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Relationship between depression and frailty in older adults: A systematic review and meta-analysis

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Highlights

- Depression and frailty are two common and pervasive conditions in older age.

- We conducted the first meta-analysis exploring the relationship between these constructs.

- In cross-sectional studies, participants with frailty had fourfold increased odds of depression.

- People with depression were at approximately fourfold increased odds of having frailty.

- Pooled data from longitudinal studies confirmed the heighted risk of comorbidity.

ABSTRACT (245/250)

Aim

Depression and frailty are prevalent and burdensome in older age. However, the relationships between these entities are unclear and no quantitative meta-analysis exists. We conducted a systematic review and meta-analysis to investigate the associations between depression and frailty.

Methods

Two authors searched major electronic databases from inception until November-2016 for cross-sectional/longitudinal studies investigating depression and frailty. The strength of the reciprocal associations between frailty and depression was assessed through odds ratios (ORs) adjusted for potential confounders.

Results

From 2306 non duplicated hits, 24 studies were included. The overall prevalence of depression in 8023 people with frailty was 38.60% (95% CI 30.07 to 47.10, I^2=94%). Those with frailty were at increased odds of having depression (OR adjusted for publication bias 4.42, 95%CI 2.66-7.35, k=11), also after adjusting for potential confounders (OR=2.64; 95%CI: 1.59-4.37, I^2=55%, k=4). The prevalence of frailty in 2167 people with depression was 40.40% (95%CI 27.00-55.30, I^2=97%). People with depression were at increased odds of having frailty (OR=4.07, 95%CI 1.93-8.55, k=8). The pooled OR for incident frailty, adjusted for a median

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of 7 confounders, was 3.72 (95%CI 1.95-7.08, I^2=98%, k=4), whilst in two studies frailty increased the risk of incident depression with an OR=1.90 (95%CI 1.55-2.32, I^2=0%).

Conclusion

This meta-analysis points to a reciprocal interaction between depression and frailty in older adults. Specifically, each condition is associated with an increased prevalence and incidence of the other, and may be a risk factor for the development of the other. However, further prospective investigations are warranted.

Key words: depression, frail, geriatrics, older adults, meta-analysis, psychiatry

INTRODUCTION

Frailty and depression are two common and pervasive medical conditions among older adults. The prevalence of depression in older age ranges from 10-20% (Rodda et al., 2011) and the prevalence of frailty is estimated to be similar (Collard et al., 2012). Recent studies have suggested that 16-35 % of frail individuals have also experienced co-existing depression, and that the prevalence of depression in frail individuals is as high as 46.5% ın older adults (Buigues et al., 2015). Both depression and frailty are associated with a range of deleterious outcomes in older age such as lower quality of life (QOL), increased use of healthcare services, increased morbidity and mortality (Clegg et al., 2013; Fugate Woods et al., 2005; Hare et al., 2014; Rodda et al., 2011). Furthermore, co-existing depression and frailty is associated with particularly worse outcomes such as accelerated cognitive impairment and disability (Potter et al., 2016). There are several reasons that may account for the high levels of commorbidity between depression and frailty. One is the overlap in some areas of diagnostic criteria, e.g. unintentional weight loss, making it difficult to distinguish from each other, particularly with advancing age. Another factor one is that depression and frailty have some common etiology that makes disentanglement difficult (Brown et al., 2014). Given the high levels of depression (Buigues et al., 2015) and frailty (Soysal P et al., 2016) in older age and the deleterious outcomes when they co-exist, understanding the relationship between these factors is of utmost importance.

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Despite the public health importance, the prevalence and incidence of depression among people with frailty and the opposite relationship is largely unknown. The convergence of the frailty and depression spectrum in mid- and late-life also give rise to the hypothesis of 'overlapping syndromes' (Katz, 2004), with possible biological mechanisms accounting for both syndromes (Vaughan et al., 2015). Most evidence to date suggests that the frailty and depression criteria consist of a highly overlapping but distinct subpopulation (Mezuk et al., 2013); moreover, the association between the two constructs cannot be fully explained by the overlapping of their symptoms (Lohman, 2013) so frailty and depression must be considered interrelated rather than overlapping syndromes. To date, previous narrative and/ or selective reviews have suggested there may be a relationship between frailty and depression (Brown et al., 2016; Buigues et al., 2015; Mezuk et al., 2012; Benraad et al., 2016; Drey et al.,2011). For instance, one previous narrative systematic review (Vaughan et al., 2015) suggested that the co-occurrence of depression and frailty was greater than 10% in older adults ≥ 55 years old, but noted that there is considerable variation in the estimates and a meta-analysis was not conducted. To date, to the best of our knowledge, no meta-analysis has been conducted to consider the relationship between depression and frailty.

Given the aforementioned, we conducted a systematic review and meta-analysis to investigate 1) the prevalence and odds of depression in people with frailty, 2) the prevalence and odds of frailty in people with depression, 3) the incidence of depression in people with frailty, and 4) the incidence of frailty in people with depression.

MATERIALS AND METHODS

This systematic review was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] criteria (von Elm et al., 2008) and the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] statement (Liberati et al., 2009). The review followed a predetermined, but unpublished protocol.

Search strategy

Two independent authors (BS and NV) searched Medline (via Ovid), Psychinfo and EMBASE for studies from inception until 11/2016 with no language restrictions. The search terms used were (frailty or frail*) and (depress* or depressive or major depressive disease). Conference abstracts were also included and the authors were contacted for obtaining missing information at least two times in a month.

Study selection

Included studies were published quantitative studies of a cross sectional or longitudinal design that: (1) Reported the prevalence or incidence of frailty <------> depression in older adults with a mean age over 60 years and older; (2) Captured frailty with a recognized criteria (e.g. Fried's criteria (Fried et al., 2001)); (3) Captured depression according to structured interview diagnostic criteria (e.g. DSM and major depressive disorder (MDD)) or depressive symptoms with a validated depression screening measure (e.g. Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977)) (henceforth called 'depression', although where possible in the results we differentiate between MDD and depressive symptoms); and (4) included a control group (pre-frail and robust as separated entities or together).

Studies were excluded if they (1) did not use clear diagnostic criteria for frailty or only used one item for its diagnosis (e.g. low gait speed) or (2) reported depression with an unvalidated screening tool or measure.

Data extraction

Two authors (NV, PS) independently extracted data from the selected studies in a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by consensus with a third author (BS). The following information was extracted: 1) characteristics of the study population (e.g. sample size, demographics, country in which the study was performed); 2) setting in which the study was performed; 3) diagnostic criteria for frailty and depression; 4) demographic characteristics (mean age and percentage of women) by frailty and depression status; 5) type and number of adjustments in the multivariate analyses (for longitudinal studies); 6) follow-up period (only for longitudinal studies).

If we required additional data to either confirm or enable study inclusion, we contacted the primary authors up to three times over a month period.

Outcomes

The primary outcomes were a) the prevalence and comorbid odds of depression/depressive symptoms in frailty and b) the prevalence and comorbid odds of frailty in people with depression/depressive symptoms. In addition, we calculated the incidence of c) depression/depressive symptoms onset in people with frailty, and d) frailty onset in people with depression/depressive symptoms.

Assessment of study quality

Study quality was assessed by two investigators (PS, BS) using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2012). A third reviewer was available for mediation (NV). The NOS assigns a maximum of 9 points based on three quality parameters: selection, comparability, and outcome (Wells et al., 2012).

Statistical analysis

Analyses were performed by two independent investigators (BS, NV) using Comprehensive Meta-Analysis (CMA) 3 (http://www.meta-analysis.com). Due to the anticipated heterogeneity, a random effects meta-analysis was undertaken. The analyses were conducted in the following steps. First, the prevalence of depression among people with frailty together with 95% confidence intervals (CIs) was calculated. Second, the odds ratio and 95% CI of frailty among people with and without depression was calculated. Third, the prevalence of frailty among people with depression and 95% CI was calculated. Fourth, the odds ratio and 95% CI of frailty among people with and without depression was calculated. For each of the above analyses, when possible, we conducted subgroup analyses investigating differences according to geographical region, study setting, depression classification (structured clinical assessment versus screening measure) and frailty measure (e.g. Fried criteria versus others) (Fried et al., 2001)). Where available, adjusted estimates of the association between frailty and depression (or the contrary) were extracted and pooled as ORs. Finally, ORs

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adjusted for the maximum number of covariates available for each study were used to assess the association between frailty (or depression) at the baseline and incident depression (or frailty) at follow-up. Study heterogeneity was measured using the Cochran's Q and I-squared statistics, assuming that a p≤0.10 for the former and a value ≥50% for the latter indicated a significant and substantial heterogeneity (Higgins and Thompson, 2002). Given significant heterogeneity, a meta-regression analysis was performed using differences in mean age, body mass index (BMI) and percentage of females among groups (frail, pre-frail, robust) as moderators in single meta regression. Publication bias was assessed by visually inspecting funnel plots, and to account for publication bias, we used the Duval and Tweedie trim-and-fill method (Duval and Tweedie, 2000), based on the assumption that the effect sizes of all the studies are normally distributed around the center of a funnel plot; in the event of asymmetries, it adjusts for the potential effect of unpublished studies.

RESULTS

The search identified 2,306 non-duplicated potentially eligible studies. Following a detailed review of title and abstracts, a total of 63 full text articles were reviewed. The eligibility criteria were applied and 39 articles were excluded (reasons summarized in **Figure 1**) with a total of 24 articles meeting the inclusion criteria (Almeida et al., 2016, 2015; Arts et al., 2016; Badalà et al., 2008; Brown et al., 2014; Chang et al., 2010; Collard et al., 2014; de Albuquerque Sousa et al., 2012; Dent and Hoogendijk, 2014; L. Feng et al., 2014; Fried et al., 2001; Hajek et al., 2016; Jarschik et al., 2012; Jung et al., 2016; Lakey et al., 2012; Lohman et al., 2016, 2014; Makizako et al., 2015; McAdams-DeMarco et al., 2016; Monin et al., 2016; Paulson and Lichtenberg, 2013; Pegorari and Tavares, 2014; Sanchez-Garcia et al., 2014; Woods et al., 2005). Of the 24 included studies, 17 studies provided only cross-sectional data, 3 studies provided only longitudinal data, and 4 studies had both cross-sectional and longitudinal data. One study (Monin et al., 2016) did not contain any data that could be included in the meta-analysis.

Study and participants' characteristics

Study and participants' characteristics of cross-sectional studies are summarized in **Supplementary Tables 1 and 2**. The majority of the studies were conducted among community-dwellers (n = 19 (79.1%)) and in North America (n=12 (50.0%)), followed by Europe (n=4), Asia (n=3), Australia (n=3), and Latin America (n=2). (**Supplementary Table 1**). The overall quality of the studies, assessed through NOS, was generally good with a median=8 (range=5-9) (Full details are available in **Supplementary Table 5).**

Overall 12 cross-sectional studies (Jurschik et al., 2012; Pegorari et al.,2014; Feng, 2014; Matheus et al., 2015; Dent and Hoogendijk EO, 2014; Chang et al., 2009; Sanchez-Garcìa et al., 2013; Patricio de Albuquerque Sousa et al., 2011; Fried L.P.et al., 2001; Fugate Woods N. et al., 2005; Jung et al., 2016; Mara A. McAdams et al., 2016) investigated the prevalence of depression in frailty including a total of 8023 frail older participants with a mean age of 74.6 years, of whom 94.0 % were female. These participants were compared with 45,775 participants with no frailty (mean age: 70.2; 88.1% females). Furthermore, the 8 cross sectional studies investigating the prevalence of frailty in people with depression (Collard et al.,2014; Lohman et al., 2016; Almeida et al., 2015; Brown et al., 2015; Lohman et al., 2014; Mezuk et al., 2013; Paulson D. and Lichtenberg, 2013; Osvaldo P. Almeida et al., 2016) included 2,164 depressed older adults with a mean age of 69.3 years, 66.5 % of which were females. These subjects were compared with 14,932 subjects with no depression.

In addition, there were 311 frail older adults in the 3 longitudinal studies (Feng et al., 2014; Makizako et al., 2015; Monin et al., 2016) (mean age 75.1, 39.1% females) investigating the incidence of depression over a mean follow up of 4.67 years. These subjects were compared with 5801 subjects with no frailty at baseline. Finally, there were 6404 depressed older adults in 4 longitudinal studies (Fugate Woods N. et al., 2005; Paulson and Lichtenberg, 2013; Lakey et al., 2012; A Hajek et al., 2016) that investigated the incidence of frailty over a mean follow up of 2.87 years. These participants were compared with 51,610 participants with no depression (**Supplementary Tables 3 and 4**).

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Measurement of frailty

Overall, 19 studies used Fried and colleagues' criteria to define frailty (≥ 3 criteria among unintentional weight loss, poor physical activity, slowness, reduced muscular strength, and exhaustion) (Fried et al., 2001). The other measures of frailty include the Women's Health Initiative Observational Study (WHI-OS) (≥ 3 criteria among slowness and exhaustion measured with Rand-36 physical function scale and vital scale and self-reported weight loss >5% in the last two years and weekly energy expenditure) (n=1) (Fugate Woods N. et al., 2005); International Association of Nutrition and Aging (Iana) Task Force definition of frailty (n=2) comprehending five relevant domains: fatigue, resistance, ambulation illnesses and loss of weight (≥ 3 criteria) (Abellan et al., 2008); the adapted frailty index including the following: wasting, weakness, slowness, fatigue or exhaustion, and falls (n=1) (Paulson and Lichtenberg, 2013); and Clinical Frailty Scale ranging from 1 (very fit) to 7 (severely frail) (n=1) (Rockwood et al.,2005).

Measurement of depression

Depressive symptoms were assessed using the CES-D scale (n=11), the Geriatric Depression Scale (GDS) (n=8) (Radloff et al, 1977), and Composite International Diagnostic Interview (CIDI) (n=2) (Wittchen et al., 1991). Three studies adopted different methods including the Patient Health Questionnaire (PHQ-9) (requiring at least 5/9 symptoms) (Kroenke et al., 2001), interview schedule based on the Diagnostic and Statistical Manual of Mental Disorders (DSM III-R) and the Burnam 8-item depression screening instrument (Burnam et al., 1988).

Cross-sectional meta-analysis findings

Prevalence of depression in people with frailty

Full details of the prevalence of depression in people with frailty are summarized in **Table 1**. The overall prevalence of depression in 8023 people with frailty was 38.6% (95% CI 30.07 to 47.10, I^2=94%). Table 1 shows the prevalence of depression in frail people stratified by geographical region, study setting,

depression outcome and definition of frailty. These moderators did not significantly affect our results, although the prevalence of frailty was higher in studies in Latin America, among community-dwellers, using screening measures for depressive symptoms (instead of structured interviews for MDD) and using the criteria suggested by Fried et al. (**Table 1**). A visual inspection of funnel plots (available from corresponding author on request) did not suggest publication bias and the trim and fill analyses all remained unchanged when any potential publication bias was adjusted for (**Table 1)**.

Odds of depression in people with frailty versus controls

Across eleven studies, taking people without frailty as the reference group, frail people had higher odds of having comorbid depression (OR=3.95, 95% CI 2.36 to 6.58, p <0.001). After adjusting for publication bias, the OR increased to 4.42 (95% CI 2.66-7.35). The between group p values for the subgroup analyses remained non-significant **(Table 1),** however, some results in the subgroups became non-significant which may be due to a small number of studies in some groupings. No study reported the odds of depression in people with frailty, adjusted for potential confounders.

Prevalence of frailty in people with depression

Full details of the meta-analysis of the prevalence of frailty in depression are presented in **Table 2**. In 2167 participants with depression, the prevalence of frailty was 40.40% (95% CI 27.00 to 55.30, I^2=97%). The prevalence of frailty was significantly higher (p=0.03) in studies capturing depression with a screening measure (49.50%, 95% CI 32.50 to 66.60) compared to a structured clinical diagnosis for MDD (17.62%, 95% CI 5.46 to 44.22) and some variation was noted according to frailty assessment methods, although some caution should be given due to small number of studies in each group (**Table 2**). The trim and fill analyses all remained unchanged.

Odds of frailty in people with depression versus controls

Taking the participants with no depression as reference, people with depression had an increased risk of having frailty (OR=4.07, 95% CI 1.93 to 8.55, p<0.0001; I^2=96%) (**Table 2**)**.** This association was significant in five studies including North Americans (OR=2.25; 95%CI 1.00-5.08, p=0.05; I^2=96%) compared to other settings (**Table 2**). As shown in **Table 2**, publication bias was unlikely.

Four studies (Chang et al., 2010; de Albuquerque Sousa et al., 2012; Jarschik et al., 2012; Pegorari and Tavares, 2014) reported the OR for frailty in adjusted analyses in depressed vs. no depressed people, taking robust participants as reference. After adjusting for a median of 6 potential confounders (range: 3-12), the pooled OR was 2.64 (95%CI: 1.59-4.37; I^2=55%; **Figure 2**). Another study (Jung et al., 2016) reported that an OR of 5.25 (95%CI: 2.55-10.83) for frailty vs. pre-frailty/robustness, after adjusting for 4 potential confounders.

Longitudinal meta-analysis findings

Studies investigating incident frailty in older people with depression

Overall, 6404 older adults with depression at baseline were followed over a mean of 2.87 years investigating incident frailty (Fugate Woods N. et al., 2005; Paulson and Lichtenberg, 2013; Lakey et al., 2012; A Hajek et al., 2016). The pooled OR for incident frailty, adjusted for a median of 7 potential confounders (range: 0-21) (**Supplementary Table 3**), was 3.72 (95%CI 1.95-7.08; p<0.0001; I^2=98%), as shown in **Figure 3**.

Studies investigating incident depression among people with frailty

Overall, two longitudinal studies (L. L. Feng et al., 2014; Makizako et al., 2015) including 4852 older adults investigated incident depression as the outcome. These two studies found that frailty at the baseline increased the risk of incident depression by about 90% (OR=1.90; 95%CI 1.55-2.32, p<0.0001; I^2=0%), after adjusting for 11 covariates (**Figure 4; Supplementary Table 4)**. One study (Monin et al., 2016) with no meta-analyzable data reported an association between depression and frailty in 1260 community-dwelling married couples.

DISCUSSION

In this meta-analysis, for the first time, we have considered the possible bidirectional relationship between frailty and depression summarizing the data of both cross-sectional and longitudinal studies. In summary, our data suggests that across cross-sectional studies, approximately forty percent of individuals with depression have frailty and a similar proportion of those with frailty have depression. Our comparative meta-analysis suggests that frail older people are four times more likely to have depression than non-frail people. A similar increased odds for frailty was evident in older people with depression versus those without depression. Longitudinal studies substantially confirmed these findings despite being more limited in number.

Frailty, is a multifactorial geriatric syndrome, which could be influenced by pain, mobility and balance problems, weakness, poor endurance etc. All of these risk factors may lead to disability, or functional dependence, and thus lead to depression (Fugate Woods N. et al., 2005). On the other hand, depression may also predict indicators of frailty due to the decrease in social ties, gait speed, and less physical activities, or due to the increase in sedentary life, fall risk, weight loss, and malnutrition, which may increase the perpetuation of affective symptoms typical of depression including sadness, anhedonia, and helplessness (A Hajek et al., 2016; Paulson et al., 2013). Additionally, depression may not only be associated with physical frailty, but also with cognitive impairment, which may be long-lasting and may persist even during affective remission (Bortolato et al., 2016). Depression-related cognitive impairment may contribute to the emergence of frailty. It is also possible that there are shared risk factors and pathophysiological pathways. First, these reciprocal associations may be at least partly explained by overlapping mechanisms such as cerebrovascular disease, chronic inflammation, oxidative stress (Black et al., 2015), mitochondrial dysfunction (Brown et al., 2016), hypothalamic-pituitary-adrenal (HPA) axis dysregulation (Belvederi et al., 2014), among others (Katz, 2004; Soysal et al., 2016; Soysal P et al., 2017). Subclinical vascular diseases that cause pre-frontal white-matter hyperintensities in patients with late-life depression have consistently been considered a key factor in prefrailty (Newberg et al., 2006). Growing evidence also supports a positive association between frailty and the inflammatory cytokines, such as interleukin 6 (IL 6) (Soysal et al., 2016),

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which is also known to be elevated in individuals with late life depression (Vaughan et al., 2015). Inflammatory cytokines are associated with both decreased muscle mass and strength, and also negatively affect the central dopaminergic function, which may result in depressive affect, fatigue, and cognitive and motor slowing (Brown et al., 2016). Mitochondrial dysfunction has also been identified in numerous neurodegenerative diseases as well as depression. Muscle biopsies in patients with depression have shown decreased ATP production, and adults with depression had also impaired mitochondrial respiration in peripheral blood mononuclear cells, most strongly correlating with the symptom of fatigue (Brown et al., 2016). The detrimental cycle between declined activity, mobility, and energy levels resembles the clinical presentation of depression as well as those with the frailty syndrome (Brown et al., 2016). Another hypothesis is that HPA axis dysregulation, as well as aberrations in other mediators, such as insulin-like growth factor, and testosterone (Belvederi et al., 2014), have been reported in frail persons with significant depressive symptoms and may account for the reciprocal association herein observed (von Zerssen et al., 1986). Moreover, the beneficial effects of the approaches to prevent frailty or depression may protect the other. For example, the successful treatment of the depression itself may result in increased behavioral and social activation, thereby increasing physical and social activity levels, improving muscle mass and strength, and the elder's overall energy levels, thereby, reducing frailty (Lakey et al., 2012). Similarly, increasing physical activity is an effective intervention for frailty in older adults, and can protect and manage depressive symptoms in the elderly through potential neurobiological changes and as a consequence of social and physical engagement (Brown et al., 2016; Stieglitz et al, 2014; Peterson et al., 2009; Schuch et al.,2016a; Schuch et al., 2016b). Other interventions such as improving balance and muscle strength, and vitamin D supplementation may also play a role in preventing or treating frailty (Brouwer-Brolsma et al., 2013). Depressive symptoms may cause vitamin D deficiency via decreased sun exposure, poorer dietary intake and more smoking (Brouwer-Brolsma et al., 2013). In fact, all these findings support the bidirectionality of the depression–frailty relationship. Clearly, future research is required to explore and understand such relationships.

Our comprehensive meta-analysis results advance the literature from previously published narrative and/ or selective reviews that have considered the relationship between depression and frailty. Meta-analyses enable the logical pooling of data and enable a more precise estimate of the prevalence and/ or odds of an outcome than when making subjective considerations of individual studies separately such as those in previous narrative reviews (Ioannidis and Lau, 1999). Nonetheless, the previous reviews have illustrated some interesting findings. One review, including 28 studies, reported that frailty and depression are comorbid geriatric syndromes in a subgroup of older individuals, and that frailty is also a risk factor for the development and persistence of depressive symptoms (Buigues et al., 2015). Another review, including both cross-sectional (n = 16) and cohort studies (n = 23) indicated that frailty, its components, and functional impairment are risk factors for depression (Mezuk et al., 2012). On the other hand, another review found that the relationship between depressive symptomatology and increased risk of incident frailty was robust, while the opposite relationship was less conclusive (Vaughan et al., 2015). However, the potential role of antidepressant medications on frailty has not been clearly evaluated in any of these reviews. Because, as shown in the review by Benraad et al, geriatric characteristics are rarely taken into account in trials on antidepressant drugs in late-life depression (Benraad et al., 2016). To differentiate from these previous reviews, the meta-analysis was performed in the present study (Buigues et al., 2015; Mezuk et al., 2012). Specifically our data established that frail older people are four times more likely to have depression compared to controls, with similar increased odds for frailty among those with depression versus controls. While cross-sectional studies are unable to clarify the directionality of the relationship between frailty and depression, it clearly indicates that there is a high level of comorbidity. Whether or not this is attributed to mutually exclusive or overlapping symptomology of each condition is not clear and future prospective research may help to disentangle this relationship and explore potential overlapping symptomology and disease onset. Nonetheless, the limited number prospective studies does suggest that after adjusting for confounders, people with depression are at increased risk of developing frailty, whilst the converse relationship also appears to be evident. However, the small number of longitudinal studies

precludes any definitive conclusions and future longitudinal research is required to specifically attempt to differentiate between the signs and symptoms of both conditions.

Some factors were identified in our analyses as being potentially important in explaining the association between depression and frailty. The prevalence of depression in frail people, in fact, was higher in studies from Latin America, among community-dwellers, those using depression screening measures (instead structured interviews) and in studies which considered criteria suggested by Fried et al. (Fried et al., 2001) A recent international study demonstrated that depressive symptoms are more pronounced within traditional family based value patterns, like Latin America, possibly because of higher expectations of the availability of family support that are often only partially fulfilled due to recent changes in family structure (Ylli et al 2016). Fried's criteria shares symptoms with the CES-D and this could partially explain the high correlation. However, some studies have found that the strong association between frailty and depression is not unique to a single definition of frailty such as the Clinical Frailty Index, and thus, our findings do not seem to be fully explained by shared symptomatology (Lohman et al., 2014). We also examined the opposite relationship, i.e. the prevalence of depression among the frail and the odds and incidence of depression in frail older individuals compared to robust ones. Depressed people showed significantly higher levels of frailty (~40%), mainly in North American studies and in one Australian study (Almedia et al., 2015).

Prospective studies of the relationship between depression and incident frailty also suggest that depression may increase the risk of frailty (Vaughan et al., 2015). Depression is associated with increased weakness, mobility deficits, and fatigue, which may thus increase the risk of frailty and increased mortality over a period of up to 5 years (Veronese et al., 2016). The role of antidepressant drug treatment in the relationship between depression and frailty deserve further investigation. Antidepressants have been associated with a higher risk of incident frailty (Lakey et al., 2012). This association could simply be explained by a more severe and chronic form of depression that required the use of antidepressant drugs (Vaughan et al., 2015), but a large prospective observational study reported that even in the absence of

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depressive symptoms, antidepressant use was associated with becoming frail (Lakey et al., 2012). Therefore, non-pharmacological interventions may be an important approach for depressed frail older adults. Clearly further research is needed to elucidate the possible role of drugs in the depression-frailty relationship (Mezuk et al., 2012).

LIMITATIONS

Whilst our data provides some novel insights, some limitations should be acknowledged. The most important lies in that the evidence is largely drawn from case-control and cross-sectional studies. Thus the directionality and degree of overlap between these two constructs is not clear. In addition, the number of prospective studies was limited, therefore future prospective research is required to allow a better elucidation of potential moderators which could influence the reciprocal prospective associations between depression and frailty. A second limitation is the high heterogeneity observed. The different methods and different cut-off values used for defining frailty and depression might play a role, but our findings suggest that these factors cannot completely explain the observed reciprocal associations. Third, there was limited information on important moderators such as physical activity, medication use, presence of dementia, and inflammatory cytokines. Fourth, depression was diagnosed through non-original methods (DSM), and only four studies (Anand et al., 2012; L. Feng et al., 2014; Fried et al., 2001; Lakey et al., 2012) reported data regarding antidepressants, thus precluding the possibility to conduct a meta-analysis. However, in one large longitudinal study, the use of antidepressants was associated with a higher incidence of frailty indicating that this factor is of importance in the association between depression and frailty (Lakey et al., 2012). Thus, future research should consider the relationship between antidepressant medication and frailty/depression. Finally, the presence of depressive symptoms in the construct of frailty may artificially contribute to the relationship between frailty and depression. More research is required to investigate the relationship between major depression and clearly defined frailty in particular. Such research might also

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consider the relationship of important potential moderators such as physical activity, antidepressant medication and inflammatory markers.

In conclusion, our results provide evidence for a consistent bidirectional relationship between frailty and depression among older people. However, the precise mechanisms underpinning those reciprocal epidemiological associations deserve further investigation. Our data suggest that over a third of people with frailty have depression and a similar proportion of people with depression have frailty, while the odds of each condition are four times higher than controls. Therefore, interventions designed to decrease one of both syndromes can prevent the emergence of other. Our data is of public health importance and may open important perspectives for the prevention and treatment of those highly co-occurring and prevalent conditions.

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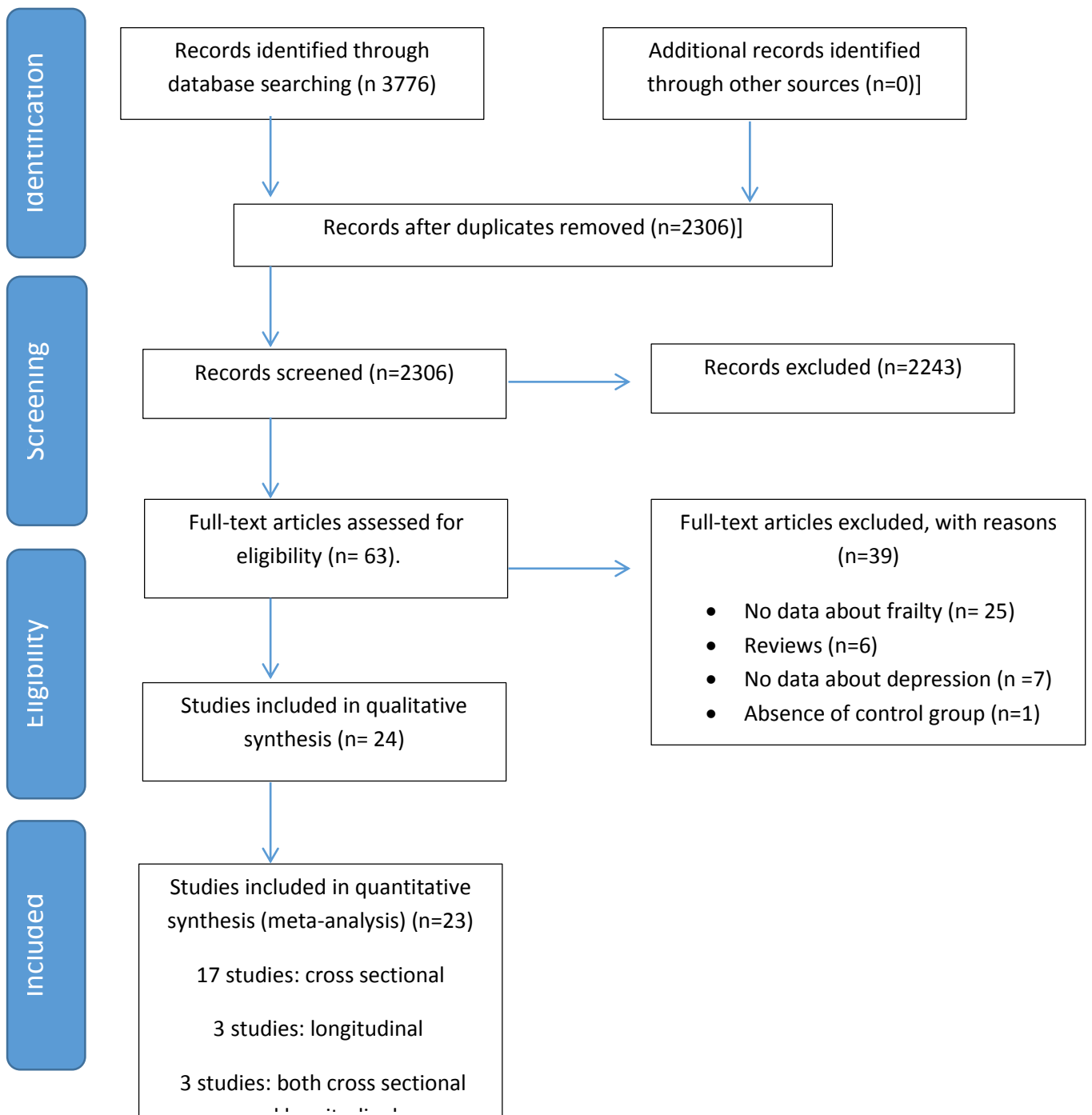
Figure 1. PRISMA flow-chart

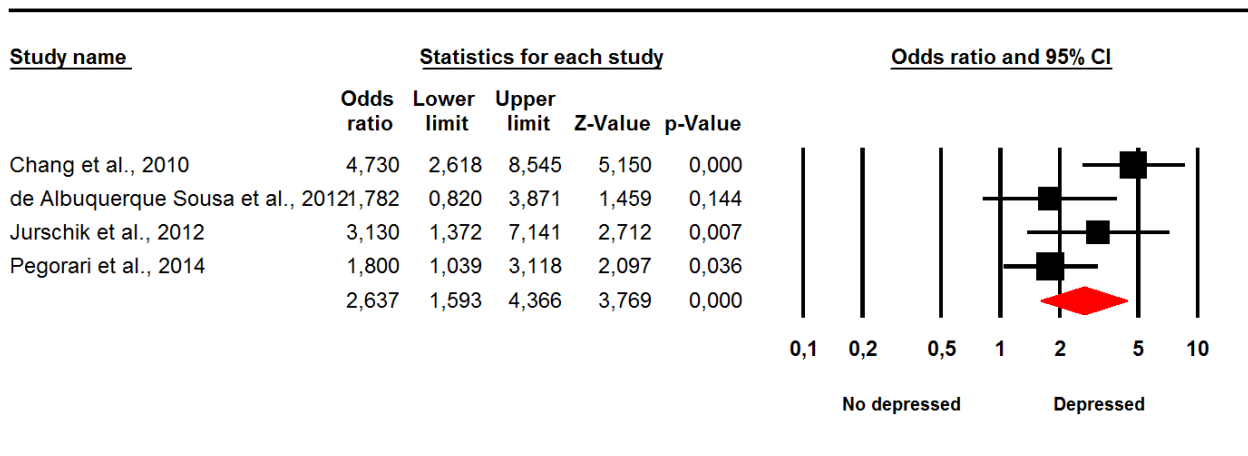Figure 2. Odds of frailty in people with depression versus controls

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Chang et al., 2010	4,730	2,618	8,545	5,150	0,000
de Albuquerque Sousa et al., 2012	1,782	0,820	3,871	1,459	0,144
Jurschik et al., 2012	3,130	1,372	7,141	2,712	0,007
Pegorari et al., 2014	1,800	1,039	3,118	2,097	0,036
	2,637	1,593	4,366	3,769	0,000

Figure 3. Odds for incident frailty in older people with depression

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Fugate Woods et al., 2005	2,200	1,882	2,572	9,886	0,000
Hajek et al., 2016	6,840	5,665	8,258	20,004	0,000
Lakey et al., 2012	2,260	1,677	3,045	5,360	0,000
Paulson et al., 2015	5,640	4,041	7,872	10,169	0,000
	3,716	1,946	7,095	3,977	0,000

Meta Analysis

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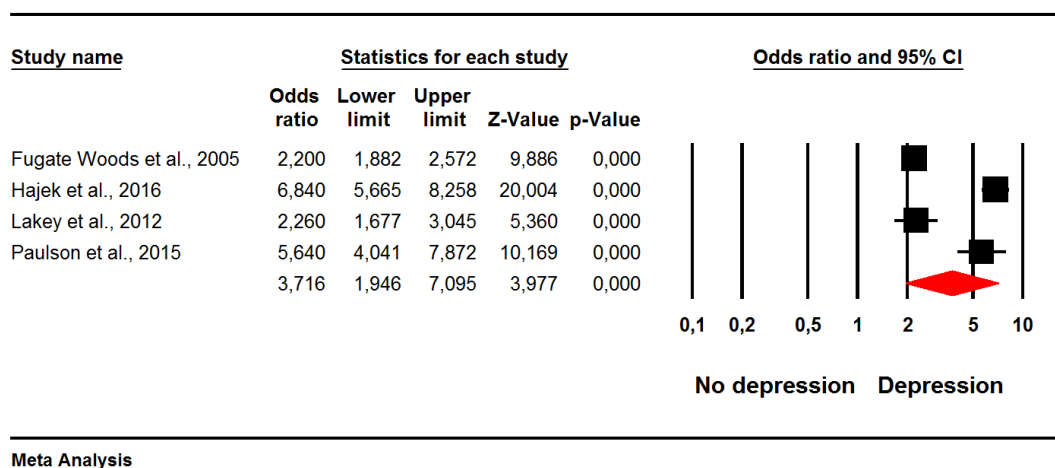
Figure 4. Odds for incident depression among people with frailty

Study name	Statistics for each study					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Feng et al., 2014	3,090	1,122	8,513	2,182	0,029	
Makizako et al., 2015	1,860	1,517	2,280	5,974	0,000	
	1,897	1,554	2,316	6,287	0,000	

0,1   0,2   0,5   1   2   5   10

No frailty   Frailty
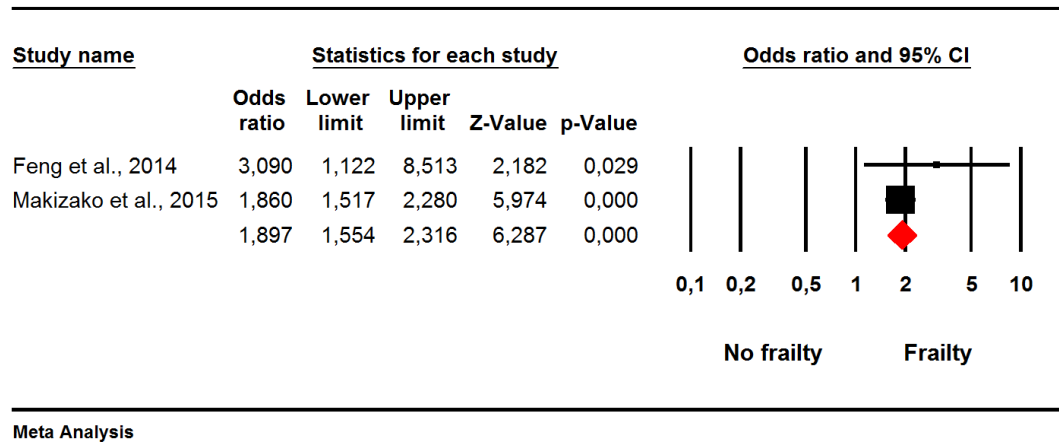
Meta Analysis

Table 1-Meta-analysis results of prevalence and odds of depression in older people with frailty

Analysis	Number of study estimates	Number of participants	Meta-analysis			Between group p value	Trim and fill effect size (95% CI) [adjusted studies]	I²
Prevalence of depression in older people with frailty								
			Prevalence	95% CI				
Main analysis	11	8023	38.60%	30.07	47.10		Unchanged	94
Geographical region						0.751		
North America	5	7478	41.08%	29.02	54.31		Unchanged	97
Asia	2	211	34.63%	17.57	56.83		N/A	46
Europe	2	147	30.12%	14.93	51.44		N/A	N/A
Latin America	2	190	44.02%	24.78	65.24		N/A	N/A
Study Setting						0.737		
Community	10	7830	39.00%	30.05	48.13		Unchanged	94
Community and inpatients	1	96	34.02%	13.84	62.32		N/A	N/A
Depression outcome						0.737		
Screening measure	10	7830	39.00%	30.05	48.13		Unchanged	94
Structured instrument	1	96	34.02%	13.84	62.32		N/A	N/A

Frailty measure						**<0.001**		
Fried	10	1302	40.04%	33.60	47.60		Unchanged	83
WHI-OS	1	6619	26.16%	12.98	45.70		N/A	N/A
Odds of depression in older people with frailty								
			OR	**95% CI**				
Main analysis	11	53626	3.94	2.36	6.58	**<0.001**	4.42 (2.66-7.35) [1]	96
Geographical region						0.312		
North America	5	49181	6.700	2.92	15.34	**<0.001**	Unchanged	98
Asia	2	2207	4.582	1.24	18.92	**0.02**	N/A	69
Europe	2	889	1.298	0.23	7.12	0.763	N/A	N/A
Latin America	2	1349	2.437	0.45	13.12	0.299	N/A	N/A
Study Setting						0.28		
Community	10	53260	4.420	2.57	7.65	**<0.0001**	4.99 (2.93-8.51) [1]	96
Outpatients and inpatients	1	366	1.240	0.24	6.20	0.86	N/A	N/A
Depression outcome						0.28		
Screening measure	10	53260	4.420	2.57	7.65	**<0.0001**	4.99 (2.93-8.51) [1]	96
Structured instrument	1	366	1.240	0.24	6.20	0.86	N/A	N/A
Frailty measure						0.34		

									Key: N/A= not appli cable.
Fried	10	12969	4.074	1.96	8.84	**0.001**	4.65 (2.30-9.38) [1]	96	
WHI-OS	1	40657	2.855	0.28	28.69	0.372	N/A	N/A	

CI: Confidence interval; OR: Odds ratio; WHI-OS: Women's Health Initiative Observational Study -

Table 2-Meta-analysis results of prevalence and odds of frailty in older people with depression

Analysis	Number of study estimates	Number of participants	Meta-analysis			Between group p value	Trim and fill effect size (95% CI) [adjusted studies]	I2
Prevalence of frailty in older people with depression								
			Prevalence	95% CI				
Main analysis	8	2167	40.40%	27.00	55.30		Unchanged	97
Geographical region						**0.027**		
North America	5	1381	31.26%	17.32	49.67		Unchanged	97
Australia	2	398	72.9%	39.1	91.9		N/A	N/A
Europe	1	378	27.24%	0.64	67.38		N/A	N/A
Study setting						0.576		
Community	7	1789	42.60%	27.10	59.70		Unchanged	97
Community and inpatient	1	378	27.24%	5.450	70.86		N/A	N/A
Depression classification						**0.03**		
Screening tool	6	1701	49.50%	32.50	66.60		Unchanged	97
Structured interview	2	466	17.62%	5.460	44.22		N/A	90
Frailty measure						**0.007**		

Fried	5	1592	27.12%	15.9	49.29		Unchanged	96
Fried adapted	1	167	51.49%	20.04	81.80		N/A	N/A
Iana Task	2	408	85.45%	54.31	96.67		N/A	N/A
Odds of frailty in older people with depression								
			OR	**95% CI**				
Main analysis	8	17099	4.068	1.93	8.55	**<0.001**	Unchanged	96
Geographical region						0.063		
North America	5	9185	2.256	1.00	5.08	**0.05**	Unchanged	96
Australia	2	7404	19.35	3.91	95.76	**<0.001**	N/A	93
Europe	1	510	3.745	0.573	24.48	0.168	N/A	N/A
Study setting						0.675		
Community	7	16589	4.11	1.82	9.28	**0.001**	Unchanged	97
Community and inpatient	1	510	3.74	0.42	33.31	0.23	N/A	N/A
Depression classification						0.655		
Screening tool	6	15906	4.60	1.93	11.80	**0.001**	Unchanged	96
Structured interview	2	1193	2.67	0.55	12.78	0.29	N/A	N/A
Frailty measure						0.056		
Fried	5	11680	2.18	0.93	5.09	0.09	Unchanged	95

Fried adapted	1	580	4.22	0.60	29.34	0.145	N/A	N/A
Iana Task	2	4839	19.12	1.23	16.13	**<0.001**	N/A	N/A

Key: N/A= not appli cable.

CI: Confidence interval; OR: Odds ratio

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