RISK OF CARDIOVASCULAR DISEASE MORBIDITY AND MORTALITY IN FRAIL AND PRE-FRAIL OLDER ADULTS: RESULTS FROM A META-ANALYSIS AND EXPLORATORY META-REGRESSION ANALYSIS

Nicola Veronese, MD[1,2,*], **Emanuele Cereda, MD, PhD**[3,*], **Brendon Stubbs, PhD**[4,5], **Marco Solmi, MD**[2,6,7], **Claudio Luchini, MD**[8,9], **Enzo Manzato, MD**[1,10], **Giuseppe Sergi, MD**[1], **Peter Manu, MD**[11], **Tamara Harris, MD**[12], **Luigi Fontana, MD**[13,14,15], **Timo Strandberg, MD**[16,17], **Helene Amieva, MD**[18,19], **Julien Dumurgier, MD**[20], **Alexis Elbaz, MD**[21], **Christophe Tzourio, MD**[22], **Monika Eicholzer, MD**[23], **Sabine Rohrmann, MD**[23], **Claudio Moretti, MD**[24], **Fabrizio D'Ascenzo, MD**[24], **Giorgio Quadri, MD**[24], **Alessandro Polidoro, MD**[25], **Roberto Alves Lourenço, MD**[26], **Virgilio Garcia Moreira, MD**[26], **Juan Sanchis, MD**[27], **Valeria Scotti, MD**[28], **Stefania Maggi, MD**[10], and **Christoph U. Correll, MD**[29,30,31,32]

[1]Department of Medicine (DIMED), Geriatrics Division, University of Padova, Italy [2]Institute of clinical Research and Education in Medicine (IREM), Padova, Italy [3]Nutrition and Dietetics Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy [4]Physiotherapy Department, South London and Maudsley NHS FoundationTrust, Denmark Hill, London SE5 8AZ, United Kingdom [5]Health Service and Population Research Department, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8 AF, United Kingdom [6]Department of Neurosciences, University of Padova, Padova, Italy [7]National Health Care System, Monselice, Padova Local Unit ULSS 17, Italy [8]Department of Pathology and Diagnostics, University and Hospital Trust of Verona, Verona, Italy [9]Surgical Pathology Unit, Santa Chiara Hospital, Trento, Italy [10]National Research Council, Neuroscience Institute - Aging Branch, Padova, Italy [11]South Oaks Hospital, Northwell Health, 400 Sunrise Highway, Amityville, NY 11701, USA, USA [12]Laboratory of Epidemiology and Population Sciences, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, USA [13]Division of Geriatrics and Nutritional Sciences and Center for Human Nutrition, Washington University School of Medicine, St. Louis, MO, USA [14]Department of Clinical and Experimental Sciences, Brescia University, Brescia, Italy [15]CEINGE Biotecnologie Avanzate, Napoli, Italy [16]University of Helsinki and Helsinki University Hospital, Helsinki, Finland [17]University of Oulu, Center for Life Course Health Research, Oulu, Finland [18]Centre de Recherche Inserm, Bordeaux, France [19]University Victor Segalen Bordeaux 2,

Corresponding Author: Nicola Veronese, MD. University of Padova, Department of Medicine, Geriatrics Division, Padova, Italy. ilmannato@gmail.com. Phone: 00390498218492; fax: 00390498211218.
[*]These two authors equally contributed to this research.

Bordeaux, France [20]CMRR Paris Nord AP-HP, Groupe Hospitalier Lariboisière Fernand-Widal Saint-Louis, INSERM, U942, Université Paris Diderot, Sorbonne Paris Cité, UMRS 942, Paris, France [21]CESP, Univ. Paris-Sud, UVSQ, INSERM, Université Paris-Saclay, Villejuif, France [22]University of Bordeaux, Neuroepidemiology, UMR897, Bordeaux, France [23]University of Zurich, Epidemiology, Biostatistics and Prevention Institute, Division of Chronic Disease Epidemiology, Hirschengraben 84, CH-8001 Zurich, Switzerland [24]Division of Cardiology, Department of Science, Città della Salute e della Scienza, Turin, Italy [25]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy [26]Department of Internal Medicine, Faculty of Medical Sciences, State University of Rio de Janeiro, Rio de Janeiro, Brazil [27]Department of Cardiology, Hospital Clínico Universitario, School of Medicine, University of Valencia, Valencia, Spain [28]Clinical Epidemiology and Biometric Unit, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy [29]The Zucker Hillside Hospital, Psychiatry Research, Northwell Health, Glen Oaks, New York, USA [32]Hofstra Northwell School of Medicine, Hempstead, NY, USA [33]The Feinstein Institute for Medical Research, Manhasset, NY, USA [32]Albert Einstein College of Medicine, Bronx, NY, USA

Abstract

Frailty is common and associated with poorer outcomes in the elderly, but its role as potential cardiovascular disease (CVD) risk factor requires clarification. We thus aimed to meta-analytically evaluate the evidence of frailty and pre-frailty as risk factors for CVD. Two reviewers selected all studies comparing data about CVD prevalence or incidence rates between frail/pre-frail vs. robust. The association between frailty status and CVD in cross-sectional studies was explored by calculating and pooling crude and adjusted odds ratios (ORs) ±95% confidence intervals (CIs); the data from longitudinal studies were pooled using the adjusted hazard ratios (HRs). Eighteen cohorts with a total of 31,343 participants were meta-analyzed. Using estimates from 10 cross-sectional cohorts, both frailty and pre-frailty were associated with higher odds of CVD than robust participants. Longitudinal data were obtained from 6 prospective cohort studies. After a median follow-up of 4.4 years, we identified an increased risk for faster onset of any-type CVD in the frail (HR=1.70 [95%CI, 1.18–2.45]; I^2=66%) and pre-frail (HR=1.23 [95%CI, 1.07–1.36]; I^2=67%) vs. robust groups. Similar results were apparent for time to CVD mortality in the frail and pre-frail groups. In conclusion, frailty and pre-frailty constitute addressable and independent risk factors for CVD in older adults.

Keywords

frailty; cardiovascular disease; meta-analysis

INTRODUCTION

Frailty is typically defined as a state of "reduced physiological reserve and increased vulnerability for poor resolution of homeostasis after a stressor event"(Clegg et al., 2013) and is common among older adults, with an estimated prevalence of 10% in community-dwellers(Collard et al., 2012) and higher in people with cardiovascular diseases (CVD).

(Afilalo, 2011; Finn and Green, 2015) Research addressing the relationship between frailty and CVD has suggested a bidirectional relationship.(Afilalo et al., 2014) On the one hand, standard CVD risk factors, increased body weight, and physical inactivity in healthy midlife are each associated with old age frailty(Savela et al., 2013; Stenholm et al., 2014). Subclinical CVD is also associated with frailty.(Newman et al., 2001) CVDs are among the strongest contributors for frailty development in people with advanced age(Afilalo et al., 2014), and the presence of frailty in older adults with CVD increases the risk of falls, institutionalization, repeated hospitalization and mortality.(Afilalo, 2011; Afilalo et al., 2014; Fukui et al., 2015) On the other hand, since frailty and CVD share some common abnormalities, such as low-grade inflammation and insulin-resistance(Clegg et al., 2013), recent research proposed that frailty could be considered a potential CVD risk factor.(Phan et al., 2008; von Haehling et al., 2013)

This issue is highly relevant in geriatric medicine, because frailty and even more its precursor intermediate state (pre-frailty) might be reversible if appropriately treated(Ng et al., 2015). The frailty phenotype is a syndromic condition requiring a comprehensive geriatric assessment for: 1) understanding which are the causes of the increased vulnerability, and 2) develop personalized plans of interventions (potentially covering physical and non-physical domains). The components of interventions for frailty may include physical exercise, nutrition, lifestyles, cognitive training, medication review(Santos-Eggimann et al., 2016), and specific therapies for underlining causes, like heart transplant for heart failure(Jha et al., 2016). Many of the interventions used for treating frailty (e.g. increasing physical activity levels and nutritional interventions) are also useful for decreasing CVD onset.(de Labra et al., 2015; Hanna and Wenger, 2005; Haskell, 2003) Whether frailty and pre-frailty are risk factors for CVD is clinically important to the extent that the detection of these conditions in older subjects might offer a pertinent window for appropriate interventions that may delay the onset of CVD and consequently reduce disability, hospitalization and mortality.(Gary, 2012)

The data regarding the relationship between frailty and future CVD have been not completely clear and, to the best of our knowledge, no meta-analysis has investigated if frailty status is associated with an increased risk of CVD and associated mortality. Therefore, the aim of the present study was to perform a systematic review and meta-analysis summarizing the evidence of frailty and pre-frailty as possible risk factors for CVD in older adults. The meta-analytical approach allows not only to overcome the limited evidence resulting from small studies, but also to provide a comprehensive quantitative review of available data and to assess the robustness as well as heterogeneity of the results, including their potential sources. We hypothesized that frail and prefrail individuals have a significantly increased risk of having and of developing CVD as well as related mortality, compared with robust older adults.

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)

Search strategy

The published literature was searched using strategies created by a medical librarian for the concepts of frailty, risk, cardiovascular disease, and age 65 or older. The search strategies were established using a combination of standardized terms (free text or MeSH terms) and key words, and were implemented in Ovid Medline 1946-, Embase via Emabse.com 1947-, Cumulative Index of Nursing and Allied Health Literature 1937-, Cochrane Database of Systematic Reviews via Wiley, Cochrane Central Register of Controlled Trials via Wiley, and Database of Abstracts of Review via Wiley. To increase the chance of generating generalizable data, we conservatively excluded intervention studies, as randomized controlled trials generally have a whole host of exclusion criteria. Thus, articles indexed by the publication type of randomized or controlled trials were eliminated with the "NOT" Boolean operator. All searches were conducted from their inception until 12/31/2015 and without language restriction. All results were exported to EndNote for the removal of duplicates. The search strategy used in Pubmed is reported in eTable 1. A similar search (adapted to the requirements of each database) was run in the other databases. Two investigators (NV, MS) independently conducted an electronic literature search and inconsistencies were resolved by consensus with a third author (VS).

References of articles included in the analysis and of others relevant to the topic were hand-searched to identify additional, potentially relevant publications. Conference abstracts were also considered, contacting the first or corresponding author for additional information at least 4 times in 4 weeks.

Study selection

We only considered studies that had a cross-sectional or longitudinal design; reported a multidimensional evaluation of the presence of frailty (such as using the criteria suggested by Fried(Fried et al., 2001), Rockwood(Rockwood et al., 2005) or Gill(Gill et al., 2002) as described in eTable 2); reported data on clinical CVD (self-reported, medical and/or hospital records, adjudicated disease diagnosis); and had a study population's mean age 65 years. Studies were excluded if they reported CVD prevalence/incidence data only for one item included in the definition of frailty (e.g. low gait speed); investigated the role of frailty in people with CVD but focusing on non-CVD outcomes (e.g. overall mortality); reported data regarding frailty as consequence of a specific disease/condition (e.g. cancer); included only sub-clinical estimates of CVD; and focused on changes produced by specific interventions.

When data regarding CVD were available only for one item included in the definition of frailty (e.g. slow gait speed), the first and corresponding authors of each paper were contacted at least 4 times in 4 weeks to obtain further information about the other frailty domains.

Data extraction

To be included in the quantitative synthesis, studies had to provide data on odds or risk estimates (or data allowing us to compute these ourselves) for any-type CVD or for specific CVD (i.e., odds ratios [ORs] and hazard ratios [HRs] for cross-sectional and longitudinal studies, respectively), together with precision estimates (95% confidence interval [95%CI]) comparing frailty status conditions (taking robustness as reference group). Two authors (NV, EC) independently recorded data extracted from the selected studies into a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by consensus with a third author (CC). The following information was extracted: i) study characteristics (e.g. sample size, demographics, country in which the study was performed); ii) study setting; iii) diagnostic criteria for frailty; iv) demographic characteristics (percentage of women and age) and risk factors for CVD prevalence (obesity, type 2 diabetes and hypertension) by frailty status; v) type and number of adjustments in the multivariate analyses; vi) follow-up period (only for longitudinal studies); vii) method of ascertainment of CVD.

When information on CVD was missing, study authors were contacted to obtain unpublished data. When two or more studies represented a cohort, all the articles were included contacting the first/corresponding author in order to have the most complete analyses available. These unpublished data were validated by the first or last authors of the studies from which these data were obtained. When raw data were shared with the main investigators of this project, these were independently analyzed by two authors of this meta-analysis (NV and EC). In addition to number of CVD by frailty status, we requested OR/HR estimates adjusted for the maximum number of the following covariates: age (as continuous variable), gender, obesity, type 2 diabetes, and hypertension. All the data were finally confirmed by the main investigator of each article.

Outcomes

The primary outcomes were the proportion and incidence of any-type of CVD according to frailty status. Secondary outcomes included the proportion and rate of onset: coronary heart disease (CHD), cerebrovascular disease (stroke and transient ischemic attack), heart failure, and peripheral vascular disease (PVD). In longitudinal studies the risk of CV mortality was also investigated.

Assessment of study quality

The Newcastle-Ottawa Scale (NOS)(Wells et al., 2012) was used to assess study quality. The NOS assigns a maximum of 9 points based on three quality parameters: selection, comparability, and outcome, with a cut-off of <5 being indicative of high risk of bias.(Wells et al., 2012) NOS scores were initially assessed by two investigators (NV, CL), and discrepancies were addressed by a joint re-evaluation of the article with a third author (BS).

Statistical analysis

Analyses were performed by two independent investigators (NV, EC) using Comprehensive Meta-Analysis (CMA) 3 (http://www.meta-analysis.com). In primary analyses, pooled ORs (crude and fully adjusted) were calculated to synthesize data from cross-sectional studies, while pooled HRs (fully adjusted) were calculated for longitudinal studies. In secondary

analyses, the same procedure was applied using specific CVD as outcome. When studies provided only estimates for specific CVDs, these were pooled with the others in both primary and secondary analyses. According to availability of data, the following comparisons were addressed: frail vs. robust; pre-frail vs. robust; frail vs. pre-frail/robust. The random effects model was used to account for anticipated between-study heterogeneity. (DerSimonian and Laird, 1986)

Study heterogeneity was assessed using the chi-squared and I-squared statistics, assuming that a p 0.05 for the former and a value 50% for the latter indicated a significant heterogeneity.(Higgins and Thompson, 2002) Whenever significant heterogeneity existed and 4 studies were available, a meta-regression analysis was performed examining the following pre-specified moderators: setting (community-dwelling vs. others), study quality (NOS score), number of adjustments (for adjusted analyses), follow-up period (for longitudinal investigations), frailty criteria (Fried's vs. others), and outcome ascertainment (self-reported, medical and/or hospital records, adjudicated disease diagnosis). Strata analyses were conducted accordingly.

Publication bias was assessed by visually inspection of funnel plots and using the Egger bias test.(Egger et al., 1997) When 3 studies were available, we used the Duval and Tweedie nonparametric trim-and-fill method to account for potential publication bias. 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, this procedure adjusts for the potential effect of unpublished (trimmed) studies.(Egger et al., 1997)

RESULTS

The search identified 8,953 non-duplicated, potentially eligible studies. After excluding 8,897 papers on the grounds of a review of their titles and abstracts, 56 full-text articles were examined, and 21 articles(Avila-Funes et al., 2014; Blaum et al., 2005; Chaves, 2005; Danon-Hersch et al., 2012; de Albuquerque Sousa et al., 2012; Dumurgier et al., 2009; Eichholzer et al., 2012; Ekerstad et al., 2011; Frisoli et al., 2015; Green et al., 2012; Hajjar et al., 2009; Khan et al., 2013; Lin et al., 2015; Moreira and Lourenco, 2013; Moretti et al., 2013; Polidoro et al., 2013; Ramsay et al., 2015; Ricci et al., 2014; Sanchis et al., 2014; Sergi et al., 2015; Wong et al., 2010) corresponding to 18 cohorts were finally included in our meta-analysis (Figure 1).

Study and patient characteristics

The 18 cohorts (Avila-Funes et al., 2014; Blaum et al., 2005; Chaves, 2005; Danon-Hersch et al., 2012; de Albuquerque Sousa et al., 2012; Dumurgier et al., 2009; Eichholzer et al., 2012; Ekerstad et al., 2011; Frisoli et al., 2015; Green et al., 2012; Lin et al., 2015; Moreira and Lourenco, 2013; Moretti et al., 2013; Polidoro et al., 2013; Ramsay et al., 2015; Ricci et al., 2014; Sanchis et al., 2014; Sergi et al., 2015; Wong et al., 2010) included 4,469 frail participants out of 31,343 older subjects (eTable 3). Ten cohorts provided data on pre-frail (n=7,294) and robust (n=6,875) participants, while 8 (Chaves, 2005; Eichholzer et al., 2012; Ekerstad et al., 2011; Green et al., 2012; Khan et al., 2013; Moretti et al., 2013; Polidoro et al., 2013; Ricci et al., 2014) compared frail (n=2,305) to pre-frail/robust participants

(n=12,705). Meta-analyzed prevalence estimates according to frailty status are presented in Table 1.

All studies used a modified version of the definition proposed by Fried et al.(Fried et al., 2001) for defining frailty, except three (two(Ekerstad et al., 2011; Polidoro et al., 2013) used the definition proposed by Rockwood et al.(Rockwood et al., 2005) and one(Khan et al., 2013) the Gill's index(Gill et al., 2002)). Ten cohorts used a self-reported history for the diagnosis of CVD(Avila-Funes et al., 2014; Danon-Hersch et al., 2012; de Albuquerque Sousa et al., 2012; Dumurgier et al., 2009; Eichholzer et al., 2012; Hajjar et al., 2009; Lin et al., 2015; Moreira and Lourenco, 2013; Polidoro et al., 2013; Ramsay et al., 2015; Ricci et al., 2014; Wong et al., 2010), five(Ekerstad et al., 2011; Green et al., 2012; Khan et al., 2013; Moretti et al., 2013; Sanchis et al., 2014) medical/hospital records, three(Blaum et al., 2005; Chaves, 2005; Sergi et al., 2015) an adjudicated disease diagnosis and one(Frisoli et al., 2015) the criteria proposed by the American Heart Association.(Frisoli et al., 2015) The majority of the studies was conducted among community-dwellers and in Europe. The quality of the studies seems to be good, as shown by the NOS values. Frail participants appeared to be older and more frequently females than pre-frail, robust or pre-frail/robust participants. Regarding potential risk factors for CVD, frail participants showed a higher presence of obesity, type 2 diabetes and hypertension (eTable 3).

Cross-sectional findings

Using crude data from ten cohorts(Avila-Funes et al., 2014; Blaum et al., 2005; Danon-Hersch et al., 2012; de Albuquerque Sousa et al., 2012; Dumurgier et al., 2009; Frisoli et al., 2015; Hajjar et al., 2009; Lin et al., 2015; Moreira and Lourenco, 2013; Ramsay et al., 2015; Sanchis et al., 2014; Wong et al., 2010) and taking 6,875 robust participants as the reference category, frail (n=1,561) and pre-frail (n=7,294) participants presented a significantly higher risk of any-type CVD: OR=3.44 [95%CI, 2.41–4.91] (p<0.001, I^2=79%) and OR=1.59 [95%CI, 1.28–1.97] (p<0.001, I^2=73%), respectively. These findings were confirmed when comparing frail vs. prefrail/ robust participants (studies=15): OR=2.06 [95%CI, 1.51–2.81] (p<0.001, I^2=89%). Similar associations were found for almost all specific CVDs (Table 2).

Table 3 shows the association between frailty and CVDs, adjusted for a median of 7 (range: 1–8) potential confounders listed for each cohort (eTable 3). Taking robust participants as the reference, frailty (OR=2.85; 95%CI=2.29–3.53, p<0.001, I^2=3%) and pre-frailty (OR=1.63; 95%CI=1.39–1.91, p<0.001, I^2=13%) were characterized by a higher risk of having any-type CVD (five studies, n=12,594)(Avila-Funes et al., 2014; Hajjar et al., 2009; Lin et al., 2015; Ramsay et al., 2015; Sergi et al., 2015). The comparison of frail vs. pre-frail/robust participants in four cohorts, n=6,517)(Hajjar et al., 2009; Lin et al., 2015; Ramsay et al., 2015; Sergi et al., 2015) led to similar results (OR=1.69; 95%CI=1.45–1.98, p<0.001, I^2=0%). Again, the association between frailty and pre-frailty remained significant when analyzing specific CVDs (Table 2). While unadjusted ORs were associated with significant heterogeneity in individual study results, the analysis of adjusted estimates resulted in no heterogeneity for almost all outcomes.

Longitudinal findings

Six prospective cohort studies (Avila-Funes et al., 2014; Dumurgier et al., 2009; Eichholzer et al., 2012; Khan et al., 2013; Moretti et al., 2013; Sanchis et al., 2014; Sergi et al., 2015) followed 18,307 participants (for a median of 4.4 (range: 1–11.4) years. Frail participants represented 16% of the baseline population (n=2,943), pre-frail 26% (n=4,875), robust 24% (n=4,488), while the remaining participants (n=6,669; 34%) were classified as pre-frail/ robust (Table 1). With the exception of one study(Khan et al., 2013) that controlled for baseline CVD, analyses were based on participants free of CVD.

Taking robust participants as the reference group and after adjusting for a median of 9 potential confounders (range: 7–13), frailty (HR=1.70 [95%CI, 1.18–2.45], p=0.004; I^2=66%) (Figure 2a) and pre-frailty (HR=1.23 [95%CI, 1.07–1.36], p=0.009; I^2=67%) (Figure 2b) were associated with significantly increased risk of shorter time to any-type CVD at follow-up. Similarly, frailty was associated with a significantly increased the risk of shorter time until CVD when compared to pre-frail/ robust participants (HR=1.56 [95%CI, 1.14–2.14], p=0.006; I^2=74%) (Figure 2c).

Compared to robustness (Figure 2a–b), frailty increased the risk of CHD of 49% (95%CI, 1.10–2.04; p=0.01)(Avila-Funes et al., 2014; Sanchis et al., 2014; Sergi et al., 2015), of heart failure of 72% (95%CI, 1.19–2.45; p=0.004)(Khan et al., 2013; Sanchis et al., 2014; Sergi et al., 2015) and resulted in about a 4-fold increased risk of CV mortality (HR=3.89 [95%CI, 2.39- 6.34], p<0.001).(Sanchis et al., 2014; Sergi et al., 2015) Conversely, pre-frailty carried a significant higher risk of heart failure (HR=1.64 [95%CI, 1.06–2.55], p=0.026; I^2=68% (Khan et al., 2013; Sanchis et al., 2014; Sergi et al., 2015)) and CV mortality (HR=2.80 [95%CI, 1.83–4.28], p<0.001; I^2=0%(Sanchis et al., 2014; Sergi et al., 2015)). Finally, frailty increased the risk of CHD(Avila-Funes et al., 2014; Moretti et al., 2013; Sanchis et al., 2014; Sergi et al., 2015) (HR=1.49 [95%CI, 1.00–2.19], p=0.045; I^2=31%) as well as of CV mortality(Sanchis et al., 2014; Sergi et al., 2015) (HR=1.73 [95%CI, 1.17–2.54], p=0.006; I^2=14%) compared to pre-frail/robust participants (Figure 2c).

Meta-regression

The analysis of adjusted risk estimates from cross-sectional studies were not characterized by substantial heterogeneity, which was detected only for the risk of having heart failure and peripheral vascular disease. However, due to the limited number of studies (3) it was not possible to conduct a meta-regression to identify potential sources of heterogeneity. Conversely, analysis of longitudinal studies showed moderate heterogeneity for the incidence of any-type CVD in all investigated comparisons. Among the moderators considered, any-type CVD was especially higher in frail and in pre-frail individuals who were community dwelling compared to robust participants, while longer follow-up period increased the risk of any-type CVD in frail compared to pre-frail/robust individuals (eTable 4).

In a meta-analysis was restricted to the community setting (4 out of 5 studies), the pooling of risks for any-type CVD for frail (HR=1.38 [95%CI, 1.13–1.68], p=0.001; I^2=0%) and pre-frail (HR=1.22 [95%CI, 1.09–1.35], p<0.001; I^2=0%) participants resulted in no

heterogeneity. However, when frail individuals were compared with pre-frail/robust individuals and studies were stratified by median duration of follow-up (4.4 years), only studies (n=3) with longer follow-up reported a significant association between frailty and incident of any-type CVD, with a reduction in heterogeneity (HR=1.22 [95%CI: 1.09–1.35], p<0.001; I^2=0%).

Publication bias

According to the visual inspection of funnel plots and using Egger's test (see Tables 2 and 3 for cross-sectional studies), no publication bias was evident for all primary and secondary outcomes included. A similar lack of publication bias was present for longitudinal studies. These findings were confirmed, using Eger's regression test (p>0.05) and after imputing for potential unpublished studies (Duval and Tweedie trim-and-fill statistic).

DISCUSSION

In this meta-analysis including a total of 31,343 older participants, we found that frailty and pre-frailty were associated with increased risk of CVD. The increased risk of CVD was evident across both cross-sectional and prospective data analysis. Moreover, frailty was associated by a ~3-fold higher risk of death due to CV causes. The association between frailty and pre-frailty with individual CVDs substantially confirmed those shown in the primary analyses. Frailty increased the risk of CHD, heart failure and CV mortality, while pre-frailty carried a significant higher risk of heart failure and CV mortality.

The prevalence of frailty and pre-frailty were about 15% and 40%, respectively. Accordingly, in agreement with other surveys about this topic(Collard et al., 2012; Kojima, 2015), frailty and pre-frailty are highly prevalent conditions among older adults with important implication for health. Frail and pre-frail study participants seemed to have had an unfavorable metabolic profile, being characterized by higher rates of established CVD risk factors, like obesity, hypertension and type 2 diabetes, than robust participants. All the associations found between frailty conditions and CVD were independent of these potentially confounding CVD risk factors. This fact was particularly evident for cross-sectional data, as the synthesis of unadjusted and adjusted risk estimates yielded similar results (with significant reduction in heterogeneity in adjusted analyses), as well as when considering community-dwellers and longitudinal prospective investigations with longer follow-up. Pooled adjusted risks were characterized by limited to no heterogeneity in individual study results. Other factors than frailty, however, likely play a role in the relationship between frailty status and CVD.

The association between frailty and CVD identified in this work does not allow a definitive causality assessment. Considering the results of prospective cohort studies, there is evidence strong suggestion for a cause-effect relationship between frailty and CVD, as analyses were substantially based on participants free of clinical CVD at study entry. Cross-sectional data analyses may also support the hypothesis of an inverse relationship (i.e. CVD precedes the onset of frailty). Unfortunately, evidence on this topic from prospective studies is limited, (Stone et al., 2014) even if some studies support the notion that subclinical CVD precedes frailty.(Newman et al., 2001; Savela et al., 2013; Stenholm et al., 2014; Strandberg et al.,

2012) It is thus likely that frail and pre-frail subjects had significant sub-clinical vascular and cardiac alterations,(Gharacholou et al., 2015; Katayama et al., 2015; Newman et al., 2001) which made the development of a clinical CVD more likely. Second, frail and pre-frail subjects seem to have several cellular and bio-humoral alterations(Zaslavsky et al., 2013) (e.g. higher oxidative stress and levels(Mulero et al., 2011), marked deoxyribonucleic acid damage(Ashar et al., 2015) and shorter telomere length(Zaslavsky et al., 2013)) that could contribute to the development of CVD.(Haycock et al., 2014; Heitzer et al., 2001; MAHMOUDI et al., 2006) Third, frail people have elevated inflammatory markers (and consequently higher markers of thrombosis(Buckley et al., 2009)), which are known to play a role in the development of CVD.(Buckley et al., 2009) Finally, endocrine dysregulations present in frail and pre-frail people could play an additional role in the development of CVD since these people, for example, usually have lower IGF-1(Cappola et al., 2009) and sex hormones levels(Hyde et al., 2010) compared to healthy controls and these factors may further increase CVD risk.(Corona et al., 2011; Ren and Anversa, 2015)

The implications for practice of present results may be substantial given the aging global population and rising levels of frailty. The importance of CVD in aging was recently discussed and the concept of frailty stressed.(Bell et al., 2015) Particularly, frailty and even more pre-frailty are reversible conditions if appropriately treated, thus reinforcing the importance of their assessment also by cardiologists. (Bell et al., 2015; Fried et al., 2001; Lee et al., 2014) Frailty, in fact, has surely more possibilities of being reversed compared to more advanced conditions typical of older people, such as disability. Very little is known if the treatment of frailty *per se* could be preventative from a cardiovascular point of view. Even if drugs commonly used for the prevention of CVD may be poorly applicable in very frail older subjects(Granziera et al., 2015; Stone et al., 2014), a recent study reported that strict adherence to guidelines for cardiovascular drugs could delay overall mortality in older adults affected by several chronic conditions.(Tinetti et al., 2015) For example, recent evidence suggests that the level of frailty among community-living older people does not interact with the efficacy of antihypertensive treatment.(Bulpitt et al., 2012) Conversely, the role of non-pharmacological interventions could represent a future topic of interest in the frail population. Reasons include evidence suggesting that comprehensive geriatric assessment seems to improve the early recognition of frailty syndromes. Therefore, the positive result of one of these tests should be followed by a comprehensive geriatric assessment of the individual for determining the underlying causes of frailty and plan personalized interventions. Regarding this topic. the application of several non-pharmacological interventions (e.g. physical exercise, dietary interventions, and reduction of unnecessary medications(Carraro et al., 2015; Sergi et al., 2015)) may delay and decrease the onset of CVD. (Bell et al., 2015) In particular, physical activity interventions might play a pivotal role in the prevention of both CVD and frailty. Research is required to establish if physical activity interventions can prevent CVD onset among people with frailty and reverse frailty status.

The findings of our meta-analysis must be considered within its limitations. First, the longitudinal studies included did not assess the transitions of participants across frailty status conditions, which could partly explain our results.(Lee et al., 2014) Second, frailty was evaluated mainly through the criteria suggested by Fried(Fried et al., 2001), but this

definition suffers from some limitations, like not considering cognitive aspects that are, on the contrary, relevant for the assessment of frailty in the elderly.(Kuller et al., 2016) The definitions are also not taking into account specific demographic and clinical variables that may define a syndrome of "biological frailty". For example, work performed by some of us has identified age 65 and older, increased blood urea nitrogen, and decreased haemoglobin and albumin levels as independent predictors for the large number of significant medical deteriorations occurring in patients hospitalized for psychiatric conditions.(Manu et al., 2012) In this large cohort, the medical deteriorations became manifest frequently as falls or febrile syndromes, and required often admissions to medical units. It is reasonable then to assume that biologically frail elderly patients receive a higher level of medical attention, leading to the discovery of pre-existent cardiovascular conditions prevalent in this age group.

The published studies included in our analysis have usually adopted modified versions of the tools originally suggested by Fried(Fried et al., 2001), and this could introduce a bias in our results.(Theou et al., 2015) However, the heterogeneity of pooled estimates was low, which could be considered a major point of strength of our study. The inclusion of different criteria for assessing frailty seems to poorly affect our results in terms of heterogeneity suggesting that, independently from the definition (and the tool used in the assessment), frailty is associated with a higher risk of CVD in the elderly. Furthermore, in ten cohorts only self-reported diagnosis of CVD was considered and this could have introduced another bias since a remarkable percentage of CVD in the elderly is asymptomatic.(Cefalu CA, Burris, 1996) Finally, due to the limited number of studies reporting detailed information, we were unable to assess if differences in the prevalence of specific CVD risk factors significantly moderated the outcomes. Despite these limitations, clear strengths of this meta-analysis include the large number of cohorts and participants analyzed, the relatively long follow-up duration of the longitudinal investigations, and the large number of relevant statistical adjustments and outcomes considered.

In conclusion, frailty and pre-frailty have a close connection with CVD and they constitute modifiable risk factors for CVD in older people. Since CVD events represent an important source of disability and mortality, our meta-analysis confirms the importance of screening for frailty status conditions. This should apply to both subjects/patients with or without and increased CV risk. Future studies are required to evaluate if addressing frailty and pre-frailty and their underlying causes could positively influence CV outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

Afilalo J. Frailty in Patients with Cardiovascular Disease: Why, When, and How to Measure. Curr. Cardiovasc. Risk Rep. 2011; 5:467–472. DOI: 10.1007/s12170-011-0186-0 [PubMed: 21949560]

Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, Popma JJ, Ferrucci L, Forman DE. Frailty assessment in the cardiovascular care of older adults. J. Am. Coll. Cardiol. 2014; 63:747–762. DOI: 10.1016/j.jacc.2013.09.070 [PubMed: 24291279]

Ashar FN, Moes A, Moore AZ, Grove ML, Chaves PHM, Coresh J, Newman AB, Matteini AM, Bandeen-Roche K, Boerwinkle E, Walston JD, Arking DE. Association of mitochondrial DNA levels with frailty and all-cause mortality. J. Mol. Med. (Berl). 2015; 93:177–86. DOI: 10.1007/s00109-014-1233-3 [PubMed: 25471480]

Avila-Funes JA, Meillon C, González-Colaço Harmand M, Tzourio C, Dartigues JF, Amieva H. Association between frailty and carotid central structure changes: The three-city study. J. Am. Geriatr. Soc. 2014; 62:1906–1911. DOI: 10.1111/jgs.13062 [PubMed: 25284354]

Bell SP, Orr NM, Dodson JA, Rich MW, Wenger NK, Blum K, Harold JG, Tinetti ME, Maurer MS, Forman DE. What to Expect From the Evolving Field of Geriatric Cardiology. J. Am. Coll. Cardiol. 2015; 66:1286–1299. DOI: 10.1016/j.jacc.2015.07.048 [PubMed: 26361161]

Blaum CS, Xue QL, Michelon E, Semba RD, Fried LP. The association between obesity and the frailty syndrome in older women: The Women's Health and Aging Studies. J. Am. Geriatr. Soc. 2005; 53:927–934. DOI: 10.1111/j.1532-5415.2005.53300.x [PubMed: 15935013]

Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. Ann. Intern. Med. 2009; 151:483–95. [PubMed: 19805771]

Bulpitt CJ, Beckett NS, Peters R, Leonetti G, Gergova V, Fagard R, Burch LA, Banya W, Fletcher AE, Beckett NS, Forette F, Tuomilehto J, Clarke R, Ritchie C, Waldman A, Walton I, Poulter R, Ma S, Comsa M, Burch LA, Fletcher AE, Bulpitt CJ, Peters R, Tuomilehto J, Swift C, Sever P, Potter J, McCormack T, Forette F, Gil-Extremera B, Dumitrascu D, Staessen JA, Thijs L, Fletcher AE, Bulpitt CJ. Blood pressure control in the Hypertension in the Very Elderly Trial (HYVET). Lancet. Neurol. 2012; 344:683–689. DOI: 10.1016/S1474-4422(08)70143-1

Cappola AR, Xue Q-L, Fried LP. Multiple hormonal deficiencies in anabolic hormones are found in frail older women: the Women's Health and Aging studies. J. Gerontol. A. Biol. Sci. Med. Sci. 2009; 64:243–8. DOI: 10.1093/gerona/gln026 [PubMed: 19182229]

Carraro S, Veronese N, De Rui M, Manzato E, Sergi G. Acute decompensated heart failure: Decision pathways for older people. Eur. Geriatr. Med. 2015; 6:456–461. DOI: 10.1016/j.eurger.2015.05.013

Cefalu CA, Burris JF. Cardiovascular disease in the elderly. Compr. Ther. 1996; 22:509–514. DOI: 10.1016/S0735-1097(87)80456-4 [PubMed: 8879918]

Chaves P. Impact of anemia and cardiovascular disease on frailty status of community-dwelling older women: the Women's Health and Aging Studies I and II. Journals …. 2005; 60:729–735.

Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013; 381:752–62. DOI: 10.1016/S0140-6736(12)62167-9 [PubMed: 23395245]

Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J. Am. Geriatr. Soc. 2012; 60:1487–92. DOI: 10.1111/j. 1532-5415.2012.04054.x [PubMed: 22881367]

Corona G, Rastrelli G, Monami M, Guay A, Buvat J, Sforza A, Forti G, Mannucci E, Maggi M. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. Eur. J. Endocrinol. 2011; 165:687–701. DOI: 10.1530/EJE-11-0447 [PubMed: 21852391]

Danon-Hersch N, Rodondi N, Spagnoli J, Santos-Eggimann B. Prefrailty and chronic morbidity in the youngest old: an insight from the Lausanne cohort Lc65+ J. Am. Geriatr. Soc. 2012; 60:1687–94. DOI: 10.1111/j.1532-5415.2012.04113.x [PubMed: 22906300]

de Albuquerque Sousa ACP, Dias RC, Maciel, álvaro CC, Guerra RO. Frailty syndrome and associated factors in community-dwelling elderly in Northeast Brazil. Arch. Gerontol. Geriatr. 2012; 54doi: 10.1016/j.archger.2011.08.010

de Labra C, Guimaraes-Pinheiro C, Maseda A, Lorenzo T, Millán-Calenti JC. Effects of physical exercise interventions in frail older adults: a systematic review of randomized controlled trials. BMC Geriatr. 2015; 15:154.doi: 10.1186/s12877-015-0155-4 [PubMed: 26626157]

DerSimonian R, Laird N. Meta-analysis in clinical trials. Control. Clin. Trials. 1986; 7:177–188. DOI: 10.1016/0197-2456(86)90046-2 [PubMed: 3802833]

Dumurgier J, Elbaz A, Ducimetière P, Tavernier B, Alpérovitch A, Tzourio C. Slow walking speed and cardiovascular death in well functioning older adults: prospective cohort study. BMJ. 2009; 339:b4460. [PubMed: 19903980]

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315:629–634. DOI: 10.1136/bmj.316.7129.469 [PubMed: 9310563]

Eichholzer M, Barbir A, Basaria S, Dobs AS, Feinleib M, Guallar E, Menke A, Nelson WG, Rifai N, Platz EA, Rohrmann S. Serum sex steroid hormones and frailty in older American men of the Third National Health and Nutrition Examination Survey (NHANES III). Aging Male. 2012; 15:208–15. DOI: 10.3109/13685538.2012.705366 [PubMed: 22822787]

Ekerstad N, Swahn E, Janzon M, Alfredsson J, Löfmark R, Lindenberger M, Carlsson P. Frailty is independently associated with short-term outcomes for elderly patients with non-ST-segment elevation myocardial infarction. Circulation. 2011; 124:2397–2404. DOI: 10.1161/CIRCULATIONAHA.111.025452 [PubMed: 22064593]

Finn M, Green P. The Influence of Frailty on Outcomes in Cardiovascular Disease. Rev. Esp. Cardiol. (Engl. Ed). 2015; 68:653–6. DOI: 10.1016/j.rec.2015.04.005 [PubMed: 26129717]

Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in older adults: evidence for a phenotype. J. Gerontol. A. Biol. Sci. Med. Sci. 2001; 56:M146–56. [PubMed: 11253156]

Frisoli A, Ingham SJM, Paes, Angela T, Tinoco E, Greco A, Zanata N, Pintarelli V, Elber I, Borges J, Camargo Carvalho AC. Frailty predictors and outcomes among older patients with cardiovascular disease: Data from Fragicor. Arch. Gerontol. Geriatr. 2015; 61:1–7. DOI: 10.1016/j.archger. 2015.03.001 [PubMed: 25921097]

Fukui S, Kawakami M, Otaka Y, Ishikawa A, Mizuno K, Tsuji T, Hayashida K, Inohara T, Yashima F, Liu M. Physical frailty in older people with severe aortic stenosis. Aging Clin. Exp. Res. 2015; doi: 10.1007/s40520-015-0507-0

Gary R. Evaluation of frailty in older adults with cardiovascular disease: incorporating physical performance measures. J. Cardiovasc. Nurs. 2012; 27:120–31. DOI: 10.1097/JCN. 0b013e318239f4a4 [PubMed: 22334147]

Gharacholou SM, Tashiro T, Cha SS, Scott CG, Takahashi PY, Pellikka PA. Echocardiographic Indices Associated With Frailty in Adults   65 Years. Am. J. Cardiol. 2015; doi: 10.1016/j.amjcard. 2015.08.023

Gill TM, Baker DI, Gottschalk M, Peduzzi PN, Allore H, Byers A. A program to prevent functional decline in physically frail, elderly persons who live at home. N. Engl. J. Med. 2002; 347:1068–74. DOI: 10.1056/NEJMoa020423 [PubMed: 12362007]

Granziera S, Cohen AT, Nante G, Manzato E, Sergi G. Thromboembolic Prevention in Frail Elderly Patients With Atrial Fibrillation: A Practical Algorithm. J. Am. Med. Dir. Assoc. 2015; 16:358–364. DOI: 10.1016/j.jamda.2014.12.008 [PubMed: 25680239]

Green P, Woglom AE, Genereux P, Daneault B, Paradis JM, Schnell S, Hawkey M, Maurer MS, Kirtane AJ, Kodali S, Moses JW, Leon MB, Smith CR, Williams M. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: A single-center experience. JACC Cardiovasc. Interv. 2012; 5:974–981. DOI: 10.1016/j.jcin. 2012.06.011 [PubMed: 22995885]

Hajjar I, Yang F, Sorond F, Jones RN, Milberg W, Cupples LA, Lipsitz LA. A novel aging phenotype of slow gait, impaired executive function, and depressive symptoms: Relationship to blood pressure and other cardiovascular risks. Journals Gerontol. - Ser. A Biol. Sci. Med. Sci. 2009; 64:994–1001. DOI: 10.1093/gerona/glp075

Hanna IR, Wenger NK. Secondary prevention of coronary heart disease in elderly patients. Am. Fam. Physician. 2005; 71:2289–2296. [PubMed: 15999866]

Haskell WL. Cardiovascular disease prevention and lifestyle interventions: effectiveness and efficacy. J. Cardiovasc. Nurs. 2003; 18:245–55. [PubMed: 14518600]

Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A, Willeit P. Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. BMJ. 2014; 349:g4227. [PubMed: 25006006]

Heitzer T, Schlinzig T, Krohn K, Meinertz T, Munzel T. Endothelial Dysfunction, Oxidative Stress, and Risk of Cardiovascular Events in Patients With Coronary Artery Disease. Circulation. 2001; 104:2673–2678. DOI: 10.1161/hc4601.099485 [PubMed: 11723017]

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat. Med. 2002; 21:1539–1558. DOI: 10.1002/sim.1186 [PubMed: 12111919]

Hyde Z, Flicker L, Almeida OP, Hankey GJ, McCaul KA, Chubb SAP, Yeap BB. Low free testosterone predicts frailty in older men: the health in men study. J. Clin. Endocrinol. Metab. 2010; 95:3165–72. DOI: 10.1210/jc.2009-2754 [PubMed: 20410223]

Jha SR, Hannu MK, Wilhelm K, Newton PJ, Chang S, Montgomery E, Harkess M, Tunnicliff P, Smith A, Hayward C, Jabbour A, Keogh A, Kotlyar E, Dhital K, Granger E, Jansz P, Spratt P, Macdonald P. Reversibility of Frailty in Advanced Heart Failure Patients Listed for Transplantation. J. Hear. Lung Transplant. 2016; 35:S29.doi: 10.1016/j.healun.2016.01.077

Katayama PL, Dias DPM, Silva LEV, Virtuoso-Junior JS, Marocolo M. Cardiac autonomic modulation in non-frail, pre-frail and frail elderly women: a pilot study. Aging Clin. Exp. Res. 2015; 27:621–629. DOI: 10.1007/s40520-015-0320-9 [PubMed: 25673231]

Khan H, Kalogeropoulos AP, Georgiopoulou VV, Newman AB, Harris TB, Rodondi N, Bauer DC, Kritchevsky SB, Butler J. Frailty and risk for heart failure in older adults: The health, aging, and body composition study. Am. Heart J. 2013; 166:887–94. DOI: 10.1016/j.ahj.2013.07.032 [PubMed: 24176445]

Kojima G. Prevalence of Frailty in Nursing Homes: A Systematic Review and Meta-Analysis. J. Am. Med. Dir. Assoc. 2015; 16:940–5. DOI: 10.1016/j.jamda.2015.06.025 [PubMed: 26255709]

Kuller LH, Lopez OL, Mackey RH, Rosano C, Edmundowicz D, Becker JT, Newman AB. Subclinical Cardiovascular Disease and Death, Dementia, and Coronary Heart Disease in Patients 80+ Years. J. Am. Coll. Cardiol. 2016; 67:1013–1022. DOI: 10.1016/j.jacc.2015.12.034 [PubMed: 26940919]

Lee JSW, Auyeung T-W, Leung J, Kwok T, Woo J. Transitions in Frailty States Among Community-Living Older Adults and Their Associated Factors. J. Am. Med. Dir. Assoc. 2014; 15:281–286. DOI: 10.1016/j.jamda.2013.12.002 [PubMed: 24534517]

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009; 6:e1000100.doi: 10.1371/journal.pmed.1000100 [PubMed: 19621070]

Lin CH, Chou CY, Liu CS, Huang CY, Li TC, Lin CC. Association between frailty and subclinical peripheral vascular disease in a community-dwelling geriatric population: Taichung Community Health Study for Elders. Geriatr. Gerontol. Int. 2015; 15:261–267. DOI: 10.1111/ggi.12265 [PubMed: 25164713]

Mahmoudi M, Mercer J, Bennett M. DNA damage and repair in atherosclerosis. Cardiovasc. Res. 2006; 71:259–268. DOI: 10.1016/j.cardiores.2006.03.002 [PubMed: 16580654]

Manu P, Asif M, Khan S, Ashraf H, Mani A, Guvenek-Cokol P, Lee H, Kane JM, Correll CU. Risk factors for medical deterioration of psychiatric inpatients: opportunities for early recognition and prevention. Compr. Psychiatry. 2012; 53:968–74. DOI: 10.1016/j.comppsych.2012.03.005 [PubMed: 22520089]

Moreira VG, Lourenco RA. Prevalence and factors associated with frailty in an older population from the city of Rio de Janeiro, Brazil: The FIBRA-RJ Study. Clinics. 2013; 68:979–985. DOI: 10.6061/clinics/2013(07)15 [PubMed: 23917663]

Moretti C, Giusto F, Quadri G, D'Ascenzo F, Di Cuia M, De Simone V, Colaci C, Reitano C, Bergerone S, Bo M, Moiraghi C, Porta M, Marinone C, Cavallo Perin P, Veglio F, Montrucchio G, Torchio M, Scaglione L, Gaita F. A comparative analysis of cardiovascular and frailty prognostic risk scores in patients with ACS. The STORM study. EuroIntervention. 2013; 9:140.

Mulero J, Zafrilla P, Martinez-Cacha A. Oxidative stress, frailty and cognitive decline. J. Nutr. Health Aging. 2011; 15:756–60. [PubMed: 22089224]

Newman AB, Gottdiener JS, Mcburnie MA, Hirsch CH, Kop WJ, Tracy R, Walston JD, Fried LP. Associations of subclinical cardiovascular disease with frailty. J. Gerontol. A. Biol. Sci. Med. Sci. 2001; 56:M158–66. [PubMed: 11253157]

Ng TP, Feng L, Nyunt MSZ, Feng L, Niti M, Tan BY, Chan G, Khoo SA, Chan SM, Yap P, Yap KB. Nutritional, Physical, Cognitive, and Combination Interventions and Frailty Reversal Among Older Adults: A Randomized Controlled Trial. Am. J. Med. 2015; 128:1225–1236.e1. DOI: 10.1016/j.amjmed.2015.06.017 [PubMed: 26159634]

Phan HM, Alpert JS, Fain M. Frailty, inflammation, and cardiovascular disease: evidence of a connection. Am. J. Geriatr. Cardiol. 2008; 17:101–7. [PubMed: 18326951]

Polidoro A, Stefanelli F, Ciacciarelli M, Pacelli A, Di Sanzo D, Alessandri C. Frailty in patients affected by atrial fibrillation. Arch. Gerontol. Geriatr. 2013; 57:325–327. DOI: 10.1016/j.archger.2013.04.014 [PubMed: 23706973]

Ramsay SE, Arianayagam DS, Whincup PH, Lennon LT, Cryer J, Papacosta AO, Iliffe S, Wannamethee SG. Cardiovascular risk profile and frailty in a population-based study of older British men. Heart. 2015; 101:616–22. DOI: 10.1136/heartjnl-2014-306472 [PubMed: 25480883]

Ren J, Anversa P. The insulin-like growth factor I system: physiological and pathophysiological implication in cardiovascular diseases associated with metabolic syndrome. Biochem. Pharmacol. 2015; 93:409–17. DOI: 10.1016/j.bcp.2014.12.006 [PubMed: 25541285]

Ricci NA, Pessoa GS, Ferriolli E, Dias RC, Perracini MR. Frailty and cardiovascular risk in community-dwelling elderly: a population-based study. Clin. Interv. Aging. 2014; 9:1677–85. DOI: 10.2147/CIA.S68642 [PubMed: 25336932]

Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005; 173:489–95. DOI: 10.1503/cmaj.050051 [PubMed: 16129869]

Sanchis J, Bonanad C, Ruiz V, Fernández J, García-Blas S, Mainar L, Ventura S, Rodríguez-Borja E, Chorro FJ, Hermenegildo C, Bertomeu-González V, Núñez E, Núñez J. Frailty and other geriatric conditions for riskstratification of older patients with acute coronary syndrome. Am. Heart J. 2014; 168:784–791. , e2. DOI: 10.1016/j.ahj.2014.07.022 [PubMed: 25440808]

Santos-Eggimann B, Sirven N, Kan GA, van, Rolland Y, Bergman H, Morley J, Kritchevsky S, Vellas B, Morley J, Vellas B, Kan G, Bergman H, Ferrucci L, Guralnik J, Chambers R, Hogan D, MacKnight C, Bergman H, Sternberg S, Schwartz AW, Karunananthan S, Bergman H, Mark C, Fried L, Tangen C, Walston J, Walston J, Fried L, Sanders J, Boudreau R, Fried L, Walston J, Harris T, Newman A, Kulmala J, Nykanen I, Manty M, Hartikainen S, Robertson D, Savva G, Kenny R, Sourial N, Bergman H, Karunananthan S, Mitnitski A, Mogilner A, Rockwood K, Searle S, Mitnitski A, Gahbauer E, Gill T, Rockwood K, Cesari M, Gambassi G, Kan G, Vellas B, Gobbens R, Assen M, Luijkx K, Schols J, Peters L, Boter H, Buskens E, Slaets J, Theou O, Brothers T, Mitnitski A, Rockwood K, Bandeen-Roche K, Xue Q, Ferrucci L, Woods N, LaCroix A, Gray S, Macklai N, Spagnoli J, Junod J, Santos-Eggimann B, Hsu H, Chang W, Espinoza S, Jung I, Hazuda H, Gill T, Gahbauer E, Allore H, Han L, Shardell M, D'Adamo C, Alley D, Fallah N, Mitnitski A, Searle S, Gahbauer E, Gill T, Rockwood K, Mitnitski A, Song X, Rockwood K, Rochat S, Cumming R, Blyth F, Gobbens R, Assen M, Au A, Puts M, Fletcher J, Sourial N, Bergman H, Theou O, Brothers T, Pena F, Mitnitski A, Rockwood K, Hoogendijk E, Hout H,

Heymans M, Ade CM, Engstrom E, Alves L, Theou O, Brothers T, Rockwood M, Haardt D, Mitnitski A, Rockwood K, Santos-Eggimann B, Cuenoud P, Spagnoli J, Junod J, Jürges H, Cesari M, Demougeot L, Boccalon H, Bari M, Profili F, Bandinelli S, Auyeung T, Lee J, Leung J, Kwok T, Woo J, Studenski S, Perera S, Patel K, Gobbens R, Assen M, Vermeulen J, Neyens J, Rossum E, Spreeuwenberg M, Witte L, Berrut G, Andrieu S, Carvalho IA, De, Turner G, Clegg A, Gordon A, Masud T, Gladman J, Robinson T, Finlayson E, Allen K, Romero-Ortuno R, O'Shea D, Sourial N, Bergman H, Karunananthan S, Pijpers E, Ferreira I, Stehouwer C, Kruseman AN, Drubbel I, Wit N, Bleijenberg N, Eijkemans R, Schuurmans M, Numans M, Drubbel I, Numans M, Kranenburg G, Bleijenberg N, Wit N, Schuurmans M, Drubbel I, Bleijenberg N, Kranenburg G, Hoogendijk E, Horst H, Deeg D, Kim H, Higgins P, Canaday D, Burant C, Hornick T, Clegg A, Young J, Iliffe S, Rikkert M, Rockwood K, Pialoux T, Goyard J, Lesourd B, Romero-Ortuno R, Rolfson D, Majumdar S, Tsuyuki R, Tahir A, Rockwood K, Ekerstad N, Swahn E, Janzon M, Graham M, Galbraith P, O'Neill D, Rolfson D, Dando C, Norris C, Purser J, Kuchibhatla M, Fillenbaum G, Harding T, Peterson E, Alexander K, Roshanravan B, Khatri M, Robinson-Cohen C, Fragoso CV, Enright P, McAvay G, Ness P, Gill T, Hamaker M, Jonker J, Rooij S, Vos A, Smorenburg C, Munster B, Kenig J, Zychiewicz B, Olszewska U, Richter P, Smets I, Kempen G, Janssen-Heijnen M, Deckx L, Buntinx F, Akker M, Puts M, Monette J, Girre V, Puts M, Monette J, Girre V, Dent E, Chapman I, Howell S, Piantadosi C, Visvanathan R, Joosten E, Demuynck M, Detroyer E, Milisen K, Wou F, Gladman J, Bradshaw L, Franklin M, Edmans J, Conroy S, Joseph B, Pandit V, Zangbar B, Hastings S, Purser J, Johnson K, Sloane R, Whitson H, Stiffler K, Finley A, Midha S, Wilber S, Townsend N, Robinson T, Farhat J, Velanovich V, Falvo A, Makary M, Segev D, Pronovost P, Revenig L, Canter D, Taylor M, Amrock L, Neuman M, Lin H, Deiner S, Cohen R, Lagoo-Deenadayalan S, Heflin M, Dasgupta M, Rolfson D, Stolee P, Borrie M, Speechley M, Revenig L, Canter D, Henderson M, Beggs T, Sepehri A, Szwajcer A, Tangri N, Arora R, Oresanya L, Lyons W, Finlayson E, Partridge J, Harari D, Dhesi J, Partridge J, Harari D, Martin F, Dhesi J, Afilalo J, Mottillo S, Eisenberg M, Singh M, Rihal C, Lennon R, Spertus J, Nair K, Roger V, Rowe R, Iqbal J, Murali-Krishnan R, Bagnall N, Faiz O, Darzi A, Athanasiou T, Sepehri A, Beggs T, Hassan A, Afilalo J, Alexander K, Mack M, Ferrucci L, Guralnik J, Studenski S, Fried L, Cutler G, Walston J, Bibas L, Levi M, Bendayan M, Mullie L, Forman D, Afilalo J, Chou C, Hwang C, Wu Y, Theou O, Stathokostas L, Roland K, Gine-Garriga M, Roque-Figuls M, Coll-Planas L, Sitja-Rabert M, Salva A, Kelaiditi E, Kan G, Cesari M, Cameron I, Fairhall N, Langron C, Fairhall N, Sherrington C, Kurrle S, Lord S, Lockwood K, Cameron I, Fairhall N, Sherrington C, Lord S, Bleijenberg N, Dam V, Drubbel I, Numans M, Wit N, Schuurmans M, Cesari M, Demougeot L, Boccalon H, Guyonnet S, Vellas B, Andrieu S, Rodriguez-Manas L, Bayer A, Kelly M, Romera L, Orfila F, Segura J, Metzelthin S, Rossum E, Witte L, Hendriks M, Kempen G, Metzelthin S, Rossum E, Witte L, Chan D, Tsou H, Yang R, Tavassoli N, Guyonnet S, Kan GA, Van, Vellas B, Balardy L, Gillette-Guyonnet S, Chen C, Chen C, Lai I, Huang G, Saczynski J, Inouye S, Clegg A, Barber S, Young J, Iliffe S, Forster A, Fragala M, Dam T, Barber V, Rest O, Zwaluw N, Tieland M, Favela J, Castro L, Franco-Marina F, Razzanelli M, Profili F, Mossello E. Screening for frailty: older populations and older individuals. Public Health Rev. 2016; 37:7.doi: 10.1186/s40985-016-0021-8 [PubMed: 29450049]

Savela SL, Koistinen P, Stenholm S, Tilvis RS, Strandberg AY, Pitkälä KH, Salomaa VV, Strandberg TE. Leisure-time physical activity in midlife is related to old age frailty. Journals Gerontol. - Ser. A Biol. Sci. Med. Sci. 2013; 68:1433–1438. DOI: 10.1093/gerona/glt029

Sergi G, Veronese N, Fontana L, De Rui M, Bolzetta F, Zambon S, Corti M-C, Baggio G, Toffanello ED, Crepaldi G, Perissinotto E, Manzato E. Pre-frailty and risk of cardiovascular disease in elderly men and women: the pro.v.a. study. J. Am. Coll. Cardiol. 2015; 65:976–83. DOI: 10.1016/j.jacc.2014.12.040 [PubMed: 25766943]

Stenholm S, Strandberg TE, Pitkälä K, Sainio P, Heliövaara M, Koskinen S. Midlife obesity and risk of frailty in old age during a 22-year follow-up in men and women: The mini-Finland follow-up survey. Journals Gerontol. - Ser. A Biol. Sci. Med. Sci. 2014; 69:73–78. DOI: 10.1093/gerona/glt052

Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Watson K, Wilson PWF. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/

American Heart Association Task Force on Practice Guidelines. J. Am. Coll. Cardiol. 2014; 63:2889–934. DOI: 10.1016/j.jacc.2013.11.002 [PubMed: 24239923]

Strandberg TE, Sirola J, Pitkälä KH, Tilvis RS, Strandberg AY, Stenholm S. Association of midlife obesity and cardiovascular risk with old age frailty: a 26-year follow-up of initially healthy men. Int. J. Obes. (Lond). 2012; 36:1153–7. DOI: 10.1038/ijo.2012.83 [PubMed: 22614054]

Theou O, Cann L, Blodgett J, Wallace LMK, Brothers TD, Rockwood K. Modifications to the frailty phenotype criteria: Systematic review of the current literature and investigation of 262 frailty phenotypes in the survey of health, ageing, and retirement in Europe. Ageing Res. Rev. 2015; doi: 10.1016/j.arr.2015.04.001

Tinetti ME, McAvay G, Trentalange M, Cohen AB, Allore HG. Association between guideline recommended drugs and death in older adults with multiple chronic conditions: population based cohort study. BMJ. 2015; 351:h4984.doi: 10.1136/bmj.h4984 [PubMed: 26432468]

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. for the STROBE initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guildelines for reporting observational studies. J. Clin. Epidemiol. 2008; 61:344–349. DOI: 10.1016/j.jclinepi.2007.11.008 [PubMed: 18313558]

von Haehling S, Anker SD, Doehner W, Morley JE, Vellas B. Frailty and heart disease. Int. J. Cardiol. 2013; 168:1745–7. DOI: 10.1016/j.ijcard.2013.07.068 [PubMed: 23931976]

Wells G, , Shea B, , O'Connell D, , Peterson J, , Welch V, , Losos M, , Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. 2012 (Available from URL http//www.ohri.ca/programs/clinical_epidemiology/oxford.asp) 2012

Wong CH, Weiss D, Sourial N, Karunananthan S, Quail JM, Wolfson C, Bergman H. Frailty and its association with disability and comorbidity in a community-dwelling sample of seniors in Montreal: a cross-sectional study. Aging Clin. Exp. Res. 2010; 22:54–62. DOI: 10.3275/6675 [PubMed: 19940555]

Zaslavsky O, Cochrane BB, Thompson HJ, Woods NF, Herting JR, LaCroix A. Frailty: a review of the first decade of research. Biol. Res. Nurs. 2013; 15:422–32. DOI: 10.1177/1099800412462866 [PubMed: 23086382]

HIGHLIGHTS

- If frailty is a potential cardiovascular risk factor is poorly known.

- In our work frailty was associated with higher prevalence and incidence of CVD.

- Interventional studies are needed to confirm our findings.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Identification

Records identified through
database searching
(n = 10258)

Additional records identified
through other sources
(n = 0)

Screening

Records after duplicates removed
(n =8953)

Records screened
(n = 8953)

Records excluded (not pertinent)
(n = 8897)

Eligibility

Full-text articles
assessed for eligibility
(n = 56)

Full-text articles excluded, with
reasons
(n = 35)
No data about CVD (n=12)
All participants with CVD (n=7)
Reviews (n=7)
Only gait speed (n=5)
No data about frailty (n=4)

Studies included in
qualitative synthesis
(n = 21)

Included

Studies included in
quantitative synthesis
(meta-analysis)
(n = 21)
(18 cohorts)

Figure 1.
PRISMA flow-chart

A   Pooled risk estimates for frail vs. robust participants

	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value	Hazard ratio and 95% CI
Any-type CVD						
3-City study. 2014	1.47	1.03	2.10	2.12	0.03	
Khan. 2013	1.88	1.02	3.47	2.02	0.04	
Sanchis. 2014	3.40	1.80	6.41	3.78	0.000	
Sergi. 2015	1.26	0.98	1.63	1.77	0.08	
TOTAL (I²=66%; p=0.034)	1.70	1.18	2.45	2.86	0.004	
Coronary heart disease						
3-City study. 2014	1.37	0.86	2.18	1.33	0.19	
Sanchis. 2014	1.60	0.79	3.30	1.30	0.19	
Sergi. 2015	1.60	0.96	2.66	1.81	0.07	
TOTAL (I²=0%; p=0.89)	1.49	1.01	2.04	2.56	0.01	
Stroke or TIA						
3-City study. 2014	1.37	0.79	2.38	1.12	0.27	
Sergi. 2015	1.44	0.52	4.00	0.70	0.48	
TOTAL (I²=0%; p=0.93)	1.386	0.852	2.254	1.31	0.19	
Heart failure						
Khan. 2013	1.88	1.02	3.47	2.02	0.04	
Sanchis. 2014	3.20	1.27	8.04	2.47	0.01	
Sergi. 2015	1.44	1.12	1.86	2.82	0.005	
TOTAL (I²=35%; p=0.22)	1.72	1.185	2.50	2.85	0.004	
CV mortality						
Sanchis. 2014	4.80	2.20	10.49	3.93	0.000	
Sergi. 2015	3.41	1.829	6.36	3.86	0.000	
TOTAL (I²=0%; p=0.50)	3.89	2.393	6.34	5.47	0.000	

0.1 0.2 0.5 1 2 5 10

B **Pooled risk estimates for pre-frail vs. robust participants**

	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value	Hazard ratio and 95% CI
Any-type CVD						
3-City study. 2014	1.13	0.93	1.38	1.21	0.23	
Khan. 2013	1.36	1.08	1.71	2.62	0.009	
Sanchis. 2014	3.10	1.61	5.95	3.40	0.001	
Sergi. 2015	1.21	1.04	1.40	2.51	0.01	
TOTAL (I^2=67%; p=0.03)	1.32	1.07	1.63	2.63	0.009	
Coronary heart disease						
3-City study. 2014	1.04	0.82	1.33	0.32	0.75	
Sanchis. 2014	1.50	0.71	3.16	1.07	0.29	
Sergi. 2015	1.45	0.59	3.56	0.81	0.42	
TOTAL (I^2=0%; p=0.54)	1.01	0.88	1.37	0.81	0.42	
Stroke or TIA						
3-City study. 2014	1.19	0.87	1.63	1.08	0.28	
Sergi. 2015	0.93	0.48	1.80	-0.22	0.83	
TOTAL (I^2=0%; p=0.51)	1.14	0.85	1.51	0.88	0.38	
Heart failure						
Khan. 2013	1.36	1.08	1.71	2.62	0.009	
Sanchis. 2014	4.40	1.79	10.83	3.22	0.001	
Sergi. 2015	1.35	0.92	2.00	1.52	0.13	
TOTAL (I^2=68%; p=0.044)	1.64	1.06	2.55	2.22	0.03	
CV mortality						
Sanchis. 2014	2.90	1.22	6.90	2.41	0.02	
Sergi. 2015	2.77	1.705	4.500	4.12	0.000	
TOTAL (I^2=0%; p=0.93)	2.80	1.834	4.277	4.77	0.000	

0.1 0.2 0.5 1 2 5 10

C Pooled risk estimates for frail vs. pre-frail/robust participants

	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value	Hazard ratio and 95% CI
Any-type CVD						
3-City study. 2014	1.370	0.979	1.918	1.835	0.067	
Eicholzer. 2014	2.130	1.599	2.838	5.165	0.000	
Moretti. 2013	2.600	0.867	7.800	1.705	0.088	
Sanchis. 2014	1.700	1.106	2.614	2.418	0.016	
Sergi. 2015	1.090	0.877	1.355	0.776	0.438	
TOTAL (I^2=74%; p=0.004)	1.562	1.137	2.146	2.750	0.006	
Coronary heart disease						
3-City study. 2014	1.34	0.86	2.09	1.29	0.20	
Moretti. 2013	3.40	1.42	8.13	2.75	0.006	
Sanchis. 2014	1.30	0.72	2.36	0.87	0.39	
Sergi. 2015	1.10	0.49	2.46	0.23	0.82	
TOTAL (I^2=31%; p=0.22)	1.49	1.01	2.19	2.00	0.05	
Stroke or TIA						
3-City study. 2014	1.24	0.74	2.08	0.81	0.42	
Sanchis. 2014	1.70	0.06	48.98	0.31	0.76	
Sergi. 2015	1.52	0.61	3.76	0.91	0.37	
TOTAL (I^2=0%; p=0.92)	1.31	0.84	2.05	1.19	0.24	
Heart failure						
Moretti. 2013	1.20	0.54	2.68	0.44	0.66	
Sanchis. 2014	1.20	0.60	2.40	0.52	0.61	
Sergi. 2015	1.00	0.72	1.40	0.000	1.00	
TOTAL (I^2=0%; p=0.85)	1.05	0.794	1.40	0.37	0.71	
CV mortality						
Sanchis. 2014	2.20	1.24	3.92	2.68	0.007	
Sergi. 2015	1.40	0.94	2.31	1.67	0.01	
TOTAL (I^2=14%; p=0.28)	1.73	1.17	2.54	2.77	0.006	

0.1 0.2 0.5 1 2 5 10

Figure 2.
Meta-analysis and pooled fully-adjusted HRs of CVDs and CV mortality in frail and pre-frail participants from prospective cohort studies: Forrest plot A, frail vs. robust; Forrest plot B, pre-frail vs. robust; Forrest plot C, frail vs. pre-frail/robust.

Table 1

Meta-analysed prevalence of frailty and pre-frailty in the studies included.

Cross-sectional studies			Longitudinal studies		
Cohorts (population)	Frail % (95%CI)	Pre-frail % (95%CI)	Cohorts (population)	Frail % (95%CI)	Pre-frail % (95%CI)
18 (31,343)	17.9 (11.4–27.0)	--	7 (18,970)	15.9 (6.8–32.9)	--
10 (16,400)	12.0 (8.3–17.0)	43.7 (38.7–48.8)	4 (10,278)	12.7 (6.9–22.1)	42.3 (36.6–48.2)

Notes:

Prevalence is reported as percentage with 95% confidence intervals. The first row is referred to the studies including frail vs. pre-frail and/or robust; the second to the studies including only studies reporting data on frail vs. pre-frail vs. robust.

Table 2

Meta-analysis of cross-sectional studies with publication bias assessment

Analysis	Number of studies	Number participants		Meta-analysis				Heterogeneity	Publication bias	
		1st group	2nd group	OR	95% CI		P-value	I^2	Egger bias & p-value	Adjusted risk estimates* (95% CI)
CVD										
Frail vs. robust	10	1561	6875	**3.44**	**2.41**	**4.91**	**<0.001**	79	1.66; 0.42	4.15 (2.78 to 6.21)
Pre-frail vs. robust	10	7294	6875	**1.59**	**1.28**	**1.97**	**<0.001**	73	−2.10; 0.18	1.65 (1.32 to 2.06)
Frail vs. pre-frail /robust	15	3866	21607	**2.06**	**1.51**	**2.81**	**<0.001**	89	1.38; 0.41	Unchanged
CHD										
Frail vs. robust	8	1363	6155	**2.79**	**2.20**	**3.35**	**<0.001**	34	0.75; 0.67	Unchanged
Pre-frail vs. robust	8	6436	6155	**1.93**	**1.14**	**3.26**	**0.01**	93	−3.03; 0.51	2.23 (1.40 to 3.36)
Frail vs. pre-frail /robust	13	3574	19453	**1.44**	**1.06**	**1.97**	**0.02**	86	0.42; 0.80	Unchanged
Stroke + TIA										
Frail vs. robust	9	1525	6354	**4.58**	**2.56**	**8.20**	**<0.001**	79	0.29; 0.91	5.70 (3.01 to 10.82)
Pre-frail vs. robust	9	6903	6354	**2.11**	**1.59**	**2.83**	**<0.001**	37	−1.78; 0.10	2.31 (1.65 to 3.24)
Frail vs. pre-frail /robust	13	2311	18719	**2.83**	**2.00**	**3.99**	**<0.001**	76	−0.52; 0.72	3.29 (2.31 to 4.70)
Heart failure										
Frail vs. robust	5	789	2365	**4.99**	**1.93**	**12.94**	**0.001**	88	−2.62; 0.58	6.95 (2.68 to 17.98)
Pre-frail vs. robust	5	3098	2365	1.49	0.62	3.59	0.38	88	−4.37; 0.28	1.95 (0.84 to 4.51)
Frail vs. pre-frail /robust	7	1047	5656	**3.25**	**1.89**	**5.60**	**<0.001**	83	−2.08; 0.53	2.37 (1.33 to 4.25)
PVD										
Frail vs. robust	6	972	2499	**3.72**	**2.55**	**5.41**	**<0.001**	37	1.17; 0.28	2.95 (1.95 to 4.47)
Pre-frail vs. robust	6	3399	2499	**2.00**	**1.37**	**2.94**	**<0.001**	54	0.51; 0.65	1.83 (1.24 to 2.70)
Frail vs. pre-frail /robust	9	2622	7539	**1.78**	**1.14**	**2.71**	**<0.001**	83	0.73; 0.75	1.43 (0.93 to 2.20)

Bold values represent significant results, as p-value <0.05

Abbreviations: CHD: coronary heart disease; CI: confidence intervals; CVD, cardiovascular diseases; OR, odds ratio; PVD: peripheral vascular disease; TIA, transient ischemic attack.

*Test for publication bias: Duval and Tweedie nonparametric trim-and-fill procedure

Table 3

Adjusted odds ratios of cross-sectional studies included with publication bias assessment.

Analysis	Number of studies	Meta-analysis			Heterogeneity	Publication bias	
		OR	95% CI	P-value	I^2	Egger bias & p-value	Adjusted risk estimates* (95% CI)
CVD							
Frail vs. robust	5	**2.85**	**2.29**	**3.53**	**<0.001**	3	2.19; 0.26	Unchanged
Pre-frail vs. robust	5	**1.63**	**1.39**	**1.91**	**<0.001**	13	2.41; 0.23	1.54 (1.29 to 1.81)
Frail vs. pre-frail /robust	4	**1.69**	**1.45**	**1.98**	**<0.001**	0	0.78; 0.31	Unchanged
CHD							
Frail vs. robust	4	**2.86**	**2.20**	**3.71**	**<0.001**	0	5.24; 0.11	2.69 (2.11 to 3.43)
Pre-frail vs. robust	4	**1.58**	**1.32**	**1.88**	**<0.001**	0	1.53; 0.55	Unchanged
Frail vs. pre-frail /robust	3	1.43	0.90	2.29	0.13	30	0.66; 0.73	Unchanged
Stroke + TIA							
Frail vs. robust	4	**3.38**	**2.37**	**4.81**	**<0.001**	0	0.20; 0.94	3.20 (2.28 to 4.47)
Pre-frail vs. robust	4	**1.98**	**1.53**	**2.57**	**<0.001**	0	3.57; 0.48	Unchanged
Frail vs. pre-frail /robust	2	**2.20**	**1.62**	**2.99**	**<0.001**	0		
Heart failure							
Frail vs. robust	3	**8.76**	**2.76**	**27.83**	**<0.001**	72	3.14; 0.17	3.83 (1.31 to 11.24)
Pre-frail vs. robust	3	**1.89**	**1.03**	**3.47**	**0.03**	29	1.83; 0.19	1.52 (0.86 to 2.69)
Frail vs. pre-frail /robust	2	**2.20**	**1.62**	**2.99**	**<0.001**	0		
PVD							
Frail vs. robust	3	**3.45**	**1.79**	**6.64**	**<0.001**	72	3.86; 0.05	Unchanged
Pre-frail vs. robust	2	2.45	0.77	7.84	0.13	80		
Frail vs. pre-frail /robust	0						

Bold values represent significant results, as p-value <0.05

Abbreviations: CHD: coronary heart disease; CI: confidence intervals; CVD, cardiovascular diseases; OR, odds ratio; PVD: peripheral vascular disease; TIA, transient ischemic attack.

*Test for publication bias: Duval and Tweedie nonparametric trim-and-fill procedure