**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](#_ENREF_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](#_ENREF_2)]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](#_ENREF_5)]

A number of studies have reported associations between OH and increased risk of adverse clinical outcomes, including cardiovascular events and stroke [[6](#_ENREF_6)], recurrent falls syncope and consequent injuries [[7](#_ENREF_7)], cognitive impairment [[8](#_ENREF_8)], impaired sleep quality [[9](#_ENREF_9)], and depression.[[10](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_13)]

***Statistical analysis***

For each meta-analysis, we re-calculated the summary effect size and its 95% CI, using random-effects models.[[14](#_ENREF_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](#_ENREF_15)] For the largest study of each meta-analysis, we evaluated whether this was statistically significant. Heterogeneity was estimated using the *I2* metric, with values > 50% indicative of high heterogeneity, and values > 75% suggesting very high heterogeneity. [[16](#_ENREF_16), [17](#_ENREF_17)] In addition, we calculated the evidence of small-study effects. In this regard, we used the regression asymmetry test [[18](#_ENREF_18)], using a p-value < 0.10. [[19](#_ENREF_19)] Finally, we applied the excess of significance test [[20](#_ENREF_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 χ2-based test. [[20](#_ENREF_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](#_ENREF_21)] 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](#_ENREF_34)], 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 I2 > 50% and, of them, 2 reported a very high heterogeneity (I2> 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](#_ENREF_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](#_ENREF_42)] and activated systematic inflammation[[43](#_ENREF_43)], which have both been involved in the pathogenesis of subclinical atherosclerosis, leading to cardiovascular disease. [[43](#_ENREF_43), [44](#_ENREF_44)] Xin et al in their analysis [[38](#_ENREF_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](#_ENREF_46)] Alternatively, OH might cause brain atrophy, microbleeds, and white matter brain lesions, resulting in falls.[[47](#_ENREF_47)] OH might also cause falls through impaired muscle microcirculation, as one study found an association of OH with muscle ischemia.[[48](#_ENREF_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](#_ENREF_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](#_ENREF_50)] Previous research has shown that cerebral blood flow is decreased in OH by electroencephalography[[50](#_ENREF_50)], besides decreased brain perfusion during orthostatic pressure was demonstrated by the method of single‐photon emission computed tomography. [[51](#_ENREF_51)] Cerebral hypoperfusion may lead to leukoaraiosis underlying the neurodegeneration process in dementia.[[52](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_55)] Some pathologies such as diabetes, alpha‐synucleinopathies, and sarcoidosis are common causes for autonomic neuropathy, and OH is prevalent among these diseases.[[56](#_ENREF_56), [57](#_ENREF_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](#_ENREF_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](#_ENREF_43), [44](#_ENREF_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](#_ENREF_5)] Baroreflex dysfunction, a marker of Autonomic nervous system imbalance implicated in the pathogenesis of OH[[59](#_ENREF_59), [60](#_ENREF_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](#_ENREF_61)]

**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 (I2<50%) was used as one of the criteria for having convincing outcomes, even if the use of the same I2 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](#_ENREF_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.

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**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** | **I2** | **Small study effect** | **Excess significance bias** | **Largest study signifcant** | **95% prediction intervals** | **Level of evidence** |
| CHD [[40](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_34)] | 4 | NA | 41972 | HR | 1.22(1.11-1.35) | 0.00009 | 0 | no | NA | no | 0.98-1.53 | **III** |
| Alzheimer[[34](#_ENREF_34)] | 2 | NA | 12977 | HR | 1.18(1.02-1.35) | 0.02 | 0 | NA | NA | no | NA | **IV** |
| Vascular dementia[[34](#_ENREF_34)] | 3 | NA | 30469 | HR | 1.40(1.04-1.89) | 0.03 | 0 | no | NA | no | 0.20-9.66 | **IV** |
| MMSE[[34](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](http://hypotension.kw/),tw. | 4934 |
| 3 | Orthostatic dysregulat\*.kw,tw. | 147 |
| 4 | Postural [hypotension.kw](http://hypotension.kw/),tw. | 1426 |
| 5 | Positional [hypotension.kw](http://hypotension.kw/%22%20%5Ct%20%22_blank),tw. | 2 |
| 6 | Orth[ostasis.kw](http://ostasis.kw/%22%20%5Ct%20%22_blank),tw. | 998 |
| 7 | Orth[ostatic.kw](http://ostatic.kw/%22%20%5Ct%20%22_blank),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](http://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 statisticallysignificant result (p < 0.05); a 95% PI that excluded the null; no large heterogeneity (I2 <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 statisticallysignificant 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**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
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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
 | **Reason for exclusion** |
| --- | --- |
| 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**

**Identification**

Records identified through database searching in PubMed, PsychInfo, Embase
(n = 982)

Duplicates were identified and removed
(n = 7)

Records screened
(n = 975)

Records after duplicates were removed
(n = 975)

**Screening**

Records excluded based on title/abstract
(n =953)

Publications excluded (n =15)

***11****Wrong study design*

***2****Wrong patient population*

***1****Abstract*

***2****Poster abstract*

**Eligibility**

Full-text articles assessed for eligibility
(n =22)

Meta-analyses included in umbrella review
(n = 7)

*12 outcomes*

**Included**