ORTHOSTATIC HYPOTENSION AND HEALTH OUTCOMES:

AN UMBRELLA REVIEW OF OBSERVATIONAL STUDIES

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KEY SUMMARY POINTS

Aim: To investigate potential relationships between Orthostatic Hypotension (OH) and negative health outcomes and mortality, through an umbrella review with integrated meta-analyses.

Findings: OH is significantly associated with several negative outcomes in older people, but a suggestive evidence is available only for higher risk of coronary heart disease, congestive heart failure, stroke, falls, dementia, and all-cause mortality.

Message: OH seems to be significantly associated with several negative health outcomes in older people, even if only associations with coronary heart disease, congestive heart failure, stroke, falls, dementia, and all-cause mortality, are supported by suggestive evidence.

ABSTRACT (242/250)

Purpose: Orthostatic Hypotension (OH) is associated with older age and many negative clinical outcomes in geriatric practice. We aimed to capture the breadth of outcomes that have been associated with the presence of OH and systematically assess the quality, strength and credibility of these associations using an umbrella review with integrated meta-analyses.

Methods: We systematically searched several major databases from their commencements through to 16th May 2019 for meta-analyses of observational studies of OH and any health-related outcome. We used these metrics to categorize the strength of evidence of significant outcomes ($p<0.05$) from class I (convincing) to class IV (weak), according to pre-established criteria.

Results: From 975 abstracts, 7 meta-analyses of 12 outcomes were included. For each outcome, the median number of studies was 4, the median number of participants was 46,493, with a median of 3,630 incident cases. There was suggestive (class III) evidence that OH was associated with significantly higher risk of coronary heart disease (HR=1.32, 95%CI: 1.12-1.56), stroke (HR=1.22, 95%CI: 1.08-1.38), congestive heart failure (HR=1.30, 95%CI: 1.09-1.55), all-cause mortality (RR=1.50, 95%CI: 1.24-1.81), falls (OR=1.84, 95%CI: 1.39-2.44), and dementia (HR=1.22, 95%CI: 1.11-1.35).

Conclusion: The current evidence base indicates that OH is significantly associated with a range of adverse cardiovascular, cognitive, and mortality outcomes in older people, although the strength of this evidence remains only suggestive. Further research in larger samples and with lower risk of bias is required to build a fuller picture of the impact of OH on health.

Keywords: orthostatic hypotension; umbrella review; meta-analysis; mortality; fall; heart failure**;** heart disease; stroke

INTRODUCTION

Orthostatic Hypotension (OH) diagnosis is often defined as a drop of at least 20 mm Hg in systolic BP (SBP) and/or 10 mm Hg in diastolic BP (DBP) upon the change in position (from sitting to standing).[1] The prevalence of OH increases with age and is estimated to be 10–30% in older adults. It is important to note that different methods used to measure OH have produced different prevalence estimates. [2-4]Reasons for the increase in prevalence of OH with age include an age-related decrease in renin-angiotensin aldosterone level, cardiac hypertrophy, and deficiency in arterial baroreflex sensitivity and vasomotor control; all of which make the management of postural blood pressure increasingly difficult with age.[5]

A number of studies have reported associations between OH and increased risk of adverse clinical outcomes, including cardiovascular events and stroke [6], recurrent falls syncope and consequent injuries [7], cognitive impairment [8], impaired sleep quality [9], and depression.[10] However, no attempt has been made to synthesize the literature on the health risks associated with OH or critically evaluate the strength of the available evidence. A better understanding of the full spectrum of health risks associated with OH is important for geriatric practice. OH has been shown to be significantly associated with older age, polyurinary incontinence, frailty, and functional impairment in daily life activities, OH can therefore be considered as a new geriatric syndrome.[11]

Therefore, the present study aimed to capture the breadth of outcomes that have been shown in observational studies to be associated with OH and systematically assess the quality, strength and credibility of these associations. We used an umbrella review with integrated meta-analyses [12] to combine evidence from a wide range of outcomes and populations.

MATERIALS AND METHODS

The present umbrella review followed a structured protocol (available upon request from the corresponding author) that was pre-registered in PROSPERO as CRD 42019126423.(https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=126423).

Data sources and searches

We searched several databases (Epistemonikos, MEDLINE through Ovid, CINAHL, EMBASE, Cochrane library and JBI Database of Systematic Reviews and Implementation Reports) from their inception through to 16th May 2019. The search strategy used in MEDLINE is reported, as an example, in **Supplementary Table 1**. Moreover, we hand-searched the reference lists of included articles. No language restrictions were applied.

Study selection

In this umbrella review, we included: 1) systematic reviews with meta-analyses that included people with a diagnosis of OH, according to The Consensus Committee of the American Autonomic Society and the American Academy of Neurology, and 2) meta-analyses of observational studies (longitudinal or case-control) that investigated the association of OH with any health-related outcome (e.g. cardiovascular events, falls, depression, cognitive impairment, mortality). OH was defined as a drop of at least 20 mm Hg in systolic BP (SBP) and/or 10 mm Hg in diastolic BP (DBP) upon the change in position.[1] Both the active standing test and Head up Tilt Table test for measuring blood pressure were accepted.

Data extraction

Two independent investigators (PS, JD) extracted the following information for each article: (1) first author name; (2) year of publication; (3) journal; (4) the number of included studies and the total number of the people included in the review; (5) the inclusion criteria for studied population; (6) the definition used for OH; (7) the effect size used in the review; (8) study design (case-control, longitudinal); (9) number of cases (i.e. people having the event of interest, e.g. falls) and controls (i.e. people without events) for each study; and (10) setting. Disagreements were resolved through consensus with another independent reviewer (NV). We

then extracted the study-specific estimated relative risk for each health outcome (risk ratio [RR], odds ratio [OR], hazard ratio [HR], mean difference [MDs]), along with the associated 95% confidence interval (CI). If two meta-analyses were available for the same outcome, we included the largest in terms of studies.

Outcomes

Any health-related outcome (e.g. cardiovascular events, falls, depression, cognitive impairment, mortality and others) were included.

Methodological quality of systematic reviews

The methodological quality of the included meta-analyses were assessed using ROBIS. The ROBIS is completed in three phases: (1) assess relevance (optional), (2) identify concerns with the review process, and (3) judge risk of bias. Phase 2 covers four domains through which bias may be introduced into an each systematic review of the umbrella review: study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis and findings. Phase 3 assesses the overall risk of bias in the interpretation of review findings and whether this considered limitations identified in any of the phase 2 domains. Signaling questions are included to help judge concerns with the review process (phase 2) and the overall risk of bias in the review (phase 3); these questions flag aspects of review design related to the potential for bias and aim to help assessors judge risk of bias in the review process, results, and conclusions Each item can be scored from low to high risk of bias.[13]

Statistical analysis

For each meta-analysis, we re-calculated the summary effect size and its 95% CI, using random-effects models.[14] Next, the 95% prediction interval was estimated which further accounts for between-study effects and estimates the certainty of the association if a new study addresses that same association. [15] For the largest study of each meta-analysis, we evaluated whether this was statistically significant. Heterogeneity was estimated using the I^2 metric, with values $\geq$ 50% indicative of high heterogeneity, and

values ≥ 75% suggesting very high heterogeneity. [16, 17] In addition, we calculated the evidence of small-study effects. In this regard, we used the regression asymmetry test [18], using a p-value < 0.10. [19] Finally, we applied the excess of significance test [20] which evaluates whether the number of studies with nominally significant results (i.e. with p< 0.05) among those included in a meta-analysis is too large based on the power that these data sets have to detect effects at α=0.05. The number of expected 'positive' (E); i.e., statistically significant studies was compared with the observed (O) number of statistically significant studies through a χ^2-based test. [20] A p-value<0.10 was considered indicating of excess statistical significance.

Sensitivity analysis in which these analyses were repeated restricted to prospective observational studies with convincing (class I) or highly suggestive (class II) evidence only were planned, but none met this criteria.

Grading the evidence

Using the results of analyses described in the statistical analysis section, associations that presented nominally statistically significant random-effects summary estimates (i.e. p<0.05) were categorized into convincing, highly suggestive, suggestive, or weak evidence (class I to IV), following a grading scheme that has already been applied in various fields of medicine. [21-33] These criteria are fully reported in **Supplementary Table 2**.

RESULTS

Literature search

We initially identified 975 papers. Of these, 22 full texts were screened and finally 7 meta-analyses [34-40], which included 12 different outcomes, were included as reported in **Figure 1**.

Meta-analyses of included studies

Table 1 summarises the main findings of our umbrella review. For each outcome, the median number of studies was 4, the median number of participants was 46,493, with a median of 3,630 incident cases.

All the studies focused on the general population as the population of interest, and all were cohort studies. Four outcomes related to cardiovascular diseases, four were cognitive outcomes and the other four outcomes regarded falls and mortality, including specific-cause deaths.

Supplementary Table 3 reports the assessment of the quality of the meta-analyses included, showing that these works (with the exception of two) had a low risk of bias, according to the ROBIS. **Supplementary Table 4** shows the main results of included primary studies of each meta-analysis. The excluded studies with reason are shown in **Supplementary Table 5.**

Overall, 10/12 studies (83%) reported significant summary results ($p < 0.05$), as shown in **Table 1**. Half of the outcomes (6/12) reported significant heterogeneity, as $I^2 \geq 50\%$ and, of them, 2 reported a very high heterogeneity ($I^2 \geq 75\%$). For one outcome (falls) we observed a small study effect, whilst the excess significance bias was present in 3/12 outcomes included. The largest study, in terms of participants, was statistically significant for five outcomes. No outcome included 95% prediction intervals excluding the null, i.e. not statistically significant.

Based on the above mentioned criteria, none of the outcomes presented convincing (class I) or highly suggestive (class II) evidence. Six outcomes presented suggestive evidence (class III): OH was associated with significantly higher risk of coronary heart disease (HR=1.32, 95%CI: 1.12-1.56), stroke (HR=1.22, 95%CI: 1.08-1.38), congestive heart failure (HR=1.30, 95%CI: 1.09-1.55), falls (OR=1.84, 95%CI: 1.39-2.44), dementia (HR=1.22, 95%CI: 1.11-1.35), and all-cause mortality (RR=1.50, 95%CI: 1.24-1.81) (**Table 1**).

DISCUSSION

This umbrella review, summarized the findings of 7 previous meta-analyses of the association between OH and 12 independent outcomes. Suggestive (i.e. class III) evidence for associations between OH and risk of coronary heart disease, stroke, congestive heart failure, all-cause mortality, falls and dementia were found.

Cardiovascular disease (CVD)

While we identified significant associations between OH and several cardiovascular outcomes (coronary heart disease, stroke, congestive heart failure), none reached the cutoff for Class I or II evidence.

Several hypotheses may be helpful in explaining the relationship between OH and increased CVD risk. First, patients with OH are likely to have increased blood pressure variability related to body posture, and a large proportion of thoracic blood volume may be displaced to lower limbs due to gravity during orthostasis. [41] Thus, both myocardial and cerebral ischemia may occur frequently as a result of OH. Moreover, subsequent acute change of hemodynamic and organ perfusion status may trigger a coronary heart disease or stroke event. Second, it has been suggested that OH is associated with higher arterial stiffness[42] and activated systematic inflammation[43], which have both been involved in the pathogenesis of subclinical atherosclerosis, leading to cardiovascular disease. [43, 44] Xin et al in their analysis [38] stated that a significant association between OH and congestive heart failure incidence can be found in middle-age subjects and those with hypertension and diabetes mellitus at baseline. These results highlight the predictive effect of OH for future congestive heart failure in both the low-risk population and the high-risk population with known congestive heart failure risks. On the other hand, polypharmacy, in particular cardiovascular drugs including antianginals, antiarrhythmics, antihypertensive such as calcium channel blockers and α-blockers are strongly associated with OH in patients with CV [45]. Therefore, careful medication review is needed to improve orthostatic blood pressure changes in routine clinical practice

Falls

Despite some studies failing to find a consistent association between OH and falls, the present review found suggestive evidence for this association meaning that this association is less significant than expected. There

are several possible explanations for the association between OH and falls. OH might cause an acute drop in cerebral oxygenation because of an impaired cerebral autoregulation, resulting in dizziness and falls.[46] Alternatively, OH might cause brain atrophy, microbleeds, and white matter brain lesions, resulting in falls.[47] OH might also cause falls through impaired muscle microcirculation, as one study found an association of OH with muscle ischemia.[48] Conversely, falls might cause OH by fear of falls, with consequent behavioral changes including lower physical activity levels, resulting in deconditioning and muscle loss.[49] However, current evidence does not support this, as OH was not found to be associated with physical activity behaviour.

Dementia

Suggestive evidence was found for an association between OH and dementia, but the association was not confirmed for vascular dementia or Alzheimer's disease.

The most frequently proposed mechanism linking OH to dementia is the recurrent transient brain hypoperfusion hypothesis. [50] Previous research has shown that cerebral blood flow is decreased in OH by electroencephalography[50], besides decreased brain perfusion during orthostatic pressure was demonstrated by the method of single-photon emission computed tomography. [51] Cerebral hypoperfusion may lead to leukoaraiosis underlying the neurodegeneration process in dementia.[52] OH was traditionally thought to be detrimental only if compensatory mechanisms are inadequate. When cerebral autoregulation is impaired, it reacts less efficiently to compensate for a drop in cerebral perfusion pressure and fails to maintain adequate cerebral blood flow which may cause ischemic cerebral damage.[53] However, one recent study reported no relationship between OH and cognitive impairment related with leukoaraiosis, subtle brain microstructural damage, or cerebral blood flow.[54] OH and cognitive function are complicated and affected by multiple factors. The autonomous nervous system has been reported to be essential for orthostatic reflex and dysfunction of this system usually results in OH. [55] Some pathologies such as diabetes, alpha-synucleinopathies, and sarcoidosis are common causes for autonomic neuropathy, and OH is prevalent among these diseases.[56, 57] On the other hand, in a recent study, it was demonstrated that the prevalence

of OH, in older patients with Alzheimer's disease was similar to those with Dementia of Lewy Body, an alpha-synucleinopathy. [58]

All-cause mortality

OH represents a condition of impaired hemodynamic homeostasis, where compensatory neuroendocrine mechanisms are intermittently activated. These mechanisms may trigger the activation of other biologic effectors, e.g. platelets or the coagulation cascade, potentially promoting the occurrence of cardio- or cerebrovascular events that can contribute to a higher mortality risk. [43, 44] Moreover, wide swings in blood pressure and supine hypertension associated with OH may provoke intermittent ischemic bouts and increased afterload, leading to permanent end-organ damage such as left ventricular hypertrophy and decreased renal function. [5] Baroreflex dysfunction, a marker of Autonomic nervous system imbalance implicated in the pathogenesis of OH[59, 60] is characterized by enhanced sympathetic activity and withdrawal of parasympathetic control, and has long been recognized as an important mediator of increased cardiovascular morbidity and mortality.[61-63]

Limitations

The results of this study should be considered in light of its limitations; some related to the umbrella review method, some to those of the individual studies included. Considering that meta-analyses included studies with significantly differing designs, populations and other basic characteristics, large heterogeneity might arise. However, a common estimate of heterogeneity (I^2<50%) was used as one of the criteria for having convincing outcomes, even if the use of the same I^2 is still discussed. Moreover, meta-analyses have important limitations and their results may also depend on choices made about what estimates to select from each study and how to report them in the meta-analysis.[64] Applying the criteria suggested by the ROBIS for evaluating the quality of meta-analyses, we observed the presence of a high risk of bias in 2 out of

the 7 meta-analyses included. This evidence is mainly associated with the second phase in which a high risk of bias in eligibility and selection of studies and synthesis and findings of evidence.

Conclusions

In summary, OH seems to be significantly associated with several negative health outcomes in older people, even if only the association with coronary heart disease, congestive heart failure, stroke, falls, dementia and all-cause mortality is supported by a suggestive evidence. However, the present review does not allow to draw firm conclusions whether OH can be considered as a risk factor for other medical conditions. For instance, it is not clear whether patients with OH benefit from anti-hypertensive treatments to the same extent as those without. Future prospective studies aiming at investigating this relationship on larger cohorts of patients and with less biases are necessary to reinforce the observed associations in this umbrella review.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest: All authors declare no conflict of interest.

Ethical approval: Was not requested being a revision of already published literature.

Informed consent: No patients were included in this review.

Sponsor's role: None.

REFERENCES

1. American Autonomic S, the American Academy of N (1996) Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Neurology 46:1470-1470
2. Low PA (2008) Prevalence of orthostatic hypotension. Clinical Autonomic Research 18:8-13
3. Soysal P, Aydin AE, Okudur SK, Isik AT (2016) When should orthostatic blood pressure changes be evaluated in elderly: 1st, 3rd or 5th minute? Archives of gerontology and geriatrics 65:199-203
4. Aydin AE, Soysal P, Isik AT (2017) Which is preferable for orthostatic hypotension diagnosis in older adults: active standing test or head-up tilt table test? Clinical interventions in aging 12:207
5. Low PA, Tomalia VA (2015) Orthostatic hypotension: mechanisms, causes, management. Journal of Clinical Neurology 11:220-226
6. Verwoert GC, Mattace-Raso FU, Hofman A, Heeringa J, Stricker BH, Breteler MM, Witteman JC (2008) Orthostatic hypotension and risk of cardiovascular disease in elderly people: the Rotterdam study. Journal of the American Geriatrics Society 56:1816-1820
7. Atkins D, Hanusa B, Sefcik T, Kapoor W (1991) Syncope and orthostatic hypotension. The American journal of medicine 91:179-185
8. Yap PLK, Niti M, Yap KB, Ng TP (2008) Orthostatic hypotension, hypotension and cognitive status: early comorbid markers of primary dementia? Dementia and geriatric cognitive disorders 26:239
9. Gupta V, Lipsitz LA (2007) Orthostatic hypotension in the elderly: diagnosis and treatment. The American journal of medicine 120:841-847
10. Schneider L, Sloane RB, Staples FR, Bender M (1986) Pretreatment orthostatic hypotension as a predictor of response to nortriptyline in geriatric depression. Journal of clinical psychopharmacology 6:172-176
11. Chen L, Xu Y, Chen X, Lee W-J, Chen L-K (2019) Association Between Orthostatic Hypotension and Frailty in Hospitalized Older Patients: A Geriatric Syndrome More Than a Cardiovascular Condition. The journal of nutrition, health & aging 23:318-322
12. Ioannidis JP (2009) Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. CMAJ 181:488-493
13. Whiting P, Savović J, Higgins JP, Caldwell DM, Reeves BC, Shea B, Davies P, Kleijnen J, Churchill R (2016) ROBIS: a new tool to assess risk of bias in systematic reviews was developed. Journal of clinical epidemiology 69:225-234
14. Avelino-Silva TJ, Jaluul O (2017) Malnutrition in Hospitalized Older Patients: Management Strategies to Improve Patient Care and Clinical Outcomes. International Journal of Gerontology 11:56-61
15. Stroud M, Duncan H, Nightingale J (2003) Guidelines for enteral feeding in adult hospital patients. Gut 52:vii1
16. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539-1558
17. Veronese N, Notarnicola M, Osella A, et al. (2018) Menopause Does Not Affect Fatty Liver Severity In Women: A Population Study in a Mediterranean Area. Endocrine, metabolic & immune disorders drug targets
18. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629-634
19. Carvalho AF, Kohler CA, Brunoni AR, Miskowiak KW, Herrmann N, Lanctot KL, Hyphantis TN, Quevedo J, Fernandes BS, Berk M (2016) Bias in Peripheral Depression Biomarkers. Psychotherapy and psychosomatics 85:81-90
20. Ioannidis JP, Trikalinos TA (2007) An exploratory test for an excess of significant findings. Clin Trials 4:245-253
21. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P (2015) Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. International journal of evidence-based healthcare 13:132-140

22. Belbasis L, Savvidou MD, Kanu C, Evangelou E, Tzoulaki I (2016) Birth weight in relation to health and disease in later life: an umbrella review of systematic reviews and meta-analyses. BMC medicine 14:147
23. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP (2016) Environmental risk factors and Parkinson's disease: An umbrella review of meta-analyses. Parkinsonism & related disorders 23:1-9
24. Dinu M, Pagliai G, Casini A, Sofi F (2017) Mediterranean diet and multiple health outcomes: An umbrella review of meta-analyses of observational studies and randomized trials. Nutrition, Metabolism and Cardiovascular Diseases 27:e21
25. Kyrgiou M, Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, Martin-Hirsch P, Tsilidis KK (2017) Adiposity and cancer at major anatomical sites: umbrella review of the literature. Bmj 356:j477
26. Li X, Meng X, Timofeeva M, Tzoulaki I, Tsilidis KK, Ioannidis PA, Campbell H, Theodoratou E (2017) Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies. Bmj 357:j2376
27. Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JPA (2014) Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ : British Medical Journal 348:g2035
28. Veronese N, Solmi M, Caruso MG, Giannelli G, Osella AR, Evangelou E, Maggi S, Fontana L, Stubbs B, Tzoulaki I (2018) Dietary fiber and health outcomes: an umbrella review of systematic reviews and meta-analyses. The American journal of clinical nutrition 107:436-444
29. Machado MO, Veronese N, Sanches M, et al. (2018) The association of depression and all-cause and cause-specific mortality: An umbrella review of systematic reviews and meta-analyses. BMC medicine 16:
30. Veronese N, Demurtas J, Celotto S, et al. (2018) Is chocolate consumption associated with health outcomes? An umbrella review of systematic reviews and meta-analyses. Clinical Nutrition
31. Veronese N, Demurtas J, Pesolillo G, et al. (2019) Magnesium and health outcomes: an umbrella review of systematic reviews and meta-analyses of observational and intervention studies. European journal of nutrition
32. Köhler CA, Evangelou E, Stubbs B, et al. (2018) Mapping risk factors for depression across the lifespan: An umbrella review of evidence from meta-analyses and Mendelian randomization studies. Journal of psychiatric research 103:189-207
33. Smith L, Luchini C, Demurtas J, et al. (2019) Telomere length and health outcomes: An umbrella review of systematic reviews and meta-analyses of observational studies. Ageing research reviews 51:1-10
34. Iseli R, Nguyen VTV, Sharmin S, Reijnierse EM, Lim WK, Maier AB (2019) Orthostatic hypotension and cognition in older adults: A systematic review and meta-analysis. Experimental gerontology
35. Min M, Shi T, Sun C, Liang M, Zhang Y, Wu Y, Sun Y (2018) The association between orthostatic hypotension and dementia: A meta-analysis of prospective cohort studies. International journal of geriatric psychiatry 33:1541-1547
36. Mol A, Hoang PTSB, Sharmin S, Reijnierse EM, van Wezel RJ, Meskers CG, Maier AB (2018) Orthostatic hypotension and falls in older adults: a systematic review and meta-analysis. Journal of the American Medical Directors Association
37. Ricci F, Fedorowski A, Radico F, Romanello M, Tatasciore A, Di Nicola M, Zimarino M, De Caterina R (2015) Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. European heart journal 36:1609-1617
38. Xin W, Lin Z, Li X (2013) Orthostatic hypotension and the risk of congestive heart failure: a meta-analysis of prospective cohort studies. PloS one 8:e63169
39. Xin W, Lin Z, Mi S (2014) Orthostatic hypotension and mortality risk: a meta-analysis of cohort studies. Heart (British Cardiac Society) 100:406-413
40. Xin W, Mi S, Lin Z, Wang H, Wei W (2016) Orthostatic hypotension and the risk of incidental cardiovascular diseases: a meta-analysis of prospective cohort studies. Preventive medicine 85:90-97
41. Smit AA, Halliwill JR, Low PA, Wieling W (1999) Pathophysiological basis of orthostatic hypotension in autonomic failure. J Physiol 519 Pt 1:1-10
42. Mattace-Raso FU, van der Cammen TJ, Knetsch AM, van den Meiracker AH, Schalekamp MA, Hofman A, Witteman JC (2006) Arterial stiffness as the candidate underlying mechanism for postural blood

pressure changes and orthostatic hypotension in older adults: the Rotterdam Study. J Hypertens 24:339-344
43. Fedorowski A, Ostling G, Persson M, Struck J, Engstrom G, Nilsson PM, Hedblad B, Melander O (2012) Orthostatic blood pressure response, carotid intima-media thickness, and plasma fibrinogen in older nondiabetic adults. J Hypertens 30:522-529
44. Fan XH, Wang Y, Sun K, Zhang W, Wang H, Wu H, Zhang H, Zhou X, Hui R (2010) Disorders of orthostatic blood pressure response are associated with cardiovascular disease and target organ damage in hypertensive patients. Am J Hypertens 23:829-837
45. Pepersack T, Gilles C, Petrovic M, Spinnewine A, Baeyens H, Beyer I, Boland B, Dalleur O, De Lepeleire J, Even-Adin D, Van Nes MC, Samalea-Suarez A, Somers A; Working Group Clinical Pharmacology, Pharmacotherapy and Pharmaceutical Care; Belgian Society for Gerontology and Geriatrics (2013). Prevalence of orthostatic hypotension and relationship with drug use amongst older patients. Acta Clin Belg. 68:107-12.

46. Mager DR (2012) Orthostatic hypotension: pathophysiology, problems, and prevention. Home Healthc Nurse 30:525-530; quiz 530-522

47. Aoki M, Tanaka K, Wakaoka T, Kuze B, Hayashi H, Mizuta K, Ito Y (2013) The association between impaired perception of verticality and cerebral white matter lesions in the elderly patients with orthostatic hypotension. J Vestib Res 23:85-93
48. Humm AM, Bostock H, Troller R, Z'Graggen WJ (2011) Muscle ischaemia in patients with orthostatic hypotension assessed by velocity recovery cycles. J Neurol Neurosurg Psychiatry 82:1394-1398
49. Chisholm P, Anpalahan M (2017) Orthostatic hypotension: pathophysiology, assessment, treatment and the paradox of supine hypertension. Intern Med J 47:370-379
50. Elmstahl S, Rosen I (1997) Postural hypotension and EEG variables predict cognitive decline: results from a 5-year follow-up of healthy elderly women. Dement Geriatr Cogn Disord 8:180-187
51. Toyry JP, Kuikka JT, Lansimies EA (1997) Regional cerebral perfusion in cardiovascular reflex syncope. Eur J Nucl Med 24:215-218
52. Brown WR, Thore CR (2011) Review: cerebral microvascular pathology in ageing and neurodegeneration. Neuropathol Appl Neurobiol 37:56-74
53. Liu H, Zhang J (2012) Cerebral hypoperfusion and cognitive impairment: the pathogenic role of vascular oxidative stress. Int J Neurosci 122:494-499
54. Foster-Dingley JC, Moonen JEF, de Ruijter W, van der Mast RC, van der Grond J (2018) Orthostatic hypotension in older persons is not associated with cognitive functioning, features of cerebral damage or cerebral blood flow. J Hypertens 36:1201-1206
55. Flachenecker P, Wolf A, Krauser M, Hartung H-P, Reiners K (1999) Cardiovascular autonomic dysfunction in multiple sclerosis: correlation with orthostatic intolerance. Journal of neurology 246:578-586
56. Lim SY, Lang AE (2010) The nonmotor symptoms of Parkinson's disease--an overview. Mov Disord 25 Suppl 1:S123-130
57. Gaspar L, Kruzliak P, Komornikova A, et al. (2016) Orthostatic hypotension in diabetic patients-10-year follow-up study. J Diabetes Complications 30:67-71
58. Isik AT, Kocyigit SE, Smith L, Aydin AE, Soysal P (2019) A comparison of the prevalence of orthostatic hypotension between older patients with Alzheimer's Disease, Lewy body dementia, and without dementia. Experimental gerontology
59. Xin W, Lin Z, Mi S (2014) Orthostatic hypotension and mortality risk: a meta-analysis of cohort studies. Heart 100:406-413
60. Robertson D (2008) The pathophysiology and diagnosis of orthostatic hypotension. Clin Auton Res 18 Suppl 1:2-7
61. Sabbah HN (2012) Baroreflex activation for the treatment of heart failure. Curr Cardiol Rep 14:326-333
62. Schwartz PJ, La Rovere MT (1998) ATRAMI: a mark in the quest for the prognostic value of autonomic markers. Autonomic Tone and Reflexes After Myocardial Infarction. Eur Heart J 19:1593-1595

63. La Rovere MT, Bigger JT, Jr., Marcus FI, Mortara A, Schwartz PJ (1998) Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 351:478-484
64. Ioannidis JP (2016) The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses. The Milbank quarterly 94:485-514

Table 1. Evidence of the association between orthostatic hypotension

Outcome [reference]	N of studies	Cases	Sample size	Type of metric	Mean effect size (95% CI)	P	I^2	Small study effect	Excess significance bias	Largest study signifcant	95% prediction intervals	Level of evidence
CHD [40]	7	5719	158446	HR	1.32 (1.12-1.56)	0.001	65.4	no	yes	no	0.81-2.15	**III**
Stroke [40]	7	3657	158446	HR	1.22 (1.08-1.38)	0.002	20.2	no	yes	yes	0.95-1.57	**III**
Congestive HF[38]	4	3603	51270	HR	1.30 (1.09-1.55)	0.004	56.5	no	no	yes	0.66-2.56	**III**
All cause mortality [39]	10	NA	65174	RR	1.50 (1.24-1.81)	0.00004	93.4	no	NA	yes	0.75-3.00	**III**
Falls [36]	15	2185	6323	OR	1.84 (1.39-2.44)	0.00002	73.2	yes	yes	no	0.68-5.01	**III**
Dementia [34]	4	NA	41972	HR	1.22 (1.11-1.35)	0.00009	0	no	NA	no	0.98-1.53	**III**
Alzheimer[34]	2	NA	12977	HR	1.18 (1.02-1.35)	0.02	0	NA	NA	no	NA	**IV**
Vascular dementia[34]	3	NA	30469	HR	1.40 (1.04-1.89)	0.03	0	no	NA	no	0.20-9.66	**IV**
MMSE[34]	4	NA	3966	MD	-0.347 (-0.560 to -0.134)	0.001	23	no	NA	yes	-1.01 to 0.31	**IV**
MCI[34]	5	NA	12969	OR	1.20 (1.001-1.43)	0.048	58.9	no	NA	no	0.71-2.01	**IV**
CV mortality[37]	3	NA	51013	RR	1.20 (0.73-2.00)	0.47	91.7	no	NA	no	0-655.7	**NS**
Non CV mortality[37]	3	NA	51013	RR	1.20 (0.96-1.50)	0.11	38.6	no	NA	yes	0.14-9.93	**NS**

Abbreviations: CHD: Congenital Heart Disease; CV: Cardiovascular; HF: Heart Failure; HR: Hazard Ratio; MCI: Mild Cognitive Impairment; MD: mean diffefence; MMSE: Mini Mental State Examination; NA: Not-Applicable; OR: Odd ratios, RR: Relative Risk

Supplementary Table 1. Example of search strategy made in Medline

#	Searches	Results
1	Orthostatic hypotension/	5481
2	Orthostatic hypotension.kw,tw.	4934
3	Orthostatic dysregulat*.kw,tw.	147
4	Postural hypotension.kw,tw.	1426
5	Positional hypotension.kw,tw.	2
6	Orthostasis.kw,tw.	998
7	Orthostatic.kw,tw.	11097
8	Meta-Analysis/	100440
9	Meta-Analy*.kw,tw.	146772
10	meta$analy*.kw,tw.	1977
11	Systematic Review/	105413
12	Systematic review.kw,tw.	129246
13	or/1-7	14638
14	or/8-12	246974
15	13 and 14	130

Supplementary Table 2. Criteria used for assessing the evidence in this umbrella review.

Evidence classification	Criteria
Convincing (class I)	Associations with $p < 0.000001$; >1,000 cases (or >20 000 participants for continuous outcomes) having the event of interest; the largest component study reporting a nominal statistically significant result ($p < 0.05$); a 95% PI that excluded the null; no large heterogeneity (I^2 <50%); no evidence of small-study effect ($p > 0.10$); no excess significance bias ($p > 0.10$).
Highly suggestive (class II)	Associations with $P < 0.000001$; >1000 cases (or >20 000 participants for continuous outcomes) having the event of interest; the largest component study reporting a statistically significant result ($p < 0.05$).
Suggestive (class III)	Associations with $P < 0.001$; >1000 cases (or >20 000 participants for continuous outcomes) having the event of interest
Weak (class IV)	Remaining statistically significant associations with $P < 0.05$.

Supplementary Table 3. ROBIS quality assessment of the included meta-analysis

Studies	Phase 2				Phase 3
	Study Eligibility Criteria	Identification And Selection Of Studies	Data Collection And Study Appraisal	Synthesis And Findings	Risk Of Bias In The Review
Xin 2016	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Xin 2014	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Xin 2013	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Ricci 2015	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Mol 2019	LOW RISK	LOW RISK	LOW RISK	UNCLEAR RISK	LOW RISK
Min 2018	HIGH RISK	HIGH RISK	LOW RISK	HIGH RISK	HIGH RISK
Iseli 2019	HIGH RISK	HIGH RISK	LOW RISK	HIGH RISK	HIGH RISK

Supplementary Table 4. The main results of the primary studies of each included meta-analysis

Authors, year	Single study	Year	Outcome	Type of metric	Summary effect size	Lower 95 CI	Higher 95 CI	N_Cases	N_Controls	Follow up (year)
Xin, 2016	ARIC	2000	CHD	HR	1,85	1,31	2,62	346	12087	7,9
	Rotterdam	2008	CHD	HR	1,2	1	1,45	668	4396	6,7
	Malmo	2010	CHD	HR	1,18	1,05	1,33	3849	28948	22,7
	Guangzhou	2011	CHD	HR	2,76	1,68	4,54	75	1099	1,1
	CHS	2013	CHD	HR	1,2	0,96	1,5	386	3124	13
	LEOGRA	2013	CHD	HR	1,25	0,83	1,88	145	871	8,4
	CAPPP	2013	CHD	HR	1	0,7	1,44	250	8538	6
Xin, 2016	ARIC	2000	Stroke	HR	2	1,24	3,23	178	12255	7,9
	Rotterdam	2008	Stroke	HR	1,1	1,89	1,36	503	4561	6,7
	Malmo	2010	Stroke	HR	1,11	0,95	1,3	2134	30663	22,7
	Guangzhou	2011	Stroke	HR	1,09	0,51	2,33	27	1147	1,1
	CHS	2013	Stroke	HR	1,18	0,97	1,44	477	3033	13
	LEOGRA	2013	Stroke	HR	1,33	0,8	2,22	93	923	8,4
	CAPPP	2013	Stroke	HR	1,48	1,07	2,05	245	8543	6
Xin,2014	Verwoert	2008	CV mortality	RR	0,81	0,54	1,22	NA	NA	7,8
	Fedorowski	2011	CV mortality	RR	1,02	0,89	1,17	NA	NA	22,7
	Rose	2006	CV mortality	RR	2,04	1,57	2,66	NA	NA	13
Xin, 2014	Verwoert	2008	Non CV mortality	RR	1,02	0,81	1,28	NA	NA	7,8
	Fedorowski	2011	Non CV mortality	RR	1,32	1,04	1,68	NA	NA	22,7
	Rose	2006	Non CV mortality	RR	1,57	0,86	2,88	NA	NA	13
Xin, 2013	Verwoert	2008	Congestive HF	HR	1,12	0,92	1,36	571	4493	6,6
	Fedorowski	2010	Congestive HF	HR	1,22	1,01	1,47	1293	31376	24
	Lin	2011	Congestive HF	HR	1,73	0,66	4,54	19	1155	1
	Jones	2012	Congestive HF	HR	1,54	1,3	1,82	1720	10643	17,5
Ricci, 2015	Sasaki	2005	All cause mortality	RR	2,02	1,57	2,62	136	168	4
	Rose	2006	All cause mortality	RR	2,72	2,42	3,07	1693	11459	13

	Cohen	2006	All cause mortality	RR	1,56	1,01	2,4	81	733	1
	Fedorowski	2011	All cause mortality	RR	1,43	1,34	1,54	7145	24923	24
	Fedorowski	2013	All cause mortality	RR	1,37	1	1,87	279	8509	6
	Raiha	1995	All cause mortality	RR	0,99	0,78	1,25	184	163	10
	Masaki	1998	All cause mortality	RR	1,67	1,29	2,15	473	3049	4
	Hossain	2001	All cause mortality	RR	1,28	0,95	1,74	134	539	0,7
	Weiss	2006	All cause mortality	RR	0,96	0,8	1,16	249	222	3,5
	Verwoert	2008	All cause mortality	RR	1,57	1,45	1,69	1835	3229	6,8
Mol, 2019	Campbell	1989	Falls	OR	3,4	2,44	4,75	507	254	1
	Chen	2009	Falls	OR	4,94	1,4	17,46	NA	NA	NA
	Coutaz	2012	Falls	OR	1,29	0,83	1,99	146	194	0,5
	Gangavati	2011	Falls	OR	1,46	0,83	2,58	203	519	1
	Gaxatte	2017	Falls	OR	1,8	1,19	2,71	205	628	0,5
	Graafmans	1996	Falls	OR	2,85	1,69	4,82	126	228	0,5
	Gray	2000	Falls	OR	2,96	0,91	9,57	70	48	0,25
	Hartog	2015	Falls	OR	0,95	0,52	1,73	59	231	1
	Kerr	2010	Falls	OR	7,57	1,11	51,83	49	52	0,5
	McDonald	2016	Falls	OR	4,89	1,57	15,24	30	49	1
	Menant	2016	Falls	OR	1,02	0,67	1,53	238	291	1
	Ooi	2000	Falls	OR	1,22	0,89	1,66	219	625	1,2
	Passant	1997	Falls	OR	2,72	1,37	5,42	54	97	NA
	Van Helden	2007	Falls	OR	1,98	0,82	4,76	42	235	0,25
	Wong	2013	Falls	OR	1,06	0,7	1,6	237	283	1
Min, 2018	Cremer	2017	Dementia	HR	1,23	1,01	1,51	760	6013	7,5
	Wolters	2016	Dementia	HR	1,15	1	1,34	1176	5028	15,3
	Rawlings	2017	Dementia	HR	1,4	1,13	1,73	1044	10459	22
	Holm	2017	Dementia	HR	1,18	0,73	1,89	428	17064	28+/-4
Min, 2018	Wolters	2016	Alzheimer's Disease	HR	1,17	0,99	1,37	935	5269	15,3

	Cremer	2017	Alzheimer's Disease	HR	1,19	0,91	1,57	512	6261	7,5
Min,2018	Wolters	2016	Vascular dementia	HR	1,2	0,73	1,96	95	6109	15,3
	Holm	2017	Vascular dementia	HR	1,99	0,91	4,35	96	17396	28+/-4
	Cremer	2017	Vascular dementia	HR	1,42	0,92	2,15	151	6622	7,5
Iseli,2019	Curreri	2016	MMSE	MD	-0,2	-0,444	-0,044	138	1270	4.4±1.2
	Enrique	2011	MMSE	MD	-0,6	-3,476	2,276	NA	NA	NA
	Huang	2017	MMSE	MD	-0,4	-0,823	0,023	NA	NA	NA
	Yap	2008	MMSE	MD	-0,6	-0,958	-0,242	1347	947	NA
Iseli, 2019	Curreri	2016	MCI	OR	1,32	1,192	1,462	NA	NA	4.4±1.2
	Elmstahl	2014	MCI	OR	1,23	0,751	2,014	123	2808	6
	Huang	2017	MCI	OR	4,05	1,143	14,354	16	116	4
	Wolters	2016	MCI	OR	1,15	0,992	1,333	NA	NA	NA
	Yap	2008	MCI	OR	0,87	0,613	1,235	NA	NA	NA

Abbreviations:

CHD: Congenital Heart Disease; CV: Cardiovascular; HF: Heart Failure; HR: Hazard Ratio; MCI: Mild Cognitive Impairment; MD: mean diffefence; MMSE: Mini Mental State Examination; NA: Not-Applicable; OR: Odd ratios, RR: Relative Risk

Supplementary Table 5. Excluded studies with reason

Reference	Reason for exclusion
1. Briggs, R.; Kenny, R. A.; Kennelly, S. P.Systematic Review: The Association between Late Life Depression and Hypotension Journal of the American Medical Directors Association 12 01 2016;17(12):1076-1088 2. Fereshtehnejad, S. M.; Lökk, J. Orthostatic hypotension in patients with Parkinson's disease and atypical parkinsonism. Parkinson's disease, 2014;2014:475854 3. Lee, Y.Orthostatic hypotension in older people Journal of the American Association of Nurse Practitioners, 2013;25(9):451-8 4. Mol, A.; Reijnierse, E. M.; Bui Hoang, P. T. S.; van Wezel, R. J. A.; Meskers, C. G. M.; Maier, A. B.Orthostatic hypotension and physical functioning in older adults: A systematic review and meta-analysis Ageing Research Reviews Dec 2018;48:122-144 5. Ometto, F.; Stubbs, B.; Annweiler, C.; Duval, G. T.; Jang, W.; Kim, H. T.; McCarroll, K.; Cunningham, C.; Soysal, P.; Isik, A. T.; Luchini, C.; Solmi, M.; Sergi, G.; Manzato, E.; Veronese, N. Hypovitaminosis D and orthostatic hypotension: a systematic review and meta-analysis. Journal of Hypertension 06 2016;34(6):1036-43 6. Pepersack, T.; Gilles, C.; Petrovic, M.; Spinnewine, A.; Baeyens, H.; Beyer, I.; Boland, B.; Dalleur, O.; De Lepeleire, J.; Even-Adin, D.; Van Nes, M. C.; Samalea-Suarez, A.; Somers, A. Prevalence of orthostatic hypotension and relationship with drug use amongst older patients. Acta Clinica Belgica March-April 2013;68(2):107-112 7. Saedon, N. I.; Tan, M. P.; Frith, J.The prevalence of orthostatic hypotension: a systematic review and meta-analysis Journals of Gerontology Series A Biological Sciences & Medical Sciences Aug 29 2018;29 8. Velseboer, D. C.; de Haan, R. J.; Wieling, W.; Goldstein, D. S.; de Bie, R. M. Prevalence of orthostatic hypotension in Parkinson's disease: a systematic review and meta-analysis Parkinsonism & Related Disorders Dec 2011;17(10):724-9 9. Zhou, Y.; Ke, S. J.; Qiu, X. P.; Liu, L. B. Prevalence, risk factors, and prognosis of orthostatic hypotension in diabetic patients: A systematic review and meta-analysis.Medicine Sep 2017;96(36):e8004 10. Udow, S. J.; Robertson, A. D.; Macintosh, B. J.; Espay, A. J.; Rowe, J. B.; Lang, A. E.; Masellis, M. 'Under pressure': Is there a link between orthostatic hypotension and cognitive impairment in alpha-synucleinopathies? Journal of Neurology, Neurosurgery and Psychiatry 01 Dec 2016;87(12):1311-1321	Wrong study design
1. Jansen, S.; Bhangu, J.; de Rooij, S.; Daams, J.; Kenny, R. A.; van der Velde, N. The Association of Cardiovascular Disorders and Falls: A Systematic Review Journal of the American Medical Directors Association Mar 01 2016;17(3):193-9 2. McCarthy, F.; Fan, C. W.; Kearney, P. M.; Walsh, C.; Kenny, R. A.What is the evidence for cardiovascular disorders as a risk factor for non-syncopal falls? Scope for future research European Geriatric Medicine September 2010;1(4):244-251	Wrong patient population
1. Velseboer, D. C.; De Haan, R. J.; Wieling, W.; Goldstein, D. S.; De Bie, R. M. Prevalence of orthostatic hypotension in Parkinson's disease: A systematic review and meta-analysis. Movement Disorders May 2011: S56-S57 2. Udow, S. J.; Lang, A. E.; Masellis, M. Association or causation? Orthostatic hypotension and cognitive impairment in alpha-synucleinopathies: A systematic review. Movement Disorders June 2016;31 (Supplement 2):S452	Poster abstract
1. Ricci, F.; Radico, F.; Romanello, M.; Tatasciore, A.; Di Nicola, M.; Zimarino, M.; De Caterina, R. Morbidity and mortality related to orthostatic hypotension: Results of a meta-analysis of non-randomized observational studies European Heart Journal August 2013;1)():817	Abstract

Figure 1. Prisma Flow Diagram