Frailty as a Predictor of Hospitalization among Community-Dwelling Older People: A Systematic Review and Meta-analysis

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Summary Box:

What is already known on this subject?

- hospitalization of older people has become a major focus because of detrimental hazards and substantial healthcare burden and costs.

- Frailty has increasingly been recognized as an important predictor of hospitalization.

- The objectives of this study were to systematically review the literature for the associations between physical frailty and hospitalization risks among community-dwelling older people and to conduct meta-analyses to synthesize pooled risk estimates.

What this study adds?

- This systematic review and meta-analysis has demonstrated that physical frailty was a significantly predictor of hospitalization among community-dwelling older people.

- The hospitalization risks according to frailty may be higher among those with advanced age.

- Interventions targeted at reducing frailty may potentially reduce hospitalization risks.

ABSTRACT
Background: Due to detrimental hazards and substantial healthcare burden and costs, hospitalization of older people has become a major focus. Frailty has increasingly been recognized as an important predictor of hospitalization. This study aims to identify studies on physical frailty as a predictor of hospitalization risks and to pool the risk estimates among community-dwelling older people.

Methods: A systematic literature search was performed in August 2015 using five databases: Embase, MEDLINE, CINAHL, PsycINFO, and Cochrane Library for prospective studies examining physical frailty as a predictor of hospitalization published in 2000 or later. Odds ratio (OR) and hazard ratio (HR) were combined to synthesize pooled effect measures using fixed-effects models. The included studies were assessed for heterogeneity, methodological quality, and publication bias. Subgroup analysis and meta-regression analysis were conducted to examine study characteristics in relation to the hospitalization risks.

Results: Of the 4,620 studies identified by the systematic review, 13 studies with average follow-up period of 3.1 years were selected. Frailty and prefrailty were significantly associated with higher hospitalization risks both among ten studies with OR (pooled OR=1.90, 95%CI=1.74-2.07, p<0.00001; pooled OR=1.26, 95%CI=1.18-1.33, p<0.00001, respectively) and three studies with HR (pooled HR=1.30, 95%CI=1.12-1.52, p=0.0007; pooled HR=1.13, 95%CI=1.04-1.24, p=0.005, respectively). Heterogeneity was low-moderate. No publication bias was detected. The studies with older populations and unadjusted outcome measures were associated with higher hospitalization risks in the subgroup analysis.

Conclusions: This systematic review and meta-analysis demonstrated physical frailty is a significant predictor for hospitalization among community-dwelling older people. Hospitalization can potentially be reduced by treating or preventing frailty.

INTRODUCTION

Older people are at a high risk of hospitalization and the risk becomes higher as they age.[1] The number of hospitalizations of older people has been steadily increasing in many countries,[2] and can increase further as both the number and proportion of older people increase. In the United States, the cost of hospitalization among Medicare beneficiaries is substantial, accounts for approximately half of all Medicare fee-for-service expenditure.[3] Some treatments and interventions are only available at hospitals and hospitalization is often necessary to treat acutely ill older people with complex medical problems. However, because of its high health care burden and costs as well as the hazards of the hospitalization, including disruption of care, functional decline due to prolonged bed rest, iatrogenic infections, falls, delirium, adverse drug reactions, and exposure to unfamiliar environments, it has been a major focus of interest for healthcare providers and policymakers to prevent the hospitalization of older people.[2, 4]

Frailty has increasingly been recognized as one of the important predictors for hospitalization. Frailty, a geriatric syndrome which has been receiving recent research attention, is characterized by a decline in physiological reserves in multiple systems and an increased vulnerability to adverse health outcomes, such as falls, disability, and death, due to age-related accumulated deficits.[5-7] Frailty has been also shown to be associated with negative psychological consequences, including depression,[8] cognitive impairment,[9] and poor quality of life.[10, 11]

Although there has been an increasing volume of frailty research in the literature, there has been no international consensus reached on how to operationalize frailty. Among various definitions and criteria proposed,[5] the one developed by Fried and colleagues from the Cardiovascular Health Study (CHS) is most frequently used.[6] They defined frailty as having three or more, and prefrailty as having one or two, of five components of physical phenotypes: (1) unintentional weight loss, (2) self-reported exhaustion, (3) weakness, (4) slow walking speed, and (5) low physical activity. Shortly afterward, the Study of Osteoporotic Fractures (SOF) criteria were proposed as a simpler version of the CHS criteria, consisting three physical components: (1) interntional or unintential weight loss >5% in the past year, (2) inability to rise from a chair five consecutive times without using the arms, and (3) self-perceived reduced energy level.[12] It may well be expected that frail older people with these negative health conditions or traits are more prone to hospitalization compared with non-frail individuals. One study found comorbidities, prior history of hospitalization, six or more primary care visits, advanced age, and unmarried status were independent risk factors for hospitalization,[13] some of which are associated with frailty.[5, 6, 14] In fact, multiple prospective studies have shown significant associations between frailty and a higher risk of hospitalization, however, some studies did not.[15, 16]

Only one systematic review was found in the literature examining frailty and hospitalization.[17] This paper reviewed studies from 1990 through to 2010 on associations between various geriatric syndromes and the risk of hospitalization.[17] The authors identified six articles on frailty and hospitalization risks among elderly populations in the community.[6, 15, 18-21] However, it should be noted that some important studies were not included[22, 23] and that a meta-analysis was not reported.[17] In addition, it is expected more related studies have been published since 2010 given that this is a rapidly progressing research field. Therefore, the current study aims to conduct (1) a systematic review to identify studies investigating prospective associations between physical frailty and future hospitalization risks and (2) a meta-analysis to synthesize pooled evidence of hospitalization risk according to physical frailty among community-dwelling older people. Given the conflicting findings from previous studies, the current systematic review and meta-analysis study providing pooled risk estimates will further increase our understanding of frailty as an important risk factor of hospitalization as well as a possible screening tool to identify the elderly at risk for hospitalization.

METHOD

Data Sources and Search Strategy

A systematic literature search was all performed in August 2015 by a US-trained clinician researcher (GK) board certified in Internal Medicine and Geriatric Medicine with experiences in both inpatient and outpatient settings based on a protocol developed in accordance with Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)[24] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) statements.[25] Five electronic databases: Embase, MEDLINE, CINAHL Plus, PsycINFO, and the Cochrane Library, were used without language restriction for studies published from 2000 through current, using an explosion function if available. The search strategy was ((Hospitalization (Medical Subject Heading (MeSH))) OR (Hospital Admission (MeSH)) OR (Hospital(s) (MeSH)) OR (Patient Admission (MeSH)) OR (Patient Readmission (MeSH)) OR (Inpatient(s) (MeSH)) OR (Hospital Patient (MeSH)) OR (Hospitalized Patient (MeSH)) OR (Hospital Utilization (MeSH)) OR (Health Resource Utilization (MeSH)) OR (Health Care Utilization (MeSH)) OR (Patient(s) (MeSH)) OR (Hospitalization*) OR (Hospitalisation*) OR (Admission*) OR (Readmission*) OR (Hospital*) OR (Utilization*) OR (Utilisation*) OR (Inpatient*)) AND ((Frailty Syndrome (MeSH)) OR (frailty)). Reference lists of included and relevant articles were also manually searched.

Study Selection

This systematic review and meta-analysis was limited to prospective studies since cross-sectional or retrospective studies are subject to some potential biases and not capable of detecting temporal associations, in this case, between frailty as a predictor and hospitalization as an outcome. The inclusion criteria were as follows:

1. Prospective study design.
2. Community-dwelling individuals.
3. Mean age of 65 years or older.
4. Frailty defined by original or modified versions of validated frailty criteria based on physical components.
5. Odds ratio (OR), risk ratio (RR), or hazard ratio (HR) provided as a risk measure or computable from available data.

The exclusion criteria were as follows:

1. Frailty defined by surrogate measures, such as walking speed, or only by frailty components.
2. Frailty defined by multidimensional criteria or definitions, such as ones including cognitive, psychological, and social factors
3. Selected samples with certain diseases, such as heart failure or Parkinson’s disease or institutionalized populations.
4. Poster presentations, dissertations, randomized controlled trials, or review articles.

When multiple eligible studies used data from the same sample or cohort, the study with the largest number of individuals was included. When multiple physical frailty criteria were used, the data according to CHS criteria, which have been used most frequently in the literature, or its modified versions were included.

Data Extraction
Data was extracted from the eligible studies using a standardized data collection sheet which included first author, publication year, location (country), sample size, proportion of female individuals, age (mean, range, or age criterion for inclusion), frailty criteria, effect measure, and follow-up period. Some studies did not analyze entire cohorts but subsamples for associations between frailty and hospitalization, therefore it was attempted to obtain the sample size, female proportion, and age from the sample actually used for the analysis of interest. If these data were not available, the data from the entire cohort was substituted. When one study used different types of physical frailty criteria, the data based on the Cardiovascular Health Study (CHS) criteria were included if available. When different lengths of follow-up periods were used, the data from the follow-up length closest to the mean of the rest of the included studies were used.

Methodological Quality Assessment
All eligible studies were assessed for their methodological quality using the Newcastle-Ottawa scale for cohort studies.[26] This nine-item scale covers selection, compatibility, and outcome domains of cohort studies. A study was considered to be of good quality to be included in the meta-analysis if five or more of the nine items were met.

Statistical Analysis
All analyses were performed using Review Manager 5 (version 5.2, The Cochrane Collaboration, Copenhagen, Denmark), IBM SPSS Statistics (version 22, IBM Corporation, New York, USA), Comprehensive Meta-Analysis (version 3.3, Biostat, New Jersey, USA), and StatsDirect (version 2.8, StatsDirect, Cheshire, UK).

The OR, RR, and HR with 95% a confidence interval (95%CI) of hospitalization risk for frailty and prefrailty compared with nonfrailty/robustness were extracted directly from the included studies, or the OR was calculated from the numbers presented in the studies using a univariate logistic regression model. No study reported a RR. Adjusted OR and HR were preferred for meta-analyses when available and otherwise unadjusted ones were extracted.

The OR and HR were transformed by calculating their natural logarithms. The standard errors of the log-transformed OR and HR were calculated by dividing the difference between log-transformed upper and lower 95%CI limits by 3.92. These numbers were used to calculate pooled estimates of OR and HR, 95%CI, and p values, using a random-effects model if high heterogeneity was detected by using I^2 statistic, and using a fixed-effects model otherwise, with the generic inverse variance method. Heterogeneity across the included studies was examined using Cochran's Q statistic. The magnitude of the heterogeneity was examined using I^2 statistic and I^2 value of 25%, 50%, and 75% were considered as low, moderate, and high heterogeneity, respectively.[27] Publication bias was examined by a visual inspection of the funnel plots and using Begg-Mazumdar's and Egger's tests.[28, 29]

Subgroup analyses were performed to explore potential factors affecting hospitalization risks by frailty. The factors considered were location (Europe vs. USA), sample size (>=4000 vs. <4000), female proportion (>=60% vs. <60%), mean age (>=75 vs. <75), frailty criteria (CHS vs. SOF), follow-up period (>2 years vs. <=2 years, >1 year vs. <=1 year), and adjustment for outcome (adjusted vs. unadjusted). A random-effects meta-regression analysis was also conducted to examine the study characteristics (sample size, female proportion of a cohort, mean age, follow-up period, and Newcastle-Ottawa scale score, all as a continuous variable) for potential moderator effects on the hospitalization risks by frailty.

RESULTS

Selection Processes

Figure 1 is a flow diagram presenting the literature search and study selection. The systematic review using five electronic databases identified 4,619 studies and the manual search found one relevant study. Of these 4,620 studies, 1,514 duplicate studies were excluded and then 3,081 studies were excluded by title and abstract review, leaving 25 studies for full-text review. An additional 12 studies were excluded for the following reasons: no effect measures of hospitalization risk for frailty category were shown (n=6), a hospitalization risk was not examined (n=3), the same cohort used (n=1), a poster presentation (n=1), or a cross-sectional study design (n=1). 13 studies remained and were examined for methodological quality using the Newcastle-Ottawa quality assessment scale for cohort studies.[26] All 13 studies were scored as five or greater and considered to have an adequate quality of methodology to be included in the meta-analysis. (**Table 1**)

Study Characteristics

Table 1 shows the characteristics of the 13 included studies involving 74,900 community-dwelling older people who were examined for hospitalization risk according to frailty status.[6, 15, 16, 18, 19, 22, 30-36] Five studies were from the United States[6, 15, 19, 22, 30], two were from Italy[34, 35], and one each from France,[18] the United Kingdom,[33] Spain,[32] Mexico,[36] Portugal,[16] and Korea.[31] The cohort sizes ranged widely with the largest one (n=40,657) from the Women's Health Initiative[22] and the smallest one including 95 individuals.[16] Two studies involved only women[15, 22] and the rest used mixed cohorts. Although most of the studies presented a mean age ranging from 65.8 to 81.5 years, some did not, but just presented numbers of individuals in age groups. Most of the included studies (10/13) used original or modified CHS criteria, [6, 15, 16, 18, 19, 22, 30-33] and the rest used modified SOF criteria.[34-36] The ORs were presented or calculated in ten studies[16, 18, 19, 22, 30, 31, 33-36] and three studies presented HRs.[6, 15, 32] Follow-up periods ranged from 10 months[16] to 8 years[30].

Frailty as a Predictor of Hospitalization

Meta-analysis of Studies Presenting OR

The ORs and 95%CIs were available for hospitalization risk according to frailty and/or prefrailty from ten studies encompassing 67,288 older people in the community.[16, 18, 19, 22, 30, 31, 33-36] Fixed-effects models were used to synthesize pooled ORs of hospitalization risk for frailty and prefrailty as heterogeneity was moderate ($p=0.02$, $I^2=54\%$) and low ($p=0.26$, $I^2=21\%$), respectively. Frailty and prefrailty were significantly associated with a higher risk of hospitalization (pooled OR=1.90, 95%CI=1.74-2.07, $p<0.00001$; pooled OR=1.26, 95%CI=1.18-1.33, $p<0.00001$, respectively) compared with non-frail individuals. (**Figure 2A**)

Meta-analysis of Studies Presenting HR

Three studies with 7,970 older people presented HRs as a risk measure of hospitalization by frailty and prefrailty.[6, 15, 32] Since heterogeneity was moderate for frailty ($p=0.09$, $I^2=58\%$) and low for prefrailty ($p=0.69$, $I^2=0\%$), fixed-effects models were employed. Frailty and prefrailty were significantly associated with a higher risk of hospitalization (pooled HR=1.30, 95%CI=1.12-1.52, $p=0.0007$; pooled HR=1.13, 95%CI=1.04-1.24, $p=0.005$, respectively) compared with non-frail individuals. (**Figure 2B**)

Publication Bias Assessment
Visual inspection of funnels plots for studies presenting OR and HR for frailty and prefrailty (**Figure 3**) did not show obvious asymmetry. No significant publication bias was observed among the studies presenting OR for frailty and prefrailty using Begg-Mazumdar's and Egger's tests (all $p>0.05$). It was not possible to use these tests for the studies with HR due to the small number of included studies.

Subgroup Analysis and Meta-Regression Analysis
The ten studies with OR of hospitalization risks for frailty were further examined by subgroup analysis. The studies were divided into subgroups according to several study characteristics including location, sample size, female proportion, mean age, frailty criteria, follow-up period, methodological quality, and outcome adjustment and were compared for subgroup differences. (**Table 2**) Higher hospitalization risks according to frailty were observed two subgroups consisting of studies with older mean ages (three studies, OR=3.09, 95%CI=2.00-4.77, p for subgroup difference=0.02) and unadjusted outcome measures (four studies, OR=2.46, 95%CI=1.87-3.24, p for subgroup difference=0.05) than the corresponding counterpart subgroups.

The study characteristics of these ten studies were further analyzed using meta-regression analysis for potential moderator effects on the hospitalization risks by frailty. The characteristics investigated were sample size female proportion of a cohort, mean age, follow-up period, and Newcastle-Ottawa scale score, and were individually entered into the meta-regression models. None of these characteristics were significant modulators in the associations between frailty and hospitalization.

DISCUSSION
This systematic review and meta-analysis shows that community-dwelling older people classified as frail or prefrail had significantly higher risks of hospitalization than those classified as robust. Despite the substantial diversity in the methodologies, such as study location, sample size, gender proportion, and follow-up period, the hospitalization risks according to frailty were fairly consistent among the included studies and the heterogeneity was low to modest across the studies (I^2=0%-58%). It was suggested by subgroup analysis that studies with older populations and unadjusted outcome measures were associated with higher hospitalization risks according to frailty.

Among the 13 studies included in this systematic review, the majority (76.9%, 10/13) used original or modified versions of CHS, while the rest of three studies used SOF criteria. Given SOF criteria is a shorter version of CHS and they share some frailty components (weight loss and exhaustion), the consistent use of CHS or SOF criteria by the included studies may have contributed to low to moderate heterogeneity across the studies.

Subgroup analysis suggested higher hospitalization risks according to frailty were associated with two study characteristics; higher mean age (>=75 years old) and unadjusted outcome measures. It is inevitable for us to age without health declines and deficits and it may be natural that older people are more predisposed to various negative health outcomes and therefore to higher hospitalization risks by frailty compared with younger people. When frail older people are being hospitalized, there should be multiple confounding factors directly and indirectly associated with the hospitalization risks. Therefore it is important to take it into consideration by adjusting these factors in statistical models to examine independent associations between frailty and hospitalization risks. It can be expected that the pooled risk estimate was smaller among the studies properly adjusting for the confounders. Another subgroup with studies with smaller sample sizes (n<4000) was found to have a tendency to have higher hospitalization risks (five studies, pooled OR=2.57, 95%CI=1.85-3.57, p for subgroup difference=0.06) compared with another five studies involving 4000 or more participants. Although it is not clear why the studies with smaller sample sizes showed higher hospitalization risks, four out of the five smaller studies provided unadjusted risk measures, which could be the cause of this subgroup difference. In general, adjustment for multiple confounding covariates may sometimes be difficult or may not always be possible especially when a sample size is very small due to lack of statistical power.

Exact mechanisms underlying the associations between frailty and subsequent higher hospitalization risks are unknown. Although causes and reasons for older people's hospitalizations can be multifactorial, falling can possibly explain the associations at least to some degree. Approximately one third of older people aged 65 and older fall every year.[37] Falls are a leading cause of mortality and morbidity, including hip fracture or head injury, and can lead to hospitalization.[38] Physical components of frailty, such as weakness or gait abnormality, may potentially increase risks of falling in frail older people.[5] In fact, frailty has been shown to be a significant predictor of future falls among community-dwelling older people.[7, 39] Despite the strong associations of falls with both frailty and hospitalization, fall-related factors, such as a history of falling or a fall as a reason for hospitalization, were not investigated in the studies included in this review.

Although this review focused on physical frailty criteria, some experts advocated that frailty should be conceptualized as a multidimensional syndrome including not only physical but also cognitive, psychological, and social factors.[40-42] Frailty Index (FI) describe frailty as a continuous score based on accumulation of age-related deficits and impairments in multidimensional domains.[43] FI were used by previous studies and showed those with higher FI (worse frailty status) were at increased risks for hospitalization among community-dwelling older people.[20, 44-46] The results of these studies were not able to be combined mainly due to different methodologies (i.e. effect sizes per FI unit, per 0.01 of FI, or per 7 groups by FI).

This study has multiple strengths and some limitations. First, this is the first systematic review and meta-analysis on associations between frailty and future hospitalization risk. Second, the robust methodology, according to the PRISMA and MOOSE statements, was employed, including conducting a comprehensive systematic review using five electronic databases and assessing the methodological quality, the publication bias, and the heterogeneity across the included studies. Third, the meta-analyses showed persistent and dose-response findings: higher degree of frailty status (frail>prefrail>robust) was associated with a higher risk of future hospitalization in both study groups presenting OR and HR. These findings seem reliable because there was no evidence of a high heterogeneity or publication bias detected among the studies. Despite these strengths, it should be recognized as a potential limitation that all processes were conducted by one investigator. It would have been ideal to have two independent investigators involved in some stages of the process, such as data extraction or methodological quality assessment. The findings of this study should, therefore, be interpreted with caution since potentially important studies may have been missed or the extracted data may have been inaccurate. Another potential limitation is that none of the included studies took into consideration a fall as a potential cause of hospitalization or a history of falls as an important confounder, which might have influenced the results.

It is still unknown which frailty criteria are the most suitable to detect older people at high risk for hospitalization and what factors or causes (i.e. falls) are involved directly and indirectly in the associations between frailty and hospitalization. Researchers can fill the gap by designing and conducting longitudinal cohort studies focusing on how frailty is related to specific causes of hospitalization. Given frailty is a dynamic state[47] and can possibly be reversed back to being prefrail or robust by appropriate interventions,[5] the findings of this review is also valuable for clinicians because there is a possibility that they could screen older people for frailty as a risk factor of hospitalization and could start the interventions if appropriate to prevent them from being hospitalized. Lastly, policymakers could make the most of this review's findings as well to conduct campaigns or create policy schemes, such as exercise promotions or public education regarding nutrition, for older people to support them to prevent onset of frailty or reverse it. All of these efforts could lead to reduce detrimental effects and related substantial health care costs of hospitalization among older people.

Conclusion

This systematic review and meta-analysis demonstrates thepooled evidence that frailty and prefrailty are significant predictors for hospitalization among community-dwelling older people. The findings are important for all related parties including clinicians, researchers, and policymakers.

LICENCE FOR PUBLICATION

COMPETING INTEREST

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Table 1. Summary of included studies on frailty and hospitalization among community-dwelling older people.

Author/Study	Year	Location	Sample size	Female (%)	Age (range)	Frailty criteria	Effect measure	Follow-up period	NOS
Coelho et al.[16]	2015	Portugal	95	67.4%	78.5 (≥65)	mCHS	cOR	10 months	5/9
Paulson et al.[30] HRS	2015	US	8844	58.8%	74.5 (65-101)	mCHS	uOR aOR	4 years	6/9
Jung et al.[31] KLoSHA	2014	Korea	693	50.8%	74.6* (≥65)	mCHS	uOR	5.57 years	5/9
Garcia-Garcia et al.[32] TSHA	2014	Spain	1638*	56.1%	75.1 (≥65)	mCHS	uHR	4 years	7/9
Bouillon et al.[33] White Hall II	2013	UK	5169	27.5%	65.8 (55-79)	mCHS	cOR	15.2 months	6/9
Bilotta et al.[34]	2012	Italy	226	71.3%	81.5 ("65+")	mSOF	uOR aOR cOR	1 year	7/9
Diaz de Leon et al.[36]	2012	Mexico	4068	53.4%	68.4 (≥60)	mSOF	aOR	2 years	8/9
Forti et al.[35] CSBA	2012	Italy	698	55.4%	74.7 (≥65)	mSOF	uOR cOR	4 years	5/9
Kiely et al.[19] MOBILIZE Boston Study	2009	US	760	63.9%	78.1 (≥70)	mCHS	uOR aOR	18 months	7/9
Avila-Funes et al.[18] Three City Study	2008	France	6078	61.3%	74.1 (65-95)	mCHS	uOR aOR	4 years	7/9
Bandeen-Roche et al.[15] WHAS	2006	US	612	100%	- (70-79)	mCHS	aHR	3 years	6/9
Woods et al.[22] WHI-OS	2005	US	40657	100%	- (65-79)	mCHS	aOR†	5.9 years‡	6/9
Fried et al.[6] CHS	2001	US	5317	57.9%	- (65-101)	CHS	uHR aHR	3 years	8/9

* Not reported but calculated from available data
‡ mean follow-up
† Average number of hospitalization per year≥0.5 compared with no hospitalizations.
95%CI= 95% confidence interval
BWHHS: British Women's Heart and Health Study
CSBA: Conselice Study of Brain Aging
HRS: Health and Retirement Study
KLoSHA: Korean Longitudinal Study on Health and Aging
(m)CHS: (Modified) Cardiovascular Health Study frailty index (Fried's phenotype)
mSOF: Modified Study of Osteoporotic Fractures frailty index
TSHA: Toledo Study for Healthy Aging
u/aHR: Unadjusted/Adjusted hazard ratio
u/a/cOR: Unadjusted/Adjusted/Calculated odds ratio
WHAS: Women's Health and Aging Studies

Table 2. Subgroup analysis among 10 studies with OR of hospitalization risk for frailty.

Subgroup	Number of studies	Pooled OR (95%CI)	p	I^2	p for subgroup difference
Location*					
Europe	5	1.85 (1.52-2.26)	<0.00001	57%	0.66
USA	3	1.95 (1.76-2.16)	<0.00001	74%	
Sample size					
n=4000+	5	1.85 (1.69-2.03)	<0.00001	65%	0.06
n<4000	5	2.57 (1.85-3.57)	<0.00001	11%	
Female proportion					
Female>=60%	5	1.91 (1.70-2.13)	<0.00001	69%	0.88
Female<60%	5	1.88 (1.64-2.16)	<0.00001	40%	
Mean age†					
>=75	3	3.09 (2.00-4.77)	<0.00001	29%	0.02
<75	6	1.77 (1.56-2.01)	<0.00001	52%	
Frailty criteria					
CHS	7	1.93 (1.76-2.12)	<0.00001	65%	0.25
SOF	3	1.64 (1.27-2.12)	0.0002	0%	
Follow-up period					
>2 years	5	1.84 (1.67-2.02)	<0.00001	24%	0.14
<=2 years	5	2.17 (1.77-2.65)	<0.00001	67%	
>1 years	8	1.89 (1.73-2.07)	<0.00001	64%	0.73
<=1 years	2	2.11 (1.13-3.93)	0.02	0%	
Outcome adjustment					
Adjusted	6	1.84 (1.68-2.02)	<0.00001	66%	0.05
Unadjusted	4	2.46 (1.87-3.24)	<0.00001	0%	

* Two studies were from Korea and Mexico, respectively.

† One study did not provide mean age.

Figure 1. Flow chart of systematic literature review

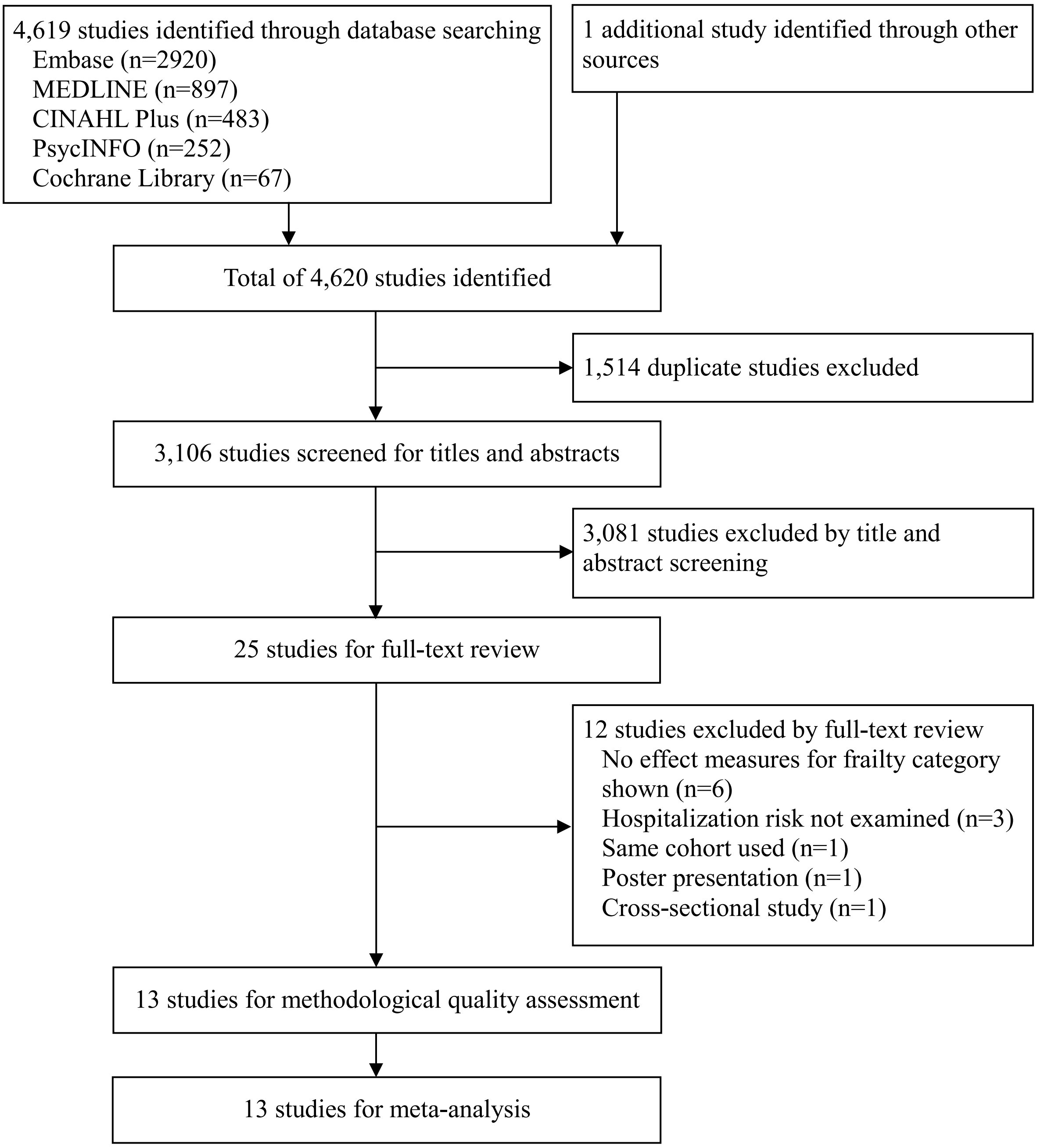
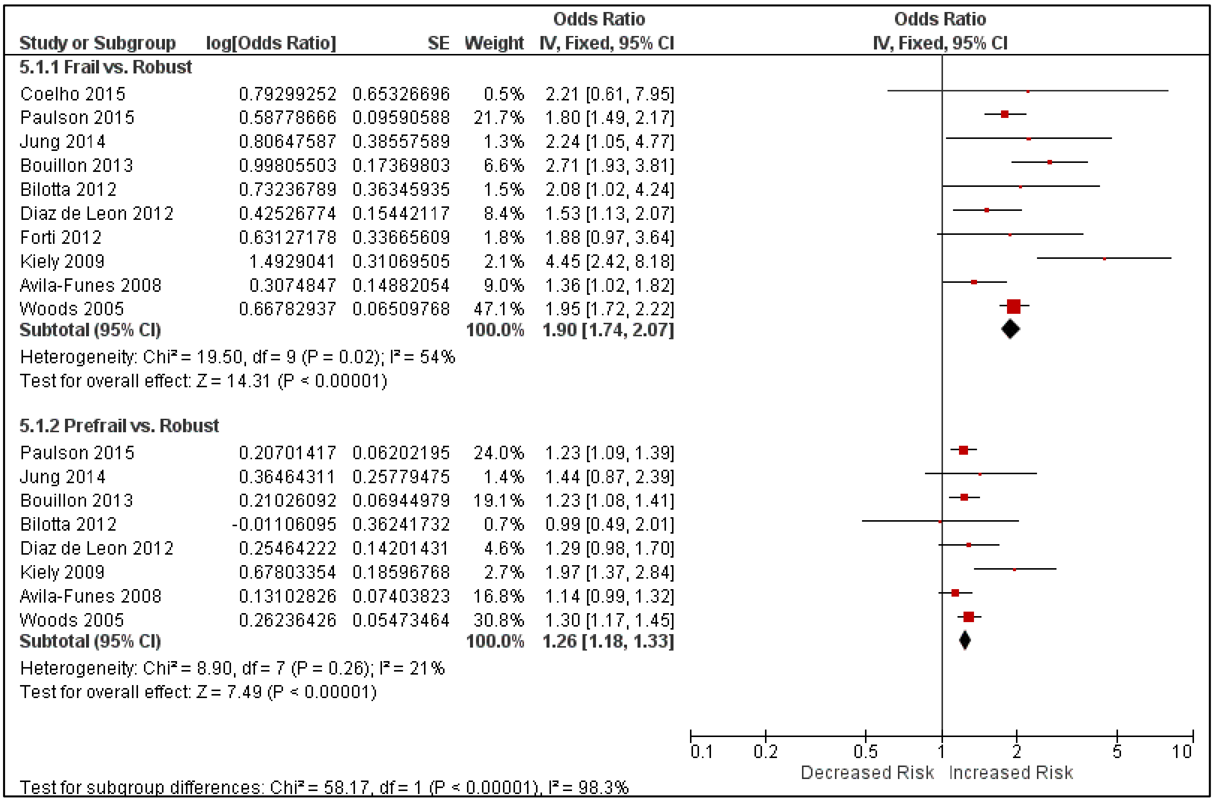


Figure 2. (A) Forest plots of hospitalisation risk (OR) according to frailty and prefrailty. (B) Forest plots of hospitalisation risk (HR) according to frailty and prefrailty.

A



B

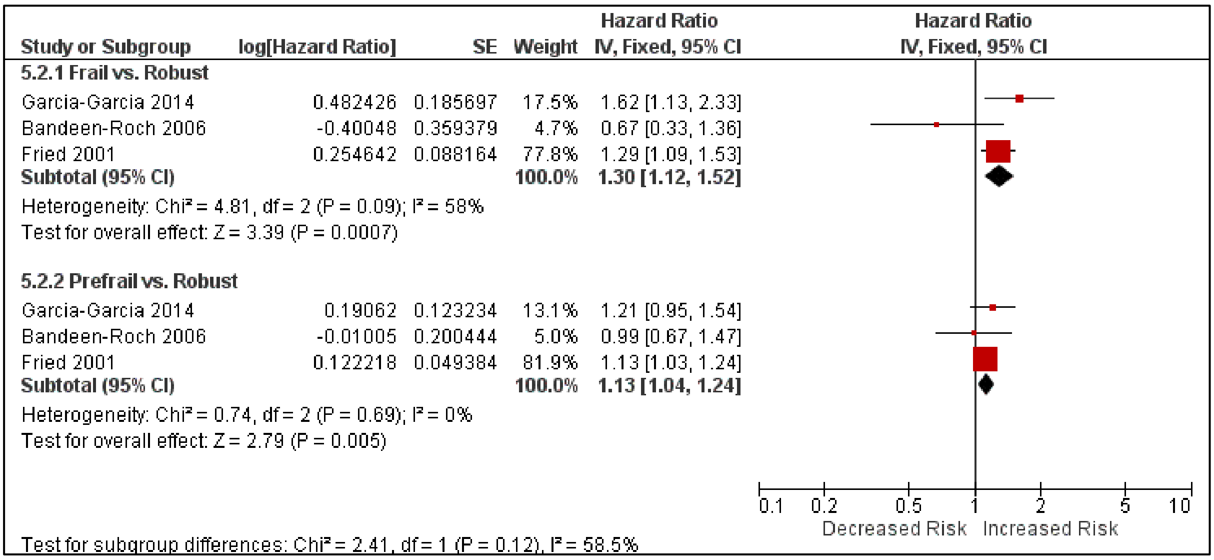


Figure 3. Funnel plots for studies presenting OR according to frailty (A) and prefrailty (B) and studies presenting HR according to frailty (C) and prefrailty (D).