WOMEN IN SCIENCE - GERIATRIC MEDICINE 2021

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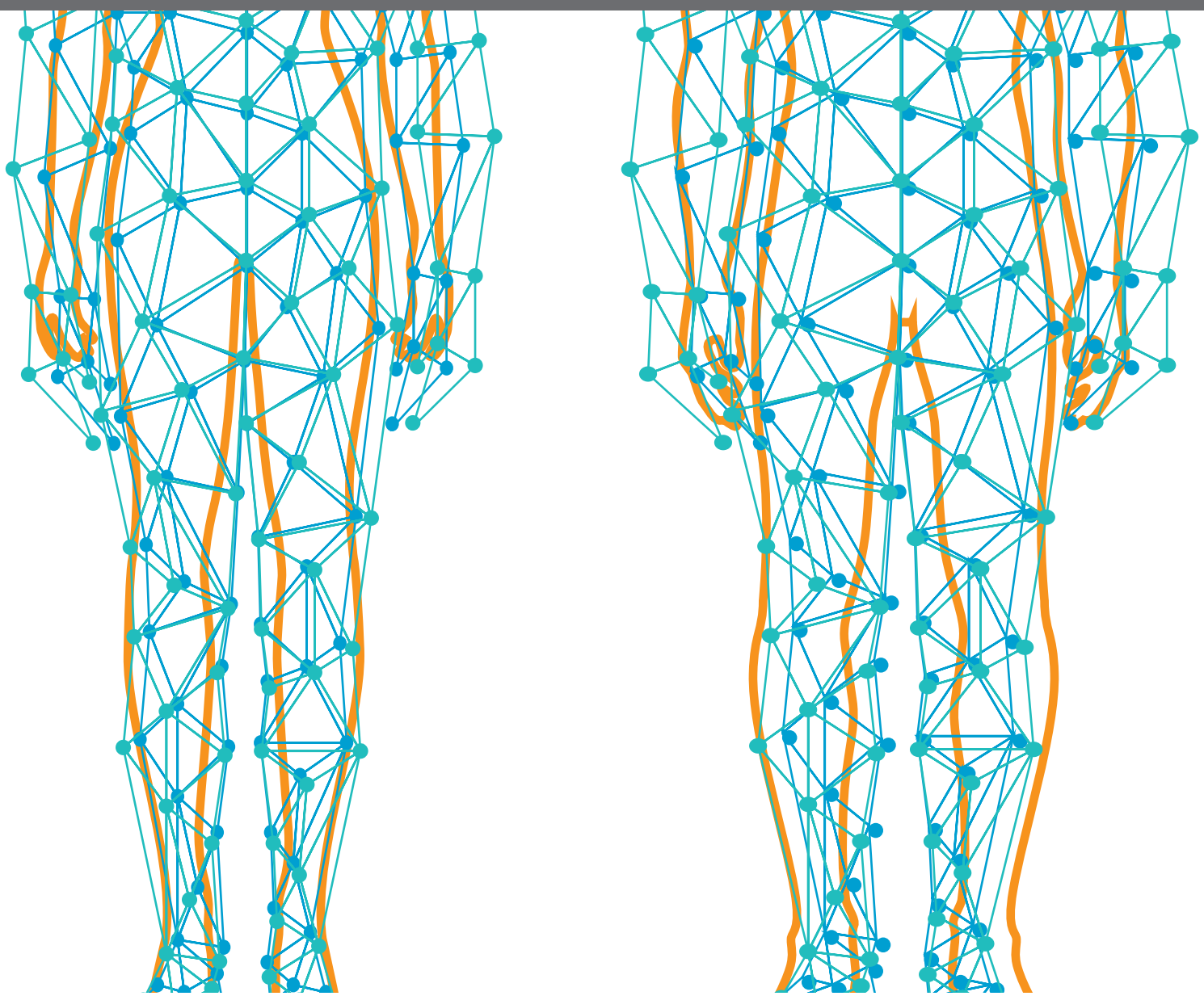

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WOMEN IN SCIENCE - GERIATRIC MEDICINE 2021

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Editorial: Women in science - geriatric medicine 2021

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Editorial on the Research Topic
Women in science - geriatric medicine 2021

In a world where the gender gap is often mentioned, where the role of women in society is often discussed, but in the same world where the strength of differences seems to be the only reality, the Research Topic in "*Women in science - geriatric medicine 2021*" tried to check the pulse of the Women researchers in all fields of the Geriatric Medicine. This topic aimed to assemble all the latest knowledge and the most recent ongoing research that sees Women as the principal responsible for the projects.

In particular, from the identification of specific features of cardiac amyloidosis, through the definition of factors associated with frailty in different settings and countries, the effect of Low and High-Density Lipoprotein Cholesterol or the use of beta-carotene on Mortality, or the medication Use with the incidence of Dementia After COVID-19 Hospitalization, to the definition of the differences in the LEVO-DOPA pharmacokinetics by gender, and the development of a new conceptual definition of severe self-neglect, the Research Topic "*Women in science - geriatric medicine 2021*" tries to explore some of the main aspects of Geriatrics, focusing on all the aspects of the elderly life.

Starting with the effects of the calcific aortic stenosis in the geriatric population, Myasoedova et al. analyze the characteristics of patients with this condition in association with cardiac amyloidosis, and the possible impact of cardiac amyloidosis on mortality of the patients with aortic stenosis, and the effect of different treatment strategies on outcomes of patients with aortic stenosis and concomitant cardiac amyloidosis. The authors suggest that several specific clinical, electrocardiographic, and echocardiographic features can be considered "red flags" of cardiac amyloidosis in patients with aortic stenosis (Myasoedova et al.).

Then, some articles focused on the factors that can conditionate the functional capacity of the elderly, with particular interest for the osteosarcopenia in Community-Dwelling Mexicans (López-Teros et al.), and Chinese older population (Chen et al.), but

also by big data analysis of Older Adults Hospitalized in Long-Term Care in Portugal (Ramos et al.).

Moreover, Moreno et al. investigated if sarcopenia influences the healthy life expectancy (HLE) and unhealthy life expectancy (ULE) among older adults from Santiago, Chile. The authors demonstrated sex differences in disability trajectories among sarcopenic older people.

Indeed, gender differences were also found by Conti et al. that investigated the gender-related differences in Levodopa pharmacokinetics in patients with Parkinson's disease at their first-ever intake of Levodopa. Women showed higher levels of AUC and Cmax when compared with men, but also multiple linear regression analyses showed that the female sex was the only predictor of AUC and Cmax.

Yuan et al. examined the association between frailty and inpatient services utilization and the mediating role of multimorbidity in the association between frailty and inpatient services utilization among older adults in rural China. The authors found that frailty among Chinese rural older adults is associated with higher inpatient services utilization, and multimorbidity mediates this association.

Then, the importance of other factors in modifying the survival of the elderly was investigated. By using the Shanghai Aging Study, Wu et al. investigated the association between the low and high-density lipoprotein cholesterol levels and 10-Year Mortality in Community-Dwelling Older adults. An inverse association of LDL and a U-shape relationship of HDL-C with long-term all-cause mortality was found in a cohort of community-dwelling older Chinese adults.

Starting by the evidence of the beneficial effects of some diet foods on humans (1–3), by performing a metanalysis, Corbi et al. checked the association between beta-carotene supplementation and mortality. The authors found no evidence of an overall preventive effect of beta-carotene supplements on total, cancer, CVD, and cerebrovascular mortality risk in a meta-analysis of RCTs published over the past 25 years. Instead, beta-carotene supplementation increased the risk of lung cancer mortality but decreased the risk of HIV-related mortality.

Finally, two other articles included in this topic faced two different aspects. Pickens et al. purposed a new definition for severe self-neglect with the development of a conceptual framework by Modifying the CREST model for Self-Neglect. Freudenberg-Hua et al. determined the 1-year incidence rate of post-COVID dementia; assessed the association between pre-COVID psychotropic medication use and post-COVID incident dementia; and explored the association between different classes and types of psychotropic medications and post-COVID incident dementia. In this cohort study of older adults hospitalized with COVID-19 at a large health system in New York, exposure to pre-COVID psychotropic medications was associated with a greater 1-year incidence of post-COVID dementia.

Finally, the Research Topic "*Women in science - geriatric medicine 2021*" shows the great involvement of women in all fields of research, including biological, clinical, therapeutical, and preventive aspects.

Author contributions

GC contributed to the conception. VC and AF contributed to the design of the Research Topic. All authors contributed to the management of submission, the revision process, and the control of the articles quality. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

Publisher's note

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HYPOTHESIS AND THEORY
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Development of a Conceptual Framework for Severe Self-Neglect (SN) by Modifying the CREST Model for Self-Neglect

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Self-neglect is an inability or refusal to meet one's own basic needs as accepted by societal norms and is the most common report received by state agencies charged with investigating abuse, neglect and exploitation of vulnerable adults. Self-neglect is often seen in addition to one or multiple conditions of frailty, mild to severe dementia, poor sleep and depression. While awareness of elder self-neglect as a public health condition and intervention has significantly risen in the past decade as evidenced by the increasing amount of literature available, research on self-neglect still lacks comprehensiveness and clarity since its inception to the medical literature in the late 1960s. With the burgeoning of the older adult population, commonness of self-neglect will most likely increase as the current incidence rate represents only the "tip of the iceberg" theory given that most cases are unreported. The COVID-19 pandemic has exacerbated the incidence of self-neglect in aged populations and the need for the use of intervention tools for aging adults and geriatric patients living alone, many of which may include in-home artificial intelligence systems. Despite this, little research has been conducted on aspects of self-neglect other than definition and identification. Substantial further study of this disorder's etiology, educating society on early detection, and conceivably preventing this syndrome altogether or at least halting progression and abating its severity is needed. The purpose of this research is to provide a definition of severe self-neglect, identify key concepts related to self-neglect, comprehensively describe this syndrome, present a conceptual framework and analyze the model for its usefulness, generalizability, parsimony, and testability.

Keywords: self-neglect, artificial intelligence, sleep, geriatrics, cognition

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INTRODUCTION

Self-neglect is the inability or refusal to meet one's own basic needs as accepted by societal norms (1). It is a commonly seen by practitioners in association with geriatric conditions of frailty and characterized by losses in physical, psychological, and social domains. Self-neglect is the most common report received by Adult Protective Services (APS), state agencies charged with investigating abuse, neglect and exploitation of vulnerable adults (2–4). Some studies indicate that

older adults who self-neglect have two and half times the mortality rate than adults who have never been reported to APS (5) and ∼2 times the 1-year mortality rate of adults who do not self-neglect (6). Other studies indicate rates as high as a six-fold increase in 1-year mortality of self-neglecters with as high as a 15-fold increase of mortality for individuals with self-neglect compared to those without self-neglect (7). With the burgeoning of the older adult population, the commonness of self-neglect will most likely increase as the current incidence rate represents only the "tip of the iceberg" theory given that most cases are unreported (8).

While awareness of elder self-neglect as a public health condition meriting investigation and intervention has significantly risen in the past decade as evidenced by the increasing amount of literature available, research on self-neglect still lacks comprehensiveness and clarity since its inception to the medical literature in the late 1960s. The literature found by these authors focuses almost exclusively on identifying and defining self-neglect, which has been a critical undertaking given the dearth of literature prior to the last decade. A number of studies report the complex nature of self-neglect, yet the lack of a standard definition or standard assessment tool makes it difficult to study and to mutually recognize its occurrence among health care professionals (1, 9–17). To date, the National Association of Adult Protective Service Administrators (NAPSA) provides the most comprehensive definition of self-neglect as:

> an adult's inability, due to physical or mental impairment or diminished capacity, to perform essential self-care tasks including: (a) obtaining essential food, clothing, shelter, and medical care; (b) obtaining goods and services necessary to maintain physical health, mental health, emotional well-being, and general safety; and (c) managing one's own financial affairs excluding an individual's lifestyle choice [(18), p. 33].

Another comprehensive definition provided by the National Centers of Elder Abuse, which excludes conscious, voluntary decisions by mentally competent adults is:

> the behavior of an elderly person that threatens his/her own health and safety. Self-neglect generally manifests itself in an older person as a refusal or failure to provide himself/herself with adequate food, water, clothing, shelter, personal hygiene, medication (when indicated), and safety precautions (19).

On the other hand, the common definition in the literature states self-neglect is the inability to meet one's own basic needs or behaviors of an individual that threatens his or her self-care (8, 20–23). These definitions are either lengthy and/or do not reflect the seriousness of elder self-neglect if left unrecognized and untreated.

These authors study self-neglect, see self-neglect in an emergency responder capacity, and/or have medically treated this population. Since little research has been conducted on aspects of self-neglect other than definition and identification, this disorder lends credibility to a life-long, academic pursuit in studying its etiology, educating society on early detection, and conceivably preventing this syndrome altogether or at least halting progression and abating its severity.

Walker and Avant (24) illustrate the processes of concept synthesis, derivation, and analyses. Application of concept synthesis is to encompass the varying definitions of self-neglect to develop a standard definition and conceptual framework. In conducting concept synthesis, a mixed method approach will be undertaken. This method includes a review of the literature and qualitative synthesis based on the authors' own observations as well as collaboration with experts in the field.

The literature review included searches in PUBMED, SCOPUS, MEDLINE, CINNAHL, Administration on Aging, NAPSA, and the National Center on Elder abuse using the following key terms: self-neglect, older adults, senile breakdown syndrome, social breakdown, Diogenes' syndrome, elder abuse, elder mistreatment, neglect, elder neglect, executive dysfunction, and impaired cognition. Inclusion criteria for article selection are those written in English and persons 65 years of age and older who self-neglect. Exclusion criteria include persons <65 years of age, focusing within specific ethnic groups or nationalities, and other forms of elder abuse such as caregiver neglect, financial exploitation, and physical abuse without mention of self-neglect. The purpose of this paper is to provide a definition of severe self-neglect, identify key concepts related to self-neglect, comprehensively describe this syndrome, present a conceptual framework and analyze the model for its usefulness, generalizability, parsimony, and testability.

Key Concepts

Self-neglect occurs along a continuum ranging from mild to severe in nature (17). For the purpose of this conceptual framework, severe self-neglect will be used. Severe self-neglect is defined as an unawareness to the hazardous and progressive decline in personal, social, physical, mental, and/or environmental domains leading to the inability to maintain culture and community standards of acceptable living that threatens one's own safety, health, and quality of life. The purpose of this definition is to define a phenomenon that is complex and progressive yet clearly highlights the lack of awareness to one's hazardous state of health (17).

The conceptualization of severe self-neglect is that it develops in the presence of known predictors or when one develops executive dysfunction as defined below in this paper. When either of these two factors is present, older adults develop functional disabilities, which may lead to a decline in their personal and/or environmental domains. Informal caregivers may attempt some form of intervention to aid self-neglecters, yet the self-neglecters refuse to accept help. When self-neglecters refuse nursing, medical, or social intervention, it is hypothesized that a progressive decline in their personal, functional, environmental, and social domains ensues. This decline manifests as poor personal hygiene, filthy environments, hoarding unnecessary items, malnourishment, rotting or spoiled food, or delirium, to name a few. What remains to be tested is the absolute presence, absence, or combination of the manifestations seen in self-neglecters (see **Figure 1** for manifestations).

The etiology of severe self-neglect has not been clearly identified although known predictors resulting in self-neglect have been identified. Predictors are defined as symptoms or indicators present at the time of disease onset. Only five research

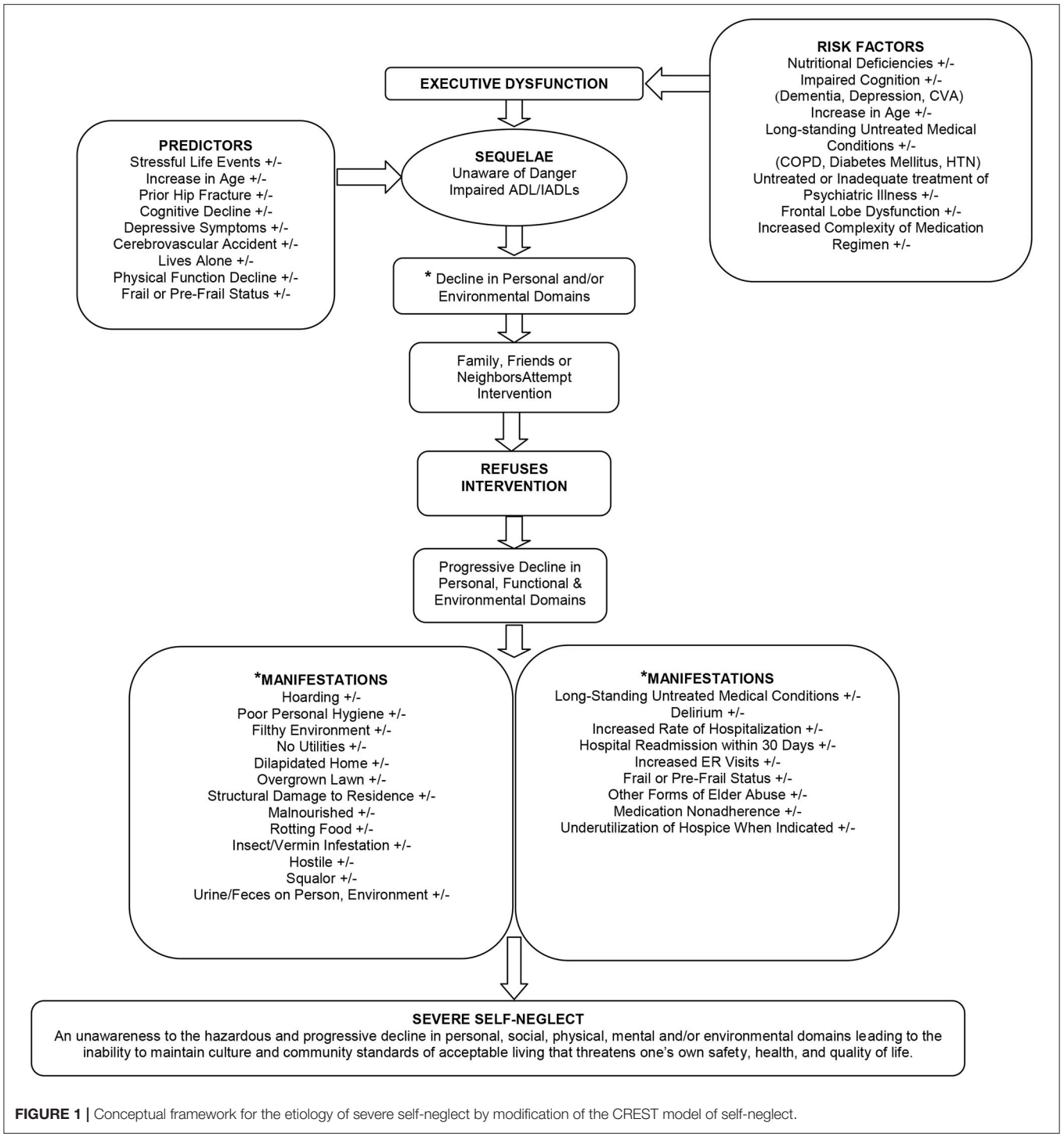

FIGURE 1 | Conceptual framework for the etiology of severe self-neglect by modification of the CREST model of self-neglect.

articles were found to report physical predicting factors for self-neglect. Stressful life events, older age, a prior history of a hip fracture or cerebrovascular accident, objective physical function decline using physical performance testing, self-reported physical function decline using the Katz Index or Rosow-Breslau Health Scale, frail or pre-frail status on the Fried Frail Phenotype test, male gender, low income, cognitive decline, and depressive symptoms have all been identified as predictors to self-neglect (10, 21, 25–27).

Executive Dysfunction

Executive dysfunction (ED) is defined as the inability to complete complex tasks such as managing financial transactions or preparing meals, actions that require high cognitive abilities

(28–30). Increasing complexity of the medication regimen has proven to be a risk factor contributing to ED and self-neglect with higher levels of regimen complexity resulting in lower levels of medication adherence (31). Medication non-adherence is a manifestation of self-neglect associated with increasing complexity of the medication regimen as well as lower physical functioning in self-neglecters (32). These results highlight the cyclical nature of self-neglect and medication in such that ED and comorbidities dictate a need for more medication which increases the risk of non-adherence which can exacerbate the ED and comorbidities. Moreover, executive dysfunction is the inability to initiate or halt actions, plan future events in the presence of novel tasks, inhibit inappropriate behaviors or alternate plans quickly when events interfere with an individual's usual routine of care (33). Several medical conditions such as major depression, diabetes mellitus, memory disorders, psychiatric illnesses, and frontal lobe dysfunction all have been associated with the development of ED (28). Brain atrophy associated with aging can also contribute to the onset of ED (29, 33). Executive dysfunction can be present even with a normal Mini-Mental State Examination (MMSE) score, as well as in highly educated individuals (29, 34).

Refusal is defined as the self-neglecter being unwilling to accept nursing, social, or medical interventions at the persuasion of family, friends, or neighbors. This refusal of care is in the presence of functional, personal, mental, and/or environmental decline. Refusal is a cardinal feature of self-neglecters and is often attributed to a life-style choice or eccentric living (14, 35). For the purpose of this framework, unawareness to dangerous living conditions indicates that eccentric life-style choices and behaviors are not optional and are self-neglect characteristics.

Lack of Standard Definition Decreases the Identification of Self-Neglect

Several authors have identified the need to define and conceptualize this problem in order to conduct more, rigorous research (1, 9, 11–17, 43). There is consensus among researchers that with a standard definition, comparison of study results among disciplines is possible. As of 2012, only 39 states and the District of Columbia include self-neglect in their state elder abuse statutes despite self-neglect being the most common allegation reported to APS agencies across the United States (44). Consequently, true incidence and prevalence rates are undetermined due to varying or lack of definitions which exist for self-neglect among states and researchers (see **Table 1**).

Lauder applied self-neglect to Orem's Self-Care Theory; however, this theory does not encompass all features of self-neglect due to its complexity (1). In 2001, Dorothy Orem argued that self-neglect needs to first be conceptualized prior to utilizing this term in the health care arena (12). As it is outlined in the literature, self-neglect occurs along a continuum; however, the focus of this conceptual framework is on the extreme form along the continuum (1, 12, 17).

Executive Dysfunction Increases the Risk of Self-Neglect

Impairments in executive function contribute to institutionalization due to patient morbidity and subsequent caregiver burden (29, 30). Research demonstrates that executive function is significantly and independently associated with functional status in older adults (29, 39, 45). An independent association has been discovered between executive function decline and an increased risk of self-neglect; however, the study showed that global cognitive function, MMSE, and episodic memory are not independently associated with a greater risk of self-neglect (45). When individuals develop ED, their decisional making abilities are questionable (39). In assessing decision making autonomy, health care providers must address not only the patient's ability to make a decision, but also the ability to carry out that decision (28). In other words, the elder must articulate then demonstrate their decision. For example, in a study of elder self-neglecters, elders reported taking their medication as prescribed yet upon a total pill count, there were discrepancies between what the elder reported, the number of pills prescribed, and the number of pills left in the medication bottle (46).

Understanding, intentionality, and voluntariness are the three components of decisional making capacity (47). Individuals with ED lack the ability to make voluntary decisions and carry out these decisions. These two important components of decisional making autonomy are often not detected with traditional mental status examinations (39). Without detection, adverse health consequences occur in individuals thought capable of making informed decisions regarding their medical regimens (28).

Pickens et al. (38) conducted a cross sectional pilot study of 100 self-neglectors aged 65 and older and 100 community matched controls, which included administering the KELS and the MMSE (see **Table 2**). Analyses revealed self-neglecters were significantly more likely to fail the KELS compared to the control group even after stratifying by normal MMSE scores (38). These results may be due to impaired executive function not identified with MMSE testing. Although no prior research directly links ED to a lack of capacity, individuals who lack capacity also have ED (39). This linkage needs to be tested with future research.

Known Predictors Increase Risk of Self-Neglect

Currently, there are no prospective, longitudinal studies as to the onset of self-neglect, but there are longitudinal studies regarding identification and related aspects of self-neglect. The literature describing this phenomenon is based on case studies, retrospective reviews of social services and Adult Protective Service reports, retrospective chart reviews, qualitative studies, and analysis of the Established Populations for Epidemiologic Studies of the Elderly (EPESE) cohort database. One exception is the landmark study by MacMillan and Shaw (35) that introduced self-neglect to the medical field. These physicians evaluated and treated 72 older adults with self-neglect and followed them over 4 years.

Of considerable note, the Chicago Health and Aging Project (CHAP) was a longitudinal study of older adults conducted in 3-year cycles beginning in 1993 which grew from 6,158 community-dwelling participants living in certain Chicago

TABLE 1 | Lack of standard definition decreases identification of Self-Neglect (SN).

References	Purpose of study	Population (*N*)	Intervention	Outcomes	Authors' conclusion	Our conclusion
Adams and Johnson (9)	SN is present in the medical literature and little attention to the nursing literature	Hospital and community nurses	Interviewed nurses to see if they could identify SN	All nurses were able to identify gross SN	Poor nutrition was a common feature identified with gross SN	Agree, and it has been identified in the literature (i.e., malnutrition, nutritional deficiencies)
Bozinovski (10)	Develop conceptual framework for SN	Qualitative interview of SNers and APS caseworkers ($N = 70$)	Qualitative interviews	Framework based on self-continuity of preserving/protecting self and maintaining customary control	Using the term SN is a misnomer rather older persons labeled as SN are engaged in a process of struggling to maintain coherency of self	Agree with some aspects of this; however, if someone is demented and lives alone with impaired ADL/IADLs it is doubtful they are attempting to maintain customary control or preservation
Dick (16)	Commentary	N/A	N/A	N/A	Need to develop a conceptual and operational definition for SN and diogenes syndrome to formalize the language, synthesize knowledge and reduce the labels applied to this population	We agree
Gibbons (15)	Propose SN as a NANDA diagnosis	N/A	Literature review	SN is either intentional or non-intentional; non-intentional is the failure to engage in self-care actions necessary for health and well-being as a result in deficits in cognition and other mental, physical, material, or social resources needed to participate in self-care	SN as a NANDA diagnosis is either intentional SN or non-intentional SN; Need a standard definition	Agree, but it doesn't describe the unawareness of the situation
Gunstone (13)	Explores the perceptions and experiences of community mental health workers who assess and manage the risk of SN and severe SN in persons with serious health problems	7 community mental health nurses	Semi-structured interviews	Nurses working in a number of areas where there is a distinct lack of clarity- "The Gray Areas" of which the most important were tolerance of workers to situations of SN/Severe SN, policies, procedures, legislation, and definitions	Need to balance safety needs of clients against their need to be treated as autonomous is a major dilemma with nurses; SN lacks a clear definition	We agree
Lauder (36)	Explore the medical constructs of SN	N/A	Literature review		SN is a symptomatic disorder of a fragmented phenomenon; recognizes unique and personal experience of each SN case vs. a universal definition; SN is a concrete human experience which must be understood within a particular historical context within its own cultures and values and interpersonal practices	Agree with parts but do not agree with the patients living in human and animal feces thinking it's 'okay'. Clearly there's a disconnect
Lauder (1)	Explore the utility of self-care theory in understanding SN		Using SC theory to understand SN	Household squalor, poor diet, failure to look after one's health, poor personal hygiene, mental and physical health problems, inability to sustain and develop interpersonal relationships, homes dirty, littered, and disrepair	SC theory can explain some aspects of SN which may be due to our inability to explain human behavior leading to SN; it may be due to the lack of self-care theories	Agree since SN is a complex phenomenon

(Continued)

TABLE 1 | Continued

References	Purpose of study	Population (*N*)	Intervention	Outcomes	Authors' conclusion	Our conclusion
Lauder et al. (14)	Provide an overview of SN and a framework for managing this problem	N/A	Lit review	Severe household squalor, major decline in personal hygiene, housing disrepair, poor personal hygiene, household untidiness	SN is a violation of acceptable social norms; competing definitions	We agree that there are so many varying definitions leading to the confusion of diagnosing and treating SNers
Orem (12)	Letter to the Editor based on Lauder's theory of SN in the SC theory	N/A	N/A	N/A	SN needs conceptualization to determine validity and reliability of the formulated and expressed concepts as it's used in health care practices. There are no formal and expressed concepts of SN. We need a detailed description of a range of instances of SN to reveal a number of clear-cut cases with evidence of essential elements and relationships among them	We agree

neighborhoods in 1993 to 9,056 participants in 2005. As of 2005, the total number of individuals found to have been reported to social services in that cohort was 1,820 (48). A plethora of data was collected, including data regarding individuals who were identified as possible self-neglecters and the traits accompanying them, often separated into mild, moderate, or severe cases of self-neglect (see **Table 3**). As of 2010, there were 4,627 individuals still participating in the study (6, 7, 25, 26, 48–52).

Self-Neglect Within Communities and Groups

The population Study of Chinese Elderly in Chicago (PINE Study), conducted from 2011 to 2013, focused on self-neglecting, community-dwelling U.S. Chinese older adults in the greater Chicago area. Within this population, the unique manifestation of suicidality and unique confounding factors of illiteracy and language barriers were discovered (53). However, based on current research available, these authors are presently unable to determine if the discoveries of the PINE study can be generalized to all populations of self-neglecters or if they are confined to specific ethnicities, so suicidality, illiteracy, and language barriers are not included within this framework.

A study conducted on elder abuse and neglect among veterans among greater Los Angeles examined the prevalance, type, and intervention outcomes of elder abuse/neglect among a veteran population. A review of medical records of 575 veterans who had received services from the Veteran's Affairs Geriatric Outpatient Clinic in Los Angeles during a 3-year period found 31 veterans (5.4%) who had an elder abuse report filed on their behalf. Prevalance of elder abuse/neglect was higher among older (80+) and Caucasian and African American veterans. Eight of 31 victims suffered from more than one type of elder abuse including self-neglect (54). A close look at this study reveals that it lacked more information about self-neglect of veterans possibly resulting from PTSD (Post Traumatic Stress Disorder) and this can be further explored to prevent future cases on self-neglect in veterans.

Depression and Cognitive

Depressive symptoms and cognitive impairment in older adults were used to predict self-neglect by analyzing data from the New Haven EPESE cohort (21). Individuals were 65 years of age and older residing in the community. Male gender, older age, low income, depressive symptoms, impaired cognition, and a prior hip fracture or cerebrovascular accident were found to predict self-neglect. These outcomes were confirmed with Connecticut's investigations between 1982 and 1991. In Bozinovski's qualitative study interviewing self-neglecters and caseworkers, the development of self-neglect was attributed to a major, life-changing event such as death of a loved one or a decline in personal health (10).

Decline in Physical Condition

Measured declines in physical and cognitive function can predict the prevalence of self-neglect. A study by Dong et al. (26) as part of the CHAP population survey utilized the MMSE and the 6-item Katz Activities of Daily Living (ADL) scale to assess cognitive function and measure limitations for performing basic

TABLE 2 | Executive dysfunction may increase the development of self-neglect.

References	Purpose of study	Population (*N*)	Intervention	Outcomes	Authors' conclusion	Our conclusion
Dyer et al. (23)	Characterize a group of self-neglectors 65 years and older	Older adults aged 65 years and older with validated SN referred to a medical team by APS ($n = 538$)	Cross sectional chart review	Average patient age was 75.6, 70% were female, 460 were 65 years of age and older, 50% had abnormal MMSE scores, 15% had abnormal GDS scores, 76.3% had abnormal PPT scores, 95% had moderate to poor social support based on the DUKE Social support index, multiple co-morbidities were noted yet more than 46% were on no meds	Underlying medical disorders leads to executive dysfunction resulting in impairments in IADLs. When there is a lack of social support services in this group, self-neglect ensues	CREST model of self-neglect needs to be adapted
Kohlman-Thomson (37)	N/A	N/A	N/A	N/A	Booklet with instructions on how to administer and score the KELS. In the introduction, the author describes its utility and how in some states it's used in the courts for determination of commitment and gravely disabled cases	
Pickens et al. (38)	Compare KELS scores between substantiated SN and matched community controls	65 years of age and older with substantiated SN by APS ($N = 100$)	CGA including the KELS	SN significantly more likely to fail the KELS compared to matched controls. When stratified by MMSE, SN with intact cognitive function still significantly more likely to fail the KELS	KELS provides clinicians with an objective measure of an individual's capacity and performance with everyday life-supporting tasks and thus provides information that can help NPs identify elders at risk for SN	We agree
Royall et al. (29)	To assess the contribution of executive control function to functional status	Non-institutionalized septuagenarians ($N = 547$)	MMSE, EXIT25, and functional status measurements conducted	The effect of the EXIT 25 on change in IADl was stronger than those of age, baseline IADLs, comorbid disease and level of care	ECF is a significant and independent correlate of functional status in normal aging	
Royall et al. (30)	To assess the contribution of changes in executive control function and memory to changes in functional status	Non-institutionalized septuagenarians ($N = 547$)	CVLT, EXIT25, functional status measurements conducted	EXIT25's effect on the rate of change in IADLs was stronger than those of age, baseline IADLs, comorbid disease or level of care	ECF is a strong, significant and independent correlate of functional status in normal aging. In contrast, memory decline has no independent association with rate of change in functional status	
Schillerstrom et al. (39)	A review of the impact of medical illness on ED and discuss practical diagnostic instruments and treatment strategies	N/A	N/A	N/A	Patients with ED are more likely to resist care and less compliant with medications. ED makes a significant contribution to impaired IADLs and longitudinal rates of change in ADL performance. Medical patients should be screened for ED. CLOX test can help detect ED	Agree
Workman et al. (28)	N/A	N/A	N/A	N/A	Impaired executive function affects intentionality and voluntariness. Evaluation of autonomous decision-making capacity is an ongoing process that requires integration of data from multiple sources and detailed questioning by an IDT	
Wecker et al. (33)	Determine if age is related to a decline in executive function	Individuals 20–79 years old ($N = 112$)	California trail making and stroop test administered	After controlling for the component skills, age had a significant effect on executive requirement (speed) but didn't have an effect on switching	Study confirms importance of partialling out components in the assessment of multidimension tasks; emphasizes specificity over generalizability when examining impact of age on cognition	

TABLE 3 | Known predictors increases self-neglect.

References	Purpose of study	Population (*N*)	Intervention	Outcomes	Authors' conclusion	Our conclusion
Abrams et al. (21)	Assess the contribution of depressive symptoms and cognitive impairment to the prediction of SN in elders residing in the community	Data analysis of the EPESE data base (*N* = 2,812)	N/A	Risk factors to developing SN are males, older age, low income, living alone, history of hip fracture or stroke, cognitive impairment and depressive symptoms	Elders residing in the community who experience depressive symptoms or impaired cognition may be at risk for SN	We agree
Bozinovski (10)	Develop conceptual framework for SN	Qualitative interview of SNers and APS caseworkers (*N* = 70)	Qualitative interviews	Framework based on self-continuity of preserving/protecting self and maintaining customary control; there deviant behavior pushes families and friends away when help is suggested	Using the term SN is a misnomer. Rather, older persons labeled as SN are engaged in a process of struggling to maintain coherency of self	Agree with some aspects of this; however, if someone is demented, lives alone with impaired ADL/IADLs, it is doubtful they are attempting to maintain customary control or preservation
Dong et al. (25)	Assess the contribution of measurable physical function decline with the prevalence of SN	1,068 of the 5,570 participants of CHAP from 1993 to 2005 who were reported to APS for suspected SN	Physical performance test, Katz ADL scale, Nagi scale, and Rosow-Breslau scale	For every 1-point decline in the physical performance test and declines in the Katz ADL or Rosow-Breslau scales were associated with an increased risk of SN	Increased physical impairment is independently associated with increased risk of SN	We agree
Dong et al. (26)	Assess the contribution of physical and mental function decline with the prevalence of SN stratified by gender and by SN factor; lower health status increased risk of SN	4,627 older adults from CHAP; 1,645 men and 2,982 women	Katz ADL scale, MMSE, and health status	Risk of SN increased as health status decreased; for each impairment on the Katz ADL scale, risk of SN increased for women in the factors of overall SN, hoarding, unsanitary conditions, and personal hygiene and for men in personal hygiene; for each lower point on the MMSE, SN increased in the factors of overall self-neglect, hoarding, house in need of repair, and unsanitary conditions for both genders	As levels of physical function, health status, and cognitive dysfunction decline, risk increases for SN and personal or environmental hazards, which are prevalent in an urban, community-dwelling aging population	Agree, but we have found these hazards to be prevalent in community-dwelling aging populations regardless of urban, suburban, or rural classifications
Lee et al. (27)	Assess the contribution of frailty status to the prediction of SN	Older adults with APS-verified SN, *N* = 37	Fried Frailty Phenotype assessment	3% of SNers were robust, 62% were pre-frail, and 35% were frail indicating that frail or pre-frail status can predict SN; individuals who are pre-frail are twice as likely to become frail	Current interventions are wise to target pre-frail older adults to delay progression from pre-frail to frail	We agree

self-care, respectively. Results showed that for each impairment on the Katz ADL scale, the prevalence of overall self-neglect, hoarding, and unsanitary conditions increased significantly in women, and inadequate personal hygiene increased for men and women, indicating that a measurable decline in physical function can contribute to self-neglect. For each lower point on the MMSE, there was a substantial increase in overall self-neglect, hoarding, house in need of repair, and unsanitary conditions for both men and women, which corroborates the findings of impaired cognition contributing to self-neglect as seen in the New Haven EPESE cohort. Additionally, the study statistically proved that lower health status correlates with increased prevalence of self-neglect. A longitudinal CHAP-related study by Dong et al. (25) focused on assessing physical function by objectively measuring decline in physical performance testing, and measuring self-reported declines in the Katz, Nagi, and Rosow-Breslau scales. The results concluded that there was an increased risk of self-neglect with every 1-point decline in the physical performance test as well as with each decline in the Katz and Rosow-Breslau scales. There was no association between increased risk of self-neglect and a decrease in the Nagi scale.

Frailty

A study conducted by Lee et al. (27) used the Fried Frailty Phenotype (FFP) in assessing the abilities of self-neglecting older adults as it had been widely presumed that frailty contributes to self-neglect. Characteristics assessed with the FFP included unintended weight loss, self-reported fatigue, low physical activity, decreased grip strength, and slow walking speed. If none of the characteristics applied, the individual was considered robust; if one or two characteristics were present, the individual was classified as pre-frail; an individual with three or more applicable characteristics was considered frail. As expected, more self-neglecters were frail as opposed to robust; however, the majority of self-neglecting adults in the study were in the pre-frail status (27). Therefore, a predicting factor for severe self-neglect is frail or pre-frail status on the FFP (see **Table 3**).

Personality Traits

One zone of predictive factors, which was found to be statistically insignificant, is personality traits. Another part of the CHAP population survey, a study was conducted to determine whether the personality traits of neuroticism, extraversion, information processing, and rigidity were associated with the development of elder self-neglect. Though initial results indicated a positive association, it was determined that potential confounding factors were responsible for the association. Once the potential confounders were accounted for, there was no longer a statistically significant association between personality traits and self-neglect (48). Therefore, we did not include the results in our conceptual framework.

Sleep

Sleep quality and self-neglect in aged adults has been minimally explored (55), evaluated the association of elder abuse and poor sleep in a rural older Malaysian population. Researchers found self-neglect was significantly associated with poor sleep and recommended the creation of interventions or treatment modalities that focus on improving sleep quality among elder self-neglect and abuse populations. Additional research has looked at the impact of poor sleep quality in associated conditions (56–58). However, further research is needed in this area to assess the association of self-neglect with poor sleep quality.

Based on the authors' experience, self-neglect occurs in both genders regardless of income. Therefore, for the purpose of this conceptual framework, known predictors will be limited to stressful life events, older age, cognitive impairment, depressive symptoms, a history of either a stroke or hip fracture, physical function decline, or frail or pre-frail status. All of these disorders can lead to functional decline (25–27, 59–63). While income is not considered a predictor of the onset of severe self-neglect, a lack of income has been proven to contribute to a lack of ability to pay for medications and other medical treatments, which compounds the previously discussed risk factor of medication non-adherence (64).

Client Refusal Increases Risk of Self-Neglect

Commonly, self-neglecters come to the attention of APS or medical professionals when informal caregivers can no longer tolerate the self-neglecter's state of living (65). These individuals refuse medical attention, home cleaning, or removal from their home. Typically, they are not bothered by their personal and environmental domains despite the presence of urine and feces on floorboards, matted hair, overgrown nails, clutter, overgrown lawns, broken windows, or rotting food in their cupboards or refrigerators (1, 2, 11, 13–15, 40–42, 66–68).

In Texas, APS has the option of emergency removals, but this option may not be available in other states or countries (69). Commonly, involuntary removal is the only means for providing any intervention (69). Once hospitalized, treatment is initiated, yet upon discharge, self-neglecters refuse outpatient services (70, 71). Americans are very independent, so the least restrictive alternative to intervention is imperative. However, when self-neglecters lack the capacity for self-care and protection, they are no longer safe to live alone (17).

Lee et al. (72) successfully conducted the first known clinical intervention in a group of APS-substantiated self-neglecters, proving that not every self-neglecter will refuse intervention. Of the 94 possible referrals, there were 59 individuals who agreed to participate and 35 who completed the two-phase trial. However, severity of the self-neglect does not appear to have been taken into account. Therefore, client refusal of care is still included in the conceptual framework as a defining characteristic of severe self-neglect. This study should be considered in future research regarding mild to moderate self-neglect as it proves positive treatment outcomes for those who agree to the proposed intervention (see **Table 4**).

While refusal of interventions increases the risk of self-neglect, self-neglect increases the risk of emergency and end of life healthcare utilization. Self-neglecters are more likely to need hospice services than elders who do not self-neglect, with severe self-neglecters experiencing the greatest increase in risk. There is also a decreased length of time spent on hospice care and time between admission into hospice care and death for

TABLE 4 | Refusing intervention increases self-neglect.

References	Purpose of study	Population (*N*)	Intervention	Outcomes	Authors' conclusion	Our conclusion
Bozinovski (10)	Develop conceptual framework for SN	Qualitative interview of SNers and APS caseworkers ($N = 70$)	Qualitative interviews	Framework based on self-continuity of preserving/protecting self and maintaining customary control; there deviant behavior pushes families and friends away when help is suggested	Using the term SN is a misnomer rather older persons labeled as SN are engaged in a process of struggling to maintain coherency of self	Agree with some aspects of this however if someone is demented, lives alone with impaired ADL/IADLs I doubt they are attempting to maintain customary control or preservation
Clark et al. (40)	describe gross neglect in old age	Elderly patients admitted to a hospital in acute illness and extreme SN ($N = 30$)	Stabilization of medical problems	All had dirty, untidy homes, filthy personal appearance, 1/3 persistently refused help; acute presentation with falls was common, deficiencies in iron, folate, B12, vitamin C, calcium and vitamin D; high mortality rate (46%); personality characteristics aloof, suspicious, emotionally labile, aggressive, reality disoriented	These features might be called diogenes syndrome	I agree
Cooney and Hamid (41)	N/A	N/A	N/A	N/A	Main obstacle in helping SNers is their reluctance to seek help and resistance to medical intervention when offered. Need to gradually develop rapport and then encourage them to accept services	Agree with both suggestions except in underlying psychosis or untreated psychiatric disorders
Lauder et al. (14)	Provide an overview of SN and a framework for managing this problem	N/A	Lit Review	Severe household squalor, major decline in personal hygiene, housing disrepair, poor personal hygiene, household untidiness, service refusal	SN is a violation of acceptable social norms; competing definitions	I agree that there are so many varying definitions leading to the confusion of diagnosing and treating SNers
Reifler (42)	Editorial on diogenes syndrome	N/A	N/A	N/A	Diogenes syndrome also known as senile squalor, senile SN or social breakdown is characterized by social withdrawal, self-induced abysmal living and lack of concern about receiving assistance. There is evidence that these patients could be treated such as depression in conjunction with severe medical illness	Agree

individuals who self-neglect (7). Emergency department usage rates for elders who self-neglect were found to be significantly higher, roughly triple, that of those who do not self-neglect, with a gradient increase in severity of self-neglect and emergency department use (51). Additionally, it was determined that elders who self-neglect have an increased rate of hospital readmission within 30 days after being discharged, again roughly triple the rate of those who do not self-neglect, with a gradient increase in severity of self-neglect and hospital readmission (50).

Recent Measurement Tools and Interventions

The Kohlman Evaluation of Living (KELS) assesses both basic and instrumental activities of daily living (37). The KELS relies on the individual's performance and self-report as well as observation by the administrator. In some states, the KELS is used in guardianship hearings to determine if someone can safely live by him/herself in the community based on their KELS' scores.

The Self-Neglect Severity Scale (SSS), proposed in 2006 by the Consortium for Research in Elder Self-neglect of Texas (CREST), laid the foundation for self-neglect severity assessment. It utilized questions clustered into the sections of personal hygiene; assessment of cognitive, health, and safety issues; and environmental assessment to determine the severity of self-neglect exhibited by an individual (2). Upon testing, the SSS was found to have sensitivity and specificity below the conventional acceptable range, thus necessitating an improved scale for a gold-standard screening tool (73). As of yet, no refinements to the SSS have been published; however, there have been several other assessment tools devised in the past decade to identify self-neglect and/or assess its severity.

Of note are the SN-37, the Elder Self-Neglect Assessment, the Abrams Geriatric Self-Neglect Scale, the IMSelf-Neglect questionnaire, and the Chicago Health and Aging Self-Neglect Scale. Many of these scales expand upon the foundation laid by the SSS (6, 74–77). The SN-37 is an instrument comprised of 37 items separated into 5 factors that contribute to self-neglect: environment, social networks, emotional and behavioral liability, health avoidance, and self-determinism. A provider based on the yes or no answers indicating the presence or absence of each item can suggest appropriate interventions. The SN-37 tool is comprehensive while remaining brief enough to avoid overwhelming the individual or the professional administering and interpreting the assessment (74). The primary limitation noted by these authors as SN-37 relates to this conceptual framework is that there did not appear to be a classification of the scoring system to define where a self-neglecter sits on the continuum from mild to severe self-neglect except that a higher score means increased severity. The purpose of SN-37 as understood by these authors was to focus more on interventions based on responses and not on classification; however, this conceptual framework attempts to define self-neglect at the severe end of the continuum and thus requires classification.

The Elder Self-Neglect Assessment (ESNA) is a psychometrically sound self-neglect assessment tool which has a long form of 62 items and a short form of 25 items. In both forms, items are divided into either behavioral characteristics or environmental factors. Using the Rasch item response theory and traditional validation approaches, it was determined that behavioral characteristics were more frequently associated with low to moderate severity of self-neglect while environmental factors were more frequently associated with moderate to high severity. The assessment is organized so that the questions are relatively in order from least to most severe (75). Like SN-37, the primary limitation noted by these authors as ESNA relates to this conceptual framework is the lack of classification of what scores constitute mild, moderate, or severe self-neglect.

The Abrams Geriatric Self-Neglect Scale (AGSS) is a 6-item assessment, but each item is its own factor with a handful of supporting questions to determine the score. The items are prescription medications, personal care, nutrition, environment/housing, financial stewardship, and socialization. The supporting questions help determine a score for each item of 0–4 for a total score range of 0–24, 0 meaning a complete absence of self-neglect and 24 meaning the most severe self-neglect (76). Given that the AGSS also does not classify which range of scores indicate mild, moderate, or severe self-neglect, the same limitation applies as it relates to this conceptual framework.

The Istanbul Medical School Elder Self-Neglect (IMSelf-neglect) questionnaire is an 11-item screening tool developed to be used by outpatient clinics in conjunction with a complete geriatric assessment. The items are separated into the clusters of personal hygiene, health habits, and social functioning, and a lower test score indicates a higher possibility of self-neglect, with the cut-off threshold to indicate that self-neglect is present at or below 7 (77). Given the nature of outpatient clinics, a screening tool with 11 items is ideal to aid in identification of individuals who need a referral for more in depth assessments and care. However, there are limitations noted by these authors as IMSelf-Neglect relates to this conceptual framework including a lack of comprehensiveness and a lack of classification of scores on the self-neglect continuum except for the cut-off threshold at 7 indicating that self-neglect is present.

The Chicago Health and Aging Self-Neglect Instrument is a 15-item assessment that encompass personal hygiene, health habits, behavioral characteristics, environmental characteristics, and financial independence. Each item receives a rating of 0–3 to notate no risk, mild risk, moderate risk, or severe risk to health and safety without additional assistance for a score range of 0–45 (6). The data could also be classified with scores of 1–15 indicating mild self-neglect, 16–30 indicating moderate self-neglect, and 31–45 indicating severe self-neglect (50). This assessment tool quantitatively classifies self-neglect severity as mild, moderate, or severe.

Each of these assessment tools has strengths, and many aspects of the tools overlap with one another while retaining their own distinct elements. With the exception of the IMSelf-Neglect questionnaire, which was developed for a specific niche, all the tools were meant to be generalizable. There is no clear "gold standard" tool to assess self-neglect, so the variety of options, while beneficial for researchers and healthcare providers who may wish to tailor an assessment to best fit the individual or patient who is self-neglecting, does nothing to provide a solution

to the quandary of standardizing the self-neglect assessment. For the purposes of identifying severe self-neglect, however, the Chicago Health and Aging Self-Neglect Instrument is the only assessment tool which provides a numerically-based system to differentiate severe from mild or moderate self-neglect.

Besides the aforementioned study by Lee et al. (72), these authors found only one other study on self-neglect interventions over the past decade. The evaluation of the elder abuse intervention program ECARE, Eliciting Change in At-Risk Elders, proved that developing relationships with at-risk elders and/or their families prior to suggesting community-based interventions produces statistically significant improvements in the elder's status. Some participants required as long as 3 months to build a working alliance with outreach specialists before moving on to interventions. Once that alliance was formed, information about available community-based resources was provided that would enhance the elder's safety and promote autonomy in whatever regard best suited the elder's situation. The results found that elder abuse risk factors decreased throughout the intervention and almost three-quarters of participants made strides in their treatment goal and advanced through at least one of Prochaska and DiClemente's stages of change (78). This study is of particular interest and important when juxtaposed with the study by Dong et al. (49). This showed that individuals who self-neglect are at a significantly increased risk of later experiencing multiple additional forms of elder abuse, even after adjusting for confounding factors with a median time between self-neglect alone and the onset of elder abuse of 3.5 years in the study's population (49). The limitations for the analysis of ECARE as it applies to the conceptual framework of severe self-neglect are that the analysis was targeted to all forms of elder abuse, which includes but is not specific to self-neglect, and it did not account for different severities of self-neglect except as a possible causative factor in the length of time required to develop a working alliance. Further studies are needed to determine the impact of ECARE if it is focused on individual aspects of elder abuse, including self-neglect or severe self-neglect.

Automated Monitoring Systems and Machine Learning

The interventions we have referred to in this study require the presence of clinical personnel or verification from a designated advocate. Prior to the COVID-19 pandemic, in-home care and visitation of aging patients, at least sporadically or upon government request was a common reality of Western society. However, the pandemic exacerbated the need for interventions that do not require person-to-person contact.

In-home monitoring systems that incorporate artificial intelligence (AI), machine learning and data science became very useful during the pandemic, but new models are needed more than ever to provide better predictions of health conditions in a larger cohort of individuals (79, 80). It is well-documented that facial recognition and systems-based algorithms used in AI do not result in accurate identification or equal outcomes for black people (81–83).

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A study published shortly before the onset of the pandemic showed that there was racial bias in a widely used algorithm of U.S. healthcare systems, further exacerbating racial and ethnic disparities in an affected health care population of ∼200 Million people (84). Reflective of health inequities, disparities and racial bias in the U.S. healthcare system, the death rate of African-Americans, Hispanic, and Native-Americans from COVID-19 is almost 3 times that of whites (85). As of January 5, 2021, Black and Indigenous Americans experienced the highest rates of death over the past 4 weeks from COVID-19, exceeding 1 in 750 nationally (86). The need for in-home health monitoring systems that accurately reflect disease symptoms and conditions based on facial attributes and whole population analysis is immense (87).

There are reported cases of elderly abuse at nursing homes which has been poorly studied. A look at the SCOPUS database reveals that only 78 out of 1,342 published articles in the last 5 years deal with abuse of the elderly in relation to nursing homes, representing a very small part (5.81% of the considered sample as compared to the number of articles on child abuse highlighting the lack of interest of research on this phenomena) (88).

A 41- Question survey was administered to healthcare professionals, working at the Internal Medicine and Geriatric Wards of two different university Hospitals of Southern Italy, representative of the Italian health public system. For the majority healthcare workers, neglect represented a type of abuse, whereas 40% of physicians and 37% of nurses considered this concept false. All professionals recognized the elder abuse as violation of basic human rights, but 46.94% were not sure about the existence of standard procedure for abuse reporting and treatment. The healthcare workers did not take any necessary action, neither report them to public authorities nor adult protective service agencies. There is still a strong need for education and specific training programs on elder abuse (89).

Parsimony

Considering the complex nature of severe self-neglect, this framework is not concise. If researchers are interested in mild self-neglect, one assumes a more concise model may be developed. What shocks communities and health care professionals is the extreme form of self-neglect since no prior research has been conducted on its etiology. A few published case studies exist on treatment modalities (70, 71, 90).

Testability

This framework has great potential for future testing. It expands on the previously published CREST model of self-neglect to include a definition, predictors, and the refusal component as well as the manifestations. Each domain can be tested individually, in parts, or as a whole. For example, elders who develop ED can be followed to determine if self-neglect ensues, or self-neglecters can be tested to determine if they have ED. Further, prospective longitudinal studies can be conducted to determine what risk factors or circumstances initiate the

onset of self-neglect. Can early intervention prevent or abate this problem?

Usefulness

Utilization by medical, social, nursing, and legal groups may benefit from this framework by having a better understanding of what occurs before the manifestations of severe self-neglect. This framework can be used to teach community agencies about the critical manifestations of which workers must be aware in order to identify severe self-neglect. For example, postal workers have an excellent opportunity to peer into an elder's home during routine mail or package delivery. Emergency medical personnel and home health care workers are in a particularly unique position to be able to assess the physical manifestations of self-neglect in the home from a medical perspective if their services are required by the individual. The primary goal of this framework is to illustrate that this disorder is not a life-style choice.

Generalizability

Currently, this framework is specific to severe self-neglect. It cannot be applied to other forms of elder abuse such as financial exploitation or physical abuse. It shares some features of elders experiencing caregiver neglect such as malnourishment, delirium, and untreated medical conditions. Extreme caution is warranted if applying this framework to mild or moderate self-neglect as signs and symptoms may differ or be much less apparent. Future research should focus on adapting this framework to abuse by caregivers. Additionally, future studies should be conducted regarding the reversal of self-neglect and determining if there is a point of severity on the self-neglect continuum at which abatement is no longer a viable option to provide a point of reference for healthcare providers and social workers in determining how best to treat or assist in cases of self-neglect.

Conclusion

A conceptual framework and a new definition for severe self-neglect is proposed as a foundation for further research. This framework can be used in clinical and community settings to aid health care professionals in identifying severe self-neglect. In doing so, treating these individuals may prevent an early death and possibly reverse this complex health problem. Current knowledge of severe self-neglect is based on studies of individuals already in a state of severe neglect. Collaboration among different disciplines is needed to intervene in these complex cases in order to arrest or reverse the progression of self-neglect. The nursing, medical, and social literature is lacking in prospective, longitudinal data, which must be addressed in the near future.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

SP provided substantial contributions to the conception of the work, acquisition and analysis of data for the work, and is the corresponding author on this paper who agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MD provided substantial contributions in the acquisition and analysis of data for the work. EJ and FJ provided substantial contributions to the design of the work, interpretation of the data for the work, and revised it critically for intellectual content. FJ also serves as a corresponding author on this paper who agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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The Association of Osteosarcopenia With Functional Disability in Community-Dwelling Mexican Adults 50 and Older

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Background: Osteosarcopenia (OS) has recently been described as a predictor of negative outcomes in older adults. However, this alteration in body composition has not been widely studied. In Mexico and Latin America, no information is available on its frequency or associated factors.

Objective: To analyze the association between OS with FD in community-dwelling Mexican adults 50 and older.

Design: Cross-sectional secondary data analysis was performed using primary data from a prospective study Frailty, Dynapenia and Sarcopenia Study in Mexican Adults (FraDySMex).

Setting and Participants: Eight hundred and twenty-five people were included, 77.1% women, aged 70.3 ± 10.8 years old.

Methods: OS was defined as when the person was diagnosed with sarcopenia (SP) plus osteopenia/osteoporosis. The SP diagnosis was evaluated in accordance with the criteria of the European Working Group for the Definition and Diagnosis of Sarcopenia (EWGSOP), and the osteoporosis diagnosis using World Health Organization (WHO) criteria. Muscle mass and bone mass were evaluated using dual-energy X-ray absorptiometry (DXA). FD was evaluated using the basic activities of daily living (BADL) and the instrumental activities of daily living (IADL). Additional sociodemographic and health co-variables were also included, such as sex, age, education, cognitive status, depression, comorbidity, hospitalization, polypharmacy, urinary incontinence, and nutrition variables such as risk of malnutrition and obesity. Associations between OS with FD were evaluated using multiple logistic regression.

Results: The prevalence of OS was 8.9% and that of FD was 8.9%. OS was associated with FD [odds ratio (OR): 1.92; CI 95%: 1.11–3.33].

Conclusions and Implications: Comprehensive OS assessment could help clinicians identify risk factors early, and thus mitigate the impact on FD in older people.

Keywords: sarcopenia, osteosarcopenia, functional disability, community-dwelling, Mexico City

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INTRODUCTION

Changes in body composition in older people, such as loss of muscle and bone mass, can increase their risk of developing geriatric conditions like sarcopenia (SP) and osteosarcopenia (OS), which is defined as the coexistence of osteopenia/osteoporosis and SP (1, 2). Both OS and SP have been associated with adverse effects on the elderly population, such as frailty, falls, a low quality of life, hospitalization, functional disability (FD), and death (3–7), all of which represent high costs in health systems (3). The muscle and bone tissue loss share several pathophysiological mechanisms which involve a high burden on the health of older adults, leading to the recognition of OS as an emerging geriatric condition (3). It is estimated that, due to the increase in older adults (60 and older) around the world, OS will also increase. The increasing number of falls and fractures will lead to a higher FD in this population (3).

The data around these clinical conditions are heterogeneous and, in some cases in Latin America, data are not available. For SP, the prevalence in Mexico ranges from 9.9 to 33.6% (4–7), while the prevalence of OS has not been reported. However, in other countries OS varies between 5 and 37% among older community-dwelling adults (3). For osteoporosis, the prevalence among Mexican older adults has been reported as, among women and men respectively, between 16 and 6% for osteoporosis of the hip, and 17 and 9% for osteoporosis of the spine (8). Older adults with OS, when compared to older adults who have only SP or osteopenia/osteoporosis, have lower physical performance and an increased risk of fracture, institutionalization, and FD (9–12).

In addition, FD is more common among older people than in the rest of the population (13, 14). A prevalence of FD among Mexican older adults (60 and older) of 26.9% has been reported for the basic activities of daily living (BADL), and 24.6% for the instrumental activities of daily living (IADL) (15). Studies of Mexican older adults have found that risk factors for FD are primarily being an older adult; being female; having polypharmacy, anorexia, weight loss, malnutrition, depression, cognitive impairment, or a comorbidity; a lack of physical activity; and smoking and alcoholism (16–19). No previous study in Mexico has explored the relationship between OS and FD, despite the fact that evidence shows that OS can be a highly predictive geriatric condition in the development of FD in older people (3, 9–12). This is particularly relevant when considering that Mexico is going through an accelerated demographic aging process. In the last 10 years, the proportion of adults 60 years and older increased from 9.1% in 2010 to 12% in 2020, and it is expected that by 2030 one in five people will belong to this age group (20).

The objective of this study is to analyze the association between OS and FD in community-dwelling Mexican adults 50 and older. Few studies have looked at this relationship, but most of those that have, have come from high-income countries. Thus, it is necessary to explore in greater detail the characteristics and epidemiology of OS and FD in a middle-income population such as Mexico, in such a way that prevention and intervention strategies more appropriate to the local context can be developed. Furthermore, while the most unfavorable outcomes due to OS occur in older adults, identifying associated factors earlier can help minimize negative impacts in that group.

MATERIALS AND METHODS

Design and Study Population

This study performs a cross-sectional analysis of women and men 50 years and older, who are community residents and participants in the FraDySMex Study (Frailty, Dynapenia, and Sarcopenia in Mexican Adults). This cohort of community-dwelling adults comes mainly from three municipalities (out of a total of 16) in southeast Mexico City (Cuajimalpa, Magdalena Contreras, and Álvaro Obregón). These three areas hold 12.5% of the total of those 60 and older in Mexico City and have high levels of poverty (Cuajimalpa: 30.1%; Magdalena Contreras: 32.6%; and Álvaro Obregón: 27.9%) (21). Participants were invited to take part in the cohort during home visits made by a psychologist or a social worker, as well as through flyers left in churches, senior community centers, social security centers, and health centers in the designated areas (22).

People eligible to participate in the study were: (1) those who were able to move around with or without assisting devices; and (2) those who were able to answer the study questionnaire by themselves or with the help of a caregiver if their Mini-Mental State Examination (MMSE) score was 10 points or less (23). People were excluded from the study if they were institutionalized, had decreased alertness with any cause, and if they had any acute or chronic condition that, in the judgment of the medical staff, could affect their ability to answer the proposed questionnaire and complete the objective evaluation. Also, people without grip strength tests or a dual-energy X-ray absorptiometry (DXA) body composition assessment were also excluded.

The study had a 3-round design. The first round consisted of the assessment of individuals from October 2014 to December 2015 ($n = 606$), and the second round from October to December 2019 ($n = 1{,}070$). In this last round, new people were added to the cohort and some individuals who had participated in the first round were reevaluated. The participants were received in the Research Laboratory on Functional Evaluation at the National Institute of Geriatrics and the Older Adult Evaluation Center at the Iberoamerican University in Mexico City. There, the medical staff, composed of geriatricians, internists, general practitioners, nurses, physical therapists, nutritionists, and specialists in geriatric rehabilitation, conducted a series of objective evaluations on participants. The selection of the study population is shown in **Figure 1**.

Measurements

Functional Disability Assessment

FD was evaluated using the Barthel scale for BADL and the Lawton scale for IADL (24, 25). A score of $\leq$90 on the BADL scale or $\geq$1 on the IADL scale were considered as FD.

Osteosarcopenia Definition

OS is a condition that describes the co-existence of osteoporosis and sarcopenia, two chronic musculoskeletal conditions associated with aging (2, 3). The sarcopenia was defined

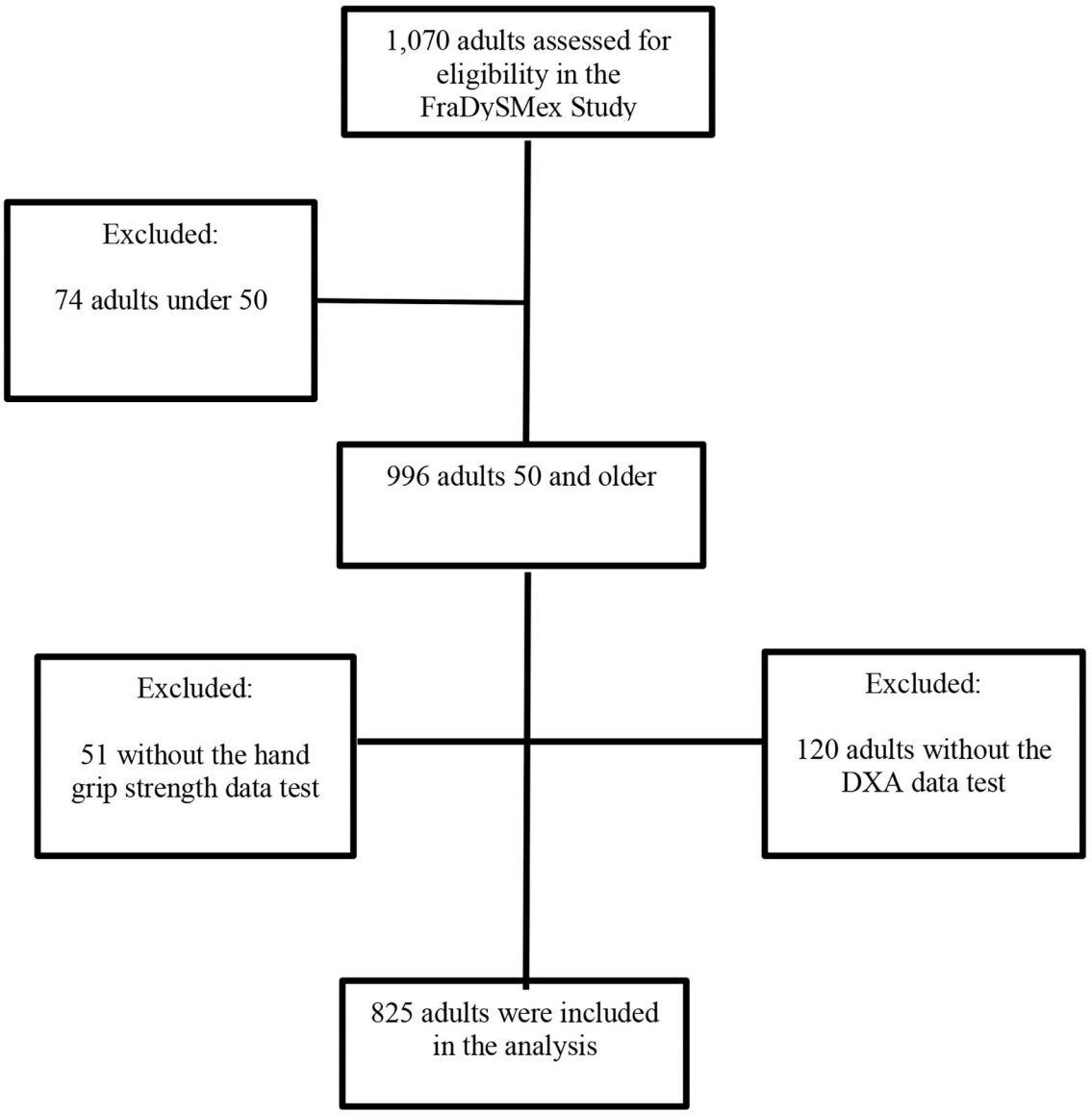

FIGURE 1 | Flowchart of FraDySMex (Frailty, Dynapenia, and Sarcopenia in Mexican adults Study (FraDySMex). DXA, dual-energy X-ray absorptiometry.

according to the criteria of the European Working Group on Sarcopenia in Older People (EWGSOP) (1), adjusted to the population studied, considering low strength, muscle mass and poor physical performance (slow gait speed) (1). Total skeletal muscle mass (kg) (SMT) and appendicular skeletal muscle mass (arms and legs) (kg) (ASM) was measured using dual-energy X-ray absorptiometry (DXA) (Hologic Discovery-WI; Hologic Inc, Bedford-MA). A manual dynamometer (JAMAR Hydraulic Hand Dynamometer, Lafayette, IN) was used to measure manual pressure force; three measurements were taken from each arm and the highest was considered for the analysis. The gait speed was measured for physical performance, which was recorded from a regular six-meter pace walk on the GAIT Rite instrumented mat (platinum 20) (204 × 35.5 × 0.25 inches, 100 Hz sample rate). The cut-off points used for these variables are described in **Table 1**. To determine osteopenia/osteoporosis, DXA was used to measure the total bone mineral density (g/cm^2) (BMD), the femur, and the lumbar spine (L1–L5). WHO criteria were used to diagnose osteopenia/osteoporosis, osteoporosis was considered when the T-score was lower than 2.5 SDs (standard deviations) and osteopenia when the T-score was between 2.5 and 1.0 SDs of the lumbar spine or femur BMD below that of the reference population of young adults (26).

Co-variates

Sociodemographic

Age (years), sex, and schooling (<10; ≥ 10 years).

TABLE 1 | Components and cut-off points used for the diagnosis of sarcopenia.

Sex	ASM[a]	Gait speed[b]	Hand-grip strength[c]	
Males	ASM≤ 6.68 kg/m^2	Height ≤ 1.65 m ≥ 5.7 s	BMI ≤ 24.3kg/m^2	≤ 22
		Height > 1.65 m ≥ 4.5 s	BMI 24.4–26.6kg/m^2	≤ 22
			BMI 26.7–28.5 kg/m^2	≤ 24
			BMI > 28.5 kg/m^2	≤ 22
Females	ASM ≤ 5.35 kg/m^2	Height ≤ 1.51 m ≥ 6.8 s	BMI ≤ 24.7 kg/m^2	≤ 12
		Height > 1.51 m ≥ 5.4 s	BMI 24.8–27.6 kg/m^2	≤ 12
			BMI 27.7–30.5 kg/m^2	≤ 12
			BMI > 30.5 kg/m^2	≤ 13

ASM, Appendicular skeletal muscle mass; BMI, Body mass index.
[a]*Cut-off points according to the lowest quintile of ASM.*
[b]*Cut-off points by height according to the lowest quintile of gait speed.*
[c]*Cut-off points by BMI quartile.*

Health Conditions

Depressive symptoms, from the Depression Scale of the Center for Epidemiological Studies (CESD-7 scale); depression was considered if subjects scored five or more (27). Cognitive status, which was assessed using the MMSE (cognitive impairment was considered when ≤23 points were obtained with 5 years of school education, ≤19 points with between 1 and 4 years of education, ≤16 without education or with <1 year of education) (28). Comorbidity was assessed using the Charlson Comorbidity Index, adapted to Mexican Spanish (≥3 points was considered high comorbidity) (29, 30). Polypharmacy was defined as taking five or more medications (31), and urinary incontinence was defined using the incontinence items on the Barthel scale (24).

Nutrition Variables and Body Composition

Malnutrition was assessed through the Mini Nutritional Assessment (MNA) test, using a cut-off point of ≤23 (risk of malnutrition) (32). The percentage of total body fat was used for women ≥40% and men ≥30% for obesity measured by DXA (33). In addition, anthropometric measurements such as weight, size and BMI (body mass index) were also used to adjust muscle strength and gait components of the sarcopenia diagnosis.

Physical Activity

Low physical activity was defined using the lowest quintile of kilocalories per week, obtained via the physical activity questionnaire for older adults (CHAMPS); <545.7 for men and <481.2 kcal/week for women (34).

Statistical Analysis

Variables were described by arithmetic means and standard deviation (SD) or proportions as appropriate. Group differences between participants with or without FD were evaluated using the *t-Student* test or the *Chi-squared* test for continuous and categorical variables. Logistic regression models (adjusted and not adjusted) were used to determine the association between SP and OS with FD, and the results are shown in terms of an odds ratio (OR). We included the known factors that may modify the effect of this association and that have been previously described in the literature. The variables included in the final models were those significantly related with FD in bivariate analysis. The model with the best fit was chosen. Differences were considered statistically significant with $p \leq 0.05$, and confidence intervals (CI) were also reported at 95%. Likewise, collinearity and interaction between variables were also verified for the final models. The data was analyzed using *Stata version 18*® (Stata Corp, College Station, Texas, USA).

RESULTS

The average age of the participants was 70.3 ± 10.8 years; 77.1% were women and 52.2% had <10 years of schooling. Regarding the health characteristics of the study population, the following incidences were found: cognitive impairment (10.9%), depression (28.8%), high comorbidity (22.3%), polypharmacy (33.1%), and urinary incontinence (8.9%). In terms of nutrition variables, 30.3% of participants were at risk of malnutrition and 53.5% of obesity. Of the total sample, 8.9% had FD. In addition, the prevalence of SP and OS was 14.9 and 8.9%, respectively. In the comparative analysis between groups (with and without FD), the variables that were significant were: age, sex (women), low education, cognitive impairment, depression, polypharmacy, high comorbidity, urinary incontinence, hospitalization, risk of malnutrition, low physical activity, SP, and OS (**Table 2**).

In the multivariate analysis, an increased risk of FD was found in adults with SP (OR: 1.70, CI 95%: 1.03–2.81, $p = 0.04$), an association that was higher in adults with OS (OR: 1.94, CI 95%: 1.10–3.42, $p = 0.02$), after adjusting for age, sex, polypharmacy, risk of malnutrition, and low physical activity (**Figure 2**).

DISCUSSION

The objective of this study was to analyze the association between OS and FD in community-dwelling adults 50 years and older in Mexico City. Our results suggest that there is a statistically significant association between OS and FD (after adjusting for age, polypharmacy, and risk of malnutrition; known factors that may modify the effect of disability association), and that this association is higher than that in those adults

TABLE 2 | Characteristics of participants by functional disability.

Characteristics	Total	With functional disability		Without functional disability		*p*-value
	N [95% CI]	*N*	% [95% CI]	*N*	% [95% CI]	
Sarcopenia	15 [12–17]	36	19 [13–24]	69	10 [7–13]	0.00
Osteosarcopenia	9 [7–11]	29	17 [11–23]	45	6 [4–8]	0.00
Sociodemographic						
Age, years	69.9 ± 9.3	207	77.5 ± 9.5	707	67.1 ± 9.4	0.00
50–65 years old	52 [46–53]	46	61 [54–68]	430	22 [16–29]	
>65 years old	48 [42–49]	161	78 [72–83]	277	39 [36–43]	0.00
Women	78 [75–80]	166	80 [74–81]	556	78 [75–81]	0.68
Low education < 10 years	58 [49–56]	146	70 [64–77]	331	46 [43–50]	0.00
Health conditions						
Cognitive impairment (MMSE)*	11 [9–13]	45	24 [18–31]	47	7 [5–9]	0.00
Depression (CESD-7 ≥ 5)	29 [26–32]	75	41 [34–48]	168	25 [21–28]	0.00
High Comorbidity (Charlson Comorbidity Index ≥ 3 points)	23 [19–25]	66	34 [29–43]	123	18 [15–21]	0.00
Hospitalization, ≥1 in the last year	12 [9–13]	41	19 [14–25]	62	8 [6–10]	0.00
Polypharmacy, ≥5 medications	31 [30–36]	92	50 [43–58]	189	28 [24–31]	0.00
Urinary incontinence	10 [7–11]	47	22 [16–28]	34	4 [3–6]	0.00
Other nutrition and body composition variables						
Risk of malnutrition (MNA ≤ 23)	30 [27–33]	86	50 [42–57]	163	24 [21–28]	0.00
Obesity (≥40% women and ≥35% men)	59 [54–60]	122	58 [52–65]	367	51 [48–55]	0.07
Low physical activity	20 [18–23]	64	3 [25–37]	60	8 [2–15]	0.00

CI, Confidence intervals.
**MMSE, Mini-Mental State Examination (cognitive impairment was considered when ≤23 points were obtained with 5 years of school education, ≤19 points with between 1 and 4 years of schooling, ≤16 without schooling or with <1 year of schooling).*
CESD, Depression Scale of the Center for Epidemiological Studies.
MNA, Mini Nutritional Assessment.

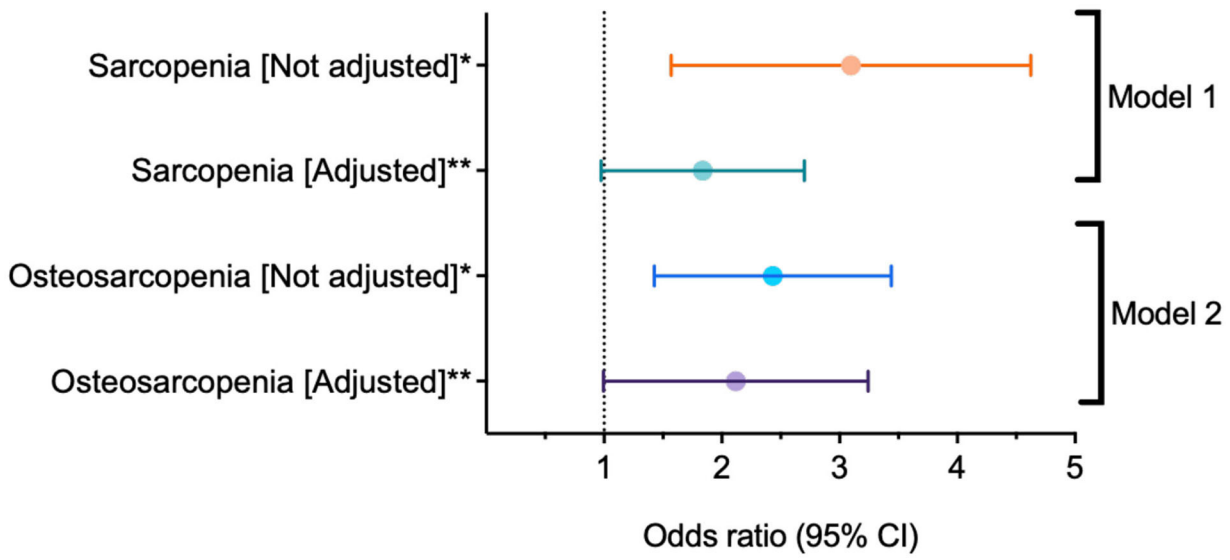

FIGURE 2 | Logistic regression between sarcopenia, osteosarcopenia, and functional disability. CI, Confidence intervals. *$p < 0.001$; **$p < 0.05$. Both models were adjusted by age, sex, polypharmacy, risk of malnutrition, and low physical activity.

with SP only. This coincides with the results of other studies. For example, Kirk et al. (3) found that Australian older people with OS were 2.6 times more at risk of developing FD than those without OS; however, that study doesn't compare that risk vs. SP alone. Drey et al. (35) showed that in pre-frail older adults, osteosarcopenic individuals had a significant reduction

in physical performance, suggesting that adults with OS have a higher risk for further functional decline when compared to sarcopenic and osteopenic/osteoporotic individuals. It is important to reiterate that there are few studies published to date that analyze the relationship between OS and FD. Furthermore, our results corroborate the conclusion that OS represents a greater risk for FD in our study's population than SP alone.

During the aging process, there are several changes in body composition, both on a molecular and tissue level. This is either due to an increase and redistribution of adipose tissue or to a loss of fat free body mass (particularly at the expense of muscle and bone mass). These changes determine the risk of developing geriatric syndromes such as SP and OS; public health problems that impact the quality of life in the geriatric population (1–4). It has also been reported that these syndromes have common risk factors and outcomes and generally interact with each other as OS; that is, one syndrome can contribute to the onset of another and incur worse results, such as functional repercussions and a loss of independence in older adults (3, 12, 35).

This is the first study in Mexico to analyze the relationship between OS with FD in older adults, although previously an association of osteosarcopenic obesity (OSO) syndrome with low physical performance and frailty had been shown as risk factors for FD among older Mexican adult women (36). This evidence indicates the importance of integrating a body composition measure, as a risk factor for FD, into the geriatric assessment. Timely detection of changes in muscle and bone tissue in older adults can help health personnel start a specific treatment (diet, physical activity, and promoting healthy behaviors) that prevents further deterioration, development of SP and OS, and subsequently FD.

It should be noted that in Mexico, this assessment of body composition (measurement of muscle mass, fat mass and bone mass) is not included in most primary and secondary care levels. Not all centers have the necessary infrastructure to perform these measurements, such as electrical bioimpedance equipment or dual-energy X-ray absorptiometry. Also, few health personnel are trained to perform and interpret these measurements in the population of older adults. Therefore, it is necessary to develop and implement protocols or algorithms based on the evaluation of body composition indicators as early predictors of FD in older adults. Similarly, it is essential to generate *ad hoc* scales or measuring systems for the Mexican population that can be used by medical personnel in health institutions where specialized equipment such as those used in this research is not available.

FD has a higher prevalence and impact on the older adult population; however, it is necessary to detect risk factors at younger ages, such as loss of muscle and bone mass starting at around age 40 or 50 and increasing with advancing age. These physiological and molecular changes begin gradually, such as with the alteration of hormones and inflammation factors, which is accentuated after the age of 60 (33). Detection of these changes at younger ages allows for effective treatments to be implemented to prevent the development of geriatric conditions like FD.

We consider it necessary to conduct further studies on this topic and to include other phenotypes associated with body composition in the analysis, such as sarcopenia obesity, OSO, and other FD-related sociodemographic variables such as socioeconomic level, race, ethnic group, quality of life and access to health services. Likewise, it is recommended to conduct this analysis with a longitudinal design and with different types of geriatric populations.

This study has some limitations that should be considered. First, the analysis used was cross-sectional; therefore, no conclusions on causality between FD and OS could be reached. However, one strength is that 825 participants were included, which could establish a significant association between the variables of interest. A second limitation is that FD was measured through self-reported scales based on limitations in BADL and IADL. A final limitation has to do with a possible selection bias, since the sample consisted of adults who were able to go, on their own, to the centers where the evaluations were carried out, and those adults who were less healthy and with a higher degree of FD could have been excluded.

CONCLUSION AND IMPLICATIONS

Comprehensive OS assessment could help clinicians identify risk factors early and thus mitigate the impact on FD in older people. FD is one of the most relevant health indicators of older adults, not only due to individual impacts, but also because of the increase in dependency and the costs implied for health systems, especially in middle- and lower-income countries. OS is a geriatric syndrome that, together with other syndromes, should be evaluated to design more appropriate interventions, based on the specific needs of the older Mexican 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

This study was approved by the Ethics Committee of the Angeles Mocel General Hospital, and registered by the National Institute of Geriatrics (DI-PI-002/2014), as well as with the National Bioethics Commission (CONBIOETICA-09-cei-013-20170517/2019). The informed written consent of all individuals was obtained.

AUTHOR CONTRIBUTIONS

ML-T contributed to the data collection, statistical data analysis, and manuscript writing. OR-C was responsible for the study design (FraDySMex) project, study approval in the ethics committee, data collection, and manuscript review. SS-G contributed data analysis and manuscript review. LC-P contributed to statistical analysis. AL-L contributed to the final manuscript review. MA-B is the corresponding author and contributed to writing and reviewing the manuscript. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Prevalence, Incidence, and Associated Factors of Possible Sarcopenia in Community-Dwelling Chinese Older Adults: A Population-Based Longitudinal Study

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Purpose: This study aimed to assess the prevalence, incidence, and associated factors of possible sarcopenia in a nationwide representative sample of the community-dwelling older Chinese population.

Methods: This study used the data of participants aged 60 years and over from the China Health and Retirement Longitudinal Study (CHARLS). Data on participants from three waves (2011–2015) of CHARLS were extracted. Possible sarcopenia was defined as low muscle strength or low physical performance, based on the Asian Working Group for Sarcopenia 2019 consensus. We first described baseline prevalence and four-year incidence of possible sarcopenia. Then multiple logistic regression and multivariable parametric proportional hazard model with Weibull distribution were used to examine the association of risk factors with baseline prevalence and four-year incidence of possible sarcopenia, respectively.

Results: The prevalence of possible sarcopenia was 46.0%. The four-year incidence of possible sarcopenia was 11.9 per 100 person-years. Multivariable analysis revealed that advanced age and depressive symptoms were associated with increased prevalence of possible sarcopenia, while receiving education and moderate or high physical activity were associated with a lower risk of possible sarcopenia prevalence. For incidence, only advanced age was associated with an increased risk of possible sarcopenia incidence.

Conclusion: Our study revealed the substantial burden of possible sarcopenia and related risk factors in community-dwelling settings in China. It highlighted the importance of early detection and intervention in this subclinical group for the prevention of sarcopenia.

Keywords: prevalence, incidence, possible sarcopenia, risk factors, epidemiology

INTRODUCTION

Advancing age is accompanied by a series of physiological changes in body composition, one of which is characterized as the gradual decrease in muscle quantity and quality (1). When low skeletal muscle mass coexisted with low muscle function (muscle strength or physical performance), this geriatric syndrome is termed sarcopenia (2). Previous evidence reported the prevalence of sarcopenia, defined by the Asian Working Group for Sarcopenia (AWGS) 2014, ranged from 5.5 to 25.7% among the Asian population (3). For Chinese community-dwelling older adults, the pooled prevalence was 11–14% (4, 5). In the eastern area of China, the prevalence rate was 9.7% (6). Sarcopenia is associated with a series of adverse health outcomes, such as falls, fractures, frailty, physical disability, and hospitalization (7). However, sarcopenia develops insidiously, even with no obvious symptom in the early stage. In general, people with sarcopenia are not aware of this disorder until progressively decreased muscle function becomes severe enough, such as the occurrence of physical dependence (8). Therefore, to enable timely intervention, early screening and identifying the vulnerable individuals who are on the way to sarcopenia before resulting in adverse outcomes should be at the forefront of sarcopenia management.

Measuring muscle mass is an indispensable procedure in the diagnosis of sarcopenia. However, assessing muscle mass is still a challenge in primary care settings where reliable and validated diagnostic equipment is not easily accessible. To promote early identification of people at risk of, or on the way to, sarcopenia and raise awareness of sarcopenia prevention in primary care settings, the AWGS 2019 consensus proposes a new concept named "possible sarcopenia," which refers to poor muscle strength or low physical performance (3). According to the AWGS 2019 algorithm for sarcopenia, the SARC-F or SARC-CalF questionnaire could be used for case-finding in community settings (3). For those whose SARC-F $\geq$ 4 or SARC-CalF $\geq$ 11, muscle strength and physical performance should be assessed to detect whether the possible sarcopenia exists. If possible sarcopenia is identified, early lifestyle intervention and preventive service should be provided for this vulnerable group (3).

The epidemiological information of possible sarcopenia is limited. At present, three cross-sectional studies have reported the prevalence of possible sarcopenia based on the AWGS 2019 consensus (9–11). One was conducted in Singapore, which recruited 536 adults aged from 21 to 90 years, with a prevalence of 15.3% (10). The other study was conducted in Korea, which recruited 2,123 older adults, with the prevalence as 20.1% in men and 29.2% in women (9), and the third one studied 6,172 Chinese participants, with the prevalence as 38.5% (11). However, no study reported the incidence of possible sarcopenia using the population-based longitudinal data, only the incidence of sarcopenia was examined in previous research (12, 13). Furthermore, no study examined the risk factors of the incidence of possible sarcopenia.

The purpose of this study was to estimate the prevalence and incidence of possible sarcopenia, according to the definition of the AWGS 2019 consensus, and to examine potential risk factors for both using a nationwide representative sample of community-dwelling older Chinese population aged 60 years and above. As a newly proposed concept in the updated guideline for sarcopenia, possible sarcopenia is less investigated. Epidemiological evidence of possible sarcopenia, such as prevalence and incidence, is the first step for decision-making regarding resource allocation in healthcare (e.g., prevention, screening, and treatment) and to develop preventive routines or healthcare services tailored to the growing older population. Identifying risk factors of possible sarcopenia could further help to prioritize screening and prevention programs for the particular subgroup(s).

METHODS

Design

This study was the secondary analysis of the China Health and Retirement Longitudinal Study (CHARLS).

Data Sources and Participants

This study used data from CHARLS, which is an ongoing longitudinal survey targeting a nationally representative sample of Chinese adults aged 45 years and over. Details of CHARLS have been reported elsewhere (14). Briefly, the baseline survey of the CHARLS was conducted in 2011, which involved 17,708 respondents (response rate: 80.5%) from 28 provinces in China. These participants were followed up every 2 years from 2011 to 2015. In this study, we included data from participants aged 60 years and over at the first wave (2011). Following previous studies on sarcopenia, we excluded participants with psychiatric or cognitive disorders, or cancer (15–18), because these conditions might affect their response to the survey or induce more uninformative censoring during follow-up. We also excluded those who had missing data either in the handgrip strength test or five-time chair stand test at baseline, because possible sarcopenia was defined based on the results of these two tests (3). Ethics approval for the data collection in CHARLS was obtained by the original authors of CHARLS from the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015).

Measures

Possible Sarcopenia

Possible sarcopenia, at all three waves, was defined based on the AWGS 2019 consensus, as low muscle strength or low physical performance (3).

Muscle strength was assessed by handgrip strength. In CHARLS, handgrip strength was measured with the mechanical dynamometer (YuejianTM WL-1000, Nantong, China). Participants were instructed to bend the elbow with 90° and squeeze the dynamometer as hard as they can for a couple of seconds. For those unable to stand unassisted, sitting was allowed. In line with AWGS 2019 recommendation, each hand was tested twice separately, and the maximum reading of four measures was used to reflect handgrip strength. Low muscle strength was defined as the handgrip strength $<$ 28 kilograms (kg) in men and $<$ 18 kg in women (3). The handgrip strength

would be coded as missing if participants did not appear to use full effort during the test, or if the measuring position was lying down or unknown, or if outlier data (defined as > 99 percentile or < 1 percentile) were recorded (19, 20).

Physical performance was assessed by the five-time chair stand test. Participants were instructed to sit down and keep their arms folded across the chest. Then they were asked to stand up and sit down at their fastest pace five times consecutively, without stopping and moving arms. The time needed to finish the test was recorded by the examiner. As recommended by AWGS 2019, low physical performance was defined as needing 12 s or more to complete the task (3). Participants who tried but could not complete this test would be regarded as having low physical performance. Similarly, outlier data (defined as > 99 percentile or < 1 percentile) of this test would be coded as missing (19).

Risk Factors for Possible Sarcopenia

Based on previous evidence on sarcopenia, similar risk factors were considered for possible sarcopenia, including age, gender, education level, marital status, residence, smoking and drinking status, physical activity (PA), depression, body mass index (BMI), and multimorbidity (10, 13).

Age was divided into three subgroups: 60–69, 70–79, and 80 and above. The highest education level was divided into four groups: illiterate, primary school, secondary school, and high school and above. The marital status of participants was categorized into two groups: married vs. single, divorced, or widowed. Rural or urban residence was determined based on the administrative division from the National Bureau of Statistics China (21).

Smoking and drinking status were grouped into three categories: never, ever but quit, and current use. As for PA level, the CHARLS collected information regarding the intensity, duration, and frequency of PA in a usual week. Three types of intensity (vigorous PA, moderate PA, and walking) and discrete time duration of PA were collected. In this study, we first calculated the volume of each type of PA by multiplying duration per day (minutes/day) with frequency (days), then transformed the volume into a metabolic equivalent value (MET) (walking = 3.3 MET, moderate PA = 4 MET, and vigorous PA = 8 MET) (22). Because CHARLS did not measure the exact duration of time per day regarding each type of PA, we could only obtain the range of duration time (0–30, 30–120, 120–240, and 240 min above). In that case, the daily duration of each type of PA was assessed by the average value of each time range. The total volume of PA (MET-minutes/week) was calculated as the sum of volumes of vigorous PA, moderate PA, and walking. Based on the IPAQ scoring protocol, the PA level was divided into three groups: low, moderate, and high PA level (22).

Depression was measured with the validated 10-item Center for Epidemiologic Studies Depression Scale short form (23, 24). Participants were asked to rate the frequency of each mood or symptom that occurred in the last week. Each item was scored ranging from 0 to 3. The total scores were calculated by summing all the item scores after reversing two items that were positively formulated (items 5 and 8). Depression was defined by the total score ≥12 (23).

Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. BMI status was categorized into four groups: obese (BMI ≥ 25 kg/m^2), overweight (23 kg/m^2 ≤ BMI < 25 kg/m^2), normal (18.5 kg/m^2 ≤ BMI < 23 kg/m^2), and underweight (BMI < 18.5 kg/m^2) (25). Multimorbidity refers to the coexisted presence of multiple chronic diseases (26). At present, the operational definition of multimorbidity in current literature varied a lot in the selection of different diseases and the cutoff point of the number of conditions (27). Based on a systematic review, the co-occurrence of two or more chronic conditions was most commonly used to define multimorbidity (27). Therefore, in this study, multimorbidity was defined as the existence of two or more chronic non-communicable diseases (28). The CHARLS investigated 14 diagnosed non-communicable diseases such as cardiovascular diseases, chronic lung diseases, liver diseases, and digestive diseases, etc. In this study, we only used 11 non-communicable diseases (psychiatric diseases, cognitive disorders, and cancer were excluded as these were the exclusion criteria of the participants) to define multimorbidity.

Statistical Analysis

Descriptive statistics on the sample characteristics were calculated for the total analytical sample. For incidence assessment, we only analyzed the data from participants who were free of possible sarcopenia at baseline. Those who lacked data to identify possible sarcopenia at both two follow-up waves (2013 and 2015) were excluded. Furthermore, to restrict interval censoring to within 2 years, we also excluded those who only lacked data on possible sarcopenia at the second wave (2013). Incidence proportion was calculated as new cases during the follow-up divided by the total number of at-risk subjects being followed. The four-year incidence rate of possible sarcopenia was calculated as new cases during 2011–2015 divided by the person-years of follow-up.

For the identification of risk factors, we only analyzed data from participants without missing data in the potential risk factors at baseline. We used multivariable logistic regression to examine the adjusted association between risk factors and prevalent possible sarcopenia at baseline. Adjusted odds ratio (OR) was estimated with 95% CIs. For the incidence of possible sarcopenia, the onset time could not be exactly detected because the CHARLS collected data every 2 years. For new cases during the four-year follow-up, the onset time was only known to lie in an interval time between the last wave of free of possible sarcopenia and the wave of the new diagnosis of possible sarcopenia. Therefore, the onset time was regarded as interval censoring. For those free of possible sarcopenia until the third wave, the data were regarded as right censoring. Right censored data can be regarded as the special case of interval censoring, with the interval unbounded on the right (29). For interval-censored data, if the lower bound, midpoint, or upper bound of the interval is assumed as the onset time, it may result in biased estimates because the inherent uncertainty of the exact onset time is ignored (30, 31). Parametric proportional

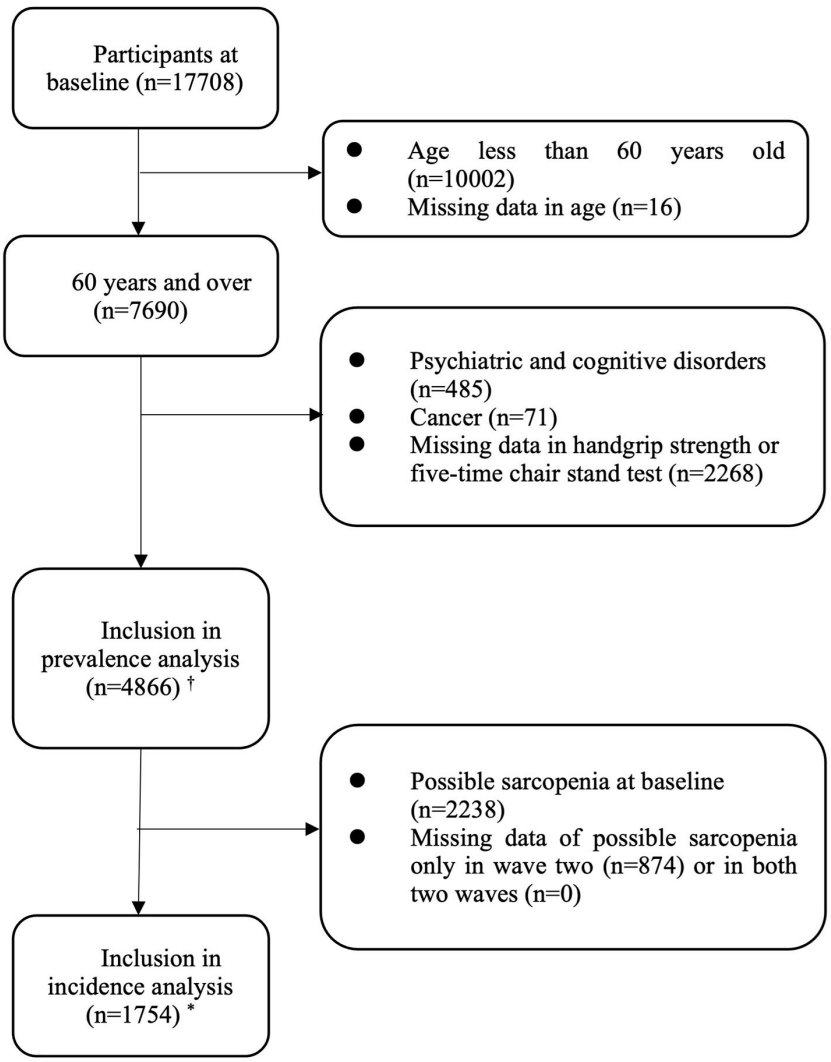

FIGURE 1 | Flowchart of participants selection.

hazards models are suitable to accommodate interval-censored data (32). Therefore, we assumed that the onset time of possible sarcopenia followed a Weibull distribution. A multivariable parametric proportional hazard model with Weibull distribution was fitted to detect the adjusted association of risk factors with the four-year incidence of possible sarcopenia. Adjusted hazard ratio (HR) was estimated with 95% CIs. When performing the above multivariable models, the potential multicollinearity was checked. The cutoff of correlation coefficient < 0.8 was considered acceptable (33).

Considering the multistage probability sampling design and non-response in the CHARLS data, individual sampling weights with non-response adjustment were taken into account in the analysis. All analyses were conducted using Stata15.0 (34). Significance was set at the 0.05 level, with the two-tailed test.

RESULTS

Prevalence and Incidence of Possible Sarcopenia

Among the 17,708 participants in the first wave, 7,690 were aged 60 years and over. After excluding those with psychiatric and cognitive disorders ($n = 485$), cancer ($n = 71$), and those with missing data either in handgrip strength or the five-time chair stand test ($n = 2,268$) at baseline, a total of 4,866 participants were eligible for inclusion in analyzing baseline prevalence (50.3% of

men, 49.7% of women; mean age: 67.7 ± 6.4 years old) (**Figure 1**). A total of 2,238 participants had possible sarcopenia at baseline, giving an overall prevalence rate of 46.0% (95% CI: 44.6–47.4%). The gender-specific prevalence of possible sarcopenia was 40.8% (95% CI: 38.8–42.7%) for men and 51.3% (95% CI: 49.3–53.3%) for women. Of those with possible sarcopenia, 304 participants (13.6%) only had low muscle strength, 1,452 participants (64.9%) only had low physical performance, and 482 participants (21.5%) had both poor muscle strength and low physical performance. Sociodemographic characteristics of those included in the prevalence analysis were shown in **Table 1**.

For incidence analysis, we only included those free of possible sarcopenia at baseline (n = 2,628). After deleting those with insufficient data to identify possible sarcopenia at the second wave (n = 874), and at both two waves (n = 0), a total of 1,754 participants were included in the incidence analysis (**Figure 1**). At the end of wave three, there were 661 new cases of possible sarcopenia. The overall incidence proportion during the four-year follow-up was 37.7% (95% CI: 35.4–40.0%), with 36.9% (95% CI: 33.8–40.0%) for men and 38.7% (95% CI: 35.4–42.1%) for women. The four-year incidence rate of possible sarcopenia was 11.9 per 100 person-years (95% CI: 11.1–12.9). The gender-specific incidence rate was 11.7 per 100 person-years (95% CI: 10.5–13.0) for men and 12.3 per 100 person-years (95% CI: 11.0–13.7) for women.

Risk Factors of Possible Sarcopenia

For risk factors analysis, we only included those free of missing data in baseline covariates (n = 1,830 for prevalence analysis and n = 666 for incidence analysis). Adjusted associations of risk factors with prevalent and incident possible sarcopenia were shown in **Table 2**. Participants who received education (primary: OR = 0.624, 95% CI: 0.479–0.812; secondary: OR = 0.558, 95% CI: 0.371–0.839; and high and above: OR = 0.250, 95% CI: 0.138–0.450, as compared to illiteracy) and had moderate or high PA level (moderate PA: OR = 0.622, 95% CI: 0.432–0.896 and high PA: OR = 0.501, 95% CI: 0.374–0.671, as compared to low PA level) were associated with lower prevalence of possible sarcopenia. However, those who were older (70–80 years: OR = 1.848, 95% CI: 1.390–2.458 and 80 years and above: OR = 3.737, 95% CI: 1.864–7.494, as compared to 60–70 years) and had depression symptoms (OR = 1.689, 95% CI: 1.316–2.167) presented an increased risk of prevalent possible sarcopenia. As for incident possible sarcopenia, only advanced age (70–80 years: OR = 1.516, 95% CI: 1.054–2.180; 80 years and above: HR = 4.035, 95% CI: 1.761–9.246, as compared with 60–70 years) was significantly associated with increased risk of incident possible sarcopenia.

DISCUSSION

This study examined the prevalence, incidence, and risk factors of possible sarcopenia in a nationwide representative sample of Chinese older adults. We found 46.0% of older adults had possible sarcopenia at baseline, which indicated that a large proportion of older adults had poor muscle function and were on the way to sarcopenia. Our estimated prevalence of possible

TABLE 1 | Characteristics of participants at baseline.

Characteristics	All sample		
	N	Unweighted	Weighted
Gender (%)			
Female	2,420	49.7	50.4
Male	2,446	50.3	49.6
Age (%)			
60–70	3,456	71.0	68.2
70–80	1,198	24.6	25.8
80 and above	212	4.4	6.0
Education (%)			
Illiteracy	1,763	36.2	35.2
Primary school	2,264	46.5	46.2
Secondary school	564	11.6	12.2
High school and above	275	5.7	6.4
Marriage (%)			
Married	3,862	79.4	76.7
Single, divorced or widowed	1,004	20.6	23.3
Residence (%)			
Urban	1,725	35.5	42.2
Rural	3,141	64.5	57.8
Physical activity (%)			
Low	431	21.5	23.4
Moderate	398	19.9	22.2
High	1,175	58.6	54.4
Smoking status (%)			
Never	2,782	57.5	58.7
Former	528	10.9	11.9
Current	1,531	31.6	29.4
Drinking status (%)			
Never	2,812	57.9	58.8
Former	554	11.4	10.9
Current	1,492	30.7	30.3
CESD score, median (interquartile range, IQR)		7.0 (9.0)	7.0 (8.0)
Depression (%)			
No	3,185	70.3	72.3
Yes	1,349	29.7	27.7
BMI, median (IQR)		22.4 (4.9)	22.6 (5.1)
BMI category (%)			
Underweight	454	9.7	9.6
Normal	2,165	46.1	43.9
Overweight	886	18.9	19.4
Obesity	1,186	25.3	27.1
Numbers of chronic conditions, median (IQR)		1.0 (2.0)	1.0 (2.0)
Multimorbidity (%)			
No	2,772	57.3	57.5
Yes	2,067	42.7	42.5
Handgrip strength, median (IQR)		29.2 (13.0)	29.0 (13.0)
Chair stand test, median (IQR)		10.8 (4.6)	10.9 (4.7)
Muscle function (%)			
Normal	2,628	54.0	53.0
Low strength only	304	6.3	6.2
Low physical performance only	1,452	29.8	30.3
Low strength and physical performance	482	9.9	10.5

TABLE 2 | Risk factors of the prevalence and incidence of possible sarcopenia.

Risk factors	Logistics regression model (n = 1,830)				Proportional hazard model (n = 666)			
	Adjusted OR	95% CI		P-value	Adjusted HR	95% CI		P-value
		Lower	Upper			Lower	Upper	
Gender				0.189				0.554
Female	1				1			
Male	0.798	0.569	1.118		1.141	0.738	1.764	
Age				<0.001				<0.001
60–70	1				1			
70–80	1.848	1.390	2.458		1.516	1.054	2.180	
80 and above	3.737	1.864	7.494		4.035	1.761	9.246	
Education				<0.001				0.462
Illiteracy	1				1			
Primary school	0.624	0.479	0.812		0.818	0.590	1.136	
Secondary school	0.558	0.371	0.839		0.702	0.397	1.242	
High school and above	0.250	0.138	0.450		0.646	0.319	1.307	
Marriage				0.311				0.968
Married	1				1			
Single, divorced or widowed	1.161	0.870	1.550		0.991	0.641	1.532	
Residence				0.609				0.084
Urban	1				1			
Rural	1.069	0.828	1.380		1.346	0.960	1.887	
Physical activity				<0.001				0.619
Inactive	1				1			
Moderate	0.622	0.432	0.896		1.230	0.754	2.005	
High	0.501	0.374	0.671		1.030	0.686	1.546	
Smoking status				0.572				0.913
Never	1				1			
Ever but quit	1.192	0.766	1.856		1.007	0.534	1.897	
Current smoke	1.189	0.844	1.675		0.922	0.572	1.485	
Drinking status				0.351				0.658
Never	1				1			
Ever but quit	0.993	0.678	1.454		0.920	0.574	1.473	
Current drink	0.808	0.598	1.093		0.836	0.569	1.228	
Depression				<0.001				0.097
No	1				1			
Yes	1.689	1.316	2.167		1.305	0.953	1.788	
BMI				0.996				0.266
Underweight	1.015	0.668	1.542		1.560	1.003	2.426	
Normal	1				1			
Overweight	0.940	0.687	1.285		1.127	0.778	1.632	
Obesity	0.947	0.715	1.253		1.155	0.789	1.693	
Multimorbidity				0.287				0.356
No	1				1			
Yes	1.137	0.898	1.440		1.154	0.852	1.563	

sarcopenia was much higher than that in Singapore (15.3%) and Korea (20.1–29.2%) (9, 10). The cross-sectional investigation in Singapore recruited relatively younger adults, with 44.5% participants aged less than 60 years (age: 21–90 years and mean age: 58.5 years), which might account for the lower prevalence than our estimate (10). Compared with the other study in Korea, the difference in prevalence estimates was probably due to different operational definitions used to define possible sarcopenia (9). Furthermore, our prevalence from CHARLS 2011 was higher than that based on CHARLS 2015 dataset (46.0 vs. 38.5%) (11). The difference in the prevalence estimates might be due to the different lifestyles (e.g., alcohol drinking: 42.1 vs.

33.1% and smoking: 42.5 vs. 47.3%) between the two samples. Given that Wu and colleagues did not examine the PA level, it was unknown whether two samples also presented different PA levels.

At present, no other study examined the incidence rate of possible sarcopenia. Compared with existing evidence regarding the incidence of sarcopenia, the coexisted low muscle mass and low muscle strength/low physical performance, the incidence of possible sarcopenia reported in this study was much higher (12, 13, 35). For example, previous literature reported that the incidence proportion over a four-year period in community-dwelling older adults in China was 8.1% (35). Another cohort study found the three-year incidence rate of sarcopenia in British older adults was 3.7 per 100 person-years (13). The present study revealed the substantial burden of possible sarcopenia in community-dwelling settings in China, which indicated the high proportion of vulnerable older residents need early prevention of sarcopenia.

This study found the cross-sectional association of age, education, PA level, and depression with prevalent possible sarcopenia. The older age group showed a higher risk of prevalence, which indicated the advanced age was a significant independent risk factor of decreased muscle function. Consistent with existing evidence (10, 36), our findings indicated that older adults who received education and were physically active might be associated with better muscle function. Furthermore, our results showed the depressive symptom was associated with an increased risk of the prevalence of possible sarcopenia, which was consistent with current evidence regarding the cross-sectional association of depression with sarcopenia and its components, though different measurements were used to assess depression (37, 38).

In terms of incidence, only age was significantly associated with incident possible sarcopenia. Biological changes in tissues and organs during the aging process, such as the gradual decline in cellular metabolism and tissue regeneration, the decrease in muscle mass combined with a progressive increase in fat mass, and the function decline in the body system, are the pathogenic mechanism for the multisystem aging syndromes, such as frailty (39). Sarcopenia is regarded as the precursor syndrome or physical component of frailty (40). Though it is well established that the loss of muscle mass and function is accelerated with aging, the decline in muscle quantity and quality can be delayed or even reversed by timely lifestyle interventions involving exercise training and nutrition management targeting the older population (3). It is never too late for older adults to rebuild their muscles and preserve their function (41). Under this circumstance, the AWGS 2019 consensus proposes the entity of "possible sarcopenia" to promote our awareness of sarcopenia prevention in community and prevention settings. Our results showed no significant association between education level and the incidence of possible sarcopenia. Similar findings were also reported in previous cohort studies (12, 13). In view of the limited literature about possible sarcopenia, future longitudinal studies could consider further examining the predictive value of socioeconomic status on incident possible sarcopenia. Though PA is a well-known risk factor of sarcopenia, our finding showed no significant association between the PA level and the four-year incidence of possible sarcopenia. Similarly, the insignificant association of self-reported PA level and the incident sarcopenia was also reported in previous literature (12, 13). The insignificant effect of self-reported PA on the incident possible sarcopenia might reveal that PA had a relatively short-term effect; hence, the incidence of possible sarcopenia or sarcopenia was not associated with a baseline level of PA which had a time gap of several years. Future research could consider examining the longitudinal association between the trajectory of PA level and the incidence of possible sarcopenia or sarcopenia. Furthermore, previous evidence suggested that aerobic exercise had little effect on muscle strength or mass compared with resistance exercise (42). However, in this study, the PA only reflected the intensity level, and no information was available to further identify the type of exercise, such as aerobic or resistant exercise. Therefore, the PA level alone might be not enough to reveal the real association between PA and possible sarcopenia or sarcopenia. Moreover, our study also found an insignificant association between depression and the incidence of possible sarcopenia. As referred to the current evidence about the risk factors of incident sarcopenia, the insignificant association between depression and the incidence of sarcopenia was also reported in previous research (13, 43). Due to different definitions of depression and sarcopenia applied in current research, the results might be less comparable across studies. Future longitudinal studies are needed to further confirm the association between depression and the incidence of possible sarcopenia or sarcopenia using the same definition or diagnosis criteria to define depression, possible sarcopenia, or sarcopenia.

The major strength of this study was that we used a nationwide representative longitudinal database with large sample size. However, this study had some limitations. First, given that the CHARLS did not investigate the exact questions of the SARC-F questionnaire, we did not use the SARC-F or SARC-CalF questionnaire for case-finding. Instead, we directly assessed the muscle strength and physical performance to detect the possible sarcopenia. Future studies could consider constructing and validating SARC-F by using similar questions collected by the CHARLS, which could promote the sarcopenia assessment using nationwide population-based data. Second, in this study, we excluded participants with psychiatric, cognitive disorders, or cancer. However, due to data availability, we did not know the specific kinds and stages of psychiatric, cognitive disorders, and cancer. Therefore, we might exclude participants with just mild conditions that should be eligible in this study. Nevertheless, we conducted a supplementary analysis to include those with psychiatric, cognitive disorders, or cancer. The prevalence and four-year incidence of possible sarcopenia were 46.7% (95% CI: 43.4–48.1%) and 12.1 per 100 person-years (95% CI: 11.2–13.0), respectively. The estimates were similar to the main results. Furthermore, findings from the risk factor analysis were also consistent with our main results (**Supplementary Table 1**). Third, participants missing physical function tests at baseline might be frailer and more likely to suffer from possible sarcopenia. Therefore, this study might underestimate the prevalence of possible sarcopenia. Nevertheless, as those with possible sarcopenia at baseline had to be excluded from the

analysis, the estimate of incidence of possible sarcopenia was less likely to be affected. Moreover, we did not include all possible risk factors of possible sarcopenia due to the lack of relevant data, such as dietary intake, nutritional status, osteoporosis, and the number of prescribed medications. Therefore, our results might be open to unmeasured confounders. Furthermore, some circulating biomarkers of sarcopenia, such as the C-reactive protein and interleukin 6, were not considered in this study. Although data about the C-reactive protein were available in the CHARLS dataset, we only focused on the risk factors of demographics and lifestyle behaviors in this study. It was because demographics and lifestyle factors were more accessible in community settings and more relevant to identify the at-risk population and inform the early lifestyle intervention. Future studies targeting the associations between biomarkers and possible sarcopenia could be conducted. Furthermore, the imprecise measurement of PA level might introduce uncertainty and might bias the estimation. Besides, there were missing values in some baseline covariates, by using the complete cases in the analysis, the statistical power might be reduced. However, we conducted a supplementary analysis with multiple imputations, and the results showed the factors identified from the complete data analysis remained significant (**Supplementary Table 2**). Finally, some baseline covariates such as PA level, smoking and drinking status, depression symptoms, and BMI might change during the four-year follow-up. However, we only examined the predictive role of the baseline level for all covariates on the four-year incidence. Future studies may investigate the association between changes in these variables and possible sarcopenia incidence.

CONCLUSION

This study examined the prevalence and incidence of possible sarcopenia as well as the associated factors in Chinese community-dwelling older adults. Advanced age, not received education, physical inactivity, and depression symptoms were associated with an increased risk of possible sarcopenia prevalence, while only advanced age was associated with an increased incidence rate of possible sarcopenia. Early screening and lifestyle intervention for these at-risk populations are encouraged in the primary care service of sarcopenia prevention.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Biomedical Ethics Review Committee of Peking University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PC, ZC, and MH: study concept and design and critical revision of the manuscript for important intellectual content. ZC: data extraction and drafting of the manuscript. ZC and PC: analysis and interpretation of data. 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/fmed.2021.769708/full#supplementary-material

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Association Between Frailty and Inpatient Services Utilization Among Older Adults in Rural China: The Mediating Role of Multimorbidity

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Introduction: Developed and developing countries have different health systems and disease patterns. There is little evidence that frailty is related to inpatient services utilization in developing countries. In addition, the underlying mechanism of this relationship also remains unclear. This study aimed to examine the association between frailty and inpatient services utilization, and further explore whether multimorbidity play a mediating role in this association.

Methods: A total of 3,242 rural older adults aged 60 and older were included in the analysis. Frailty was measured by the physical frailty phenotype (PFP). Multimorbidity and inpatient services utilization was measured based on participants' self-report and validated by village doctors. Ordered logistic regression analyses were performed to examine the association between frailty, multimorbidity and inpatient services utilization. Bootstrap analysis was further to explore the mediation effect of multimorbidity on frailty and inpatient services utilization.

Results: The utilization of inpatient services was 20.1% (one: 15.8%, two or more: 4.3%). The prevalence of prefrailty and frailty was 64.7 and 18.1%, respectively. Frail older adults experienced a higher risk of multimorbidity and inpatient services utilization. Multimorbidity partially mediated the association between frailty and inpatient services utilization [95% confidence interval (CI): 0.005-0.016, $p < 0.001$]. The mediating effect of multimorbidity accounted for 19.0% of the total effect.

Conclusions: Among Chinese rural older adults, frailty is associated with higher inpatient services utilization, and multimorbidity mediates this association. Recommendations are to increase frailty risk screening, chronic disease monitoring, and to do timely interventions.

Keywords: frailty, multimorbidity, inpatient services utilization, older adults, rural

INTRODUCTION

China is the most populous country with the world's largest aging population. In 2018, about 250 million people were aged 60 years and above in China, and the number is expected to nearly double by 2050 (491 million) (1, 2). Such an enormous size of the aging population has put tremendous pressure on medical and health service supply in China. The Fifth National Health Service Survey in China found the utilization of inpatient services among older adults was higher than that of other age groups, and this utilization showed a rapid growth trend in the past decades (3). A recent study found that the inpatient services utilization among Chinese older people was higher in rural than in urban areas (4). The number of older people has increased dramatically. Therefore, to identify the influencing factors of inpatient services utilization among rural older adults is of great significance for the medical and health system.

Frailty is defined as a "clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems" (5). Frailty is strongly associated with a wide range of adverse health outcomes, such as falls, fractures, hospitalization, and death (6–8). Some studies examined the association between frailty and healthcare utilization using data from developed countries, such as Spain, Australia, and the United States, which indicated frailty was associated with higher hospitalization rates (9–12). There are different health systems in developed and developing countries (13). To date, it is largely unknown whether frailty is associated with inpatient services utilization among older adults in developing countries such as China. Previous studies found that the prevalence of frailty among Chinese older adults in rural areas was higher than that in urban areas (14, 15). However, there is no evidence that frailty is related to inpatient services utilization among Chinese rural older adults. In addition, the underlying mechanism of this relationship also remains unclear.

An increasing number of older people were found to be affected by more than one physical conditions (16). The co-occurrence of two or more physical chronic conditions in an individual was known as multimorbidity (17). Recently, more and more studies have focused on the association between frailty and multimorbidity. Studies found frailty was associated with multimorbidity among older adults, and frailty might predispose persons to the development of multiple chronic diseases (18, 19). A prospective cohort study in Italy found there was a significant association between frailty at baseline and incident multimorbidity in HIV outpatients (20). Furthermore, previous research revealed multimorbidity was associated with a reduction in life expectancy as well greater chances of hospitalization, poorer quality of life, and functional impairment (21). A prospective cohort study in the United States indicated that multimorbidity was independent predictors of higher inpatient utilization after considering conventional predictors (22). Disease patterns in developing countries differ from those in developed countries (23). There is evidence that 69.3% of older inpatients in China have multimorbidity (24). Thus, multimorbidity might be a mediator between frailty and inpatient services utilization.

In the current study, using the Shandong Rural Elderly Health Cohort (SREHC) baseline survey databases, we aim to 1) examine the association between frailty and inpatient services utilization, and 2) explore the mediating role of multimorbidity in the association between frailty and inpatient services utilization among older adults in rural China.

METHODS

Data Source and Sample

Cross-sectional data were from the baseline survey of SREHC, which was conducted from May to June 2019 in Shandong province, China. Shandong is the second most populous province in China with 107 million people in 2018, with largest aging populations (1). We used a multistage stratified random sampling method to select the participants. More information about sample selection and data collection has been described in our previous publication (25). A total of 3,242 rural older adults with complete data were included in the analysis.

MEASURES

Inpatient Services Utilization

Inpatient services utilization was evaluated by the question that "Have you ever been hospitalized during the past 12 months?" Respondents with the answer of "yes" were further asked, "How many times have you been hospitalized?" The corresponding questionnaire covered main healthcare sectors of inpatient treatment in hospitals (including general hospital, specialized hospital, Chinese traditional medicine hospital, and township hospital), community healthcare center, and others. In this study, frequency of inpatient services utilization during the one year preceding the survey date was classified as zero, one or two or more times.

Frailty

Frailty was measured by the physical frailty phenotype (PFP). The PFP included five criteria: shrinking, exhaustion, low physical activity level, slowness, and weakness (25, 26). The shrinking criterion was met if the respondent self-reported unintentional loss of at least 4.5 kilograms or 5% of body mass index (calculated from self-reported height and measured weight) in the past year. The exhaustion criterion was met if the participant answered "A moderate amount of time (3 to 4 days)" or "Most of the time (5 to 7 days)" when asked "How often during the last week did you feel this way?" to either of the two questions from the Center for Epidemiological Studies-Depression scale: "I felt everything I did was an effort" and "I could not get going". The low physical activity was met if the total weekly of physical activity measured by International Physical Activity Questionnaire Short Form was <383 Kcal for men and <270 Kcal for women. The slowness criterion was met when gait speed, measured as the timed walk tests over a 4.6-metercourse, was at or below the gender- and height-specific cut-points. The weakness criterion was met when handgrip strength, assessed as the average of 3 readings by the dominant hand held dynamometer, was at or below the sex- and body mass index-specific cut-points.

The respondents were scored 1 point for meeting one of the criteria. The total score ranges from 0 to 5 points. 0 point indicates nonfrail, 1-2 points indicates prefrail, and ≥3 points indicates frail.

Multimorbidity

Multimorbidity was measured by the questions: "Have you ever been diagnosed with a chronic disease by a physician?". If the answer was "yes," the respondents would be further asked the questions that "How many chronic diseases have you ever been diagnosed?," which was validated by the chronic disease case management system. In this study, multimorbidity referred to one individual with two or more chronic diseases. Participants were classified as having or not having multimorbidity. Participants with multimorbidity were further classified as having two chronic conditions or three or more. The list of diseases for the operationalization of chronic diseases was described in **Supplementary File 1**.

TABLE 1 | Characteristics of participants according to inpatient services utilization.

Characteristics	Total, *N* (%)	Inpatient services utilization			*p*-value
		Zero (*n* = 2,591)	One (*n* = 512)	Two or more (*n* = 139)	
Age (years), mean ± SD	70.1 ± 6.2	70.0 ± 6.1	70.7 ± 6.2	71.1 ± 6.7	0.007
Gender					0.094
Male	1,181 (36.4)	920 (35.5)	205 (40.0)	56 (40.3)	
Female	2,061 (63.6)	1,671 (64.5)	307 (60.0)	83 (59.7)	
Education					0.609
Illiteracy	1,353 (41.7)	1,093 (42.2)	204 (39.8)	56 (40.3)	
Primary school	1,257 (38.8)	1,006 (38.8)	200 (39.1)	51 (36.7)	
Junior high school and above	632 (19.5)	492 (19.0)	108 (21.1)	32 (23.0)	
Marital status					0.784
Married	2,415 (74.5)	1,937 (74.8)	376 (73.4)	102 (73.4)	
Unmarried/widowed/divorced	827 (25.5)	654 (25.2)	136 (26.6)	37 (26.6)	
Living arrangement					0.939
Non-empty-nester	590 (18.2)	469 (18.1)	96 (18.7)	25 (18.0)	
Empty-nester	2,652 (81.8)	2,122 (81.9)	416 (81.3)	114 (82.0)	
Household income					0.910
Quartile 1 (the poorest)	816 (25.1)	661 (25.5)	123 (24.0)	32 (23.0)	
Quartile 2	803 (24.8)	646 (24.9)	126 (24.6)	31 (22.3)	
Quartile 3	809 (25.0)	638 (24.6)	134 (26.2)	37 (26.6)	
Quartile 4 (the richest)	814 (25.1)	646 (25.0)	129 (25.2)	39 (28.1)	
Physical exercise					0.648
No	1,579 (48.7)	1,256 (48.5)	250 (48.8)	73 (52.5)	
Yes	1,663 (51.3)	1,335 (51.5)	262 (51.2)	66 (47.5)	
MMSE (score), mean ± SD	22.9 ± 5.1	23.1 ± 5.0	22.6 ± 5.5	21.4 ± 5.1	<0.001
Mild cognitive impairment	1,263 (39.0)	1,004 (38.8)	195 (38.1)	64 (46.0)	
Moderate cognitive impairment	485 (15.0)	372 (14.4)	83 (16.2)	30 (21.6)	
Severe cognitive impairment	34 (1.0)	24 (0.9)	10 (2.0)	—	
Self-reported health status					<0.001
Good	1,456 (44.9)	1,292 (49.9)	136 (26.6)	28 (20.1)	
Normal	923 (28.5)	737 (28.4)	157 (30.6)	29 (20.9)	
Bad	863 (26.6)	562 (21.7)	219 (42.8)	82 (59.0)	
Frailty status					<0.001
Nonfrail	558 (17.2)	486 (18.7)	60 (11.7)	12 (8.7)	
Prefrail	2,097 (64.7)	1,701 (65.7)	317 (61.9)	79 (56.8)	
Frail	587 (18.1)	404 (15.6)	135 (26.4)	48 (34.5)	
Multimorbidity					<0.001
Zero or one chronic disease	2,101 (64.8)	1,792 (69.2)	252 (47.5)	57 (41.0)	
Two chronic diseases	801 (24.7)	578 (22.3)	170 (34.2)	53 (38.1)	
Three or more chronic diseases	340 (10.5)	221 (8.5)	90 (18.3)	29 (20.9)	

SD, standard deviation; MMSE, Mini-Mental State Examination.

TABLE 2 | Spearman's correlation analysis results of frailty, multimorbidity, and inpatient services utilization among older adults in rural China.

Variable	1	2	3
Frailty	1.000		
Multimorbidity	0.168***	1.000	
Inpatient services utilization	0.139***	0.190***	1.000

*** $p < 0.001$.

TABLE 3 | The association between frailty and multimorbidity among older adults in rural China.

Variable	OR	95% CI	*p*-value
Frailty status			
Nonfrail	1.00	1	
Prefrail	1.38	1.10–1.74	0.005
Frail	2.12	1.60–2.81	<0.001
Age (years)	0.99	0.98–1.01	0.465
Gender			
Male	1.00		
Female	1.46	1.23–1.72	<0.001
Education			
Illiteracy	1.00		
Primary school	1.08	0.90–1.30	0.416
Junior high school and above	0.94	0.74–1.20	0.645
Marital status			
Married	1.00		
Unmarried/widowed/divorced	1.06	0.88–1.28	0.541
Living arrangement			
Non-empty-nester	1.00		
Empty-nester	1.44	1.15–1.82	0.002
Household income			
Quartile 1 (the poorest)	1.00		
Quartile 2	1.00	0.80–1.24	0.978
Quartile 3	1.05	0.84–1.32	0.645
Quartile 4 (the richest)	1.12	0.87–1.43	0.375
Physical exercise			
No	1.00		
Yes	1.11	0.96–1.30	0.169
MMSE (score)	1.04	1.03–1.06	<0.001
Self-reported health status			
Good	1.00		
Normal	2.71	2.25–3.26	<0.001
Bad	5.04	4.15–6.11	<0.001

OR, odds ratio; CI, confidence interval; MMSE, Mini-Mental State Examination.

Covariates

Demographic characteristics included age (continuous), gender (male, female), education (illiteracy, primary school, junior high school and above), marital status (married, unmarried/widowed/divorced), living arrangement (non-empty-nester, empty-nester), and household income [quintile 1 (the poorest), quintile 2, quintile 3, quintile 4 (the richest)]. Health status characteristics included physical exercise (no, yes), cognitive function (continuous), and self-reported health status (good, normal, bad). Physical exercise was measured by levels of frequency of exercise (27). Once a month or less is no physical exercise, more than once a month is physical exercise. Cognitive function was measured using the 30-item Chinese version of the Mini-Mental State Examination (MMSE) (28). The maximum score is 30 points, with higher scores indicating better cognitive function. MMSE was categorized further into mild/moderate/severe cognitive impairment (29).

Statistical Analysis

We compared the characteristics of participants according to whether they use inpatient services, using Kruskal–Wallis test for continuous variables and Chi-square test for categorical variables. We examined the association among the main variables using Spearman's correlation analysis. The mediation test was based on the technique proposed by Wen and Ye (30). First, ordered logistic regression was employed to estimate the association between frailty and multimorbidity, and between frailty and inpatient services utilization, respectively. Second, ordered logistic regression was employed to further explore the association between frailty and inpatient services utilization when multimorbidity was included. We controlled covariates in above analyses. Finally, we performed bootstrap tests (sampling process was repeated 1,000 times) to examine the total, indirect and direct effect of the model (31). The indirect effect was regarded as statistically significant if the 95% confidence interval (CI) excluded zero. All tests were 2-sided with a significance level of $p < 0.05$. We conducted all analyses in Stata 14.2 (Stata Corp, College Station, TX).

RESULTS

Sample Description

Table 1 shows the characteristics of the participants. Of the 3,242 respondents, 651 (20.1%) used inpatient services during the one year preceding the survey date. The utilization of inpatient services for prefrail and frail rural elderly was 18.9 and 29.5%, respectively. Approximately 64.7% of the respondents were prefrail, and 18.1% of those were frail. About one-third of respondents had two or more chronic diseases. Compared with respondents who did not use inpatient services, those who used inpatient services more likely to be older, be frail, and have multimorbidity. Diseases noted in groups with frailty and in groups with hospitalizations see **Supplementary File 2**.

Correlation Analysis

Table 2 presents the correlation matrix of the association among frailty, multimorbidity and inpatient services utilization. Frailty was positively associated with inpatient services utilization ($\rho = 0.139$, $p < 0.001$). Multimorbidity was positively associated with frailty ($\rho = 0.168$, $p < 0.001$) and also positively associated with inpatient services utilization ($\rho = 0.190$, $p < 0.001$).

Mediating Effect of Analysis

Table 3 shows the relationship between frailty and multimorbidity among older adults in rural China. Frailty

TABLE 4 | The mediating effect of multimorbidity on association between frailty and inpatient services utilization among older adults in rural China.

Variable	Model without mediators			Model with mediators		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Frailty status						
Nonfrail	1.00			1.00		
Prefrail	1.22	0.92–1.62	0.170	1.17	0.88–1.56	0.286
Frail	1.74	1.24–2.44	0.001	1.59	1.13–2.24	0.008
Multimorbidity						
Zero or one chronic disease				1.00		
Two chronic diseases				1.78	1.45–2.19	<0.001
Three or more chronic diseases				2.21	1.69–2.90	<0.001
Age (years)	1.02	1.00–1.03	0.040	1.02	1.00–1.03	0.029
Gender						
Male	1.00			1.00		
Female	0.74	0.61–0.91	0.003	0.70	0.58–0.86	<0.001
Education						
Illiteracy	1.00			1.00		
Primary school	1.06	0.85–1.33	0.598	1.06	0.84–1.33	0.617
Junior high school and above	1.35	1.01–1.80	0.041	1.37	1.03–1.84	0.032
Marital status						
Married	1.00			1.00		
Unmarried/widowed/divorced	1.11	0.89–1.39	0.363	1.10	0.88–1.38	0.401
Living arrangement						
Non-empty-nest elderly	1.00			1.00		
Empty-nest elderly	1.04	0.79–1.36	0.782	0.98	0.75–1.28	0.887
Household income						
Quartile 1 (the poorest)	1.00			1.00		
Quartile 2	1.24	0.95–1.61	0.116	1.23	0.94–1.61	0.123
Quartile 3	1.37	1.04–1.79	0.024	1.37	1.04–1.78	0.024
Quartile 4 (the richest)	1.50	1.11–2.02	0.008	1.48	1.10–2.00	0.010
Physical exercise						
No	1.00			1.00		
Yes	1.17	0.98–1.41	0.086	1.16	0.96–1.39	0.117
MMSE (score)	0.97	0.95–0.99	0.008	0.96	0.94–0.98	0.001
Self-reported health status						
Good	1.00			1.00		
Normal	1.91	1.51–2.40	<0.001	1.67	1.31–2.11	<0.001
Bad	3.91	3.11–4.92	<0.001	3.11	2.45–3.95	<0.001

OR, odds ratio; CI, confidence interval; MMSE, Mini-Mental State Examination.

status were associated with multimorbidity. Prefrail (OR = 1.38, 95% CI: 1.10–1.74, $p = 0.005$) and frail (OR = 2.12, 95% CI: 1.60–2.81, $p < 0.001$) older people were more likely to have multimorbidity.

Table 4 shows the mediating role of multimorbidity on association between frailty and inpatient services utilization among older adults in rural China. The model without mediators (multimorbidity) showed that frailty was associated with inpatient services utilization (OR = 1.74, 95% CI: 1.24–2.44, $p = 0.001$). When the mediator was included, frailty was still associated with inpatient services utilization (OR = 1.59, 95% CI: 1.13–2.24, $p = 0.008$). Pre-frailty was not related to inpatient services utilization. Multimorbidity was also associated with inpatient services utilization. The more severe the multimorbidity, the more inpatient services may be used.

Moreover, bootstrap test suggested that after adjusting for covariates, the total effect of frailty on inpatient services utilization was 0.058 (95% CI: 0.025–0.090, $p < 0.001$). The direct effect of frailty on inpatient services utilization was 0.047 (95% CI: 0.014–0.079, $p = 0.005$). The indirect mediating effect via multimorbidity was 0.011 (95% CI: 0.005–0.016, $p < 0.001$). These effects were significant since the 95% CI excluded zero. The association between frailty and inpatient

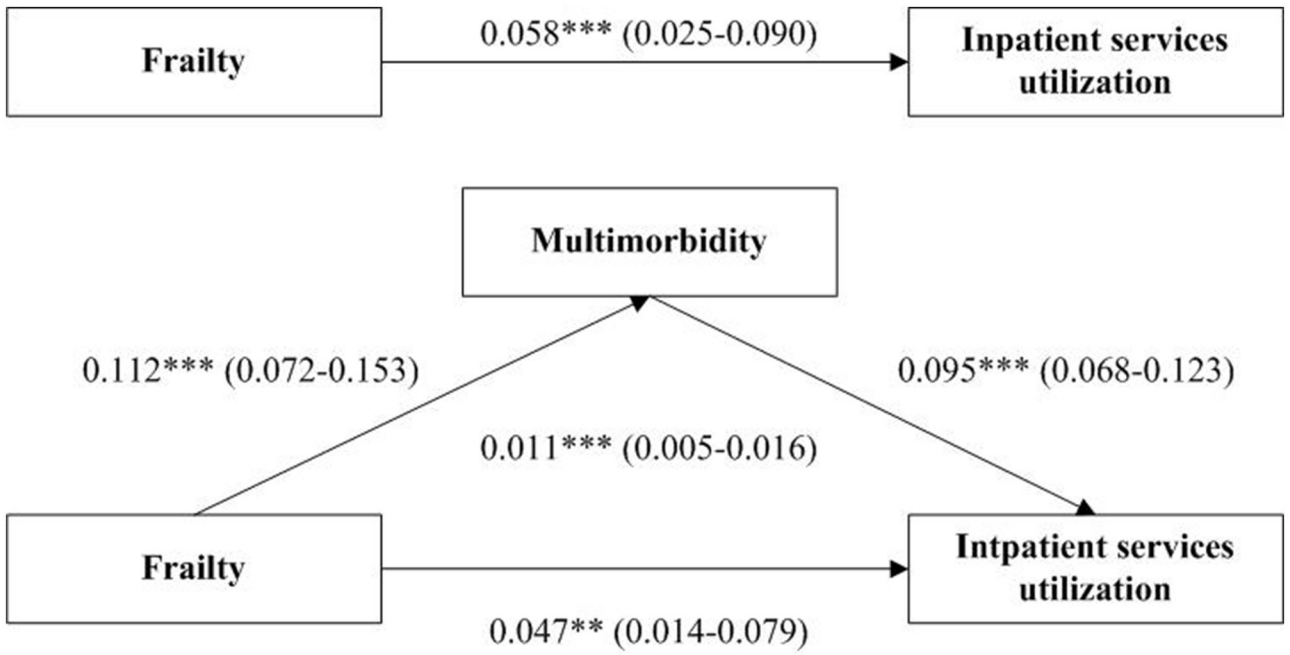

FIGURE 1 | Path diagram of the association between frailty and inpatient services utilization in with multimorbidity as a mediator. $^{**}p < 0.01$. $^{***}p < 0.001$. The coefficient and 95% confidence interval in the parentheses are shown. Models are adjusted for age, gender, education, marital status, living arrangement, household income, physical exercise, Mini-Mental State Examination score and self-reported health status.

services utilization was partially mediated by multimorbidity, of which, the indirect effect accounted for 19.0% of the total effect. **Figure 1** illustrates the mediation pathway model with coefficients.

DISCUSSION

The current study found that frailty was associated with inpatient services utilization among older adults in rural China. Moreover, multimorbidity was associated with inpatient services utilization and partially mediated the association between frailty and inpatient services utilization.

This study found the utilization of inpatient services among Chinese rural older adults (60+) was 20.1%, higher than the national average (9.0%) of all age groups in rural areas (3), which indicated that older adults, as a special group, had a large demand for health services. The utilization of inpatient services in present study was higher than the 14.9% among older adults (60+) in rural Shandong province in 2013 (32). The finding suggests that the inpatient services utilization of older people is on the rise, which may be related to the deepening of medical reform and the basic coverage of medical insurance in recent years (33). Prefrail (18.9%) and frail (29.5%) rural elderly in Shangdong utilize more inpatient services than national average. In developed countries, the utilization of inpatient services for the prefrail elderly ranges from 24.2 to 50.2% (9–11, 34). The utilization of inpatient services for the frail elderly varies from 38.7 to 51.6% (9–11). These utilization rates are significantly higher than in our study. This could be attributed to better welfare in developed countries, since Chinese population would have to pay out of pocket.

Consistent with previous studies in developed countries, we found that frailty was positively associated with higher inpatient services utilization among rural older adults in China. A population-based study in Australia found that frailty was a risk factor for the use of inpatient services in the past year in older men, including spending at least one night in a hospital or nursing home (10). A prospective cohort study in the United States showed that frail older women had higher inpatient services utilization after accounting for multimorbidity and functional limitations (11). The association of frailty and inpatient services utilization may be related to the decline of various system functions among frail older adults (35). Frailty accelerates the process of functional decline and makes older adults more vulnerable to adverse health conditions. At the same time, the muscle strength of the frail elderly decreased and they were prone to fall, leading to fracture and head injury, etc. (36), which may increase the inpatient services utilization.

Inconsistent with prior studies in developed countries, we did not find a correlation between prefrailty and higher inpatient services utilization among older adults. A previous longitudinal study of older adults residing in Boston, United States found that prefrail participants were more likely to report hospitalization during the subsequent 10 months (37). Another longitudinal cohort study in Italy revealed that prefrail older adults account for the highest percentage of costs generated by using hospital services, as well as for the highest number of used hospital services (34). This difference in the association between

prefrailty and inpatient services utilization may be attributed to the discrepancy between the level of economic and medical development across countries and regions. A formal welfare system for older adults is largely lacking in rural China. Moreover, there are a large number of low-income groups. For them, using inpatient services could consume most of their wealth, so they would not use the inpatient service at the stage of prefrailty. Perhaps when their physical conditions were getting worse, they and their family would choose to use inpatient services.

We also found that frailty was positively associated with multimorbidity, and frail older adults were more likely to have multiple chronic diseases. A recent systematic review and meta-analysis study found frailty was associated with an increasing risk of developing multimorbidity among older people (18). One possible explanation is the biological mechanism of the system failure process (35, 38). This frail system is more vulnerable to any stressor for older adults, hence increasing the risk of adverse health outcomes due to the inability to recover homeostasis. These adverse health outcomes would lead to an increased risk of multimorbidity. Multimorbidity was positively associated with inpatient services use, which was in consistent with previous studies (22). Some previous studies demonstrated that health care utilization and spending increased with the number of chronic conditions among older adults (39, 40). Agborsangaya et al. showed that persons with multimorbidity were twice as likely to be hospitalized or visit an emergency department compared to persons without multimorbidity (41). Since the aging process implies physiological decline, the probability of the occurrence of disease and functional disability increases with an increasing age. Multimorbidity may lead to more serious disability and deconditioning that have direct effects on health care utilization. From social aspects, the co-occurrence of chronic diseases requires regular medical appointments and special dietary needs. Due to a low income status, a lack of informal assistance and timely access to public and private healthcare systems, regular medical care and special dietary cannot be met. This means that multimorbid patient in rural areas do not having access to regular care, which increases inpatient utilization.

Furthermore, our results demonstrated multimorbidity played as a partial mediator between frailty and inpatient services utilization. Older adults with frailty were more likely to experience the co-occurrence of chronic diseases, which was related to a higher utilization of inpatient services. Although the prevalence of multimorbidity increases with an increasing age, it is not uncommon for an individual to experience multimorbidity before old age (42). Thus, regular surveillance for multimorbidity status (i.e., before a first chronic disease progresses to multimorbidity) could timely reduce adverse effects. Besides, multimorbidity was associated with a reduction in life expectancy as well a poorer quality of life and depression (21), which may increase the risk of hospitalization.

Our findings provided several implications. Recommendations are to increase risk screening, monitoring, and to do timely interventions. Firstly, frailty needs to be appropriately recognized in primary care rather than erroneously considered to be part of the normal aging process. General practitioner could lead risk screening initiatives to detect early frailty among older adults, thus enabling the health system to target these individuals more effectively. Secondly, better monitoring of multimorbidity and timely interventions might help to improve population health, to decrease inappropriate frequent access to more inpatient services. Moreover, to encourage general practitioner to follow them up regularly and meet their basic health service needs.

According to China's 7th national population census, 11 provinces have a total elderly population of more than 10 million, with Shandong being the only one with a population of more than 20 million. Perhaps our results have some reference significance for other provinces with large elderly population in China. In addition, the Chinese experience may also be beneficial to some less developed countries, as the living condition of rural China resembles that in other developing countries.

This study has several limitations. First, using self-reported data to measure variables may cause recall bias in some information. Second, due to the cross-sectional data, we could not determine the casual inference between frailty and inpatient services utilization. Future longitudinal studies are needed to elucidate the causal association. Finally, the proportion of mediating effect suggests that there may be other mechanisms, and future research can explore more factors which can explain other variance between frailty and inpatient services utilization.

CONCLUSIONS

In conclusion, the utilization of inpatient services was 20.1% among Chinese rural older adults. Our findings revealed that frailty was associated with inpatient services utilization, and multimorbidity mediated this association. Recommendations are to increase frailty risk screening, chronic disease monitoring, and to do timely interventions.

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 protocol for this study was approved by the Ethical Committee of School of Public Health, Shandong University (approval number, 20181228). Participants were voluntary, and in review they had the right to withdraw from the study at any time. Written informed consent was obtained for all participants.

AUTHOR CONTRIBUTIONS

YY: conceptualization, methodology, formal analysis, writing-original draft, and writing-review and editing. JL: methodology and writing-review and editing. PF: investigation, resources, and data curation. CZ: conceptualization, supervision, writing-review

and editing, and funding acquisition. SL: conceptualization, supervision, and writing-review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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BRIEF RESEARCH REPORT
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Forecasting Healthy Life Expectancy Among Chilean Community-Dwelling Older Adults With and Without Sarcopenia

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Background: Sarcopenia is an important risk factor for disability and dependency at old age. The prevalence of sarcopenia among the Chilean older population is high.

Objective: To estimate life expectancy, healthy life expectancy and unhealthy life expectancy among sarcopenic and non-sarcopenic older adults from Santiago, Chile.

Methods: A sample of 1,897 community-dwelling older adults aged 60 years or more, living in Santiago, was observed between 5–15 years. Disability was defined as the unhealthy state, assessed through self-reported difficulties in activities of daily living. Sarcopenia was determined via HTSMayor software. Total and marginal life expectancies were estimated using the Interpolated Markov Chain method "IMaCh".

Results: At 60 years, estimated life expectancy for sarcopenic and non-sarcopenic older adults was similar (22.7 and 22.5 years, respectively). The proportion of years to be lived with disability was three times greater in sarcopenic adults, compared to non-sarcopenic people. This difference was observed up to 80 years. Non-sarcopenic women had a higher proportion of years to be lived with disabilities compared to non-sarcopenic men of the same age, but this proportion was higher among sarcopenic men, compared to sarcopenic women until 70 years of age.

Discussion: People with sarcopenia expect to live a higher proportion of years with disabilities. Sarcopenic men until 70 years expected to live a higher proportion of years with disability, compared to sarcopenic women. Monitoring sarcopenia among older people may help to identify individuals with higher risk of disability onset. Future research should focus on disentangling the mechanisms explaining sex differences.

Keywords: disability-free life expectancy, life expectancy, sarcopenia, gender, longitudinal studies

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BACKGROUND

Since 2016, sarcopenia has been recognized as a condition with its own code (M62.84) in the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10CM) (1). Sarcopenia is defined as a progressive and generalized skeletal muscle disorder, characterized by loss of muscle mass, strength and function, associated with age and with an increased risk

of falls, fractures, morbidity, disability, mortality, and poor quality of life (2, 3). There are also economic costs for healthcare systems, individuals and families, associated with sarcopenia, due to the increased risk of hospitalization and higher costs during hospital stay, compared to people of the same age without sarcopenia (4).

Worldwide prevalence of sarcopenia is high. A recent review concluded that different definitions resulted in wide variation of estimations, and according to studies that employed the definition of the European Working Group on Sarcopenia in Older People (EWGSOP) (5), considering low muscle mass and low muscle strength or low physical performance, the average prevalence was 9.9% and increased with increasing age, reaching 19.4% in the oldest old (6). In Chile, sarcopenia prevalence estimated with the EWGSOP algorithm is 19.1%, similar for men and women, and it is associated with age (7).

In Chile, the population aging is advanced, with the highest life expectancy (LE) at birth (80 years) of South America, along with French Guiana (8). It is important to determine if those years are lived in good health or if the additional years of life result in an expansion of morbidity among the older population (9). Considering that sarcopenia is a highly prevalent condition among older adults, and that its is associated with disability (10), it is necessary to determine the impact of sarcopenia on health expectancies.

Health expectancies integrate health status to the LE indicator, providing information with respect to the total number of years expected to be lived at a certain age, and the number of years expected to be lived in a certain health status, such as free of disability (9). Estimations of health expectancies in Chile are scarce. Previous Chilean studies reported that women at 60 years expected to live a higher proportion of years with disabilities, compared to men of the same age (11–13).

The aim of this study was to estimate LE, healthy life expectancy (HLE) and unhealthy life expectancy (ULE) among sarcopenic and non-sarcopenic older adults from Santiago, Chile.

METHODS

This is a dynamic cohort study. The sample included 1,897 people aged 60 years and older, living in the community in Santiago, Chile, who were originally recruited to the Alexandros (14) and HTS Mayor (15) projects, aimed to study disability associated with obesity and sarcopenia in Chilean older people. The Alexandros sample ($N = 2,311$) was recruited between 2003 and 2008, and the HTS Mayor sample ($N = 169$), in 2012. Baseline information was collected between 2003–2012. People who died in the following 6 months from baseline (1.5%), and those who had missing data in the outcome variables (3.8%) were excluded from the analyses. Sixty-eight people (2.7%) rejected to take part in this study. From a total of 2,281 people who were eligible and accepted to take part in this study, 384 (16.8%) were lost to follow-up (**Supplementary Material 1**). One thousand eight hundred ninety-seven participants were followed-up between 5–15 years (interquartile range 5.17 years), until 2017.

Data were collected via face-to-face interviews, carried out by trained interviewers at the Institute of Nutrition and Food Technology. The interviews included a structured questionnaire to gather sociodemographic information and self-reported health problems, including chronic diseases and functional status. The 5 item Geriatric Depression Scale (GDS-5) (16) was used to determine depressive symptoms. Cognitive status was assessed via the Mini-Mental State Examination (MMSE) (17) and the Functional Activities Questionnaire (FAQ) (18). Anthropometric measurements included weight, knee height, waist, hip, and calf circumference. Handgrip strength was measured in the dominant hand, with calibrated dynamometers, following the Southampton protocol. Mobility was assessed with questions about the ability to walk several blocks, climbing stairs, pushing or pulling heavy objects, lifting or carrying weights over ten 5 kg, and picking up a coin from a table. The details of the operationalization of sarcopenia are described below.

Functional status was determined according to the criteria proposed by Albala et al. (19) for the Chilean older population, considering limitation in at least one activity of daily living (ADL), or in two instrumental activities of daily living (IADL), or in three advanced activities of daily living (AADL), or a score of MMSE<13 and PFAQ>5.

Sarcopenia was defined as an adapted version of the diagnostic algorithm of the European Working group on Sarcopenia in Older People (EWGSOP1) in 2010 (5), considering low physical performance, low muscle strength, and/or low muscle mass. Participants with sarcopenia were identified by means of HTSMayor software (14). A prediction model for the Chilean population (18) was employed to estimate appendicular skeletal muscle mass (ASM):

ASM (kg) = 0.107(weight) + 0.251(knee-height) + 0.197(calf-circumference) + 0.047(dynamometry) - 0.034 (hip-circumference) + 3.4178 (male) - 0.020 (age) - 7.646;

Coefficient of determination = 0.89;

Standard Error of the Estimation = 1.346 kg.

Cut-off points of the skeletal muscle mass index (SMI = ASM/height^2) for the Chilean population were obtained from this prediction model, resulting in 7.45 kg/m^2 for men, and 5.88 kg/m^2 for women (20). Muscle strength was assessed considering the best two scores obtained with a handgrip dynamometer, using the dominant hand. Cut-off points previously estimated for the Chilean population (21, 22) were employed. A combination of two physical performance tests was used to assess this dimension, since not all participants had the three meters (3 m) walking speed register. The tests used were 3 m walking speed and timed up and go (TUG) speed, in this order (23).

Mortality data were confirmed via death certificates obtained from the National Civil Registry until July 30, 2017. Vital status of all participants was known by the end of follow-up.

Descriptive analyses were carried out with Stata 15 (StataCorp.2015. Stata Statistical Software, Release 14. College Station, TX, StataCorp LP). To estimate life expectancies and disability-free life expectancies, multistate methods were employed. Three states were considered—healthy, disabled, and

TABLE 1 | Baseline characteristics of the sample.

Variable	Total (n = 1,897) %	Men (n = 612) %	Women (n = 1,285) %	*P*-value
Age (years)*	69.2 ± 6.8	69.3 ± 6.4	69.2 ± 7.0	0.7651
Age groups				0.029
60–69.9	70.0	68.0	71.0	
70–79.9	20.5	23.7	18.9	
≥80	9.5	8.3	10.1	
Education> 8 years	40.4	41.1	40.0	0.5831
Living alone	10.0	8.9	10.5	0.290
Functional limitation	16.6	11.4	19.1	<0.001
Multimorbidity (≥2 CD)	47.4	42.8	49.6	<0.001
Depression (GDS-5)	30.9	26.3	33.0	0.0031
BMI*	28.6±5.0	27.5±4.4	29.1±5.2	<0.001
Nutritional status				<0.001
Underweight	2.1	2.3	2.0	
Normal	21.0	26.0	18.6	
Overweight	43.5	47.1	41.8	
Obese	33.4	24.7	37.6	
Sarcopenia	22.4	22.1	22.6	0.804
Falls	32.6	27.8	34.8	0.003
ADL limitation ≥ 1	11.9	11.3	12.2	0.553
IADL limitation ≥ 1	26.8	31.2	24.8	0.003
MMSE	6.8	6.4	7.0	0.649

**Mean and standard deviation.*

TABLE 2 | Total life expectancy, healthy life expectancy and unhealthy life expectancy, among sarcopenic and non-sarcopenic Chilean older men and women.

	Without sarcopenia (n = 1,472)			With sarcopenia (n = 425)		
	TLE	HLE*	ULE**	TLE	HLE*	ULE**
Total						
60 years	22.5	20.5	2.0	22.7	16.8	5.8
95% CI	21.5–23.5	19.6–21.4	1.5–2.5	21.0–24.3	15.2–18.4	4.5–7.1
70 years	14.5	12.7	1.8	14.4	8.9	5.5
95% CI	13.6–15.4	11.8–13.6	1.3–2.3	13.2–15.6	7.7–10.1	4.4–6–6
80 years	8.3	6.7	1.6	7.8	3.3	4.5
95% CI	7.4–9.2	5.8–7.6	0.9–2.3	6.9–8.7	2.4–4.2	3.6–5.4
Men						
60 years	20.1	19.0	1.2	18.3	10.7	7.6
95% CI	18.7–21.6	17.5–20.3	0.7–1.8	15.4–21.2	6.7–14.8	4.0–11.2
70 years	12.1	11.1	1.0	11.4	6.4	5.0
95% CI	10.9–13.4	9.9–12.4	0.5–1.5	9.6–13.2	4.9–8.0	3.5–6.5
80 years	6.6	5.9	0.7	6.4	3.5	2.9
95% CI	5.3–7.8	4.6–7.3	0.1–1.2	5.0–7.8	2.5–4.4	2.1–3.8
Women						
60 years	23.8	21.5	2.4	25.6	19.5	6.1
95% CI	22.5–25.2	20.2–22.8	1.6–3.1	23.8–26.6	17.7–21.4	4.7–7.6
70 years	15.7	13.5	2.2	16.4	10.6	5.8
95% CI	14.5–17.0	12.3–14.7	1.4–3.0	14.9–17.9	9.0–12.2	4.5–7.1
80 years	9.2	7.2	2.0	8.8	4.1	4.8
95% CI	7.9–10.4	5.9–8.4	1.1–2.9	7.6–10.1	2.8–5.3	3.6–5.9

**Healthy life expectancy (without disability). **Unhealthy life expectancy (with disability).*

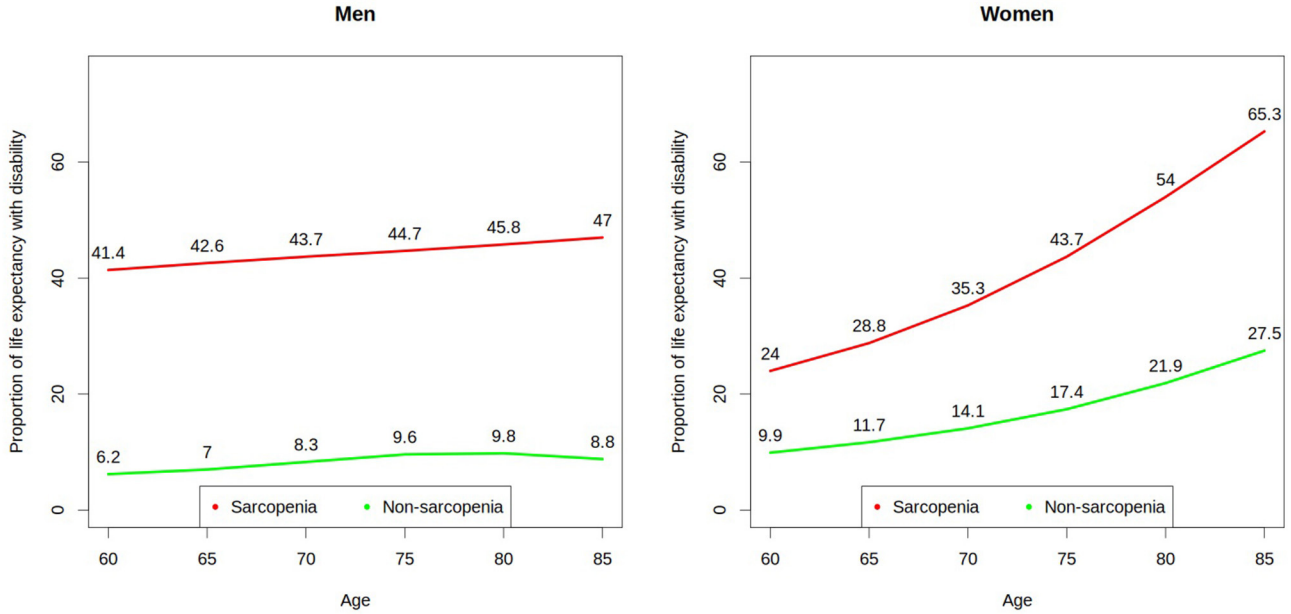

FIGURE 1 | Proportion of life expectancy to be lived with disability by Chilean older men and women with and without baseline sarcopenia.

dead—with five possible transitions: healthy-healthy, healthy-disabled, disabled-healthy, healthy-dead, disabled-dead. The Interpolated Markov Chain (IMaCh) software was employed for the calculations (24, 25). Estimations were expressed as number of years and percentages, and 95% confidence intervals were calculated.

Cox proportional hazards models were used to estimate the association between sarcopenia and the incidence of functional limitation, including sociodemographic variables, body mass index, multimorbidity (defined as two or more self-reported chronic diseases, including high blood pressure, diabetes, coronary heart disease, stroke, chronic obstructive pulmonary disease, cancer, and arthritis), depressive symptoms, and falls. Self-reported depression was not included in this variable, due to the underdiagnosis of depression by health care providers in Chile (26). No violations of the proportional hazards' assumption were detected. Since falls and depression have been previously reported as risk factors of functional limitation (27–30), interaction terms between sarcopenia and each of these variables were tested.

Study protocols and consent forms were approved by the ethics committee of the Institute of Nutrition and Food Technology. All participants gave signed informed consent.

RESULTS

As observed in **Table 1**, the sample had a higher proportion of women (67.7%), and the mean age was 69.2 years (SD = 6.8). Baseline prevalence of sarcopenia was 22.4%, with no difference between men and women ($p = 0.8$). Functional limitation had a prevalence of 16.6% (men = 11.4%, women = 19.1%). Participants were followed-up for a median of 5.8 years, and a total of 6,358.6 person years. During the follow-up, 105 new cases of functional decline were observed, 127 people with baseline functional limitation had recovered and 492 deaths occurred.

Table 2 shows that LE of sarcopenic and non-sarcopenic older adults at 60 years was 22.7 and 22.5 years, respectively. There were no differences in LE between both groups, but at every age, non-sarcopenic older adults had more healthy years and less ULE. Total LE was significantly longer for women than men at all ages, with the exception of participants with sarcopenia at 80 years. No significant difference was observed in total LE among sarcopenic and non-sarcopenic men. Among women, there were no differences in total LE between groups, but sarcopenic women expected to live more years with disabilities, compared to non-sarcopenic women, and had a shorter healthy life expectancy at age 70 and 80.

As observed in **Figure 1**, sarcopenic men had a higher proportion of expected ULE, compared to non-sarcopenic men, with a proportion of ULE 6.6 times higher at 60 years, 5.3 times higher at 70 and 4.7 times higher at 80 years. The proportion of ULE among sarcopenic women was 2.4 times higher at age 60, 2.5 times higher at age 70 and 4.0 times higher at age 80, compared to non-sarcopenic women. Sarcopenic men at 60 and 70 years of age had a higher proportion of expected ULE, compared to sarcopenic women of the same age, with a difference of 17.4 and 8.4 percent points, at the respective age. On the contrary, among non-sarcopenic people at ages 69, 70, and 80, a higher proportion of LE was expected to be lived with disabilities among women, compared to men (3.7, 5.8, and 12.1 percent point, respectively).

Cox proportional hazards models showed that sarcopenia and age were the only variables associated with the incidence of

TABLE 3 | Hazard ratio of functional limitation among Chilean older people from the Alexandros and HTS Mayor studies, 2003–2017.

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Sarcopenia	3.40 (2.11–5.49)	3.65 (2.02–6.62)	3.69 (1.99–6.86)	3.85 (2.05–7.22)
Age (years)	1.07 (1.03–1.11)	1.07 (1.03–1.11)	1.07 (1.03–1.11)	1.07 (1.03–1.11)
Women	0.80 (0.49–1.31)	0.79 (0.49–1.30)	0.88 (0.52–1.48)	0.82 (0.48–1.40)
Nutritional state				
BMI<20		1.06 (0.39–2.86)	0.80 (0.25–2.52)	0.78 (0.25–2.47)
BMI: 25–29.9		0.94 (0.54–1.64)	0.97 (0.54–1.74)	0.97 (0.54–1.74)
BMI: ≥30		1.17 (0.54–2.53)	1.22 (0.55–2.70)	1.22 (0.55–2.72)
Multimorbidity*			0.99 (0.61–1.61)	0.98 (0.60–1.60)
Depression**			1.10 (0.66–1.85)	1.04 (0.61–1.75)
Falls				1.43 (0.87–2.37)

*≥2 chronic diseases; **GDS-5.

functional limitation (**Table 3**). Interaction terms of sarcopenia with falls and with depression were not significant.

DISCUSSION

Our study found no difference in LE between sarcopenic and non-sarcopenic older people, but more ULE among the former. In absolute terms, at 60 years of age, sarcopenic men expected to live more years with disability, compared to non-sarcopenic men and women with or without sarcopenia. From 70 years, sarcopenic women expected to live more years with disability, compared to the other groups. With respect to the proportion of ULE, sarcopenic men expected to live a higher proportion of LE with disabilities, up to the age of 70 years.

According to our results, baseline sarcopenia had a differential impact on HLE and ULE of men and women. Sarcopenic men had a shorter HLE and more ULE, compared to sarcopenic women. This suggests that sarcopenia could be associated with a higher and earlier onset of disability among older men. A Brazilian study found that sarcopenia was associated with osteoporosis among older men, but not women (31). Among a Japanese sample without baseline restrictions in ADL, almost twice as much sarcopenic men (38.8%) as sarcopenic women (18.8%) developed restrictions in ADL (32).

A previous study found that Chilean older women had a higher proportion of ULE, compared to men of the same age (10). However, the results of the present study show the importance of considering baseline sarcopenia to describe disability trajectories of older men and women. Women with sarcopenia had a higher proportion of ULE, compared to non-sarcopenic women. Sarcopenic older men, for their part, expected to live a greater proportion of their total LE with disabilities, compared not only to non-sarcopenic men, but to sarcopenic women as well.

Genetic, nutritional, physical activity and age-related factors are associated with the onset of sarcopenia (33). Two systematic reviews have concluded that physical activity is a protective factor against sarcopenia in men and women (34, 35). Nevertheless, some studies suggest that the effect of physical activity on sarcopenia onset and progression differs between sexes (36, 37). Rivera et al. (38) found that age and physical activity were related with muscle volume and performance in men, but not in women. According to those results, sedentarism during the life-course resulted in loss of muscular mass among men, with a negative impact on function. In the case of older women, it was observed that muscular performance and functionality was preserved despite the sarcopenic process. The role of physical activity on different trajectories of disability among sarcopenic older men and women should be further studied. Also, other potential factors associated with these differences, which act as protective factors for women or negatively affect men, should be elucidated.

This study has some limitations that should be considered. ASM was estimated by an anthropometric equation instead of dual-energy X-ray absorptiometry (DXA), which is considered the gold standard to measure body composition (39). However, this equation and DXA had a high concordance correlation coefficient (0.94) in a previous Chilean study (40). On the other hand, considering the technical difficulties to assess muscle mass and quality, and the ability of muscle strength and physical performance to predict adverse outcomes, these latter measures of physical performance are primarily used (2, 4). The sample size affected the precision of our estimations, particularly in stratified analyses and for older ages. Nevertheless, we found significant differences between groups. The participants of the study were recruited among older people living in Santiago. Hence, our results are not representative at a national level. Also, the sample did not include people living in rural areas. According to previous research, Chilean older people living in rural areas have worse health status and higher levels of disability (41). Lastly, attrition bias cannot be ruled out, which could have affected out estimations, in case the distribution of sarcopenia or disability incidence varied between the participants in our study and those lost to follow-up. A higher or lower incidence of disability among men or women with or without sarcopenia who were not followed-up, could result in over or underestimation of years to be

lived with disability, in one or several of the groups. This limitation should be taken into account when interpreting the results.

In conclusion, our results stress the importance of monitoring sarcopenia among older adults, to identify those individuals at a greater risk of disability onset. Sex differences observed in disability trajectories among sarcopenic older people should be disentangled by future research.

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 Ethics Committee of the Institute of Nutrition and Food Technology. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LL and CA designed the primary studies. CM coordinated the data collection. LL and XM designed the secondary analyses that are reported here and wrote the draft of the manuscript. LL performed the statistical analyses. All authors revised, commented, and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.841810/full#supplementary-material

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Low and High-Density Lipoprotein Cholesterol and 10-Year Mortality in Community-Dwelling Older Adults: The Shanghai Aging Study

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Background: The relationship between serum cholesterol and mortality remains disputed. This study aimed to examine the association of low and high-density lipoprotein cholesterol (LDL-C and HDL-C) with all-cause mortality among community-dwelling older adults in the Shanghai Aging Study.

Methods: We followed 3,239 participants free of lipid-lowering agents for a median of 10 years. Levels of LDL-C and HDL-C were measured at baseline using fasting blood samples. Survival status was confirmed by the local mortality surveillance system. The associations between the levels of LDL-C, HDL-C, and all-cause mortality were assessed by Cox proportional hazards models.

Results: The increment of LDL-C concentration was related to a lower risk of mortality (p for trend < 0.05). Using the highest quintile of LDL-C (≥4.10 mmol/L) as a reference, the lowest quintile of LDL-C (<2.61 mmol/L) was associated with the highest risk of mortality, after adjusting for confounders (HR 1.67; 95% CI 1.26–2.21), exclusion of death within the first 2 years of follow-up (HR 1.57; 95% CI 1.17–2.11), and exclusion of functionally impaired participants (HR 1.46; 95% CI 1.07–2.00). A U-shape relationship was found between HDL-C level and the mortality risk. Using the third quintile of HDL-C (1.21–1.39 mmol/L) as a reference, HR (95% CI) was 1.46 (1.09–1.95) for the lowest quintile (<1.09 mmol/L) and 1.45 (1.07–1.96) for the highest quintile (≥1.61 mmol/L) of HDL-C, after adjusting for confounders; and 1.57 (1.15–2.15) for the lowest quintile and 1.45 (1.04–2.01) for the highest quintile of HDL-C, after exclusion of death within the first 2 years of follow-up; and 1.55 (1.11–2.16) for the lowest quintile and 1.42 (1.00–2.02) for the highest quintile of HDL-C, after exclusion of functionally impaired participants.

Conclusions: We found an inverse association of LDL-C and a U-shape relationship of HDL-C with long-term all-cause mortality in a cohort with community-dwelling older Chinese adults. Levels of LDL-C and HDL-C are suggested to be managed properly in late life.

Keywords: LDL-C, HDL-C, mortality, older adults, cohort study

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INTRODUCTION

The health status of older individuals is complicated, owing to multiple subclinical and clinical diseases. Considering the complex and potentially diverse biochemical roles of cholesterol on and beyond the cardiovascular system, exploring the association between cholesterol and all-cause mortality may help to evaluate its role in late life from a comprehensive perspective.

Serum cholesterol is transported in the blood attached to lipoproteins, such as low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). The relation between late-life LDL-C, HDL-C, and all-cause mortality has been reported by population-based cohort studies. Some studies reported either a lack of an association or an inverse association for LDL-C and mortality (1–11). Some studies concluded a U-shape association for HDL-C, with both lower and higher HDL-C concentrations associated with an elevated risk of mortality (3, 12). One major methodological concern of most previous studies was lack of the adjustment of lipid-lowering therapy, a strong confounder in the association analysis. Additionally, most of the findings were from high-income countries, while large-sampled studies with long-term follow-up in the low and middle-income countries are still limited. The Shanghai Aging Study recruited a large cohort of community-dwelling older adults during 2010–2012 and prospectively monitored the survival status of the participants until the end of 2020. In this study, we aimed to examine the association between LDL-C, HDL-C level, and all-cause mortality in older Chinese adults.

METHODS

Study Site and Population

Between 2010 and 2012, permanent residents aged 50 years or older from Jingansi community in Jingan District, Shanghai were recruited in the Shanghai Aging Study. Details of the recruiting procedure were previously published elsewhere (13). The original sample size of the Shanghai Aging Study was 3,836. In the present study, participants from the Shanghai Aging Study were excluded if they: (1) did not measure LDL-C and HDL-C at baseline ($n = 336$); (2) took lipid-lowering medication ($n = 261$). The final sample size for the current study was 3,239.

Cholesterol Assessment

For each participant, a 2-ml fasting blood sample was drawn by a research nurse during the baseline clinical interview. Serum LDL-C and HDL-C concentration were measured by Hitachi 7 600 full-automatic biochemical analyzer with the direct method at the central lab of Huashan Hospital (13).

Covariates

At baseline, demographic and lifestyle characteristics of the participants were collected via an interviewer-administered questionnaire including age, sex, formal educational year, family income, cigarette smoking, tea and alcohol consumption, and physical activity. Low family income was defined as per capita income <170 USD per month. Cigarette smoking status was defined if the participant had smoked daily within the past month. Alcohol consumption was defined if the participant had at least one serving of alcohol weekly during the past year. Tea consumption was defined if the participant had drunk tea more than three times a week for 6 months or over during the past year. Physically active was defined as having a total physical activity of more than 10.5 metabolic equivalent value (MET)-hours per week (14). Medical conditions such as type II diabetes, hypertension, heart diseases (including coronary heart disease, valvular heart disease, cardiomyopathy, heart failure, heart rhythm problems), stroke, and cancer were asked and further confirmed from the medical records. The Center for Epidemiologic Studies Depression Scale (CESD) was administered to assess psychiatric status. Depression was present if CESD was ≥ 16 (13). Activities of Daily Living (ADL) were used for evaluating the functional ability. Participants were defined as functionally impaired if ADL was >20 (15). Anthropometry was performed by research nurses. Height and weight were used to calculate the body mass index (BMI). Obesity was defined as BMI $\geq$27.5 kg/m^2 based on the World Health Organization (WHO)'s definition for Asian populations (16).

Mortality Surveillance

The survival status of participants from baseline to December 31, 2020, was confirmed by access to the mortality surveillance system in the Center of Disease Control (CDC) in Jingan District, Shanghai. According to the regulations on household registration of Shanghai, once the death of the resident occurs, the CDC in his/her registered permanent residence is responsible for verifying the date of death and fundamental cause of death, which is coded by the International Classification of Diseases, tenth edition (ICD-10) from the death certificate.

Statistical Analysis

Mean with standard deviation (SD) and number with frequency (%) were used to describe continuous and categorical variables, respectively. Participants were categorized into subgroups according to the quintiles of LDL-C and HDL-C concentration. *T*-test was used to analyze the differences for continuous variables and Pearson's chi-squared test was used for categorical variables, between participants who took lipid-lowering medications and those who did not.

Participants were followed up for their survival status from baseline (2010–2012) to December 31, 2020. For those deceased, survival time was defined as the difference between the date of death and the date of baseline when levels of LDL-C and HDL-C were measured. Participants were censored as long as they were alive until December 31, 2020. The follow-up length was then defined as the difference between the date of baseline examination and the date of December 31, 2020. The crude mortality rate was calculated as the number of deaths divided by the cumulative person-years of follow-up. The hazard ratios (HRs) of mortality for LDL-C and HDL-C quintiles were estimated using Cox proportional hazards models. Model 1 adjusted for age, sex, years of formal education, low family income, cigarette smoking, tea and alcohol consumption, physical activity, and obesity. Model 2 further adjusted for a history of type II diabetes, hypertension, heart diseases, stroke,

cancer, and depression. Model 3 excluded those who died within the first 2 years of follow-up based on model 2. Model 4 excluded those who were functionally impaired based on model 2. The linear trend was tested by entering LDL-C and HDL-C as continuous variables. Adjusted cumulative survival curves were plotted based on the results of model 2. Subgroup analysis was also conducted according to the median age and sex, based on model 2. We have tested the proportional hazards (PH) assumption using Schoenfeld residuals methods and Log-log survival curves. The result of Schoenfeld residuals methods and the curves of Log-log survival analysis suggested that the PH assumption was not violated for all variables included in the Cox models.

All the *p*-values and 95% CIs were estimated in two-tailed tests. The data analysis was conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Comparison of the baseline characteristics between participants who took lipid-lowering medications ($n = 261$) and those who did not ($n = 3{,}239$) was shown in **Supplementary Table**. In general, participants who took medications were older and had a higher prevalence of chronic diseases such as hypertension, diabetes, stroke, and heart diseases, compared to those who did not. Also, those who took medications had a significantly lower level of LDL-C and HDL-C.

In total, 3,239 participants were included in this study. The baseline characteristics of the study participants were shown in **Table 1**. Participants' mean age was 69.41 ± 8.05 years old and the average year of education was 11.67 ± 4.02 years. Half of the participants had hypertension, and the prevalence of other medical conditions was about 10%. The means of LDL-C and HDL-C concentrations were 3.35 ± 0.91 mmol/L and 1.35 ± 0.35 mmol/L. Participants with higher LDL-C were younger, more likely to be female, had a higher level of BMI, had a lower prevalence of type II diabetes, and had a higher level of HDL-C.

Five hundred and forty-six deaths (16.9%) were identified during a median of 10-year follow-up. **Figure 1A** revealed a monotonic decrease of the crude mortality rate with the increment of LDL-C concentration, from 26.36 (95% CI: 22.24–30.49) per 1 000 person-years in the lowest quintile to 11.71 (95% CI: 9.06–14.36) per 1 000 person-years in the highest quintile. **Figure 1B** presented a curvilinear trend between HDL-C and mortality, with the lowest mortality rate of 14.40 (95% CI: 11.16–17.64) per 1 000 person-years in the group of HDL-C concentration of 1.21–1.39 mmol/L.

As shown in **Table 2**, the increment of LDL-C concentration was related to decreasing risk of mortality (p for trend < 0.05). Using the highest quintile of LDL-C (≥4.10 mmol/L) as a reference, the lowest quintile (<2.61 mmol/L) was associated with the highest risk of mortality, after adjusting for confounders (HR 1.67; 95% CI 1.26–2.21), exclusion of death within the first two years of follow-up (HR 1.57; 95% CI 1.17–2.11), and exclusion of functionally impaired participants (HR 1.46; 95% CI 1.07–2.00).

A U-shape relationship was found between HDL-C level and mortality risk, with both the lowest and highest quintile of HDL-C being associated with increased mortality risk. Using the third quintile of HDL-C (1.21–1.39 mmol/L) as a reference, HR (95% CI) was 1.46 (1.09–1.95) for the lowest quintile (<1.09 mmol/L) and 1.45 (1.07–1.96) for the highest quintile (≥1.61 mmol/L) of HDL-C, after adjusting for confounders; and 1.57 (1.15–2.15) for the lowest quintile and 1.45 (1.04–2.01) for the highest quintile of HDL-C, after exclusion of death within the first 2 years of follow-up; and 1.55 (1.11–2.16) for the lowest quintile and 1.42 (1.00–2.02) for the highest quintile of HDL-C, after exclusion of functionally impaired participants.

Figure 2 demonstrated the cumulative survival curves of participants according to the quintiles of LDL-C and HDL-C levels. Participants with the lowest LDL-C concentration (Q1) showed the worst survival, followed by those in the second and third quintile (Q2, Q3). Participants with LDL-C in the fourth and fifth quintiles (Q4, Q5) shared the best cumulative survival. The difference in the cumulative survival between Q1, Q2 and Q3, Q4 and Q5 of LDL-C expanded over time **(Figure 2A)**. The best survival was found for participants in the third HDL-C quintile. Both the lowest and the highest HDL-C quintiles presented a worse survival compared to the third HDL-C quintile **(Figure 2B)**.

The results of the subgroup analysis were shown in **Table 3**. The inverse association between LDL-C and 10-year all-cause mortality risk was observed among participants ≥68 years old ($p < 0.001$), both females ($p < 0.001$) and males ($p = 0.016$). The U-shape relationship in which both the lowest and highest quintile of HDL-C were related to increased mortality risk was observed among participants ≥68 years old (HR 1.60; 95% CI 1.18–2.19 for the lowest quintile, HR 1.64; 95% CI 1.19–2.25 for the highest quintile) and males (HR 1.57; 95% CI 1.08–2.29 for the lowest quintile, HR 1.72; 95% CI 1.21–2.26 for the highest quintile). For females, only the lowest quintile of HDL-C was related to increased mortality risk (HR 1.94; 95% CI 1.27–2.96).

DISCUSSION

In this population-based prospective study, we observed an inverse association between LDL-C and 10-year all-cause mortality risk among 3,239 older adults without using lipid-lowering agents. The relationship of HDL-C with all-cause mortality demonstrated a U-shape, both the lowest and highest quintile of HDL-C were related to increased mortality risk.

Evidence was limited regarding the association of late-life LDL-C, HDL-C, and all-cause mortality in low and middle-income countries. Our study was conducted in a large sample of Chinese community-dwellers through a long-term follow-up. The information on the participants' survival status in our study was from the mortality surveillance system in the local CDC with a follow-up rate of 100%. We excluded older adults who were on lipid-lowering medication, a potentially strong confounder for lipids and mortality. Additionally, we excluded participants

TABLE 1 | Baseline characteristics of study participants.

	Total	Quintiles of LDL-C				
		<2.61 mmol/L	2.61–3.09 mmol/L	3.10–3.50 mmol/L	3.51–4.09 mmol/L	≥4.10 mmol/L
Age, years, mean (SD)	69.41 (8.05)	70.18 (8.01)	69.84 (8.13)	69.55 (7.95)	69.24 (8.40)	68.31 (7.68)
Male, *n* (%)	1,476 (45.57)	362 (54.77)	302 (50.25)	303 (44.23)	268 (43.37)	241 (35.76)
Education, years, mean (SD)	11.67 (4.02)	11.64 (4.13)	11.39 (4.15)	11.75 (3.99)	11.73 (4.01)	11.80 (3.82)
BMI, mean (SD)	24.30 (3.45)	23.99 (3.59)	24.05 (3.53)	24.17 (3.42)	24.50 (3.42)	24.76 (3.22)
Low family income, *n* (%)	60 (1.86)	9 (1.37)	17 (2.83)	8 (1.18)	13 (2.11)	13 (1.94)
Cigarette smoking, *n* (%)	356 (10.99)	76 (11.50)	63 (10.48)	80 (11.68)	63 (10.19)	74 (10.98)
Alcohol consumption, *n* (%)	271 (8.37)	53 (8.02)	38 (6.32)	72 (10.51)	54 (8.74)	54 (8.01)
Tea drinking, *n* (%)	1,381 (42.93)	282 (42.86)	246 (41.07)	303 (44.69)	262 (42.74)	288 (43.05)
Physically active, *n* (%)	2,003 (62.28)	393 (60.00)	383 (64.05)	440 (64.99)	383 (62.18)	404 (60.30)
Obesity, *n* (%)	545 (16.87)	108 (16.34)	95 (15.86)	107 (15.64)	105 (17.07)	130 (19.37)
Hypertension, *n* (%)	1,601 (49.43)	334 (50.53)	309 (51.41)	328 (47.88)	316 (51.13)	314 (46.59)
Type II diabetes, *n* (%)	408 (12.60)	118 (17.85)	72 (11.98)	85 (12.41)	69 (11.17)	64 (9.50)
Stroke, *n* (%)	351 (10.83)	73 (11.04)	72 (11.98)	72 (10.51)	68 (11.00)	66 (9.79)
Heart diseases, *n* (%)	300 (9.26)	65 (9.83)	47 (7.82)	72 (10.51)	60 (9.71)	56 (8.31)
Cancer, *n* (%)	318 (9.87)	78 (11.85)	60 (10.03)	63 (9.24)	69 (11.24)	48 (7.15)
Depression, *n* (%)	557 (17.20)	116 (17.55)	104 (17.30)	117 (17.08)	101 (16.34)	119 (17.66)
LDL-C, mmol/L, mean (SD)	3.35 (0.91)	2.15 (0.40)	2.87 (0.12)	3.29 (0.13)	3.78 (0.15)	4.64 (0.55)
HDL-C, mmol/L, mean (SD)	1.35 (0.35)	1.27 (0.40)	1.32 (0.34)	1.35 (0.33)	1.36 (0.33)	1.43 (0.32)

BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

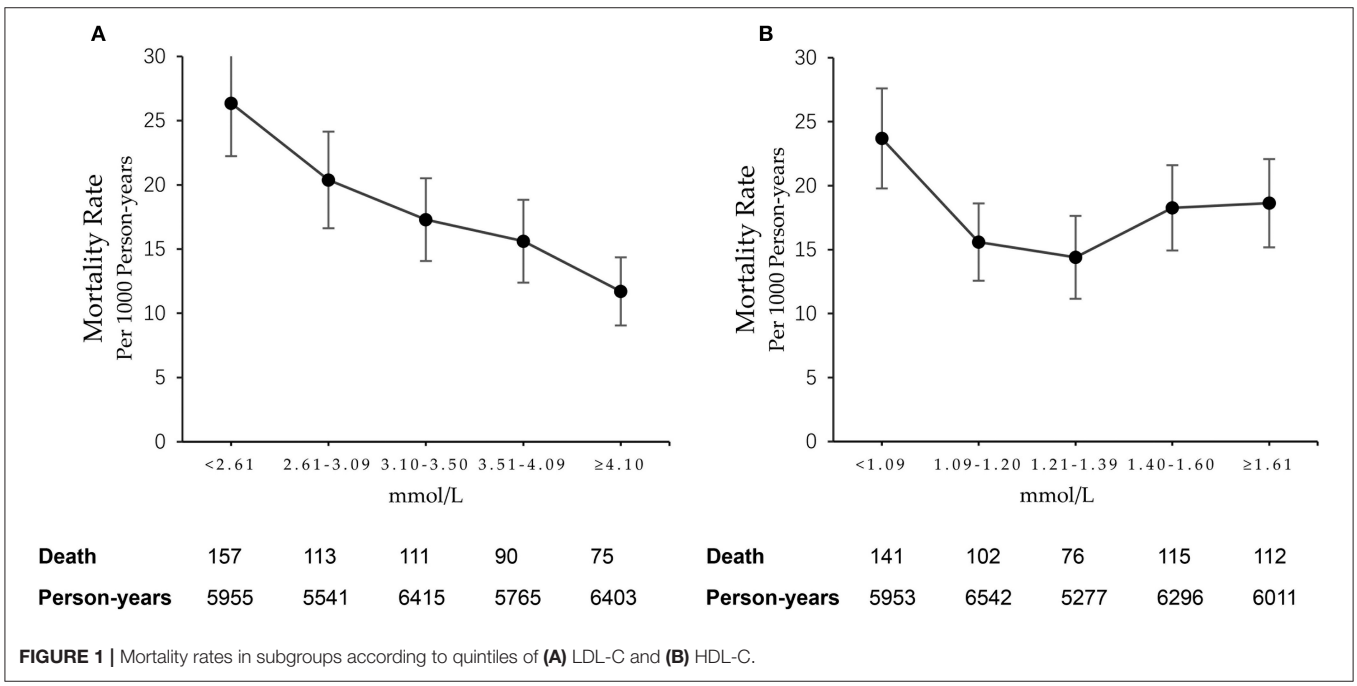

FIGURE 1 | Mortality rates in subgroups according to quintiles of **(A)** LDL-C and **(B)** HDL-C.

who died within the first 2 years of follow-up and those with functional impairment to prevent reverse causality.

Our finding is consistent with previous studies where an inverse association of LDL-C with all-cause mortality was found among older adults (2–7). Using a large sample size ($N = 13,733$), a population-based register study in Region Zealand reported an increased risk of death for older adults with LDL-C <2.5 mmol/L (3). Another observational study in Italy found that the risk of death was reduced by 16% for every 1 mmol/L of LDL-C increment (2). Similar inverse associations of LDL-C with risk of death were also reported in other population-based observational studies from the USA, Finland, Netherland, Japan, and China

TABLE 2 | Adjusted hazard ratio (95% confidence interval) of all-cause mortality.

	Model 1	*p* for trend	Model 2	*p* for trend	Model 3	*p* for trend	Model 4	*p* for trend
LDL-C		<0.001		<0.001		<0.001		0.011
<2.61 mmol/L	1.70 (1.28–2.25)*		1.67 (1.26–2.21)*		1.57 (1.17–2.11)*		1.46 (1.07–2.00)*	
2.61–3.09 mmol/L	1.30 (0.97–1.75)		1.28 (0.95–1.73)		1.20 (0.88–1.64)		1.17 (0.84–1.62)	
3.10–3.50 mmol/L	1.20 (0.89–1.61)		1.14 (0.85–1.54)		1.18 (0.87–1.61)		1.12 (0.81–1.55)	
3.51–4.09 mmol/L	1.05 (0.77–1.43)		1.02 (0.75–1.39)		0.96 (0.69–1.33)		0.95 (0.67–1.35)	
≥4.10 mmol/L	1		1		1		1	
HDL-C		0.732		0.878		0.494		0.426
<1.09 mmol/L	1.48 (1.11–1.98)*		1.46 (1.09–1.95)*		1.57 (1.15–2.15)*		1.55 (1.11–2.16)*	
1.09–1.20 mmol/L	1.04 (0.77–1.41)		1.05 (0.77–1.42)		1.11 (0.81–1.54)		1.19 (0.84–1.67)	
1.21–1.39 mmol/L	1		1		1		1	
1.40–1.60 mmol/L	1.20 (0.89–1.61)		1.21 (0.89–1.63)		1.27 (0.92–1.74)		1.37 (0.98–1.92)	
≥1.61 mmol/L	1.41 (1.05–1.91)*		1.45 (1.07–1.96)*		1.45 (1.04–2.01)*		1.42 (1.00–2.02)*	

Model 1 adjusted for age, sex, educational years, low family income, cigarette smoking, alcohol drinking, tea-drinking, physical activity, and obesity.
Model 2 further adjusted for hypertension, type II diabetes, stroke, heart diseases, cancer, and depression.
Model 3 excluded those who died within 2 years of initial cholesterol measurement (n = 60) on the basis of model 2.
Model 4 excluded those who were functionally impaired (n = 212) on the basis of model 2.
LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
*$p < 0.05$.

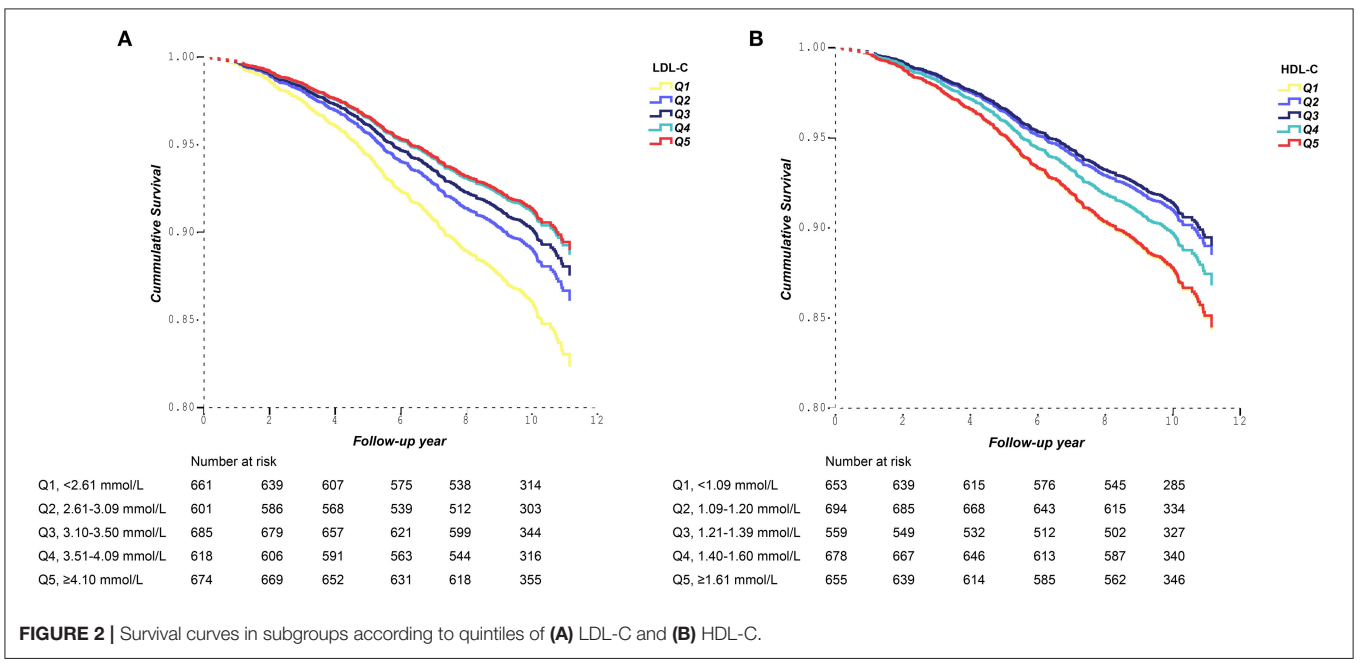

FIGURE 2 | Survival curves in subgroups according to quintiles of **(A)** LDL-C and **(B)** HDL-C.

(1, 4–7). Several studies reported no significant association between LDL-C and all-cause mortality (8–11). For example, the Cardiovascular Health Study found LDL-C was inversely associated with mortality in the crude model, but not in the model adjusting for potential confounders (8). Although LDL-C is a well-established risk factor for atherosclerotic cardiovascular disease and results from the Cooper Center Longitudinal Study showed that high levels of LDL-C were independently associated with an increased risk of cardiovascular disease mortality (17), to our knowledge, no studies reported a positive association between late-life LDL-C and all-cause mortality. Combined, these studies indicate that high late-life LDL-C levels do not seem to be definitely harmful in the general population. High LDL-C might not be a risk indicator at old age and thus be used to identify older adults at risk and start cardiovascular disease management. Instead, those with low LDL-C in late life might warrant further attention. An adjustment of diet may help to increase their level of LDL-C and avoid extra risk of all-cause mortality.

Our findings could be explained by that among older individuals, lower LDL-C levels are partially a surrogate marker of frailty. Evidence shows that LDL-C gradually decreases

TABLE 3 | Adjusted hazard ratio (95% confidence interval) of all-cause mortality among the subgroups.

Age < 68 years		Age ≥ 68 years		Female		Male	
LDL-C							
<2.70 mmol/L	1.76 (0.94, 3.31)	<2.60 mmol/L	1.76 (1.28, 2.43)*	<2.71 mmol/L	2.29 (1.47, 3.57)*	<2.50 mmol/L	1.58 (1.10, 2.28)*
2.71–3.14 mmol/L	1.19 (0.61, 2.31)	2.61–3.01 mmol/L	1.27 (0.91, 1.76)	2.71–3.20 mmol/L	1.24 (0.77, 1.99)	2.50–2.98 mmol/L	1.08 (0.73, 1.59)
3.15–3.60 mmol/L	1.13 (0.58, 2.22)	3.02–3.45 mmol/L	1.27 (0.91, 1.77)	3.21–3.64 mmol/L	1.19 (0.72, 1.97)	2.99–3.39 mmol/L	1.31 (0.89, 1.92)
3.61–4.16 mmol/L	0.79 (0.37, 1.70)	3.46–4.00 mmol/L	1.06 (0.75, 1.49)	3.65–4.20 mmol/L	1.21 (0.73, 1.98)	3.40–3.90 mmol/L	1.08 (0.74, 1.59)
≥4.17 mmol/L	1	≥4.01 mmol/L	1	≥4.21 mmol/L	1	≥3.91 mmol/L	1
p for trend	0.104	*p* for trend	<0.001	*p* for trend	<0.001	*p* for trend	0.016
HDL-C							
<1.09 mmol/L	1.14 (0.62, 2.10)	<1.09 mmol/L	1.60 (1.18, 2.19)*	<1.10 mmol/L	1.94 (1.27, 2.96)*	<1.00 mmol/L	1.57 (1.08, 2.29)*
1.09–1.20 mmol/L	0.90 (0.47, 1.72)	1.09–1.20 mmol/L	1.14 (0.83, 1.57)	1.10–1.29 mmol/L	0.95 (0.62, 1.45)	1.00–1.11 mmol/L	1.18 (0.81, 1.73)
1.21–1.39 mmol/L	1	1.21–1.40 mmol/L	1	1.30–1.49 mmol/L	1	1.12–1.29 mmol/L	1
1.40–1.61 mmol/L	1.14 (0.60, 2.17)	1.41–1.60 mmol/L	1.39 (1.00, 1.93)	1.50–1.70 mmol/L	0.94 (0.61, 1.46)	1.30–1.49 mmol/L	1.15 (0.78, 1.68)
≥1.62 mmol/L	0.87 (0.43, 1.76)	≥1.61 mmol/L	1.64 (1.19, 2.25)*	≥1.71 mmol/L	1.20 (0.78, 1.86)	≥1.50 mmol/L	1.72 (1.21, 2.46)*
p for trend	0.239	*p* for trend	0.855	*p* for trend	0.088	*p* for trend	0.155

Hazard ratio (95% confidence interval) were adjusted for age, sex, educational years, low family income, cigarette smoking, alcohol drinking, tea-drinking, physical activity, obesity, hypertension, type II diabetes, stroke, heart diseases, cancer, and depression. LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

*$p < 0.05$.

in the latter decades of life (18). The ability to preserve a higher level of LDL-C in late life may represent a better global health condition and protect individuals from death. Large-scale epidemiologic studies, such as the Whitehall Study, the Framingham Study, and the Honolulu Study have related low cholesterol to a higher cancer incidence and mortality, suggesting a potential role of cholesterol in cancer development and survival (19). Higher serum cholesterol also promotes inflammatory responses, including augmentation of toll-like receptor signaling, inflammasome activation, and the production of monocytes and neutrophils in the bone marrow and spleen (20).

Our finding of a U-shape relationship between HDL-C and all-cause mortality is consistent with the findings of the Health and Retirement Study (HRS) and the population-based register study in Region Zealand (3, 12). Both low and high HDL-C were associated with an increased risk of death. In HRS, the risk of death was increased by 72% and 56% for participants with HDL-C < 30 mg/dl and HDL-C ≥ 90 mg/dl, respectively, compared with those with HDL-C of 70–79 mg/dl (12). Other studies reported either no association or only low HDL-C was associated with high all-cause mortality (1, 4, 6, 11, 21). In a prospective cohort in Finland, older adults in the lowest quartile of HDL-C were over twice as likely to die as those in the highest quartile (1). Although the diverse results and potential mechanisms could not be well explained, these findings add to the uncertainty of the role of HDL-C for mortality in old people.

Subgroup analysis showed a similar association between LDL-C/HDL-C and 10-year all-cause mortality risk among participants ≥68 years old, both females and males. Although we did not observe an inverse association of LDL-C with all-cause mortality among participants < 68 years, the risk estimates for the lowest quintile of LDL-C were similar between those younger than 68 and those ≥68. Thus, a limited number of deaths among participants < 68 years may account for the insignificant finding. For females, although the lowest quintile of HDL-C was related to increased mortality risk, the increased risk for the highest quintile of HDL-C did not reach a statistical significance. The effect of a higher level of HDL-C on mortality might be varied across sex.

The limitations of our study are listed as the following. First, the current study relied on a single measurement of LDL-C and HDL-C at baseline. Measurement error and biological variability would impact the association estimation. Second, reverse causality may be of concern due to the potential underlying chronic diseases of older adults. However, in our study, the inverse association remained unchanged after excluding those who died in the first 2 years of follow-up and those who were functionally impaired. Rather, the difference of cumulative survival between high and low LDL-C levels expanded over time, which strengthens the evidence against reverse causality. Third, despite adjustment for important covariates in our analysis, the possibility of residual confounding from unmeasured variables such as diets, occupation history, and air pollution could also affect the results. Fourth, our study only focused on all-cause mortality because the relatively

small number of events has limited the ability to study cause-specific mortality. In addition, the current analysis is a *post-hoc* analysis. The sample size was not calculated according to mortality rate. Last, our study participants were recruited from communities in downtown Shanghai using a government-maintained "residents list". The population-based nature of the Shanghai Aging Study indicates that the study sample well-represented the characteristics of older adults living in downtown Shanghai. However, our findings may not be generalized to other populations in China in which the demographic characteristics could be varied.

In conclusion, we found an inverse association of LDL-C and a U-shape relation of HDL-C with long-term all-cause mortality in a cohort with community-dwelling older Chinese adults. Levels of LDL-C and HDL-C are suggested to be managed properly in late life. The role of LDL-C and HDL-C in health status in late life needs further validation in diverse regions and ethnic populations. The causal relation cannot be answered with the observational design, whereas the randomized clinical trials so far indicate that treatment with cholesterol-lowering drugs is of benefit also in older age. The decision whether or not to treat older people with cholesterol-lowering drugs needs to weigh the "costs" and the "benefits" for the individual and society.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DD was responsible for the study's concept and design. WW, DD, ZX, XL, and QZ collected the data. WW did the analyses with support from JL. WW prepared the manuscript. DD, XL, ZX, QZ, and JL revised the manuscript. DD is the guarantor of this article. 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/fmed.2022.783618/full#supplementary-material

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Red Flags, Prognostic Impact, and Management of Patients With Cardiac Amyloidosis and Aortic Valve Stenosis: A Systematic Review and Meta-Analysis

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Background: Cardiac amyloidosis (CA) has been recently recognized as a condition frequently associated with aortic stenosis (AS). The aim of this study was to evaluate: the main characteristics of patients with AS with and without CA, the impact of CA on patients with AS mortality, and the effect of different treatment strategies on outcomes of patients with AS with concomitant CA.

Materials and Methods: A detailed search related to CA in patients with AS and outcomes was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Seventeen studies enrolling 1,988 subjects (1,658 AS alone and 330 AS with CA) were included in the qualitative and quantitative analysis of main patients with AS characteristics with and without CA, difference in mortality, and treatment strategy.

Results: The prevalence of CA resulted in a mean of 15.4% and it was even higher in patients with AS over 80 years old (18.2%). Patients with the dual diagnosis were more often males, had lower body mass index (BMI), were more prone to have low flow, low gradient with reduced left ventricular ejection fraction AS phenotype, had higher E/A and E/e', and greater interventricular septum hypertrophy. Lower Sokolow–Lyon index, higher QRS duration, higher prevalence of right bundle branch block, higher levels of *N*-terminal pro-brain natriuretic peptide, and high-sensitivity troponin T were significantly associated with CA in patients with AS. Higher overall mortality in the 178 patients with AS + CA in comparison to 1,220 patients with AS alone was observed [odds ratio (OR) 2.25, $p = 0.004$]. Meta-regression analysis showed that younger age and diabetes were associated with overall mortality in patients with CS with CA (Z-value −3.0, $p = 0.003$ and Z-value 2.5, $p = 0.013$, respectively). Finally, patients who underwent surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI) had a similar overall mortality risk, but lower than medication-treated only patients.

Conclusion: Results from our meta-analysis suggest that several specific clinical, electrocardiographic, and echocardiographic features can be considered "red flags" of CA in patients with AS. CA negatively affects the outcome of patients with AS. Patients with concomitant CA and AS benefit from SAVR or TAVI.

Keywords: aortic stenosis (AS), cardiac amyloidosis (CA), outcome, surgical aortic valve replacement, transcatheter aortic valve implantation (TAVI)

INTRODUCTION

In the geriatric population, calcific aortic stenosis (AS) is one of the most prevalent cardiovascular diseases. It affects 3% of the general population older than 65 years (1). AS is an age-related disease (2, 3) and, therefore, the number of affected patients will drastically increase in the coming decades due to the aging of the world population (4). Nowadays, the only therapeutic strategies available for AS are surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI).

Cardiac amyloidosis (CA) is characterized by extracellular amyloid infiltration into the heart, in most cases of light chain (AL) or transthyretin (TTR) types. Acquired TTR amyloidosis (ATTRwt) is also called "senile amyloidosis" and is highly prevalent in the elderly (5).

The prevalence of CA in patients with AS is variable although consistent, ranging from 8 (6) to 16%, as reported in patients undergoing TAVI (7). The uncertainty about the prevalence of CA in the context of AS probably originates from the limited number of patients enrolled in most of the published studies. However, a different prevalence could be also explained by some specific patient's characteristics, in particular age and gender (6, 7). Two recent meta-analyses report a prevalence of CA in patient with AS of 9 and 14.4%, respectively (8, 9). Thus, the true prevalence of CA in patients with AS is still undefined and probably underestimated in some studies. A further increase in prevalence is expected in the next years, both due to the aging of the population and the improvement of the diagnostic algorithm (10), including multimodality imaging (11, 12).

The identification of "red flags" of CA in the context of AS is particularly challenging because the two diseases share common features. Some studies observed the clinical characteristics of patients with concomitant AS and CA and concluded that such patients show manifestations of more advanced disease, such as higher levels of *N*-terminal pro-brain natriuretic peptide (NT-proBNP), greater left ventricular (LV) hypertrophy, and advanced diastolic dysfunction (7, 8).

The outcome of patients with both the AS and CA is another important open question. There are conflicting reports on the prognostic significance of CA in patients with AS and on the potential impact of CA on aortic valve replacement benefits. Some studies attribute to CA an important role in AS prognosis (6, 13, 14), while other reports show that CA does not significantly worse AS outcome (15–17). It remains also to be clarified if there is a better therapeutic strategy in patients with both the AS and CA and if the presence of CA should be considered as an additive factor to be evaluated in the choice of AS treatment modality (SAVR or TAVI).

We performed a systematic review and meta-analysis to clarify: (1) the prevalence of CA in patients with AS; (2) the "red flags" of CA in the context of AS; (3) the impact of CA on patients with AS outcome; (4) the impact of aortic valve replacement in patients with concomitant CA and AS; and (5) if there is a treatment of choice (SAVR or TAVI) in patients with concomitant CA and AS.

MATERIALS AND METHODS

Search Strategy

To perform a complete search and analysis, a detailed protocol for this review was prospectively developed, specifying objectives, criteria for study selection, outcomes, and statistical methods.

To identify all the available studies, a systematic search was evaluated in the electronic databases (PubMed, Web of Science, and Scopus). A detailed search relating to CA in patients with AS and outcomes was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (18). Following the search, terms were used in all the possible combinations: cardiac amyloidosis, aortic stenosis, aortic valve stenosis, outcome, adverse event, prognosis, risk stratification, and apical sparing. The last search was performed on December 29, 2021. The reference lists of all the retrieved articles were manually reviewed. Two independent authors (VAM and VP) analyzed each article and performed the data extraction independently. In case of disagreement, a third investigator was consulted (PP). Discrepancies were resolved by consensus.

Data Extraction and Quality Assessment

According to the prespecified protocol, all the studies evaluating the prevalence and/or outcomes of concomitant CA and AS and the impact on cardiovascular risk factors were included. Case reports, case series not reporting data on prevalence and outcomes, reviews, and animal studies were excluded. We included in the analysis only studies on patients with AS with suspected or confirmed CA at echocardiography, cardiac magnetic resonance (CMR), and bone scintigraphy. In particular, we included two echocardiographic studies that identified patients with concomitant CA and severe AS with apical sparing pattern at LV strain analysis (19, 20). In each study, data regarding major clinical, demographic, echocardiographic, electrocardiographic variables, and prevalence of cardiovascular risk factors in patients with AS with and without CA were extracted. The quality analysis for each included study was performed accordingly to the Newcastle–Ottawa Scale

(NOS). The result of the NOS quality assessment is given in **Supplementary Table 1**.

Statistical Analysis and Risk of Bias Assessment

Statistical analysis was performed using Comprehensive Meta-analysis Version 3.3.070 (Biostat, Englewood, New Jersey, 2014). Differences among cases and controls in dichotomous variables were expressed as odds ratio (OR) with pertinent 95% CI and the differences in continuous variables were expressed as a standardized mean difference (SDM) and 95% CI. The overall effect was tested using Z scores and significance was set at $p < 0.05$. Statistical heterogeneity among studies was assessed with the chi-squared Cochran's Q-test and with I^2 statistic, which measures the inconsistency across study results and describes the proportion of total variation in study estimates, that is due to heterogeneity rather than sampling error. In detail, I^2 values of 0% indicate no heterogeneity, 25% low, 25–50% moderate, and 50% or more high heterogeneity (21).

Publication bias was assessed by Egger's test and represented graphically by funnel plots of the standard difference in means vs. the SE. Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect and Egger's test was used to assess publication bias, over and above any subjective evaluation (22). The value $p < 0.05$ was considered as statistically significant. In order to be as conservative as possible, the random-effect method was used for all the analyses to consider the variability among the included studies (22). In the case of significant publication bias, Duval and Tweedie's trim and fill method was used to allow for the estimation of adjusted effect size (22).

Meta-Regression Analyses

The differences in mortality among patients with AS with and without CA may be affected by clinical and demographic characteristics of patients included in different studies [mean age, diabetes, dyslipidemia, hypertension, body mass index (BMI), and coronary artery disease presence], echocardiographic characteristics (peak aortic jet velocity, mean aortic valve gradient, aortic valve area, LV ejection fraction, E/A ratio, E/e' ratio, interventricular septum, stroke volume index, and LV mass index), electrocardiographic characteristics (low voltage, Sokolow–Lyon Index, QRS duration, and right bundle branch block), and biochemical parameters. To assess the possible effect of such variables in explaining the different results observed across studies, meta-regression analyses after implementing a regression model with the mortality as dependent variables (y) and the variables mentioned above as independent variables (x) were performed (23).

RESULTS

The search strategy identifies 110 articles (**Figure 1**). Duplicate results were excluded and after a screening of the titles and the abstracts, thirty-one articles were selected for full-text evaluation. The revision of full-length articles allowed the exclusion of fourteen studies due to wrong study design or irrelevant information in their content. Thus, seventeen studies (6, 7, 13–17, 19, 20, 24–31), enrolling 1,988 subjects (1,658 AS alone and 330 AS with CA), were included in the qualitative and quantitative analyses of main patients with AS characteristics with and without CA (14 studies), difference in mortality (9 studies), and treatment strategy (10 studies).

Prevalence of CA and Characteristics of AS Patients With and Without CA

The prevalence of CA was accessed in 14 studies (6, 7, 13–17, 19, 20, 25, 28–31), including 1,934 subjects (276 with concomitant CA and AS), resulting in a mean of 15.4%. Our results suggest that the prevalence of CA is lower in patients with AS under 80 years old compared with patients over 80 years old (7.1 vs. 18.2%, respectively). Of note, we found a positive correlation between the prevalence of CA in each study and the age of these patients (**Figure 2**).

Clinical and demographic characteristics as well as cardiovascular risk factors associated with CA prevalence in patients with AS were reported in 12 studies (6, 7, 13, 15–17, 19, 20, 28–31), including 1,772 subjects (1,506 AS alone and 266 AS with CA) (**Table 1**; **Supplementary Figures 1, 2**).

Patients with concomitant CA and AS were more often males, 68 vs. 52%, with a corresponding odds ratio (OR) of 2.01 (95% CI: 1.13, 3.56; $p < 0.0001$) and had lower BMI, SDM of −0.32 (95% CI: −0.51; −0.12, $p = 0.002$). Analysis of echocardiographic parameters found that patients with AS and CA were more prone to have low flow, low gradient with reduced LV ejection fraction (LVEF), OR of 2.26 (95% CI: 1.44; 3.54, $p < 0.001$), lower aortic valve mean gradient SDM of −0.33 (95% CI: −0.54; 0.11, $p = 0.003$), and higher E/A and E/e' ratios SDM of 2.26 (95% CI: 1.3; 4.7, $p < 0.001$) and 0.48 (95% CI: 0.29; 0.67, $p < 0.001$), respectively. Interventricular septum (IVS) was thicker in patients with dual diagnosis (SDM 0.67, 95% CI: 0.46; 0.88, $p < 0.001$), while stroke volume index (SVi) was higher in patients with AS alone (SDM −0.52, 95% CI: −0.68; −0.35, $p < 0.001$). Electrocardiographic parameters significantly associated with AS and CA were: lower Sokolow–Lyon Index (SDM −1.3, 95% CI: −2.02; 0.54, $p < 0.001$); higher QRS duration (SDM 0.36, 95% CI: 0.05; 0.66, $p = 0.002$); and higher prevalence of right bundle branch block (RBBB) (OR 3.55, 95% CI: 2.32; 5.41, $p < 0.001$). Finally, higher levels of both the NT-proBNP and high-sensitivity troponin T (Hs-TnT) were significantly associated with AS and CA in comparison with the patients with AS alone, SDM of 0.76 (95% CI: 0.43; 1.09, $p < 0.001$) and 0.93 (95% CI: 0.72; 1.13, $p < 0.001$), respectively. The heterogeneity of all the analyzed variables is given in **Supplementary Table 2**. In particular, data of male sex, aortic valve mean gradient, E/A ratio, IVS, Sokolow–Lyon Index, NT-proBNP, and Hs-TnT showed significant heterogeneity, while no heterogeneity was observed for BMI, presence of low flow, low gradient with reduced LVEF, E/e' ratio, and QRS duration.

Publication Bias

Funnel plots of effect size vs. SE for all the performed analyses were rather symmetrical and Egger's test showed the absence of publication bias, except for three variables, such as age,

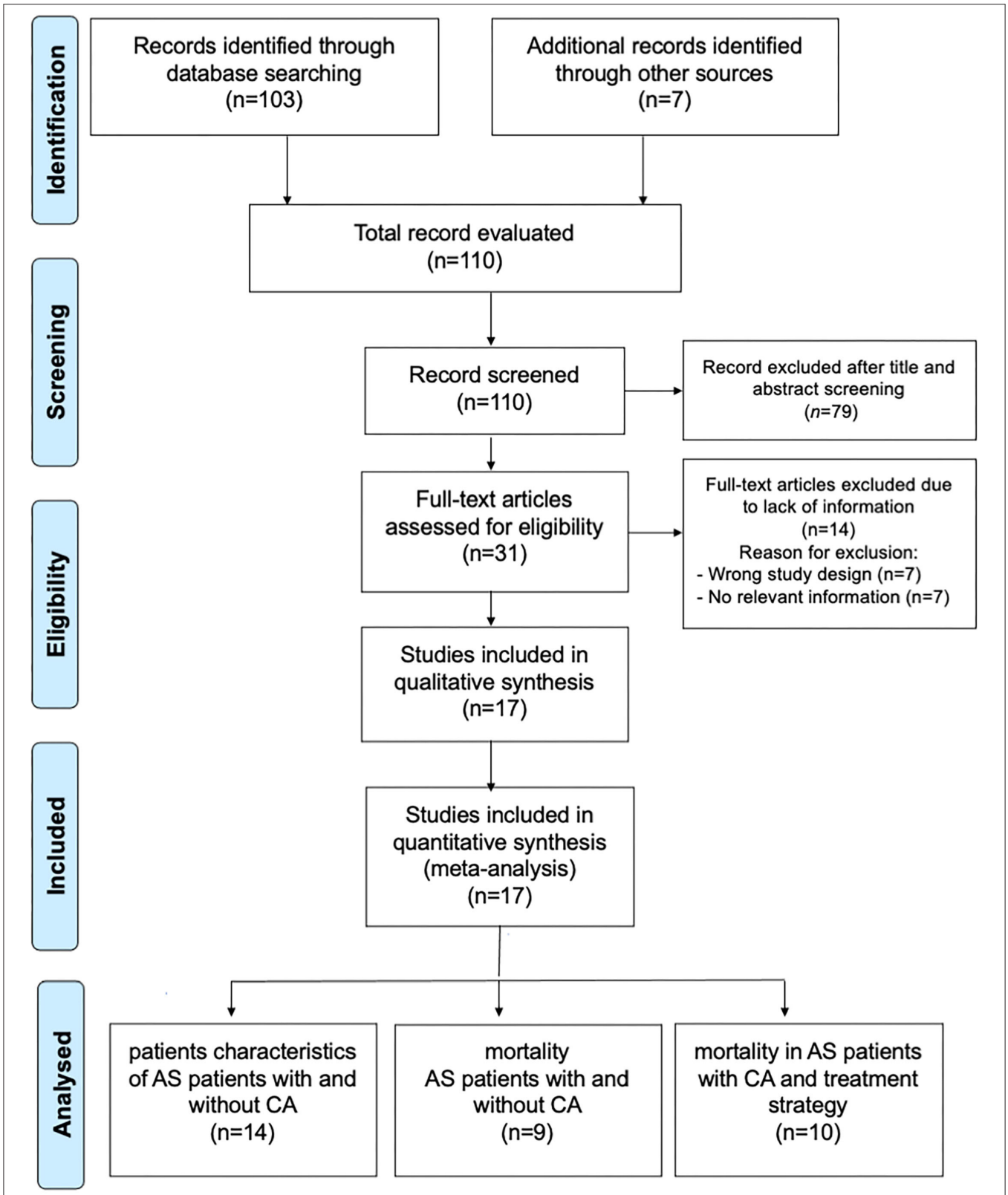

FIGURE 1 | Prisma Flow Chart. The flow chart represents the number of studies evaluated according to PRISMA guidelines.

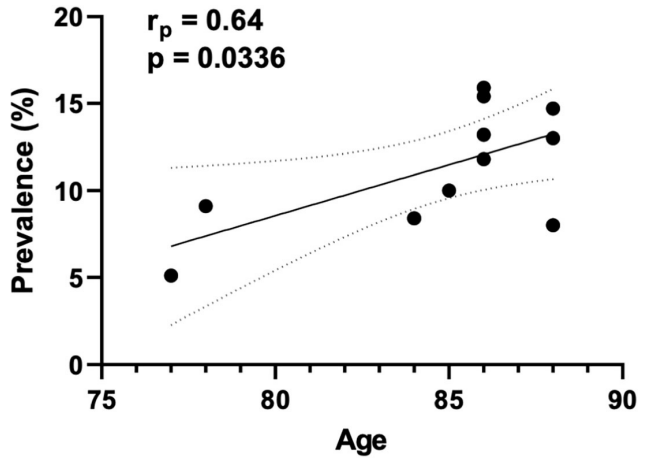

FIGURE 2 | Correlation between the prevalence of CA and age. The correlation plot indicates the results of 11 studies. The abscissa (x axis) represents the mean age of patients with both conditions (CA and AS), while the ordinate (y axis) represent the prevalence of CA in each included study.

E/A ratio, and LV mass index. These variables showed an asymmetric distribution and Egger's test confirmed the presence of a significant publication bias (Egger's $p = 0.023$, $p = 0.019$, and $p = 0.045$, respectively; **Supplementary Table 3**). However, the Duval and Tweedie's trim and fill analysis showed that, after adjusting for publication bias, results were confirmed (age, SDM of 0.33, 95% CI: 0.13, 0.53; E/A ratio, SDM of 1.4, 95% CI: 0.35, 2.44; LV mass index 0.49, 95% CI: 0.15, 0.82; **Supplementary Figure 3**).

Increased Mortality in Patients With AS and Concomitant CA

The presence of CA was associated with an increased mortality rate in patients with AS. Nine studies (6, 13–17, 19, 25, 31) showed higher overall mortality in the 178 patients with AS with CA in comparison with 1,220 patients with AS alone with an OR of 2.25 (95% CI: 1.23–3.94, $p = 0.004$), with a moderate heterogeneity among studies (I^2: 43% $p = 0.082$; **Figure 3**).

Funnel plots of effect size vs. SE for overall mortality in patients with AS with and without CA showed an asymmetric distribution and Egger's test confirmed the presence of a significant publication bias (Egger's $p = 0.048$, **Supplementary Figure 4**). After adjusting for publication bias (Duval and Tweedie's trim and fill analysis), results were consistently confirmed with an OR of 1.85 (95% CI: 1.01, 3.40).

Sensitivity analysis showed that, excluding the study of Ferreira et al. (19), due to different methods of CA evaluation, considering eight studies (6, 13–17, 25, 31) including 139 patients with AS with CA and 1,170 patients with AS without CA, the results were confirmed with an OR of 1.83 (95% CI: 1.11, 3.03, $p = 0.019$), without low heterogeneity among studies (I^2: 26% $p = 0.219$).

Meta-Regression Analysis

For the evaluation of the impact of major clinical and demographic characteristics on the difference in overall mortality between patients with AS alone and with CA, meta-regression models were performed (**Supplementary Table 4**). Our results showed that with increasing age, the difference in overall mortality rate between patients with AS with and without CA declines, suggesting that the presence of CA in younger age in patients with AS could lead to higher mortality risk (Z-value: −3.0; $p = 0.003$, **Figure 4A**). In addition, diabetes was positively associated with overall mortality in patients with AS with CA (Z-value: 2.5; $p = 0.013$, **Figure 4B**).

Different Treatment Strategies and Overall Mortality in Patients With Concomitant CA and AS

To evaluate the role of CA in patients with AS who underwent a different type of medical intervention, we analyzed data from ten studies (6, 13–17, 24, 26, 27, 31), four studies reported data on medical/pharmacological treatment (6, 13, 24, 26), four studies reported data on SAVR (14, 26, 27, 31), and eight studies included data regarding TAVI (6, 13, 15–17, 24, 26, 27). Results of our analysis suggested a significant difference in overall mortality between the three groups ($p = 0.002$, **Figure 5)**. As expected, patients who underwent SAVR or TAVI showed a lower risk of overall mortality compared with the patients pharmacologically treated only. However, no difference was observed between patients treated with SAVR *vs.* TAVI ($p = 0.217$).

Funnel plots of effect size vs. SE for all the performed analyses were rather symmetrical and Egger's test showed the absence of publication bias (**Supplementary Table 5**).

DISCUSSION

In the present systematic review and meta-analysis, we report that: (1) in elderly patients with AS, the prevalence of CA increases with age; (2) specific clinical, electrocardiographic, and echocardiographic features can be considered "red flags" of CA in patients with AS; (3) CA negatively affects the outcome of patients with AS; (4) patients with concomitant CA and AS benefit from aortic valve replacement; and (5) in patients with concomitant CA and AS, there is not a treatment of choice.

The prevalence of CA in patients with AS is highly variable in literature. In the analyzed studies, it ranges from 8 to 16% (6, 7). This variability could be in part explained by the use of different imaging diagnostic techniques. However, the variability of CA prevalence in patients with AS remains high even among studies based on the same diagnostic method (7, 15). Another possible explanation could be the limited number of patients enrolled in most of the studies, but also two recent meta-analysis report a different prevalence of CA in patients with AS ranging from 9 to 14.4% (8, 9). Thus, it is plausible that specific patient's characteristics of the populations included in the studies could explain such differences. In this study, the overall prevalence of CA in patients with AS was of 15.4%. Although all the patients included were elderly, we observed a higher prevalence of CA in

TABLE 1 | Characteristics of patients with AS with and without CA.

Variable	AS + CA	*n*	AS	n	Effect size	*P*-value
Age, years	85.4 ± 5.5	259	82.4 ± 8.8	1,441	0.38 (0.24; 0.51)	**<0.001**
Male, *n* (%)	180 (67.7)	266	784 (52.1)	1,506	2.01 (1.13; 3.56)	**0.017**
BMI, kg/m^2	25.6 ± 3.9	181	26.1 ± 4.8	893	−0.32 (−0.51; −0.12)	**0.002**
Hypertension, *n* (%)	212 (80.9)	262	1,170 (79.6)	1,470	1.12 (0.71; 1.77)	0.638
Diabetes, *n* (%)	48 (22.7)	211	297 (25.5)	1,166	0.95 (0.59; 1.51)	0.811
Dyslipidemia, *n* (%)	66 (43.7)	151	332 (47.8)	674	0.80 (0.54; 1.18)	0.261
CAD, *n* (%)	108 (49.1)	220	555 (46.1)	1,203	1.15 (0.75; 1.77)	0.530
Stage D1	63 (54.8)	115	605 (72.2)	838	0.45 (0.30;0.68)	**<0.001**
Stage D2	37 (29.8)	124	171 (18.2)	942	2.26 (1.44; 3.54)	**<0.001**
Stage D3	24 (20.9)	115	118 (14.1)	838	1.77 (0.86; 3.61)	0.119
AV mean gradient, mmHg	39.5 ± 15.6	259	42.9 ± 13.6	1,441	−0.33 (−0.54; 0.11)	**0.003**
AV peak velocity, cm/s	3.9 ± 0.8	195	4.2 ± 0.6	1,112	−0.41 (−0.68; −0.14)	**0.003**
AV Area, cm^2	0.7 ± 0.23	259	0.7 ± 0.19	1,441	−0.006 (−0.29; 0.28)	0.964
E/A ratio	1.7 ± 1.1	141	0.9 ± 07	930	2.26 (1.3; 4.7)	**<0.001**
E/e' ratio	21.8 ± 11.0	129	17.5 ± 8.6	836	0.48 (0.29; 0.67)	**<0.001**
LVEF, %	53 ± 14	262	58 ± 14	1,470	−0.40 (−0.59; −0.20)	**<0.001**
IVS, mm	14.5 ± 3.3	224	12.9 ± 2.5	1,456	0.67 (0.46; 0.88)	**<0.001**
SVi, mL/m^2	30 ± 10	224	38 ± 15	1,427	−0.52 (−0.68; −0.35)	**<0.001**
LV Mass index, g/m^2	139 ± 42	220	117 ± 33	1,391	0.75 (0.45; 1.05)	**<0.001**
Low voltage, *n* (%)	9 (4.2)	214	52 (4.0)	1,316	1.59 (0.77; 3.27)	0.209
Sokolow-Lyon Index, mV	1.9 ± 0.7	154	2.4 ± 0.9	1,060	−1.3 (−2.02; 0.54)	**0.001**
QRS duration, ms	128 ± 27	184	102 ± 25	1,266	0.36 (0.05; 0.66)	**0.002**
RBBB, *n* (%)	48 (30.0)	160	121 (10.7)	1,134	3.55 (2.32; 5.41)	**<0.001**
NT-proBNP, ng/l	3,338 ± 3,362	160	1,558 ± 2,273	978	0.76 (0.43; 1.09)	**<0.001**
Hs-TnT, ng/l	41.2 ± 34.4	106	23.4 ± 17.8	830	0.93 (0.72; 1.13)	**<0.001**

AS, aortic stenosis; CA, cardiac amyloidosis; BMI, body mass index; CAD, coronary artery disease; D1, high gradient; D2, low-flow, low-gradient with reduced LVEF; D3, low-flow, low-gradient with normal LVEF; AV, aortic valve; LV, left ventricular; LVEF, left ventricular ejection fraction; IVS, interventricular septum; SVi, stroke volume index; RBBB, right bundle branch block; NT-proBNP, N-terminal pro-brain natriuretic peptide; Hs-TnT, high-sensitivity troponin T. statistically significative values (p <0.05) are reported in bold.

those with more than 80 years old (18.2 vs. 7.1%). Among the analyzed demographic and clinical variables, age, male—gender, and BMI were significantly associated with the presence of CA in patients with AS. Cavalcante et al. (6) described that, in a population of 113 patients with severe AS, the prevalence of CA increased from 8 to 25% when only older (≥80 years) and male patients were considered. Thus, we can argue that the more "red flags" are present in a selected population, the higher the CA prevalence will be. In the present systematic review and meta-analyses, by pooling data of 226 patients (6, 7, 13, 15–17, 19, 20, 28–31), we identified the factors associated to CA in patients with AS. We observed that patients with both the CA and AS, together with the described demographic and clinical variables, are characterized by a low-flow low-gradient AS phenotype, worse diastolic LV function, greater LV hypertrophy, higher NT-proBNP and Hs-TnT, and specific ECG features (RBBB, reduced Sokolow–Lyon Index, and increased QRS duration). A recent expert consensus of the European Society of Cardiology (10) suggests that the presence of LV hypertrophy (LV wall thickness ≥12 mm) is sufficient in patients with AS to arise the suspicion of CA and proceed in the diagnostic algorithm based on bone scintigraphy/CMR coupled to assessment for monoclonal proteins. However, in clinical practice the systematic use of bone scintigraphy and/or CMR could not be feasible in all the patients, both for logistic and economic reasons (32). Thus, the identification and validation of "red flags" scores for CA in patients with AS is probably the most important challenge. Nitsche et al. (13) proposed the remodeling, age, injury, systemic, and electrical (RAISE) score to standardize the CA assessment in patients with AS. These authors assigned a different weight to each factor and suggested that patients with a score of >2 points necessitate of further screening by bone scintigraphy and light-chain assessment. Given its impact on AS prognosis, the identification of CA in patients with AS is particularly important. Our results confirm the evidence of previous meta-analyses (8, 9) on the adverse outcome of patients with both the pathologies. We analyzed data from 9 studies (6, 13–17, 19, 25, 31) with an overall population of 1,398 patients, 178 affected by both the AS and CA. At a mean follow-up of 19 months, 245 (21%) and 56 (32%) patients died in the lone AS and CA-AS pooled study groups, respectively. The negative impact of CA on patients with AS was also confirmed when data were adjusted for publication bias. We confirmed that CA is associated to a worse prognosis in patients with AS even after a sensitivity analysis without the study including patients with only a probability of CA, based on echocardiographic strain analysis (19). Interestingly, the

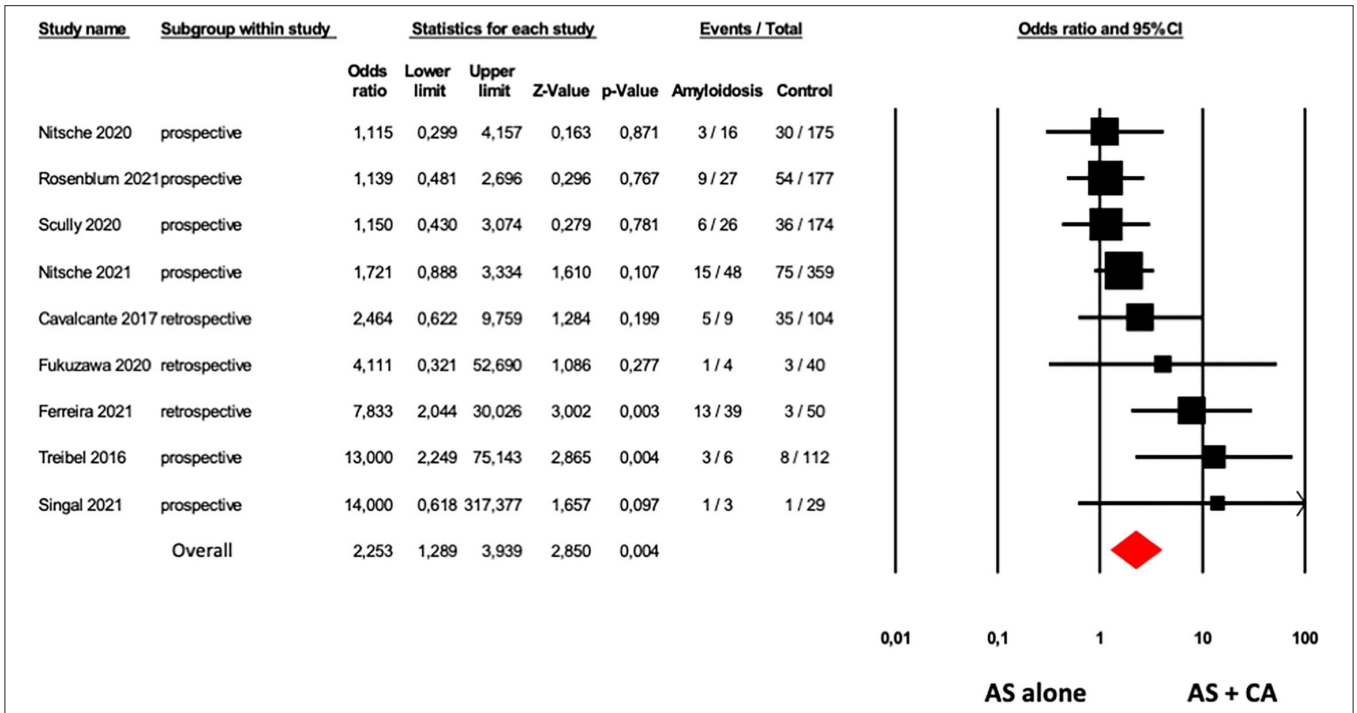

FIGURE 3 | Forest plots of overall mortality in AS patients with and without CA. Overall mortality was evaluated with the difference in Odds Ratio (OR) between AS patients with and without CA. The diamond represents the estimated overall effect, while the squares represent each study with 95%CI.

negative effect of CA on AS outcome appears to be reduced in older subjects, thus suggesting the importance of CA assessment especially in patients with AS younger than 80 years old. On the contrary, the presence of diabetes further increases the mortality risk of patients with both the CA and AS. Although the negative impact of CA on patient's outcome, this study confirms the benefits of aortic valve replacement with respect to medical therapy even in patients with both the diseases. The benefit of aortic valve replacement has been questioned by some authors that, in a small population, reported that patients with CA and AS died at the same rate as those with CA alone, despite some having undergone SAVR (33). On contrast, other authors recently reported that TAVI significantly improves the prognosis of patients with both the AS and CA, with a similar survival rate to patients with AS alone (15, 17).

An important open question is whether CA should be considered an additive factor able to influence the choice of treatment modality (SAVR or TAVI) in a single patient. Conflicting evidence is reported in the literature on possible postprocedural complications in patients with both the CA and AS. Some authors suggest a high risk for TAVI because of operative and postoperative complications, including atrioventricular blocks with need for permanent pacemaker implantation and risk of LV rupture (33–35). Java et al. reported possible complications even after SAVR, such as postoperative tamponade and low-output syndrome (27). In this study, we included 10 studies with an overall population of 120 patients referred to TAVI and 29 patients to SAVR. We compared the outcome of patients undergone TAVI and SAVR and we observed that the two treatments are similar in term of survival benefits. Indeed, as patients with CA are elderly and with more advanced disease, it is plausible that the evaluation of each single case by the heart team frequently favors the choice of TAVI. In the analyzed data, far fewer patients were referred to SAVR (only 29), thus indicating that, in clinical practice, clinicians often prefer TAVI in patients with both the CA and AS. It is important to underline that we could only analyze the differences of the two treatment modalities on mortality, without considering the benefits in terms of symptoms, heart failure progression, and patients' functional capacity recovery, all the items which could make the difference among the two treatment strategies. Finally, further studies are required to establish the benefits of concomitant aortic valve replacement and tafamidis in patients with AS and TTR amyloidosis.

Study Limitations

This study has some potential limitations. In the analyzed publications, the diagnosis of CA was made by different imaging techniques; however, data were confirmed even without studies with uncertain CA diagnoses. Systemic red flags of CA, such as carpal tunnel syndrome, were not included in the analysis due to a lack of relevant data on concomitant carpal tunnel syndrome and CA in patients with AS. In articles evaluating outcomes, also patients with moderate AS were included, leading to an underestimation of overall mortality in particular of patients with AS referred to medical treatment. The small sample size in the

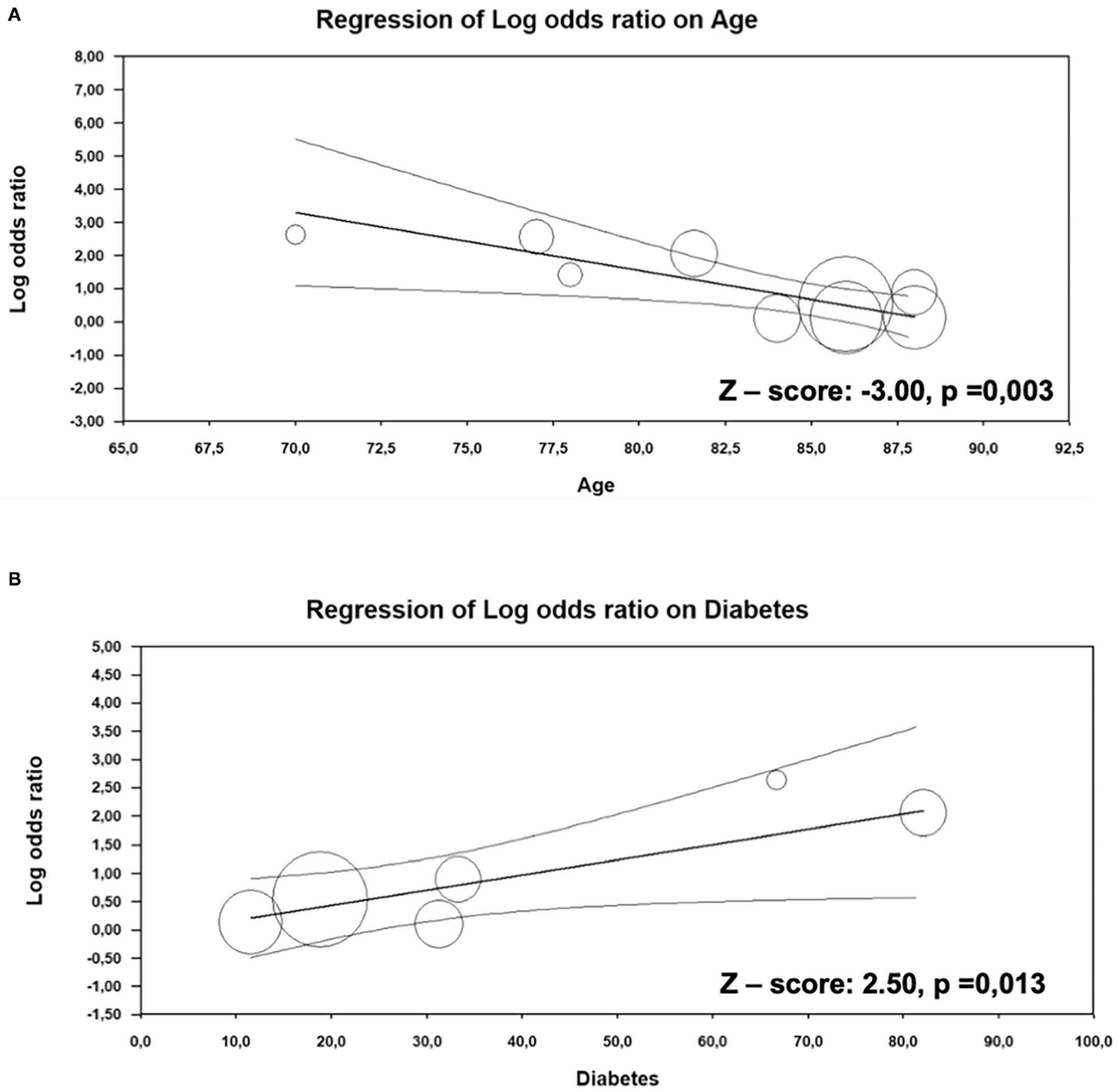

FIGURE 4 | Meta-regression analysis. Impact of age **(A)** and diabetes **(B)** on the difference in overall mortality between AS patients with and without CA.

different treatment strategies could explain the slightly decreased risk of overall mortality of patients with SAVR compared to pharmacologically treated ones. Finally, the results of this study were focused on overall mortality; however, the assessment of cardiovascular mortality, rehospitalization, and functional status could improve our understanding of CA role in AS context.

CONCLUSION

The prevalence of CA in AS is consistent and increases with age. Patients with concomitant CA and AS are characterized by advanced age, male sex, lower BMI, and features of more advanced disease. The presence of CA confers a worse prognosis to patients with AS; however, the benefits of aortic valve replacement remain significant even in presence of both the diseases. Based on the analyzed studies, there is not a treatment of choice between SAVR and TAVI, but due to the low number of patients who undergo SAVR in clinical practice, randomized further studies are required to better define this issue. There are currently no data on the cumulative benefit of aortic valve replacement and tafamidis in patients with concomitant CA and AS.

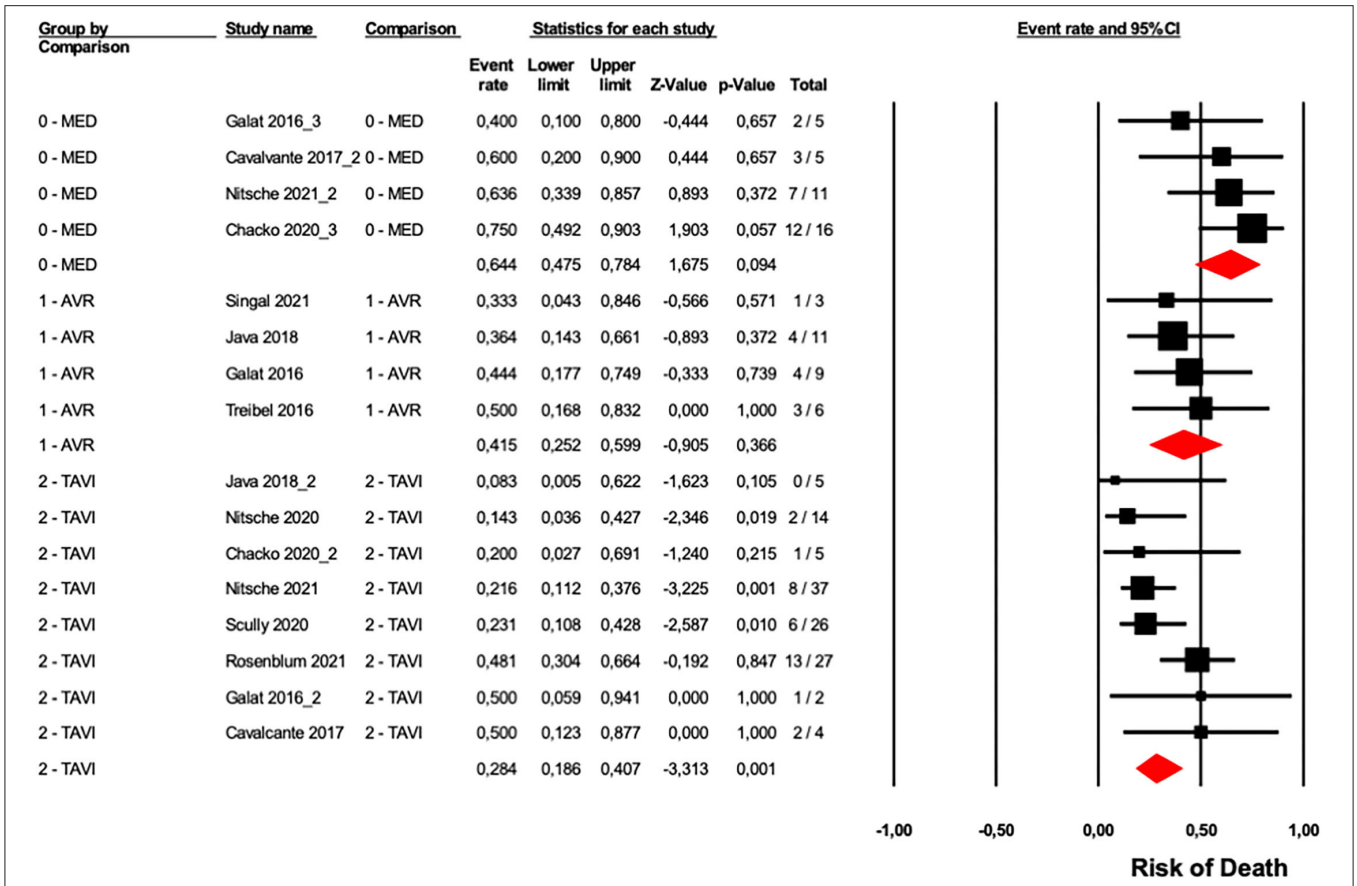

FIGURE 5 | Forest plots of overall mortality in a different type of treatment in AS patients with CA. Overall mortality was evaluated with the difference in event rate between different types of AS patients treatments with and without CA. The diamond represents the estimated overall effect, while the squares represent each study with 95%CI.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

VM and MC conceived of the presented manuscript. VM, PP, and VP analyzed each article and performed the data extraction independently. VV, DM, and IM draft the method and result section with the input of VM and PP. LP and DL draft the introduction and discussion section with the input of MC and VP. All authors discussed the results and contributed to the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.858281/full#supplementary-material

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METHODS
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Assessment of Functioning in Older Adults Hospitalized in Long-Term Care in Portugal: Analysis of a Big Data

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Background: Functioning assessment is a key tool for health professionals to characterize the person's degree of dependence and plan care.

Objectives: The objectives were: (1) know the functioning components of older adults hospitalized in the National Network of Continuous Integrated Health Care (NNCIHC) in Portugal; and (2) compare the conceptual frameworks used in this network with the International Classification of Functioning, Disability and Health (ICF).

Methods: A longitudinal retrospective study is made with 171,414 individuals aged 65 years and over. The Principal Components Analysis (PCA) was realized to reduce the number of variables, previously suggested by a scoping review, about the concepts that characterize the functionality. Then, a consensus meeting was held, where the items were matched with the ICF.

Results: The average age of the sample is 80.17 years old (SD = 7.383), predominantly female (59%), without a spouse (54%), and with <6 years of education (56.4%). Four concepts were grouped: mobility, life daily activities, instrumental activities, and cognitive status that demonstrated good internal consistency. Most items correspond to ICF, except for the item "taking medication."

Conclusion: Theoretical and conceptual similarities support the use of instruments based on the ICF in Portugal's healthcare network. We suggest that ICF also encompasses a specific dimension related to medication management, given its importance for people's health.

Keywords: functioning, older adults, ICF, long-term care, self-care

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INTRODUCTION

The aging of the population poses a growing challenge on a global scale in regard to better respond to the needs of the older adults, particularly in terms of health care. With older age, there is an increased risk of developing chronic and degenerative diseases, which represent more than 50% of the global disease burden, with profound implications for independence and the use of health

care and services (1–3). In addition, death from chronic diseases has been increasing over time, rising from 67% of deaths worldwide in 2010 to 74% in 2019 (1). In Portugal, a recent study with people over 65 years old institutionalized or supported in day centers found that 68.2% had multimorbidity, that is, they suffered from more than one chronic disease (4). A recent study concluded, in a cross-sectional analysis, that people between 60 and 69 years old who suffer from three or more diseases fit into a complex morbidity profile, which over the years refers to those who develop a severe disability in carrying out activities of daily living and have a moderate risk of mortality (5). Moreover, multimorbidity significantly increases the risk of dependence when combined with conditions that affect cognitive and mental status (6, 7).

Thus, it is to be expected that older adults with multimorbidity have a higher risk of becoming dependent. Dependence can be defined as the inability to satisfy one or more needs, essential to the maintenance of life and well-being, without a supplementary or total action on the part of another (8, 9). As such, it is a product of the combination of impairment and need, which means that it is not just a loss of aptitude, faculty, or competence to perform one or more activities. The level of dependence varies, as it incurs the degree and type of disability. It can be permanent or temporary, which means that it can be prevented, reduced, or reversed, if there is an appropriate environment and assistance (10). Dependence is not necessarily restricted to self-care, but it is in this domain that it gains special importance for individuals and is particularly sensitive for health professionals. For the WHO, self-care can be understood as an ability for individuals, families, and communities to promote and maintain health, prevent disease and deal with dependence and disability with or without the support of health professionals (11).

Health-care professionals play a key role in promoting self-care for the person with some degree of dependency. Functioning assessment is a key tool for health professionals to characterize the person's degree of dependence and plan care, being a useful tool for the assessment of health outcomes (12). To this end, the WHO developed the International Classification of Functioning, Disability and Health (ICF) in a more comprehensive attempt to classify health concepts (13, 14). The ICF is a classification system, based on an integrative biopsychosocial health model, addressing functioning and disability (14). The ICF is composed of four constructs: Body Functions (b); Body Structure (s); Activity and Participation (d), and Environmental Factors (e). Each construct of ICF is arranged in a hierarchy (chapter, second, third, and fourth level domains), e.g., Chapter 2: Sensory Functions and Pain (b2); Second level: Seeing Functions (b210); Third level: Quality of vision (b2102); and Fourth level: Color vision (b21021) (14). The ICF is used internationally to describe health and functioning, and some of the health instruments have been mapped (15). Providing care with a high level of excellence is a priority in health systems, for the provision of efficient and effective services that result in ideal results for people, especially for dependent older adults, as they are more exposed to vulnerability (16, 17).

National Network of Continuous Integrated Health Care (NNCIHC)

The increase in situations of dependence in self-care and the need to reduce the length of hospital stay posed new challenges to health teams and families, related to the preparation for discharge. To meet this emerging need, it was created in 2006 in Portugal, the National Network of Continuous Integrated Health Care (NNCIHC) (18). Its mission is to ensure the promotion of the continuity of care in an integrated manner to people in a situation of dependency, at any age, who need continued health care and social support, of a preventive, rehabilitative, or palliative nature, provided through a unit of inpatients or outpatient clinics and hospitals and domiciliary teams, comprising a set of public and private institutions (Decree-Law no. 101/2006, of June 6). This network has a few key characteristics that are important to highlight: (1) have a dual-advice, the Ministry of Health, and the Ministry of Labor and Social Solidarity, combining health care with social care; (2) focuses on dependency and functioning gains; (3) aims at the integration and continuity of care.

These inpatient units constitute three types of networks: Convalescence, Medium Duration and Rehabilitation, and Long-Term and Maintenance. The Convalescent Units have the objective of clinical and functional stabilization, being more advisable for people recovering from an acute process or decompensation of a chronic disease, with great recovery potential with a predictable stay of up to 30 consecutive days. The Medium Duration and Rehabilitation Units are designed for transitory situations, where, for the promotion of rehabilitation, autonomy, and control of the acute or chronic process, there is a need for hospitalization ranging from 30 to 90 days. The Long-Term and Maintenance Units are intended to ensure care that prevents and/or delays the exacerbation of the dependency condition, with a likely hospital stay of more than 90 days. This time frame is extended given that care is envisioned for people with chronic diseases of slow evolution and with a high degree of complexity, which cannot and is not advised to be provided at home (Decree-Law no. 101/2006). Before admission to the Network, people are submitted to a multidisciplinary assessment and, according to their recovery potential, they are placed in a certain Inpatient Unit. Since its creation and up to 2017, an integrated assessment, based on multiple variables, was used to assess the functioning of its users. However, there is a lack of evidence about the concepts that permit to evaluate the functional capacity of older people, subsequently, to understand the correspondence of these items with the domains of the ICF. To improve the evaluation of functionality, the NNCIHC implemented, in February of 2017, a framework for developing instruments: the ICF, to allow for a more rigorous definition of outcome indicators and international comparability. The data presented in the database prior to this date included various variables about the health conditions and level of functionality. Several studies report insufficient information on the performance and results of the NNCIHC in self-care capacity (10, 19, 20) so it is relevant to analyze its impact, until the introduction of a new measurement instrument.

Mobility capacity: walking, the performance of basic life activities and instruments, and cognitive status are equally important dimensions in self-care, in long-term care. Their relationship has been studied, and they are also facilitators or inhibitors of self-care capacity (21). In this way, we can analyze the data carefully, and understand the evolution of the functioning of the inpatients of the NNCIHC in further studies.

In this sense, the objectives of this research were: (1) know the functioning components of older adults hospitalized in the NNCIHC in Portugal; and (2) compare the conceptual frameworks used in this network with the ICF.

MATERIALS AND METHODS

Type of Study and Sample

A longitudinal retrospective study is made with a sample of 171,414 older adults, aged 65 years and over and hospitalized in health units belonging to the NNCIHC. The Long-Term and Maintenance Units were the ones with the most hospitalized people (34.7%; $N = 59{,}516$), followed by the Medium Term and Rehabilitation Units (34.4%; $N = 59{,}013$) and, finally, the Convalescent Units (30.9%; $N = 52{,}885$).

Collect Data/Procedures

After authorization from the National Data Protection Commission and the Ethics Committee, the informatics services of the NNCIHC provided the data without information that would allow the identification of patients. So, data were obtained by analyzing the records of health professionals, mostly nurses, on the portal of the NNCIHC, called Network GestCare, from 2010 to 2017.

After collecting data, we performed the following steps:

1) Analysis of the functioning components of older adults hospitalized in the NNCIHC in Portugal.
2) Compare the conceptual frameworks used in this network with the ICF.

A New ICF-Based Instrument

In the Network GestCare set of information from the electronic health, the record is available, based on several items of validated international scales. The variables present included sociodemographic characteristics, health complaints, nutritional status, falls, mobility, physical autonomy based on Katz Index of Independence in Activities of Daily Living (22), instrumental autonomy on Instrumental Activities of Daily Living (23), emotional complaints and cognitive state, based on the Mini-Mental State Examination (24). The data received from the GestCare Network were the results of the assessment of patients in the units using the ICF-based instrument. This instrument is not validated yet, so we intend to analyze some of its variables and test its reliability.

Data Analysis

Descriptive statistics were used to analyze the sociodemographic characteristics by type of care.

To address objective 1: assess to the variables that characterize the functioning concepts of older adults hospitalized in the national network of integrated continuous health care in Portugal; we conducted the following steps:

(a) Tested the construction of the concepts, a PCA was performed, as it is a multivariate exploratory analysis technique that transforms a set of correlated variables into a smaller set of independent variables. When studying a database with many information and variables, PCA was performed as one of the most common data reduction methods. It is a multivariate exploratory analysis technique that transforms a set of variables correlated with each other into a smaller set of independent variables, with linear combinations of the original variables, called main components (25). We can reduce it to a total of 22 variables (indicators) into 4 variables (concepts), to simplify the process of analysis.
(b) Analyzed the importance of the different variables to the global concept. The Kaiser–Meyer–Olkin (KMO) was analyzed, and an examination of the commonalities (h^2) was performed to identify which variables were more or less important, in terms of the variance explained for the analysis of the components. A value of 0.5 was defined as the acceptable lower limit for the inclusion of variables. Bartlett's test of sphericity presented a $p < 0.001$ in all concepts, so we reject the null hypothesis and conclude that the variables are significantly correlated.
(c) Calculated Cronbach's α to analyze the internal consistency of the items and each of the domains (26). According to Murteira (27), missing's in big data, characterized by their high number of data, are irrelevant, so they were not included in the statistical analysis.

To address objective 2: compare the conceptual frameworks used in this network with the ICF, we conducted the following steps:

Step 1) To match the variables of self-care with the ICF items, the focus group method was used, and an evaluation was performed by experts in the field. The criteria for belonging to the focus group were as follows: experience in functionality assessment and in-depth knowledge of the ICF. The focus group consisted of 5 participants (one physician, two nurses, and two physical therapists) and it was moderated by one of the group's researchers.
Step 2) Analyzed the final concepts and their compatibility to the ICF, as in a previous study (15), the concepts and the relationship to the ICF items were discussed. All had more than 80% agreement, so there was no need to resolve convergences. We have taken the ICF linking rules into consideration in this process (28, 29).

RESULTS

Sociodemographic Characteristics

The sample consisted of 171,414 older adults, with an average age of 80.17 years (SD = 7.383), between 65 and 109 years. Most of the sample is female (59.0%), does not have a spouse, given that 37.2% have the marital status of widowhood, 13.0% are single and 3.8% are divorced/separated and have <6 years of schooling

TABLE 1 | Sociodemographic characterization of the sample ($N = 171,414$).

Sociodemographic variables	Global *n* (%)	Convalescent units *n* (%)	Medium term and rehabilitation units *n* (%)	Long term and maintenance units *n* (%)
Age				
65–74	40,409 (23.6)	15,320 (29.0)	14,498 (24.6)	10,591 (17.8)
75–84	79,899 (46.6)	24,987 (47.2)	28,414 (48.1)	26,498 (44.5)
≥ 85	51,106 (29.6)	12,578 (23.8)	16,101 (27.3)	22,427 (37.7)
Sex				
Female	101,150 (59.0)	32,535 (61.5)	34,215 (58.0)	34,400 (57.8)
Male	70,264 (41.0)	20,350 (38.5)	24,798 (42.0)	25,116 (42.0)
Marital Status				
Single	19,945 (11.6)	6,193 (11.7)	6,332 (10.7)	7,420 (12.5)
Married	70,491 (41.2)	20,883 (39.5)	24,832 (42.1)	24,776 (41.6)
Divorced	5,782 (3.4)	2,018 (3.8)	2,166 (3.7)	1,598 (2.7)
Widow	57,076 (33.3)	17,578 (33.2)	19,510 (33.1)	19,988 (33.6)
Unknown	18,120 (0.2)	109 (0.2)	90 (0.2)	97 (0.2)
Missing	17,824(10.4)	6,104 (11.5)	6,083 (10,3)	5,637 (9.5)
Education (years)				
No education	33,596 (19.6)	8,244 (15.6)	10,933 (18,5)	14,419 (24.2)
1 to 6	51,879 (30.3)	15,802 (29.9)	18,564 (31,5)	17,513 (29.4)
7 to 12	3,395 (2.0)	1,087 (2.1)	1,346 (2,3)	962 (1.6)
≥ 13	3,164 (1.8)	1,047 (20)	1,248 (2,1)	869 (1.5)
Missing	79,380 (46.3)	26,705 (50.5)	26,922 (45.6)	25,753 (43.3)
Portugal Region				
Alentejo	15,165 (8.8)	4,913 (9.3)	4,668 (7.9)	5,584 (9.4)
Algarve	8,937 (5.2)	3,659 (6.9)	2,761 (4.7)	2,517 (4.2)
Center	42,802 (25.0)	11,937 (22.6)	15,233 (25.8)	15,632 (26.3)
Lisbon and Vale do Tejo	45,872 (26.8)	11,362 (21,5)	18,663 (31.6)	15,847 (26.6)
North	49,565 (28.9.5)	18,805 (35.6)	14,778 (25.0)	15,982 (26.9)
Missing	18,146 (5.3)	2,209 (4.2)	2,910 (4.9)	3,954 (6.6)

(56.4%) (**Table 1**). The number of individuals may be smaller in some of the analyzed variables, triggered by the existence of missing's (missing values).

Reliability Analysis

The factors or components of self-care were selected according to the theoretical framework, a scoping review carried out previously (21) and with the objective of the study. These components include (1) mobility: walking; (2) Activities of Daily Living (ADL); (3) Instrumental Activities of Daily Living (IADL); and (4) cognitive state: orientation in time and space. The sample consisted of 159,084 assessments of the health status of the elderly.

The analysis of the commonalities (h^2) is important to identify which variables are more or less important, in terms of the explained variance for the analysis of the components. In view of the literature (26), it was considered that variables with commonality lower than 0.5 have low explanatory power in the variance of the components, being defined as the acceptable lower limit for the inclusion of variables. It was found that the KMO statistic is an indicator of partial correlations between high variables, namely in the concept of basic (KMO = 0.885) and instrumental (KMO = 0.917) activities. The concept related to mobility: walking (KMO = 0.743) and cognitive status (KMO = 0.593) assume lower values, probably due to the smaller number of items, respectively three and two, as shown in **Table 2**. Bartlett's test of sphericity presented a $p < 0.001$ in all concepts, so we concluded that the variables are significantly correlated.

The overall Cronbach's α (for the 22 items) had a value of 0.95, demonstrating excellent internal consistency. Regarding the Cronbach's α of the concepts, the cognitive state had the highest alpha ($\alpha = 0.97$), followed by the concept self-care: basic activities ($\alpha = 0.94$), the concept self-care: instrumental activities ($\alpha = 0.92$), and mobility: walking ($\alpha = 0.89$).

Corresponding ICF Concepts

From the similarity analysis of the concept mapping obtained with the ICF, it is possible to verify that there is a correspondence between the cognitive state: orientation in time and space with the functions of orientation (b114), orientation in relation to time (b1140) and orientation in relation to place (b1141), inserted in the mental functions.

TABLE 2 | Analysis of the main components and the alpha coefficients ($N = 159,084$).

Indicators	Concepts				
	Mobility—walking				
	Component matrix				h^2
Walk in the street	**0.932**				0.869
Use stairs	**0.893**				0.798
Walk at home/inside buildings	**0.895**				0.800
	Activities of daily living (ADL)				
Use toilet, potty and/ or urinal (use, clean up, clothes, flush)		**0.906**			0.822
Lay down/ Get up from the bed (move, transfer, walk)		**0.905**			0.818
Sit down/ get up from chairs (move, transfer, walk)		**0.902**			0.814
Get dressed/take off clothing (choose, prepare, and get dressed)		**0.888**			0.789
Wash up/take a shower (go in/out, be, clean up)		**0.852**			0.725
Control feces		**0.818**			0.668
Control of urine		**0.808**			0.652
Feed/eat (serve, prepare food, eat)		**0.769**			0.592
	Instrumental activities of daily living (IADL)				
Meal preparations		**0.911**			0.880
Laundry		**0.910**			0.920
Housework		**0.909**			0.925
Shop		**0.897**			0.847
Use transports		**0.857**			0.754
Manage money		**0.809**			0.818
Take medication		**0.749**			0.787
Use of telephone		**0.681**			0.785
	Cognitive state—Time and space orientation				
Time and Space Orientation (global assessment)				**0.995**	0.990
Space Orientation				**0.960**	0.921
Time Orientation				**0.970**	0.941
Cronbach's Alpha	0.889	0.938	0.922	0.974	0.951
Kaiser- Meyer-Olkin	0.743	0.885	0.917	0.593	
Bartlett's Test of Sphericity	379,877.629	6,645,154.241	1,457,746.534	3,811,525.473	
	3	28	28	3	
	0.000	0.000	0.000	0.000	

The meaning of bold values is most relevant information in this table.

The concept of mobility, more particularly walking on the street, fits into walking long distances (d501), just as walking on stairs can translate into going up/down (d4551), just as walking at home/inside buildings is similar to walking short distances (d500).

Relatively, the activities of life that involve lying down/getting out of bed and sitting down or getting up from chairs fall under the ICF in changing the basic position of the body (d410). Using the toilet, potty, and/or urinal, as well as controlling the sphincters, its association in the ICF with care related to the excretion processes is suggested (d530). Dressing and undressing with similar semantics fits into dressing (d540), as well as washing/bathing with washing (d510) and eating/eating with eating (d550) and drinking (d650).

Instrumental life activities that include using transport fit in the ICF to the use of transports (d470); using the phone when using communication devices (d3600); housework chores to performing housework chores (d640); make purchases to buy (d6200) or the acquisition of goods and services (d620) and manage money for basic economic transactions (d860). Preparing meals uses exactly the same terminology (d630) as washing clothes (d6400).

More detailed information is shown in **Table 3**.

DISCUSSION

This study has two main objectives, first, we intend to know the functioning components of older adults hospitalized in the

TABLE 3 | Instrument's items x aligned with the corresponding ICF (*International Classification of Functioning, Disability and Health*) concepts.

ICF component	ICF chapter	ICF chapter concepts	Integrated assessment instrument		ICF correspondence
			Concept	Items	
Body functions (B)	B1	Mental functions	Cognitive state - time and space orientation	Time and space orientation (global assessment)	b114 Orientation functions
				Time Orientation	b1140 Orientation to time
				Space Orientation	b1144 Orientation to space
Activities and participation (D)	D4	Mobility	Mobility: walk	Walk in the street	d450 Walking: d4501 walking short or long distances
				Use stairs	d455 Moving around: d4551 Going up and down stairs
				Walk at home/inside buildings	d450 Walking: d4500 Walking short distances
			Instrumental activities	Use transports	d470 Using transportation
			Basic activities	Lay down/ Get up from the bed (move, transfer, walk)	d410 Changing basic body position: d4100 Laying down; d4104 Standing
				Sit down/ get up from chairs (move, transfer, walk)	d410 Changing basic body position: d4103 Sitting; d4104 Standing
	D5	Self-care	Basic activities	Use toilet, potty and/ or urinal (use, clean up, clothes, flush)	d530 Toileting
				Get dressed/take off clothing (choose, prepare and get dressed)	d540 Dressing: d5400 Putting on clothes; d5401 taking off clothes; d5404 Choosing appropriate clothing
				Wash up/take a shower (go in/out, be, clean up)	d510 Washing oneself: d5101 Washing whole body
				Control feces	d530 Toileting: d5301 Regulating defecation
				Control of urine	d530 Toileting: d5300 Regulating urination
				Feed/eat (serve, prepare food, eat)	d550 Eating: d560 Drinking
	D3	Communication		Use of telephone	d360 Using communication devices and techniques: d3600 Using telecommunication devices
	D6	Domestic life	Instrumental activities	Meal preparations	d630 Preparing meals
				Housework	d640 Doing housework
				Laundry	d640 Doing housework: d6400 Washing and drying clothes and garments
				Shop	d620 Acquisition of good and services: d6200 Shopping
	D8	Main life areas		Manage money	d860 Basic economic transactions
				Take medication	

NNCIHC in Portugal; and second, we aimed to compare the conceptual frameworks used in this network with ICF.

Regarding the sociodemographic profile, older adults between 65 and 74 years were hospitalized in greater numbers in Convalescence Units (29.0%) and less in Long-Term Units (17.8%). Older people (85 or over) were the most frequent in Long-Term and Maintenance Units (37.7%). While, in the Medium Duration and Rehabilitation groups, individuals aged between 75 and 84 years predominated (48.1%). Fluctuations in the three typologies were little accentuated in marital status, highlighting the absence of a spouse/sentimental partner. There was a great predominance of widowed and single/divorced women, with a greater number of married men. Older adults who did not attend school (42.7%) were more concentrated in Long-Term and Maintenance Units, probably related to the older age of people.

Integrated Assessment Instrument and ICF Concepts

The principal components that described the functional capacity, used by health professionals from the NNCIHC, had excellent internal consistency. In the matrix of components, most of the very high correlation coefficients (> 0.8) are detected, which reinforces the results found for the sphericity test and the KMO measure.

So, regarding our second goal, it was possible to obtain correspondence with the ICF in almost all items present in the Integrated Assessment Instrument, with the exception of the item "Taking medications," as this concept is not in the ICF. However, we can fit it into the Self-Care dimension of the ICF. The item "Maintaining one's health," according to the ICF, refers to caring for oneself by doing what is required to look after one's health (11). We consider that taking medication is an activity that is

related to taking care of one's own health. Although it does not specify the taking of the medication, it is the category where the item "Taking medications" best fits. However, the definition of the concept itself does not clearly address medication management. Furthermore, we consider that this activity is extremely relevant for the maintenance of health, especially in the management of one or more chronic diseases, and should be considered as a unique dimension of self-care. A scoping review that evaluated interventions to improve self-care in patients with a chronic condition reported that maintenance behaviors focused primarily on physical activity (70%), food intake (59%), and medication intake (52%). However, monitoring of medication intake was rarely included (9%) and was mainly done in studies with patients with heart failure (15%) and asthma (20%) (30).

Components of Self-Care

This study highlighted self-care as the main aspect of functioning that affects the lives of older adults. As reflected in the results, we developed concepts of functioning, which in turn interfere with self-care: mobility; basic activities; instrumental activities; and cognitive status. Self-care can be considered a broad concept that encompasses the other concepts (31), so there is a need for a systematic assessment of geriatric conditions (32). There are several factors that can influence self-care, such as taking sedative or psychotropic medications, cognitive impairment, depression, and a history of falling (33, 34). In this study, patients hospitalized in the NNCIHC present changes in self-care due to impairments in functioning caused either by disorders or temporary loss of function due to a specific situation, such as a fall.

The changes in self-care are related to the following disease-related factors, reported by Palmer (35) multimorbidity (difficulty in integrating self-care in all conditions); and life events that interact with the disease to interfere with healthy behavior. In the case of our sample, life events are diverse: dependence on life activities, need for teaching the person/informal caregiver, rehabilitation, post-surgical care, and pressure ulcers. It is also highlighted as a reason for hospitalization, the management of the caregiver's therapeutic regimen and rest, with the need for continuous integrated care.

The care models should describe more specific individual levels of activities and processes (36). A recent literature review defines a self-care model that encompasses functioning components related to body functions, cognition, and emotional functions, highlighting the importance of self-management of life activities (37).

Self-Care and the Person-Centered Care

Since people have specific individual and environmental characteristics, more and more person-centered care should be chosen in the healthcare units (38).

Person-centered care has increasingly demonstrated effectiveness in health outcomes, and functioning assessment is the key to promote self-care, as it allows for the assessment of the evolution of functional status and planning of care accordingly. Studies demonstrate the importance of person-centered care in increasing the activation of hospitalized older adults, enhancing their capacity for selfcare (30).

To implement person-centered care, we consider that there are other concepts that should be introduced in the evaluation of the functioning of older adults admitted to the NNCIHC, such as communication and environmental factors, such as support from networks (family, friends, other providers), given their interference in self-care. The Elderly Nursing Core Set (ENCS) is a recently constructed and validated instrument for the Portuguese population, which is already being used in research studies (4, 39) and addresses the concepts: self-care, learning, and mental functions, communication and social relationships. It was built using the ICF concepts and some of them coincide with those presented here. It is, however, organized differently and considers a fundamental concept, the environmental factors, which are not used in the NNCIHC. Several studies have emphasized the importance of environmental factors, such as social support. For example, in the USA, there are Acute Care Units for the Older Adults (ACE) which are based on a person-centered care model that objectives to prevent the loss of independence of the patient. In these units, functional status is assessed on admission and throughout hospitalization, considering the same domains: ADL, mobility, mood/affect, cognition, living situation, social support, and nutritional status (35). In a study developed with seniors over the age of 80, the results suggest that affectionate relationships are necessary for maximal adaptation in old age (40). Besides that, several studies have found that social support can have a significant positive effect on recovery from surgery, total mortality rates, healthcare utilization, depression, teenage pregnancy, and several other conditions. Most of these studies highlight the ability of social support to moderate or buffer the impact of psychosocial stress on physical and mental health (41, 42).

Limitations

As limitations to this study, we highlight the fact that we only have data until 2017. As of the year 2018, the data in the Integrated Continuous Health Care Network in Portugal have changed and it is for this reason that we only have data up to 2017.

CONCLUSION

Theoretical and conceptual similarities support the use of instruments based on the ICF in Portugal's national integrated continuing health care network. The mobility concepts: walking; life activities; instrumental activities and cognitive status: orientation in time and space, similarly to the ICF, contribute to measuring and understanding people's health status, self-care capacity, and functioning, particularly in the context of long-term care (43–46). We suggest that ICF also encompasses a specific dimension related to medication management, given its importance for people's health.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Scientific Research in the Areas of Human Health and Welfare of the University of Évora (report number 17036 and date of approval April 26, 2017). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AR contributed to conceptualization. AR, CF, RB, and LP contributed to methodology. AR and RB contributed to formal analysis and software. CF, ML, and AH contributed to validation, writing, reviewing, and editing. CF and ML contributed to investigation, project administration, and funding acquisition. AR and LP contributed to writing original draft preparation and resources. RB contributed to data curation. All authors have read and agreed to the published version of the manuscript.

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BRIEF RESEARCH REPORT
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Psychotropic Medication Use Is Associated With Greater 1-Year Incidence of Dementia After COVID-19 Hospitalization

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Background: COVID-19 has been associated with an increased risk of incident dementia (post-COVID dementia). Establishing additional risk markers may help identify at-risk individuals and guide clinical decision-making.

Methods: We investigated pre-COVID psychotropic medication use (exposure) and 1-year incidence of dementia (outcome) in 1,755 patients (≥65 years) hospitalized with COVID-19. Logistic regression models were used to examine the association, adjusting for demographic and clinical variables. For further confirmation, we applied the Least Absolute Shrinkage and Selection Operator (LASSO) regression and a machine learning (Random Forest) algorithm.

Results: One-year incidence rate of post-COVID dementia was 12.7% ($N = 223$). Pre-COVID psychotropic medications (OR = 2.7, 95% CI: 1.8–4.0, $P < 0.001$) and delirium (OR = 3.0, 95% CI: 1.9–4.6, $P < 0.001$) were significantly associated with greater 1-year incidence of post-COVID dementia. The association between psychotropic medications and incident dementia remained robust when the analysis was restricted to the 423 patients with at least one documented neurological or psychiatric diagnosis at the time of COVID-19 admission (OR = 3.09, 95% CI: 1.5–6.6, $P = 0.002$). Across different drug classes, antipsychotics (OR = 2.8, 95% CI: 1.7–4.4, $P < 0.001$) and mood stabilizers/anticonvulsants (OR = 2.4, 95% CI: 1.39–4.02, $P = 0.001$) displayed the greatest association with post-COVID dementia. The association of psychotropic medication with dementia was further confirmed with Random Forest and LASSO analysis.

Conclusion: Confirming prior studies we observed a high dementia incidence in older patients after COVID-19 hospitalization. Pre-COVID psychotropic medications were associated with higher risk of incident dementia. Psychotropic medications may be risk markers that signify neuropsychiatric symptoms during prodromal dementia, and not mutually exclusive, contribute to post-COVID dementia.

Keywords: COVID-19, dementia, cognitive impairment, post-COVID, psychotropic medication, geriatric

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INTRODUCTION

Emerging literature suggests that neurological and psychiatric disorders are common complications of Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection (1, 2). COVID-19 has also been associated with an increased risk of incident dementia (post-COVID dementia) (3–5). Taquet et al. found that the 6-month post-COVID dementia incidence was 2-fold higher than the incidence following influenza (4). As typical in dementia syndromes, this risk was predominantly seen in older adults and appeared to be correlated with disease severity, as those requiring hospitalization for COVID-19 had higher rates of subsequent dementia (4, 5).

Identification of risk markers associated with post-COVID dementia is important to guide clinical decision-making as well as future research on preventative measures in at-risk individuals. Recent large studies using electronic health record (EHR) data have investigated the interplay of psychiatric illness and COVID-19. Their findings indicate that not only does COVID-19 have profound mental health sequelae for those previously healthy, but pre-existing psychiatric illness was associated with worse short-term outcomes including mortality (6, 7). Yet, these studies did not evaluate the use of pre-COVID psychotropic medications.

In non-COVID studies there is conflicting evidence regarding the association between psychotropic medications and dementia risk (8–11). Interestingly, several COVID-related studies have even reported potentially beneficial effects of psychotropic medications (e.g., antidepressants) in preventing SARS-CoV-2 infection, severe illness, and mortality (12–14). Given that psychotropic medications are broadly prescribed among older adults (15–17) and their use is potentially modifiable, the role of psychotropic medications in incident post-COVID dementia requires systematic investigation.

In this article, we leveraged EHR data of 1,755 older adults (≥65 years) hospitalized for COVID-19 to: (1) determine the 1-year incidence rate of post-COVID dementia; (2) assess the association between pre-COVID psychotropic medication use and post-COVID incident dementia; and (3) explore the association between different classes and types of psychotropic medications and post-COVID incident dementia.

METHODS

Study Design and Population

This retrospective cohort study was performed within Northwell Health, a large integrated academic health system in the greater New York metropolitan area, and conducted following the statement of Standard Reporting of Observational Studies in Epidemiology (STROBE) (18) (**Supplementary Table 1**). The study protocol was approved by the local Institutional Review Board.

Demographic and clinical data was extracted from the EHR by the data management team. We included adults aged 65 years or older, who were hospitalized in one of 11 health system hospitals between March 1st, 2020 and April 20th, 2020, with a positive SARS-CoV-2 test result (19). Index COVID-19 hospitalization was defined as the first admission with a SARS-CoV-2 infection confirmed by a positive reverse-transcriptase–polymerase-chain-reaction (RTPCR) test in nasopharyngeal specimens. Inclusion for this study required that patients were discharged alive after their index admission and had at least one follow-up visit within the health system (outpatient, inpatient, or emergency department) by April 20th, 2021. Patients were excluded if they had a previous diagnosis of dementia or cognitive impairment [International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) codes starting with F01, F02, F03, F04, F09, G30, G31, G32, and R41] prior to the index admission or if they were prescribed a medication used for dementia (**Supplementary Table 2**; **Figure 1**).

Outcome Variable

The primary outcome was 1-year incident dementia, defined as either of the following: (1) any new diagnosis of dementia or cognitive impairment (ICD-10 codes starting with F01, F02, F03, F04, F05, F09, G30, G31, G32, and R41) that was recorded in the EHR during any follow-up visit until April 20th, 2021; and/or (2) a new prescription for medications used for dementia (**Supplementary Table 2**). One-year incidence of post-COVID dementia was compared between patients with documented use of at least one psychotropic medication prior to the index COVID-19 hospitalization (pre-COVID) vs. patients without pre-COVID psychotropic medication use (defined below).

Psychotropic Medication Use, Demographic and Clinical Variables

Pre-COVID psychotropic medication use was defined as any documented prescription before the index COVID-19 hospitalization (**Supplementary Table 2**). The list included antipsychotics, antidepressants, anticonvulsants and mood stabilizers (including lithium), benzodiazepines, and antiparkinson medications. We extracted pre-COVID psychotropic "home medications" as recorded in the "admission medication reconciliation" document, as well as those prescribed within the first 24 h of the index admission. During the initial pandemic peak, home medications were often entered directly into the hospital orders rather than being reconciled separately in the appropriate location. The "home medications" filled at registered pharmacies in New York were automatically populated into the EHR leading to comprehensive documentation. Based on the guiding pharmacological principles of treating delirium in acutely medically ill (20), new psychotropic medications were not initiated as standing medication to treat delirium in the first 24 h. Psychotropic medications ordered "as needed" (i.e., pro re nata) for behavioral symptoms during index admission were excluded. Neurological and psychiatric diagnoses (ICD-10 F codes and G codes, I6x, and R56) were extracted from "past medical history" of index admission.

Demographic variables included age, sex, chart documented race (Asian, Black, White, "other or unknown"), and ethnicity (Hispanic or Other). Patient characteristics included dichotomized smoking history ("current or formal smoker" or "never smoker"); body mass index (BMI), which was calculated from weight and height, using the formula BMI

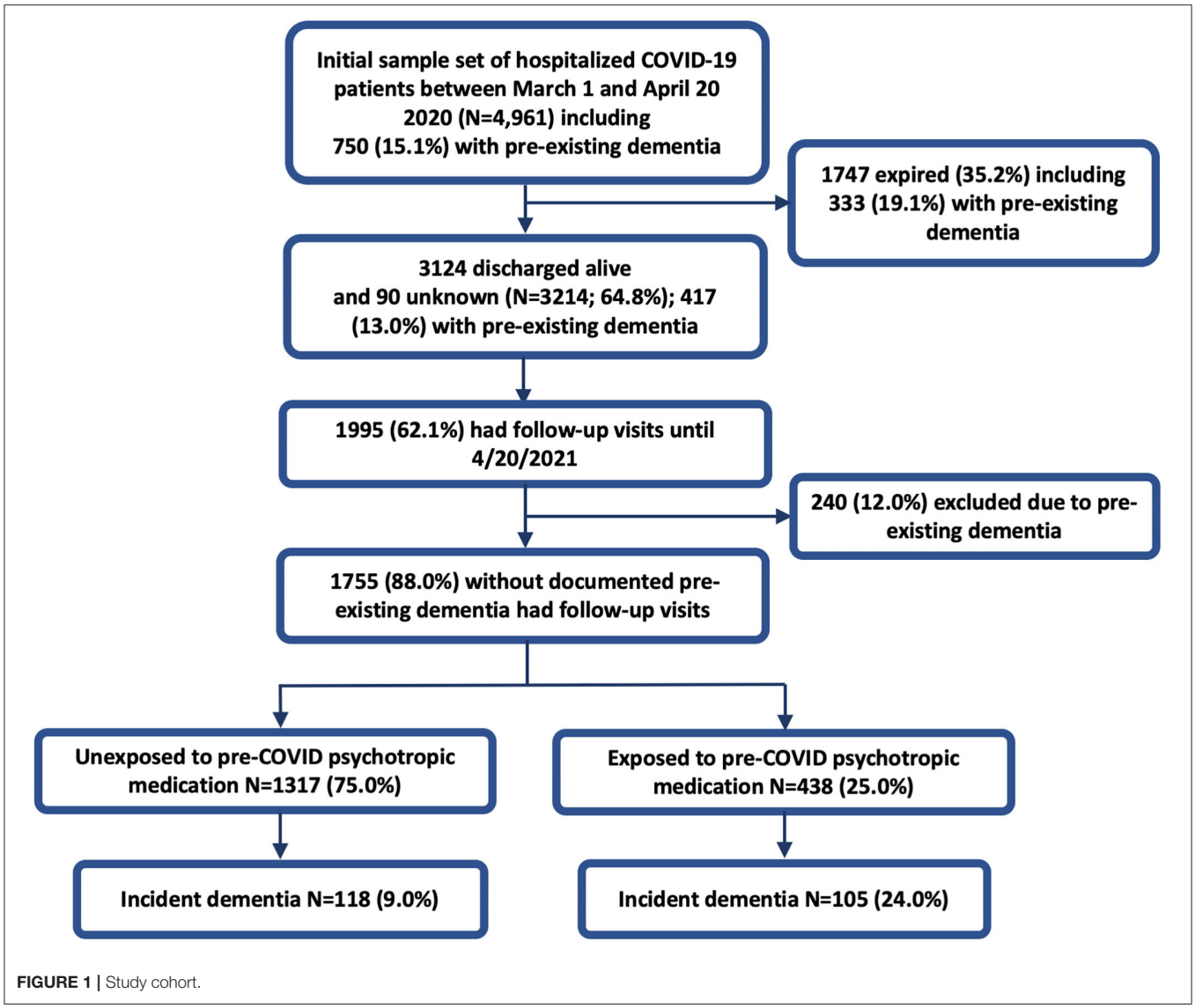

FIGURE 1 | Study cohort.

= weight (kg)/height (m)^2; and comorbidity index, which was derived using the Charlson Comorbidity Index without the age component of the score (21, 22). BMI < 14 (below one percentile of our data; $N = 20$) was regarded as missing, due to likely data input errors. Clinical variables representing severity of the acute COVID-19 illness included the Modified Early Warning Score (MEWS) (23) at the time of admission and highest level of oxygen requirement during index hospitalization. The MEWS is an objective score designed to assess severity of illness (23). The highest level of oxygen support during the index COVID-19 admission were collapsed into three categories (in increasing order of severity): "0" for room air or nasal cannula; "1" for Venturi Mask, non-rebreather, high flow, and non-invasive positive-pressure ventilation; "2" for invasive mechanical ventilation. Delirium during the index COVID-19 hospitalization was defined as ICD10 code F05.

Statistical Analysis

We applied several types of analyses to investigate the association between predictor variables and post-COVID incident dementia. First, unadjusted analyses included Fisher's exact or Chi-square tests for categorical factors as well as *t*-test or its non-parametric version (Wilcoxon test), if needed, for continuous variables. Second, multivariable (multiple) logistic regression with corresponding variable selection was utilized. Multivariable logistic regression was also performed in the subgroup including only patients with at least one documented history of neurological or psychiatric diagnosis. For Cox proportional hazard ratio model, we calculated time-to-event (days) based on time point of index COVID-19 admission, time point of first dementia diagnosis and time point of last follow-up visit without a dementia diagnosis. Two additional methods were applied to confirm the robustness of multiple regression

results. First, we applied a machine learning algorithm—random forest (RF) (24) to identify the importance of the predictor variables for outcome prediction (25). RF has been frequently used in EHR data due to its robustness to noise, such as collinearity, in high dimensional data (26, 27). Next, we applied Least Absolute Shrinkage and Selection Operator (LASSO) regression to minimize overfitting of variables (28) (**Supplementary Material**). Using these performance-based methods to evaluate input variables can be considered as an alternative to the *p*-values in a regression model (29). Lastly, in secondary exploratory analyses, we evaluated associations between individual psychotropic medications and post-COVID dementia using univariable Fisher's exact test.

All statistical analyses were carried out on the R platform (version 4.0.3) (30) (https://www.r-project.org). The R statistical packages used for this study include glmnet package for LASSO, randomForest package for RF and imputation for missing values, and tableone (31) for presentation. A power analysis for testing the association of an individual medication with the outcome was performed using two-sample test for proportions with unequal sample sizes and implemented in pwr package (32).

RESULTS

Incidence of Post-COVID Dementia and Unadjusted Analysis

Of the 4,961 older adults hospitalized with COVID-19 between March 1st, 2020 to April 20th, 2020 that were previously reported (19), 1,755 patients (mean age 75.3 years) without pre-COVID dementia had at least one follow-up visit in Northwell within 1-year following the index COVID-19 admission (**Figure 1**; **Table 1**). A total of 223 (12.7%) patients developed incident dementia within 1-year follow-up. Of the 438 (25.0%) patients exposed to at least one pre-COVID psychotropic medication, 105 (24.0%) developed dementia, compared to 118 (9.0%) of the 1,317 patients without the exposure (OR = 3.20, 95% CI: 2.37-−4.32, Fisher's exact $P = 1.19 \times 10^{-14}$) who developed dementia. Among the psychotropic medication users, 121 were on antipsychotics, 244 on antidepressants, 110 on benzodiazepines, 95 on mood stabilizers or anticonvulsants, and 46 on antiparkinson medications. Univariable analysis (**Table 1**) demonstrated that age, BMI, Comorbidity Index, delirium during index COVID-19 admission, prior use of antipsychotics, antidepressants, benzodiazepines and mood stabilizers/anticonvulsants, were significantly associated with a higher risk of incident post-COVID dementia.

Multiple Regression Analysis

We applied three multiple regression models. **Model 1** examined the relationship between "any psychotropic medication" use and post-COVID dementia, adjusting for age, gender, race, ethnicity, BMI, smoking history, Comorbidity Index, MEWS, highest level of oxygen requirement, and delirium. Pre-COVID use of any psychotropic medication was significantly associated with post-COVID dementia (OR = 2.68, 95% CI: 1.79–4.01, $P < 0.001$) (**Table 2**, Model 1). Model 2 examined the association of each class of psychotropic medications (i.e., antipsychotics, antidepressants, mood stabilizers/anticonvulsants, benzodiazepines, and antiparkinson medications listed in **Supplementary Table 2**), adjusting for all variables in Model 1, except for "any psychotropic medication." After adjusting, antipsychotics and mood stabilizers/anticonvulsants remained significant (**Table 2**, Model 2). Model 3 included all variables that were significant at $P \leq 0.05$ in Model 2. In Model 3 (**Table 2**), antipsychotic medications (OR = 2.75, 95% CI: 1.69–4.38, $P < 0.001$) and mood stabilizers/anticonvulsants (OR = 2.39, 95% CI: 1.39–4.02, $P = 0.001$) were associated with a more than 2-fold increased risk of incident post-COVID dementia. Additionally, delirium during the index COVID-19 admission was associated with a 2-fold increased risk of incident post-COVID dementia (OR = 2.36, 95% CI: 1.65–3.35, $P < 0.001$). Model 3 also demonstrated that each additional year of age was associated with a 5% increase of post-COVID dementia (OR = 1.05, 95% CI: 1.03-−1.07, $P < 0.001$) and each unit increase of the comorbidity index was associated with a 6% increased risk of post-COVID dementia (OR = 1.07, 95% CI: 1.02–1.12, $P = 0.009$). On the other hand, each unit increase of BMI was associated with a 4% decreased risk of post-COVID dementia (OR = 0.96, 95% CI: 0.93-−0.99, $P = 0.003$) (**Table 2**). Furthermore, we analyzed hazard ratios (HR) for incident dementia using days between the index COVID-19 hospitalization and dementia diagnosis for the variables in Model 1 and Model 2 (**Supplementary Table 3**). The results of HRs are comparable with the ORs.

We further performed a sensitivity analysis in the subset of 423 patients who had at least one neurological and psychiatric diagnosis that were documented during the index COVID-19 hospitalization, adjusting for all variables in **Model 1**. Pre-COVID psychotropic medication use remained significantly associated with post-COVID dementia (OR = 3.09, 95% CI: 1.52–6.57, $P = 0.002$; **Supplementary Table 4**).

Secondary Unadjusted Analyses

In exploratory secondary unadjusted analyses, we examined the unadjusted association between individual psychotropic medications and post-COVID dementia (see sample size power analysis in **Supplementary Figure 1**). Among the top 20 most frequently prescribed medications in our cohort, valproic acid (OR = 11.57, 95% CI: 3.59-−38.18, $P < 0.001$), haloperidol (OR = 8.44, 95% CI: 3.19–21.83, $P < 0.001$), mirtazapine (OR = 6.02, 95% CI: 3.12-−11.34, $P < 0.001$), levetiracetam (OR = 5.91, 95% CI: 3.17-−10.80, $P < 0.001$), clonazepam (OR = 3.97, 95% CI: 1.58-−9.16, $P = 0.002$), quetiapine (OR = 3.9, 95% CI: 1.64-−8.61, $P = 0.001$), and escitalopram (OR = 3.49, 95% CI: 1.54-−7.33, $P = 0.002$) were significantly associated with increased risk for post-COVID dementia (at Bonferroni corrected *P*-value threshold of <0.0025) (**Table 3**).

The lack of association of post-COVID dementia with COVID-19 severity, as measured by MEWS and highest level of oxygen delivery, is counterintuitive. We therefore asked whether MEWS/oxygen delivery (e.g., information on COVID-19 severity) is to a certain extent included in the delirium variable. In unadjusted analysis, MEWS were associated with delirium (OR = 1.19, $P = 0.004$), but this association could be explained by

TABLE 1 | Patient demographics and characteristics stratified by post-COVID incident dementia (unadjusted).

Variable	Level	No incident dementia	Incident dementia	*P*-value	Missing (%)
N		1,532	223		
Sex (%)	F	669 (43.7)	103 (46.2)	0.53	0
	M	863 (56.3)	120 (53.8)		
Age [mean (SD)]		74.85 (7.46)	78.40 (8.02)	<0.001	0
Race (%)	Asian	103 (6.7)	13 (5.8)	0.05	0
	Black	389 (25.4)	43 (19.3)		
	Other or unknown	362 (23.6)	47 (21.1)		
	White	678 (44.3)	120 (53.8)		
Ethnicity (%)	Hispanic	237 (16.2)	27 (12.6)	0.2	4.6
	Non-hispanic	1,222 (83.8)	188 (87.4)		
Smoking (%)	No	1,408 (93.9)	196 (92.9)	0.69	2.5
	Yes	92 (6.1)	15 (7.1)		
BMI [mean (SD)]		27.61 (5.94)	25.47 (6.05)	<0.001	4.1
Comorbidity index [mean (SD)]		3.25 (2.85)	4.12 (3.00)	<0.001	0.1
MEWS [mean (SD)]		3.48 (1.16)	3.63 (1.30)	0.13	18.9
Highest oxygen delivery (%)	0	1,068 (69.7)	162 (72.6)	0.01	0
	1	319 (20.8)	34 (15.2)		
	2	145 (9.5)	27 (12.1)		
Delirium (%)	No	1,351 (88.2)	151 (67.7)	<0.001	0
	Yes	181 (11.8)	72 (32.3)		
Antipsychotic (%)	No	1,449 (94.6)	185 (83.0)	<0.001	0
	Yes	83 (5.4)	38 (17.0)		
Antidepressant (%)	No	1,345 (87.8)	166 (74.4)	<0.001	0
	Yes	187 (12.2)	57 (25.6)		
Benzodiazepine (%)	No	1,444 (94.3)	201 (90.1)	0.03	0
	Yes	88 (5.7)	22 (9.9)		
Mood stabilizer/ anticonvulsant (%)	No	1,468 (95.8)	192 (86.1)	<0.001	0
	Yes	64 (4.2)	31 (13.9)		
Antiparkinson (%)	No	1,496 (97.7)	213 (95.5)	0.1	0
	Yes	36 (2.3)	10 (4.5)		
Any psychotropic (%)	No	1,199 (78.3)	118 (52.9)	<0.001	0
	Yes	333 (21.7)	105 (47.1)		

Ethnicity, Hispanic or not-Hispanic; Smoking, "No" is defined as never smoker and "Yes" as current or past smoker; BMI, body mass index; Comorbidity Index, Charlson Comorbidity Index without the age component; MEWS, Modified Early Warning Score. Highest Oxygen Delivery: the highest level of oxygen support during index hospitalization. "0": room air or nasal cannula; "1": Venturi Mask, non-rebreather, high flow, non-invasive positive-pressure ventilation; "2": invasive mechanical ventilation. Any Psychotropic: medications including all subcategories of psychotropic medications: antipsychotics, antidepressants, benzodiazepines, mood stabilizers/anticonvulsants (including lithium), and Parkinson's disease medications (Antiparkinson).

age (OR = 1.09, $P = 0.24$ after adjusting for age). Levels of oxygen support was not associated delirium (OR = 1.14, $P = 0.20$) in unadjusted analysis.

From all patients who did not expire during the index hospitalization ($N = 3{,}214$), 1995 (62.1%) had available 1-year follow-up data within our health system. We compared the demographic and clinical variables between those with and without follow-ups (potentially seeking care elsewhere; **Supplementary Table 5**). Among relevant features for post-COVID dementia, significantly higher comorbidity index (3.46 vs. 2.61, $P < 0.001$), higher BMI (27.65 vs. 26.81, $P = 0.005$), as well as higher proportion of exposure to "Any Psychotropic" (30.9 vs. 25.4%, $P = 0.001$) were observed in those with follow-ups. However, antipsychotic medications (8.8 vs. 8.4%, $P = 0.74$) and mood stabilizers/anticonvulsants (6.0 vs. 4.8%, $P = 0.15$), the two classes highly associated with post-COVID dementia, did not differ significantly between the two groups.

Random Forest (RF) Analyses and LASSO Regression

Next, we applied RF to determine the importance of predictor variables in Model 2, in predicting post-COVID dementia. Using the parameters optimized for unequal sample sizes, the RF model had an out-of-bag (OOB) error rate of 25.41%. The importance of a variable for the prediction

TABLE 2 | Multivariable logistic regression for variables associated with 1-year incident dementia in older adults hospitalized with COVID-19 (n = 1,755).

	Model 1			Model 2			Model 3		
Predictors	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Age	1.03	1.00 – 1.06	**0.04**	1.04	1.01 – 1.07	**0.01**	1.05	1.03 – 1.07	**<0.001**
Sex (ref = "female")	0.84	0.57 – 1.24	0.37	0.83	0.56 – 1.22	0.34	___	___	___
Race, Asian (ref = "white")	1.09	0.47 – 2.29	0.83	1.07	0.46 – 2.24	0.87	___	___	___
Race, Black (ref = "white")	0.68	0.40 – 1.12	0.14	0.66	0.39 – 1.10	0.12	___	___	___
Race, other/unknown (ref = "white")	1.17	0.61 – 2.18	0.63	1.19	0.62 – 2.24	0.59	___	___	___
Ethnicity (ref = "hispanic")	1.13	0.57 – 2.31	0.74	1.1	0.55 – 2.25	0.80	___	___	___
Smoking	0.86	0.39 – 1.73	0.69	0.88	0.40 – 1.78	0.74	___	___	___
BMI	0.96	0.93 – 1.00	**0.04**	0.96	0.93 – 1.00	**0.04**	0.96	0.93 – 0.99	**0.003**
Comorbidity index	1.07	1.00 – 1.14	0.06	1.07	1.00 – 1.14	**0.04**	1.07	1.02 – 1.12	**0.009**
Delirium	3.01	1.94 – 4.63	**<0.001**	2.78	1.77 – 4.32	**<0.001**	2.36	1.65 – 3.35	**<0.001**
MEWS	0.99	0.82 – 1.19	0.92	1	0.82 – 1.19	0.97	___	___	___
Highest oxygen delivery	1.18	0.88 – 1.57	0.27	1.19	0.88 – 1.58	0.25	___	___	___
Any psychotropic	2.68	1.79 – 4.01	**<0.001**	___	___	___	___	___	___
Antipsychotic	___	___	___	2.27	1.20 – 4.19	**0.01**	2.75	1.69 – 4.38	**<0.001**
Mood stabilizer/ anticonvulsant	___	___	___	2.48	1.25 – 4.72	**0.007**	2.39	1.39 – 4.02	**0.001**
Antidepressant	___	___	___	1.59	0.97 – 2.53	0.06	___	___	___
Benzodiazepine	___	___	___	1.36	0.66 – 2.64	0.39	___	___	___
Antiparkinson	___	___	___	1.36	0.47 – 3.38	0.54	___	___	___

OR, odds ratio; For binary variables Smoking, Delirium, Any Psychotropic, Antipsychotic, Mood Stabilizer/Anticonvulsant, Antidepressant, Benzodiazepine, and Antiparkinson, the reference values were "No" or "not exposed." Ethnicity, Hispanic or not-Hispanic; Smoking, never smoker or current/past smoker; BMI, body mass index; Comorbidity Index, Charlson Comorbity Index; MEWS, Modified Early Warning Score. Highest Oxygen Delivery: Highest level of oxygen support during index hospitalization; Any Psychotropic: medications including all subcategories of psychotropic medications: antipsychotics, antidepressants, benzodiazepines, mood stabilizers/anticonvulsants (including lithium), and Parkinson's disease medications (Antiparkinson). Significant P values are in bold.

accuracy is measured by "Mean Decrease Accuracy," which represents how much predictive accuracy is lost if a variable is removed from the model. A higher importance score indicates that the variable is more useful for the prediction of incident post-COVID dementia. The model identified the following as the most relevant predictors of incident post-COVID dementia (in declining order of importance): delirium, antipsychotics, mood stabilizers/anticonvulsants, Comorbidity Index, benzodiazepines, and antidepressants (**Supplementary Figure 2**).

Finally, we applied LASSO regression, which addresses the possibility of overfitting and collinearity of variables. Using the variables in Model 2 the LASSO coefficient profile (**Supplementary Figure 3**) showed that the predictor variables selected (in declining order) were: delirium, age, antipsychotics, mood stabilizers/anticonvulsants, antidepressants, BMI, and Comorbidity Index. Thus, results from analyses that are less sensitive to collinearity are consistent with our standard regression analysis above and increase confidence in the statistical model.

DISCUSSION

In this retrospective cohort study of 1,755 older adults hospitalized with COVID-19, the overall 1-year incidence rate of dementia was 12.7%. Pre-COVID psychotropic medication use was associated with higher 1-year incidence of dementia, after controlling for patient demographics, characteristics, and severity of acute COVID-19 illness. To our knowledge, this is the first study to systematically demonstrate an association between pre-COVID psychotropic medications and post-COVID dementia. While recent literature has reported an association between pre-COVID psychiatric illness and post-COVID dementia (6, 7), the use of psychotropic medications until now has been unexplored. Yet, it has been suggested that pre-COVID psychotropic medication use in itself may modulate vulnerability to COVID-19 (33), thereby highlighting the importance of this investigation.

The mechanisms that underlie the observed association between psychotropic medications and post-COVID incident dementia are unknown. It is intuitive that psychotropic medications indicate pre-existing neuropsychiatric conditions in which COVID-19 occurs. It is possible that psychotropic medications may potentiate the neurostructural changes that have been found in the brain of those who have recovered from COVID-19 (34). Our sensitivity analysis in patients with documented neurological and psychiatric diagnoses supports this interpretation. Not mutually exclusive, COVID-19 may have accelerated the underlying brain disorders for which psychotropic medications were prescribed, leading to the greater incidence of post-COVID dementia. In general, severe infections requiring hospitalization had been associated with increased long-term risk of all-cause dementia (35). In pre-COVID literature, the association between psychiatric illness and

TABLE 3 | Association of individual psychotropic medications with post-COVID dementia.

Medication	Counts	Odds ratio	95% CI	*P*
Levetiracetam	57	**5.91**	**3.17 – 10.80**	**<0.001**
Mirtazapine	51	**6.02**	**3.12 – 11.34**	**<0.001**
Sertraline	51	2.48	1.08 – 5.19	0.02
Alprazolam	46	0.97	0.25 – 2.74	1
Escitalopram	43	**3.49**	**1.54 – 7.33**	**0.002**
Quetiapine	36	**3.9**	**1.64 – 8.61**	**0.001**
Carbidopa-Levodopa	35	3.51	1.41 – 7.96	0.004
Clonazepam	32	**3.97**	**1.58 – 9.16**	**0.002**
Trazodone	28	2.77	0.90 – 7.22	0.04
Olanzapine	25	3.2	1.03 – 8.55	0.02
Haloperidol	22	**8.44**	**3.19 – 21.83**	**<0.001**
Risperidone	22	2.98	0.85 – 8.63	0.04
Duloxetine	21	2.39	0.58 – 7.49	0.12
Lorazepam	21	3.17	0.89 – 9.266	0.04
Paroxetine	18	2.03	0.37 – 7.33	0.22
Bupropion	16	3.38	0.78 – 11.38	0.05
Citalopram	16	1.45	0.17 – 6.44	0.65
Valproic acid	15	**11.57**	**3.59 – 38.18**	**<0.001**
Aripiprazole	14	2.77	0.49 – 10.68	0.13
Fluoxetine	13	1.85	0.20 – 8.61	0.33

Counts: number of patients taking the medication. Bonferroni corrected P-value significance threshold is 0.0025 for 20 univariable associations (Fisher's exact test). Significant P values are in bold.

dementia has been described (11, 36–39). Several hypotheses have been proposed to explain this relationship, including that psychiatric disorders may: share a common pathology with dementia, signify prodromal dementia, or may be an independent risk factor for dementia (36, 40, 41). Further studies are critical to evaluate whether psychotropic medications may serve as a modifiable risk factor for post-COVID dementia.

Within the psychotropic medication classes studied, we found that antipsychotics and anticonvulsants/mood stabilizers were associated with a greater risk of post-COVID dementia. Their relative importance as predictors for post-COVID dementia in this cohort was also highlighted by our machine learning model and LASSO regression analysis. A previous study reported that exposure to antipsychotics in very-late onset schizophrenia-like psychosis was associated with increased dementia risk (38). In contrast, another study showed that antipsychotics were associated with a lower risk of dementia among schizophrenia patients (11). Our results add to these reports regarding associations between antipsychotic use and dementia risk in psychotic disorders. Furthermore, our finding on anticonvulsants and mood stabilizers are consistent with previous literature reporting that regular use of anticonvulsants was associated with a significantly greater risk of incident dementia (42).

In order to gain a deeper understanding of the individual medications that could drive the association signals, we performed explorative analysis on the association of commonly used psychotropic medications (16, 43, 44) with incident post-COVID dementia. We found that valproic acid and haloperidol had the largest effect sizes. Interestingly, valproic acid was associated with an increased risk of dementia in patients with bipolar disorder in a previous non-COVID study (45) and the authors speculated that reduced brain-derived neurotrophic factor expression in the hippocampus lead to less cell proliferation and inhibition of neurite outgrowth (45). To our knowledge, haloperidol use has not been individually linked with increased long-term risk of non-COVID dementia (11, 38). Notably, typical antipsychotics may have an inhibitory effect on SARS-CoV-2 (46), and haloperidol has been previously reported to reduce tau phosphorylation, a hall mark of Alzheimer's dementia, in a mouse model (47). Furthermore, while antidepressants as a class were not associated with post-COVID dementia in our study, the potential effects of two commonly prescribed antidepressants in older adults (16, 48)—mirtazapine and escitalopram—warrant further investigation.

Another new and important finding from our study was the high 1-year incident rate (12.7%) of post-COVID dementia. Al-Aly et al. (5) and Taquet et al. (4) reported a 0.95 and 2.7% 6-month incidence rate of dementia, respectively. However, there are several key differences between these studies and ours: (1) their cohorts included all patients with and without hospitalization, unlike the hospitalized 65+ cohort in our study; (2) the follow-up period was only 6 months, as opposed to 1-year; and (3) they only considered new diagnoses while our study also included new prescriptions of cognitive enhancers such as donepezil as a proxy for new onset of cognitive impairment. In the article by Taquet et al. (4), the 6-month dementia incidence rate for hospitalized patients across all ages was 1.46%, which was 2.2-fold of the incidence (0.67%) for the whole cohort the regardless of hospitalization or age. The authors further reported a 2.66% incidence for patients over the age of 65 regardless of hospitalization, which was 4-fold of the rate for the whole cohort (0.67%). Although the dementia incidence for patients who were both over 65 and hospitalized were not specifically reported, one might extrapolate that it would be around 6% ($0.67\% \times 4 \times 2.2$) at 6-month, assuming the risk increase is linear. Given the doubled follow-up time in our study, the dementia incidences observed in our study are not inconsistent with their report. The differences in study design likely accounted for the differences of incidence rates but also highlight the importance of focusing on at-risk population.

In our study, the prevalence of pre-existing dementia was 15.1% among all 4,961 COVID-19 hospitalizations, 19.1% among those who expired, and 12.0% among those who had follow-ups. Reynish et al. (49) reported a 13.9% prevalence for dementia or cognitive impairment among people aged 65+ with an emergency medical admission (9.4% known dementia and 4.5% unspecified cognitive impairment). Bellelli et al. (50), employing a formal cognitive assessment, identified a dementia prevalence of 24% in patients aged 65+ in acute hospitals across Italy. The patients in their study were on average older than the patients in our study. The lower dementia prevalence in our follow-up study likely resulted from a combination of factors: (1) survival bias—dementia is associated with the higher

COVID-19 mortality (51); (2) age differences; (3) a lack of formal cognitive assessment, which may lead to underestimation of pre-existing cognitive impairment. Moreover, among the patients without pre-existing dementia, the prevalence of antipsychotic medication use was 6.9%. This is higher than those previously reported prevalence of 2–3% among older adults (52, 53). A possible explanation could be that people with severe mental illness have multifold higher odds of hospitalization related to COVID-19 (54).

With regard to other variables found to be associated with post-COVID dementia, we confirmed the previously reported association between delirium and post-COVID dementia (4, 5). In agreement with literature on non-COVID dementia (55), we found that older age was associated with higher incidence of post-COVID dementia. Of interest, COVID-19 severity, as indicated by MEWS and oxygen delivery, was not associated with post-COVID dementia. This might be due to a potential survival bias, as all patients in our study were older and hospitalized (indicating severe COVID-19) and many older adults with severe COVID-19 did not survive their index admissions. Among survivors of COVID-19 hospitalization, MEWS had a weak unadjusted correlation with delirium that could be explained by age and oxygen delivery was not correlated with delirium.

We furthermore investigated the study's validity by comparing the features between patients who had followed up within our healthy system (thus included) and those who did not. While pre-COVID psychotropic exposure was higher among the included subjects, the difference was driven by higher number of antidepressant users, while no significant differences were observed for antipsychotics and anticonvulsants/mood stabilizers—the two drug classes associated with a greater risk of post-COVID dementia.

This study has several strengths. First, we focus on older patients hospitalized with COVID-19, a cohort that appears to be the most vulnerable for the development of post-COVID dementia. Second, our cohort included a diverse patient population with a longer follow-up period then previously reported. Third, our data set included clinically rich variables that underwent vigorous process of data harmonization–ensuring that the data fields represent clinically relevant information. Fourth, we were able to increase the sensitivity of post-COVID dementia detection by not only using documented ICD-10 codes, but also newly started dementia medications. Fifth, our statistical model included not only patient demographics but also a comorbidity score as well as markers of COVID-19 illness severity (MEWS and level of oxygen delivery). Sixth, due to the large sample size, our study was able to systematically investigate different classes of psychotropic medications. Lastly, the robustness of our results was demonstrated by using different statistical methods, including machine learning (Random Forest) and LASSO, which allowed for controlling for overfitting.

This study also has several limitations. First, due to incomplete integration of psychiatric diagnoses in the accessible EHR, a common impediment of EHR studies (56), our study could not comprehensively delineate whether the psychotropic medications or the pre-existing neurological and psychiatric illnesses predicted post-COVID dementia. To infer a causal effect of psychotropic medication use on post-COVID dementia, future studies with comprehensive integration of psychiatric diagnoses are necessary. Second, the method of identifying dementia (EHR documentation and medications) was not amenable to validation given the lack of formal cognitive assessments and could lead to underestimation of pre-existing cognitive impairment. Third, even though the patients were admitted to 11 different hospitals, it still reflects a single health system, which may limit generalizability. Fourth, the associations of individual medications with post-COVID dementia should be interpreted with caution, as the sample sizes did not permit adjustments for covariables. Fifth, no information on lifestyle and economic factors were included, which may influence medication prescription. Lastly, it is also possible that some cases of newly diagnosed dementia could have included long-COVID syndrome, for which cognitive impairment could be part of the clinical presentation (57).

CONCLUSION

In this cohort study of older adults hospitalized with COVID-19 at a large health system in New York, exposure to pre-COVID psychotropic medications was associated with greater 1-year incidence of post-COVID dementia. Psychotropic medications may contribute to post-COVID dementia, and not mutually exclusive, serve as a risk marker that signifies neuropsychiatric conditions during prodromal dementia, which was accelerated by COVID-19.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

YF-H, AM, and LS conceived the study, designed the study, and authored the manuscript. YL and MQ performed data extraction. YF-H and WL conducted the analysis. AM, MC, BG, JMK, MD, EB, and JK contributed to data interpretation, discussion, and manuscript preparation. 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/fmed.2022.841326/full#supplementary-material

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Gender Differences in Levodopa Pharmacokinetics in Levodopa-Naïve Patients With Parkinson's Disease

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Background: Levodopa (LD) is the most effective drug in the treatment of Parkinson's disease (PD). Unfortunately, prolonged use of LD leads to complications, mainly motor/non-motor fluctuations (MNMF) and dyskinesias (DYS). Women seem more prone to develop such LD-related complications. Nonetheless, there is a paucity of prospective studies examining gender-related predictors of MNMF and DYS. Among several factors, which concur with a very complex scenario, changes in LD pharmacokinetics influence the drug's effectiveness. The present study aimed to assess gender-related differences in LD pharmacokinetics in patients with PD at their first-ever intake of LD.

Materials and Methods: This is a multicentric study enrolling patients with PD, who were LD-naïve and received a single dose of LD/benserazide (100/25 mg) formulation. All participants gave their written informed consent, and the study was approved by the local Ethics Committees. To measure plasma LD concentrations and pharmacokinetic parameters (AUC, Cmax, Tmax, $t_{1/2}$), fasting blood samples were collected before drug intake and then at 8-time points until 260 min. LD concentrations were measured by ultra-high-performance liquid chromatography coupled with mass spectrometry (UHPLC-MS). Multiple linear regression analyses were performed to identify the predictors of the parameters.

Results: Thirty-five patients (16 women and 19 men) were consecutively enrolled. Area under curve (AUC) and maximum plasma concentration (Cmax) were significantly higher in women than men ($p = 0.0006$ and $p = 0.0014$, respectively). No statistically significant difference was found regarding Tmax and $t_{1/2}$. Multiple linear regression analyses revealed that female sex (β = 1.559116, 95% CI 0.8314479 2.286785; $p < 0.0001$) and body mass index (BMI) (β = −0.0970631, 95% CI −0.1733004 −0.0208258; $p = 0.014$) significantly predicted AUC. Only female sex significantly predicted Cmax (β = 1,582.499, 95% CI 731.581 2,433.417; $p = 0.001$). Moreover, only BMI significantly

predicted $t_{1/2}$ (β = 0.0756267, 95% CI 0.0143407 0.1369126; p = 0.017). Stratifying by gender, BMI was confirmed to significantly predict $t_{1/2}$ in women (β = 0.1300486, 95% CI 0.0172322 0.242865; p = 0.027), but not in men.

Conclusion: This study provides novel insights on gender differences in LD pharmacokinetics, possibly contributing to the later development of motor complications and dyskinesia in PD.

Keywords: gender, Parkinson's disease, levodopa, pharmacokinetics, motor/non-motor fluctuations, dyskinesia, body weight, body mass index

INTRODUCTION

Levodopa (LD), combined with dopa-decarboxylase inhibitors (DDCI) carbidopa or benserazide, remains the gold standard of therapy in Parkinson's disease (PD) since the 1970s (1).

In the early stages of the disease, LD/DDCI formulations are well tolerated and are so effective in controlling the main PD-associated symptoms with a favorable benefit-to-risk ratio that the expression "honeymoon period" is commonly used (2).

Unfortunately, prolonged use of LD leads to complications, mainly motor/non-motor fluctuations (MNMF) and dyskinesia (DYS), which are among the most important determinants of patients' disability (3).

Since plasma LD concentrations are strongly linked with drug effects, it is important to better investigate the LD pharmacokinetics (PK) to improve the drug efficacy and safety (4). In particular, increased LD absorption during chronic administration may contribute to the wearing-off phenomenon (5). Moreover, the risk for developing DYS is related to the patients' drug exposure and is reported to rise mostly at LD dosages greater than 4 mg/kg (6).

Moreover, the occurrence of LD-related complications is dependent on several other factors, including age at onset, disease duration and severity, the length of treatment, body weight (BW), and not the least, gender. The latter is one of the most important factors since women are more prone to develop LD-related complications compared with men (7). Women show higher LD bioavailability than men as assessed by higher values of the AUC and maximum plasma concentration (Cmax) (8, 9).

Nonetheless, there is a dearth of prospective studies examining the relationship between adverse events and LD PK. Moreover, no previous study has investigated factors possibly influencing plasma LD concentrations and PK parameters in female and male patients with PD assuming LD for the first time.

In this paper, we aim to present baseline gender differences in plasma LD concentrations and PK parameters in LD-naïve patients with PD enrolled in a 2-year multicentric prospective study, which was designed to assess predictors of the development of NMMF and DYS according to gender.

MATERIALS AND METHODS

The present investigation is part of a 2-year Italian multicentric study aimed to investigate gender-related predictors of the development of MNMF and DYS in patients who are LD-naïve. The study was approved by the Ethics Committees of the participating centers (n.4_r.p.s.o./2019 for the

TABLE 1 | Clinical characteristics of the study population.

	Men (n = 19)	Women (n = 16)	P-value
Age (years)	61 (±8.7)	62 (±11.8)	NS
BW median value (Kg)	80	70	0.0228
BMI median value (Kg/m^2)	26	26	NS
Duration of the disease (months)	34 (±28.5)	59 (±24.5)	NS
Daily energy consumption (Kcal)	1798.688 (±381)	1330.875 (±319)	0.0069
Lean mass (Kg)	62.737 (±12.5)	46.7 (±4.3)	0.0021
Fat mass (Kg)	20.125 (±16.3)	25.3 (±9)	NS
Motor symptoms:			
Bradykinesia	16 (100%)	14 (100%)	NS
Rigidity	16 (100%)	13 (92,8%)	NS
Tremor	15 (93,75%)	13 (92,8%)	NS
Postural instability	1 (6,25%)	1 (7,14%)	NS
Antiparkinsonian drugs use:			
DA	12 (63,1%)	6 (37,5%)	NS
iMAO-B	11 (58%)	6 (37,5%)	NS
DA and iMAO-B	9 (47,3%)	5 (31,2%)	NS
No DA and iMAO-B	5 (26,3%)	9 (56%)	NS
Comorbidities:			
Arterial hypertension	7 (43%)	7 (50%)	NS
Hypercholesterolemia	2 (12,5%)	4 (28,6%)	NS
Chronic gastritis	2 (12,5%)	2 (14,2%)	NS
Type II diabetes	2 (12,5%)	0 (0%)	NS

Except for body weight (BW) and body mass index (BMI), the values are expressed as mean and standard deviation (SD) or number and percentage of patients.
Abbreviations: BW, body weight; BMI, body mass index; DA, dopamine agonists; iMAO-B, monoamine oxidase-B inhibitors.

Abbreviations: LD, levodopa; DDCI, dopa-decarboxylase inhibitors; PD, Parkinson's disease; MNMF, motor/non-motor fluctuations; DYS, dyskinesias; PK, pharmacokinetics; BW, body weight; AUC, area under the curve; Cmax, maximum plasma concentration; MDS, Movement Disorder Society; EDTA-2Na, ethylenediaminetetracetic acid disodium; UHPLC-MS, ultra-high performance liquid chromatography coupled with mass; TFA, trifluoroacetic acid; HFBA, heptafluorobutyric acid; ISTD, internal standard; PFP, pentafluorophenyl; Tmax, time to reach Cmax; $t_{1/2}$, half-life; AUCw, AUC adjusted for body weight; Cmax/w, Cmax adjusted for body weight; BMI, body mass index; iMAO-B, monoamine oxidase-B inhibitors; DA, dopamine agonists; COMT, catechol-*O*-methyltransferase.

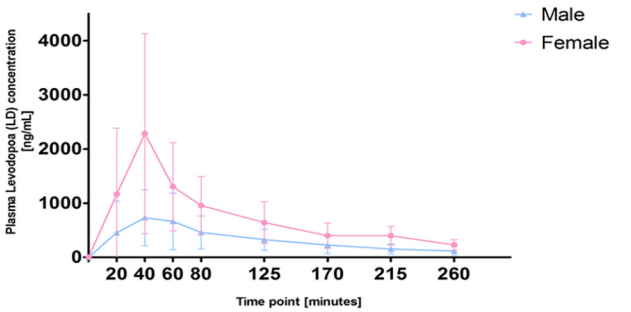

FIGURE 1 | Differences in plasma levodopa (LD) concentrations between men and women.

Coordinating Center of Salerno). All participants gave their informed consent.

Thirty-five patients with PD, diagnosed using MDS clinical diagnostic criteria (10), were consecutively enrolled at the Center for Neurodegenerative Diseases (CEMAND), Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana," University of Salerno-Italy; Movement Disorders Centre, Hermitage-Capodimonte, Naples; Dipartimento "G.F. Ingrassia," Neuroscience Unit- University of Catania-Italy; I.R.C.C.S.- "Istituto di Scienze Neurologiche and DIBINEM"- "Alma Mater Studiorum"–University of Bologna-Italy. The questionnaire for eating habits "Grana Padano nutritional observatory" was administered (11).

All patients were LD-naïve and received a single dose of LD/benserazide (100/25 mg) formulation.

Pharmacokinetics of Levodopa

Pharmacokinetic analysis was centralized at the Clinical Pharmacology Unit, University Hospital of Salerno.

Samples of venous blood were collected in EDTA-2Na, in fasting condition, through an indwelling catheter before and 20, 40, 60, 80, 125, 170, 215, and 260 min after drug intake.

Plasma was obtained by centrifugation (3,000 *g* for 10 min) and stored in new EDTA-2Na vacutainers at −80°C until further analysis.

The LD concentrations were measured by UHPLC-MS after protein precipitation of plasma samples, using a mixture composed of 10% TFA/1% HFBA. An appropriate volume of internal standard (ISTD) was added to the precipitation mixture at a final concentration of 2.5 μg/ml. LD was extracted from 50 μL of plasma and added to 150 μL of precipitation mixture containing ISTD. After first centrifugation (16,000 × *g*, 10 min, 4°C; 5415R Sigma-Aldrich), 150 μL of supernatants were recovered and centrifuged for other 5 min at the same speed, and 100 μL of clear supernatants were transferred to clean glass vials. The analysis was carried out on a Thermo Scientific TSQ Endura triple quadrupole mass spectrometer coupled to a Dionex UltiMate 3000 UHPLC system (Thermo Fisher Scientific, Milan, Italy) equipped with a Kinetex PFP column (50 × 2.1 mm: 2.6 μm particle size) (Phenomenex, Torrance, CA, United States). LD elution was obtained by using a two-component mobile phase,

TABLE 2 | Plasma levodopa (LD) concentrations and pharmacokinetics (PK) parameters, unadjusted and adjusted by body weight, measured in men and women.

Plasma LD concentration measured at each time point (ng/mL)				Plasma LD concentration measured at each time point corrected by BW (ng/mL)/w			
Time (min.)	**M**	**W**	***P*-value**	**Time (min.)**	**M**	**W**	***P*-value**
20	454.1053 ± 5583.694	1168.42 ± 11220.535	0.0313	20	5.936316 ± 0.93631635	18.14667 ± 819.6273	0.0189
40	732.1368 ± 32.136835	2284.08 ± 1846.953	0.0014	40	9.411579 ± 0.6.893599	34.02933 ± 426.90424	0.0005
60	662.7263 ± 62.726324	1305.037 ± 305.03724	0.0080	60	8.817368 ± 0.8.099045	19.63 ± 912.91515	0.0049
80	459.0368 ± 59.036815	957.55 ± 57.556815	0.0016	80	5.974211 ± 0.4.441285	14.315 ± 48.191977	0.0005
125	324.9421 ± 24.942177	640.9813 ± 4385.7052	0.0035	125	4.402105 ± 0.3.1499	9.516875 ± 0.5.957967	0.0027
170	228.0568 ± 2159.6823	400.2706 ± 00.270623	0.0134	170	3.094211 ± 0.2.54934	5.9375 ± 0.3.454692	0.0085
215	153.3053 ± 53.305392	398.5067 ± 98.506792	0.0000	215	2.066842 ± 0.1.515395	5.848 ± 2.600281	0.0000
260	115.5556 ± 15.555628	229.1933 ± 296.75774	0.0008	260	1.572222 ± 0.1.235321	3.414 ± 0.1.520925	0.0006
PK parameters				**PK parameters corrected by BW**			
AUC mcg*h/mL	1.126805 ± 0.126805et	2.583994 ± 0.51.49891	0.0006	AUC/w (mcg*h/mL)/w	0.0147789 ± 0.00996	0.0387062 ± 0.0.02404	0.0385
Cmax ng/mL	909.8947 ± 09.89474 4	2405.094 ± 405.09447	0.0014	Cmax/w (ng/mL)/w	12.15474 ± 2.15474	36.31375 ± 6.31375w	0.0004
Tmax min.	45.26316 ± 5.26316w	46.25 ± 6.25316w	NS				
$t_{1/2}$ hours	1.533158 ± 0.0.534977	1.494375 ± 0.1.237298	NS				

Values are expressed as mean ± SD.

Abbreviations: LD, levodopa; BW, body weight; PK, pharmacokinetics; AUC, area under the curve; Cmax, maximum plasma concentration; Tmax, time to reach Cmax; $t_{1/2}$, half-life; AUCw, AUC adjusted for body weight; Cmax/w, Cmax adjusted for body weight.

consisting of a solution (A) of 0.1% formic acid in water and (B) of 0.1% formic acid in acetonitrile used in a gradient mode (from 0 to 30% of B in 2 min). Then, the column was washed for 1 min at 70% of B and restored to the initial condition for column equilibration. The total runtime was 4.5 min. The flow rate was 0.4 ml/min and the column temperature was set at +20°C. The injection volume was 5 μL and all samples were analyzed in triplicates. The limit of detection and the limit of quantification of the analysis was 50 and 125 ng/ml, respectively.

The PK parameters, AUC, Cmax, time to reach Cmax (Tmax), and half-life ($t_{1/2}$) were calculated using the R 3.5.1 version (12) and Prism 8.0.1 version (GraphPad Software, Inc., La Jolla, CA, United States) considering a non-compartmental study model.

The AUC and Cmax values were also adjusted for BW and referred to as AUCw and Cmax/w.

STATISTICAL ANALYSIS

To determine PK parameters, analysis of variance (ANOVA) with Tukey's or Dunnett's multiple comparisons test was employed.

To test the correlation between variables, we performed several linear regression analyses. AUC, Cmax, Tmax, and $t_{1/2}$ were sequentially used as dependent variables, while age, sex, and alternatively BW or BMI were introduced as independent variables.

All values were expressed as mean and standard deviation (SD). A $p < 0.05$ was considered statistically significant. Statistical analysis was performed using STATA 16 version.

RESULTS

The LD concentrations were measured in plasma from 35 Caucasian patients (19 men and 16 women) with PD. All of them were LD-naïve patients and received a single dose of oral LD/benserazide (100/25 mg) formulation.

The study population appeared to be homogenous for the age and duration of the disease. No differences were found in BMI median value between men and women, while women had a median value of BW lower than men. Daily energy consumption and lean mass were higher in men than in women, while women showed higher fat mass compared with men without reaching a statistical significance. There was no difference in PD symptoms, monoamine oxidase-B inhibitors (iMAO-B), dopamine agonists (DA) use, and comorbidities between genders. The main characteristics of the study population are listed in **Table 1**. No differences were found in dietary habits (data not shown).

The differences in plasma LD concentrations between men and women over time are shown in **Figure 1**. The mean values measured in men and women at each time point (20–260 min) and PK parameters are reported in **Table 2**.

As shown in **Figure 2**, women showed plasma LD concentrations, unadjusted (panel A) and adjusted for BW (panel B), higher than men at each time point.

The AUC (**Figure 3A**) and AUCw (**Figure 4A**) were higher in women than in men ($p < 0.0006$ and $p < 0.0004$, respectively). As

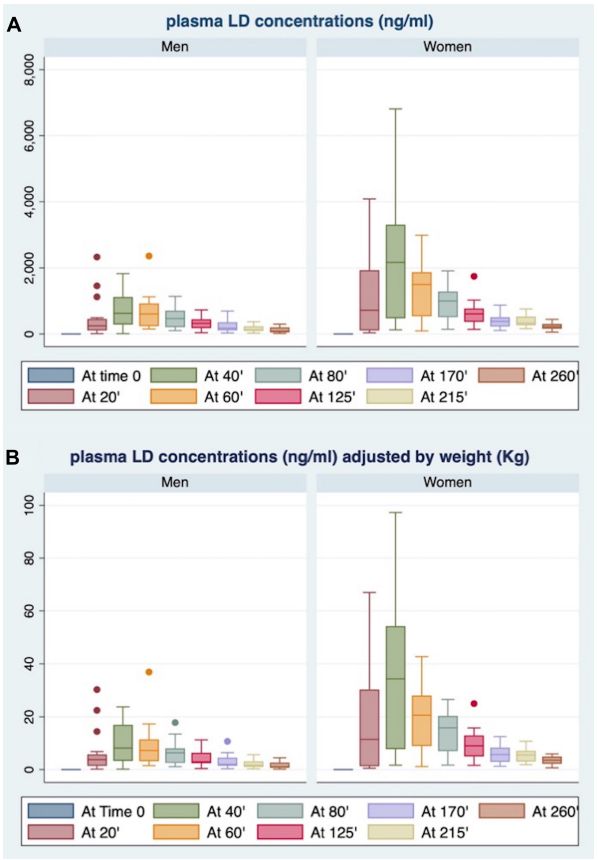

FIGURE 2 | Gender differences in plasma LD concentrations at each time point, unadjusted **(A)** and adjusted for body weight (BW) **(B)**.

shown in **Figures 3B**, **4B**, women also revealed higher Cmax and Cmax/w when compared with men ($p < 0.0014$ and $p < 0.0004$, respectively). Conversely, there were no statistically significant differences in Tmax and $t_{1/2}$ (**Figures 3C,D**).

By stratifying the study population according to median BW (i.e., 73 Kg) or BMI (i.e., 26) values, women showed higher plasma LD concentrations compared with men (**Figure 5**). Notably, BMI median value was 26 for both men and women. The most relevant differences emerged by comparison between men and women with BMI of <26 (**Figure 5C**).

Table 3 reports the differences in plasma LD concentrations, measured at each time point (20–260 min), and PK parameters between men and women stratified by BMI median value. Women with BMI < 26 showed plasma LD concentrations significantly higher than men with BMI of <26. Considering BMI of ≥26, women demonstrated higher LD concentrations as compared with men in the range of 20–60 min after LD administration without reaching a statistical significance. By contrast, the concentration levels measured in the range of 80–260 min were significantly higher in women as compared with men (**Table 3**).

The AUC and Cmax were significantly higher in women than in men irrespective of BMI stratification (**Table 3** and

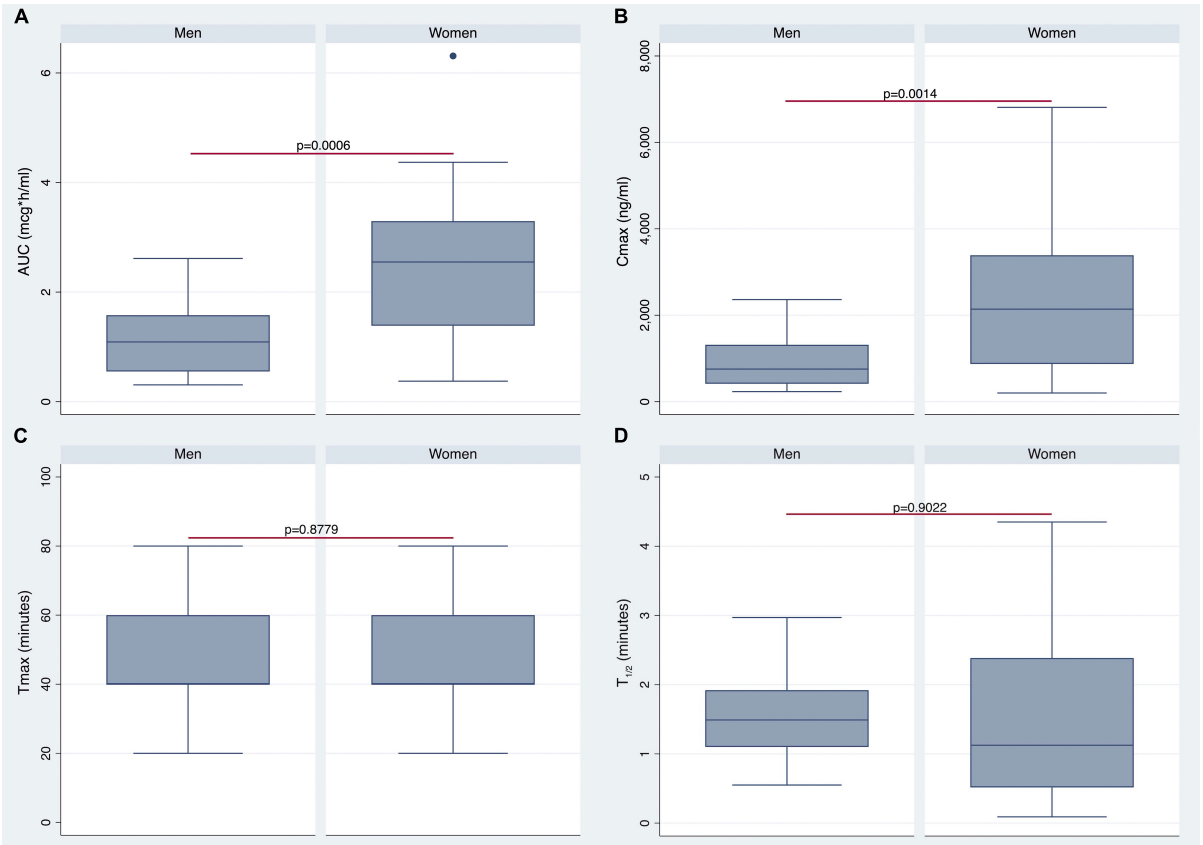

FIGURE 3 | Differences in pharmacokinetics (PK) parameters between men and women. Gender differences in area under the curve (AUC), maximum plasma concentration (Cmax), Tmax, and $t_{1/2}$ are shown in panels **(A–D)**, respectively.

Figures 6A,B). A similar finding was observed considering values adjusted for BW (**Figures 7A,B**). No gender differences were found regarding Tmax and $t_{1/2}$ neither for BMI $<$ 26 nor BMI $\geq$ 26 values (**Table 3** and **Figures 6C,D**).

Linear Regression Analyses

Multiple linear regression analyses were sequentially performed to test the predictors of AUC, Cmax, Tmax, and $t_{1/2}$ using age, sex, and BW as independent variables. The first analysis tested if age, sex (female), and BW significantly predicted AUC. The fitted regression model was: 4.729196 −0.0220806* (Age) + 1.181306* (female sex) −0.0279986* (BW). The overall regression was statistically significant [$r2$ = 0.3841, $F(3,31)$, p = 0.0016]. It was found that only the female sex significantly predicted AUC (β = 1.181306, 95% CI 0.3589598 2.003652; p = 0.006).

The second analysis tested if age, sex (female) and BW significantly predicted Cmax. The fitted regression model was: 3,889.778 −23.72423* (Age) + 1,314.009* (female sex) −19.01502* (BW). The overall regression was statistically significant [$r2$ = 0.3131, $F(3,31)$, p = 0.0080]. It was found that only female sex significantly predicted Cmax (β = 1,314.009, 95% CI 367.4519 2,260.566; p = 0.008).

The third linear regression analysis, testing if age, sex (female), and BW significantly predicted Tmax, did not identify any significant association. The fitted regression model was: 37.0304 + 0.2527491* (Age) −0.124896* (female sex) −0.0896137* (BW). The overall regression was not statistically significant [$r2$ = 0.0274, $F(3,31)$, p = 0.8318].

The same results were found by considering $t_{1/2}$. The fitted regression model was: −1.265975 + 0.0264122* (Age) + 0.0958726* (female sex) + 0.0147279* (BW). The overall regression was not statistically significant [$r2$ = 0.1020, $F(3,31)$, p = 0.1020].

Another set of multiple linear regression analyses was performed to test the predictors of sequentially AUC, Cmax, Tmax, and $t_{1/2}$ using age, sex, and BMI (instead of BW) as independent variables. The first analysis tested if age, sex (female), and BMI significantly predicted AUC. The fitted regression model was: 4.531093 −0.0123913* (Age) + 1.559116* (female sex) −0.0970631* (BMI). The overall regression was statistically significant [$r2$ = 0.4390, $F(3,31)$, p = 0.0004]. It was found that female sex (β = 1.559116, 95% CI 0.8314479 2.286785; $p < 0.0001$) and BMI (β = −0.0970631, 95% CI −0.1733004 −0.0208258; p = 0.014) significantly predicted AUC (**Figure 8**).

The second analysis tested if age, sex (female), and BMI significantly predicted Cmax. The fitted regression model was: 4,083.443 −16.89948* (Age) + 1,582.499* (female sex) −78.50151* (BMI). The overall regression was statistically

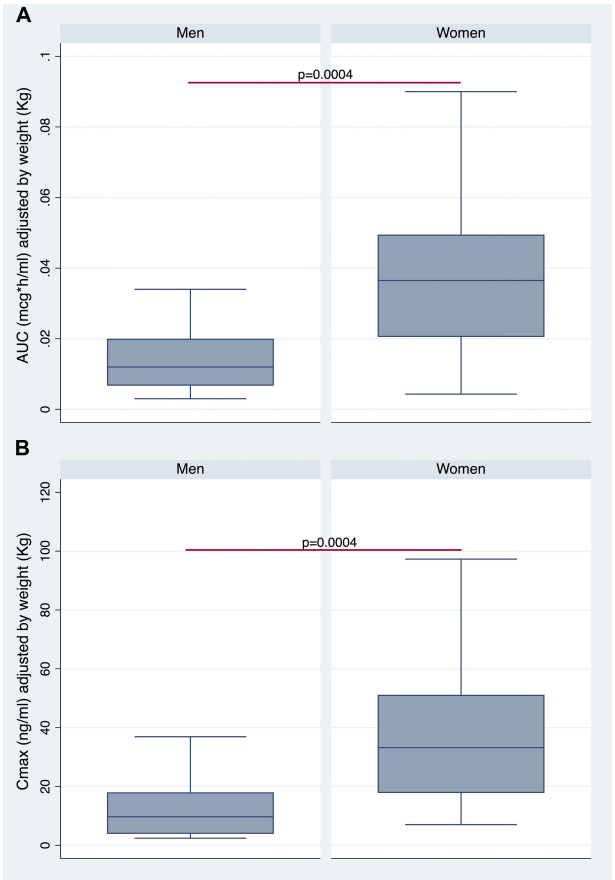

FIGURE 4 | Gender differences in AUC **(A)** and Cmax **(B)** adjusted for BW.

significant [$r2 = 0.3542$, $F(3,31)$, $p = 0.0032$]. It was found that only female sex significantly predicted Cmax (β = 1,582.499, 95% CI 731.581 2,433.417; $p = 0.001$).

The third linear regression analysis, testing if age, sex (female), and BMI significantly predicted Tmax, did not identify any significant association. The fitted regression model was: 19.30049 + 0.2710341* (Age) + 0.4642899* (female sex) + 0.3447133* (BMI). The overall regression was not statistically significant [$r2 = 0.0318$, $F(3,31)$, $p = 0.7972$].

Finally, considering $t_{1/2}$, the fitted regression model was −1.802667 + 0.0208382* (Age) −0.1261094* (female sex) + 0.0756267* (BMI). The overall regression was statistically significant [$r2 = 0.2213$, $F(3,31)$, $p = 0.0487$]. It was found that only BMI significantly predicted $t_{1/2}$ (β = 0.0756267, 95% CI 0.0143407 0.1369126; $p = 0.017$) (**Figure 9A**).

Then, stratifying by gender, we tested if age and BMI predicted the $t_{1/2}$. For men, the fitted regression model was 1.660209 −0.0018911* (Age) −0.0004214* (BMI). The overall regression was not statistically significant [$r2 = 0.0009$, $F(2,16)$, $p = 0.9928$].

For women, the fitted regression model was −3.432078 + 0.0203022* (Age) + 0.1300486* (BMI). The overall regression was statistically significant [$r2 = 0.4132$, $F(2,13)$, $p = 0.0313$]. It was confirmed that in women BMI significantly predicted $t_{1/2}$ (β = 0.1300486, 95% CI 0.0172322 0.242865; $p = 0.027$) (**Figure 9B**).

DISCUSSION

Despite LD being considered the most effective antiparkinsonian drug since the 1970s, the balance between drug effectiveness and side effects has not yet been determined (1). This is crucial in women who are particularly prone to develop LD-related complications, mainly DYS (7). However, the few available studies focused on the gender-related differences in LD pharmacodynamics, and PK enrolled patients previously treated with LD and with different formulations and dosages (13, 14).

In the present study, plasma concentrations and PK parameters were measured in LD-naïve patients, who received the same LD formulation, and the results were compared between men and women.

Women showed higher levels of AUC and Cmax when compared with men, confirming the few data available in the literature. Notably, plasma LD concentrations were significantly higher in women than in men at each time point, covering a time of 4 h and 30 min.

Gender differences in PK and pharmacodynamics have been investigated in recent times. Oral bioavailability and distribution were reported to exert the most important influence on the PK of several compounds. Such differences seem to be mainly related to BW; however, they can persist also after adjusting for this biometric variable (15).

The data on the differences in LD PK between men and women are scarce and mainly regarding the LD administration routes other than the oral one (14).

Several studies suggested considering BW and BW loss during therapy because of an inverse relationship between plasma LD levels and BW (16, 17). Martinez-Ramirez et al. (18) described women in a subgroup of extremely sensitive patients reporting a brittle response, defined as the presence of highly disabling DYS after LD standard doses. No less important is the fact that these women have lower BW than patients who were better responders (18).

Conversely, Kumagai et al. (9), in a population of elderly Japanese patients on LD chronic treatment, reported that women had a significantly greater LD bioavailability compared with men irrespective of BW. This finding is consistent with our results, obtained in LD-naïve patients after the first LD administration, showing that plasma concentrations, as well as AUC and Cmax, were higher in women than in men, also after adjusting for BW. We found that AUC and AUCw were 2.29 times and 2.62 times higher in women than in men, respectively. Similar behavior was found for Cmax and Cmax/w, which were 2.64 and 2.98 times higher in women than in men, respectively.

Multiple linear regression analyses showed that the female sex was the only predictor of AUC and Cmax. No correlation was found neither with Tmax nor with $t_{1/2}$.

Stratifying the study population according to the BMI median value (i.e., 26 for both women and men), it was possible to highlight the most important differences between

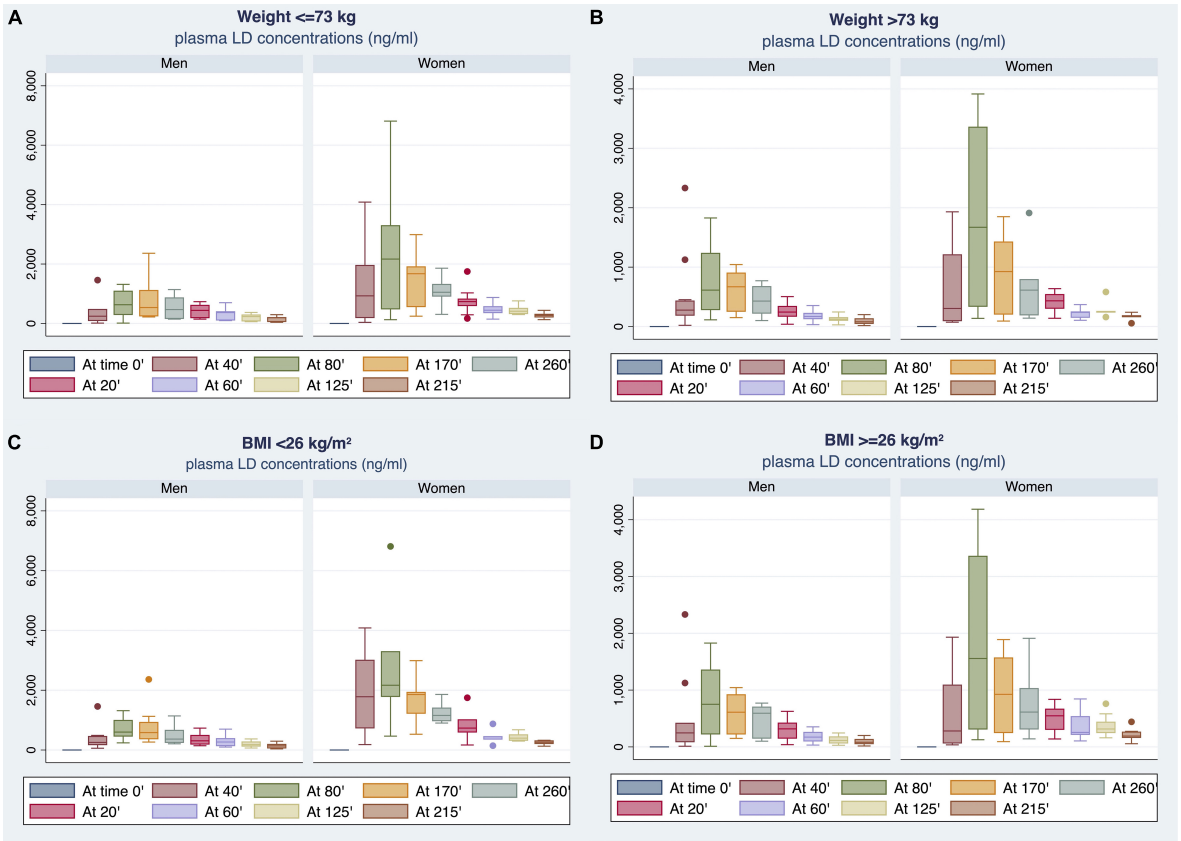

FIGURE 5 | Gender differences observed in plasma LD concentrations by stratifying the study population according to median BW **(A,B)** or body mass index (BMI) **(C,D)** values.

TABLE 3 | Differences in plasma LD concentrations and PK parameters between men and women stratified by the BMI median value.

BMI < 26				BMI ≥ 26			
Plasma LD concentration measured at each time point (ng/ml)							
Time (min.)	**M**	**W**	***P*-value**	**Time (min.)**	**M**	**W**	***P*- value**
20	411.1375 ± 11.1375D	1812.371 ± 812.371D	0.0168	20	485.3545 ± 85.3545D	604.962576 ± 04.962576	NS
40	707.75 ± 07.75 576	2785.6 ± 785.6 576	0.0121	40	749.8727 ± 49.872776	1845.25 ± 845.25 76	NS
60	798.425 ± 98.425 76	1732.271 ± 732.27176	0.0262	60	564.0364 ± 64.036476	972.7444 ± 72.744476	NS
80	487.275 ± 87.275476	1227.457 ± 227.45776	0.0010	80	438.5 ± 38.505776	747.6222 ± 47.622276	NS
125	357.7 ± 215.7421	802.7571 ± 02.757121	0.0367	125	301.1182 ± 01.118221	515.1556 ± 15.1556 1	0.0345
170	298.025 ± 98.0256 1	444.2714 ± 44.2714 1	NS	170	177.1709 ± 77.1709 1	366.0478 ± 66.0478	0.0292
215	198.9875 ± 98.9875 1	433.35 ± 33.35 5	0.0056	215	120.0818 ± 68.60688	375.2778 ± 192.1556	0.0006
260	140.05 ± 40.05 155	249.75 ± 80.20506	0.0441	260	95.96 ± 5.961 506	215.4889 ± 15.4889 6	0.0082
PK parameters							
AUC mcg*h/mL	1.216038 ± 0.216038me	3.332286 ± 0.332286 et	0.0050	AUC mcg*h/mL	1.061909 ± 0.061909 et	2.001989 ± 0.001989 e	0.0385
Cmax ng/mL	941.5125 ± 41.5125 et	2986.786 ± 986.786	0.0149	Cmax ng/mL	886.9 ± 86.9 6 e	1952.667 ± 952.667 et	0.0474
Tmax min.	57.5 ± 7.574 7 e	40 ± 0 5	NS	Tmax min.	38.18182 ± 8.18182 e	62.22222 ± 0.22222 e	NS
$t_{1/2}$ hours	1.4225 ± 0.4225 2 e	1.051429 ± 0.051429 e	NS	$t_{1/2}$ hours	1.613636 ± 0.613636 et	1.838889 ± 0.838889 e	NS

Values are expressed as mean ± SD.
Abbreviations: LD, levodopa; PK, pharmacokinetics; AUC, area under the curve; Cmax, maximum plasma concentration; Tmax, time to reach Cmax; $t_{1/2}$, half-life.

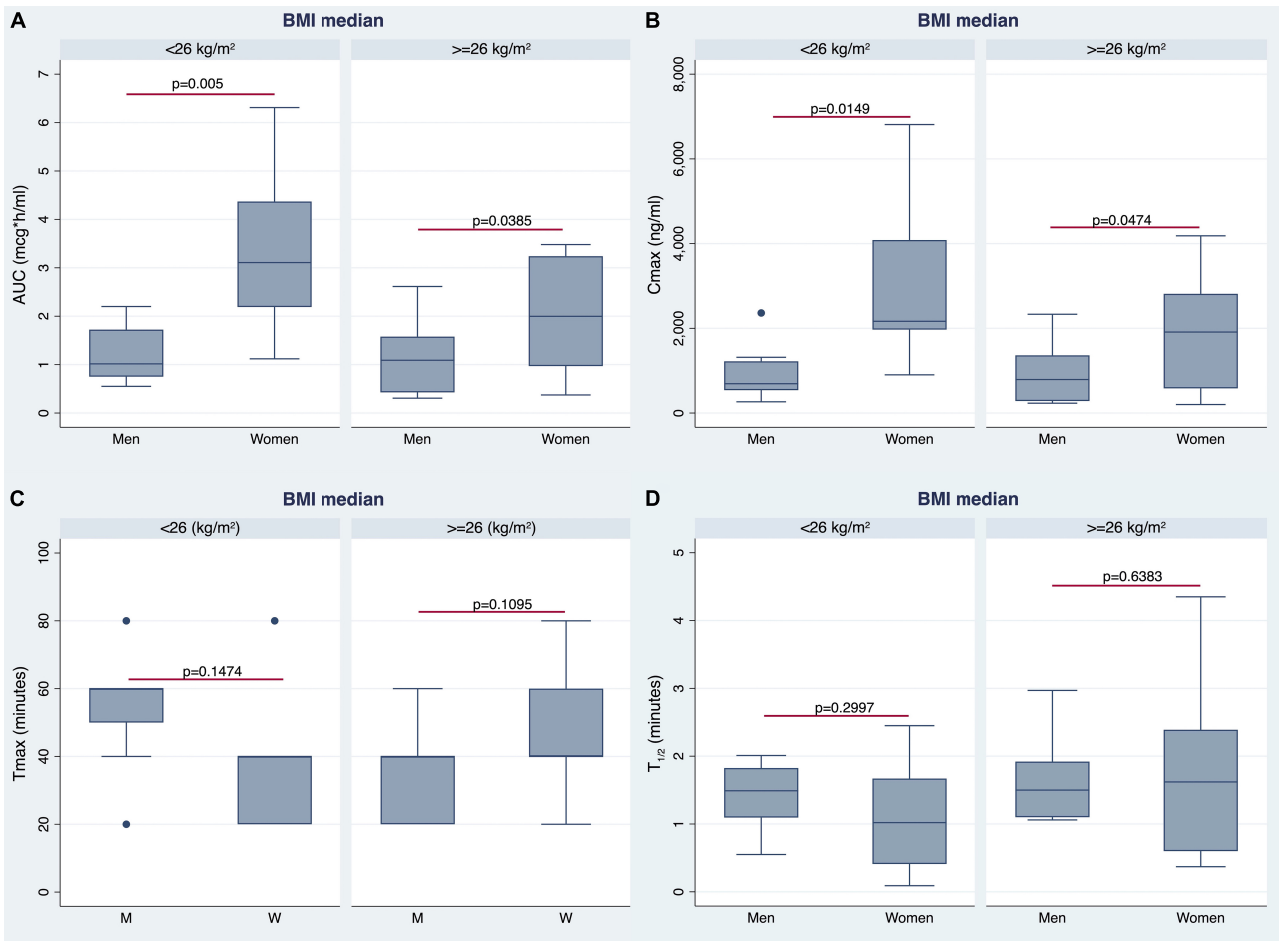

FIGURE 6 | Gender differences observed in AUC **(A)**, Cmax **(B)**, time to reach Cmax (Tmax) **(C)**, and $t_{1/2}$ **(D)** by stratifying the study population according to median BMI value.

lighter women and lighter men, especially in the time range of 20–80 min corresponding to LD peak. Women demonstrated higher values than men also in the group with a BMI of ≥26. However, significant differences were found only in the time range of 125–260 min, corresponding to through PK.

It is of particular interest that, using BMI as an independent variable instead of BW, a significant association was found with $t_{1/2}$, as well as with AUC and Cmax. The best predictors of AUC were female sex ($p < 0.0001$) and BMI ($p = 0.014$), Cmax was predicted only by the female sex, while only BMI significantly predicted $t_{1/2}$. Higher BMI was associated to lower AUC and higher $t_{1/2}$ values. Moreover, stratifying by sex, BMI was confirmed to significantly predict $t_{1/2}$ in women, but not in men.

This is an important finding, especially considering that, after repeated drug intake, both wearing-off and DYS are associated with the short plasma half-life of LD. As a matter of fact, stabilizing the plasma LD levels is considered the best way to attenuate these adverse events (1).

Besides the low BW values of female patients, other variables have been considered to explain gender differences in the LD PK and LD effects.

Women show a slower gastric emptying time compared with men (19) and the variability of transit times is crucial for drugs with pronounced intestinal regional differences in absorption, such as LD (20). Moreover, it has been reported that women have about 25% lower catechol-*O*-methyltransferase (COMT) enzyme activity than men (21).

Some studies evaluating the possible influence on LD PK of other antiparkinsonian drugs failed to demonstrate pharmacokinetic-drug interactions (8). In the present study, there was no statistically significant difference in the use of DA and/or iMAO-B between women and men. However, given the small sample size, further studies are required to confirm this finding. Nonetheless, this is the first study assessing gender differences in LD PK in LD-naïve patients with PD and suggests that gender significantly affects LD PK parameters since the first intake. Another strength of the study is the prospective design and the homogeneity of the study population regarding age, disease duration, and use of other antiparkinsonian drugs.

Adjusting plasma LD levels by BMI allowed us to observe the most relevant pharmacokinetic differences according to gender. This biometric variable, even more than the BW, could be useful

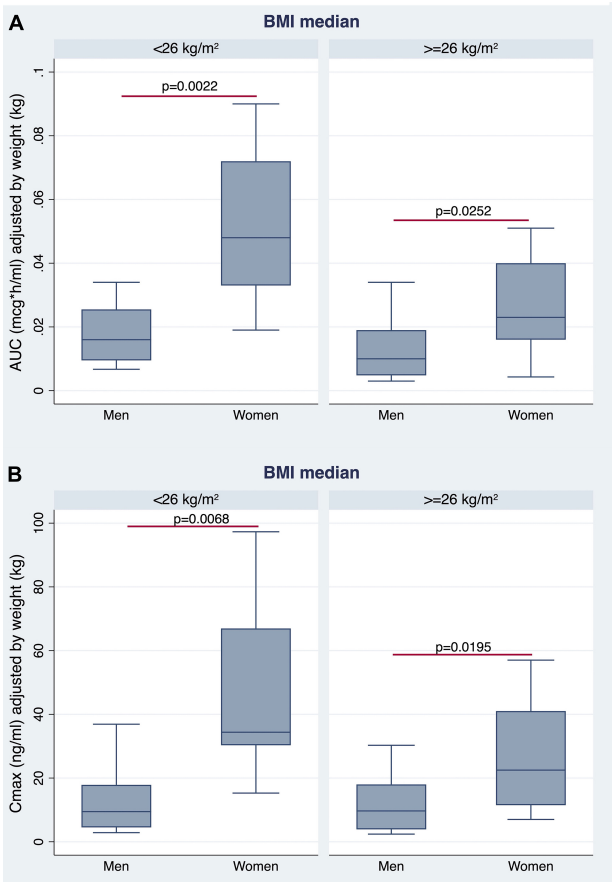

FIGURE 7 | Gender differences observed in AUC **(A)** and Cmax **(B)**, adjusted for BW, by stratifying the study population according to median BMI value.

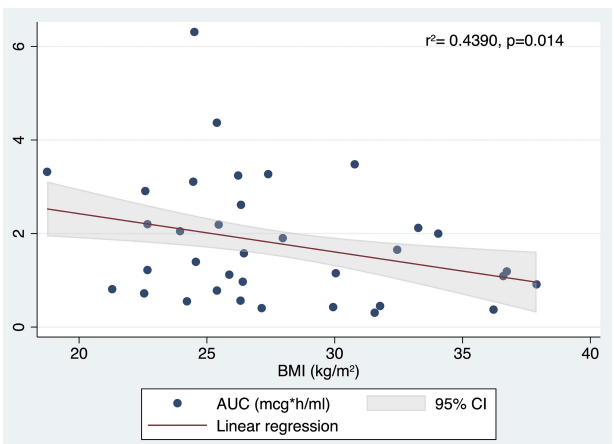

FIGURE 8 | Correlation between AUC (mcg*h/ml) values and BMI (kg/m^2).

to set up the best-personalized approach. In particular, BMI emerged as the only predictor of $t_{1/2}$ in women and not in men. Thus, it is important considering that this finding regards patients receiving LD for the first time.

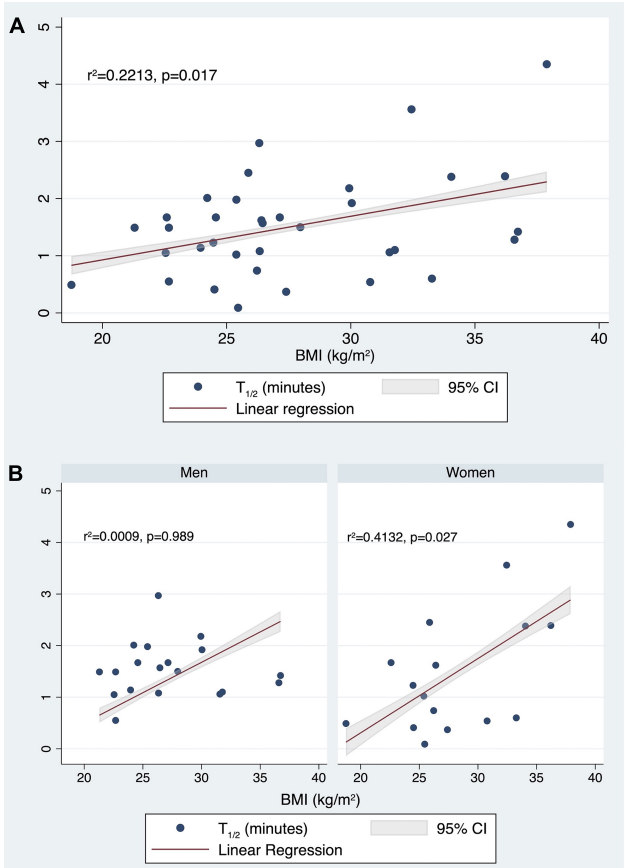

FIGURE 9 | Correlation between $t_{1/2}$ (min) values and BMI (kg/m^2) in the whole population **(A)** and stratifying by sex **(B)**.

CONCLUSION

Taken together, our findings provide novel insights into gender differences in LD pharmacokinetics, possibly contributing to the later development of motor complications and dyskinesia in PD. The results refer to parameters measured at the first drug intake of patients enrolled in an ongoing study with a 2-year follow-up. Future analyses will allow us to assess whether the highlighted differences translate into different patterns of adverse events in men and women.

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 Comitato Etico Campania Sud-A.S.L. Napoli 3. The

patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VC conceptualized the study and drafted the manuscript. VI conceptualized the study and oversaw the data analysis. MR, MP, MA, CS, AN, IC, and CC enrolled the patients. ED participated in data analysis and drafting of the manuscript. BC and VG performed the experiments and data analysis. GS performed the experiments. GC performed data analysis and participated in the drafting of the manuscript. PB and AF oversaw the drafting of the manuscript. MTP conceptualized the study and oversaw the drafting of the manuscript. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Association Between Beta-Carotene Supplementation and Mortality: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: Aging is a phenomenon universally involving all organisms, genetically determined, and epigenetically influenced by the environment. Numerous observational studies have shown the positive impact of non-pharmacological approaches started in younger age on chronic conditions affecting the elderly health and survival. This meta-analysis aimed to investigate the effect of beta-carotene on the total and cause-specific mortality as reported by randomized controlled trials (RCTs).

Methods: We searched Medline, Scopus, Web of Science, and CENTRAL Cochrane from inception to September 2021. Studies were eligible if enrolled adults with any health condition, compared beta-carotene supplements at any dose with placebo or no intervention, provided information on deaths from any cause, and were RCTs, in English. The risk of bias was assessed by the Cochrane risk of bias tool and the GRADE. Risk ratios and their 95% confidence intervals were used and a *P*-value less than 0.05 was considered statistically significant.

Results: Among 3,942 articles searched, 44 articles on 31 RCTs, which included 216,734 total subjects, 108,622 in beta-carotene supplement groups, and 108,112 in the placebo or no-intervention groups, were involved in the final analyses. In a random-effects meta-analysis of all 31 trials, beta-carotene supplements were found to have no preventive effect on mortality (risk ratio 1.02, 95% confidence interval 0.98–1.05, I^2 = 42%). Further, the analysis showed no preventive effect on cancer, cardiovascular, cerebrovascular, and other mortality causes. Instead, beta-carotene supplementation significantly increased the risk of lung cancer mortality (RR 1.14, 95% CI 1.02, 1.27, I^2 = 3%) but decreased the risk of human immunodeficiency virus-related mortality (RR 0.55, 95% CI 0.33, 0.92, I^2 = 0).

Conclusion: More studies should be performed to better define the role of beta-carotene on survival, to confirm or deny our results. Therefore, the possible beneficial or harmful effects of the beta-carotene supplementation on mortality must not be overstated.

Systematic Review Registration: [https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=259354], identifier [CRD42021259354].

Keywords: mortality, meta-analysis, randomized controlled trials, aging, beta-carotene

INTRODUCTION

Aging is a phenomenon universally involving all organisms, genetically determined, epigenetically influenced by the environment, and characterized by a progressive decline of physiological function, mainly the cardiovascular and metabolic profile, leading to death. Numerous observational studies have shown the positive impact of non-pharmacological approaches started in younger age on chronic conditions affecting the elderly health and survival (1–4).

Nutrition is a modifiable lifestyle factor that has been consistently associated with various aspects, including greater adherence to healthy dietary patterns, the intake of specific nutrients, or the consumption of specific foods (5).

Beta-carotene is a fat-soluble phytochemical found naturally in yellow/orange and green leafy plants, and also produced by some microorganisms (6). It is a single homolog of nearly 600 known carotenoids, several of which can be converted into vitamin A and occur as cis-trans forms at a varying ratio (7, 8). As the main carotenoids, beta-carotene can be metabolized into bioactive retinol and other beta-carotene compounds essential for maintaining homeostasis and human physiology (9). Several studies reveal that the beta-carotene is a potent antioxidant, able to function against oxidative stress, maintaining health, and preventing diseases such as cancer and cardiovascular disease (CVD) (10–15). Observational evidence also suggests that a high dietary intake of beta-carotene is associated with a reduced risk of cancer and CVD (16). Moreover, serum beta-carotene has also been inversely correlated with systemic inflammation and insulin resistance (17, 18). However, there is also evidence that beta-carotene may possess a pro-oxidant property and act as a cocarcinogen (19).

Several studies, including meta-analyses, assessing the health effects of beta-carotene showed inconsistent results in humans. Although there have been mixed results for the risk of mortality from cancer (20–22), several observational studies indicated that individuals with a high dietary intake or high circulatory levels of beta-carotene have a lower risk of all-cause (21) and CVD mortality (20, 23, 24). According to a meta-analysis of prospective studies, dietary or circulating beta-carotene has an inverse association with total mortality (25). In addition, in another recent dose-response meta-analysis of observational studies, higher circulating concentrations of beta-carotene were significantly associated with a lower risk of CVD mortality, whereas higher dietary intake of beta-carotene did not appear to have protective effects (26). As a supplement, the findings were inconsistent. Large controlled trials reported either no benefits or unpredicted adverse effects of beta-carotene supplementation, including increased lung cancer incidence and mortality among subjects exposed to asbestos and tobacco (27–30). In these treatment trials, beta-carotene also led to a small but significant increase in CVD and augmented total mortality. In 2012, a meta-analysis of RCTs was conducted by the Cochrane group. In trials with a low risk of bias, the results demonstrated that beta-carotene used singly or in combination with other antioxidants significantly increases overall mortality (31). Furthermore, the same review group performed a meta-regression analysis and reported significant effects of the dose of beta-carotene on mortality (32).

There has been substantial attention to the health effects of beta-carotene, and a systematic review and meta-analysis of the association between beta-carotene supplementation and all-cause mortality in RCTs have already been reported (31). However, the last analyses referred to data available until 2012, and a better and more updated understanding of the beta-carotene-mortality association to examine cause-specific mortality is needed. Therefore, this meta-analysis investigates the association between beta-carotene supplementation and the risk of cause-specific mortality among population subgroups in RCTs, including the most recent results in the literature.

MATERIALS AND METHODS

This study was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 (33). The protocol for this review was registered on PROSPERO (CRD42021259354).

Inclusion and Exclusion Criteria

Studies were eligible if they enrolled adults (age $\geq$ 18) with any health condition; if they compared beta-carotene supplements at any dose with placebo or no intervention, provided information on deaths from any cause; and if they were randomized controlled trials (RCTs). On the contrary, we excluded studies if all the participants received beta-carotene; if they included pregnant women or critically ill patients; and if they used beta-carotene analogs.

Search Strategy

We searched four databases: Medline, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials

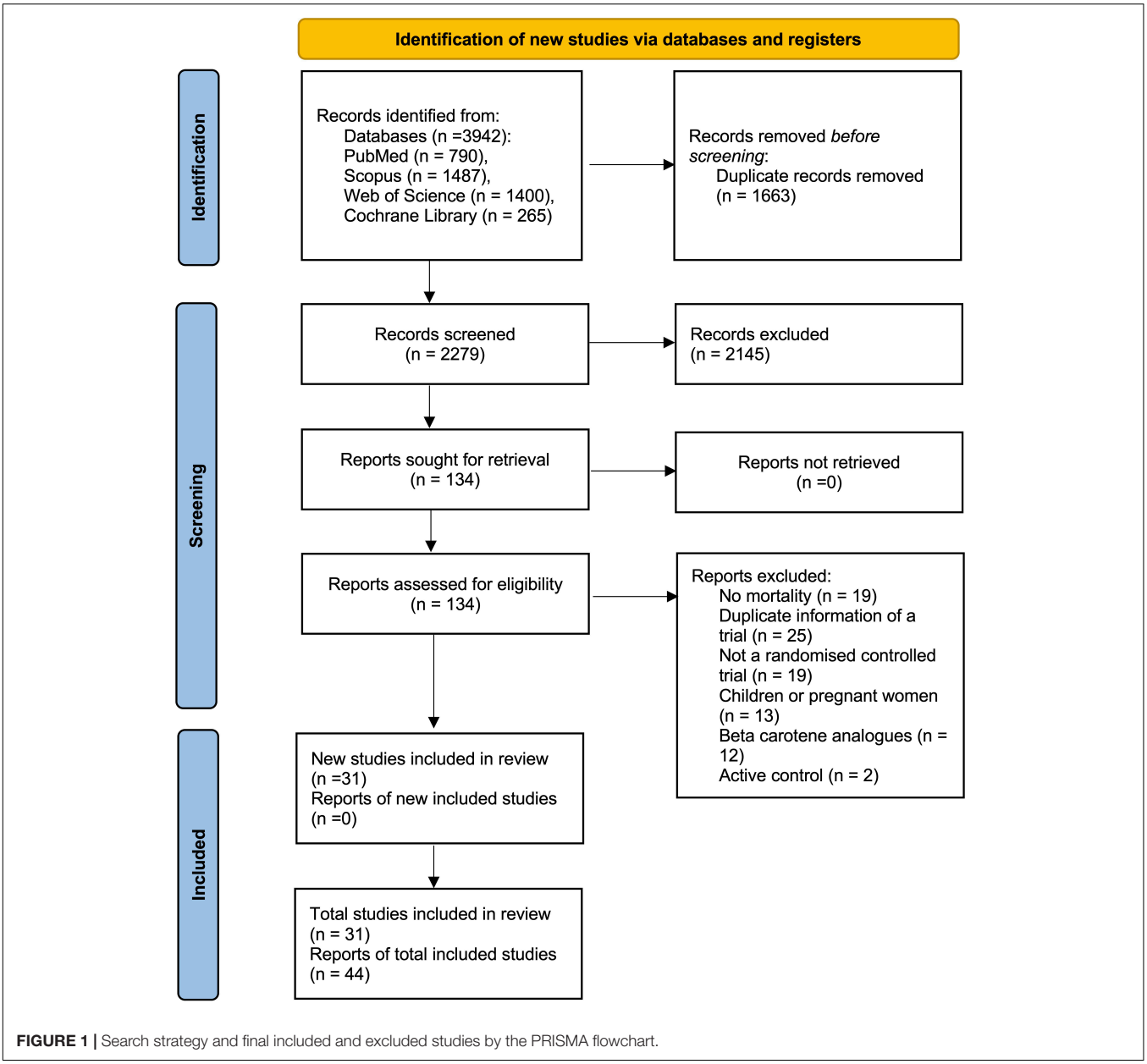

FIGURE 1 | Search strategy and final included and excluded studies by the PRISMA flowchart.

(CENTRAL) of the Cochrane library, from inception to September 2021. We also checked the bibliography of identified studies and systematic reviews to increase the search for relevant articles. We applied English language restriction. No restriction on the type of publication was used. We selected the following keywords for the literature search: "carotenoid*," or "beta-carotene," or "b-carotene" and "mortality," or "death." At the same time, similar queries were, respectively, used for controlled vocabulary search: "beta-carotene" [Mesh] AND "mortality" [Mesh], INDEX TERMS "beta-carotene" AND "mortality."

Study Selection and Data Extraction

After removing duplicates with reference management software EndNote X9 (Clarivate Analytics, Philadelphia, PA, United States), Two raters screened the title/abstract of articles independently. Potentially eligible articles were then accessed in full. Divergences between raters on article eligibility were resolved by a third rater, who screened the studies independently (100% consensus on article eligibility was reached). A data extraction spreadsheet was then developed, and the information from the included studies was extracted and tabulated. When RCTs had more than two arms, data from the separate treatment arms were pooled. The following data were extracted: study name (along with the year of publication), country, study characteristics (participant number, age, gender, health status, and study design), treatment duration/follow-up period, intervention and dosage, mortality causes, and the amount of death/number of participants in each intervention group.

Study Quality Assessment

The quality of all included trials was assessed using the Cochrane Collaboration risk of bias tool (34). The Cochrane risk of bias tool is made up of 7 components: (1) sequence generation, (2) allocation sequence concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other bias. Moreover, we also performed the GRADEpro GDT (GRADEpro Guideline Development Tool Software (35) assessment for the quality of evidence.

Statistical Analyses

We performed statistical analyses using RevMan (version 5.3.3; The Cochrane Collaboration) and the meta package in R Software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), and the interface R-Studio version 1.4.1717 (R studio, PBC, Boston, MA, United States). We used risk ratios and their associated 95% confidence intervals to assess outcomes and considered a *P*-value less than 0.05 to be statistically significant. We assessed heterogeneity using the I^2-test (34). We used random-effects models for our analysis and the possibility of small study effects was assessed qualitatively by a visual estimate of the funnel plot and quantitatively by calculation of the Egger and Begg's tests (36).

We evaluated the effects of beta-carotene supplements according to mortality cause (cancer mortality, CVD mortality, cerebrovascular disease mortality, and mortality from other causes). Besides, we performed several additional subgroup analyses to test interactions according to: the number of participants (≥1,000 and <1,000, by using the median value for stratification), the number of events (≥100 and <100 by using the median value for stratification), the gender (men, women, and both), the mean age (≥65 and < 65 years to evaluate the aging effect), the beta-carotene dose (>20 and <20 mg/day by using the median value for stratification), the length of follow-up (at least four years and less than four years, by using the median value for stratification), the intervention (beta-carotene singly and beta-carotene combined with vitamins, minerals, or other interventions), the participant health status (healthy and unhealthy), and the control group (placebo and no intervention) in all the included trials. Moreover, a subgroup analysis was also performed by country (**Supplementary Figure 7**).

TABLE 1 | Summary characteristics of included studies.

Characteristics	No. of trials (No. of participants)
Eligible studies	
Total No. of trials (No. of participants)	31 (216,734)
Median (IQR) follow-up (years)	4.6 (1.7–8.8)
Follow-up at least 4 years	16 (171,578)
Median (IQR) No. of participants	382 (85, 5,883)
Total No. of deaths	45,907
Median (IQR)% women	49 (15.45–58.44)
Median (IQR) age (years)	60.2 (54.2–67.7)
Country	
American	17 (119,297)
European	9 (63,937)
Asian-pacific	5 (33,500)

RESULTS

Study Selection

We initially identified 3,942 records after searching databases and relevant bibliographies. After excluding 1,663 duplicated articles and 2,145 articles that did not satisfy the selection criteria, we reviewed the full texts of 134 articles and included 44 articles (27, 29, 30, 37–77) on 31 RCTs in the final analysis (**Figure 1**).

Study Characteristics

Table 1 summarizes the characteristics of included trials, and **Table 2** gives details of those trials. The final analysis comprised 216,734 participants, 108,622 in the beta-carotene supplement group and 108,112 in the placebo or no intervention groups, from 31 RCTs reported in 44 articles. In the studies in which age and gender were reported, the median age was 60.2 years (age range 32–85 years), and 49% of the subjects were women. The median treatment and follow-up periods were 3 and 4.6 years, respectively. There were 45,907 deaths, of which 4,609 deaths were from cancer, 3,796 deaths were from CVD, and 956 deaths were from cerebrovascular disease.

The selected articles were published from 1993 through 2018, spanning 25 years. The countries in which the studies were conducted were as follows: United States (n = 13), Canada (n = 3), United Kingdom (n = 3), China (n = 2), France (n = 2), Italy (n = 2), Finland (n = 1), Netherlands (n = 1), Venezuela (n = 1), India (n = 1), Thailand (n = 1), and Australia (n = 1). The studies included healthy subjects (general population, physicians, and nurses); patients with oral premalignancy, skin, lung, and head and neck cancer; adults with underlying CVD or cerebrovascular diseases, and acquired immunodeficiency syndrome (AIDS), primary biliary cirrhosis, and age-related eye diseases; persons at risk of esophageal/gastric cardia cancer; smokers or asbestos-industry workers; and institutionalized elderlies.

Among the 31 trials, 30 had a placebo group, and 1 had a no-intervention group as the control (77). Further, 16 trials used the parallel design, 14 used the factorial design, and one study used a cross-over design (67). The following 3 trials were reported in 16 articles: the Alpha-Tocopherol Beta-Carotene Prevention Study (n = 11), Nutrition Intervention Trial; The General Population Trial (n = 3), and the Physicians' Health Study (n = 2).

Quality of the Included Trials

Supplementary Figures 1, **2** show the quality of the included trials. Twenty-four trials were classified as having a low risk of bias. The remaining 4 trials had one or more inadequate components (64, 66, 72, 76), and 1 trial had an unclear risk of bias (63). **Supplementary Figures 3**, **4** show the GRADE assessment of the quality. The overall results showed a high quality of the studies.

TABLE 2 | Data summary of randomized controlled trials assessing the effects of beta-carotene supplementation on mortality (*n* = 44).

References	Country	Study characteristics	Treatment duration/follow-up period (median)	Intervention (dose)	Mortality cause	Intervention (death/total)	Control (death/total)
Albanes et al. (37)	Finland	*N* = 29,133 (mean age 57.2 y) Women: 0% Health status: smokers (5 + cigarettes/day) Design: 2.2 factorial	6.1/6.1 y	Beta-carotene (20 mg/d) + alpha-tocopherol (50 mg/d) vs. beta-carotene placebo	Colorectal cancer	23/14,560	23/14,573
Austin et al. (38)	Canada	*N* = 331 (median age 39.5 y) Women: 10.5% Condition: acquired immunodeficiency syndrome Design: Parallel	13/13 m	Beta-carotene (72 mg/d) + multivitamins and trace elements vs. beta-carotene placebo	HIV-related mortality	13/165	23/166
Bairati et al. (39)	Canada	*N* = 156 (mean age 62.5 y) Women: 21% Condition: stage I or II head and neck cancer Design: Parallel	3.1/6.5 y	Beta-carotene (30 mg/d) + alpha-tocopherol (400 UI/d) vs. placebo	All-cause	37/79	30/77
Blot et al. (40)	China	*N* = 29,450 (age range 40–69 y) Women: 55% Health status: at risk of esophageal/gastric cardia cancer Design: 2.2.2.2 factorial	5.25/5.25 y	Beta-carotene (15 mg/d) + vitamin E and selenium + micronutrients vs. beta-carotene placebo	Cancer Cerebrovascular disease	369/14,729 249/14,729	423/14,721 274/14,721
Brown et al. (41)	United States	*N* = 80 (mean age 53 y) Women: 13% Health status: coronary disease Design: 2.2 factorial	3/3 y	Antioxidant vitamins (beta-carotene 25 mg/d) vs. placebo	All-cause Cardiovascular cause	11/42 3/42	12/38 7/38
Chew et al. (42)	United States	*N* = 4,757 (median age 69 y) Women: 56% Health status: age-related eye disease Designs: 2.2 factorial	6.3/10 y	Beta-carotene (15 mg/d) + vitamin C (500 mg/d) + vitamin E (400 IU/d) ± zinc (80 mg/d) vs. placebo	All-cause	439/2,370	427/2,387
Chylack et al. (43)	United States	*N* = 297 (mean age 68 y) Women: 59% Condition: age-related cataract Design: Parallel	3/3 y	Antioxidant micronutrients (beta-carotene 18 mg/d) vs. placebo	All-cause	9/149	3/148
Garbagnati et al. (44)	Italy	N = 34 (mean age 66.75 y) Women: 44.5% Condition: stroke Designs: 2.2 factorial	1/1 y	Antioxidants (beta-carotene 19 mg/d) vs. placebo	Cardiovascular disease	1/16	3/18
Gaziano et al. (45)	United States	*N* = 14,641 (mean age 64.3 y) Women: 0% Health status: General population Design: 2.2.2.2 factorial	11.2/11.2 y	Beta-carotene (50 mg/alternate days) + multivitamins vs. beta-carotene placebo	All-cause Cancer	1,345/7,317 403/7,317	1,412/7,324 456/7,324
Girodon et al. (46)	France	*N* = 362 (mean age 83.9 y) Women: 74.58% Condition: Institutionalized elderly Design: 2.2 factorial	2/2 y	Vitamins (beta-carotene 6 mg/d) vs. placebo	All-cause	45/180	51/182
Goodman et al. (47)	United States	*N* = 18,314 (median age 58 y) Women: 34% Health status: Smoker or asbestos exposed Designs: Parallel	4/10 y	Beta-carotene (30 mg/d) + retinyl palmitate (25,000 IU/d) vs. placebo	All-cause Lung cancer Cardiovascular disease	1,855/9,420 294/9,420 354/9,420	1,509/8,894 227/8,894 319/8,894
Graat et al. (48)	Netherlands	*N* = 316 (mean age 73.2 y) Women: 48.5% Condition: non-institutionalized elderly Design: 2.2 factorial	15/15 m	Multivitamin-mineral capsule (beta-carotene 2.4 mg/d) vs. placebo	All-cause	0/163	5/153
Greenberg et al. (49)	United States	*N* = 1,805 (mean age 63.2 y) Women: 30% Health condition: Basal cell or squamous cell carcinoma Designs: Parallel	4.3/8.2 y	Beta-carotene (50 mg/d) vs. placebo	All-cause Cardiovascular disease Cancer	146/913 68/913 38/913	139/892 59/892 44/892

(Continued)

TABLE 2 | (Continued)

References	Country	Study characteristics	Treatment duration/follow-up period (median)	Intervention (dose)	Mortality cause	Intervention (death/total)	Control (death/total)
Grieger et al. (50)	Australia	*N* = 115 Women: 52% Health condition: aged care residents Designs: Parallel	6/6 m	Multivitamin (beta-carotene 3 mg/d) vs. placebo	All-cause	3/58	4/57
Heart Protection Study Collaborative Group (51)	United Kingdom	*N* = 20,536 (age range 40–80 y) Women: 24.74% Health status: coronary disease, occlusive arterial disease, or diabetes Design: 2.2 factorial	5/5 y	Antioxidant vitamins (20 mg/d beta-carotene) vs. placebo	All-cause Coronary heart disease Stroke	1,446/10,269 664/10,269 108/10,269	1,389/10,267 630/10,267 107/10,267
Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group (27)	Finland	*N* = 29,133 (mean age 57.2 y) Women: 0% Health status: Smokers (5 + cigarettes/day) Design: 2.2 factorial	6.1/6.1 y	Beta-carotene (20 mg/d) + alpha-tocopherol (50 mg/d) vs. beta-carotene placebo	Cancer Lung cancer	582/14,560 302/14,560	534/14,573 262/14,573
Heinonen et al. (52)	Finland	*N* = 29,133 (mean age 57.2 y) Women: 0% Health status: Smokers (5 + cigarettes/day) Design: 2.2 factorial	6.1/6.1 y	Beta-carotene (20 mg/d) + alpha-tocopherol (50 mg/d) vs. beta-carotene placebo	Prostate cancer	33/14,560	29/14,573
Hennekens et al. (29)	United States	*N* = 22,071 (mean age 53 y) Women: 0% Health status: General population Design: 2.2 factorial	12/12 y	Beta-carotene (50 mg/alternate days) + aspirin vs. beta-carotene placebo	All-cause Cardiovascular disease Malignant neoplasm	979/11,036 338/11,036 386/11,036	968/11,035 313/11,035 380/11,035
Hercberg (53)	France	*N* = 13,017 (mean age 49 y) Women: 60.5% Health status: General population Designs: Parallel	7.5/12.5 y	Antioxidant vitamins and minerals (beta-carotene 6 mg/d) vs. placebo	All-cause	156/6,481	178/6,536
Jiamton et al. (54)	Thailand	*N* = 481 (mean age 32 y) Women: 61% Health status: HIV-infected Designs: Parallel	48/48 w	Immunace Micronutrient supplement (beta-carotene 6 mg/d) vs. placebo	HIV-related mortality	8/242	15/239
Kataja-Tuomola et al. (55)	Finland	*N* = 1,700 (mean age 57.2 y) Women: 0% Health status: Smokers (5 + cigarettes/day) with diabetes Design: 2.2 factorial	6.1/6.1 y	Beta-carotene (20 mg/d) + alpha-tocopherol (50 mg/d) vs. beta-carotene placebo	Diabetes-related mortality	168/877	150/823
Lai et al. (56)	Finland	*N* = 29,133 (mean age 57.2 y) Women: 0% Health status: Smokers (5 + cigarettes/day) Design: 2.2 factorial	6.1/24 y	beta-carotene (20 mg/d) + alpha-tocopherol (50 mg/d) vs. beta-carotene placebo	Chronic liver disease	121/14,560	116/14,573
Lamas et al. (57)	United States	*N* = 1,708 (median age 65 y) Women: 18% Health status: Post myocardial infarction Design: 2.2 factorial	31/55 m	Multivitamin and multimineral mixture (beta-carotene 25,000 IU/d) + IV chelation infusions vs. placebo	All-cause Cardiovascular disease	87/853 45/853	93/855 56/855
Lee et al. (30)	United States	*N* = 39,876 (mean age 54.6 y) Women: 100% Health status: Healthy Design: 2.2.2 factorial	2.1/4.1 y	Beta-carotene (55 mg on alternate days) + aspirin and vitamin E vs. beta-carotene placebo	All-cause Cardiovascular disease Cancer	59/19,939 14/19,939 31/19,939	55/19,937 12/19,937 28/19,937
Leppälä et al. (58)	Finland	*N* = 28,519 (mean age 57.2 y) Women: 0% Health status: Stroke-free smokers (5 + cigarettes/day) Design: 2.2 factorial	6.1/6.1 y	Beta-carotene (20 mg/d) + alpha-tocopherol (50 mg/d) vs. beta-carotene placebo	Stroke	82/14,246	78/14,273

(Continued)

TABLE 2 | (Continued)

References	Country	Study characteristics	Treatment duration/follow-up period (median)	Intervention (dose)	Mortality cause	Intervention (death/total)	Control (death/total)
Li et al. (59)	China	*N* = 3,318 (mean age 54 y) Women: 56% Health status: Esophageal dysplasia Design: Parallel	6/6 y	Vitamins and minerals (15 mg/d beta-carotene) vs. placebo	All-cause Cancer Cerebrovascular disease	157/1,657 87/1,657 22/1,657	167/1,661 89/1,661 35/1,661
Lin et al. (60)	United States	*N* = 8,171 (mean age 60.4 y) Women: 100% Health status: High risk of cardiovascular disease Design: 2.2.2.2 factorial	9.4/9.4 y	Beta-carotene (50 mg every other day) + antioxidants vs. beta-carotene placebo	Cancer	80/4,084	96/4,087
Liu et al. (61)	Canada	*N* = 763 (mean age 85 y) Women: 70% Health status: Institutionalized elderly Design: Parallel	19/19 m	Multivitamin and multimineral (beta-carotene 16 mg/d) vs. placebo	All-cause	96/379	97/384
Margalit et al. (62)	United States	*N* = 383 (median age 73 y) Women: 0% Health status: Prostate cancer Design: 2.2 factorial	12/22.5 y	Beta-carotene (50 mg/alternate days) ± aspirin vs. placebo	Prostate cancer	20/192	25/191
Mayne et al. (63)	United Kingdom	*N* = 264 (mean age 68 y) Women: 19% Health status: Head and neck cancer Design: Parallel	4.25/4.25 y	Beta-carotene (50 mg/d) vs. placebo	All-cause	21/135	26/129
Papadimitrakopoulou et al. (64)	United States	*N* = 84 (mean age 56 y) Women: 48.9% Health status: Oral premalignancy Design: Parallel	3/5 y	Beta-carotene (50 mg/d) + retinyle palmitate vs. beta-carotene placebo	All-cause	1/47	0/37
Age-Related Eye Disease Study 2 Research Group (65)	United States	*N* = 4,203 (median age 74 y) Women: 56.75% Health status: AMD Design: 2.2 factorial	5/5 y	Macular xanthophylls (10 mg/d lutein + 2 mg/d zeaxanthin) + omega-3 fatty acids (350 mg/d DHA + 650 mg/d EPA) vs. macular xanthophylls placebo	All-cause	746/2,123 *PC*	727/2,080 *PC*
Pathak et al. (66)	India	*N* = 136 (median age 56 y) Women: 14.6% Health status: Advanced non-small cell lung cancer Design: Parallel	2/2 y	Antioxidants (60 mg/d beta-carotene) + chemotherapy vs. chemotherapy	All-cause	54/64	64/72
Plummer et al. (67)	Venezuela	*N* = 1,980 (mean age 35–69 y) Women: 52.7% Condition: Precancerous gastric lesions Design: Parallel	3/3 y	Antioxidant vitamins (beta-carotene 18 mg/d) vs. placebo	All-cause	16/990	11/990
Prince et al. (68)	United Kingdom	*N* = 61 (mean age 58 y) Women: 92% Health condition: primary biliary cirrhosis Design: Cross-over	12/12 w	Antioxidant supplementation (beta-carotene 3 mg/d) vs. placebo	Ischemic heart disease	1/29	0/32
Qu et al. (69)	China	*N* = 29,450 (age range 40–69 y) Women: 55% Health status: At risk of esophageal or stomach cancer Design: 2^4 partial factorials	5.25/15.2 y	Beta-carotene (15 mg/d) + vitamin E and selenium vs. placebo	Liver cancer	68/14,729	83/14,721
Rautalahti et al. (70)	Finland	*N* = 29,133 (mean age 75.7 y) Women: 0% Health status: Smokers (5 + cigarettes/day) Design: 2.2 factorial	6.1/6.1 y	Beta-carotene (20 mg/d) + alpha-tocopherol (50 mg/d) vs. beta-carotene placebo	Pancreatic carcinoma	35/14,560	48/14,573
Richer et al. (71)	United States	*N* = 60 (mean age 75.3 y) Women: 5% Condition: Atrophic age-related macular degeneration Design: Parallel	12/12 m	Lutein (10 mg/d) vs. placebo	All-cause	1/29	2/31

(Continued)

TABLE 2 | (Continued)

References	Country	Study characteristics	Treatment duration/follow-up period (median)	Intervention (dose)	Mortality cause	Intervention (death/total)	Control (death/total)
Toma et al. (72)	Italy	*N* = 214 (median age 60.5 y) Women: 9.8% Health condition: Stage I-II head and neck cancer Design: Parallel	3/4.9 y	Beta-carotene (75 mg/d) vs. no treatment	All-cause Head and neck tumor	9/104 5/104	15/110 6/110
Törnwall et al. (73)	Finland	*N* = 29,133 (mean age 57.7 y) Women: 0% Health status: Smokers at risk of major coronary event Design: 2.2 factorial	6.1/6.1	Beta-carotene (20 mg/d) + alpha-tocopherol (50 mg/d) vs. beta-carotene placebo	Coronary heart disease	456/14,560	449/14,573
Virtamo et al. (74)	Finland	*N* = 29,133 (mean age 57.7 y) Women: 0% Health status: Smokers (5 + cigarettes/day) Design: 2.2 factorial	6.1/6.1 y	Beta-carotene (20 mg/d) + alpha-tocopherol (50 mg/d) vs. beta-carotene placebo	Urothelial cancer Renal cell cancer	13/14,560 16/14,560	11/14,573 25/14,573
Virtamo et al. (75)	Finland	*N* = 29,133 (mean age 57.7 y) Women: 0% Health status: Smokers (5 + cigarettes/day) Design: 2.2 factorial	6.1/14.1 y	Beta-carotene (20 mg/d) + alpha-tocopherol (50 mg/d) vs. beta-carotene placebo	All-cause	5,555/14,560	5,276/14,573
Wang et al. (76)	China	*N* = 29,450 (median age 52 y) Women: 55% Health status: At risk of esophageal/gastric cardia cancer Design: 2.2.2.2 factorial	5.25/30 y	Beta-carotene (15 mg/d) + vitamin E and selenium + micronutrients vs. beta-carotene placebo	All-cause	9,910/14,729	9,824/14,721
Wright et al. (77)	Finland	*N* = 29,133 (mean age 57.7 y) Women: 0% Health condition: Smokers (5 + cigarettes/day) Design: 2.2 factorial	6.1/6.1 y	Beta-carotene (20 mg/d) + alpha-tocopherol (50 mg/d) vs. beta-carotene placebo	Oral/pharyngeal cancer Esophageal cancer laryngeal cancer	10/14,560 6/14,560 5/14,560	7/14,573 9/14,573 5/14,573

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; NIT1, Nutrition Intervention Trial (NIT); The General Population Trial; HATS, The HDL-Atherosclerosis Treatment Study; AREDS, Age Related Eye Disease Study; REACT, The Roche European American Cataract Trial; PHSII, Physicians Health Study; CARET, The Beta-Carotene and Retinol Efficacy Trial; SCPS, Skin Cancer Prevention Study; HPS, Heart Protection Study; PHS, Physicians Health Study; SUVIMAX, The Supplementation en Vitamines et Mineraux Antioxydants; WHS, Women's Health Study; AREDS2, Age-Related Eye Disease Study 2; PC, personal contact; LAST, Lutein Antioxidant Supplementation Trial.

Meta-Analysis of the Effect of Beta-Carotene Supplements on Mortality Risk

Overall, in a random-effects model meta-analysis of all the 31 trials (27, 29, 30, 37–77), there was no statistically significant difference in total mortality between the beta-carotene supplementation group and the control group (RR 1.02, 95% CI 0.98–1.05, I^2 = 42%; **Figure 2**). Funnel plot analysis showed no asymmetry (**Figure 3**); additionally, the Egger test (P = 0.25) and Begg's test (P = 0.85) detected no significant small-study effects.

Subgroup analyses according to the number of participants, the number of events, gender, age groups, beta-carotene dose, follow-up duration, type of intervention (singly or combined beta-carotene supplements), participant health status, and the control group did not show any difference in total mortality among the participants (**Table 3**). **Table 4** shows the results of the subgroup analyses on cause-specific mortality. Beta-carotene supplementation was not associated with cancer mortality (RR 0.98, 95% CI 0.90–1.07, I^2 = 37%). However, the use of beta-carotene supplements significantly increased mortality among lung cancer patients (RR 1.14, 95% CI 1.02, 1.27, I^2 = 3%). As for CVD mortality, we found no statistically significant difference between the groups (RR 1.04, 95% CI 0.98, 1.11, I^2 = 0%). Similarly, beta-carotene supplementation did not reduce the risk of death from cerebrovascular disease (RR 0.94, 95% CI 0.82, 1.06, I^2 = 0%). However, a significant beneficial effect of beta-carotene on mortality risk was observed in participants with human immunodeficiency virus (HIV) infection (RR 0.55, 95% CI 0.33, 0.92, I^2 = 0%).

DISCUSSION

The current meta-analysis found that the administration of beta-carotene supplements had no preventive effect on total mortality, mortality from cancer, and vascular and non-vascular diseases. Furthermore, no association was found within subgroup meta-analyses based on the number of participants, the

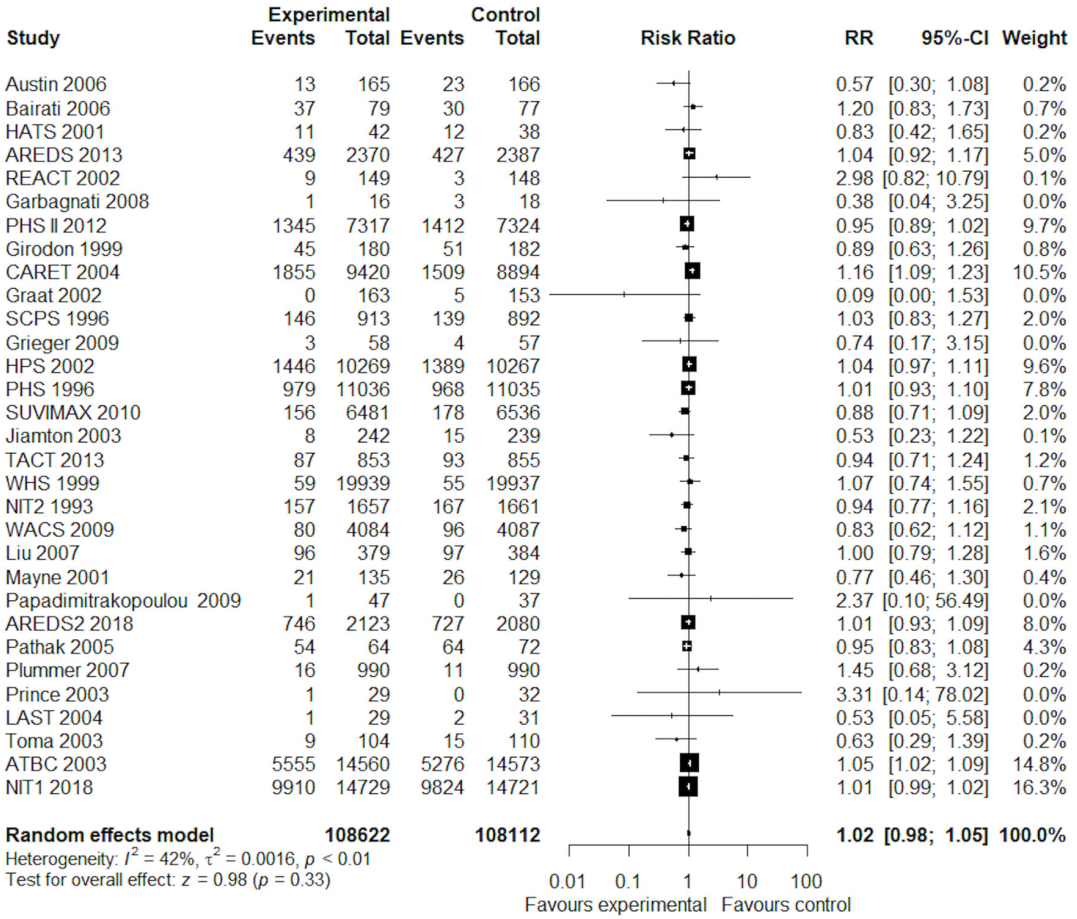

FIGURE 2 | Forest plot showing the effect of beta-carotene supplementation on total mortality in 31 randomized controlled trials.

number of events, sex, age groups, beta-carotene dose, follow-up duration, type of intervention (singly or combined beta-carotene supplements), participant health status, and control group. However, beta-carotene supplementation was significantly related to an increased risk of lung cancer mortality (RR 1.14, 95% CI 1.02, 1.27, I^2 = 3%, n = 5). The effects of beta-carotene supplementation on increased lung cancer incidence and mortality among smokers have already been described, and several possible biological mechanisms have been proposed. In general, beta-carotene supplementation has not been shown to positively impact cancer prevention. In a systematic review and meta-analysis, no effect of beta-carotene supplementation was observed on the incidence of the total, pancreatic, colorectal, prostate, breast, melanoma, and non-melanoma skin cancers. However, a significant harmful effect of beta-carotene supplementation on the incidence of lung and stomach cancers was observed in people supplemented with beta-carotene at 20–30 mg/day, in smokers and asbestos workers compared to placebo (78). Beta-carotene may act as a pro-oxidant in the presence of chronic oxidative stress such as smoking (79) and it may enhance the oxidative stress initiated by cigarette smoking and stimulate toxic effects in tissues (80). Our study also found significant inverse associations of beta-carotene supplementation with the risk of HIV-related mortality; however, this was reported in only two studies. This is in line with previous evidence illustrating that persons in all stages of HIV infection generally have low circulating levels of micronutrients, including carotenoids, and low micronutrient concentrations are correlated with HIV disease progression and mortality (38).

Overall, the findings of the present meta-analysis of RCTs are inconsistent with previous meta-analyses of observational studies suggesting beneficial effects from high dietary or circulatory beta-carotene-rich fruits and vegetables on all-cause and CVD mortality (25, 26). Intervention studies are commonly considered to provide conclusive answers, whereas observational studies represent a better picture of the real-world population. There are evident differences between the findings of published trials, which could be explained by population characteristics (general, ill, or at high-risk subjects), the different doses of supplementation (dietary levels or higher), which can be associated with harmful health effects (81), and the type of supplement (alone or in association). In this last condition, when subgroup analysis was performed, only 4 out of 31

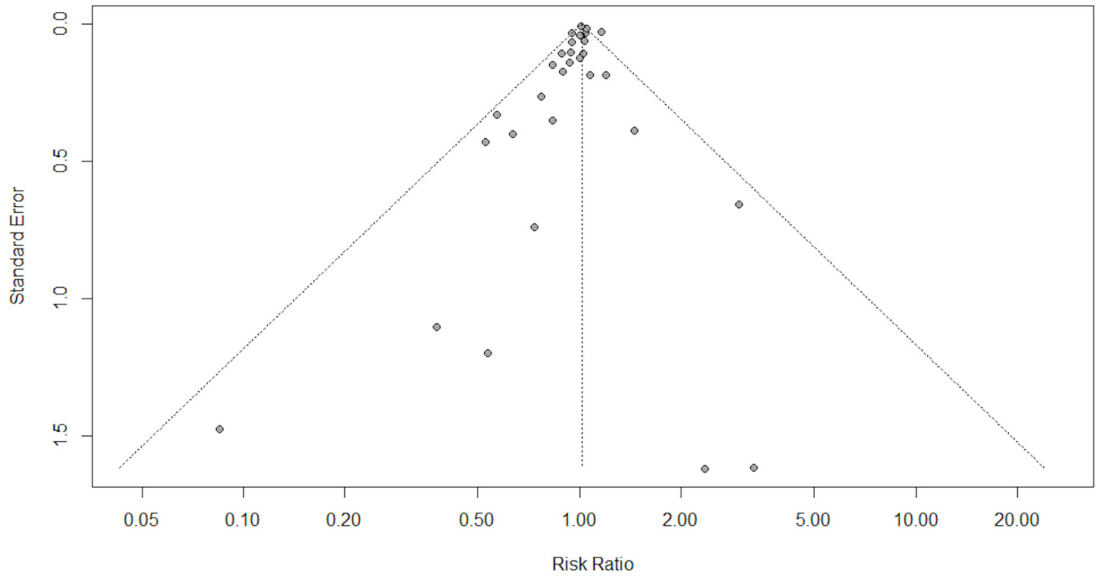

FIGURE 3 | Funnel plot for publication bias in 31 randomized controlled trials.

TABLE 3 | Subgroup analyses of the effect of beta-carotene on total mortality.

Subgroup title	No. of trials	No. of participants	I^2 (%)	Risk ratio (95% CI)	*P*-value
Overall	31	216,734	42.0	1.02 (0.98, 1.05)	0.3
No of participants					
≥1,000	15	212,980	58.0	1.02 (0.98, 1.05)	0.1
<1,000	16	3,754	4.0	0.93 (0.83, 1.04)	0.2
No of events					
≥100	16	211,899	55.0	1.02 (0.99, 1.05)	0.2
<100	15	4,835	15.0	0.88 (0.71, 1.09)	0.3
Age (years)					
≥65	11	12,879	0.0	1.00 (0.94, 1.07)	0.9
<65	20	203,855	56.0	1.02 (0.98, 1.06)	0.3
Gender					
Women	2	48,047	9.0	0.92 (0.72, 1.17)	0.5
Men	3	65,845	73.0	1.01 (0.95, 1.08)	0.8
Women and men	26	102,842	39.0	1.02 (0.97, 1.06)	0.5
Daily dose equivalent (mg)					
≥ 20	15	155,812	55.0	1.02 (0.97, 1.08)	0.5
< 20	16	60,922	0.0	1.01 (0.99, 1.02)	0.4
Follow up					
At least 4 years	16	171,578	57.0	1.02 (0.98, 1.06)	0.3
Less than 4 years	15	45,156	2.0	0.94 (0.85, 1.04)	0.2
Intervention					
Beta carotene alone	4	2,343	0.0	0.96 (0.79, 1.16)	0.6
Combined	27	214,391	47.0	1.02 (0.98, 1.05)	0.3
Participant health status					
Healthy	5	89,921	19.0	0.97 (0.91, 1.04)	0.4
Unhealthy	26	126,813	42.0	1.03 (0.99, 1.07)	0.1
Control group					
Placebo	30	216,520	43	1.02 (0.99, 1.05)	0.3
No intervention	1	214	-	0.63 (0.29, 1.39)	0.25

studies reported the use of beta-carotene alone. Although no significant difference was found in all-cause mortality ($p = 0.64$), a very low heterogeneity was discovered among these studies ($I^2 = 3.60\%$) with a trend in reduced mortality with beta-carotene supplementation (RR = 0.95, 95% CI 0.74. 1.16, **Supplementary Figure 5**). Indeed, it appears that optimal effects may be obtained with a combination of nutrients at similar levels to a healthy diet. A single antioxidant, such as beta-carotene, given at high doses in subjects with a high risk of diseases, such as smokers and asbestos-exposed workers, might not have considerable benefits and can even have adverse outcomes (82). Another possible reason for the harmful effect

TABLE 4 | Effects of beta-carotene supplements vs. placebo or no intervention on cause-specific mortality.

Mortality cause	No. of trials	Risk ratio (95% CI)	I2 (%)	Model used
Cancer	13	0.98 (0.90, 1.07)	37.0	Random effects
Colorectal cancer	2	0.97 (0.68, 1.38)	0.0	Random effects
Esophagus and stomach cancer	2	0.93 (0.82, 1.06)	0.0	Random effects
Prostate cancer	3	0.93 (0.73, 1.18)	0.0	Random effects
Lung cancer	5	1.14 (1.02, 1.27)*	3.0	Random effects
Lung cancer in smokers	2	1.14 (1.03, 1.27)*	0.0	Random effects
Lung cancer in mixed smokers and non-smokers	3	0.94 (0.74, 1.20)	0.0	Random effects
Urinary tract cancer	2	0.82 (0.55, 1.21)	0.0	Random effects
Pancreatic cancer	2	0.85 (0.62, 1.16)	0.0	Random effects
Other cancer	6	0.86 (0.70, 1.06)	0.0	Random effects
Cardiovascular disease	12	1.04 (0.98, 1.11)	0.0	Random effects
Cerebrovascular disease	5	0.94 (0.82, 1.06)	0.0	Random effects
HIV-related causes	2	0.55 (0.33, 0.92)*	0.0	Random effects
Non-cancer, non-vascular cause	5	1.04 (0.95, 1.14)	0.0	Random effects

**Statistically significant.*

in clinical trials involving beta-carotene may be attributed to the purified synthetic form (83, 84). The effective uptake of synthetic all-trans beta-carotene seems to make the synthetic form more suitable for efficient absorption. However, the fact that synthetic beta-carotene can change normal serum trans/cis ratios favoring the trans-isomer may lead to an unfavorable effect. The effects of using all-trans synthetic beta-carotene are still not well-understood (84). It is assumed that synthetic beta-carotene rather than natural mixed carotenoids may stimulate cancer formation (85). Ultimately, higher antioxidant intakes, including beta-carotene, are associated with a better diet quality, which indicates higher intakes of nutrients such as fibers, minerals, and flavonoids, and lower intakes of unhealthy nutrients.

The present study has several possible limitations. Firstly, in the majority of the studies, synthetic beta-carotene was used. Clinical consequences of using natural beta-carotene are not well-understood because RCTs have yet to be conducted. Additional trials are required to understand the differential results of synthetic beta-carotene as an alternative to natural beta-carotene. Secondly, the results were accompanied by some evidence of heterogeneity. However, the subgroup analyses were performed to overcome this problem, implying that some of the study and participant characteristics were possible sources of the heterogeneity in the data. Thirdly, the database sources did not include EMBASE. However, CENTRAL and Scopus include several articles from EMBASE as the original source.

Our study has several strengths, as well. We updated the association of beta-carotene with total mortality, assessed its effects on cause-specific mortality, and showed a significant inverse association between beta-carotene intake and HIV-related mortality. Second, because of no evidence of publication bias, the results have not been altered by this type of bias.

In conclusion, we found no evidence of an overall preventive effect of beta-carotene supplements on total, cancer, CVD, and cerebrovascular mortality risk in our meta-analysis of RCTs published over the past 25 years. Instead, beta-carotene supplementation increased the risk of lung cancer mortality but decreased the risk of HIV-related mortality. Surely more studies should be performed to better define this issue, by confirming or denying our results. Therefore, beta-carotene supplementation's possible beneficial or harmful effects on mortality must not be overstated.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

GC and SD conceived of the presented manuscript. SA, SM, MI, and GS analyzed each article and performed the data extraction independently. VC, MI, and SM drafted the method and result section with the input of GC and SD. GS and VC drafted the introduction and discussion section with the input of SA, GC, and SD. All authors discussed the results and contributed to the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.872310/full#supplementary-material

Supplementary Figure 1 | Quality of the included trials by using the Cochrane Collaboration risk of bias tool.

Supplementary Figure 2 | Quality of the included trials by using the Cochrane Collaboration risk of bias tool in summary with the studies.

Supplementary Figure 3 | The GRADE assessment of the study's quality for the all-cause mortality outcome.

Supplementary Figure 4 | The GRADE assessment of the study's quality for the all-cause mortality outcome with beta carotene alone.

Supplementary Figure 5 | Subgroup analysis by the type of supplement (alone or in association).

Supplementary Figure 6 | PRISMA checklist.

Supplementary Figure 7 | Subgroup analysis by country.

Supplementary Table 1 | Publication bias evaluation of each study by using the Cochrane Collaboration risk of bias tool.

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