiable

TABLE 3 | Spearman correlations between pre–post variations (Δ%) in the CEP group of salivary hormones and anti-microbial proteins, mental well-being, functional fitness, and health status scores of older women after 14 weeks of intervention.

Delta percentage score[#]		1	2	3	4	5	6	7	8	9	10
1. Cortisol											
2. Testosterone	*r*	0.303									
	p	0.092									
3. State of Depression Scale	*r*	−0.151	−0.008								
	p	0.410	0.965								
4. Perceived Stress Scale	*r*	0.237	0.055	0.169							
	p	0.191	0.764	0.355							
5. Happiness Face Scale	*r*	−0.137	0.111	**−0.356***	−0.069						
	p	0.454	0.544	**0.046**	0.708						
6. Satisfaction with Life Scale	*r*	−0.244	−0.107	−0.189	**−0.347**	−0.025					
	p	0.179	0.561	0.300	**0.050**	0.891					
7. Hand grip strength test	*r*	**−0.483****	−0.205	0.338	0.006	0.078	0.165				
	p	**0.005**	0.261	0.058	0.975	0.671	0.367				
8. 4.6 meters gait speed test	*r*	0.177	0.022	−0.193	−0.014	−0.030	−0.095	**−0.349***			
	p	0.334	0.904	0.291	0.939	0.870	0.605	**0.050**			
9. Tandem Stance Balance Test	*r*	**−0.358***	−0.068	−0.123	−0.090	0.300	0.218	0.198	−0.051		
	p	**0.044**	0.712	0.502	0.624	0.095	0.231	0.278	0.781		
10. Lysozyme	*r*	0.219	0.042	**−0.423***	−0.135	0.083	0.045	**−0.390***	−0.043	−0.116	
	p	0.229	0.821	**0.016**	0.460	0.652	0.805	**0.027**	0.816	0.528	
11. Immunoglobulin-A	*r*	**0.449***	−0.064	−0.219	0.243	−0.192	−0.190	−0.275	**0.342**	−0.027	−0.021
	p	**0.010**	0.730	0.228	0.181	0.292	0.297	0.127	**0.050**	0.883	0.907

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

[#]delta percentage scores = [post-value/pre-value]-1. Bold values represent statistically significant correlations.

through exercise and PA (Windle et al., 2010). In our study, participants exposed to exercise showed increasing levels of positive feelings (happiness and satisfaction with life) and decreased negative feelings (depression and stress). On the other hand, the non-exercise CG showed worse results with a tendency to a decrease in SWLS.

Positive effects of exercise participation have been reported suggesting increases on older adults' physical self-efficacy that might increase more positive perceptions of subjective well-being and effectively enhancing health-related quality of life (Atlantis et al., 2004; Elavsky et al., 2005; McAuley et al., 2006). The increase in physical functionality in our study may partly justify the results on the psychological side. However, we cannot rule out the influence of the effect of altering the context provided by the exercise program because all participants in the study had never participated in a systematic exercise with specialist teachers and regularity of practice.

Other studies show that systematic PA plays a key role in improving mood states (Oken et al., 2006), self-esteem (Opdenacker et al., 2009; Gothe et al., 2011), and life satisfaction in older adults (Fisher and Li, 2004; Elavsky et al., 2005), all relevant indicators of mental health and well-being. Further evidence for these positive effects of exercise on mental health and well-being in older people have recently been provided as a guideline for PA, and health policies in the United States, offering a strong evidence base for both preventive and therapeutic benefits of regular exercise in improving adult and elderly subjective well-being (National Institute of Aging - U.S, 2018). In European population, a research carried out in 15 countries for the Eurobarometer Study found a strong positive relationship between PA and mental health, revealing the need to implement strategic policies for active, healthy, and participative aging (Abu-Omar et al., 2004).

Functional Fitness

Our results suggest that CEP attenuated the decrease in functional fitness, even in very aged persons, which can be interpreted as a very positive result, because the physical abilities tested here have a direct connection with their daily life activities. Several studies that assessed multimodal, combined (or multicomponent) exercise-based interventions reported significant improvements in gait speed compared with CGs without exercise (Cadore et al., 2014; Eggenberger et al., 2015). Our results are in accordance with a previous study that concluded that physical exercise, especially when multiple conditioning components are used, is a key factor for the maintenance of the functionality of institutionalized older adults (Cadore et al., 2014).

Emerging evidence suggests that CEP seems to be the most helpful intervention for the prevention of functional decline in people living in social and health care institutions, especially

for the preservation or increase of gait speed ability (Giné-Garriga et al., 2010). Recent studies show that low to moderate intensity exercise programs could be enough to develop several functional fitness capacities consistently (Tarazona-Santabalbina et al., 2016). The dose–response relationship between the intensity of the exercises and functional fitness performance was the trademark of the satisfactory results obtained in this study because intensity progression was applied over the 14-week program course.

Correlations of Δ% Scores

The results of the statistical analysis on correlations confirmed the hypothesis that COR has an association with physical performance. In the study carried out recently, lower levels of diurnal COR were associated with lower levels of global functional fitness, and the opposite was also found regarding highly active subjects (Sousa et al., 2017). That feature led us to raise the hypothesis–also supported by a study from our group (Furtado et al., 2016)–that increasing the levels of COR, to clinically acceptable levels, can benefit the physical–functional performance of older adults.

On the other hand, the negative correlation between the increase of COR and the decrease in IgA promoted by exercise here was in agreement with similar studies already published, including those analyzing Δ% correlations of hormonal markers (Ahn and Kim, 2018). Also, some studies have reported that biological stress can lead to a stressor response at the biological level, causing an immune suppressive effect (Aw et al., 2007). However, many other behavioral factors may have influenced this change.

Other salivary markers, like Lys, also demonstrated significant correlation with psychological (CES-D) and functional physical performance markers (HGT), which may reveal clues about associations between these dimensions. Also, the identified correlations between negative and positive dimensions of MWB and exercise programs suggest that CEP can trigger beneficial psychological effects even in pre-frail old institutionalized populations (Stubbe et al., 2007).

Limitations

Participants cannot be blinded to group allocation, and we cannot confirm that local and social aspects did not influence the participants' perception of happiness, well-being, and other psychological status. Our discussion was carried out based on a study with older populations with similar characteristics because comparable previous studies with pre-frail individuals (focusing on the same variables) are still scarce. Other limitations are the number of participants (could be higher) and the fact that only women participated in this study.

Practical Applications

This study shows that combined CEPs can be safely and easily implemented in older adult populations. The results here (and other similarities) can be extended to a more contemporary approach, through the elaboration of practical application manuals, aimed to inform the benefits of this type of exercises. A good percentage of exercise engagement and significant effects in all dimensions reveal that combined chair-based exercises have high effectiveness in improving the well-being of these populations.

CONCLUSION

In conclusion, this study showed that the 14-week CEP program improved functional fitness, subjective well-being, and salivary TT levels in institutionalized older women. Therefore, CEPs could strongly contribute to trigger active behaviors, which could prevent an exponential and early increase of frail individuals in the population.

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 Faculty of Sport Sciences and Physical Education Ethical Committee–University of Coimbra reference code CE/FCDEF-UC/000202013. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GF was responsible for data collection and organized the writing of the manuscript. JT, AC, RR, AV-P, and CM helped in the writing of the manuscript. RL performed the statistical analysis. AT and JF coordinated the research, and together with MPB and EH, meticulously reviewed the language and helped with data interpretation. All authors critically revised the article for important intellectual content and approval of the final version.

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Clinical and Objective Cognitive Measures for the Diagnosis of Cognitive Frailty Subtypes: A Comparative Study

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Background: Cognitive frailty (CF) includes reversible and potentially reversible subtypes; the former is known as concurrent physical frailty (PF) and pre-mild cognitive impairment subjective cognitive decline (pre-MCI SCD), whereas the latter is known as concurrent PF and MCI. The diagnoses of pre-MCI SCD and MCI are based on clinical criteria and various subjective cognitive decline questionnaires. Heterogeneous assessment of cognitive impairment (CI) results in significant variability of CI, CF, and their subtype prevalence in various population-based studies.

Objective: This study aimed to compare the classification differences in CI and CF subtypes from PF and normal cognition by applying clinical and objective cognitive criteria. Clinical criteria comprised Fried PF and clinical MCI criteria combined with the SCD questionnaire, whereas objective criteria comprised Fried PF and objective cognitive criteria based on the norm-adjusted six neuropsychological test scores.

Methods: Of the 335 volunteers (age $\geq$ 60 years) in this study, 191 were diagnosed with CI based on clinical cognitive diagnosis criteria, and 144 were identified as robust normal based on objective cognitive assessment from the community-dwelling older adult cohort. Individuals with clinical CI, including 94 with MCI and 97 with pre-MCI SCD, were reclassified into different *z*-score-derived MCI, pre-MCI SCD, and normal subgroups based on objective cognitive criteria. The classification diagnostic accuracy of normal cognition, PF, pre-MCI, MCI, CF, and CF subtypes based on clinical and objective criteria was compared before and after adjusting for age, sex, and education level.

Results: The reclassification of objective assessments indicated better performance than that of clinical assessments in terms of discerning CI severity among different subgroups before adjusting for demographic factors. After covariate adjustment, clinical assessments significantly improved the ability to cognitively discriminate normal individuals from those with pre-MCI SCD and MCI but not the *z*-score-derived pre-MCI SCD and MCI groups from the robust normal group. Furthermore, the adjustment did

not improve the ability to discriminate among individuals with reversible CF from those with potentially reversible CF and pre-MCI only SCD from MCI only SCD.

Conclusions: Objective criteria showed better performance than clinical criteria in the diagnosis of individuals with CI or CF subtypes. Rapid clinical cognitive screening in combination with normative *z*-scores criteria is cost effective and sustainable in clinical practice.

Keywords: neuropsychological test, mild cognitive impairment, pre-mild cognitive impairment subjective cognitive decline, physical pre-frailty, physical frailty, reversible cognitive frailty, potential reversible cognitive frailty

INTRODUCTION

Cognitive frailty (CF) is defined as a clinical disorder with concurrent physical frailty (PF) and cognitive impairment (CI) but without dementia (Kelaiditi et al., 2013). Numerous epidemiological studies have shown that PF increases the risk of future cognitive decline and all-type dementia (Robertson et al., 2013; Kojima et al., 2016; Ma et al., 2019; Wallace et al., 2019). The combination of PF/physical prefrailty (PPF) and CI could better assess the risk for adverse outcomes in older adults (Forti et al., 2014; Yu et al., 2018; Aliberti et al., 2019; Meiner et al., 2020). CF can further be classified into two subtypes: reversible CF (RCF) and potentially reversible CF (PRCF). RCF is an optimal target for preventing elderly dependence (Ruan et al., 2015). However, the incidences of RCF and PRCF reportedly vary—from 2.5 and 1% to 19.86 and 6.3%, respectively—according to various population-based studies (Panza et al., 2018; Sugimoto et al., 2018; Ruan et al., 2020a). The use of different CF models, such as PPF or premild CI (MCI) subjective cognitive decline (SCD) that includes early (or cognitive compensation stage) and two later stages of subtle cognitive decline (Jessen et al., 2014), is considered a cause of such diversity; moreover, the different tools available for the assessment of PF have contributed to a marked variability in results (Canevelli and Cesari, 2017). The PF phenotype that includes PPF and PF, developed in the US Cardiovascular Health Study, is widely used by researchers to screen PF. Typically, CF models only contain the PF phenotype that was assessed using these modified criteria (Fried et al., 2001). Most studies involved PRCF resulting from the combination of PF and MCI. Only two studies have involved RCF resulting from the combination of PF and pre-MCI SCD (Solfrizzi et al., 2017) and that of PF/PPF and pre-MCI SCD (Ruan et al., 2020a).

Another more important cause of the significant variability of CF prevalence in various population-based studies is the heterogeneous assessment of CI. For the assessment of MCI, major studies have adopted global cognition screening measures, such as the Mini-Mental State Evaluation (MMSE) and the Montreal Cognitive Assessment (MoCA), to diagnose CI according to predetermined cutoff ranges (Trzepacz et al., 2015; Bosco et al., 2017, 2020). Although these measures can assess cognitive performance in different cognitive domains, the MMSE was less likely to detect early MCI because of ceiling effects in healthy controls (Trzepacz et al., 2015). The MoCA is a more difficult test than the MMSE, has fewer floor and ceiling effects, and is more sensitive than the latter for the detection of early cognitive decline (Larner, 2012; Trzepacz et al., 2015). However, the MoCA may yield scores lower than the cutoff values owing to the effect of demographic factors (Rossetti et al., 2011). A Clinical Dementia Rating (CDR) score of 0.5 is unlikely to differentiate MCI severity and MCI subtypes (Chang et al., 2011). To date, only two studies have adopted pre-MCI SCD for RCF diagnosis (Solfrizzi et al., 2017; Ruan et al., 2020a). Although the pre-MCI SCD criteria frame proposed by the SCD-I Working Group (Solfrizzi et al., 2017) was adopted, it is not suitable for the identification of slightly abnormal cognitive performance or subtle cognitive decline. Furthermore, pre-MCI SCD diagnosis in major studies is based on various self-reported questionnaires related to the memory domain (Rami et al., 2014; Rabin et al., 2015). Therefore, establishing objective cognitive criteria is essential for accurately diagnosing CI, CF, and their subtypes.

In the past few years, normative *z*-scores on the neuropsychological test battery have been established based on data collected in a cognitively normal population (Weintraub et al., 2009; Weintraub et al., 2018; Ruan et al., 2020b). It was possible to objectively identify pre-MCI SCD, MCI, and MCI subtypes. The false-positive diagnostic errors caused by the clinical MCI criteria (Edmonds et al., 2015a,b) significantly decreased using normative *z*-scores of domain-specific tests. When process *z*-scores obtained from learning and memory tests were integrated into non-invasive objective criteria, early pre-MCI SCD could be objectively diagnosed (Thomas et al., 2018). Moreover, patients with objective pre-MCI SCD showed early entorhinal pathological changes and faster amyloid accumulation but less widespread medial temporal neurodegeneration than the observations in patients with MCI (Thomas et al., 2020). Therefore, if objective criteria for MCI and pre-MCI SCD are integrated into the CF criteria, the accuracy of the diagnosis of CF subtypes would significantly improve.

The differentiating factor between the clinical and objective criteria is the number of tasks used—only screening tests versus additional tests for each cognitive domain. Objective criteria are more effective when they are based on additional cognitive tests. The present study aimed to explore the diagnostic accuracy of CI, CF, and their subtypes by comparing the discordance between clinical [clinical MCI criteria combined with the Spanish SCD questionnaire (SCD-Q) MyCog scores] (Rami et al., 2014) and objective assessments of CI in different subgroups based on cognitive status and CF stratifications.

MATERIALS AND METHODS

Participants

Overall, 367 volunteers (age ≥ 60 years) were recruited from communities across Shanghai via face-to-face communication in each setting. Clinical assessment and neuropsychological tests were conducted from September 2018 to June 2019. After excluding individuals with severe disability, complete loss of hearing and vision, and dementia, 335 eligible individuals (age ≥ 60 years) were included in the study. Among these participants, 94 met the clinical criteria for MCI (Petersen et al., 2001), and 97 met the criteria for pre-MCI SCD based on the SCD-Q MyCog scores (Rami et al., 2014) after excluding individuals with MCI. Furthermore, 144 robust normal individuals having at least 1 year of follow-up data and meeting the normal cognition criteria based on objective diagnosis (the *z*-scores of six neuropsychological tests) at the second annual study visit were used as controls in the study (Sliwinski et al., 1996; Ruan et al., 2020b). The 191 participants diagnosed with MCI or pre-MCI SCD using clinical cognitive criteria were further reclassified by objective cognitive diagnosis. This study was approved by the Ethics Committee of Huadong hospital, and written informed consent was obtained from each volunteer or authorized representative.

Clinical Evaluation

Participants were classified as MCI if they met the following criteria: (1) subjective memory complaint if their MyCog score was ≥7 (Rami et al., 2014); (2) CDR score of 0.5; (3) an MMSE score of 19–30 for education levels (cutoff scores: >19 for illiteracy, >22 for primary school, and >26 for middle school and above; Petersen et al., 2001); (4) no or minimal impairment in activities of daily living as determined by a clinical interview with the patient and informant (Lawton and Brody, 1969); and (5) not demented based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (American Psychiatric Association, 1994). Participants were classified as pre-MCI SCD if their MyCog score was ≥7 (Rami et al., 2014) after excluding MCI. Depression symptomatology was excluded using the short form of the Geriatric Depression Scale (GDS) (Chau et al., 2006). The cognitive and non-cognitive subscales of the Alzheimer's Disease Assessment Scale (ADAS-Cog and ADAS-Non-cog, respectively) were used to evaluate the severity of CI and behavior alteration (Rosen et al., 1984). The self-report severity scores based on a brief version of the Neuropsychiatric Inventory Questionnaire (NPI-Q) were used to evaluate the severity of neuropsychiatric symptoms (Kaufer et al., 2000).

Neuropsychological Evaluation

According to the criteria reported in the literature with minor modification (Edmonds et al., 2015b; Thomas et al., 2018), MCI and pre-MCI SCD status were assessed using the normative *z*-scores of six neuropsychological tests and process *z*-scores of the Hopkins Verbal Learning Test-Revised (HVLT-R) (Ruan et al., 2020b). The tests are as follows: Trail Making Test A and B (TMT A and B) for executive or attention domain; Boston Naming Test and Animal List generation for language domain; HVLT-R for memory domain, including delayed free correct responses and HVLT-R recognition; and three process scores from the HVLT-R for identifying early pre-MCI SCD. Briefly, the HVLT-R is a 12-item (4 words from 3 semantic categories) word-list learning and memory test that includes three learning trials (List A, Trials 1–3); an interference trial with a different list (List B); a short-delay free recall trial (Trial 4) for List A; a long-delay free recall trial (Trial 5) for List A after 25 min; and delayed recognition of 24 words, including 12 List A words and 6 related and 6 unrelated non-List A words. The three process scores from the HVLT-R included the following: learning slope [(List A Trial 3–List A Trail 1)/3], retroactive interference (List A Trial 4/List A Trial 3), and intrusion errors (total number of extralist intrusion errors across all recall trials). Other neuropsychological test batteries, including digit span forward or backward and digit symbol (Ruan et al., 2020b), to assess attention/processing speed domain were also performed for verifying the correction of objective criteria based on six previous neuropsychological test batteries and three memory process scores.

MCI and Pre-MCI SCD Evaluation by Normative *Z*-Scores

All raw total or process scores were converted to age-, education-, and sex-adjusted *z*-scores based on regression coefficients derived from our robust normal samples (Ruan et al., 2020b). If a participant had *z*-scores of >1 standard deviation (SD) from the norm on TMT A, TMT B, and intrusion errors or *z*-scores of <1 SD from the norm on the other measures of six neuropsychological test batteries, the individual was considered to have an impaired total score (the normative *z*-scores of six neuropsychological tests) or process score (**Supplementary Table 1**). The 191 participants with CI as diagnosed by clinical criteria were further classified by *z*-scores as pre-MCI SCD [two impaired process scores or one impaired process score and one impaired total score or impaired total score on two measures across different cognitive domains or Functional Assessment Questionnaire (FAQ) score of 6–8] or MCI [impaired total score on two measures in the same domain or one impaired score in each of three cognitive domains (memory, executive function, and language domains) or FAQ score of ≥9]; the remainder were classified as cognitively normal after exclusion of CI.

PF Evaluation

The five-item Fried PF scale (fatigue, weakness, slowness, low physical activity, and weight loss) with Chinese reference values (Hao et al., 2017) was used to assess PF phenotypes in the sample. Scores on the Fried PF scale ranged from 0 to 5, with scores of 1–2 representing pre-frail and 3–5 representing frail.

Evaluation of CF Subtypes

Participants were classified as RCF if they had both PPF/PF and pre-MCI SCD and as PRCF if they had both PPF/PF and MCI (Ruan et al., 2015).

ApoE Genotyping

Two single-nucleotide polymorphisms (rs429358 and rs7412) were genotyped to identify the APOE genotypes containing the APOE ε2, ε3, and ε4 alleles using a SNaPshot minisequencing assay from peripheral whole blood samples (Kim et al., 2010). The individuals were divided into the following subgroups according to the frequency of ε4: 0, 1, and 2.

Statistical Analysis

All continuous variables were assessed using one-sample Kolmogorov–Smirnov test and were deemed to be non-normally distributed. Descriptive statistics were reported as medians and interquartile ranges for continuous variables and as absolute numbers and percentages for categorical variables. The differences among the demographic, neuropsychological, and clinical characteristics of subgroups based on objective cognitive criteria were compared using the Kruskal–Wallis and chi-squared tests. Statistical significance was determined using a cutoff *P*-value of 0.050. These multiple comparisons of clinical and objective measures were further analyzed using nominal regression analyses after adjusting for age, sex, and education level. Data were analyzed using the SPSS 18.0 software.

RESULTS

Comparison Between Clinical and Objective Assessments of CI

The 191 participants with pre-MCI SCD or MCI diagnosed using clinical cognitive criteria were divided into *z*-score-derived pre-MCI SCD and MCI and *z*-score-derived normal subgroups based on objective cognitive criteria. The characteristics of the three subgroups and robust normal controls are presented in **Table 1**. Age in the *z*-score-derived MCI group was higher than that in the *z*-score-derived normal groups ($P < 0.05$). The education level of the *z*-score-derived MCI and pre-MCI SCD groups was significantly lower than that of the robust normal control group ($P < 0.001$); furthermore, the education level of the *z*-score-derived MCI group was lower than that of the *z*-score-derived normal groups ($P < 0.01$). The frequency of ApoE ε4 was significantly lower in the robust normal control group, whereas ApoE ε4/ε4 was only observed in the *z*-score-derived MCI and pre-MCI SCD groups. Among the 94 individuals with MCI diagnosed using clinical criteria, only 34 (36.2%) were accurately diagnosed, whereas the other 26 (27.7%) had normal cognitive function. The remaining 34 (36.2%) individuals were diagnosed with pre-MCI SCD using objective criteria (**Table 1** and **Figure 1A**). Among the 97 individuals with pre-MCI SCD diagnosed using clinical criteria, only 27 (27.8%) were accurately diagnosed; 30 (30.9%) individuals had MCI, and the remaining 40 (41.24%) had normal cognitive function as determined by objective criteria (**Table 1** and **Figure 1A**). The *z*-score-derived pre-MCI SCD group showed the highest prevalence of PPF, whereas the *z*-score-derived MCI group exhibited the highest prevalence of PF. The *z*-score-derived normal group had a significantly higher prevalence of PF and PPF than the robust normal control group. Only 68.8% of the individuals with *z*-score-derived MCI had PRCF and 72.1% of the individuals with *z*-score-derived pre-MCI SCD had RCF (**Table 1**).

All raw scores of objective measures, excluding the process scores of intrusion errors, revealed significant differences among the four subgroups (**Table 1**). However, clinical measures demonstrated less ability to discriminate CI severity compared with objective raw scores. Only ADAS-Cog scores were significantly different between the *z*-score-derived normal or robust normal groups and the *z*-score-derived MCI and pre-MCI SCD groups and could differentiate between the *z*-score-derived MCI and pre-MCI SCD groups as well as between the *z*-score-derived normal and robust normal groups (**Table 1**). The MMSE scores were significantly higher in the *z*-score-derived normal or robust normal groups than in the *z*-score-derived MCI and pre-MCI SCD groups. However, the MMSE scores did not significantly differ between the *z*-score-derived MCI and pre-MCI SCD groups. ADAS Non-Cog scores were significantly different between the *z*-score-derived normal and pre-MCI SCD groups and between the pre-MCI SCD and MCI groups. The CDR scores and SCD-Q MyCog scores were not significantly different among the *z*-score-derived normal, MCI, and pre-MCI SCD groups.

After adjusting for demographic factors, the scores of objective cognitive measures, including TMT A, TMT B, HVLT-R recognition, learning slope, retroactive interference, digit span forward, digit span backward, and digit symbol, were significantly different between the *z*-score-derived normal or robust normal and the *z*-score-derived MCI and pre-MCI SCD groups and not between the *z*-score-derived normal or robust normal groups (**Table 2**). Only the scores of intrusion errors showed no significant difference among the four groups. The discriminating ability of clinical measures for CI evidently improved after adjusting for age, sex, and education level. The MMSE, ADAS-Cog, and SCD-Q MyCog scores significantly differed between the *z*-score-derived normal or robust normal and the *z*-score-derived MCI and pre-MCI SCD groups as well as between the *z*-score-derived normal and robust normal groups (**Table 2**). Compared with the robust normal control, the scores of the non-cognitive measures ADAS Non-Cog, GDS, FAQ, and NPI-Q were significantly higher in the *z*-score-derived MCI and pre-MCI SCD groups. In addition, the GDS and NPI-Q scores were significantly or marginally high in the *z*-score-derived normal group.

Comparison Between Clinical and Objective Assessments of CF

Characteristics of CF, PF/PPF only, CI only (*z*-scored derived pre-MCI SCD/MCI), and normal (no PF/PPF and CI) subgroups reclassified according to the Fried PF/PPF, objective cognitive, and CF criteria are presented in **Table 3**. There were significant differences in age and education level but not in sex. The frequency of ApoE ε4 was lower in the normal group (12.96%) than in other subgroups, and individuals with ApoE ε4/ε4 were only observed in the CF and CI groups.

TABLE 1 | Demographic, neuropsychological, and clinical characteristics [medians and interquartile ranges (Q25–Q75) for continuous variables and absolute numbers or percentages for categorical variables] of experimental samples after reclassification by adopting objective cognitive assessment (neuropsychological test *z*-scores) criteria and for the robust normal control group.

	***Z*-scores derived MCI (*n* = 64)**	***Z*-scores derived pre MCI SCD (*n* = 61)**	***Z*-scores derived normal (*n* = 66)**	**Robust normal (*n* = 144)**	χ^2	***p***
Demographics						
Age (years)	75.00 (69.25, 81.00)[b]	72.00 (67.00, 78.00)	71.00 (66.75, 76.25)	72.00 (67.00, 79.75)	5.081	0.166
Education (years)	9.00 (8.00, 12.00)[a,b]	9.00 (9.00, 12.50)[a]	12.00 (9.00, 14.00)[a]	12.00 (9.00, 16.00)	32.492	0.000
Gender (% male)	29 (45.313%)	19 (31.148%)	30 (45.50%)	72 (50.00%)	6.392	0.094
Apoe ε4/ε4 frequency (*n* = 184)	38/64	38/61	40/66	68/144	13.409	0.037
0	32	30	27	62		
1	5	7	13	6		
2	1	1	0	0		
Clinical stratification						
MCI (*n* = 94)	34	34	26	–	–	–
Pre-MCI SCD (*n* = 97)	30	27	40	–	–	–
Physical frailty					37.488	0.000
Without PF or PPF	20 (31.3%)	16 (26.2%)	24 (36.4%)	78 (54.167%)		
PPF	26 (40.6%)	38 (62.3%)	36 (54.5%)	59 (40.972%)		
PF	18 (28.1%)	7 (11.5%)	6 (9.1%)	7 (4.861%)		
Cognitive frailty					441.183	0.000
Without CF	20 (31.3%)	16 (26.2%)	66 (100%)	144 (100%)		
RCF	–	45 (73.8%)	–	–		
PRCF	44 (68.8%)	–	–	–		
Objective measures (raw)						
TMT. A	78.00 (59.00, 121.00)[a,b,c]	54.00 (41.00, 71.50)[a,b]	43.00 (36.00, 59.00)	42.00 (35.00,52.00)	77.000	0.000
TMT. B	118.00 (86.25, 192.50)[a,b,c]	74.00 (60.50, 100.50)[a]	71.50 (58.00, 90.25)[a]	65.00 (52.00, 79.75)	63.926	0.000
HVLT-R delayed recall	2.00 (0.00, 3.50)[a,b,c]	3.00 (1.00, 5.00)[a,b]	5.00 (4.00, 7.00)	6.00 (4.00, 8.00)	90.794	0.000
HVLT-R recognition	10.00 (7.50, 11.00)[a,b]	10.00 (9.00, 11.00)[a,b]	11.00 (10.00, 12.00)	11 (10.00, 12.00)	35.883	0.000
Learning slope	1.00 (0.50, 1.333)[a,b]	1.00 (0.333, 1.00)[a,b]	1.333 (1.00, 1.667)	133 (1.00, 1.67)	39.026	0.000
Intrusion errors	3.00 (1.00, 6.00)	4.00 (1.25, 6.00)	3.00 (2.00, 4.750)	3.00 (1.00, 5.00)	3.312	0.346
Retroactive interference	0.600 (0.330, 0.817)[a]	0.500 (0.298, 0.788)[a,b]	0.667 (0.500, 0.871)	0.75 (0.58, 0.88)	24.456	0.000
BNT	23.00 (20.00, 25.00)[a,b,c]	25.00 (22.75, 27.00)[a,b]	26.000 (25.00, 28.00)[a]	28.00 (26.00, 29.00)	97.207	0.000
Animal fluency	12.00 (10.00, 14.00)[a,b,c]	14.00 (12.00, 17.00)[a,b]	16.50 (15.00, 19.00)[a]	18.00 (16.00, 21.00)	107.188	0.000
Digital span forward	6.00 (5.00, 7.00)[a,b]	6.00 (5.00, 7.00)[a,b]	7.00 (6.00, 8.00)	7.00 (6.00, 8.00)	29.697	0.000
Digital span backward	4.00 (3.00, 4.00)[a,b]	4.00 (3.00, 5.00)[a,b]	4.00 (3.00, 5.00)	4.00 (4.00, 5.00)	18.402	0.000
Digital symbol	22.00 (16.25, 30.00)[a,b]	27.00 (20.50, 35.00)[a,b]	31.00 (23.50, 37.00)	33.00 (27.00, 39.75)	39.047	0.000
Clinical measures						
MMSE	26.00 (25.00, 28.00)[a,b]	26.00 (25.00, 27.50)[a,b]	27.00 (26.00, 28.75)[a]	28.00 (27.00, 29.00)	78.825	0.000
CDR = 0.000/0.5 (% = 0.5)	54/6 (10%)	54/1 (1.8%)	63/1 (1.6%)	125/0.000 (0.000)	16.519	0.001
ADAS Cog	20.70 (13.670, 25.330)[a,b,c]	16.660 (13.668, 21.000)[a,b]	13.660 (10.00, 17.340)[a]	10.83 (7.31, 16.00)	60.689	0.000
ADAS Non-Cog	3.00 (1.00, 6.00)[a,b]	2.00 (1.00, 4.00)[a]	2.00 (0.000, 4.00)	2.00 (0.25, 3.00)	14.691	0.002
GDS	3.00 (2.00, 6.00)[a]	4.00 (2.50, 7.00)[a]	3.00 (2.00, 6.00)[a]	2.00 (1.00, 5.00)	20.239	0.000
SCD-Q, MyCog	10.50 (5.25, 13.00)[a]	10.00 (6.50, 12.50)[a]	9.00 (6.75, 13.00)[a]	3.000 (1.00, 4.00)	139.046	0.000
Function *Q*	1.00 (0.00, 6.00)[a,b]	1.00 (0.00, 3.00)[a,b]	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	28.484	0.000
NPI-Q score	0.00 (0.00, 2.00)[a]	1.00 (0.00, 3.00)[a]	0.00 (0.00, 3.00)[a]	0.00 (0.00, 1.00)	16.362	0.001

[a]Significantly different from robust normal control, [b]significantly different from Z-scores derived normal control, [c]significantly different from Z-scores derived pre-MCI SCD. Number of subjects with data. Qi, i^{th} quantile.

BNT, Boston Naming Test; TMT. Part A and B, Trail Making Test A and B; HVLT-R, the Hopkins Verbal Learning Test-Revised; MMSE, the Mini Mental State evaluation; CDR, Clinical Dementia Rating; ADAS Cog, cognitive subscale of the Alzheimer's Disease Assessment Scale; ADAS Non-Cog, non-cognitive subscale of the Alzheimer's Disease Assessment Scale; GDS, the Geriatric Depression Scale; SCD-Q, subjective cognitive decline questionnaire; FAQ, Functional Assessment Questionnaire; NPI-Q, neuropsychiatric inventory questionnaire; PRCF, Potentially reversible cognitive frailty; RCF, Reversible cognitive frailty; PF, Physical frailty; PPF, Physical pre-frailty.

When the clinical cognitive criteria were integrated into the CF criteria, 63 of 94 individuals were diagnosed with PRCF and 68 of 97 were diagnosed with RCF (**Table 3**). However, when objective cognitive criteria replaced the clinical criteria in the CF criteria, only 22 of 63 (34.9%) individuals were diagnosed with PRCF. Conversely, 25 (39.7%) individuals were diagnosed with

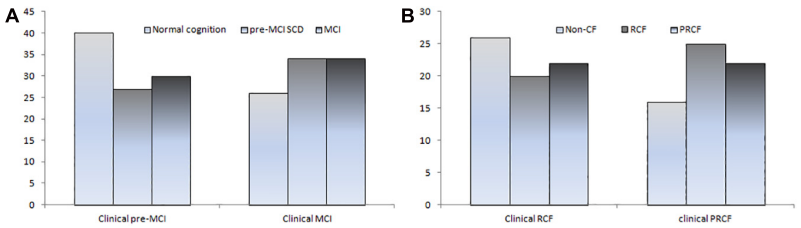

FIGURE 1 | Number of CI **(A)** and CF subtypes **(B)** based on clinical criteria was reclassified according to objective cognitive criteria.

TABLE 2 | Results from nominal regression analyses that evaluated the difference of cognitive stratification by clinical or objective measures after adjusting by sex, age, and education level (the reference category is robust normal).

	Z-scores derived MCI			*Z*-scores derived pre-MCI SCD			*Z*-scores derived normal		
	***B* (standard error)**	**OR(95%CI)**	***p***	***B* (standard error)**	**OR(95%CI)**	***p***	***B* (standard error)**	**OR(95%CI)**	***p***
Objective measures									
TMT A	0.067 (0.010)	1.069 (1.048, 1.091)	0.000	0.047 (0.010)	1.048 (1.028, 1.068)	0.000	0.017 (0.010)	1.017 (0.997, 1.038)	0.094
TMT B	0.038 (0.006)	1.039 (1.026, 1.052)	0.000	0.012 (0.006)	1.012 (1.000, 1.025)	0.050	0.010 (0.006)	1.010 (0.998, 1.023)	0.092
HVLT-R delayed recall	−0.721 (0.098)	0.486 (0.401, 0.589)	0.000	−0.551 (0.087)	0.576 (0.486, 0.683)	0.000	−0.141 (0.069)	0.868 (0.759, 0.994)	0.040
HVLT-R recognition	−0.560 (0.107)	0.571 (0.463, 0.705)	0.000	−0.396 (0.108)	0.673 (0.545, 0.831)	0.000	−0.054 (0.121)	0.947 (0.748, 1.200)	0.654
Learning slope	−0.856 (0.283)	0.425 (0.244, 0.740)	0.002	−1.198 (0.282)	0.302 (0.174, 0.524)	0.000	0.227 (0.272)	1.254 (0.737, 2.136)	0.404
Intrusion errors	0.078 (0.056)	1.082 (0.969, 1.207)	0.162	0.090 (0.053)	1.094 (0.987, 1.213)	0.089	0.015 (0.055)	1.015 (0.911, 1.131)	0.786
Retroactive interference	−0.746 (0.439)	0.474 (0.201, 1.121)	0.089	−1.043 (0.489)	0.352 (0.135, 0.919)	0.033	−0.518 (0.425)	0.596 (0.259, 1.371)	0.223
BNT	−0.609 (0.081)	0.544 (0.464, 0.638)	0.000	−0.405 (0.075)	0.667 (0.576, 0.772)	0.000	−0.257 (0.071)	0.774 (0.673, 0.889)	0.000
Animal fluency	−0.471 (0.063)	0.624 (0.551, 0.706)	0.000	−0.297 (0.054)	0.743 (0.669, 0.826)	0.000	−0.129 (0.043)	0.879 (0.808, 0.956)	0.003
Digital span forward	−0.349 (0.118)	0.705 (0.559, 0.889)	0.003	−0.240 (0.113)	0.787 (0.630, 0.982)	0.034	−0.059 (0.111)	0.943 (0.759, 1.171)	0.595
Digital span backward	−0.412 (0.176)	0.663 (0.469, 0.935)	0.019	−0.223 (0.159)	0.800 (0.587, 1.092)	0.160	0.082 (0.139)	1.085 (0.827, 1.424)	0.555
Digital symbol	−0.101 (0.023)	0.904 (0.863, 0.946)	0.000	−0.072 (0.021)	0.931 (0.893, 0.970)	0.001	−0.024 (0.018)	0.976 (0.942, 1.011)	0.182
Clinical measures									
MMSE	−0.687 (0.111)	0.503 (0.405, 0.626)	0.000	−0.707 (0.110)	0.493 (0.397, 0.612)	0.000	−0.524 (0.104)	0.592 (0.483, 0.726)	0.000
ADAS Cog	0.196 (0.031)	1.217 (1.146, 1.293)	0.000	0.158 (0.029)	1.172 (1.106, 1.241)	0.000	0.062 (0.028)	1.064 (1.008, 1.124)	0.024
ADAS Non-Cog	0.189 (0.057)	1.208 (1.081, 1.350)	0.001	0.072 (0.062)	1.075 (0.952, 1.214)	0.244	0.051 (0.061)	1.053 (0.934, 1.186)	0.399
GDS	0.137 (0.055)	1.147 (1.030, 1.277)	0.012	0.161 (0.052)	1.174 (1.060, 1.301)	0.002	0.103 (0.051)	1.109 (1.002, 1.226)	0.045
SCD-Q, MyCog	0.485 (0.062)	1.625 (1.440, 1.833)	0.000	0.491 (0.062)	1.633 (1.448, 1.843)	0.000	0.510 (0.061)	1.665 (1.476, 1.877)	0.000
FAQ sore	0.418 (0.091)	1.519 (1.271, 1.815)	0.000	0.306 (0.092)	1.359 (1.135, 1.626)	0.001	0.067 (0.115)	1.069 (0.854, 1.339)	0.559
NPI-Q score	0.210 (0.078)	1.234 (1.060, 1.437)	0.007	0.248 (0.076)	1.281 (1.103, 1.488)	0.001	0.142 (0.084)	1.153 (0.978, 1.358)	0.089

TMT. Part A and B, Trail Making Test A and B; HVLT-R, the Hopkins Verbal Learning Test-Revised; BNT, Boston Naming Test; MMSE, the Mini Mental State evaluation; ADAS Cog, cognitive subscale of the Alzheimer's Disease Assessment Scale; ADAS Non-Cog, non-cognitive subscale of the Alzheimer's Disease Assessment Scale; GDS, the Geriatric Depression Scale; SCD-Q, subjective cognitive decline questionnaire; FAQ, Functional Assessment Questionnaire; NPI-Q, neuropsychiatric inventory questionnaire.

RCF, and 16 (25.4%) were cognitively normal. Similarly, only 20 of 68 (29.4%) individuals were diagnosed with RCF. Of the remaining individuals, 22 (32.4%) were diagnosed with PRCF, and 26 (38.2%) were cognitively normal (**Figure 1B**).

The raw scores of objective tests demonstrated better discriminative ability than clinical cognitive assessment scores. Apart from the scores of intrusion errors, the scores of the other nine objective tests could accurately discriminate the cognitive status of CF, PF/PPF only, pre-MCI SCD/MCI only, and normal groups; only TMT A and HVLT-R delayed recall scores could not accurately discriminate the cognitive status between PF/PPF only and normal groups. However, the clinical MMSE and SCD-Q MyCog scores could accurately discriminate the cognitive status among CI groups (CF and pre-MCI SCD/MCI only groups), PF/PPF only, and normal groups (**Table 3**). Furthermore, only ADAS-Cog scores could accurately discriminate the cognitive status of the four groups.

After covariate adjustment, the discriminating ability of objective and clinical measures for CI showed distinct improvement. Apart from the scores of the two processes (intrusion errors and retroactive interference) and the measure digit span backward, the other objective measures for CI diagnosis could accurately discriminate the cognitive status of CF, PF/PPF only, pre-MCI SCD/MCI only, and normal groups (**Table 4**). The MMSE, SCD-Q MyCog, and ADAS-Cog scores could accurately discriminate the cognitive status of the four abovementioned groups (**Table 4**). Compared with the CF group, the scores of non-cognitive measures were significantly lower in the other three groups.

TABLE 3 | Demographic, neuropsychological, and clinical characteristics (medians and interquartile ranges [Q25–Q75] for continuous variables, and absolute numbers or percentages for categorical variables) of experimental samples in four stratifications after reclassification by adopting objective cognitive assessment (neuropsychological test *z*-scores) combined with Fried PF score criteria.

	CF (RCF + PRCF) (*n* = 89)	Only PF/PPF (*N* = 108)	Only *z*-score-derived pre-MCI SCD/MCI (Pre-MCI SCD + MCI) (*N* = 36)	Normal (no PF/PPF and cognitive impairment) (*N* = 102)	χ^2	*p*
Demographics						
Age (years)	75.00(69.00, 86.00)	73.00(68.00, 80.00)	70.00(65.00, 75.00)[a,b]	71.00(65.00, 76.25)[a,b]	19.782	0.000
Education (years)	9.00(8.00, 13.50)	12.00(9.00, 16.00)[a]	9.00(9.00, 12.00)[b]	12.00(9.00, 15.00)[a,c]	26.092	0.000
Gender (% male)	33.00(37.08%)	55.00(50.93%)	15.00(41.67%)	47.00(46.08%)	3.789	0.285
Apoe ε4/ε4 frequency (*n* = 184)	52/89	54/108	24/36	54/102	5.389	0.495
0	43	42	19	47		
1	8	12	4	7		
2	1	0	1	0		
Clinical stratification						
MCI (*n* = 94)	25 + 22	16	9 + 12	10	–	–
Pre-MCI SCD (*n* = 97)	20 + 22	26	7 + 8	14	–	–
Objective stratification					342.654	0.000
Z-scores derived MCI	44	0	20	0		
Z-scores derived pre MCI SCD	45	0	16	0		
Z-scores derived normal	0	42	0	24		
Robust normal	0	66	0	78		
Objective measures						
TMT. A	56.50(41.75, 84.25)	44.00(37.00, 58.00)[a]	59.50(42.75, 99.75)[b]	40.50(33.75, 50.00)[a,b,c]	66.307	0.000
TMT. B	74.5(58.75, 108)	68.00(57.50, 83.00)[a]	79.00(67.00, 146.00)[b]	65.00(51.00, 84.00)[a,c]	40.333	0.090
HVLT-R delayed recall	3.41(1, 5)	5.00(4.00, 7.00)[a]	2.00(0.00, 4.00)[b]	6.00(4.00, 8.00)[a,b,c]	93.872	0.000
HVLT-R recognition	10.5(9, 11)	11.00(10.00, 12.00)[a]	9.50(9.00, 10.00)[b]	11.00(10.00, 12.00)[a,c]	36.627	0.000
Learning slope	1(0.33, 1.33)	1.33(1.00, 1.67)[a]	1.00(0.33, 1.33)[b]	1.33(1.00, 1.67)[a,c]	38.097	0.000
Intrusion errors	4(2, 6.75)	3.00(1.00, 5.00)	3.00(1.00, 5.00)	3.00(2.00, 5.00)	2.513	0.473
Retroactive interference	0.5(0.29, 0.66)	0.75(0.50, 0.88)[a]	0.59(0.34, 0.80)[b]	0.71(0.60, 0.86)[a,c]	20.922	0.000
BNT	25.00(22.00, 27.00)	27.00(25.00, 28.00)[a]	24.00(23.00, 25.75)[b]	27.50(26.00, 29.00)[a,c,]	78.540	0.000
Animal fluency	14(11, 17)	18.00(15.00, 19.25)[a]	13.50(12.00, 15.75)[b]	18.00(15.00, 21.00)[a,c]	92.347	0.000
Digital span forward	6(5, 7)	7.00(6.00, 8.00)[a]	6.00(5.00, 7.00)[b]	7.00(6.00, 8.00)[a,c]	27.074	0.000
Digital span backward	4(3, 5)	4.00(4.00, 5.00)[a]	4.00(3.00, 4.00)[b]	4.00(4.00, 5.00)[c]	17.758	0.000
Digital symbol	26(19.5, 32)	33.00(24.00, 36.50)[a]	30.00(23.25, 38.25)[a]	33.00(28.25, 41.00)[a,c]	44.288	0.000
Clinical measures						
MMSE	26.00(25.00, 27.00)	28.00(27.00,29.00)[a]	25.00(26.00, 28.00)[b]	28.00(27.00, 29.00)[a,b,c]	59.598	0.000
CDR = 0.000/0.5 (% = 0.5)	75.00/6.00(7.41%)	99.00/1.00(1.00%)	32/1(3.03%)	88.00/0.00(0.00%)	10.579	0.0014
ADAS Cog	17.33(13.92, 20.75)	13.00(8.00, 17.00)[a]	16.48(9.75, 22.47)[b]	10.83(7.32, 15.66)[a,c]	62.342	0.000
ADAS Non-Cog	3(2, 4)	2.00(1.00, 4.00)[a]	2.00(1.00, 4.00)	1.00(0.00, 3.00)[a]	18.732	0.059
GDS	4(2.5, 7)	3.00(1.00, 6.00)[a]	3.00(2.00, 6.00)	2.00(1.00, 4.00)[a,b]	19.924	0.000
SCD-Q, MyCog	10(6, 12)	5.00(3.00, 8.00)[a]	8.00(5.00, 12.75)[b]	3.00(1.00, 5.00)[a,b,c]	72.395	0.000
Function Q	2(2, 5.5)	0.00(0.00, 1.00)[a]	0.00(0.00, 1.00)[a]	0.00(0.00, 1.00)[a]	42.160	0.000
NPI-Q score	0(0, 2.5)	0.00(0.00, 2.00)[a]	0(0.00, 2.00)	0.00(0.00, 1.00)[a]	13.885	0.003

[a]Significantly different from CF, [b]significantly different from only PF/PPF, [c]significantly different from pre-MCI SCD/MCI. N, Number of subjects. Qi, i[th] quantile. SCD, subjective cognitive decline; MCI, mild cognitive impairment; CF, cognitive frailty; PF, physical frailty; PPF, physical pre-frailty; BNT, Boston Naming Test; TMT. A and B, Trail Making Test A and B; HVLT-R, the Hopkins Verbal Learning Test-Revised; MMSE, the Mini Mental State evaluation; CDR, Clinical Dementia Rating; ADAS Cog, cognitive subscale of the Alzheimer's Disease Assessment Scale; ADAS Non-Cog, non-cognitive subscale of the Alzheimer's Disease Assessment Scale; GDS, the Geriatric Depression Scale; SCD-Q, subjective cognitive decline questionnaire; FAQ, Functional Assessment Questionnaire; NPI-Q, neuropsychiatric inventory questionnaire.

Comparison Between Clinical and Objective Assessments of CF Subtypes

The CF and pre-MCI SCD/MCI only groups in **Table 3** were divided into two subtypes according to CI severity (**Table 5**). Significant differences were noted in RCF, PRCF, pre-MCI SCD only, MCI only, and normal groups with respect to age and education level but not sex. ApoE ε4/ε4 was only observed in the RCF and MCI only groups.

Five of six total raw scores (excluding HVLT-R recognition) for objective cognitive assessment were significantly different between the RCF and PRCF groups, and two of six total raw scores were significantly different in the pre-MCI SCD only and MCI only groups. However, two scores (MMSE and SCD-Q

TABLE 4 | Results from nominal regression analyses that evaluated the difference of cognitive stratification by clinical or objective measures after adjusting by sex, age, and education level (the reference category is cognitive frailty).

	Only PF/PPF			Only pre-MCI SCD or MCI			Normal		
	B (standard error)	OR(95%CI)	*p*	*B* (standard error)	OR(95%CI)	*P*	*B* (standard error)	OR(95%CI)	*p*
Objective measures									
TMT A	−0.045 (0.009)	0.956 (0.939, 0.972)	0.000	−0.001 (0.006)	0.999 (0.988, 1.011)	0.897	−0.054 (0.010)	0.948 (0.929, 0.967)	0.000
TMT B	−0.021 (0.005)	0.979 (0.969, 0.989)	0.000	0.002 (0.004)	1.002 (0.995, 1.010)	0.546	−0.020 (0.005)	0.981 (0.971, 0.991)	0.000
HVLT-R delayed recall	0.485 (0.083)	1.624 (1.381, 1.910)	0.000	−0.171 (0.105)	0.843 (0.686, 1.036)	0.104	0.586 (0.087)	1.796 (1.514, 2.132)	0.000
HVLT-R recognition	0.424 (0.106)	1.528 (1.242, 1.880)	0.000	−0.079 (0.090)	0.924 (0.774, 1.103)	0.379	0.429 (0.110)	1.536 (1.239, 1.905)	0.000
Learning slope	1.086 (0.280)	2.961 (1.712, 5.123)	0.000	0.220 (0.304)	1.246 (0.687, 2.259)	0.470	1.299 (0.289)	3.667 (2.081, 6.462)	0.000
Intrusion errors	−0.097 (0.053)	0.907 (0.818, 1.006)	0.065	−0.058 (0.067)	0.944 (0. 827, 1.076)	0.386	−0.094 (0.053)	0.910 (0.820, 1.011)	0.078
Retroactive interference	0.573 (0.401)	1.773 (0.808, 3.888)	0.153	−0.521 (0.633)	0.594 (0.172, 2.053)	0.410	0.605 (0.410)	1.831 (0.821, 4.088)	0.140
BNT	0.359 (0.065)	1.432 (1.260, 1.628)	0.000	0.030 (0.067)	1.031 (0.905, 1.175)	0.648	0.430 (0.072)	1.537 (1.335, 1.769)	0.000
Animal fluency	0.327 (0.052)	1.386 (1.251, 1.537)	0.000	0.064 (0.058)	1.066 (0.952, 1.193)	0.271	0.361 (0.054)	1.435 (1.290, 1.596)	0.003
Digital span forward	0.339 (0.113)	1.404 (1.125, 1.750)	0.003	0.070 (0.143)	1.073 (0.811, 1.420)	0.622	0.237 (0.114)	1.268 (1.014, 1.585)	0.037
Digital span backward	0.370 (0.154)	1.448 (1.070, 1.959)	0.017	−0.203 (0.220)	0.816 (0.530, 1.257)	0.356	0.170 (0.159)	1.185 (0.867, 1.620)	0.287
Digital symbol	0.087 (0.022)	1.091 (1.045, 1.138)	0.000	0.055 (0.027)	1.056 (1.002, 1.113)	0.042	0.105 (0.022)	1.111 (1.063, 1.160)	0.000
Clinical measures									
MMSE	0.388 (0.093)	1.474 (1.227, 1.770)	0.000	0.007 (0.110)	1.007 (0.812, 1.249)	0.949	0.558 (0.103)	1.747 (1.428, 2.137)	0.000
ADAS Cog	−0.164 (0.029)	0.849 (0.802, 0.898)	0.000	−0.061 (0.032)	0.940 (0.883, 1.002)	0.056	−0.186 (0.031)	0.830 (0.782, 0.882)	0.000
ADAS Non-Cog	−0.111 (0.051)	0.895 (0.809, 0.990)	0.031	−0.158 (0.076)	0.854 (0.736, 0.991)	0.037	−0.232 (0.064)	0.793 (0.699, 0.899)	0.000
GDS	−0.087 (0.048)	0.916 (0.834, 1.007)	0.070	−0.145 (0.069)	0.865 (0.756, 0.990)	0.035	−0.234 (0.057)	0.792 (0.708, 0.884)	0.000
SCD-Q, MyCog	−0.118 (0.032)	0.889 (0.835, 0.945)	0.000	−0.018 (0.038)	0.983 (0.912, 1.059)	0.645	−0.255 (0.041)	0.775 (0.716, 0.840)	0.000
FAQ sore	−0.328 (0.081)	0.721 (0.614, 0.845)	0.000	−0.228 (0.092)	0.796 (0.6655, 0.953)	0.013	−0.480 (0.117)	0.618 (0.492, 0.777)	0.000
NPI-Q score	−0.142 (0.062)	0.867 (0.768, 0.979)	0.021	−0.137 (0.090)	0.872 (0.730, 1.040)	0.128	−0.307 (0.093)	0.735 (0.613, 0.883)	0.001

TMT. Part A and B, Trail Making Test A and B; HVLT-R, the Hopkins Verbal Learning Test-Revised; BNT, Boston Naming Test; MMSE, the Mini Mental State evaluation; ADAS Cog, cognitive subscale of the Alzheimer's Disease Assessment Scale; ADAS Non-Cog, non-cognitive subscale of the Alzheimer's Disease Assessment Scale; GDS, the Geriatric Depression Scale; SCD-Q, subjective cognitive decline questionnaire; FAQ, Functional Assessment Questionnaire; NPI-Q, neuropsychiatric inventory questionnaire.

MyCog) for clinical cognitive assessment were not significantly different between the RCF and PRCF groups and between the pre-MCI SCD only and MCI only groups.

After covariate adjustment, the six total scores for objective cognition assessment were significantly different between the RCF and PRCF groups (**Table 6**). Among the six total scores, the TMT A and TMT B scores significantly differed between the RCF and MCI only groups, whereas the HVLT-R delayed recall and HVLT-R recognition scores marginally differed between the RCF and only MCI groups. Among the three process scores, the learning slope scores significantly differed between the RCF and normal groups. Moreover, the digit span backward and digit symbol scores significantly differed between the RCF and PRCF groups but not between the RCF and only MCI groups. However, the clinical MMSE and SCD-Q MyCog scores did not significantly differ between the RCF and PRCF groups and between the RCF and MCI only groups. The ADAS-Cog scores significantly differed between the RCF and PRCF groups but not between the RCF and MCI only groups. The non-cognitive performance scores significantly differed between the normal and other groups. Compared with the RCF group, the ADAS Non-Cog and FAQ scores were significantly higher in the PRCF group, and the GDS and NPI-Q scores were significantly lower in the MCI only group.

DISCUSSION

In this comparative study, we established objective criteria for CI and CF subtypes based on the normative *z*-scores of six neuropsychological test batteries (two memory, two attention or executive, and two language domains) and three process scores of memory domain. According to objective criteria, 191 individuals with pre-MCI SCD or MCI were reclassified into *z*-score-derived pre-MCI SCD, MCI, and *z*-score-derived normal subgroups and compared with the robust normal group. The main findings are as follows:

(1) The normative *z*-scores could improve the differentiation performance for CI subtypes (**Tables 1**, **2**), CF (**Tables 3**, **4**), and CF subtypes (**Tables 5**, **6**) among four different subgroups compared with the raw scores of six neuropsychological test batteries.
(2) The three other neuropsychological test batteries (digit span forward or backward and digit symbol) further confirmed the previous finding.
(3) Among the clinical measures, only ADAS-Cog scores could differentiate the *z*-score-derived normal subgroup from the *z*-score-derived pre-MCI SCD and MCI groups and RCF from the PRCF before and after adjusting for demographic factors.

TABLE 5 | Demographic, neuropsychological, and clinical characteristics (medians and interquartile ranges [Q25–Q75] for continuous variables, and absolute numbers or percentages for categorical variables) of experimental samples in four stratifications after reclassification by adopting objective cognitive assessment (neuropsychological test *z*-scores) combined with Fried PF score criteria.

	RCF(*n* = 45)	PRCF(*n* = 44)	Only pre- MCI SCD (*n* = 16)	Only MCI (*n* = 20)	Normal (*N* = 102)	χ^2	*p*
Demographics							
Age (years)	75(69.00, 78.00)	77.00(72.00, 81.75)	70.00(64.00, 73.50)[a,b]	71.50(67.00, 75.75)[b]	71.00(65.00, 76.00)[a,b]	21.729	0.00
Education (years)	9.00(8.00, 13.50)	9.00 (8.00, 12.00)	11.50(9.00, 12.75)	9.00(6.75, 12.00)	12.00(9.00, 15.00)[a,b,d]	22.088	0.00
Gender (% male)	12.00(26.67%)	21(47.73%)	7(43.75%)	8(40%)	47(46.08%)	5.840	0.211
Apoe ε4/ε4 frequency (*n* = 130)						7.027	0.543
0	20	23	10	9	47		
1	5	3	2	2	7		
2	1	0	0	1	0		
Objective measures							
TMT. A	56.50(41.75,84.25)	81.00(61.00, 124.00)[a]	50.50(35.75, 66.50)[b]	65.50(54.25, 119.50)[c]	40.00(33.50, 50.00)[a,b,c,d]	71.045	0.00
TMT. B	74.50(58.75, 108.00)	124.50(91.75, 226.00)[a]	71.00(66.00, 93.00)[b]	100.00(68.75, 180.00)[a,c]	65.00(51.00, 85.50)[a,b,d]	53.774	0.00
HVLT-R delayed recall	4.00(1.00, 5.00)	2.00(0.00, 3.00)[a]	2.00(1.00, 3.75)	1.50(0.00, 4.75)	6.00(4.75, 8.00)[a,b,c,d]	83.918	0.00
HVLT-R recognition	10.50(9.00, 11.00)	10.00(6.50, 11.00)	10.00(9.00, 10.75)	9.00(8.25, 10.00)[a]	11.00(10.00, 12.00)[a,b,c,d]	32.961	0.00
Learning slope	1.00(0.33, 1.33)	0.67(0.50, 1.33)	0.67(0.33, 1.00)	1.00(0.42, 1.67)	1.33(1.00, 1.67)[a,b,c]	34.024	0.00
Intrusion errors	4.00(2.00, 6.75)	3.00(1.00, 7.00)	3.50(0.25, 5.00)	2.50(1.25, 5.75)	3.00(2.00, 5.00)	3.038	0.55
Retroactive interference	0.50(0.29, 0.66)	0.60(0.27, 0.86)	0.65(0.33, 0.96)	0.59(0.38, 0.75)	0.72(0.62, 0.86)[a,b,d]	23.350	0.00
BNT	25.00(22.00, 27.00)	22.00(19.00, 24.50)[a]	25.00(24.00, 27.00)[b]	24.00(22.00, 25.00)	28.00(26.00, 29.00)[a,b,c,d]	75.301	0.00
Animal fluency	14.00(11.00, 17.00)	12.00(9.00, 14.00)[a]	14.50(12.00, 16.75)[b]	13.00(11.00, 15.00)	18.00(15.00, 21.00)[a,b,c,d]	77.079	0.00
Digital span forward	6.00(5.00, 7.00)	5.00(4.25, 7.00)	6.00(5.00, 7.00)	6.00(5.00, 7.00)	7.00(5.00, 8.00)[a,b]	18.536	0.001
Digital span backward	4.00(3.00, 5.00)	4.00(3.00, 4.00)[a]	3.00(3.00, 4.00)	4.00(4.00, 4.00)[b,c]	4.00(4.00, 5.00)[b,c]	19.281	0.001
Digital symbol	26.00(19.50, 32.00)	19.00(16.00, 27.50)[a]	32.00(26.00, 38.75)[b]	29.50(19.25, 36.75)[b]	33.00(28.00, 41.00)[a,b]	46.111	0.00
Clinical measures							
MMSE	26.00(25.00,27.00)	26.00(25.00, 28.00)	26.00(25.00, 28.00)	26.00(25.00, 28.00)	28.00(27.00, 29.00)[a,b,c,d]	52.055	0.00
CDR = 0.000/0.5(% = 0.5)	41/1(2.38%)	35/5(12.5%)	13/0(0.00%)	19/1(5.00%)	88/0(0.00%)	13.739	0.008
ADAS Cog	17.33(13.92, 20.745)	21.66(15.00, 29.99)[a]	16.15(10.83, 21.68)[b]	18.00(9.41, 22.66)[b]	10.30(7.00, 15.66)[a,b,c,d]	55.900	0.00
ADAS Non-Cog	3.00(2.00, 4.00)	4.00(1.00, 8.00)	2.00(0.25, 3.00)[b]	2.00(1.00, 4.75)	1.00(0.00, 3.00)[a,b]	20.966	0.00
GDS	4.00(2.50, 7.00)	4.00(2.00, 7.00)	4.00(2.25, 6.75)	2.00(1.00, 5.00)[a,b,c]	2.00(1.00, 4.00)[a,b,c]	25.386	0.00
SCD-Q, MyCog	10.00(6.00, 12.00)	11.50(7.00, 13.75)	10.50(7.00, 13.00)	7.50(3.25, 11.50)	3.00(1.00, 5.00)[a,b,c,d]	67.197	0.00
Function *Q*	2.00(0.00, 5.00)	2.50(0.00, 9.75)	0.00(0.00, 1.00)[a,b]	0.00(0.00, 1.75)[b]	0.00(0.00, 1.00)[a,b]	38.876	0.000
NPI-Q score	0.00(0.00, 2.00)	2.00(0.00, 4.00)	1.00(0.00, 3.00)	0.00(0.00, 0.00)[a,b,c]	0.00(0.00, 1.00)[a,b,c]	21.806	0.00

[a]Significantly different from RCF, [b]significantly different from PRCF, [c]significantly different from only pre-MCI SCD, [d]significantly different from only MCI. N, number of subjects. Qi, i^{th} quantile. SCD, subjective cognitive decline; MCI, mild cognitive impairment; CF, cognitive frailty; PF, Physical frailty; PPF, Physical pre-frailty; BNT, Boston Naming Test; TMT. A and B, Trail Making Test A and B; HVLT-R, the Hopkins Verbal Learning Test-Revised; MMSE, the Mini Mental State evaluation; CDR, Clinical Dementia Rating; ADAS Cog, cognitive subscale of the Alzheimer's Disease Assessment Scale; ADAS Non-Cog, non-cognitive subscale of the Alzheimer's Disease Assessment Scale; GDS, the Geriatric Depression Scale; SCD-Q, subjective cognitive decline questionnaire; FAQ, Functional Assessment Questionnaire; NPI-Q, neuropsychiatric inventory questionnaire.

(4) The raw MMSE scores could differentiate the *z*-score-derived normal from the *z*-score-derived MCI and pre-MCI SCD groups (**Table 1**) and the CF and pre-MCI SCD/MCI only groups from the PF/PPF only and normal groups (**Table 3**) but not the *z*-score-derived MCI group from the pre-MCI SCD group (**Table 1**) and the RCF group from the PRCF group (**Table 5**).

(5) SCD-Q MyCog raw scores were not significantly different among the *z*-score-derived normal, MCI, and pre-MCI SCD groups (**Table 1**). However, the scores varied between the CF and pre-MCI SCD/MCI only groups from PF/PPF only and normal groups (**Table 3**) but not between the RCF and PRCF groups and pre-MCI SCD only and MCI only groups (**Table 5**).

TABLE 6 | Results from nominal regression analyses that evaluated the difference of cognitive stratification by clinical or objective measures after adjusting by sex, age, and education level (the reference category is RCF).

	PRCF			Only pre-MCI SCD			Only MCI			Normal		
	***B* (standard error)**	**OR (95%CI)**	***p***	***B* (standard error)**	**OR (95%CI)**	***P***	***B* (standard error)**	**OR (95%CI)**	***p***	***B* (standard error)**	**OR (95%CI)**	***p***
Objective measures												
TMT A	0.021 (0.008)	1.021 (1.006, 1.037)	0.006	−0.004 (0.012)	0.996 (0.973, 1.021)	0.774	0.017 (0.009)	1.017 (1.000, 1.034)	0.047	−0.041 (0.011)	0.960 (0.939, 0.981)	0.000
TMT B	0.031 (0.007)	1.031 (1.016, 1.047)	0.000	0.006 (0.011)	1.006 (0.985, 1.028)	0.573	0.030 (0.008)	1.030 (1.014, 1.046)	0.000	−0.005 (0.007)	0.995 (0.981, 1.010)	0.531
HVLT-R delayed recall	−0.251 (0.109)	0.778 (0.628, 0.963)	0.021	−0.342 (0.156)	0.7106 (0.523, 0.964)	0.028	−0.236 (0.136)	0.790 (0.605, 1.031)	0.083	0.479 (0.102)	1.615 (1.322, 1.973)	0.000
HVLT-R recognition	−0.256 (0.117)	0.774 (0.615, 0.974)	0.029	−0.218 (0.148)	0.804 (0.601, 1.076)	0.142	−0.242 (0.135)	0.785 (0.602, 1.024)	0.074	0.397 (0.143)	1.487 (1.123, 1.970)	0.006
Learning slope	0158 (0.363)	1.171 (0.575, 2.386)	0.663	−0.219 (0.467)	0.804 (0.322, 2.008)	0.640	0.724 (0.468)	2.062 (0.824, 5.160)	0.122	1.480 (0.364)	4.395 (2.154, 8.968)	0.000
Intrusion errors	0.000 (0.071)	1.000 (0.870, 1.150)	0.996	−0.068 (0.099)	0.935 (0.770, 1.135)	0.495	−0.058 (0.089)	0.944 (0.792, 1.124)	0.516	−0.090 (0.062)	0.914 (0.809, 1.033)	0.150
Retroactive interference	0.549 (0.567)	1.731 (0.569, 5.264)	0.334	0.530 (0.812)	1.698 (0.346, 8.335)	0.514	−0.504 (0.853)	0.604 (0.113, 3.216)	0.555	0.924 (0.548)	2.518 (0.861, 7.366)	0.092
BNT	−0.254 (0.079)	0.775 (0.664, 0.906)	0.001	−0.044 (0.108)	0.957 (0.775, 1.182)	0.685	−0.126 (0.094)	0.882 (0.733, 1.061)	0.184	0.350 (0.085)	1.420 (1.202, 1.677)	0.000
Animal fluency	−0.212 (0.073)	0.809 (0.701, 0.933)	0.004	−0.009 (0.082)	0.991 (0.845, 1.163)	0.915	−0.086 (0.081)	0.918 (0.784, 1.075)	0.288	0.212 (0.061)	1.236 (1.097, 1.392)	0.001
Digital span forward	−0.229 (0.171)	0.795 (0.569, 1.112)	0.181	−0.031 (0.215)	0.970 (0.636, 1.479)	0.886	0.059 (0.205)	1.060 (0.710, 1.584)	0.775	0.137 (0.144)	1.147 (0.866, 1.520)	0.339
Digital span backward	−0.697 (0.263)	0.498 (0.298, 0.834)	0.008	−1.106 (0.384)	0.331 (0.156, 0.702)	0.004	−0.087 (0.278)	0.917 (0.531, 1.583)	0.755	−0.100 (0.189)	0.905 (0.624, 1.312)	0.597
Digital symbol	−0.065 (0.032)	0.937 (0.881, 0.998)	0.042	0.015 (0.037)	1.015 (0.944, 1.091)	0.686	0.030 (0.035)	1.030 (0.962, 1.103)	0.394	0.071 (0.026)	1.073 (1.020, 1.129)	0.006
Clinical measures												
MMSE	0.002 (0.115)	1.002 (0.800, 1.255)	0.985	0.040 (0.166)	1.041 (0.751, 1.441)	0.811	0.042 (0.145)	1.043 (0.785, 1.386)	0.772	0.594 (0.123)	1.811 (1.424, 2.302)	0.000
ADAS Cog	0.066 (0.033)	1.068 (1.001, 1.139)	0.046	−0.025 (0.046)	0.976 (0.891, 1.068)	0.591	−0.044 (0.043)	0.957 (0.879, 1.042)	0.316	−0.161 (0.035)	0.851 (0.794, 0.912)	0.000
ADAS Non-Cog	0.152 (0.072)	1.165 (1.010, 1.342)	0.035	−0.113 (0.127)	0.893 (0.696, 1.146)	0.374	−0.054 (0.104)	0.948 (0.773, 1.162)	0.604	−0.168 (0.081)	0.845 (0.722, 0.991)	0.038
GDS	0.040 (0.071)	1.041 (0.906, 1.195)	0.570	−0.036 (0.099)	0.965 (0.795, 1.171)	0.717	−0.251 (0.112)	0.778 (0.625, 0.968)	0.025	−0.242 (0.071)	0.785 (0.682, 0.902)	0.001
SCD-Q, MyCog	0.037 (0.046)	1.038 (0.949, 1.135)	0.419	0.089 (0.064)	1.094 (0.965, 1.239)	0.161	−0.028 (0.058)	0.972 (0.868, 1.090)	0.631	−0.249 (0.050)	0.780 (0.707, 0.860)	0.000
FAQ sore	0.120 (0.052)	1.128 (1.018, 1.250)	0.021	−0.426 (0.262)	0.653 (0.391, 1.092)	0.104	−0.085 (0.092)	0.918 (0.766, 1.101)	0.356	−0.416 (0.122)	0.660 (0.519, 0.838)	0.001
NPI-Q score	0.020 (0.058)	1.020 (0.911, 1.142)	0.731	0.059 (0.094)	1.061 (0.882, 1.276)	0.531	−0.533 (0.244)	0.587 (0.364, 0.947)	0.029	−0.276 (0.100)	0.759 (0.623, 0.923)	0.006

TMT. Part A and B, Trail Making Test A and B; HVLT-R, the Hopkins Verbal Learning Test-Revised; BNT, Boston Naming Test; MMSE, the Mini Mental State evaluation; ADAS Cog, cognitive subscale of the Alzheimer's Disease Assessment Scale; ADAS Non-Cog, non-cognitive subscale of the Alzheimer's Disease Assessment Scale; GDS, the Geriatric Depression Scale; SCD-Q, subjective cognitive decline questionnaire; FAQ, Functional Assessment Questionnaire; NPI-Q, neuropsychiatric inventory questionnaire.

(6) After adjusting for demographic factors, the MMSE and SCD-Q MyCog scores could differentiate between the *z*-score-derived normal or robust normal and *z*-score-derived MCI and pre-MCI SCD groups, between the *z*-score-derived normal and robust normal groups (**Table 2**), and between the PF/PPF only and normal groups and the CF and pre-MCI SCD/MCI only groups (**Table 4**). However, the scores could not distinguish RCF from PRCF and pre-MCI SCD only from MCI (**Table 6**).
(7) The Non-Cog scores were higher in the CF group than in other subgroups, and the GDS and NPI-Q scores were significantly lower in the MCI only group than in the RCF group.

Although clinical criteria, including the MMSE and SCD-Q MyCog scores, could better differentiate CI or CF from those with normal cognitive function after covariate adjustment, these clinical tools failed to differentiate between the subtypes of CI (pre-MCI SCD and MCI) and CF (RCF and PRCF). The construct of MCI clinical criteria including SCD may be one of the critical factors owing to which covariate adjustment improves the differentiation in some groups but not in others. Therefore, as indicated by our findings, clinical cognitive criteria based on conventional MCI criteria combined with the SCD questionnaire may be important causes of prevalence variability in CI and CF subtypes in different population studies. The ADAS-Cog scores, typically used as an outcome measure in AD clinical trials (Wattmo and Wallin, 2017), is a better tool for differentiating pre-MCI SCD from MCI and RCF from PRCF. Furthermore, demographic factors had a minor influence on ADAS-Cog scores. A previous study demonstrated the adequacy of the ADAS-Cog scores for assessing psychometric properties in older low-literacy adults in sub-Saharan Africa (Paddick et al., 2017). However, a small-sample study showed that the ADAS-Cog scores were significantly affected by age and education (Ben Jemaa et al., 2017). The different effects of demographic factors on the ADAS-Cog scores, as demonstrated in our study, require further investigation in the future.

Objective criteria for pre-MCI SCD used in the present study have previously been verified to provide more sensitive criteria for individuals at risk for progression to MCI, indicate early pathological alterations in the brain (Thomas et al., 2020), and improve diagnostic precision, biomarker associations, and progression rates of MCI (Bondi et al., 2014; Edmonds et al., 2015a). While determining our *z*-scores criteria, we only replaced the Auditory Verbal Learning Test with a relatively brief measure—the HVLT-R (Ruan et al., 2020b). Moreover, the normative *z*-scores of the remaining three neuropsychological test batteries (digit span forward or backward and digit symbol) further verified the abovementioned objective cognitive criteria. Therefore, we conclude that objective cognitive criteria were better than clinical criteria for classifying MCI and pre-MCI SCD as well as RCF and PRCF. The diagnostic errors caused by clinical criteria for CI and normal cognition decreased after covariate adjustment.

Few studies have operationally defined pre-MCI SCD (Jessen et al., 2014; Solfrizzi et al., 2017; Margioti et al., 2020; Ruan et al., 2020a), and SCD is often substituted for pre-MCI SCD (Rami et al., 2014; Rabin et al., 2015), particularly for preclinical Alzheimer's disease (Ávila-Villanueva and Fernández-Blázquez, 2017; Lin et al., 2019). The composite score can be disproportionally influenced by poor cognitive performance on only one test; our pre-MCI SCD criteria required two impaired scores, including process scores (1 SD below or above the normative mean) in two different cognitive domains, thereby significantly improving the sensitivity and specificity of the pre-MCI SCD diagnosis (Thomas et al., 2018). Meanwhile, the clinical MCI criteria also included SCD, which further increased the diagnostic errors of pre-MCI SCD and MCI. SCD occurs with different objective cognitive function trajectories, which could result from various causes (Ávila-Villanueva and Fernández-Blázquez, 2017; Jessen et al., 2020). Reversible SCD is related to depressive symptoms, personality features, side effects from medication, and intermittent sleep disturbances (Reid and Maclullich, 2006; Jessen et al., 2020). Furthermore, our results showed that the RCF group experienced significantly higher depression scores than the MCI group (**Table 6**). Thus, the SCD-Q MyCog score may be a primary source of diagnostic errors. Conventional MCI criteria may be another source of diagnostic errors. The global CDR is not sensitive to MCI severity and prognosis (Chang et al., 2011), is susceptible to recall bias, and is influenced by psychiatric factors (Saxton et al., 2009). Furthermore, the MMSE and SCD-Q MyCog scores significantly improved in categorizing individuals with CI from those without CI after covariate adjustment (**Tables 2**, **4**). However, the adjustments did not indicate an improvement in discriminating the cognitive status among RCF, PRCF, pre-MCI only, and MCI only groups (**Tables 5**, **6**). Instead, the ADAS-Cog scores indicated better consistency with the neuropsychological test scores and could discriminate *z*-score-derived MCI and pre-MCI SCD from cognitively normal and robust normal controls (**Table 2**), CF from only PF/PPF and normal groups (**Table 4**), and RCF from other subgroups (**Table 6**). These findings indicate that clinical criteria results in several diagnostic errors in CF subtypes. In addition, the scores of non-cognitive measures were significantly higher in individuals of the PRCF group than in those of the RCF group and in individuals of the CF group than in those of the PF/PPF, only MCI, only pre-MCI SCD, and normal groups.

A limitation of this study was the small sample size of normative *z*-scores from robust normal controls (Ruan et al., 2020b), resulting in a failure to discriminate pre-MCI SCD from cognitively normal individuals in *z*-scores of intrusion errors and retroactive interference. Increasing the sample size of normative *z*-scores from robust normal controls from community-dwelling individuals will improve diagnostic accuracy. Another limitation was the small sample size of the MCI only and pre-MCI SCD only groups. In addition, although the normative *z*-scores contain the memory, language, and attention/executive domains, the visuospatial domain was not

evaluated in our sample, and this limits the possibility to detect the deficits of the visuospatial domain. The visuospatial domain should be evaluated in subsequent studies. Nevertheless, some tests, such as digit span forward, digit span backward, digit symbol, and TMT A for attention or processing speed, also indicated consistent changes.

In summary, the use of clinical criteria for distinguishing MCI from pre-MCI SCD and cognitively normal individuals resulted in numerous diagnostic errors. Covariate adjustment could improve the discriminating ability of clinical cognitive measures. The combination of clinical criteria with objective criteria is implementable and cost effective and will considerably reduce the number of diagnostic errors in CI and CF subtypes in clinical practice.

DATA AVAILABILITY STATEMENT

The original contributions generated for this study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the study protocol was approved by Hudong Hospital Research Ethics Committee, Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QR and ZY: conceptualization. QR, ZY, and JC: data curation. QR, WZ, and JR: analysing and interpretation of data. QR, WZ, JR, JC, and ZY: investigation and methodology. QR: original writing. ZY and JC: reviewing and editing. 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/fpsyg.2021.603974/full#supplementary-material

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