BMJ Open

# Hypertension and Frailty: a Systematic Review and Meta-analysis



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2018-024406 |
| Article Type: | Research |
| Date Submitted by the Author: | 28-May-2018 |
| Complete List of Authors: | Vetrano, Davide<br>Palmer, Katie<br>Galluzzo, Lucia; ISS National Centre for Epidemiology, Surveillance and Health Promotion<br>Giampaoli, Simona; Istituto Superiore di Sanita',<br>Marengoni, Alessandra; Geriatric Unit, Department of Clinical and Experimental Sciences - University of Brescia - Italy,<br>Bernabei, Roberto; Universita Cattolica del Sacro Cuore Sede di Roma, Geriatrics<br>Onder, G; Università Cattolica del Sacro Cuore, Rome, Italy, |
| Keywords: | Hypertension < CARDIOLOGY, GERIATRIC MEDICINE, EPIDEMIOLOGY |
| | |

# Hypertension and Frailty: a Systematic Review and Meta-analysis

Davide L Vetrano*[1,2], Katie Palmer* [3], Lucia Galluzzo[4], Simona Giampaoli [4], Alessandra Marengoni [5], Roberto Bernabei [2], Graziano Onder [2] on behalf of the Joint Action ADVANTAGE

*These authors contributed equally to this work.

[1] Aging Research Center, Department of Neurobiology, Health Care Sciences and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden

[2] Department of Geriatrics, Università Cattolica del Sacro Cuore, Rome, Italy

[3] San Camillo Hospital IRCCS, Venice, Italy

[4] Department of Cardiovascular, Dysmetabolic and Ageing-Associated Diseases, Istituto Superiore di Sanità, Rome, Italy

[5] Department of Clinical and Experimental Sciences, University of Brescia, Italy

**Word count: 2814 words, 55 references, 3 figures**

**Running title:** Hypertension and Frailty

**Conflicts of interest:** none declared.

**Correspondence to:**
Graziano Onder
Centro Medicina dell'Invecchiamento
Fondazione Policlinico A. Gemelli
Università Cattolica del Sacro Cuore, Rome, Italy
Tel: 0039 0630154341
Email: graziano.onder@unicatt.it

**ABSTRACT**

**Objective -** To review studies assessing the association of hypertension and frailty in observational studies.

**Design -** A systematic review of the PubMed, Web of Science, and Embase databases was performed. A meta-analysis was performed if at least three studies used the same definition of frailty and a dichotomous definition of hypertension.

**Setting, participants and measures** - Studies providing information on the association between frailty and hypertension in adult persons, regardless of the study setting, study design, or definition of hypertension and frailty were included.

**Results -** Among the initial 964 articles identified, 27 were included in the review. Four longitudinal studies examined the incidence of frailty according to baseline hypertension status, providing conflicting results. Twenty-three studies assessed the cross-sectional association between frailty and hypertension: 13 of them reported a significantly higher prevalence of frailty in hypertensive participants and 10 found no significant association. The pooled prevalence of hypertension in frail individuals was 72% (95% Confidence Interval [95%CI] 66%-79%) and the pooled prevalence of frailty in individuals with hypertension was 14% (95%CI 12%-17%). Five studies, including a total of 7,656 participants, reported estimates for the association between frailty and hypertension (pooled OR 1.33; 95%CI 0.94-1.89).

**Conclusions -** Frailty is common in persons with hypertension. Given the possible influence of frailty on the risk-benefit ratio of treatment for hypertension and its high prevalence it is important to assess the presence of this condition in persons with hypertension.

**PROSPERO REGISTRATION NUMBER:** CRD42017058303

***Keywords:*** Frailty; Hypertension

**Article Summary - Strengths and limitations of this study**

- A greater number of potentially eligible articles were screened and included in the review.
- Absence of evident publication bias, and low-to-moderate risk of methodological bias increase the reliability of our findings.
- Heterogeneity in the definitions of frailty and hypertension across studies.
- Cross-sectional design of most studies included in the review which limits the opportunity of generating hypotheses regarding a causal link between the conditions of interest.

## INTRODUCTION

The accumulation of biological deficits and dysfunctions occurring with age impairs the homeostatic balance of organisms, leading to a condition called "frailty". Frailty confers extreme vulnerability to stressors and increases the risk of a range of adverse health-outcomes (1). Its prevalence ranges between 8% and 16% in community-dwelling older adults (2,3) and it is associated with shorter survival, poor quality of life, and increased risk of disability, hospitalization, and institutionalization (4). Frailty has been shown to be correlated with morbidity and mortality in persons suffering from cardiovascular disease, and it was suggested that the recognition of frailty status can help physicians in establishing prognosis, determining procedural risks, and guiding treatments (5). In some cases, the assessment of frailty may be critical in guiding the patient towards a certain therapeutic choice (6).

Several studies have assessed the association of frailty with hypertension. In older adults, it has been suggested that frailty can explain the paradoxical relationship between lower blood pressure and increased mortality documented in several studies (7-10). For example, data from the National Health and Nutrition Examination Survey (NHANES) demonstrated an effect modification of hypertension according to frailty level in terms of walking speed (11); in fit persons, elevated blood pressure was associated with greater mortality, while in frail participants higher blood pressure was associated with lower mortality risk. The SPRINT trial showed that compared to standard blood pressure control, intensive control confers a benefit on cardiovascular morbidity and mortality both in frail and non-frail persons, but this study did not show any effects of intensive blood pressure control on risk of frailty related outcomes, such as gait speed and mobility limitation (12,13). Notably, the hypertension clinical practice guidelines released in 2017 precisely point out that blood pressure lowering therapy is one of the few interventions shown to reduce mortality risk in frail older individuals (14).

Assessing the association of frailty and hypertension may be the first step for understanding their complex interplay and might ultimately lead to optimize the treatment of hypertension and to set therapeutic goals in persons with frailty. However, the evidence on the association between these conditions has never been comprehensively summarized. The aim of the present study is to systematically review the literature, and provide pooled estimations of evidence regarding the association of frailty and hypertension.

## METHODS

We reviewed studies providing information on the association between frailty and hypertension in adult persons (*i.e.* 18 years old or older), regardless of the study setting, study design, or definition of hypertension and frailty. The protocol of the present study was registered in the international prospective register of systematic reviews PROSPERO (registration number 58303). This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.

### Data sources and searching

We searched three databases for relevant articles published from 01/01/2002 to 26/10/2017: 1) PubMed electronic database of the National Library of Medicine, 2) Web of Science and; 3) Embase. The detailed search queries are reported in the Appendix. References from the selected papers and from other relevant articles were screened for potential additional studies.

### Study selection and data extraction

Two assessors independently screened the title and abstract of the selected studies. The inclusion criteria were: 1) Articles reporting information on the association of frailty with hypertension or blood pressure (BP) values; 2) Articles in English or another European language; 3) Study design: cross-sectional, case-control, or cohort studies. Articles were excluded if they 1) Did not investigate the aims of the review; 2) Included persons younger than 18 years; 3) Did not report original data (e.g., editorial, review, or congress abstract); 4) Did not provide an explicit definition of frailty and; 5) If frailty was assessed only with a single symptom/measure (e.g. only gait speed or grip strength); 6) Were not in English or another European language. The full text of the articles selected by one or both of the assessors were retrieved for full evaluation. Two assessors read the full texts and independently extracted the information from the selected studies. A third assessor reviewed the data extraction, and any disagreement was resolved through consensus. Articles that were written in another European language than English were sent for translation by a native speaker who conducted the data extraction.

### Assessment of risk of bias

Quality of the studies was evaluated independently by the two assessors with the qualitative evaluation of observational studies Newcastle Ottawa Scale (NOS). Any disagreement in quality assessment was resolved through consensus. Studies scoring >7 were considered at low risk of bias, scores of 5-7 indicated moderate risk of bias, and scores of <5 indicated high risk of bias.

### Statistical analysis

For each measure of interest (*i.e.* proportions and association estimates), a meta-analysis was performed if at least three studies used the same definition of frailty and a dichotomous definition of hypertension (rather than using continuous BP values). Considering the observational design of the

retrieved studies, and the methodological differences potentially responsible for a significant share of the variance within the measures of interest, the pooled estimates were obtained through random effect models and Mantel-Haenszel weighting. Lack of homogeneity within the pooled studies was tested through the $I^2$ statistics (significant if ≥50%). Additional analyses were performed selecting 1) Studies with NOS≥5, in order to exclude studies with high risk of methodological bias; 2) Studies with a sample size ≥ 500 participants. Publication bias was assessed by mean of the Egger's and the Begg's tests. All statistical analyses were performed with STATA version 14 (StataCorp, TX, USA). A P value <0.05 was considered statistically significant for all analyses.

**Patient and public involvement**

Patients and public were not involved in this study.

## RESULTS

Through the literature search, we retrieved 1369 articles (**Figure 1**). An additional 8 articles were identified after reading references from the selected papers. Out of 1369 articles, 670 (48.9%) were screened after duplicates removal. Of these, 604 were excluded after screening and 34 after full-text reading. Thirty-two articles were part of the final qualitative and/or quantitative assessment (15-46) (see table e1 in the Appendix).

### Study description

The studies' sample size ranged from 56 to 144403 participants, with a mean age ranging from 60 to 81 years. Only 4 studies had a longitudinal design (15-18). Most studies included community-dwelling participants, and only 3 studies included in-hospital participants (41,45,46). Most of the studies were carried out in Asia (n=10), Europe (n=9) and South America (n=9), and fewer in North America (n=4).

***Frailty and hypertension definitions.*** Most of the studies (n=23) defined frailty according to the Cardiovascular Health Study (CHS) criteria (15-17,19,20,22,23,25-28,32,34-37,39-45). The rest of the studies evaluated frailty based on a frailty index (n=6) (18,21,24,30,36,38), by a composite score (n=3) (29,31,33) or using the Clinical Frailty Scale (n=1) (46). One study assessed frailty adopting both CHS criteria and FI (36).

In the longitudinal studies, frailty incidence ranged from 3% to 16%, in cross-sectional studies, frailty prevalence ranged from 3% to 68%. A diagnosis of hypertension was reported in 28 studies (15-21,23-35,37,39-45), while 3 studies analyzed BP as a continuous variable (22,36,46) and 1 classified BP in 4 groups (38). Diagnosis of hypertension was based on a BP cut-point in 12 studies (15,16,20,26,27,29-32,34,37,39), assessed only by self-reported in 5 studies (19,23,41,43,44), based on evaluation of medical records in 1 study (33) and on pharmacological treatment in 1 study (21). In 9 studies, hypertension diagnosis was not defined (17,18,24,25,28,35,40,42,45). Prevalence of hypertension ranged from 28% to 100%.

***Assessment of risk of bias.*** The majority of the studies presented a moderate risk of bias (n=25), and six studies presented a high risk, according to the NOS. In most of the cases, the self-reported nature of information was responsible for a lower score. However, according to the Egger's and the Begg's tests, no strong evidence of publication bias was detected in our meta-analyses (P=0.150 and P=0.987, respectively).

### Association between hypertension and frailty

***Longitudinal studies.*** Four longitudinal studies examined the risk of incidence of frailty according to baseline hypertension status. Two studies found that baseline hypertension did not significantly predict incidence of frailty (15,18), but Boullion et al found that hypertension was associated with an

increased incidence of the combined outcome prefrailty/frailty (p=0.009) (16). However, data from this study were not adjusted for possible confounders. Similarly, Castrejon Perez et al (17) found that hypertension was associated with incident frailty at univariate analysis (HR=2.11, 95%CI 1.03-4.31), but this association was not confirmed in the multivariate analysis (HR=1.58, 95%CI 0.83-3.01).

***Cross-sectional studies.*** Twenty-three studies assessed the cross-sectional association between frailty and hypertension (19,20,23-35,37,39-45). Results were very different across studies, with 13 studies reporting a significantly higher prevalence of frailty in hypertensive participants (20,24-26,29,30,31,32,34,35,37,42,43) and 10 finding no significant association (19,23,27,28,33,39-41,44,45).

Seventeen of these studies assessed frailty by the use of CHS criteria, for a total sample of 23304 individuals (19,20,23,25,26,28,32,34,35,37,39-45). Analyzing data from these studies, the pooled prevalence of hypertension in frail individuals was 72% (95% Confidence Interval [95%CI] 66% to 79%; I2=93.1%; **Figure 2a**) and the pooled prevalence of frailty in individuals with hypertension was 14% (95% CI 12% to 17%; $I^2$=96.2%; **Figure 2b**).

Three studies assessed blood pressure as a continuous variable, finding conflicting results: one study showed significantly higher SBP and DBP values in frail participants (22), while in two other studies frailty was associated with significantly lower blood pressure values (36,46). A small study including only participants receiving pharmacological treatment for hypertension, showed an inverse association between blood pressure levels and frailty (21). Finally, a large study performed in more than 140000 community dwelling older adults aged ≥ 80 years, classified SBP in 5 groups, showing that frailty was associated with lower SBP (38).

Among studies adopting the CHS definition of frailty and a dichotomous definition of hypertension, 5 reported estimates (odds ratios) for the association between frailty and hypertension, for a total sample of 7656 individuals (27,37,40,43,45). The pooled estimate for the association of frailty and hypertension based on these studies was 1.33 (95% CI 0.94 to 1.89; $I^2$=79.2%; **Figure 3**). These results were confirmed when only studies with NOS≥5 (OR 1.39; 95% CI 0.70 to 2.75; $I^2$=88.1%) or studies with a sample size ≥ 500 participants (OR 1.25; 95% CI 0.79 to 1.99; $I^2$=88.4%) were analyzed.

**DISCUSSION**

This systematic review and meta-analysis shows that 7 out of 10 frail adults have hypertension, while about 1 out of 7 hypertensive adults present with frailty. In addition, this study shows that the association between frailty and hypertension is uncertain: few longitudinal studies have assessed the impact of hypertension on incident frailty, providing conflicting results. Further, no studies have been preformed to examine whether frailty predicts incident hypertension. Finally, the meta-analysis of cross sectional studies failed to find a significant association between these conditions.

Frailty has become a high-priority theme in cardiovascular medicine due to the aging and the increasingly complex nature of patients suffering for cardiovascular conditions (5,6). This is confirmed by the observation that 14% of persons with hypertension are frailty. Frailty might indeed influence the therapeutic choices for many cardiovascular diseases. For example, assessment of frailty is considered important for determining which patients are likely to benefit from the treatment of aortic stenosis or left ventricular assist device therapy, in terms of both survival and improved quality of life (47,48).

Similarly, therapeutic choices in hypertension might be influenced by presence of frailty. First, frail older people are almost always excluded from randomized controlled trials (RCTs) assessing the effects of treatments of cardiovascular diseases, including hypertension. Logistic barriers limiting the retention in the study, the higher propensity to present adverse effects from the treatments and the higher drop out for mortality of frail individuals are the main causes for exclusion from RCTs. (49). This limits the generalizability of RCTs findings and makes difficult estimating the efficacy and safety of treatments for chronic diseases in persons with frailty. This is extremely important if we consider that according to our results 70% of frail individuals present also with hypertension. In this context, the SPRINT trial showed that compared to standard blood pressure control, intensive control leads to a benefit on cardiovascular morbidity and mortality both in frail and non-frail persons (12), but this trial excludes persons with various chronic diseases, cognitive impairment, psychiatric disorders, and those institutionalized or at risk of poor medication adherence. The lack of evidence regarding the treatment of hypertension in frail older people has been highlighted in the recently issued guidelines for the management of hypertension that recognize the role of blood pressure lowering therapy as one of the few interventions to reduce mortality risk in frail older individuals, but did not make any specific recommendations regarding treatment of hypertension in frailty individuals (14).

Second, frailty is associated with limited life expectancy; estimates from the SHARE study suggests that life expectancy for frail individuals at age of 70 years ranges between 0.1 and 1.8 years in men and between 0.4 and 5.5 years in women (50). This clearly suggests that several preventive treatments for chronic diseases, including hypertension, might have limited benefits in persons with

frailty, given that the time-until-benefit might exceed the actual life expectancy of the frail individuals.

Third, frailty is associated with an increased rate of negative events associated with pharmacological treatments. Cullian et al. showed that frail inpatients were twice as likely to develop an adverse drug reaction compared to robust persons (51). Finally, frailty might be associated with unintentional non-adherence. A recent study of 300 hypertensive patients aged 65 to 91 years, showed that frailty is associated with a significant reduction in treatment adherence (52).

These data underline the importance of assessing frailty when treating hypertension and possibly to set individual targets of blood pressure control for persons with frailty. Interestingly, in the SPRINT trial frail participants in the intensive blood pressure control group, experienced a significantly lower reduction of systolic blood pressure compared with non-frail participants (10.8 vs. 13.5 mm Hg, p=0.01), underling possible difficulties in lowering blood pressure in frail persons (12).

The meta-analysis of cross-sectional studies did not show any significant association between frailty and hypertension. Chronic diseases, including hypertension, are considered to be major determinants of frailty in theoretical models, and the negative effect of hypertension on cardiovascular outcomes can lead to frailty (53). However, our findings might be explained by the fact that cross-sectional data assess a single time-point and are unable to evaluate the role of hypertension at differing stages of the frailty process.

Only four longitudinal studies assessed the impact of hypertension on incident frailty, providing conflicting results. This observation is in line with results of RCTs that were not able to show any impact of treatment of hypertension on onset of frailty (13,54). A further explanation could be that that persons developing frailty related to functional impairment might be more likely to be lost to follow-up, and this selective drop out makes it difficult to draw any firm conclusions about the effect of the treatment on these frailty-related outcomes (55).

**Strengths and limitations**

The major strength of the present study is its comprehensive literature search that, together with the careful study selection and quality assessment, provides a reliable overview of the evidence in this field. Moreover, the generalizability of our findings is enhanced by the representativeness of the retrieved studies that mainly involved community-dwelling adults and older adults. However, our findings must be read in light of several limitations. First, we detected a significant heterogeneity among the studies that was only partially buffered by subgroup analyses. The different definitions of frailty and hypertension, the use of adapted scales and the demographic differences encountered, might explain such high level of heterogeneity. However, the absence of evident publication bias, and the low-to-moderate risk of methodological bias increase the reliability of our findings. Second, the cross-sectional design of 28 out of 32 studies limits the opportunity of generating hypotheses

regarding a causal link between the conditions of interest. In addition, the three longitudinal studies retrieved by our literature search, provided conflicting evidence on the association between frailty and hypertension. Finally, most of the studies included in the review were not aimed to assess hypertension and its relationship with frailty. For this reason, hypertension was poorly defined in most studies and this might lead to possible concerns about the methodology used to assess this condition.

**CONCLUSION**

The present study shows that frailty is common in persons with hypertension. Given the possible influence of frailty on risk-benefit ratio of treatment for hypertension and its high prevalence it is important to assess the presence of this condition in persons with hypertension. In addition, limited studies assessing the association of these conditions are available. Further research, including a more rigorous and agreed assessment of frailty, and based on longitudinal designs, is needed to untangle the relationship between frailty and hypertension and to allow for the identification of pros and the cons of the pharmacological treatment, and possible targets for therapy in this population, leading ultimately to the development of specific recommendations for the treatment of hypertension in frail people.

**FUNDING STATEMENT**

The work reported in this publication was co-funded by the European Commission through the 3rd Health Programme, under the Grant Agreement n° 724099. The European Commission support for the production of this publication does not constitute an endorsement of the contents which reflects the views only of the authors, and the Commission cannot be held responsible for any use which may be made of the information contained therein.

**AUTHORS CONTRIBUTIONS**

Conception of the work: DLV, KP, GO. Articles evaluation DLV, KP. Data analysis: DLV. Results interpretation: all the co-authors. Drafting the article: DLV, GO. Critical revision of the manuscript: all the co-authors. Final approval of the manuscript: all the co-authors. All the authors fulfill the ICMJE criteria for authorship.

**DISCLAIMER**

The authors declare no financial relationships with any organisations that might have an interest in the submitted work, no other relationships or activities that could appear to have influenced the submitted work.

**COMPETING INTERESTS**

None

**PATIENT CONSENT**

Not required

**DATA SHARING STATEMENT**

All data are available within the appendices.

**Legend to Figures**

Figure 1 - Systematic review and meta-analysis flow-chart

Figure 2a - Proportion of participants presenting with hypertension among those with frailty. Frailty was defined according to the CHS criteria.

Figure 2b - Proportion of participants presenting with frailty among those with hypertension. Frailty was defined according to the CHS criteria.

Figure 3 - Cross-sectional association of frailty (CHS criteria) with hypertension. Frailty was defined according to the CHS criteria.

**REFERENCES**

1. World Health Organization. World report on ageing and health. Geneva, Switzerland: World Health Organization. 2015
2. 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.
3. Santos-Eggimann B, Cuénoud P, Spagnoli J, Junod J. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. J Gerontol A Biol Sci Med Sci. 2009;64:675–81.
4. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013 Mar 2;381:752-62.
5. Onder G, Vetrano DL, Marengoni A, Bell JS, Johnell K, Palmer K; Optimising Pharmacotherapy through Pharmacoepidemiology Network (OPPEN). Accounting for frailty when treating chronic diseases. Eur J Intern Med. 2018 Mar 8.
6. 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;63:747-62.
7. Molander L, Lovheim H, Norman T, Nordstrom P and Gustafson Y. Lower systolic blood pressure is associated with greater mortality in people aged 85 and older. J Am Geriatr Soc. 2008;56:1853-1859.
8. Hakala SM, Tilvis RS and Strandberg TE. Blood pressure and mortality in an older population. A 5-year follow-up of the Helsinki Ageing Study. Eur Heart J. 1997;18:1019-1023.
9. Satish S, Freeman DH, Jr., Ray L and Goodwin JS. The relationship between blood pressure and mortality in the oldest old. J Am Geriatr Soc. 2001;49:367-374.
10. Van Bemmel T, Gussekloo J, Westendorp RG and Blauw GJ. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. J Hypertension. 2006;24:287-292.
11. Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. Arch Intern Med. 2012;172:1162-8.
12. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, Fine LJ, Haley WE, Hawfield AT, Ix JH, Kitzman DW, Kostis JB, Krousel-Wood MA, Launer LJ, Oparil S, Rodriguez CJ, Roumie CL, Shorr RI, Sink KM, Wadley VG, Whelton PK, Whittle J, Woolard NF, Wright JT Jr, Pajewski NM; SPRINT Research Group. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years: A Randomized Clinical Trial. JAMA. 2016;315:2673-82.
13. Odden MC, Peralta CA, Berlowitz DR, Johnson KC, Whittle J, Kitzman DW, Beddhu S, Nord JW, Papademetriou V, Williamson JD, Pajewski NM; Systolic Blood Pressure Intervention Trial (SPRINT) Research Group. Effect of Intensive Blood Pressure Control on Gait Speed and Mobility Limitation in Adults 75 Years or Older: A Randomized Clinical Trial. JAMA Intern Med. 2017;177:500-507.
14. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD,

Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 7.

15. Barzilay JI, Blaum C, Moore T, Xue QL, Hirsch CH, Walston JD, Fried LP. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. Arch Intern Med. 2007;167:635-41.

16. Bouillon K, Kivimäki M, Hamer M, Shipley MJ, Akbaraly TN, Tabak A, Singh-Manoux A, Batty GD. Diabetes risk factors, diabetes risk algorithms, and the prediction of future frailty: the Whitehall II prospective cohort study. J Am Med Dir Assoc. 2013;14:851.e1-6.

17. Castrejón-Pérez RC, Jiménez-Corona A, Bernabé E, Villa-Romero AR, Arrivé E, Dartigues JF, Gutiérrez-Robledo LM, Borges-Yáñez SA. Oral Disease and 3-Year Incidence of Frailty in Mexican Older Adults. J Gerontol A Biol Sci Med Sci. 2017;72:951-957.

18. Doba N, Tokuda Y, Goldstein NE, Kushiro T, Hinohara S. A pilot trial to predict frailty syndrome: the Japanese Health Research Volunteer Study. Exp Gerontol. 2012;47:638-43.

19. de Albuquerque Sousa ACP, Dias RC, Maciel TCC, Guerra RO. Frailty syndrome and associated factors in community-dwelling elderly in Northeast Brazil. Arch Gerontol Geriatr 2012;54:e95-e101.

20. Avila-Funes JA, Helmer C, Amieva H, Barberger-Gateau P, Le Goff M, Ritchie K, Portet F, Carrière I, Tavernier B, Gutiérrez-Robledo LM, Dartigues JF. Frailty among community-dwelling elderly people in France: the three-city study. J Gerontol A Biol Sci Med Sci. 2008;63:1089-96.

21. Basile G, Catalano A, Mandraffino G, Maltese G, Alibrandi A, Ciancio G, Lasco A, Cesari M. Relationship between blood pressure and frailty in older hypertensive outpatients. Aging Clin Exp Res. 2016 Nov 21.

22. Bastos-Barbosa RG, Ferriolli E, Coelho EB, Moriguti JC, Nobre F, Lima NK. Association of frailty syndrome in the elderly with higher blood pressure and other cardiovascular risk factors. Am J Hypertens 2012;25:1156-61.

23. Calado LB, Ferriolli E, Moriguti JC, Martinez EZ, Da Costa Lima NK. Frailty syndrome in an independent urban population in Brazil (FIBRA study): A cross-sectional populational study. Sao Paulo Med J. 2016;134(5):385-92.

24. Castrejón-Pérez RC, Gutiérrez-Robledo LM, Cesari M, Pérez-Zepeda MU. Diabetes mellitus, hypertension and frailty: A population-based, cross-sectional study of Mexican older adults. Geriatr Gerontol Int. 2017;17:925-930.

25. Chang SF, Yang RS, Lin TC, Chiu SC, Chen ML, Lee HC. The Discrimination of Using the Short Physical Performance Battery to Screen Frailty for Community-Dwelling Elderly People. J Nurs Scholarsh. 2014;46(3):207-15.

26. Chung CP, Chou KH, Chen WT, Liu LK, Lee WJ, Chen LK, et al. Cerebral microbleeds are associated with physical frailty: a community-based study. Neurobiol Aging. 2016;44:143-50.

27. Fattori A, Santimaria MR, Alves RMA, Guariento ME, Neri AL. Influence of blood pressure profile on frailty phenotype in community-dwelling elders in Brazil - FIBRA study. Arch Gerontol Geriatr. 2013;56:343-9.

28. Frisoli A Jr, Ingham SJ, Paes ÂT, 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.

29. Guessous I, Luthi JC, Bowling CB, Theler JM, Paccaud F, Gaspoz JM, McClellan W. Prevalence of frailty indicators and association with socioeconomic status in middle-aged and older adults in a swiss region with universal health insurance coverage: a population-based cross-sectional study. J Aging Res. 2014;2014:198603.

30. Kang MG, Kim SW, Yoon SJ, Choi JY, Kim KI, Kim CH. Association between Frailty and Hypertension Prevalence, Treatment, and Control in the Elderly Korean Population. Sci Rep. 2017;7:7542.

31. Klein BE, Klein R, Knudtson MD, Lee KE. Frailty, morbidity and survival. Arch Gerontol Geriatr. 2005;41:141-9.

32. Lahousse L, Maes B, Ziere G, Loth DW, Verlinden VJA, Zillikens MC, et al. Adverse outcomes of frailty in the elderly: The Rotterdam Study. Eur J Epidemiol. 2014;29:419-27.

33. Lee JS, Auyeung TW, Leung J, Kwok T, Leung PC, Woo J. Physical frailty in older adults is associated with metabolic and atherosclerotic risk factors and cognitive impairment independent of muscle mass. J Nutr Health Aging. 2011;15:857-62.

34. Nadruz W Jr, Kitzman D, Windham BG, Kucharska-Newton A, Butler K, Palta P, Griswold ME, Wagenknecht LE, Heiss G, Solomon SD, Skali H, Shah AM. Cardiovascular Dysfunction and Frailty Among Older Adults in the Community: The ARIC Study. J Gerontol A Biol Sci Med Sci. 2017;72:958-964.

35. Ng TP, Feng L, Nyunt MS, Larbi A, Yap KB. Frailty in older persons: multisystem risk factors and the Frailty Risk Index (FRI). J Am Med Dir Assoc. 2014;15:635-42.

36. O'Connell MDL, Savva GM, Fan CW, Kenny RA. Orthostatic hypotension, orthostatic intolerance and frailty: The Irish Longitudinal Study on Aging-TILDA. Arch Gerontol Geriatr. 2015;60:507-13.

37. 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.

38. Ravindrarajah R, Hazra NC, Hamada S, Charlton J, Jackson SHD, Dregan A, Gulliford MC. Systolic Blood Pressure Trajectory, Frailty, and All-Cause Mortality >80 Years of Age: Cohort Study Using Electronic Health Records. Circulation. 2017;135:2357-2368.

39. 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.

40. Serra-Prat M, Papiol M, Vico J, Palomera E, Sist X, Cabré M. Factors associated with frailty in community-dwelling elderly population. A cross-sectional study. European Geriatric Medicine. 2016;7(6):531-7.

41. Tavares DMD, Colamego CG, Pegorari MS, Ferreira PCD, Dias FA, Bolina AF. Cardiovascular risk factors associated with frailty syndrome among hospitalized elderly people: a cross-sectional study. Sao Paulo Med J. 2016;134:393-9.

42. Vaingankar JA, Chong SA, Abdin E, Picco L, Chua BY, Shafie S, Ong HL, Chang S, Seow E, Heng D, Chiam PC, Subramaniam M. Prevalence of frailty and its association with

sociodemographic and clinical characteristics, and resource utilization in a population of Singaporean older adults. Geriatr Gerontol Int.2016 Aug 31.

43. Watanabe Y, Hirano H, Arai H, Morishita S, Ohara Y, Edahiro A, Murakami M, Shimada H, Kikutani T, Suzuki T. Relationship Between Frailty and Oral Function in Community-Dwelling Elderly Adults. J Am Geriatr Soc. 2017;65:66-76.

44. 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.

45. Wu IC, Shiesh SC, Kuo PH, Lin XZ. High Oxidative Stress Is Correlated with Frailty in Elderly Chinese. J Am Geriatr Soc. 2009;57:1666-71.

46. Yanagita I, Fujihara Y, Eda T, Tajima M, Yonemura K, Kawajiri T, Yamaguchi N, Asakawa H, Nei Y, Kayashima Y, Yoshimoto M, Kitajima Y, Harada M, Araki Y, Yoshimoto S, Aida E, Yanase T, Nawata H, Muta K. Low glycated hemoglobin level is associated with severity of frailty in Japanese elderly diabetes patients. J Diabetes Investig. 2017 May 27.

47. Mack MJ, Stoler R. Intervention for Aortic Stenosis: The Measurement of Frailty Matters. J Am Coll Cardiol. 2017;70:701-703.

48. Joseph SM, Manghelli JL, Vader JM, Keeney T, Novak EL, Felius J, Martinez SC, Nassif ME, Lima B, Silvestry SC, Rich MW. Prospective Assessment of Frailty Using the Fried Criteria in Patients Undergoing Left Ventricular Assist Device Therapy. Am J Cardiol. 2017;120:1349-1354.

49. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA. 2007;297:1233-40.

50. Romero-Ortuno R, Fouweather T, Jagger C. Cross-national disparities in sex differences in life expectancy with and without frailty. Age Ageing. 2014;43:222-8.

51. Cullinan S, O'Mahony D, O'Sullivan D, Byrne S. Use of a frailty index to identify potentially inappropriate prescribing and adverse drug reaction risks in older patients. Age Ageing. 2016;45:115-20.

52. Chudiak A, Jankowska-Polańska B, Uchmanowicz I. Effect of frailty syndrome on treatment compliance in older hypertensive patients. Clin Interv Aging. 2017;12:805-814.

53. 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.

54. Applegate WB, Pressel S, Wittes J, Luhr J, Shekelle RB, Camel GH, Greenlick MR, Hadley E, Moye L, Perry HM Jr, et al. Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. Arch Intern Med. 1994;154:2154-60.

55. Di Bari M, Pahor M, Franse LV, Shorr RI, Wan JY, Ferrucci L, Somes GW, Applegate WB. Dementia and disability outcomes in large hypertension trials: lessons learned from the systolic hypertension in the elderly program (SHEP) trial. Am J Epidemiol. 2001;153:72-8.

Figure 1

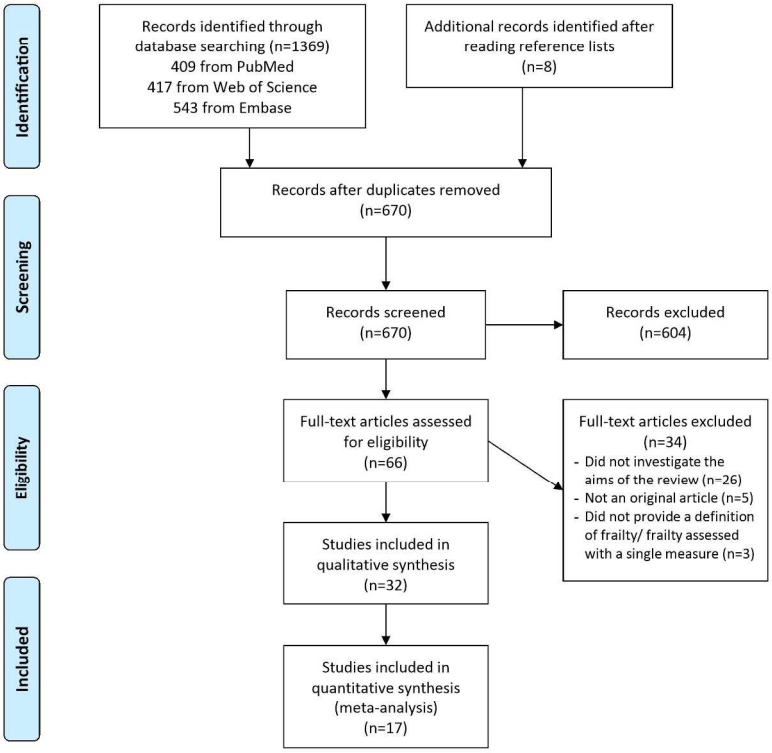


Figure 1 - Systematic review and meta-analysis flow-chart

215x279mm (300 x 300 DPI)

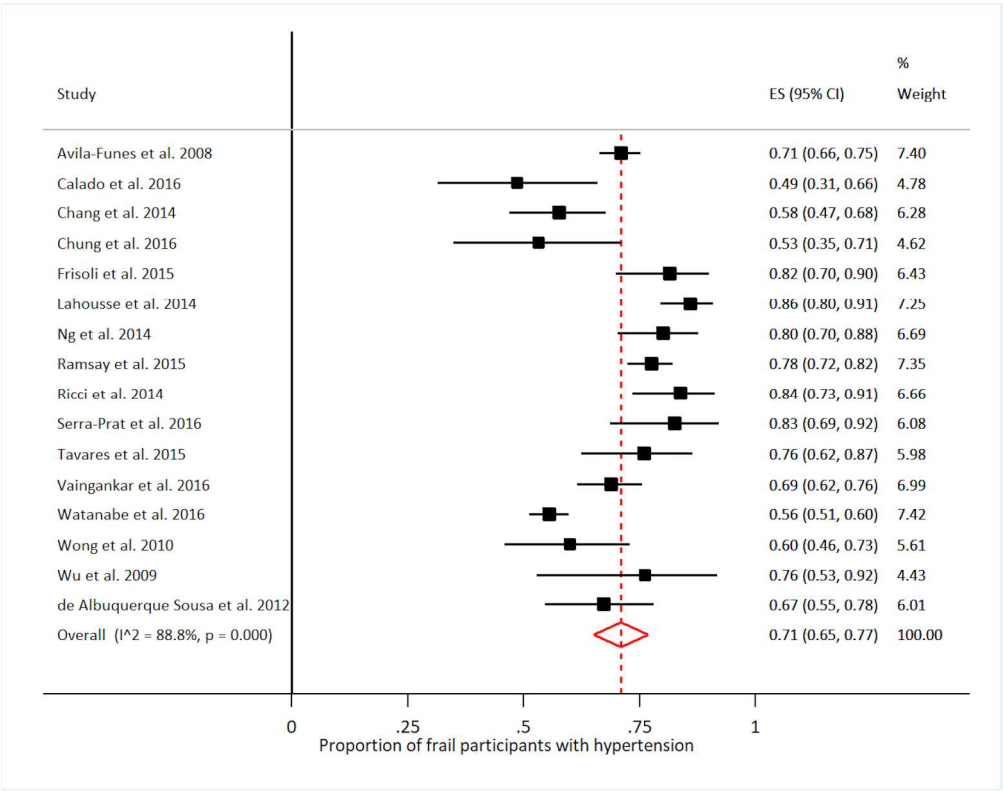


Figure 2a - Proportion of participants presenting with hypertension among those with frailty. Frailty was defined according to the CHS criteria.

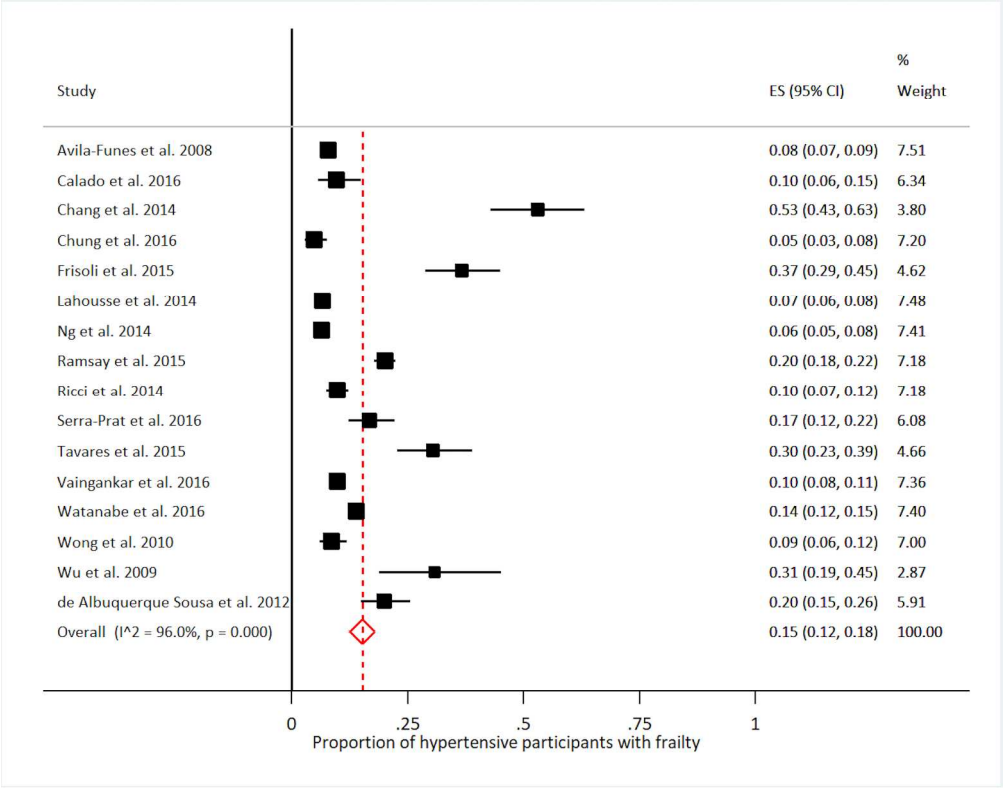


Figure 2b - Proportion of participants presenting with frailty among those with hypertension. Frailty was defined according to the CHS criteria.

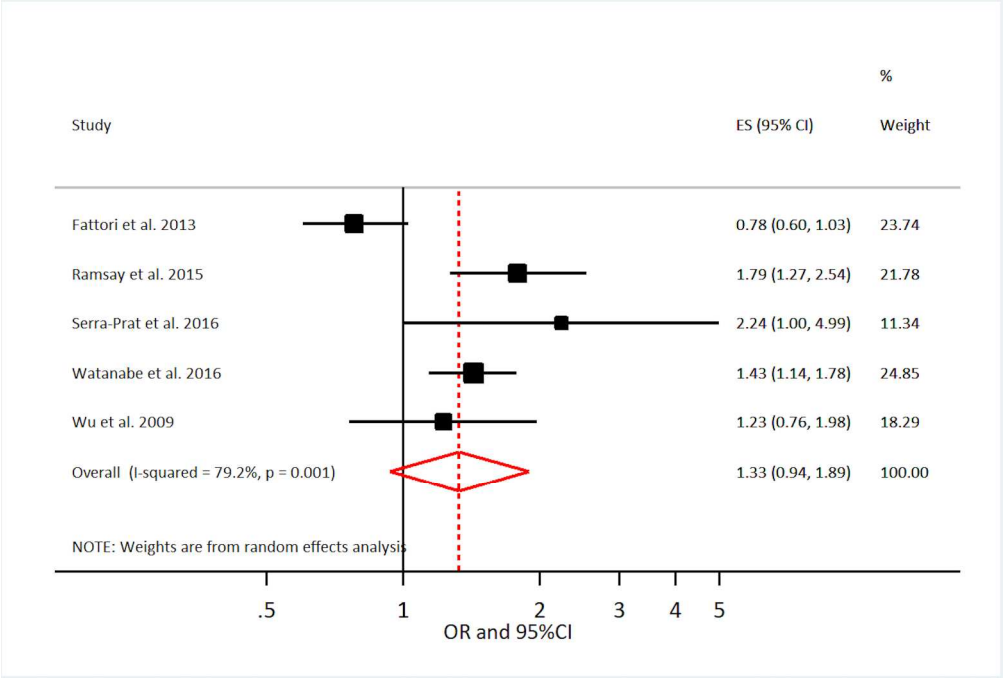


Figure 3 - Cross-sectional association of frailty (CHS criteria) with hypertension. Frailty was defined according to the CHS criteria. ‼ ┼

# Appendix

## Search terms used

### Pubmed

("hypertension"[MeSH Terms] OR "hyperten*"[Title/Abstract] OR "hypertension"[Title/Abstract] OR "hypertensive"[Title/Abstract] OR "high blood pressure"[Title/Abstract] OR "systolic blood pressure"[Title/Abstract] OR "diastolic blood pressure"[Title/Abstract] OR "raised blood pressure"[Title/Abstract]) AND ("frail elderly"[MeSH Terms] OR "frail*"[Title/Abstract] OR "frailty"[Title/Abstract])

### Web of Science and Embase

("hyperten*" OR "hypertension" OR "hypertensive" OR "high blood pressure" OR "systolic blood pressure" OR "diastolic blood pressure" OR "raised blood pressure" ) AND ("frail*" OR "frailty" )

**Table e1**. Characteristics of the studies included in the systematic review.

| First Author (year) | Study characteristics | n | Hypertension definition | Hypertension prevalence | Frailty definition | Frailty Incidence (longitudinal studies) or prevalence (cross-sectional studies) | % hypertension in frailty groups | Other results | NOS |
|---|---|---|---|---|---|---|---|---|---|
| **LONGITUDINAL STUDIES** | | | | | | | | | |
| Barzilay (2007) | Country: USA<br><br>Name: Cardiovascular Health Study (CHS)<br><br>Setting: community<br><br>Age: ≥ 65 y | 2826 | BP ≥ 130/85 mm Hg or treated hypertension | 37% | CHS criteria | Prefrail: 66%<br>Frail: 8% | Robust=34%<br>Prefrail=38%<br>Frail=43% | Incident frailty (5 and 9 y follow-up) was not predicted by hypertension diagnosis or blood pressure levels. SBP at baseline was not independently associated with frailty: HR=0.96 (95% CI 0.89-1.04) for prefrailty and HR=1.01 (95% CI 0.88-1.17) for frailty. | 7 |
| Bouillon (2013) | Country: UK<br><br>Name: Whitehall II Study<br><br>Setting: community<br><br>Age (range): 45-69 y | 2707 | BP ≥ 130/85 mm Hg or treated hypertension | 40% | CHS criteria | Prefrail: 37%<br>Frail: 3% | Robust=38%<br>Prefrail/frail=43% | - | 6 |
| Castrejón-Pérez (2017) | Country: Mexico<br><br>Name: Mexican Study of Nutritional and Psychosocial Markers of Frailty<br><br>Setting: community<br><br>Age (range): 70-95 y | 237 | Not defined | 58% | CHS criteria | Frail=15% | Robust=55%<br>Frail=74% | At univariate analysis hypertension was associated with incident frailty (HR=2.11, 95%CI 1.03-4.31), but this association was not confirmed in the multivariate analysis (HR=1.58, 95%CI 0.83-3.01) | 6 |
| Doba (2012) | Country: Japan<br><br>Name: Japanese Health Research Volunteer Study | 351 | Not defined | 28% | FI | Frail: 16% | Robust=28%<br>Frail=29% | Baseline SBP was lower in persons who developed frailty vs non frail SBP=135±17 vs 140±21 (p=0.046) . In multivariate analyses, no | 7 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Setting: community<br><br>Age (mean±SD): 78±4 y | | | | | | | significant association between SBP and frailty was observed | |
| **CROSS-SECTIONAL STUDIES** | | | | | | | | | |
| de Albuquerque Sousa (2012) | Country: Brazil<br><br>Name: Network of Studies on the Frailty of Elderly Brazilians<br><br>Setting: Community<br><br>Age (mean±SD): 74±7 y | 391 | Self-reported | 58% | CHS criteria | Prefrail: 60%<br>Frail: 17% | Robust=53%<br>Prefrail=57%<br>Frail=67% | - | 5 |
| Ávila-Funes (2008) | Country: France<br><br>Name: Three-City Study<br><br>Setting: community<br><br>Age (mean±SD): 74±5 y | 6078 | Self-reported or BP≥160/95 or treated hypertension | 64% | CHS criteria | Prefrail: 48%<br>Frail: 7% | Robust=64%<br>Prefrail=63%<br>Frail=71% | - | 5 |
| Basile (2017) | Country: Italy<br><br>Setting: community<br><br>Age (mean): 81±8 y | 56 | Treated hypertension | 100% | FI | - | - | Participants with SBP≥140 mmHg had lower FI compared to those with SBP<140 mmHg (p=0.006) | 5 |
| Bastos-Barbosa (2012) | Country: Brazil<br><br>Name: Research Network of Studies of Brazilian Elderly Individuals<br><br>Setting: community<br><br>Age (mean±SD): 74±7 y | 77 | BP reported as a continuous measure | 63% | CHS criteria | Prefrail: 40%<br>Frail: 30% | Not reported | Ambulatory BP of frail group demonstrated significantly higher systolic and diastolic BP values over the 24 h (135/74 mm Hg) than nonfrail group (122/68 mm Hg). | 5 |
| Calado (2016) | Country: Brazil<br><br>Setting: community | 385 | Self-reported | 46% | CHS criteria | Prefrail: 50%<br>Frail: 9% | Robust=44%<br>Prefrail=48%<br>Frail=49% | - | 5 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Age (mean): 74±6 y | | | | | | | | |
| Castrejón-Pérez (2017) | Country: Mexico<br><br>Name: Mexican Health and Nutrition Survey<br><br>Setting: community<br><br>Age (mean±SD): 71±8 y | 7164 | Not defined | 38% | FI | Mean FI score=0.18 | - | Multiple linear regression for FI for hypertension only (without diabetes) Beta: 0.31 (0.55-0.69) | 5 |
| Chang (2014) | Country: Taiwan<br><br>Setting: community<br><br>Age: ≥65 y | 234 | Not defined | 43% | CHS criteria | Frail: 39% | Robust=33%<br>Frail=58% | Hypertension significantly associated with frailty OR=2.21 (1.16–4.21) in multivariate analysis. | 4 |
| Chung (2016) | Country: Taiwan<br><br>Name: I-Lan Longitudinal Aging Study<br><br>Setting: community<br><br>Age (mean±SD): 62±9 y | 962 | Self-reported or BP≥140/90 or treated hypertension | 37% | CHS criteria | Prefrail: 33%<br>Frail: 3% | Robust=34%<br>Prefrail=42%<br>Frail=53% | - | 6 |
| Fattori (2013) | Country: Brazil<br><br>Name: Research Network of Studies of Brazilian Elderly Individuals<br><br>Setting: community<br><br>Age: ≥65 y | 900 | BP ≥ 140/90 mm Hg | 52% | CHS criteria | Prefrail: 52%<br>Frail: 8% | Not reported | Hypertension not associated with frailty OR=0.78 (0.60–1.03) in univariate analysis. | 7 |
| Frisoli (2015) | Country: Brazil<br><br>Name: FRAgilidade em idosos com doenças CardiOvasculaRes<br><br>Setting: outpatient | 172 | Not defined | 84% | CHS criteria | Prefrail: 51%<br>Frail: 38% | Robust=100%<br>Prefrail=83%<br>Frail=81% | - | 4 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | clinic<br><br>Age (mean±SD):77±6 y | | | | | | | | |
| Guessous (2014) | Country: Switzerland<br><br>Name: BusSanté study<br><br>Setting: community<br><br>Age (mean): 60 y | 2930 | BP ≥ 140/90 mm Hg or treated hypertension | 47% | Frailty scale based on 4 indicators (weakness, shrinking, exhaustion, and low activity) | 1 indicator=29%<br>≥2 indicators=8% | 0 indicators =42%<br>1 indicator =54%<br>≥2 indicators =65% | Hypertension significantly associated with frailty indicators in multivariate analyses. OR for 1 indicator (vs. 0 indicators) 1.40 (1.15-2.68)- OR for ≥2 indicators 1.88 (1.32-2.68). | 7 |
| Kang (2017) | Country: Korea<br><br>Name: Korea National Health and Nutrition Examination Survey<br><br>Setting: community<br><br>Age (mean±SD): 73±5 y | 4352 | BP ≥ 140/90 mm Hg or treated hypertension | 62% | FI | Prefrail: 39%<br>Frail: 44% | Robust=49%<br>Prefrail=61%<br>Frail=68% | - | 6 |
| Klein (2005) | Country: USA<br><br>Name: Beaver Dam Eye Study<br><br>Setting: community<br><br>Age (range): 53-86 y | 2515 | BP ≥ 160/95 mm Hg or treated hypertension | 47% | Frailty scale based on 5 indicators (gait speed, peak expiratory flow rate, hand grip strength, chair stand test and visual acuity) | Not reported | - | In multivariate analysis hypertension significantly associated with frailty scale in men OR for 1-point increment in scale =1.22 (1.00-1.49) and women OR=1.22 (1.02-1.46) | 6 |
| Lahousse (2014) | Country: The Netherlands<br><br>Name: Rotterdam Study<br><br>Setting: community<br><br>Age (median): 74 y | 2833 | BP ≥ 160/100 mm Hg or treated hypertension | 75% | CHS criteria | Prefrail: 51%<br>Frail: 6% | Robust=71%<br>Prefrail=77%<br>Frail=85% | - | 6 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Lee (2011) | Country: China<br><br>Setting: community<br><br>Age (mean±SD): 72±5 y | 4000 | Medical records | 43% | Composite frailty score (range 0-20) | Mean frailty score=12.2 | - | In multivariate analysis hypertension not significantly associated with composite frailty score | 5 |
| Nadruz 2017) | Country: USA<br><br>Name: Atherosclerosis Risk in Communities Study<br><br>Setting: community<br><br>Age (mean±SD): 76±5 y | 3991 | BP ≥ 160/100 mm Hg or treated hypertension | 82% | CHS criteria | Frail=5% | Robust=81%<br>Frail=92% | - | 6 |
| Ng (2014) | Country: Singapore<br><br>Name: Singapore Longitudinal Ageing Studies I and II<br><br>Setting: community<br><br>Age (mean±SD): 67±8 y | 1685 | Not defined | 62% | CHS criteria | Prefrail: 42%<br>Frail: 5% | Robust=58%<br>Prefrail=64%<br>Frail=80% | Hypertension not associated with frailty in multivariate analysis (data not provided) | 6 |
| O'Connell (2015) | Country: Republic of Ireland<br><br>Name: Irish Longitudinal Study on Aging<br><br>Setting: community<br><br>Age (mean±SD): 63±9 y | 5692 | BP reported as a continuous measure | - | CHS criteria & FI | CHS criteria<br>Prefrail: 34%<br>Frail: 4%<br><br>Mean FI score=0.10 | - | In adjusted linear regression analyses, frailty significantly associated with lower seated and standing SBP and DBP. Seated SBP -1.9 (-2.52to-1.27), standing SBP -1.79 (-2.46 to-1-13), seated DBP -1.14 (-1.51to-0.77), standing DBP -1.10 (-1.48to-0.73). | 7 |
| Ramsay (2015) | Country: UK<br><br>Name: British Regional Heart Study<br><br>Setting: community<br><br>Age (range): 71-92 y | 1622 | BP ≥ 160/90 mm Hg or treated hypertension | 72% | CHS criteria | Prefrail: 54%<br>Frail: 19% | Robust=65%<br>Prefrail=74%<br>Frail=78% | Hypertension associated with frailty age-adjusted OR=1.79 (1.27-2.54) | 6 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Ravindrarajah (2017) | Country: UK<br><br>Name: Clinical Practice Research Datalink<br><br>Setting: community<br><br>Age: ≥80 y | 144403 | SBP values classified as follows (mmHg): <110, 110-119, 120-139, 140-159, ≥160 | <110 =3%<br>110-119=7%<br>120-139=37%<br>140-159=41%<br>≥160=12% | FI | Mild frailty=40%<br>Moderate frailty=21%<br>Severe frailty=7%<br><br>Any frailty=68% | Any frailty:<br><110 =78%<br>110-119=77%<br>120-139=72%<br>140-159=64%<br>≥160=58% | Frailty was associated with lower BP. In participants with SBP <110 mmHg, 22% were fit, 28% had moderate frailty, and 12% had severe frailty. In those with SBP ≥160 mm Hg, 42% were fit, 16% had moderate frailty, and 4% had severe frailty. | 7 |
| Ricci (2014) | Country: Brazil<br><br>Name: Fragilidade em Idosos Brasileiros Network Study<br><br>Setting: community<br><br>Age (mean±SD): 72±6 y | 761 | Self-reported or BP≥140/90 or treated hypertension | 84% | CHS criteria | Prefrail: 48%<br>Frail: 10% | Robust=81%<br>Prefrail=87%<br>Frail=84% | - | 5 |
| Serra-Prat (2016) | Country: Spain,<br><br>Setting: community<br><br>Age (mean±SD): 80±3 y | 324 | Not defined | 71% | CHS criteria | Prefrail: 54%<br>Frail: 14% | Robust=66%<br>Prefrail=70%<br>Frail=82% | Hypertension associated with frailty OR=2.24 (1.00-4.99) at univariate analysis. Association not confirmed in multivariate analysis (data not provided). | 5 |
| Tavares (2016) | Country: Brazil<br><br>Name: Study of Frailty in Elderly People<br><br>Setting: hospital<br><br>Age: ≥ 60 y | 205 | Self-reported | 66% | CHS criteria | Prefrail: 52%<br>Frail: 26% | Robust=62%<br>Prefrail=62%<br>Frail=76% | - | 4 |
| Vaingankar (2016) | Country: Singapore<br><br>Name: Well-being of the Singapore Elderly study<br><br>Setting: community<br><br>Age (mean): 69 y | 2102 | Not defined | 59% | CHS criteria | Prefrail: 40%<br>Frail: 6% | Robust=55%<br>Prefrail=62%<br>Frail=70% | Hypertension not associated with frailty in multivariate analysis (data not provided) | 4 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Watanabe (2017) | Country: Japan<br><br>Name: Obu Study of Health Promotion for the Elderly<br><br>Setting: community<br><br>Age (mean): 71 y | 4720 | Self reported | 46% | CHS criteria | Prefrail: 57%<br>Frail: 11% | Robust=39%<br>Prefrail=47%<br>Frail=55% | Hypertension significantly associated with frailty in multivariate analysis (OR 1.43, 95% CI = 1.14–1.78) | 4 |
| Wong (2010) | Country: Canada,<br><br>Name: Montreal Unmet Needs Study<br><br>Setting: community<br><br>Age (mean±SD): 80±4 y | 740 | Self-reported | 52.3% | CHS criteria | Prefrail: 50%<br>Frail: 7% | Robust=47%<br>Prefrail=55%<br>Frail=60% | - | 5 |
| Wu (2009) | Country: Taiwan<br><br>Setting: community and hospital<br><br>Age (mean±SD): 77±6 y | 90 | Not defined | 58% | CHS criteria | Prefrail: 62%<br>Frail: 23% | Robust=69%<br>Prefrail=48%<br>Frail=76% | No significant association between frailty and hypertension at univariate analysis, OR=1.23 (0.76–1.98) | 4 |
| Yanagita (2017) | Country: Japan<br><br>Setting: hospital<br><br>Age (mean±SD): 78±8 y | 132 | BP reported as a continuous measure | - | Clinical Frailty Scale | Frail=42% | - | Frail participants had lower SBP values. In multivariate analyses frailty associated with significantly lower SBP values. | 4 |

NOS = Newcastle-Ottawa Scale; CHS = Cardiovascular Health Study; OR = Odds Ratio; FI = Frailty Index; BP=Blood Pressure; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure

# MOOSE Checklist for Meta-analyses of Observational Studies

| Item No | Recommendation | Reported on Page No |
|---|---|---|
| Reporting of background should include | | |
| 1 | Problem definition | 4 |
| 2 | Hypothesis statement | 4 |
| 3 | Description of study outcome(s) | 4 |
| 4 | Type of exposure or intervention used | 4 |
| 5 | Type of study designs used | 4 |
| 6 | Study population | 4 |
| Reporting of search strategy should include | | |
| 7 | Qualifications of searchers (eg, librarians and investigators) | 5 |
| 8 | Search strategy, including time period included in the synthesis and key words | 5 |
| 9 | Effort to include all available studies, including contact with authors | 5 |
| 10 | Databases and registries searched | 5 |
| 11 | Search software used, name and version, including special features used (eg, explosion) | 6 |
| 12 | Use of hand searching (eg, reference lists of obtained articles) | 5 |
| 13 | List of citations located and those excluded, including justification | 5 |
| 14 | Method of addressing articles published in languages other than English | 5 |
| 15 | Method of handling abstracts and unpublished studies | 5 |
| 16 | Description of any contact with authors | NA |
| Reporting of methods should include | | |
| 17 | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | 5 |
| 18 | Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | 5 |
| 19 | Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability) | 5 |
| 20 | Assessment of confounding (eg, comparability of cases and controls in studies where appropriate) | NA |
| 21 | Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results | 5 |
| 22 | Assessment of heterogeneity | 5-6 |
| 23 | Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | 6 |
| 24 | Provision of appropriate tables and graphics | See tables and graphs |
| Reporting of results should include | | |
| 25 | Graphic summarizing individual study estimates and overall estimate | See figures 2 and 3 |
| 26 | Table giving descriptive information for each study included | See table e1 |
| 27 | Results of sensitivity testing (eg, subgroup analysis) | 8 |
| 28 | Indication of statistical uncertainty of findings | 8 |

| Item No | Recommendation | Reported on Page No |
|---|---|---|
| Reporting of discussion should include | | |
| 29 | Quantitative assessment of bias (eg, publication bias) | 10 |
| 30 | Justification for exclusion (eg, exclusion of non-English language citations) | NA |
| 31 | Assessment of quality of included studies | 10 |
| Reporting of conclusions should include | | |
| 32 | Consideration of alternative explanations for observed results | 10 |
| 33 | Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) | 11 |
| 34 | Guidelines for future research | 11 |
| 35 | Disclosure of funding source | 12 |

*From*: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

Transcribed from the original paper within the NEUROSURGERY® Editorial Office, Atlanta, GA, United Sates. August 2012.

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 5 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 5 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 5 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 5 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 6 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 6 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 5 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 6 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 7 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 7 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 7 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 7-8 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 8 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 7 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 8 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 9 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 10 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 11 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 12 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

# Hypertension and Frailty: a Systematic Review and Meta-analysis

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2018-024406.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 31-Aug-2018 |
| Complete List of Authors: | Vetrano, Davide; Karolinska Institutet and Stockholm University, Aging Research Center, Department of Neurobiology, Health Care Sciences and Society<br>Palmer, Katie; Ospedale San Camillo<br>Galluzzo, Lucia; ISS National Centre for Epidemiology, Surveillance and Health Promotion<br>Giampaoli, Simona; Istituto Superiore di Sanita',<br>Marengoni, Alessandra; Geriatric Unit, Department of Clinical and Experimental Sciences - University of Brescia - Italy,<br>Bernabei, Roberto; Universita Cattolica del Sacro Cuore Sede di Roma, Geriatrics<br>Onder, G; Università Cattolica del Sacro Cuore, Rome, Italy, |
| Primary Subject Heading: | Geriatric medicine |
| Secondary Subject Heading: | Epidemiology |
| Keywords: | Hypertension < CARDIOLOGY, GERIATRIC MEDICINE, EPIDEMIOLOGY |
| | |

# Hypertension and Frailty: a Systematic Review and Meta-analysis

Davide L Vetrano*[1,2], Katie Palmer* [3], Lucia Galluzzo[4], Simona Giampaoli [4], Alessandra Marengoni [5], Roberto Bernabei [2], Graziano Onder [2] on behalf of the Joint Action ADVANTAGE

*These authors contributed equally to this work.

[1] Aging Research Center, Department of Neurobiology, Health Care Sciences and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden

[2] Department of Geriatrics, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy.

[3] Fondazione Ospedale San Camillo IRCCS, Venice, Italy

[4] Department of Cardiovascular, Dysmetabolic and Ageing-Associated Diseases, Istituto Superiore di Sanità, Rome, Italy

[5] Department of Clinical and Experimental Sciences, University of Brescia, Italy

**Word count: 2983 words, 57 references, 4 figures**

**Running title:** Hypertension and Frailty

**Conflicts of interest:** none declared.

**Correspondence to:**
Graziano Onder
Centro Medicina dell'Invecchiamento
Fondazione Policlinico A. Gemelli
Università Cattolica del Sacro Cuore, Rome, Italy
Tel: 0039 0630154341
Email: graziano.onder@unicatt.it

**ABSTRACT**

**Objective -** To review the association between hypertension and frailty in observational studies.

**Design -** A systematic review of the PubMed, Web of Science, and Embase databases was performed. A meta-analysis was performed if at least three studies used the same definition of frailty and a dichotomous definition of hypertension.

**Setting, participants and measures** - Studies providing information on the association between frailty and hypertension in adult persons, regardless of the study setting, study design, or definition of hypertension and frailty were included.

**Results -** Among the initial 964 articles identified, 27 were included in the review. Four longitudinal studies examined the incidence of frailty according to baseline hypertension status, providing conflicting results. Twenty-three studies assessed the cross-sectional association between frailty and hypertension: 13 of them reported a significantly higher prevalence of frailty in hypertensive participants and 10 found no significant association. The pooled prevalence of hypertension in frail individuals was 72% (95% Confidence Interval [95%CI] 66%-79%) and the pooled prevalence of frailty in individuals with hypertension was 14% (95%CI 12%-17%). Five studies, including a total of 7,656 participants, reported estimates for the association between frailty and hypertension (pooled OR 1.33; 95%CI 0.94-1.89).

**Conclusions -** Frailty is common in persons with hypertension. Given the possible influence of frailty on the risk-benefit ratio of treatment for hypertension and its high prevalence it is important to assess the presence of this condition in persons with hypertension.

**PROSPERO REGISTRATION NUMBER:** CRD42017058303

***Keywords:*** Frailty; Hypertension

**Article Summary - Strengths and limitations of this study**

- A greater number of potentially eligible articles were screened and included in the review.
- Absence of evident publication bias, and low-to-moderate risk of methodological bias increase the reliability of our findings.
- Heterogeneity in the definitions of frailty and hypertension across studies.
- Cross-sectional design of most studies included in the review which limits the opportunity of generating hypotheses regarding a causal link between the conditions of interest.

## INTRODUCTION

Frailty is a condition characterized by the accumulation of biological deficits and dysfunctions which occurs with age and impairs the homeostatic balance of organisms (1). Frailty confers extreme vulnerability to stressors and increases the risk of negative health-outcomes, including mortality, disability, poor quality of life, hospitalization and institutionalization (2). This condition has a high prevalence, ranging from 8% to 16% in community dwelling older adults (3,4). Frailty has been shown to be correlated with morbidity and mortality in persons suffering from cardiovascular disease, and it was suggested that the recognition of frailty status can help physicians in establishing prognosis, determining procedural risks, and guiding treatments (5). In some cases, the assessment of frailty may be critical in guiding the patient towards a certain therapeutic choice (6).

Several studies have assessed the association of frailty with hypertension. In older adults, it has been suggested that frailty can explain the paradoxical relationship between lower blood pressure and increased mortality documented in several studies (7-10). For example, data from the National Health and Nutrition Examination Survey (NHANES) demonstrated an effect modification of hypertension according to frailty level in terms of walking speed (11); in fit persons, elevated blood pressure was associated with greater mortality, while in frail participants higher blood pressure was associated with lower mortality risk. The SPRINT trial showed that compared to standard blood pressure control, intensive control reduce the incidence of cardiovascular events both in frail and non-frail persons, but this study did not show any effects of intensive blood pressure control on risk of frailty related outcomes, such as gait speed and mobility limitation (12,13). Notably, the hypertension clinical practice guidelines released in 2017 precisely point out that blood pressure lowering therapy is one of the few interventions shown to reduce mortality risk in frail older individuals (14).

Assessing the association of frailty and hypertension may be the first step for understanding their complex interplay and might ultimately lead to optimize the treatment of hypertension and to set therapeutic goals in persons with frailty. However, the evidence on the association between these conditions has never been comprehensively summarized. The aim of the present study is to systematically review the literature, and provide pooled estimations of evidence regarding the association of frailty and hypertension.

## METHODS

We reviewed studies providing information on the association between frailty and hypertension in adult persons (*i.e.* 18 years old or older), regardless of the study setting, study design, or definition of hypertension and frailty. The protocol of the present study was registered in the international prospective register of systematic reviews PROSPERO (registration number CRD42017058303). This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.

### Data sources and searching

We searched three databases for relevant articles published from 01/01/2002 to 26/10/2017: 1) PubMed electronic database of the National Library of Medicine, 2) Web of Science and; 3) Embase. The detailed search queries are reported in the Appendix. References from the selected papers and from other relevant articles were screened for potential additional studies.

### Study selection and data extraction

Two assessors independently screened the title and abstract of the selected studies. The inclusion criteria were: 1) Articles reporting information on the association of frailty with hypertension or blood pressure (BP) values; 2) Articles in English or another European language; 3) Study design: cross-sectional, case-control, or cohort studies. Articles were excluded if they 1) Did not investigate the aims of the review; 2) Included persons younger than 18 years; 3) Did not report original data (e.g., editorial, review, or congress abstract); 4) Did not provide an explicit definition of frailty and; 5) If frailty was assessed only with a single symptom/measure (e.g. only gait speed or grip strength); 6) Were not in English or another European language. The full text of the articles selected by one or both of the assessors were retrieved for full evaluation. Two assessors read the full texts and independently extracted the information from the selected studies. A third assessor reviewed the data extraction, and any disagreement was resolved through consensus. Articles that were written in another European language than English were sent for translation by a native speaker who conducted the data extraction.

### Assessment of risk of bias

Quality of the studies was evaluated independently by the two assessors with the qualitative evaluation of observational studies Newcastle Ottawa Scale (NOS). Any disagreement in quality assessment was resolved through consensus. Studies scoring >7 were considered at low risk of bias, scores of 5-7 indicated moderate risk of bias, and scores of <5 indicated high risk of bias.

### Statistical analysis

For each measure of interest (i.e. proportions and association estimates), a meta-analysis was performed if at least three studies used the same definition of frailty and a dichotomous definition of hypertension (rather than using continuous BP values). Considering the observational design of the

retrieved studies, and the methodological differences potentially responsible for a significant share of the variance within the measures of interest, the pooled estimates were obtained through random effect models and Mantel-Haenszel weighting. Lack of homogeneity within the pooled studies was tested through the I2 statistics (significant if ≥50%). Additional analyses were performed selecting 1) Studies with NOS≥5, in order to exclude studies with high risk of methodological bias; 2) Studies with a sample size ≥ 500 participants. Publication bias was assessed by mean of the Egger's and the Begg's tests. All statistical analyses were performed using the metan and metaprop packages included in the software for statistical analyses STATA 14.0 (StataCorp, TX, USA). Metan was used to provide pooled estimations of the association between frailty and hypertension, Metaprop was used to provide pooled measures of prevalence of frailty and hypertension (15,16). A P value <0.05 was considered statistically significant for all analyses.

**Patient and public involvement**

Patients and public were not involved in this study.

## RESULTS

Through the literature search, we retrieved 1369 articles (**Figure 1**). An additional 8 articles were identified after reading references from the selected papers. Out of 1369 articles, 670 (48.9%) were screened after duplicates removal. Of these, 604 were excluded after screening and 34 after full-text reading. Thirty-two articles were part of the final qualitative and/or quantitative assessment (17-48) (see table e1 in the Appendix).

### Study description

The studies' sample size ranged from 56 to 144403 participants, with a mean age ranging from 60 to 81 years. Only 4 studies had a longitudinal design (17-20). Most studies included community-dwelling participants, and only 3 studies included in-hospital participants (43,47,48). Most of the studies were carried out in Asia (n=10), Europe (n=9) and South America (n=9), and fewer in North America (n=4).

***Frailty and hypertension definitions.*** Most of the studies (n=23) defined frailty according to the Cardiovascular Health Study (CHS) criteria (17-19,21,22,24,25,27-30,34,36-39,41-47). The rest of the studies evaluated frailty based on a frailty index (n=6) (20,23,26,32,38,40), by a composite score (n=3) (31,33,35) or using the Clinical Frailty Scale (n=1) (48). One study assessed frailty adopting both CHS criteria and FI (38).

In the longitudinal studies, frailty incidence ranged from 3% to 16%, in cross-sectional studies, frailty prevalence ranged from 3% to 68%. A diagnosis of hypertension was reported in 28 studies (17-23,25-37,38,41-47), while 3 studies analyzed BP as a continuous variable (24,38,48) and 1 classified BP in 4 groups (40). Diagnosis of hypertension was based on a BP cut-point in 12 studies (17,18,22,28,29,31-34,36,39,41), assessed only by self-reported in 5 studies (21,25,43,45,46), based on evaluation of medical records in 1 study (35) and on pharmacological treatment in 1 study (21). In 9 studies, hypertension diagnosis was not defined (19,20,26,27,30,37,42,44,47). Prevalence of hypertension ranged from 28% to 100%.

***Assessment of risk of bias.*** The majority of the studies presented a moderate risk of bias (n=25), and six studies presented a high risk, according to the NOS. In most of the cases, the self-reported nature of information was responsible for a lower score. However, according to the Egger's and the Begg's tests, no strong evidence of publication bias was detected in our meta-analyses (P=0.150 and P=0.987, respectively).

### Association between hypertension and frailty

***Longitudinal studies.*** Four longitudinal studies examined the risk of incidence of frailty according to baseline hypertension status. Two studies found that baseline hypertension did not significantly predict incidence of frailty (17,20), but Boullion et al found that hypertension was associated with an

increased incidence of the combined outcome prefrailty/frailty (p=0.009) (18). However, data from this study were not adjusted for possible confounders. Similarly, Castrejon Perez et al (19) found that hypertension was associated with incident frailty at univariate analysis (HR=2.11, 95%CI 1.03-4.31), but this association was not confirmed in the multivariate analysis (HR=1.58, 95%CI 0.83-3.01).

***Cross-sectional studies.*** Twenty-three studies assessed the cross-sectional association between frailty and hypertension (21,22,25-37,39,41-47). Results were very different across studies, with 13 studies reporting a significantly higher prevalence of frailty in hypertensive participants (22,26-28,31,32,33,34,36,37,39,44,45) and 10 finding no significant association (21,25,29,30,35,41-43,46,47).

Seventeen of these studies assessed frailty by the use of CHS criteria, for a total sample of 23304 individuals (21,22,25,27,28,30,34,36,37,39,41-47). Analyzing data from these studies, the pooled prevalence of hypertension in frail individuals was 72% (95% Confidence Interval [95%CI] 66% to 79%; $I^2$=93.1%; **Figure 2**) and the pooled prevalence of frailty in individuals with hypertension was 14% (95% CI 12% to 17%; $I^2$=96.2%; **Figure 3**). When the analyses were limited to 13 studies enrolling participants with a mean age ≥ 70 years (21,22,25,27,30,34,36 39,41,42,45-47) the pooled prevalence of hypertension in frail individuals was 71% (95% CI 62% to 80%; $I^2$=95.4%) and the pooled prevalence of frailty in individuals with hypertension was 14% (95% CI 11% to 17%; $I^2$=97.0%).

Three studies assessed blood pressure as a continuous variable, finding conflicting results: one study showed significantly higher SBP and DBP values in frail participants (24), while in two other studies frailty was associated with significantly lower blood pressure values (38,48). A small study including only participants receiving pharmacological treatment for hypertension, showed an inverse association between blood pressure levels and frailty (23). Finally, a large study performed in more than 140000 community dwelling older adults aged ≥ 80 years, classified SBP in 5 groups, showing that frailty was associated with lower SBP (40).

Among studies adopting the CHS definition of frailty and a dichotomous definition of hypertension, 5 reported estimates (odds ratios) for the association between frailty and hypertension, for a total sample of 7656 individuals (29,39,42,45,47). *All 5 studies enrolled a sample with a mean age ≥ 70 years.* The pooled estimate for the association of frailty and hypertension based on these studies was 1.33 (95% CI 0.94 to 1.89; $I^2$=79.2%; **Figure 4**). These results were confirmed when only studies with NOS≥5 (OR 1.39; 95% CI 0.70 to 2.75; $I^2$=88.1%) or studies with a sample size ≥ 500 participants (OR 1.25; 95% CI 0.79 to 1.99; $I^2$=88.4%) were analyzed.

## DISCUSSION

This systematic review and meta-analysis shows that 7 out of 10 frail adults have hypertension, while about 1 out of 7 hypertensive adults present with frailty. In addition, this study shows that the association between frailty and hypertension is uncertain: few longitudinal studies have assessed the impact of hypertension on incident frailty, providing conflicting results. Further, no studies have been performed to examine whether frailty predicts incident hypertension. Finally, the meta-analysis of cross sectional studies failed to find a significant association between these conditions.

Frailty has become a high-priority theme in cardiovascular medicine due to the aging and the increasingly complex nature of patients suffering for cardiovascular conditions (5,6). This is confirmed by the observation that 14% of persons with hypertension are frail. Frailty might indeed influence the therapeutic choices for many cardiovascular diseases. For example, assessment of frailty is considered important for determining which patients are likely to benefit from the treatment of aortic stenosis or left ventricular assist device therapy, in terms of both survival and improved quality of life (49,50).

Similarly, therapeutic choices in hypertension might be influenced by presence of frailty. First, frail older people are almost always excluded from randomized controlled trials (RCTs) assessing the effects of treatments of cardiovascular diseases, including hypertension. Logistic barriers limiting the retention in the study, the higher propensity to present adverse effects from the treatments and the higher drop out for mortality of frail individuals are the main causes for exclusion from RCTs. (51). This limits the generalizability of RCTs findings and makes difficult estimating the efficacy and safety of treatments for chronic diseases in persons with frailty. This is extremely important if we consider that according to our results 70% of frail individuals present also with hypertension. In this context, the SPRINT trial showed that intensive control leads to a reduction in cardiovascular events both in frail persons (12), but this trial excludes most complex older adults, such as those presenting with cognitive impairment or psychiatric disorders, and those institutionalized. The lack of evidence regarding the treatment of hypertension in frail older people has been highlighted in the recently issued guidelines for the management of hypertension that recognize the role of blood pressure lowering therapy as one of the few interventions to reduce mortality risk in frail older individuals, but did not make any specific recommendations regarding treatment of hypertension in frailty individuals (14).

Second, frailty is associated with limited life expectancy; as described by results of the SHARE study life expectancy for frail individuals at age of 70 years ranges between 0.1 and 1.8 years in men and between 0.4 and 5.5 years in women (52). Therefore, in frail individuals the time-until-benefit of a given treatment might exceed the life expectancy and this might modify the risk-benefit ratio of

preventive treatments for chronic diseases, including hypertension, which may require several years before showing a beneficial effect.

Third, frail individuals have an increased risk of iatrogenic illness. Cullian et al. showed among hospitalized older adults frailty doubles the risk of developing an adverse drug reaction (53). Finally, frailty might be associated with poor medication adherence to antihypertensive medications. (54).

These data underline the importance of assessing frailty when treating hypertension and possibly to set individual targets of blood pressure control for persons with frailty. Interestingly, in the SPRINT trial frail participants in the intensive blood pressure control group, experienced a significantly lower reduction of systolic blood pressure compared with non-frail participants (10.8 vs. 13.5 mm Hg, p=0.01), underling possible difficulties in lowering blood pressure in frail persons (12).

The meta-analysis of cross-sectional studies did not show any significant association between frailty and hypertension. Chronic diseases, including hypertension, are considered to be major determinants of frailty in theoretical models, and the negative effect of hypertension on cardiovascular outcomes can lead to frailty (55). However, our findings might be explained by the fact that cross-sectional data assess a single time-point and are unable to evaluate the role of hypertension at differing stages of the frailty process.

Only four longitudinal studies assessed the impact of hypertension on incident frailty, providing conflicting results. This observation is in line with results of RCTs that were not able to show any impact of treatment of hypertension on onset of frailty (13,56). A possible explanation for this lack of effect could be that that persons developing frailty might be more likely to be lost to follow-up, and this selective drop out makes it difficult to draw any firm conclusions about the effect of the treatment on these frailty-related outcomes (57).

**Strengths and limitations**

We performed a comprehensive literature search and a careful study selection and quality assessment, providing a reliable overview of the evidence in the field of hypertension and frailty. In addition, selected studies enrolled mainly community dwelling samples and this enhances the generalizability of our findings. However, our findings present some limitations. First, we detected a significant heterogeneity among the studies which can be explained by the different definitions of frailty and hypertension and the demographic differences across studies. This heterogeneity is partially buffered by the absence of evident publication bias, and the reliability of our findings is increased by the low-to-moderate risk of methodological bias. Second, the cross-sectional design of 28 out of 32 studies limits the opportunity of assessing a cause-effect association between frailty and hypertension. In addition, the four longitudinal studies retrieved by our literature search, provided conflicting evidence on the association between frailty and hypertension. Third, the meta-analyses included only studies that defined frailty based on the CHS criteria. Therefore, we can not exclude

that the described association of frailty with hypertension varies if different criteria for frailty definition are adopted. Finally, most of the studies included in the review were not aimed to assess hypertension and its relationship with frailty. For this reason, hypertension was poorly defined in most studies and this might lead to possible concerns about the methodology used to assess this condition.

**CONCLUSION**

The present study shows that frailty is common in persons with hypertension. Given the possible influence of frailty on risk-benefit ratio of treatment for hypertension and its high prevalence it is important to assess the presence of this condition in persons with hypertension. In addition, limited studies assessing the association of these conditions are available. Further research, including a more rigorous and standardized assessment of frailty, and based on longitudinal designs, is needed to untangle the relationship between frailty and hypertension and to allow for the identification of pros and the cons of the pharmacological treatment, and possible targets for therapy in this population, leading ultimately to the development of specific recommendations for the treatment of hypertension in frail people.

**FUNDING STATEMENT**

The work reported in this publication was co-funded by the European Commission through the 3rd Health Programme, under the Grant Agreement n° 724099. The European Commission support for the production of this publication does not constitute an endorsement of the contents which reflects the views only of the authors, and the Commission cannot be held responsible for any use which may be made of the information contained therein.

**AUTHORS CONTRIBUTIONS**

Conception of the work: DLV, KP, GO. Articles evaluation DLV, KP. Data analysis: DLV. Results interpretation: DLV, KP, GO, AM. Drafting the article: DLV, GO. Critical revision of the manuscript: RB, SG, LG, AM, KP. Final approval of the manuscript: all the authors. All the authors fulfill the ICMJE criteria for authorship.

**DISCLAIMER**

The authors declare no financial relationships with any organisations that might have an interest in the submitted work, no other relationships or activities that could appear to have influenced the submitted work.

**COMPETING INTERESTS**

None

**PATIENT CONSENT**

Not required

**DATA SHARING STATEMENT**

All data are available within the appendices.

**Legend to Figures**

Figure 1 - Systematic review and meta-analysis flow-chart

Figure 2 - Proportion of participants presenting with hypertension among those with frailty. Frailty was defined according to the CHS criteria.

Figure 3 - Proportion of participants presenting with frailty among those with hypertension. Frailty was defined according to the CHS criteria.

Figure 4 - Cross-sectional association of frailty (CHS criteria) with hypertension. Frailty was defined according to the CHS criteria.

**REFERENCES**


1. World Health Organization. World report on ageing and health. Geneva, Switzerland: World Health Organization. 2015
2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013 Mar 2;381:752-62.
3. 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.
4. Santos-Eggimann B, Cuénoud P, Spagnoli J, Junod J. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. J Gerontol A Biol Sci Med Sci. 2009;64:675–81.
5. Onder G, Vetrano DL, Marengoni A, Bell JS, Johnell K, Palmer K; Optimising Pharmacotherapy through Pharmacoepidemiology Network (OPPEN). Accounting for frailty when treating chronic diseases. Eur J Intern Med. 2018 Eur J Intern Med. 2018;56:49-52.
6. 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;63:747-62.
7. Molander L, Lovheim H, Norman T, Nordstrom P and Gustafson Y. Lower systolic blood pressure is associated with greater mortality in people aged 85 and older. J Am Geriatr Soc. 2008;56:1853-1859.
8. Hakala SM, Tilvis RS and Strandberg TE. Blood pressure and mortality in an older population. A 5-year follow-up of the Helsinki Ageing Study. Eur Heart J. 1997;18:1019-1023.
9. Satish S, Freeman DH, Jr., Ray L and Goodwin JS. The relationship between blood pressure and mortality in the oldest old. J Am Geriatr Soc. 2001;49:367-374.
10. Van Bemmel T, Gussekloo J, Westendorp RG and Blauw GJ. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. J Hypertension. 2006;24:287-292.
11. Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. Arch Intern Med. 2012;172:1162-8.
12. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, Fine LJ, Haley WE, Hawfield AT, Ix JH, Kitzman DW, Kostis JB, Krousel-Wood MA, Launer LJ, Oparil S, Rodriguez CJ, Roumie CL, Shorr RI, Sink KM, Wadley VG, Whelton PK, Whittle J, Woolard NF, Wright JT Jr, Pajewski NM; SPRINT Research Group. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years: A Randomized Clinical Trial. JAMA. 2016;315:2673-82.
13. Odden MC, Peralta CA, Berlowitz DR, Johnson KC, Whittle J, Kitzman DW, Beddhu S, Nord JW, Papademetriou V, Williamson JD, Pajewski NM; Systolic Blood Pressure Intervention Trial (SPRINT) Research Group. Effect of Intensive Blood Pressure Control on Gait Speed and Mobility Limitation in Adults 75 Years or Older: A Randomized Clinical Trial. JAMA Intern Med. 2017;177:500-507.
14. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD,

Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 7.

15. Harris R, Bradburn M, Deeks J, Harbord R, Altman D, Sterne J. Metan: fixed-and random-effects meta-analysis. Stata journal. 2008;8(1):3.

16. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Archives of Public Health. 2014;72(1):39.

17. Barzilay JI, Blaum C, Moore T, Xue QL, Hirsch CH, Walston JD, Fried LP. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. Arch Intern Med. 2007;167:635-41.

18. Bouillon K, Kivimäki M, Hamer M, Shipley MJ, Akbaraly TN, Tabak A, Singh-Manoux A, Batty GD. Diabetes risk factors, diabetes risk algorithms, and the prediction of future frailty: the Whitehall II prospective cohort study. J Am Med Dir Assoc. 2013;14:851.e1-6.

19. Castrejón-Pérez RC, Jiménez-Corona A, Bernabé E, Villa-Romero AR, Arrivé E, Dartigues JF, Gutiérrez-Robledo LM, Borges-Yáñez SA. Oral Disease and 3-Year Incidence of Frailty in Mexican Older Adults. J Gerontol A Biol Sci Med Sci. 2017;72:951-957.

20. Doba N, Tokuda Y, Goldstein NE, Kushiro T, Hinohara S. A pilot trial to predict frailty syndrome: the Japanese Health Research Volunteer Study. Exp Gerontol. 2012;47:638-43.

21. de Albuquerque Sousa ACP, Dias RC, Maciel TCC, Guerra RO. Frailty syndrome and associated factors in community-dwelling elderly in Northeast Brazil. Arch Gerontol Geriatr 2012;54:e95-e101.

22. Avila-Funes JA, Helmer C, Amieva H, Barberger-Gateau P, Le Goff M, Ritchie K, Portet F, Carrière I, Tavernier B, Gutiérrez-Robledo LM, Dartigues JF. Frailty among community-dwelling elderly people in France: the three-city study. J Gerontol A Biol Sci Med Sci. 2008;63:1089-96.

23. Basile G, Catalano A, Mandraffino G, Maltese G, Alibrandi A, Ciancio G, Lasco A, Cesari M. Relationship between blood pressure and frailty in older hypertensive outpatients. Aging Clin Exp Res. 2016 Nov 21.

24. Bastos-Barbosa RG, Ferriolli E, Coelho EB, Moriguti JC, Nobre F, Lima NK. Association of frailty syndrome in the elderly with higher blood pressure and other cardiovascular risk factors. Am J Hypertens 2012;25:1156-61.

25. Calado LB, Ferriolli E, Moriguti JC, Martinez EZ, Da Costa Lima NK. Frailty syndrome in an independent urban population in Brazil (FIBRA study): A cross-sectional populational study. Sao Paulo Med J. 2016;134(5):385-92.

26. Castrejón-Pérez RC, Gutiérrez-Robledo LM, Cesari M, Pérez-Zepeda MU. Diabetes mellitus, hypertension and frailty: A population-based, cross-sectional study of Mexican older adults. Geriatr Gerontol Int. 2017;17:925-930.

27. Chang SF, Yang RS, Lin TC, Chiu SC, Chen ML, Lee HC. The Discrimination of Using the Short Physical Performance Battery to Screen Frailty for Community-Dwelling Elderly People. J Nurs Scholarsh. 2014;46(3):207-15.

28. Chung CP, Chou KH, Chen WT, Liu LK, Lee WJ, Chen LK, et al. Cerebral microbleeds are associated with physical frailty: a community-based study. Neurobiol Aging. 2016;44:143-50.

29. Fattori A, Santimaria MR, Alves RMA, Guariento ME, Neri AL. Influence of blood pressure profile on frailty phenotype in community-dwelling elders in Brazil - FIBRA study. Arch Gerontol Geriatr. 2013;56:343-9.

30. Frisoli A Jr, Ingham SJ, Paes ÂT, 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.

31. Guessous I, Luthi JC, Bowling CB, Theler JM, Paccaud F, Gaspoz JM, McClellan W. Prevalence of frailty indicators and association with socioeconomic status in middle-aged and older adults in a swiss region with universal health insurance coverage: a population-based cross-sectional study. J Aging Res. 2014;2014:198603.

32. Kang MG, Kim SW, Yoon SJ, Choi JY, Kim KI, Kim CH. Association between Frailty and Hypertension Prevalence, Treatment, and Control in the Elderly Korean Population. Sci Rep. 2017;7:7542.

33. Klein BE, Klein R, Knudtson MD, Lee KE. Frailty, morbidity and survival. Arch Gerontol Geriatr. 2005;41:141-9.

34. Lahousse L, Maes B, Ziere G, Loth DW, Verlinden VJA, Zillikens MC, et al. Adverse outcomes of frailty in the elderly: The Rotterdam Study. Eur J Epidemiol. 2014;29:419-27.

35. Lee JS, Auyeung TW, Leung J, Kwok T, Leung PC, Woo J. Physical frailty in older adults is associated with metabolic and atherosclerotic risk factors and cognitive impairment independent of muscle mass. J Nutr Health Aging. 2011;15:857-62.

36. Nadruz W Jr, Kitzman D, Windham BG, Kucharska-Newton A, Butler K, Palta P, Griswold ME, Wagenknecht LE, Heiss G, Solomon SD, Skali H, Shah AM. Cardiovascular Dysfunction and Frailty Among Older Adults in the Community: The ARIC Study. J Gerontol A Biol Sci Med Sci. 2017;72:958-964.

37. Ng TP, Feng L, Nyunt MS, Larbi A, Yap KB. Frailty in older persons: multisystem risk factors and the Frailty Risk Index (FRI). J Am Med Dir Assoc. 2014;15:635-42.

38. O'Connell MDL, Savva GM, Fan CW, Kenny RA. Orthostatic hypotension, orthostatic intolerance and frailty: The Irish Longitudinal Study on Aging-TILDA. Arch Gerontol Geriatr. 2015;60:507-13.

39. 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.

40. Ravindrarajah R, Hazra NC, Hamada S, Charlton J, Jackson SHD, Dregan A, Gulliford MC. Systolic Blood Pressure Trajectory, Frailty, and All-Cause Mortality >80 Years of Age: Cohort Study Using Electronic Health Records. Circulation. 2017;135:2357-2368.

41. 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.

42. Serra-Prat M, Papiol M, Vico J, Palomera E, Sist X, Cabré M. Factors associated with frailty in community-dwelling elderly population. A cross-sectional study. European Geriatric Medicine. 2016;7(6):531-7.

43. Tavares DMD, Colamego CG, Pegorari MS, Ferreira PCD, Dias FA, Bolina AF. Cardiovascular risk factors associated with frailty syndrome among hospitalized elderly people: a cross-sectional study. Sao Paulo Med J. 2016;134:393-9.

44. Vaingankar JA, Chong SA, Abdin E, Picco L, Chua BY, Shafie S, Ong HL, Chang S, Seow E, Heng D, Chiam PC, Subramaniam M. Prevalence of frailty and its association with sociodemographic and clinical characteristics, and resource utilization in a population of Singaporean older adults. Geriatr Gerontol Int.2016 Aug 31.

45. Watanabe Y, Hirano H, Arai H, Morishita S, Ohara Y, Edahiro A, Murakami M, Shimada H, Kikutani T, Suzuki T. Relationship Between Frailty and Oral Function in Community-Dwelling Elderly Adults. J Am Geriatr Soc. 2017;65:66-76.

46. 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.

47. Wu IC, Shiesh SC, Kuo PH, Lin XZ. High Oxidative Stress Is Correlated with Frailty in Elderly Chinese. J Am Geriatr Soc. 2009;57:1666-71.

48. Yanagita I, Fujihara Y, Eda T, Tajima M, Yonemura K, Kawajiri T, Yamaguchi N, Asakawa H, Nei Y, Kayashima Y, Yoshimoto M, Kitajima Y, Harada M, Araki Y, Yoshimoto S, Aida E, Yanase T, Nawata H, Muta K. Low glycated hemoglobin level is associated with severity of frailty in Japanese elderly diabetes patients. J Diabetes Investig. 2017 May 27.

49. Mack MJ, Stoler R. Intervention for Aortic Stenosis: The Measurement of Frailty Matters. J Am Coll Cardiol. 2017;70:701-703.

50. Joseph SM, Manghelli JL, Vader JM, Keeney T, Novak EL, Felius J, Martinez SC, Nassif ME, Lima B, Silvestry SC, Rich MW. Prospective Assessment of Frailty Using the Fried Criteria in Patients Undergoing Left Ventricular Assist Device Therapy. Am J Cardiol. 2017;120:1349-1354.

51. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA. 2007;297:1233-40.

52. Romero-Ortuno R, Fouweather T, Jagger C. Cross-national disparities in sex differences in life expectancy with and without frailty. Age Ageing. 2014;43:222-8.

53. Cullinan S, O'Mahony D, O'Sullivan D, Byrne S. Use of a frailty index to identify potentially inappropriate prescribing and adverse drug reaction risks in older patients. Age Ageing. 2016;45:115-20.

54. Chudiak A, Jankowska-Polańska B, Uchmanowicz I. Effect of frailty syndrome on treatment compliance in older hypertensive patients. Clin Interv Aging. 2017;12:805-814.

55. 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.

56. Applegate WB, Pressel S, Wittes J, Luhr J, Shekelle RB, Camel GH, Greenlick MR, Hadley E, Moye L, Perry HM Jr, et al. Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. Arch Intern Med. 1994;154:2154-60.

57. Di Bari M, Pahor M, Franse LV, Shorr RI, Wan JY, Ferrucci L, Somes GW, Applegate WB. Dementia and disability outcomes in large hypertension trials: lessons learned from the systolic hypertension in the elderly program (SHEP) trial. Am J Epidemiol. 2001;153:72-8.

Figure 1

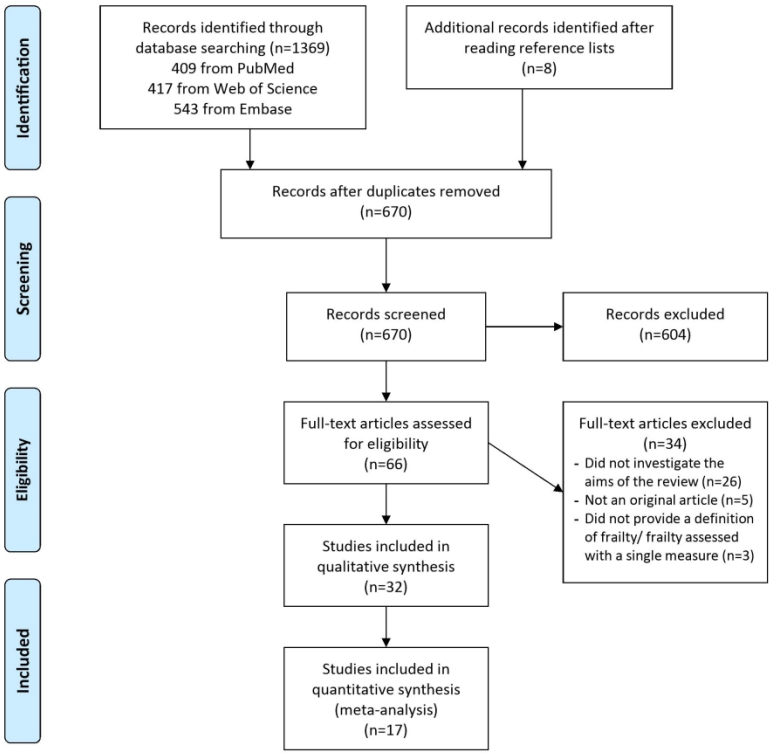


Figure 1 - Systematic review and meta-analysis flow-chart

215x279mm (300 x 300 DPI)

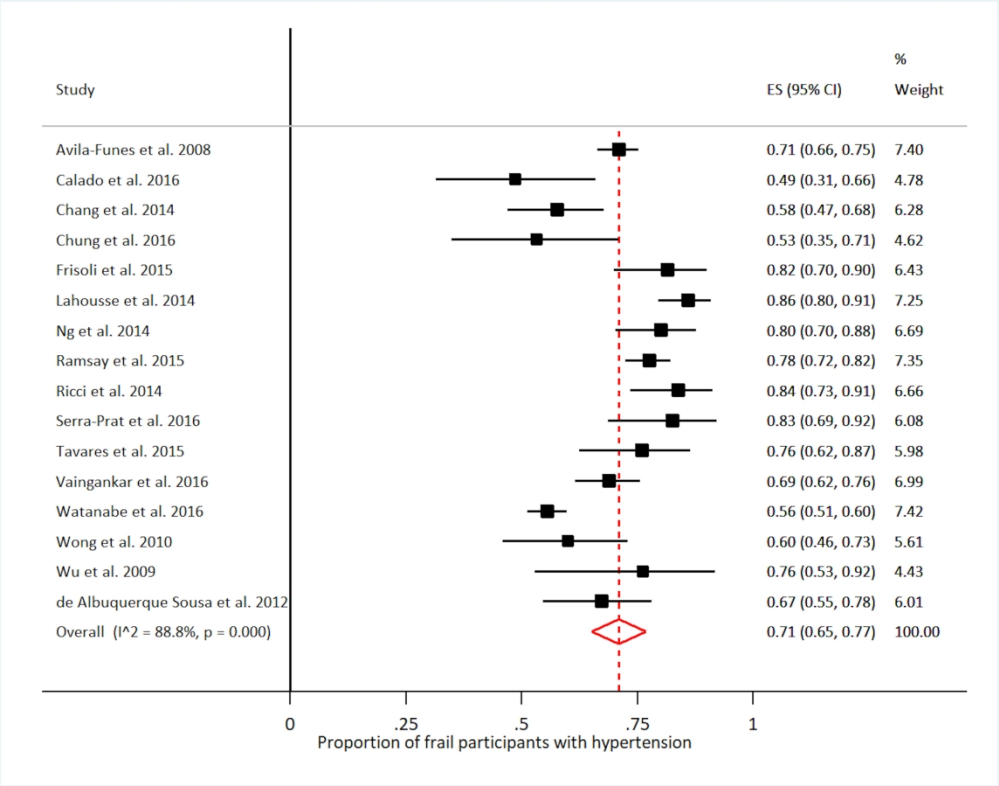


Figure 2 - Proportion of participants presenting with hypertension among those with frailty. Frailty was defined according to the CHS criteria.

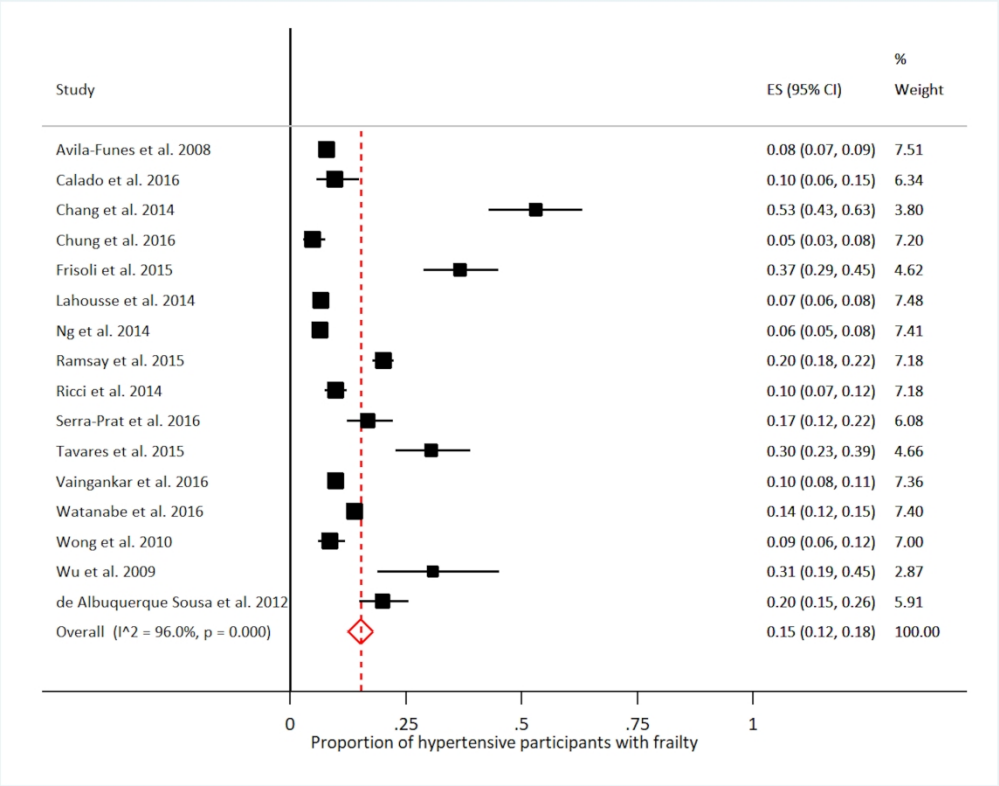


Figure 3 - Proportion of participants presenting with frailty among those with hypertension. Frailty was defined according to the CHS criteria.

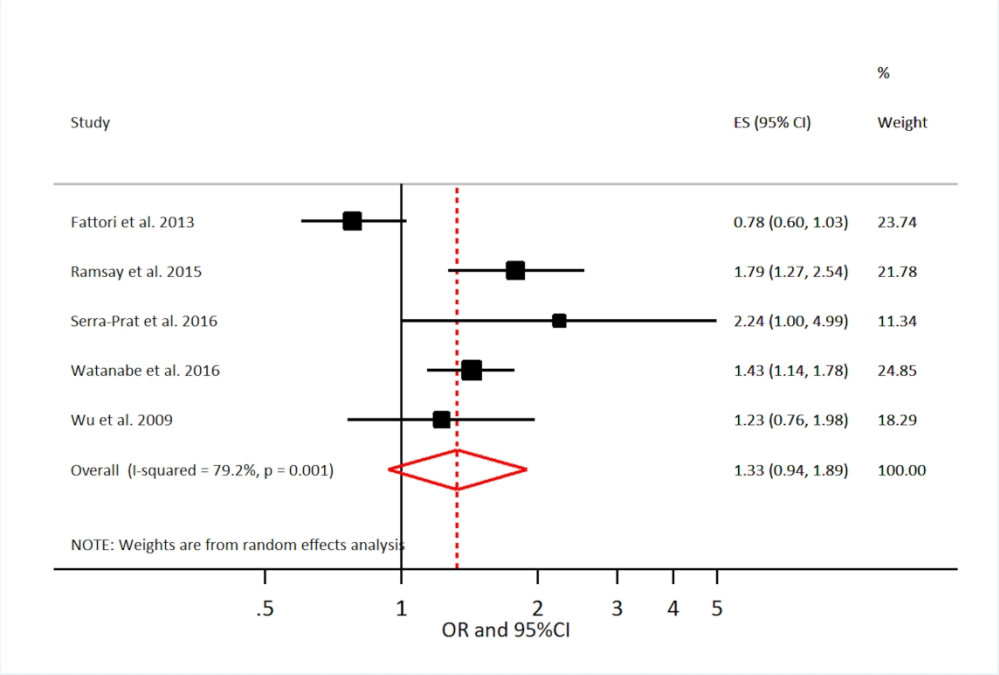


Figure 4 - Cross-sectional association of frailty (CHS criteria) with hypertension. Frailty was defined according to the CHS criteria.

# Appendix

## Search terms used

### Pubmed

(“hypertension”[MeSH Terms] OR “hyperten*”[Title/Abstract] OR “hypertension”[Title/Abstract] OR “hypertensive”[Title/Abstract] OR “high blood pressure”[Title/Abstract] OR “systolic blood pressure”[Title/Abstract] OR “diastolic blood pressure”[Title/Abstract] OR “raised blood pressure”[Title/Abstract]) AND ("frail elderly"[MeSH Terms] OR "frail*"[Title/Abstract] OR "frailty"[Title/Abstract])

### Web of Science and Embase

(“hyperten*” OR “hypertension” OR “hypertensive” OR “high blood pressure” OR “systolic blood pressure” OR “diastolic blood pressure” OR “raised blood pressure” ) AND ("frail*" OR "frailty" )

**Table e1**. Characteristics of the studies included in the systematic review.

| First Author (year) | Study characteristics | n | Hypertension definition | Hypertension prevalence | Frailty definition | Frailty Incidence (longitudinal studies) or prevalence (cross-sectional studies) | % hypertension in frailty groups | Other results | NOS |
|---|---|---|---|---|---|---|---|---|---|
| **LONGITUDINAL STUDIES** | | | | | | | | | |
| Barzilay (2007) | Country: USA<br><br>Name: Cardiovascular Health Study (CHS)<br><br>Setting: community<br><br>Age: ≥ 65 y | 2826 | BP ≥ 130/85 mm Hg or treated hypertension | 37% | CHS criteria | Prefrail: 66%<br>Frail: 8% | Robust=34%<br>Prefrail=38%<br>Frail=43% | Incident frailty (5 and 9 y follow-up) was not predicted by hypertension diagnosis or blood pressure levels. SBP at baseline was not independently associated with frailty: HR=0.96 (95% CI 0.89-1.04) for prefrailty and HR=1.01 (95% CI 0.88-1.17) for frailty. | 7 |
| Bouillon (2013) | Country: UK<br><br>Name: Whitehall II Study<br><br>Setting: community<br><br>Age (range): 45-69 y | 2707 | BP ≥ 130/85 mm Hg or treated hypertension | 40% | CHS criteria | Prefrail: 37%<br>Frail: 3% | Robust=38%<br>Prefrail/frail=43% | - | 6 |
| Castrejón-Pérez (2017) | Country: Mexico<br><br>Name: Mexican Study of Nutritional and Psychosocial Markers of Frailty<br><br>Setting: community<br><br>Age (range): 70-95 y | 237 | Not defined | 58% | CHS criteria | Frail=15% | Robust=55%<br>Frail=74% | At univariate analysis hypertension was associated with incident frailty (HR=2.11, 95%CI 1.03-4.31), but this association was not confirmed in the multivariate analysis (HR=1.58, 95%CI 0.83-3.01) | 6 |
| Doba (2012) | Country: Japan<br><br>Name: Japanese Health Research Volunteer Study | 351 | Not defined | 28% | FI | Frail: 16% | Robust=28%<br>Frail=42% | Baseline SBP was lower in persons who developed frailty vs non frail SBP=135±17 vs 140±21 (p=0.046) . In multivariate analyses, no | 7 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Setting: community<br><br>Age (mean±SD): 78±4 y | | | | | | | significant association between SBP and frailty was observed | |
| **CROSS-SECTIONAL STUDIES** | | | | | | | | | |
| de Albuquerque Sousa (2012) | Country: Brazil<br><br>Name: Network of Studies on the Frailty of Elderly Brazilians<br><br>Setting: Community<br><br>Age (mean±SD): 74±7 y | 391 | Self-reported | 58% | CHS criteria | Prefrail: 60%<br>Frail: 17% | Robust=53%<br>Prefrail=57%<br>Frail=67% | - | 5 |
| Ávila-Funes (2008) | Country: France<br><br>Name: Three-City Study<br><br>Setting: community<br><br>Age (mean±SD): 74±5 y | 6078 | Self-reported or BP≥160/95 or treated hypertension | 64% | CHS criteria | Prefrail: 48%<br>Frail: 7% | Robust=64%<br>Prefrail=63%<br>Frail=71% | - | 5 |
| Basile (2017) | Country: Italy<br><br>Setting: community<br><br>Age (mean): 81±8 y | 56 | Treated hypertension | 100% | FI | - | - | Participants with SBP≥140 mmHg had lower FI compared to those with SBP<140 mmHg (p=0.006) | 5 |
| Bastos-Barbosa (2012) | Country: Brazil<br><br>Name: Research Network of Studies of Brazilian Elderly Individuals<br><br>Setting: community<br><br>Age (mean±SD): 74±7 y | 77 | BP reported as a continuous measure | 63% | CHS criteria | Prefrail: 40%<br>Frail: 30% | Not reported | Ambulatory BP of frail group demonstrated significantly higher systolic and diastolic BP values over the 24 h (135/74 mm Hg) than nonfrail group (122/68 mm Hg). | 5 |
| Calado (2016) | Country: Brazil<br><br>Setting: community | 385 | Self-reported | 46% | CHS criteria | Prefrail: 50%<br>Frail: 9% | Robust=44%<br>Prefrail=48%<br>Frail=48% | - | 5 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Age (mean): 74±6 y | | | | | | | | |
| Castrejón-Pérez (2017) | Country: Mexico<br><br>Name: Mexican Health and Nutrition Survey<br><br>Setting: community<br><br>Age (mean±SD): 71±8 y | 7164 | Not defined | 38% | FI | Mean FI score=0.18 | - | Multiple linear regression for FI for hypertension only (without diabetes) Beta: 0.31 (0.55-0.69) | 5 |
| Chang (2014) | Country: Taiwan<br><br>Setting: community<br><br>Age: ≥65 y | 234 | Not defined | 43% | CHS criteria | Frail: 39% | Robust=33%<br>Frail=58% | Hypertension significantly associated with frailty OR=2.21 (1.16–4.21) in multivariate analysis. | 4 |
| Chung (2016) | Country: Taiwan<br><br>Name: I-Lan Longitudinal Aging Study<br><br>Setting: community<br><br>Age (mean±SD): 62±9 y | 962 | Self-reported or BP≥140/90 or treated hypertension | 37% | CHS criteria | Prefrail: 33%<br>Frail: 3% | Robust=34%<br>Prefrail=42%<br>Frail=53% | - | 6 |
| Fattori (2013) | Country: Brazil<br><br>Name: Research Network of Studies of Brazilian Elderly Individuals<br><br>Setting: community<br><br>Age: ≥65 y | 900 | BP ≥ 140/90 mm Hg | 52% | CHS criteria | Prefrail: 52%<br>Frail: 8% | Not reported | Hypertension not associated with frailty OR=0.78 (0.60–1.03) in univariate analysis. | 7 |
| Frisoli (2015) | Country: Brazil<br><br>Name: FRAgilidade em idosos com doenças CardiOvasculaRes<br><br>Setting: outpatient | 172 | Not defined | 84% | CHS criteria | Prefrail: 51%<br>Frail: 38% | Robust=100%<br>Prefrail=83%<br>Frail=81% | - | 4 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | clinic<br><br>Age (mean±SD):77±6 y | | | | | | | | |
| Guessous (2014) | Country: Switzerland<br><br>Name: BusSante´study<br><br>Setting: community<br><br>Age (mean): 60 y | 2930 | BP ≥ 140/90 mm Hg or treated hypertension | 47% | Frailty scale based on 4 indicators (weakness, shrinking, exhaustion, and low activity) | 1 indicator=29%<br>≥2 indicators=8% | 0 indicators =42%<br>1 indicator =54%<br>≥2 indicators =65% | Hypertension significantly associated with frailty indicators in multivariate analyses. OR for 1 indicator (vs. 0 indicators) 1.40 (1.15-2.68)- OR for ≥2 indicators 1.88 (1.32-2.68). | 7 |
| Kang (2017) | Country: Korea<br><br>Name: Korea National Health and Nutrition Examination Survey<br><br>Setting: community<br><br>Age (mean±SD): 73±5 y | 4352 | BP ≥ 140/90 mm Hg or treated hypertension | 62% | FI | Prefrail: 39%<br>Frail: 44% | Robust=49%<br>Prefrail=61%<br>Frail=68% | - | 6 |
| Klein (2005) | Country: USA<br><br>Name: Beaver Dam Eye Study<br><br>Setting: community<br><br>Age (range): 53-86 y | 2515 | BP ≥ 160/95 mm Hg or treated hypertension | 47% | Frailty scale based on 5 indicators (gait speed, peak expiratory flow rate, hand grip strength, chair stand test and visual acuity) | Not reported | - | In multivariate analysis hypertension significantly associated with frailty scale in men OR for 1-point increment in scale =1.22 (1.00-1.49) and women OR=1.22 (1.02-1.46) | 6 |
| Lahousse (2014) | Country: The Netherlands<br><br>Name: Rotterdam Study<br><br>Setting: community<br><br>Age (median): 74 y | 2833 | BP ≥ 160/100 mm Hg or treated hypertension | 75% | CHS criteria | Prefrail: 51%<br>Frail: 6% | Robust=71%<br>Prefrail=77%<br>Frail=85% | - | 6 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Lee (2011) | Country: China<br><br>Setting: community<br><br>Age (mean±SD): 72±5 y | 4000 | Medical records | 43% | Composite frailty score (range 0-20) | Mean frailty score=12.2 | - | In multivariate analysis hypertension not significantly associated with composite frailty score | 5 |
| Nadruz 2017) | Country: USA<br><br>Name: Atherosclerosis Risk in Communities Study<br><br>Setting: community<br><br>Age (mean±SD): 76±5 y | 3991 | BP ≥ 160/100 mm Hg or treated hypertension | 82% | CHS criteria | Frail=5% | Robust=81%<br>Frail=12% | - | 6 |
| Ng (2014) | Country: Singapore<br><br>Name: Singapore Longitudinal Ageing Studies I and II<br><br>Setting: community<br><br>Age (mean±SD): 67±8 y | 1685 | Not defined | 62% | CHS criteria | Prefrail: 42%<br>Frail: 5% | Robust=58%<br>Prefrail=64%<br>Frail=80% | Hypertension not associated with frailty in multivariate analysis (data not provided) | 6 |
| O'Connell (2015) | Country: Republic of Ireland<br><br>Name: Irish Longitudinal Study on Aging<br><br>Setting: community<br><br>Age (mean±SD): 63±9 y | 5692 | BP reported as a continuous measure | - | CHS criteria & FI | CHS criteria<br>Prefrail: 34%<br>Frail: 4%<br><br>Mean FI score=0.10 | - | In adjusted linear regression analyses, frailty significantly associated with lower seated and standing SBP and DBP. Seated SBP -1.9 (-2.52to-1.27), standing SBP -1.79 (-2.46 to-1-13), seated DBP -1.14 (-1.51to-0.77), standing DBP -1.10 (-1.48to-0.73). | 7 |
| Ramsay (2015) | Country: UK<br><br>Name: British Regional Heart Study<br><br>Setting: community<br><br>Age (range): 71-92 y | 1622 | BP ≥ 160/90 mm Hg or treated hypertension | 72% | CHS criteria | Prefrail: 54%<br>Frail: 19% | Robust=65%<br>Prefrail=74%<br>Frail=78% | Hypertension associated with frailty age-adjusted OR=1.79 (1.27-2.54) | 6 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Ravindrarajah (2017) | Country: UK<br><br>Name: Clinical Practice Research Datalink<br><br>Setting: community<br><br>Age: ≥80 y | 144403 | SBP values classified as follows (mmHg): <110, 110-119, 120-139, 140-159, ≥160 | <110 =3%<br>110-119=7%<br>120-139=37%<br>140-159=41%<br>≥160=12% | FI | Mild frailty=40%<br>Moderate frailty=21%<br>Severe frailty=7%<br><br>Any frailty=68% | Any frailty:<br><110 =78%<br>110-119=77%<br>120-139=72%<br>140-159=64%<br>≥160=58% | Frailty was associated with lower BP. In participants with SBP <110 mmHg, 22% were fit, 28% had moderate frailty, and 12% had severe frailty. In those with SBP ≥160 mm Hg, 42% were fit, 16% had moderate frailty, and 4% had severe frailty. | 7 |
| Ricci (2014) | Country: Brazil<br><br>Name: Fragilidade em Idosos Brasileiros Network Study<br><br>Setting: community<br><br>Age (mean±SD): 72±6 y | 761 | Self-reported or BP≥140/90 or treated hypertension | 84% | CHS criteria | Prefrail: 48%<br>Frail: 10% | Robust=81%<br>Prefrail=87%<br>Frail=84% | - | 5 |
| Serra-Prat (2016) | Country: Spain,<br><br>Setting: community<br><br>Age (mean±SD): 80±3 y | 324 | Not defined | 71% | CHS criteria | Prefrail: 54%<br>Frail: 14% | Robust=66%<br>Prefrail=70%<br>Frail=82% | Hypertension associated with frailty OR=2.24 (1.00-4.99) at univariate analysis. Association not confirmed in multivariate analysis (data not provided). | 5 |
| Tavares (2016) | Country: Brazil<br><br>Name: Study of Frailty in Elderly People<br><br>Setting: hospital<br><br>Age: ≥ 60 y | 205 | Self-reported | 66% | CHS criteria | Prefrail: 52%<br>Frail: 26% | Robust=62%<br>Prefrail=62%<br>Frail=76% | - | 4 |
| Vaingankar (2016) | Country: Singapore<br><br>Name: Well-being of the Singapore Elderly study<br><br>Setting: community<br><br>Age (mean): 69 y | 2102 | Not defined | 59% | CHS criteria | Prefrail: 40%<br>Frail: 6% | Robust=55%<br>Prefrail=62%<br>Frail=80% | Hypertension not associated with frailty in multivariate analysis (data not provided) | 4 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Watanabe (2017) | Country: Japan<br><br>Name: Obu Study of Health Promotion for the Elderly<br><br>Setting: community<br><br>Age (mean): 71 y | 4720 | Self reported | 46% | CHS criteria | Prefrail: 57%<br>Frail: 11% | Robust=39%<br>Prefrail=47%<br>Frail=52% | Hypertension significantly associated with frailty in multivariate analysis (OR 1.43, 95% CI = 1.14–1.78) | 4 |
| Wong (2010) | Country: Canada,<br><br>Name: Montreal Unmet Needs Study<br><br>Setting: community<br><br>Age (mean±SD): 80±4 y | 740 | Self-reported | 52.3% | CHS criteria | Prefrail: 50%<br>Frail: 7% | Robust=47%<br>Prefrail=55%<br>Frail=66% | - | 5 |
| Wu (2009) | Country: Taiwan<br><br>Setting: community and hospital<br><br>Age (mean±SD): 77±6 y | 90 | Not defined | 58% | CHS criteria | Prefrail: 62%<br>Frail: 23% | Robust=69%<br>Prefrail=48%<br>Frail=76% | No significant association between frailty and hypertension at univariate analysis, OR=1.23 (0.76–1.98) | 4 |
| Yanagita (2017) | Country: Japan<br><br>Setting: hospital<br><br>Age (mean±SD): 78±8 y | 132 | BP reported as a continuous measure | - | Clinical Frailty Scale | Frail=42% | - | Frail participants had lower SBP values. In multivariate analyses frailty associated with significantly lower SBP values. | 4 |

NOS = Newcastle-Ottawa Scale; CHS = Cardiovascular Health Study; OR = Odds Ratio; FI = Frailty Index; BP=Blood Pressure; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure

# MOOSE Checklist for Meta-analyses of Observational Studies

| Item No | Recommendation | Reported on Page No |
|---|---|---|
| Reporting of background should include | | |
| 1 | Problem definition | 4 |
| 2 | Hypothesis statement | 4 |
| 3 | Description of study outcome(s) | 4 |
| 4 | Type of exposure or intervention used | 4 |
| 5 | Type of study designs used | 4 |
| 6 | Study population | 4 |
| Reporting of search strategy should include | | |
| 7 | Qualifications of searchers (eg, librarians and investigators) | 5 |
| 8 | Search strategy, including time period included in the synthesis and key words | 5 |
| 9 | Effort to include all available studies, including contact with authors | 5 |
| 10 | Databases and registries searched | 5 |
| 11 | Search software used, name and version, including special features used (eg, explosion) | 6 |
| 12 | Use of hand searching (eg, reference lists of obtained articles) | 5 |
| 13 | List of citations located and those excluded, including justification | 5 |
| 14 | Method of addressing articles published in languages other than English | 5 |
| 15 | Method of handling abstracts and unpublished studies | 5 |
| 16 | Description of any contact with authors | NA |
| Reporting of methods should include | | |
| 17 | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | 5 |
| 18 | Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | 5 |
| 19 | Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability) | 5 |
| 20 | Assessment of confounding (eg, comparability of cases and controls in studies where appropriate) | NA |
| 21 | Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results | 5 |
| 22 | Assessment of heterogeneity | 5-6 |
| 23 | Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | 6 |
| 24 | Provision of appropriate tables and graphics | See tables and graphs |
| Reporting of results should include | | |
| 25 | Graphic summarizing individual study estimates and overall estimate | See figures 2 and 3 |
| 26 | Table giving descriptive information for each study included | See table e1 |
| 27 | Results of sensitivity testing (eg, subgroup analysis) | 8 |
| 28 | Indication of statistical uncertainty of findings | 8 |

| Item No | Recommendation | Reported on Page No |
|---|---|---|
| Reporting of discussion should include | | |
| 29 | Quantitative assessment of bias (eg, publication bias) | 10 |
| 30 | Justification for exclusion (eg, exclusion of non-English language citations) | NA |
| 31 | Assessment of quality of included studies | 10 |
| Reporting of conclusions should include | | |
| 32 | Consideration of alternative explanations for observed results | 10 |
| 33 | Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) | 11 |
| 34 | Guidelines for future research | 11 |
| 35 | Disclosure of funding source | 12 |

*From*: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

Transcribed from the original paper within the NEUROSURGERY® Editorial Office, Atlanta, GA, United Sates. August 2012.

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 5 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 5 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 5 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 5 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 6 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 6 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 5 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 6 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 7 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 7 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 7 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 7-8 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 8 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 7 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 8 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 9 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 10 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 11 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 12 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.