Sarcopenia and frailty in individuals with dementia: a systematic review

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Abstract

Background: Population aging has resulted in an increase in age-related conditions. Sarcopenia, the progressive loss of muscle mass and strength, and frailty, vulnerability to poor resolution of homeostasis after a stressor, are common causes of functional decline in older individuals. There is a paucity of work on how they interrelate with dementia. The objective of this review was to examine the literature on sarcopenia and frailty in dementia.

Methods and results: Studies of sarcopenia and frailty in dementia were searched for in EMBASE, PubMed and Web of Science, and via hand-searching. Citations were screened for independently by two reviewers, with disagreements resolved by a third reviewer. To be eligible for inclusion, the articles needed to fulfil: (1) English language; (2) human studies; and (3) full-text available. Dementia of any aetiology was included. 303 non-duplicate records were identified, of which 270 irrelevant papers were excluded. Of the remaining 33, 27 examined frailty and 13 sarcopenia, with six of these measuring both. An increased prevalence of frailty and sarcopenia was noted in dementia patients. However, nine papers did not specify dementia aetiologies. Of those that did (n=21), 20 examined Alzheimer's disease, with three also including Lewy body dementia, three vascular dementia, and one Parkinson's disease dementia.

Conclusion: Most papers examined frailty, rather than sarcopenia, in dementia. The studies were heterogeneous, using different protocols and non-validated definitions. However, dementia patients may have an increased prevalence of frailty and sarcopenia. This review highlights key gaps in accurate diagnosis of frailty/sarcopenia and in non-Alzheimer's dementia.

Key words: aging; sarcopenia; frailty; dementia; Alzheimer's; Lewy bodies.

1.1 Introduction

Population aging is progressing rapidly in many industrialised countries, resulting in a substantial increase in the prevalence of age-related health conditions. In the UK, 1.3% of the population are diagnosed with dementia, and the total number with dementia is predicted to rise to over 1 million by 2025, and 2 million by 2051 (Prince et al. 2014). However, dementia is one of many aging conditions increasingly recognised by clinicians. Sarcopenia, meaning 'poverty of the flesh', is a progressive and generalised muscle disorder with sequential loss of muscle strength, mass, and subsequently function (Cruz-Jentoft and Sayer. 2019, Cruz-Jentoft et al. 2010, Cruz-Jentoft et al. 2019), and is present in 10% of those aged 60 years or older (Shafiee et al. 2017). It is a common cause of functional decline and loss of independence in older individuals (Tanimoto et al. 2013, Dufour et al. 2012, Marsh et al. 2011, Xue et al. 2011), largely owing to an increased risk of falls, vulnerability to injury, and disability (Szulc et al. 2005, Fukagawa et al. 1995, Tinetti and Williams, 1997).

Sarcopenia is strongly associated with frailty, which is defined as a state of increased vulnerability after a stressor event due to an age-associated decline in reserve and function across multiple physiological systems (Clegg et al. 2013). Like sarcopenia, frailty is associated with an increased risk of adverse outcomes, including falls, disability, hospitalisation and delirium (Fried et al. 2001, Gale et

al. 2014, Fried and Mor. 1997, Verloo et al. 2016, Eeles et al. 2012). Prevalence of frailty among those over 65 ranges from 10-60% depending on the diagnostic criteria used (Collard et al. 2012).

Frailty is defined either according to the cumulative deficit model (Rockwood et al. 2005), or the phenotype model (Fried et al. 2001). The cumulative deficit model defines frailty according to a cumulative effect of a number of individual deficits, whereas the phenotype model defines frailty as three or more of the following: weight loss, weakness, poor endurance, slowness, and low energy expenditure. Diagnosis of sarcopenia includes measures of skeletal muscle strength, skeletal muscle mass and physical performance. According to the new European Working Group on Sarcopenia in Older People (EWGSOP2) definition, sarcopenia is probable when low muscle strength is identified. A sarcopenia diagnosis is then confirmed by the presence of low muscle mass. When low muscle strength, low muscle mass and low physical performance are all observed, sarcopenia is considered severe (Cruz-Jentoft et al. 2019).

Dementia, sarcopenia and frailty are of great public concern as their prevalence continue to rise, likely due to a secular trend in populations across the globe. Although sarcopenia and frailty are increasingly recognised, there is currently limited work on how they interrelate with age-related neurological diseases, such as dementia. The significance of both sarcopenia and frailty has gained increasing importance due to their association with poorer health-related outcomes, their frequency in older adults, and their potentially reversible nature. The objective of this review was to examine the existing literature investigating the relationship between sarcopenia and/or frailty and dementia.

2.1 Methods

2.1.1 Search strategy

A systematic review was undertaken in order to map the current evidence in this area in a structured yet reflexive manner to identify research gaps, according to the framework set out by Arksey and O'Mally (2005), and Levac's team (2010). As part of this systematic review, a comprehensive search was conducted for potentially relevant studies of sarcopenia and frailty in dementia in the electronic bibliographic databases EMBASE, PubMed and Web of Science. A hand-search for relevant papers was also performed. The literature search was conducted January 2020, and the search-term applied was "(sarcopenia OR skeletal muscle OR muscle mass OR muscle strength OR dynapenia OR grip strength) AND (frailty OR frail OR non-frail OR nonfrail OR prefrail OR pre-frail) AND (dementia OR neurodegeneration OR neurodegenerative OR degeneration) NOT (systematic review OR clinical trial OR review OR animal OR case study)". No restrictions were placed on study location or publication date.

2.1.2 Study selection

The titles and abstracts of all citations were then screened for relevance independently by two reviewers (SW and SM). When relevance could not be ascertained from the abstract, the full paper was retrieved and reviewed. Any disagreements were resolved by a third reviewer (AJY). To be eligible for inclusion, the articles needed to fulfil the following criteria: (1) English language, (2) human studies, (3) full-text available. Dementia (but not mild cognitive impairment) of any aetiology was included. After reviewing the papers, we selected the studies for data extraction and analysis based on the following criteria: (a) studies using human participants; (b) no clinical trials.

2.1.3 Data extraction

The data were extracted using a data abstraction form. Research settings from which the participants were recruited, demographics, study design, numbers, and main findings were noted.

Frailty, sarcopenia and dementia diagnostic measures and definitions were also recorded, in addition to numbers for each condition where available. Incidence and prevalence of sarcopenia and/or frailty in dementia conditions were recorded where stated.

2.1.4 Assessment of study quality

The included studies were evaluated using appropriate quality assessment tools. Cross-sectional studies were given a quality score using the Appraisal Tool for Cross-Sectional Studies (AXIS) (range 0-20) (Downes et al. 2016) (see table 3), and longitudinal studies were scored according to a STROBE checklist (range 0-34) (Vandenbroucke et al. 2007) (see table 4).

3.1 Results

3.1.1 Study selection and characteristics

375 potentially relevant records were initially retrieved from PubMed, EMBASE and Web of Science (Figure 1). A further 14 were identified through hand-searching. After excluding for duplicates, 303 records remained. Following screening, 269 irrelevant publications were excluded. Therefore, a total of 33 papers were selected for the purposes of this review, as shown in *figure 1*. Of these 33 papers, 13 included measures of sarcopenia and 27 included measures of frailty, with six investigating both conditions. Ultimately, 33 studies involving 27 study groups were included, totalling over 100,000 participants (Table 1). The sample size in these studies ranged from 28-49,283, with an average of 3217 participants in each study. Of those studies providing specifics on gender (n = 40) and age (n = 25), 56.2% of subjects were female, and mean age was 75.4 years.

3.1.2 Study quality

Of the 16 longitudinal studies, the average score on the STROBE checklist of quality was 20.6 (range 15-26). They were generally low quality due to non-validated measures of frailty (n=10), sarcopenia (n=2) and dementia (n=4), lack of justification of sample size (n=15), or ambiguity regarding eligibility criteria (n=5) or number of non-consenters (n=12). For the cross-sectional studies, mean AXIS was 13.9 (range 10-17). Of the 17 cross-sectional studies, the majority were of low quality due to non-validated definitions of frailty (n = 7), sarcopenia (n=4) and dementia (n=6), and lack of justification of sample size (n=17).

3.1.3 Methodology of frailty assessment

The 27 included studies were heterogeneous, with many using different assessment tools, as displayed in Table 2. The phenotype model (Fried et al. 2001) was the most commonly adopted tool to assess frailty (Hsueh et al. 2018, Albala et al. 2017, Avila-Funes et al. 2012, Evenhuis et al. 2012, Ni Mhaolain et al. 2011, Gray et al. 2013, Namioka et al. 2017, Chong et al. 2015, Buchman et al. 2007, Buchman et al. 2008, Ohta et al. 2019, Cezar et al. 2017, Peball et al. 2019). Some studies used non-validated versions of the Fried criteria, with modified cut-off points (Gray et al. 2013, Namioka et al. 2017), or missing variables (Buchman et al. 2007, Buchman et al. 2008, Chong et al. 2015). Of note, some studies assessed physical frailty as only the presence of slow walking speed or weak handgrip strength (HGS) (Hooghiemstra et al. 2017, Shimada et al. 2018), which, when combined with signs of cognitive impairment, was defined as cognitive frailty in the study conducted by Shimada and co-workers (Shimada et al. 2018).

Six papers defined frailty using the frailty index (Peball et al. 2019, Borda et al. 2019, Wallace et al. 2019, Armstrong et al. 2010, De Cock et al. 2018, Rogers et al. 2017). However, many of these gathered this information retrospectively from existing data (Borda et al. 2019, Wallace et al. 2019,

Armstrong et al. 2010), which is not validated and may result in suboptimal measures being used. However, Borda and co-workers (Borda et al. 2019) argued that use of the frailty index is preferable when examining patients with dementia with Lewy bodies (DLB), as physical variables and measurements may be biased by the illness of DLB itself due to the symptoms of the disease (e.g., executive function impairment).

Other studies assessed frailty using different criteria: the Study of Osteoporotic Fractures (SOF) criteria (Bilotta et al. 2012); Edmonton Frail Scale (EFS) (Cezar et al. 2017, Armstrong et al. 2010); and assessments of only physical function, such as the physical performance test (Burns et al. 2010), timed-up-and-go (TUG) (Takechi et al. 2012, Lee et al. 2018) and HGS (Takechi et al. 2012, Shin et al. 2012). Although TUG and HGS measurements have been used previously in the assessment of frailty (Kim et al. 2010, Syddall et al. 2003), neither technique has been validated as a single measure of frailty. One study measured frailty using the Changes in Health, End-Stage Disease and Signs and Symptoms (CHESS) scale (Armstrong et al. 2010), which is not explicitly a frailty measure, rather, it is described as a measure of health 'instability' and is predictive of mortality. However, it is important to note that utilisation of different frailty definition protocols may result in varying results in the same study population. For example, Cezar and colleagues noted an association between frailty and Alzheimer's disease (AD) when using the EFS definition, but not when using the phenotype definition (Cezar et al. 2017). This may be reflective of the fact that the EFS includes assessment of cognition. However, it is important to note that this was a cross-sectional study, and therefore longitudinal data would be of value in elucidating the variations between frailty models.

3.1.4 Methodology of sarcopenia assessment

Until 2010, sarcopenia had no broadly accepted clinical definition or consensus diagnostic criteria. The European Working Group on Sarcopenia was formed in order to develop operational definitions and diagnostic criteria for sarcopenia to be used in clinical practice as well as in research studies (Cruz-Jentoft et al. 2010), which was then recently refined again (Cruz-Jentoft et al. 2019). Therefore, research undertaken in this area before 2010 utilised a variety of assessment tools in order to characterise age-associated changes in lean muscle. For example, studies undertook measures of muscle strength (Shin et al. 2012, Boyle et al. 2009, Hatabe et al. 2020) or body composition (Burns et al. 2010, Moon et al. 2019) independently, without combining these with other core measures of sarcopenia. One study assessed body composition and physical performance, but without measurements of muscle strength (Burns et al. 2010), and another study examined muscle strength and physical performance, but with no measures of body composition (Wang et al. 2006). Moon and colleagues (2019) investigated muscle mass and muscle strength, using dual-energy X-ray absorptiometry (DXA) scans and an isokinetic knee extensor test, respectively. In addition, they did not apply measurements of physical performance. No studies in this review utilised the European Working Group on Sarcopenia in Older People 2019 definition of sarcopenia, and only two used the previous European Working Group definition (Ohta et al. 2019, Sarabia Cobia et al. 2014), although some studies predated the original publication (Burns et al. 2010, Boyle et al. 2009, Wang et al. 2006). One Japanese study defined sarcopenia according to the consensus of the Asian Working Group for Sarcopenia (Ogawa et al. 2018), utilising measures of muscle strength, appendicular muscle mass and gait speed. Many studies included in this review did not utilise cut-off points in order to categorise scores as normal and sarcopenic. Instead, they calculated average scores in subgroups and assessed for statistically significant differences between groups (Chong et al. 2015, De Cock et al. 2018, Burns et al. 2010, Shin et al. 2012, Wang et al. 2006), but the majority of these were prior to publication of age-standardised normalised scores (Dodds et al. 2014). A study by Peball and colleagues (2019) ascertained sarcopenia using the SARC-F questionnaire, a five-item

screening test that assesses strength, assistance with walking, rising from a chair, climbing stairs, and falls (Malmstrom and Morley. 2013).

3.1.5 Methodology of dementia assessment

The majority of studies in this review did not specify dementia aetiologies, rather, dementia was broadly defined using questionnaires and neuropsychological scores (Hseuh et al. 2018, Albala et al. 2017, Shin et al. 2012), or reported based on health records (Evenhuis et al. 2012, Armstrong et al. 2010, Rogers et al. 2017, Lee et al. 2018, Sarabia Cobo et al. 2014). Across the studies that did investigate dementia more thoroughly, AD, DLB, vascular dementia (VaD) and Parkinson's disease (PD) were considered, with a mean number of participants in each sub-group of 180, 34, 75 and 100, respectively. AD was the most commonly investigated dementia sub-type, with 20 studies assessing the condition (Avila-Funes et al. 2012, Ni Mhaolain et al. 2011, Gray et al. 2013, Namioka et al. 2017, Chong et al. 2015, Buchman et al. 2007, Buchman et al. 2008, Ohta et al. 2019, Cezar et al. 2017, Borda et al. 2019, Wallace et al. 2019, Burns et al. 2010, Takechi et al. 2012, Boyle et al. 2009, Hatabe et al. 2020, Moon et al. 2019, Wang et al. 2006, Ogawa et al. 2018, Allan et al. 2009, Moon et al. 2019). The majority of these studies utilised a combination of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Alzheimer's Criteria, Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV or DSM-5 for AD diagnosis (Avila-Funes et al. 2012, Ni Mhaolain et al. 2011, Gray et al. 2013, Namioka et al. 2017, Buchman et al. 2007, Ohta et al. 2019, Chong et al. 2015, Borda et al. 2019, Wallace et al. 2019, Burns et al. 2010, Takechi et al. 2012, Boyle et al. 2009, Hatabe et al. 2020, Moon et al. 2019, Wang et al. 2006, Ogawa et al. 2018, Allan et al. 2009, Moon et al. 2019). These accepted criteria are fulfilled in a two-step diagnostic process, initial identification of a dementia syndrome, and then application of criteria based on clinical characteristics of the AD phenotype. However, one study diagnosed AD at brain autopsy using Bielschowsky silver stain to visualize neuritic plaques, diffuse plaques, and neurofibrillary tangles in the frontal, temporal, parietal, and entorhinal cortex and the hippocampus (Buchman et al. 2008).

Lewy body dementia was considered in three studies (Buchman et al. 2008, Borda et al. 2019, Takechi et al. 2012), and was assessed using the 1996 (Takechi et al. 2012) or 2005 (Borda et al. 2019) McKeith consensus criteria, or at autopsy by staining for Lewy bodies (Buchman et al. 2008). PD was considered by Peball and colleagues (Peball et al. 2019) using the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (Hughes et al. 1992), with medical history used to examine dementia in these individuals. VaD was examined in three studies (Avila-Funes et al. 2012, Takechi et al. 2012, Hatabe et al. 2020), where diagnosis was based on the National Institute of Neurological Disorders and Stroke, and Association Internationale pour la Recherche et l'Enseignement en Neurosciences.

3.1.6 Associations between frailty and dementia

The majority of the studies included identified a positive association between frailty and dementia (Hsueh et al. 2018, Albala et al. 2017, Avila-Funes et al. 2012, Evenhuis et al. 2012, Namioka et al. 2017, Buchman et al. 2007, Buchman et al. 2008, Ohta et al. 2019, Peball et al. 2019, Borda et al. 2019, Wallace et al. 2019, Armstrong et al. 2010, De Cock et al. 2018, Takechi et al. 2012) and this relationship often remained after adjusting for basic demographics and potential confounding factors (Hsueh et al. 2018, Avila-Funes et al. 2012, Ohta et al. 2019). However, work undertaken by Gray and colleagues (2013) in a population-based prospective cohort study (n = 2,619) reported that frailty was only associated with all-cause dementia in those with higher cognitive scores at baseline, but not in those with lower baseline scores, highlighting the importance of adjusting for potential

confounding factors and indicating a complex nature in the relationship between frailty and dementia-causing conditions (Gray et al. 2013). In 2018, Shimada and colleagues undertook a prospective cohort study (n = 4570) in which they observed that individuals with comorbid physical frailty and cognitive impairment could have a higher risk of dementia than healthy older adults or older adults with either physical frailty or cognitive impairment alone, suggesting shared underlying pathways (Shimada et al. 2018). However, this study did not collect data about dementia subtypes.

When dementia aetiologies were considered with frailty, AD was most often examined (Avila-Funes et al. 2012, Ni Mhaolain et al. 2011, Namioka et al. 2017, Buchman et al. 2007, Buchman et al. 2008, Ohta et al. 2019, Cezar et al. 2017, Chong et al. 2015, Hooghiemstra et al. 2017, Borda et al. 2019, Wallace et al. 2019, Takechi et al. 2012), with 3 considering DLB (Buchman et al. 2008, Borda et al. 2019, Takechi et al. 2012), 2 VaD (Avila-Funes et al. 2012, Takechi et al. 2012), and 1 PD (Peball et al. 2019). Regarding AD, mixed findings have been noted in studies conducted thus far. Wallace and colleagues (2019) and Ohta and co-workers (2019) recently reported an association between increased frailty and AD. Similarly, when Cezar and colleagues assessed frailty in individuals with amnesic mild cognitive impairment (aMCI) as a result of AD using the phenotype model and the EFS, they reported a significantly increased prevalence of frailty in those with aMCI compared with healthy controls when utilising the EFS definition, but not the phenotype model (Cezar et al. 2017).

Other papers have suggested that increased frailty is associated only with non-AD dementia (Avila-Funes et al. 2012, Gray et al. 2013). A seven-year longitudinal study assessing frailty in those with dementia (n = 5480) reported that frailty was not associated with incident AD, but frailty status was independently associated with incident VaD (Avila-Funes et al. 2012). This is supported by the work of Gray and colleagues in which frailty was linked with a higher risk of non-AD dementia but not AD (Gray et al. 2013). Individuals with DLB are reported to be frailer than those with AD across multiple studies (Borda et al. 2019, Takechi et al. 2012). In a cross-sectional study undertaken in 2012, Takechi and co-workers investigated frailty in individuals with dementia using TUG and HGS (Takechi et al. 2012). They reported that DLB patients (n = 13) were frailer than those with AD. Similarly, when a frailty index of 35 deficits was used in DLB, the proportion of frailty was twice as high in DLB compared to AD patients (Borda et al. 2019). One longitudinal clinicopathological study of frailty in DLB reported that presence of Lewy bodies was not associated with frailty (Buchman et al. 2008), however, the number with DLB was very small (n=3), and frailty was defined using continuous composite measures of four of the five components of the phenotypic frailty model, and some of the individual components were assessed using non-validated tools, which may have resulted in an underestimation of change in frailty.

Prevalence rates of frailty in individuals with PD are noted to be significantly greater than in healthy, age-matched controls (Peball et al. 2019). This study also reported that of the 19 PD patients with dementia, 15 had frailty (Peball et al. 2019), suggesting a potential relationship between Parkinson's disease dementia (PDD) and frailty. However, dementia was defined using medical history and therefore further studies may be required in order for this relationship to be further elucidated. Frailty is reported to be associated with a more adverse course of PD, with frail individuals displaying longer disease duration, higher motor impairment, decreased quality of life, higher frequency of falls, a higher non-motor symptom burden, institutionalization, and higher care levels compared to non-frail PD patients (Peball et al. 2019).

Frailty may predate a diagnosis of dementia, and a number of studies have examined this. For example, dementia is linked with unintentional weight loss beginning years before the diagnosis of AD (Johnson et al. 2006), and poor standing balance is reported to be significantly associated with a higher risk of future dementia occurrence after controlling for other factors (Wang et al. 2006).

Many studies conducted thus far have established that incident dementia and cognitive decline frequently occur in individuals characterised as frail (Albala et al. 2017, Avila-Funes et al. 2012, Gray et al. 2013, Buchman et al. 2007, Hooghiemstra et al. 2017, Shimada et al. 2018, Wallace et al. 2019, Armstrong et al. 2010, Rogers et al. 2017, Bilotta et al. 2012, Lee et al. 2018, Hatabe et al. 2020, Halloway et al. 2019), meaning frailty may be a predictor of dementia.

3.1.7 Associations between sarcopenia and dementia

Of the papers investigating muscle mass or quality in dementia, few directly reference sarcopenia, rather, studies may examine individual characteristics of the condition independently, without combining these with other measures in order to characterise sarcopenia (Burns et al. 2010, Shin et al. 2012, Boyle et al. 2009, Moon et al. 2019). For example, a South Korean cross-sectional study (Shin et al. 2012) measured HGS and sit-to-stand scores in those with and without dementia (number with dementia = 114), however, they did not undertake measurements of muscle mass or physical performance in order to characterise sarcopenia in these individuals. In addition, this study did not utilise cut-off points in order to categorise scores as normal or sarcopenic. Females with dementia had a significantly weaker average HGS than females without. Similarly, men and women with dementia displayed a significantly reduced ability in the sit-to-stand test compared with their non-demented counterparts ($p < 0.001$ for both males and females). It is important to note that the average HGS's of both the male and female individuals with dementia were in the sarcopenic range according to the EWGSOP2 (Cruz-Jentoft et al. 2019). This was also true for male and female participants with AD in the 2019 Ohta and co-workers study and in the Ogawa and colleagues (2018) study. It was not possible to ascertain whether this is true for the other studies as they did not report average scores for males and females, rather, they gave mean scores as a whole for dementia and non-dementia groups or percentage change in HGS over many years.

Decreased muscle strength has been reported to be associated with an increased risk of cognitive decline and the development of AD (Boyle et al. 2009). These findings are supported by the work of Chong and colleagues (Chong et al. 2015) in which significantly lower HGS and Short Physical Performance Battery scores were noted in those with mild and moderate AD, when compared with individuals with mild cognitive impairment (MCI). However, when lean muscle mass was assessed in this cohort using DXA scans, no significant differences between those with MCI, mild AD and moderate AD were reported, although there was a trend for reduced lean mass in individuals with moderate AD compared to mild AD and MCI, suggesting other factors may influence this process. It is important to note that DXA methods have been known to overestimate skeletal muscle mass (Kim et al. 2009), and thus interpretation of DXA measures can lead to elevated expectations regarding the diagnosis of sarcopenia. The trend reported in the Chong study is supported by the results from a recent longitudinal study undertaken by Moon and colleagues (Moon et al. 2019), in which appendicular skeletal muscle mass as measured by DXA scans in a group of 69 AD participants was found to predict dementia progression. This group carried out another study in 2019 in which they reported that muscle strength was related to left hippocampal volume ratio, and this relationship remained after adjusting for potential confounding factors (Moon et al. 2019). However, muscle strength only demonstrated a relationship to brain regional volume ratio when in the moderate stages of the disease, and not the mild. It was positively related to both the right and the left hippocampal volume ratio. Work conducted in 2010 reported an accelerated reduction in lean mass in AD, with an association between loss of lean mass and AD-related brain atrophy (Burns et al. 2010). Similarly, decreased skeletal muscle mass index has been noted in those with cognitive decline, and reduced skeletal lean appendicular mass, total lean skeletal muscle mass and fat free mass in those with mild and moderate dementia compared to those with MCI (De Cock et al. 2018).

The latter study also observed significantly reduced gait speed and slower timed get-up and go test scores in those classified as having dementia.

When sarcopenia was examined in individuals with PD using the SARC-F questionnaire, sarcopenia was reported to be significantly more prevalent in those with PD compared with age-matched healthy controls (Peball et al. 2019). In addition, the reports from this study noted that, of the 19 PD patients with dementia, 16 also had sarcopenia, suggesting a potential link between the conditions. The 2010 EWGSOP consensus definition of sarcopenia (Cruz-Jentoft et al. 2010) was used by Ohta and colleagues (Ohta et al. 2019) in order to characterise sarcopenia in individuals with MCI and AD. They reported a significant association between physical functions linked with sarcopenia and cognitive/affective functions of MCI/AD. This association was especially present in females compared to males. When sarcopenia has been assessed in AD outpatients (n=285) using the Asian Working Group for Sarcopenia consensus, individuals with AD, even the early stages of AD, show a high prevalence rate of sarcopenia (Ogawa et al. 2018). However, the data reported in this area thus far indicate that those individuals with dementia may have more sarcopenic qualities than those without, however, limited work has been undertaken investigating sarcopenia in those with non-AD dementia. In addition, it is important to note that the majority of work thus far has assessed muscle in those with dementia, with very limited work investigating dementia in individuals with sarcopenia. Therefore, further studies looking at dementia in sarcopenic patients are required in order to address this gap, and elucidate this potentially complex relationship.

4.1 Discussion

The heterogeneous methodologies utilised in this area reflect the relatively novel nature of sarcopenia and frailty research, and supports the need for clear consensus criteria for the diagnosis and management of these conditions. Nonetheless, studies undertaken thus far have been reasonably consistent in their findings, indicating that individuals with dementia may present an increased prevalence of frailty and features of sarcopenia. In addition, frailty may be a predictor of the development of dementia. However, limited work has been performed investigating frailty and sarcopenia in non-AD dementia. As such, further research is required in order to elucidate these relationships

4.1.1 Associations between frailty and dementia conditions

The majority of studies aimed to investigate frailty rather than sarcopenia in patients with dementia conditions. Of those studies examining frailty in dementia, many did not specify dementia subtype, and diagnosed dementia using non-validated criteria. This lack of detail makes for difficult interpretation of the data, however, the majority of the studies included in this review identified a positive association between frailty and dementia (Hsueh et al. 2018, Albala et al. 2017, Avila-Funes et al. 2012, Evenhuis et al. 2012, Namioka et al. 2017, Buchman et al. 2007, Buchman et al. 2008, Borda et al. 2019, Wallace et al. 2019, Armstrong et al. 2010, De Cock et al. 2018, Takechi et al. 2012). Three studies did not report any significant associations between frailty and dementia (Ni Mhaolain et al. 2011, Hooghiemstra et al. 2017, Bilotta et al. 2012), and four reported mixed findings. However, as many did not collect data about dementia aetiologies, inferences could not be made regarding frailty and specific dementia pathology.

4.1.2 Frailty in dementia subtypes

When dementia subtypes have been considered in the assessment of frailty, increased frailty has been associated with a greater risk of non-AD dementia (Avila-Funes et al. 2012, Gray et al. 2013). However, it is important to note that utilisation of different frailty definition protocols may result in

varying results in the same study population. As the degree of frailty among people of the same age may modify the association between AD pathology and Alzheimer's dementia (Wallace et al. 2019), individuals with even a low level of AD pathology might be at risk for dementia if they have high amounts of frailty. It is therefore possible that frailty might decrease the threshold of AD pathology required to cause clinical disease, or it could be a marker of impaired repair processes that might otherwise allow for AD pathology to be better tolerated. A possible explanation for the discrepancies between AD studies could be the lack of consideration of other dementia-causes. Despite its frequency, there is a paucity of research in DLB. The limited research that has been undertaken in this area generally indicates that DLB patients may be frailer than those with AD (Borda et al. 2019, Takechi et al. 2012), suggesting the trajectories of frailty and DLB share neurobiological underpinning. However, research thus far has utilised very few participants and less comprehensive assessments of frailty than those used in studies examining frailty in AD. Future studies in this area may benefit from use of consistent and validated tools for the characterisation of frailty.

As dementia is linked with poor standing balance (Wang et al. 2006) and unintentional weight loss beginning years before the diagnosis of AD (Johnson et al. 2006), frailty may occur before individuals present with symptoms of dementia. This indicates that frailty may give rise to underlying mechanisms provoking the onset of dementia, increase an individual's vulnerability to the development of dementia, or is a confounding factor. Although the mechanisms underlying these associations are as yet unclear, oxidative stress and inflammation have been proposed to play a role (Namioka et al. 2017).

4.1.3 Associations between sarcopenia and dementia conditions

Very few studies have comprehensively examined sarcopenia as a condition, therefore it is difficult to draw conclusions relating to its associations with dementia. However, characteristics of sarcopenia often present in individuals with dementia (Ohta et al. 2019, Chong et al. 2015, De Cock et al. 2018, Burns et al. 2010, Shin et al. 2012, Boyle et al. 2009, Hatabe et al. 2020, Wang et al. 2006, Sarabia Cobo et al. 2014). As loss of lean mass has been associated with AD-related brain atrophy (Burns et al. 2010), it is possible that brain atrophy and loss of muscle mass may co-occur. Presentation of sarcopenia in these individuals may be due to the reduction in physical activity levels that is both observed in those with dementia and linked with reductions in gray matter volumes (Abel et al. 2019, Halloway et al. 2019).

As with frailty, it is possible that sarcopenia is a predictor of dementia. Characteristics of sarcopenia, are linked with a significantly higher risk of future dementia occurrence (Lee et al. 2018, Shin et al. 2012, Boyle et al. 2009, Hatabe et al. 2020, Wang et al. 2006), suggesting poor mobility and lower extremity function may occur years before presentation of dementia. Although this relationship is currently poorly understood, loss of lean mass has been reported to be associated with brain atrophy (Burns et al. 2010). Therefore, this link may be either as a direct or indirect consequence of AD pathophysiology or through shared mechanisms common to both dementia and sarcopenia. For example, elevated levels of circulating inflammatory mediators are detectable in patients in both sarcopenia and dementia (Rong et al. 2018, Bano et al. 2017, Koyama et al. 2013, Scalzo et al. 2010). However, as little is currently understood regarding this, future studies may benefit from further investigating the potential associations between sarcopenia and dementia, and also the biological underpinnings of this relationship.

4.1.4 Conclusions

Work undertaken in this area has generally reported an increase in the prevalence of frailty and features of sarcopenia in those with dementia. However, methodologies have often been poor, with less comprehensive methods used for the diagnosis of sarcopenia and dementia, and a lack of consistency for definitions of frailty. Moreover, causes of dementia other than AD have rarely been considered. As non-validated methods were often used for dementia diagnosis, the reported findings may be influenced by misdiagnosis of dementia aetiologies. In future studies, prevalence of frailty and sarcopenia in those with different dementia-causing conditions must be examined so as to make clear whether the relationships between sarcopenia, frailty and dementia are applicable for dementia as a whole, or whether these conditions are specifically associated with certain dementia subtypes, such as AD or DLB. In addition, as limited work has been undertaken investigating how these relationships may change over time, current understanding in this area would benefit from monitoring these conditions in individuals with dementia over a period of years. Therefore, comprehensive, longitudinal studies, including gold standard methodologies for the diagnosis of sarcopenia, frailty and dementia, are required in order to elucidate the relationships between these conditions. With increased knowledge in this area, clinicians may be able to detect those more likely to develop dementia and prevent progression to dementia by addressing the sarcopenia and frailty syndromes. Further research into the link between sarcopenia, frailty, and dementia may not only facilitate our understanding of the conditions, but may also be pivotal in the future management of those at risk of developing dementia, by providing a new avenue for early identification and prompt intervention.

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Competing interests

Declarations of interest: none

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Key characteristics of studies included in systematic review

Study #	Study population				Study design
	Study	n	Mean age	Country	
1	Hsueh et al., 2018	205 (107 female)	75.5 ± 7.6 years	Taiwan	CSS
2	Gray et al., 2013	2,619 (1,573 female)	76.8 years	US	PCS
3	Albala et al., 2017	2,098 (1,406 female)	68.3 ± 6.3	Chile	LCS
4	Bilotta et al., 2012	265 (189 female)	81.5 ± (6.8)	Italy	PCS
5	Avila-Funes et al. 2012	5480 (3381 female)	74.0 ± 5.2	France	LCS
6	Armstrong et al. 2010	23,952	81.7 ± 7.4	Canada	CSS
7	Buchman et al. 2007	823 (614 females)	80.4 +/- 6.9 years	US	Data from LCPI
8	Namioka et al. 2017	140	80	Japan	CSS
9	Buchman et al. 2008	165 (93 female)	84.6 ± 5.6	USA	LCPI
10	Takechi et al., 2012	201 (132 female)	78.8 ± 6.9 years	Japan	CSS
11	Borda et al., 2019	186 (117 female)	76.10 ± 7.59	International	CSS
12	Wallace et al., 2019	456 (316 female)	83.1 ± 5.9	USA	CSS
13	Evenhuis et al., 2012	848 (412 female)	Mean not stated	Netherlands	CSS
14	Boyle et al., 2009	970 (729 female)	80.3 ± 7.5	USA	PCS
15	De Cock et al., 2018	516 (gender n numbers not stated)	Mean not stated	Belgium	CSS
16	Burns et al., 2010	140 (81 female)	73.3 ± 7.3 (control), 74.9 ± 6.7 (early AD)	USA	CSS
17	Chong et al., 2015	122 (72 female)	75.4 ± 7.2 years	Singapore	PCS
18	Mhaolain et al., 2011	115 (71 female)	74 years	Ireland	CSS
19	Shin et al., 2012	1038 (675 female)	72.8 ± 6.5 (no dementia), 78.1 ± 7.6 (dementia)	South Korea	CSS
20	Shimada et al., 2018	4570 (2326 female)	71.9 +/- 5.5 years	Japan	CSS
21	Hooghiemstra et al., 2017	309 (108 female)	69.6 ± 8.5 years	The Netherlands	Longitudinal multicentre study
22	Rogers et al., 2017	8,722 (4792 female)	64.4 ± 9.8 years	UK	LCS
23	Lee et al., 2018	49,283 (24,891 females)	All 66 years at baseline	Korea	LCS
24	Allan et al., 2009	179 (73 females)	Aged 65+	UK	LCS
25	Wang et al., 2006	2581 (1060 females)	73.5 ± 5.2 (dementia-free), 78.7±6.1 (dementia)	US	PCS
26	Hatabe et al., 2020	1,055 (606 females)	60 – 79 years	Japan	LCS
27	Ohta et al., 2019	297 (175 females)	71.6 ± 11.0 (control), 78.2 ± 6.2 (MCI), 80.6 ± 6.1 (AD)	Japan	CSS
28	Peball et al., 2018	434 (203 females)	73.8 ± 5.2 years	Austria	CSS
29	Ogawa et al., 2018	352 (220 females)	68 – 94 years	Japan	CSS
30	Cezar et al., 2017	66 (53 females)	>70 years	Brazil	CSS
31	Moon et al., 2019	69	76.8 ± 7.14 years	South Korea	LCS

32	Moon et al., 2019 ²	28 (25 females)	76.9 ± 7.6 years	South Korea	CSS
33	Sarabia Cobo et al. 2014	189 (140 females)	69 - 101 years	Spain	CSS

Table 1: CSS, cross-sectional study; PCS, prospective cohort study; LCS, longitudinal cohort study; LCPI, longitudinal clinical-pathologic investigation.

Methodologies and main conclusions of papers included in systematic review

Study #	Methodologies			Main conclusions
	Frailty assessments	Sarcopenia assessments	Dementia assessments	
1	Fried	N/A	AD8	Higher AD8 scores were associated with frailty.
2	Fried	N/A	DSM-IV, NINCDS-ADRD	Frailty was associated with higher risk of developing non-AD dementia but not AD.
3	Fried	N/A	MMSE and Pfeffer Activities	Frail individuals had a significantly increased risk of dementia.
4	SOF criteria	N/A	DSM-IV-TR	Frailty was not significantly associated with dementia.
5	Fried	N/A	DSM-IV-TR	Frailty was a risk factor for incident VaD.
6	CHESS, EFS, FI	N/A	Clinical notes	Frail individuals had a higher proportion of dementia diagnosis.
7	HGS, GS, body composition, and fatigue	N/A	Neuropsych, NINCDS-ADRD, CAPIT, McKeith (1996)	Increasing frailty was associated with incident AD.
8	Fried (revised)	N/A	DSM-5	Physical frailty was common in older and female AD patients.
9	HGS, GS, body composition, and fatigue	N/A	Brain autopsy	Frailty was associated with AD pathology.
10	TUG and HGS	N/A	AD = DSM-IV, NINCDS-ADRD, VD = NINDS-AIREN, DLB = McKeith's, MCI = Petersen's.	DLB patients were frailer and had higher care ranks than AD patients.
11	FI	N/A	DSM-IV, AD = NINCDS-ADRD, DLB = McKeith	The prevalence of frailty was higher in those with DLB compared to AD.
12	FI	N/A	NINCDS -ADRD	The degree of frailty modified the association between AD pathology and Alzheimer's dementia.
13	Fried	N/A	Clinical notes	Dementia was significantly associated with frailty.
14	N/A	Muscle strength	NINCDS- ADRD	Reduced grip strength was noted in those with dementia.
15	FI, BIA, gait analysis, TUG, CS	BIA, gait analysis, TUG, CS	DSM-IV, CDR	Frailty was associated with dementia
16	PPT	MRI, DXA, PPT	NINCDS-ADRD, CDR, Neuropsych	Skeletal muscle mass significantly lower, and frailty was significantly higher in individuals with dementia
17	Modified Fried, SPPB and DXA	DXA, SPPB, HGS	CMMSE, CDR, NINCDS-ADRD, CT scans, MRI scans	Frailty was not associated with dementia.
18	Fried	N/A	NINCDS-ADRD	Increased frailty is observed in dementia.
19	N/A	HGS, STS, BMI	GMS B3, CSID, mod 10-word list learning from CERAD	Reduced grip strength and poor sit-to-stand scores were independently associated with dementia.
20	GS, HGS	N/A	NCGG-FAT, ICD-10.	Individuals with comorbid physical frailty and cognitive impairment presented a higher risk of dementia than older adults with either physical frailty or cognitive impairment alone
21	GS, HGS	N/A	DSM-IV-TR, NIA-AA, neuropsych	Slower gait speed and weaker grip strength associated with cognitive impairment.
22	FI	N/A	Self-report of doctor diagnosis	Increased frailty was independently associated with an increased risk of dementia, however, not in adults who had low cognitive scores at baseline.
23	TUG test	N/A	Medical records	Poor TUG test results increased the risk of future dementia occurrence.
24	Falls diaries	N/A	DSM-IV, NINCDS-ADRD, McKeith (1999), NINDS-AIREN, Gibb (1987)	During the one year follow up period, 65.7% of participants with dementia had at least one fall, compared with 35.9% of controls.
25	10-ft timed walk, CS, standing balance, and HGS.	GS, CS, balance, and HGS.	DSM-IV, NINCDS-ADRD.	Noted an association between low levels of physical function with an increased risk of future dementia.
26	HGS	N/A	DSM, NINCDS-ADRD, NINDS-AIREN	Greater decline in handgrip strength from midlife to late life is associated with dementia.
27	Fried	EWGSOP	DSM	Noted significant associations between poor physical functions and cognitive dysfunctions, especially in females compared to males.
28	Fried	SARC-F	UK PD's Society Brain Bank clinical diagnostic criteria	Sarcopenia and frailty were more common in PD, and are associated with a more adverse course of the disease.

29	N/A	Asian Working Group for Sarcopenia consensus	DSM-5 criteria	Participants with AD showed a high prevalence rate of sarcopenia.
30	Fried, EFS.	N/A	National Institute on Aging-Alzheimer's Association	The identification of frailty features in amnesic MCI depend on the protocol used for evaluation.
31	N/A	DXA	NINCDS-ADRDA	Muscle profile was not found to predict dementia progression.
32	N/A	DXA, isokinetic knee extensor	NINCDS-ADRDA	Muscle strength was associated with hippocampal volume ratio in moderate AD.
33	N/A	BIA, dynamometry, and PPT	Clinical notes	There was a high percentage of sarcopenia amongst institutionalised elderly with dementia.

Table 2: SOF, Study of Osteoporotic Fractures criteria; CHES, Changes in Health, End-Stage Disease and Signs and Symptoms; EFS, Edmonton Frail Scale; FI, frailty index; HGS, hand-grip strength; TUG, timed-up-and-go; PPT, physical performance test; CS, chair stand; GS, gait speed; SPPB, short physical performance battery; BIA, bioimpedance analysis; DXA, dual-energy X-ray absorptiometry scans; MRI, Magnetic Resonance Imaging; STS, sit-to-stand; BMI, body mass index; EWGSOP, European Working Group on Sarcopenia in Older People consensus diagnostic criteria for sarcopenia; AD8, The Alzheimer's Disease 8; DSM, Diagnostic and Statistical Manual of Mental Disorders; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Alzheimer's Criteria; MMSE, Mini Mental State Examination; CAPIT, Core assessment program for intracerebral transplantations; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; CDR, Clinical Dementia Rating; CMMSE, Chinese Mini Mental State Examination; CT scans, computerised tomography scans; GMS B3, Geriatric Mental State Schedule B3; CSID, Community Screening Interview for Dementia; CERAD, Consortium to Establish a Registry of Alzheimer's Disease; NCGG-FAT, Center for Geriatrics and Gerontology Functional Assessment Tool; ICD-10, International Classification of Diseases-10; NIA-AA, National Institute of Aging – Alzheimer's Association criteria for Alzheimer's disease; MDS, MDS research criteria for prodromal Parkinson's disease (Berg et al., 2015); UPDRS-III, Unified Parkinson's Disease Rating Scale.

Risk of bias in cross-sectional studies included in this systematic review

Study first author	AXIS score (max 20)
Hseuh	10
Shin	14
Armstrong	12
Namioka	13
De Cock	14
Takechi	12
Ni Mhaolain	16
Burns	12
Borda	13
Wallace	14
Evenhuis	16
Ohta	13
Peball	17
Ogawa	15
Cezar	16
Moon ²	15
Sarabia Cobo	14

Table 3: AXIS, Appraisal Tool for Cross-Sectional Studies (Downes et al. 2016).

Risk of bias in longitudinal studies included in this systematic review.

Study first author	Quality score (max 34)
Shimada	21
Gray	22
Albala	15
Hooghiemstra	23
Bilotta	26
Avila-Funes	21
Buchman (2007)	16
Buchman (2008)	15
Chong	17
Wang	26
Lee	21
Allan	22
Rogers	24
Boyle	21
Hatabe	18
Moon	22

Table 4: STROBE appraisal tool (Vandenbroucke et al. 2007)

Study identification and selection flow chart.

Figure 1: Flow diagram of the systematic search of the literature, and study selection process.