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Orthostatic hypotension and symptomatic sub-clinical orthostatic hypotension increase risk of cognitive impairment. An integrated evidence review and analysis of a large older adult hypertensive cohort.

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Short title: Orthostatic fall and cognitive decline

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Abstract

Aims

Systematically reviewing the literature found Orthostatic Hypotension (OH) to be associated with an increased risk of incident dementia but limited data were available in those at highest risk, the hypertensive oldest-old. Our aim was to analyse the relationship between OH and incident cognitive decline or dementia in this group and to synthesize the evidence base overall.

Method and results

Participants aged≥ 80 years, with hypertension, were from the Hypertension in the Very Elderly Trial (HYVET) cohort. OH was defined as a fall of >=15mmHg in systolic and or >=7mmHg in diastolic pressure after two minutes standing from a sitting position. Subclinical orthostatic fall with symptoms (SOH) was defined as a fall<OH but with unsteadiness, light-headedness or faintness in the week before blood pressure measurement. Proportional hazard regression was used to examine the relationship between baseline OH, SOH and cognitive outcomes. There were 3121 in the analytical sample, 538 with OH. OH was associated with increased risk of cognitive decline (906 events) Hazard Ratio(HR)1.36 (95%Confidence Interval 1.14:1.59). For incident dementia (241 events) HR1.34(0.98:1.84). When competing risk of cardiovascular events were taken into account results were HR1.39(1.19:1.62) and HR1.34 (1.05:1.73) respectively. SOH was associated with an increased risk of cognitive decline HR1.56(1.12:2.17) and dementia HR1.79(1.00:3.20). Combining the results from the HYVET cohort in a meta-analysis with the existing published literature in this area found a 21%(9%:35%) increased risk of dementia with OH.

Conclusion

OH indicates an increased risk of dementia and cognitive decline. SOH may also be considered a risk factor, at least in older hypertensive adults. Questions remain regarding the mechanisms and whether interventions to reduce impact of OH could protect cognition.

Keywords

Dementia Cognitive decline

Orthostatic hypotension Hypertension

Older adult

Introduction

Orthostatic hypotension (OH) is a relatively common autonomic failing and is often associated with functional impairment (1). It is commonly defined as a fall in systolic Blood Pressure (BP) of at least 20mmHg and /or a fall of at least 10 mmHg in diastolic BP within 3 minutes of standing,

Older adults are at increased risk of OH due to impaired compensatory mechanisms including decreased baroreceptor (pressure) sensitivity, increased arterial stiffness and reduced parasympathetic tone (2,3). OH is likely to be a risk factor for a variety of negative health consequences, including cardiovascular events, falls, mortality and poor cognition. This is particularly relevant in older adults where hypertension is prevalent and where levels of frailty and comorbidity may also be high (1-3). In 2014 a systematic review found OH to be associated with an increased risk of cardiovascular events (4). The evidence for an association between OH and cognitive decline in the same systematic review was equivocal. The review found only two eligible studies; one reported no relationship between OH and cognitive outcomes (5) and one other reported an increased risk of cognitive decline with OH (6). There remains a lack of high quality evidence, and remaining uncertainty, relating to the association between OH and cognitive decline or dementia.

A link between OH and increased risk of cognitive decline is plausible, either directly via variable cerebral perfusion or via increased cardiovascular risk, clinical or subclinical ischaemic events, or, via failing homeostatic mechanisms associated with both OH and cognitive decline (7). This is also particularly relevant to older adults and those with hypertension in whom cerebral auto-regulatory mechanisms may be less able to adapt (1). With an ageing population and an increased risk of cardiovascular, and cognitive, outcomes associated with increasing age alongside recent work on the role of OH (1-4,7) it is timely to evaluate OH as a predictor for cognitive decline and dementia. To give an updated and unbiased background overview of the current evidence we used systematic methods to review the literature relating to OH as a risk factor for incident cognitive decline and dementia. See supplementary figure 1 and text file 1 for details. Briefly, 21 longitudinal studies on the relationship between orthostatic hypotension and incident cognitive decline or incident dementia were found (5,6,9-27) including populations from Sweden (22 23), Italy(24), the Netherlands (25), Singapore (6) , the United States (26) and France (27). See supplementary tables 1, 2. Study sample mean age ranged from mid (23,26) to late-life (6,24,25,27,33) and follow-up from ~1-28 years (6,23- 27,33).

Three studies reported presence of OH was associated with an increased risk of dementia (22,

25, 27). One study found no relationship between baseline OH and dementia (23), one found no relationship between OH and cognitive decline (26). Two found no association between OH and risk of a fall in cognitive screening score (6,24). Study quality was adequate although details were often lacking, see supplemental table 3.

Overall, evidence suggests that a diagnosis of OH may be associated with a subsequent increased risk of dementia. However, there are no data available on those at highest risk of hypertension, OH and cognitive decline or dementia (the oldest old). Furthermore, few studies have investigated the relationship between the magnitude of the orthostatic fall and the degree of risk (i.e. the potential dose response), or the possible influence of 'sub-clinical' orthostatic fall. A greater understanding of relationship between orthostatic fall and cognitive outcome in older adults is essential to be able to identify those at risk of cognitive decline or dementia and to provide appropriate clinical support.

Our aim was to examine the relationship between orthostatic fall and subsequent cognitive decline or dementia in an older adult hypertensive population using data collected as part of the Hypertension in the Very Elderly Trial and to combine our results with the existing evidence base using meta-analysis.

Methods

HYVET was a double blind placebo controlled trial of an antihypertensive regimen (thiazide-like diuretic, indapamide 1.5 sustained release, with the optional addition of an angiotensin converting enzyme inhibitor, perindopril 2-4mg) in those aged 80 and over. Participants with hypertension were recruited from over 90 primary and secondary care centres in 13 countries and randomised to receive trial treatment or matching placebo. All required ethical approvals were obtained. Participants were seen during a two-month placebo run-in phase, at baseline, every three months during the first year and every six months thereafter. Cognitive function was assessed at baseline and annually thereafter using the Mini-Mental State Exam (MMSE). A reduction in MMSE score to below 24 or by more than three points in twelve months was classified as cognitive decline and triggered a dementia assessment. Dementia was diagnosed in accordance with the Diagnostic Statistical Manual IV (DSMIV). Dementia was classified as present or absent. An independent expert dementia committee blind to trial treatment allocation had access to all data and reviewed and validated all dementia endpoints. Other trial endpoints were reported as they occurred and included death, stroke, myocardial infarction and incident or worsening heart failure. Validation of trial endpoints was carried out by a trial endpoint committee of international experts blinded to trial treatment allocation and with full access to supporting documentation, for example, death certificates, hospitalisation reports etc:

To collect data on self-reported symptom burden HYVET trial participants were also asked to self-complete a symptom questionnaire at baseline and annually thereafter. This questionnaire was based on the Bulpitt and Fletcher questionnaire and included a list of symptoms relevant to hypertension and its treatment (28). Participants were asked to rate the level to which they had been affected by a symptom over the last week. The symptoms light-headedness, unsteadiness and faintness were selected as relevant to orthostatic drop.

The full details of the HYVET protocol have been published elsewhere (29,30). In brief, to enter the HYVET trial participants were required to be aged 80 or over at randomisation, to have no clinical diagnosis of dementia, a mean systolic BP 160 to 199mm Hg and a standing systolic BP ≥140mm Hg. The sitting BP was taken twice after sitting for five minutes and the standing BP taken twice after standing for two minutes. At study baseline BP was measured using a mercury sphygmomanometer. As supine BP was unavailable OH was calculated

based on a fall of >=15mmHg systolic BP and or a fall of >=7mmHg diastolic BP from sitting to standing (31, 32). A novel category of subclinical orthostatic fall with recent symptoms (SOH) was also created. SOH was defined as any fall in systolic BP of <15mmHg on standing and any fall in diastolic BP of <7mmHg on standing plus symptoms of light-headedness and or unsteadiness and or faintness reported by the participant as having bothered them 'a lot' or 'extremely' during the preceding week. The SOH category was adapted from the orthostatic intolerance definition used by Elmståhl et al (22) and intended to examine a potential subclinical population (3).

Statistical Methods

The analytical data set consisted of HYVET trial participants who had at least one repeated assessment of cognitive function (allowing evaluation of cognitive decline), complete baseline BP measurements and, in accordance with the literature (6,22,25) were without prior stroke. OH was classified as present or absent at baseline.

The difference in baseline characteristics between those who were included in the analytical sample and those who were excluded, and between those with and without OH, was assessed using Chi squared and Wilcoxon tests, as appropriate. Proportional hazard (Cox) regression was used to assess the relationship between those classified as having OH and subsequent cognitive decline or incident dementia. Time to event was calculated from trial entry (the date of first cognitive and blood pressure measure) to the earliest date of event, date of death or date of last follow up. The date of the study visit where cognitive decline was identified was taken as the date of event for cognitive decline. The date that cognitive decline was identified was also used for date of dementia where further testing confirmed dementia diagnosis. This is a pragmatic choice since the time interval between the visit where cognitive decline was identified and the subsequent examination to verify diagnosis of dementia varied and as the onset of dementia is an insidious process. Models were stratified (by age (80-84, >=85), sex and education) and adjusted for key cardiovascular and cognitive risk factors (baseline sitting systolic and diastolic BP, trial treatment (antihypertensive or placebo) and presence of diabetes). Proportional hazard assumptions were checked using Grambsch and Therneau tests (33). Overall model fit was assessed visually by plotting the Nelson-Aalen cumulative hazard function against the Cox-Snell residuals. Analyses carried out using SAS 9.3, Stata and Statsdirect 3.

The incidence of mortality, cardiovascular events (myocardial infarction, stroke or heart failure), cognitive decline and/or dementia may be interrelated or may all be considered manifestations of the same cardiovascular disease process. We therefore performed two further Cox regression analyses, each using a composite endpoint combining cognitive and cardiovascular events in a time to first event model to give greater statistical power and a more holistic outcome measure. In the first, incident dementia or fatal and non-fatal cardiovascular events (heart failure, myocardial infarction, stroke) were defined as an event and in the second, incident cognitive decline and fatal and non-fatal cardiovascular events (heart failure, myocardial infarction, stroke) were defined as an event.

Additional analyses were performed with adjustment for incident OH occurring during study follow-up; and, because blood pressure variability may increase the risk of both OH and cognitive decline, analyses were rerun with additional adjustment for visit to visit variability calculated as the standard deviation of the sitting systolic BP values.

Further analyses in the subset of participants who also had symptom data (i.e. had completed the symptom questionnaire) allowed comparison of those with OH, SOH and neither. The baseline characteristics of these three groups were compared using chi squared and analysis of variance tests for categorical and continuous variables, as appropriate. Pairwise differences were investigated post-hoc using the Tukey-Kramer (equal variances) or W test (unequal variances) for continuous variables and by inspection of the adjusted chi-squared residuals for categorical variables.

Proportional hazards (Cox) regression was used to assess the relationship between orthostatic status and subsequent cognitive decline or incident dementia with orthostatic status categorised as a 3-level variable (OH, SOH or neither (reference group)). There were no missing data for the exposure, outcome or confounding variables used in the analyses.

Sensitivity analyses

The Cox regression analysis was repeated: (i) in those with baseline MMSE >26 (those scoring above 26 at baseline are considered unlikely to have pre-existing cognitive decline, the selection of this population therefore allowed us to rerun the analyses with less risk of including undiagnosed dementia cases.); (ii) for systolic and diastolic OH separately; (iii) for

continuous BP fall and risk of subsequent cognitive decline or incident dementia; (iv) using the traditional and more severe classification of OH (a fall of >20mmHg systolic and or >10mmHg diastolic);

Finally, the association between baseline OH and subsequent attrition (mortality or drop out) was examined in the analytical sample and inverse probability weighting used to evaluate potential bias stemming from including only those with data on cognitive decline and without stroke.

Meta-analysis

Where possible the results from the HYVET analyses were combined with the existing evidence base was combined with using meta-analytical techniques.

Results

Study population

There were 3845 participants randomised into the HYVET trial with a mean follow up of 2.0 years. Of those, 508 were excluded from the analysis because they had no cognitive follow-up assessment and a further 216 due to prior stroke. The analytical sample therefore included 3121 with data on OH and outcome. The subset of those with symptom data and in whom SOH could be calculated contained 2109 participants. (See supplementary Figure 2 for details).

Orthostatic hypotension (OH)

Characteristics of the sample (OH)

There were 538 participants with OH and 2583 without. Those with OH had higher sitting systolic BP (P<0.0001) and lower standing systolic (P<0.0001) and diastolic pressure (P<0.0001) as would be expected. There were also older (P=0.004), They also had a lower mean MMSE score at baseline (P=0.0003), shorter follow-up (P<0.0001) and a higher percentage of this group were classified as having incident cognitive decline (P<0.0001) (see Table 1 for details).

Table 1 here

Proportional hazard regression (OH)

The estimates of the hazard ratios from the Cox regression models for the association between baseline OH and risk of cognitive decline (Hazard Ratio (HR) 1.36 (1.15:1.59)), and between baseline OH and development of dementia (HR1.34 (0.98:1.84)), were similar. (Table 2). There was little change in the estimates of hazard ratios when composite endpoints combining cognitive and cardiovascular outcomes were used, HR1.39 (1.19:1.62) for cognitive decline and cardiovascular events, and HR1.34 (1.05:1.72) for dementia and cardiovascular events. There was no relationship between OH and mortality or cardiovascular events alone. Further adjustment for blood pressure variability did not change the direction, magnitude or significance of the results.

There were 315 incident OH cases occurring during study follow-up n=169 (5.6/100 patient years of follow-up) in the placebo and n=146 (4.5/100 patient years) in the actively treated

group. Additional adjustment for incident OH resulted in the relationship between OH and incident dementia reaching statistical significance.

Further sensitivity analyses rerunning fully adjusted models in those with baseline MMSE scores >26 (n=1648) resulted in a similar pattern of results and statistical significance as seen when analysing the whole cohort. The only difference was a loss of statistical significance for one analysis, the relationship between OH alone and cognitive decline.

Table 2 here

Subclinical orthostatic fall with recent symptoms (SOH) and orthostatic hypotension (OH)

Characteristics of the sample (SOH, OH)

In the subset of those for whom symptom data were available (n=2109) 105 reported SOH, 381 OH and 1623 neither. The baseline characteristics of the three groups are summarised in Supplementary Table 4.

When examining the participants with both cognitive and symptom data there were 105 with subclinical orthostatic fall and positive symptoms, seven with symptoms but neither subclinical nor clinical orthostatic fall and four with symptoms and clinical fall. There are significant differences in the majority of measures between these groups at baseline (all except sitting systolic BP) but there is no consistent suggestion of a linear trend and the only clinically significant differences were between those without any orthostatic fall and those with OH.

Proportional hazard regression (SOH, OH)

The estimates of HRs from the Cox regression models are shown with the associated 95% confidence intervals in Table 3 and Figure 1. Both SOH and OH were associated with an increased risk of cognitive decline. For SOH, HR1.56 (95%CI 1.12:2.17) and for OH HR1.40 (95%CI 1.15:1.69). For cognitive decline and cardiovascular events the results were SOH, HR1.51 (95% CI 1.11:2.06) and OH, HR1.43 (95% CI 1.20:1.72), respectively). SOH was also associated with an increased risk of dementia HR1.79 (95% CI 1.00:3.20) and dementia and cardiovascular events HR1.79 (95%CI 1.15:2.78).

Further adjustment for blood pressure variability did not change the direction, magnitude or significance of the results. Additional adjustment for incident OH resulted in the relationship

between OH and the composite endpoint, incident dementia with cardiovascular, events reaching statistical significance.

Further sensitivity analyses rerunning fully adjusted models in those with baseline MMSE scores >26 and symptom data (n=914) resulted in a similar pattern of results but the association between OH and cognitive decline was no longer significant.
Additional analyses examining cardiovascular events and mortality alone found SOH to be associated with an increased risk of cardiovascular events HR2.28 (95% CI 1.25:4.14) and mortality HR2.97 (95% CI 1.76:5.01).

Figure 1 here. Table 3 here

Further examination of the role of symptoms (from the symptoms questionnaire) revealed that presence of self-reported light-headedness and or unsteadiness and or faintness alone (regardless of orthostatic fall) and experienced over the preceding week were not associated with incident cognitive decline or dementia. Rerunning the analysis without the inclusion of symptom data (i.e. SOH classified based on subclinical orthostatic fall alone) resulted in non-significant relationships between sub-clinical orthostatic fall and cognitive decline HR1.01 (0.82:1.24) and dementia HR 1.05(0.70:1.58).

Model fit was adequate in all cases and the proportional hazards assumption was not violated.

Sensitivity analyses

Systolic hypotension and diastolic hypotension.

The analyses were repeated with OH defined using systolic blood pressure fall, systolic OH (n=218) or diastolic blood pressure fall, diastolic OH (n=400) (Supplementary table 5). Diastolic OH was associated with an increased relative risk of; cognitive decline HR1.47 (1.23:1.75), dementia HR1.69 (1.22:2.34), cognitive decline and cardiovascular events HR1.49 (1.26:1.75) and dementia and cardiovascular events HR1.54 (1.18:2.00).There were no significant associations for systolic OH.

Repeating the analyses selecting only those with systolic OH but without diastolic OH (n=138) and diastolic OH without systolic OH (n=320) did not materially change the results.

Orthostatic fall

We investigated the relationship between magnitude of the orthostatic fall at baseline and risk of cognitive decline by repeating the Cox regression analysis with orthostatic fall as a continuous variable and for systolic and diastolic BP separately. On average there was a 26% increased relative risk of cognitive decline per 10mmHg increase (i.e. greater fall in BP) in orthostatic drop in diastolic BP HR1.26 (1.09:1.42). For systolic BP the results were HR1.04 (0.94:1.15) per 10mmHg increase.

Traditional and more severe classification of OH (a fall of >20mmHg systolic and or >10mmHg diastolic);

The Cox regression analysis was repeated using the classic, more conservative, definition of OH (see methods section) and the results presented in Supplementary Table 6. Orthostatic hypotension was associated with an estimated 49% increased relative risk of developing cognitive decline HR=1.49 (95%CI 1.16 to 1.90). This did not change markedly when cognitive decline and cardiovascular events were combined.

Attrition and inverse probability weighting:

There was no association between OH and subsequent drop out or death (events=650) OR0.86 (95% CI 0.67 to 1.10). Inverse probability weighting weighted by age, sex and baseline MMSE score found similarly positive associations between OH and incident cognitive decline (β0.078 (95%CI 0.045:0.130)) P<0.0001 and dementia (β0.027 (0.003:0.052)) P=0.034. This implies that the exclusion of those with prior stroke and without follow-up cognitive assessment did not bias the sample in such way as to materially affect the results.

Meta-analysis combining the results from the systematic review and HYVET study.

Summary data showing the relationship between presence or absence of OH and incident dementia was reported in the published literature for the Rotterdam Study (HR1.15 (95%CI 1.00:1.34)), the 3 City Study (HR 1.19 (95%CI0.98:1.46)), the Malmö study (HR 1.18 (0.73:1.89)), the Swedish Good Aging in Skåne Study (OR 1.93 (95%CI1.19:3.14)), and the HYVET study (HR 1.34 (95%CI 0.98:1.84)) (22,23,25,27).

The meta-analysis suggested that increased relative risk of dementia was associated with presence of OH. The pooled ratio was 1.21 (1.09:1.35) for fixed effects analysis. See supplementary analyses 1 for details of the meta-analysis and forest plot showing the five

included studies. The I^2 value for the meta-analysis was 10.4% and there was no significant risk of publication bias (Egger bias p=0.1463). There were insufficient data available from the previously published studies to allow separate meta-analysis relating to systolic, diastolic or subclinical OH.

See supplementary tables 1-2 for details of the studies included in the meta-analysis (populations, age, sex, follow-up, assessment of OH, assessment of cognitive function, analysis methods and results for these studies). Supplementary table 3 further details the assessment of study quality and risk of bias.

Discussion

These analyses present new data and shed new light on the relationship between OH and cognitive impairment and dementia.

Orthostatic hypotension and HYVET

When the relationship between OH and incident cognitive decline and dementia was assessed in an older adult hypertensive population from the HYVET trial, baseline OH (sitting to standing) was associated with a 36% increased risk of cognitive decline HR1.36 (1.15:1.59) and a similar point estimate but non-significant relationship with incident dementia HR1.34 (0.98:1.84). Using composite endpoints (i.e. including cardiovascular events) resulted in significant associations with both cognitive decline and dementia, and did not change the magnitude of the point estimates. Further examination of the relationship between subclinical orthostatic drop and cognitive outcomes revealed SOH to be associated with a 56% increased risk of cognitive decline HR1.56(1.12:2.17)) and a 79% increased risk of incident dementia HR1.79 (1.00:3.20)). Results were similar for composite cognitive-cardiovascular endpoints. When systolic and diastolic OH were examined separately results were significant only for diastolic drop.

The relationships between OH and cognitive outcomes in the HYVET trial are not entirely congruent with the literature. In the HYVET data the relationship between OH and cognitive decline was stronger than the equivalent relationship with dementia although both were of similar magnitude, however, there were fewer dementia cases than cases of cognitive decline and thus less power to detect a relationship. The strength of the relationship with SOH and cognitive decline was also greater than the relationship between SOH and incident dementia, however both were statistically significant despite the restricted numbers available for these analyses. Neither presence of symptoms alone, nor subclinical orthostatic fall without symptoms were associated with an increased risk of cognitive decline or dementia therefore the presence of symptoms alongside orthostatic drop may be of particular importance in identifying those at risk of cognitive decline or dementia. Unfortunately there were too few cases of OH and presence of symptoms to allow evaluation of this category.

The stronger relationship between diastolic as compared to systolic OH and cognitive

outcomes in the HYVET trial must be interpreted with caution. Although it is similar to that reported for the Swedish Malmo study and may represent a particular risk associated with a more pulsatile flow and decrease of perfusion in diastole, another explanation relevant to the HYVET data is that the trial inclusion criteria are based on systolic rather than diastolic pressures meaning that the systolic pressures were more homogeneous and clustered just above the required cut-point for trial entry. To enter the HYVET trial participants were required to have a mean systolic BP 160 to 199mmHg and a standing systolic BP ≥140mmHg. This resulted in a study population without severe OH and, since there were fewer entrants with very high systolic BP, a mean baseline systolic BP close to the entry threshold. Diastolic pressures did not suffer from the same limitation.

Further limitations include the potential for unmeasured confounding and use of a clinical trial population with randomly allocated antihypertensive treatment and placebo arms. Although we found no relationship between trial treatment group and cognitive outcomes (34) and the analyses were adjusted for trial treatment group it remains possible that there may have been an undetected impact of trial treatment on the relationship between orthostatic drop and cognitive outcomes. The relatively short follow up and the potential for interaction between blood pressure and cognitive function over a decades long prodromal period prior to the identification of decline is an additional limitation. We have a lack of understanding relating to the long term relationship between blood pressure and cognition over the life-course and a lack of data prior to participant entry into the HYVET trial at ~80 years of age which inevitably restricts our ability to evaluate causality. There is also a challenge in disentangling the potential relationship between early cognitive decline, impaired medication adherence and subsequent change in BP control and OH. Despite this, the results from the HYVET population are in line with those of longer population studies (22,23,25,27). It may be that OH had been present and incrementally increasing risk either directly or indirectly for many years prior to study start, however, we have no data on OH prior to entry into the HYVET trial. Alternatively, the association of OH and cognitive outcomes in this very elderly population may represent failing homeostatic mechanisms and increased blood pressure variability associated with both OH and cognitive decline. Additional adjustment for visit to visit variability had no impact on the results, however, a lack of sufficient data relating to 24 hour blood pressure variability (112 HYVET participants had ambulatory blood pressure measurement at baseline) prevented further examination of this area. In fact, since studies with both long and short term follow up demonstrate a relationship between OH and

increased risk, the exact causal pathways, whilst still needing to be established (35), do not change the overall categorization of OH as an easily measurable factor signalling increased risk.

Orthostatic hypotension and meta-analysis combining the published literature and the HYVET results

The meta-analysis combining HYVET with the published literature found OH to be associated with a 21% increased risk of dementia. Inevitable limitations include variation in length of follow-up, confounders, population characteristics and in the definition and assessment of OH and cognitive outcome plus risk of bias present in the constituent studies. This means that generalisability is limited and, as is common in meta-analyses, caution must be applied.

Summary

The literature overall, including HYVET, is remarkably similar in showing a relationship between OH and risk of dementia. In addition, a possible dose response may mean that even subclinical orthostatic fall is associated with raised risk especially in the presence of symptoms associated with OH. However, our analyses cannot establish causality and further research is needed to more fully understand the nature of the relationship between orthostatic drop, speed of recovery, potential difference between systolic and diastolic drop, role of symptoms, related measures such as blood pressure variability, arterial stiffness, impact of early cognitive change on medication availability or adherence and causal pathways (35, 36). Causality in this area is complex and although we know from the Discontinuation of Antihypertensive Treatment in Elderly People on Cognitive Functioning trial that stopping antihypertensives, at least in those with mild cognitive deficit, increased probability of recovery from OH, this association was not present in the intention to treat analysis, and had no impact on cognitive measures (37). Furthermore there was no relationship between antihypertensive use and OH in HYVET and antihypertensive use reduced risk of cardiovascular events and mortality (30) meaning we cannot simply recommend the cessation or reduction of antihypertensives. A key question therefore is whether other interventions to minimise the impact of OH (35-38) have any impact of cognitive outcomes.

Conclusion

Orthostatic hypotension appears to be associated with an increased risk of dementia and of cognitive decline and may be a clinically useful indicator of increased risk. Attention should also be paid to those with subclinical orthostatic drops alongside symptoms indicative of variable cerebral perfusion.

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RP designed the systematic review and analyses of the orthostatic hypotension exposure, was one of the systematic reviewers, carried out the analyses and drafted the manuscript.
KA aided in the design of the systematic review and commented on the manuscript
AB aided in the design of the systematic review and commented on the manuscript
NB aided in the design of the OH analyses and commented on the manuscript
JW aided in the design of the OH analyses, carried out the analyses and commented on the manuscript
RA aided in the design of the OH analyses and commented on the manuscript
KR aided in the design of the OH analyses and commented on the manuscript
JP aided in the design of the systematic review, was one of the reviewers and commented on the manuscript
CB was the CI for the HYVET trial and commented on the manuscript.

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HYVET coordinating team at Imperial College London (1999 to 2008);

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Conflict of interest

KR founded DGI Clinical Inc., which has contracts with pharma for individualised outcome measurement and for data analytics, including in dementia studies with Otsuka and Roche. In 2017 he participated in an Advisory Board meeting on dementia for Lundbeck and in 2014 spoke at a satellite symposium at the Alzheimer Association International Conference, sponsored by Nutricia.

No other conflicts of interest are reported.

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Figure 1 - Showing the Hazard Ratios and 95% Confidence Intervals for risk of cognitive decline and dementia for Orthostatic Hypotension (OH) and Subclinical Orthostatic Hypotension with symptoms (SOH) compared to neither.

Table 1 - Characteristics of those with Orthostatic Hypotension (OH) compared to those without OH in the HYVET population

Population characteristics mean (Standard Deviation) or n (%)	With OH N=538	Without OH N=2583	P=
Age	83.9 (3.3)	83.5 (3.1)	P=0.004
Female	61.5 (331)	61.5 (1588)	P=0.984
Sitting systolic BP	174.5 (9.8)	173.3 (9.2)	P<0.0001
Sitting diastolic BP	91.1 (8.7)	90.9 (9.0)	P=0.688
Standing systolic BP	162.0 (10.9)	169.3 (10.2)	P<0.0001
Standing diastolic BP	82.8 (9.1)	89.9 (8.9)	P<0.0001
Systolic orthostatic fall	13.4 (7.5)	4.0 (5.5)	P<0.0001
Diastolic orthostatic fall	8.3 (4.8)	1.0 (4.3)	P<0.0001
Diabetes	46 (8.6)	249 (9.6)	P=0.4666
Mini Mental State Exam (MMSE) score	24.9 (3.7)	25.4 (3.8)	P=0.0003
Incident dementia	50 (9.3)	191 (7.4)	P=0.133
Incident cognitive decline (Protocol definition: MMSE fall)	194 (36.1)	712 (27.6)	P<0.0001
Incident cardiovascular event (stroke, myocardial infarction, heart failure)	37 (6.9)	157 (6.1)	P=0.485
Death	31 (5.8)	183 (7.1)	P=0.269
Follow up in years (baseline to last available data)	2.2 (1.5)	2.4 (1.5)	P<0.0001
Number randomised to trial treatment placebo arm	268 (49.8)	1273 (49.3)	P=0.8497

Table 2 Hazard ratios (HR) and associated 95% confidence intervals (CI) for the effect of Orthostatic Hypotension on risk of cognitive decline, dementia and cardiovascular events.

Stratified by age (80-84, >=85 years), sex and education. Adjusted for baseline sitting systolic and diastolic BP, trial treatment and presence of diabetes.

Outcome	Cognitive decline		Dementia		Cognitive decline and cardiovascular events**		Dementia and cardiovascular events*	
Orthostatic Hypotension (OH)	Number of participants (events)	HR (95% CI)	Number of participants (events)	HR (95% CI)	Number of participants (events)	HR (95% CI)	Number of participants (events)	HR (95% CI)
No	2,583 (712)	1.00	2392 (191)	1.00	1778 (805)	1.00	2256 (327)	1.00
Yes	538 (194)	1.36 (1.15:1.59)	488 (50)	1.34 (0.98:1.84)	322 (216)	1.39 (1.19:1.62)	457 (81)	1.34 (1.05:1.72)

* incident dementia, fatal and non-fatal cardiovascular events (heart failure, myocardial infarction, stroke) were defined as an event

**cognitive decline, fatal and non-fatal cardiovascular events (heart failure, myocardial infarction, stroke) were defined as an event.

Table 3 - Hazard Ratios and 95% Confidence Intervals for effect of Subclinical orthostatic fall with recent symptoms and orthostatic hypotension on risk of adverse events (N=2100).

Stratified by age (80-84, >=85 years), sex and education. Adjusted for baseline sitting systolic and diastolic BP, trial treatment and presence of diabetes.

	Cognitive decline		Dementia		Cognitive decline and cardiovascular events **		Dementia and cardiovascular events *	
	Number of events	Hazard Ratio (95% Confidence Intervals (CI)	Number of events	HR (95% CI)	Number of events	HR (95% CI)	Number of events	HR (95% CI)
Neither	641	1.00	180	1.00	720	1.00	293	1.00
SOH		1.56 (1.12:2.17)		1.79 (1.00:3.20)		1.51 (1.11:2.06)		1.79 (1.15:2.78)
OH		1.40 (1.15:1.69)		1.26 (0.87:1.84)		1.43 (1.20:1.72)		1.32 (0.98:1.78)

* incident dementia, fatal and non-fatal cardiovascular events (heart failure, myocardial infarction, stroke) were defined as an event

**cognitive decline, fatal and non-fatal cardiovascular events (heart failure, myocardial infarction, stroke) were defined as an event.

Supplemental material

Supplementary text 1 Systematic review

Methods , search strategy and study selection

The databases MEDLINE and MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Embase Classic+Embase were searched using search terms including orthostatic hypotension, dementia, multi-infarct dementia, vascular dementia, alzheimer*, or cognit* adapted for optimised searching with Medline and Embase. (See supplement for details). Understanding of the relationship between BP and cognition has developed extensively over the last 20 years and search results were limited to those from 1997 to July 2017, further limitations included human rather than animal studies and articles in English (no resources were available for translation). Conference abstracts, editorials, comment, letters and review articles were excluded. The resulting abstracts were evaluated independently by two reviewers (RP and JP) and potentially eligible articles were selected for full text review. Any discrepancies were resolved by discussion between the two reviewers. All full text articles were extracted using a standardised data extraction table. Data from the included studies relating to population source, percentage of the sample that were female, length of follow-up, assessment of orthostatic hypotension, cognitive outcomes, analysis methods and results were extracted. In order to ensure the most robust assessment of incident dementia or cognitive decline data relating to samples that were pre-specified as cognitively intact at baseline were preferentially extracted.

For inclusion, articles were required to report on prospective longitudinal studies and on the relationship between orthostatic hypotension and incident cognitive decline (using cognitive measures collected at a minimum of two time points) or incident dementia. To ensure a broad assessment of the literature there were no minimum requirements for length of follow up, definition of OH or of cognitive decline or dementia. Study quality was examined per study using key questions based on the Critical Appraisal Skills Programme (8).
The systematic review is registered with the PROSPERO International prospective register of systematic reviews no. CRD42017075003

Results

Six hundred and twenty four abstracts were identified from database searching of Medline, 2805 from Embase and a further seven from reference searches. Abstract review resulted in 21 articles selected for full text evaluation of which seven were found to be eligible. Of the 14 that were excluded six were cross sectional (9-14), one was a case-control study (21), six lacked information on OH (15-20) one did not report results for incident cognitive decline (5). See supplemental figure 1, PRISMA flow chart. The seven eligible papers reported on longitudinal population studies from Sweden (22 23), (The Swedish Good Aging in Skåne Study (SGASS) and the Malmö Preventive Project), Italy (the Progetto Veneto Anziani study (PVA)), (24), the Netherlands (25), (the Rotterdam study), Singapore (Chinese adults) (6) (the Singapore longitudinal Aging Studies Cohort (SLASC)), the United States (USA) (the Atherosclerosis in the Community (ARIC) study) (26) and France (the 3-City study)(27).
The Malmö study population had a mean age of 45 (Standard Deviation (SD) 7)) years at baseline (23). The ARIC study included those aged between 45-64 at baseline and reported mean ages of 53.9 without OH and 57.3 with OH (26). The Rotterdam and Singapore studies recruited those aged 55 and older at baseline and had mean ages of 68.5 (SD 8.6) (25)

and 65.5 (SD 7.4) (6) years respectively. The Swedish SGASS study selected from nine age cohorts ranging from 60 to 93, mean age 68 (SD 8.5) at baseline (33). The Italian PVA study and the French 3-City study recruited those aged 65 and over. The PVA study also over sampled older adults. Baseline mean age in the PVA study was 71.4 (5.2) (24) and in the 3-City study 73.4 (SD4.9) (27). Follow up varied widely from one-two years (6), 4.4 years (24), six years (22), 7.5 years (27), ~6-9 years (26), 15.3 years (median) (25) and 28 years (SD 4) (23). The Swedish populations were 37% and 54% female respectively (22, 23), in the ARIC study 44.9% were female in those without OH and 45.8% in those with OH (26)**,** in the Italian study females made up 59.4%(24), the Netherlands study 59.7% (25), the 3-City Study 60.5% (27) and in Singapore 65.8% (6).

OH was defined with slight differences in all five studies (supplemental table 2). All studies calculated orthostatic fall from a supine to standing position, however, the Skåne Study used a BP fall of >20mmHg systolic BP (BP) or >10mmHg diastolic BP after standing for 1-10 minutes or a fall of >40mmHg systolic or >20 diastolic immediately after standing (22). The other five studies used a fall of >=20mmHg systolic or >=10mmHg diastolic but within three minutes of standing (25), after three minutes of standing (7), after one minute of standing (23) after either one or three minutes of standing (24) immediately after standing (27) or with BP taken every two seconds for two minutes after standing (26).

The 3-City study also calculated mild OH as a fall of >10mmHg systolic or >5 diastolic and severe OH as a fall of >30mmHg systolic or >15 diastolic immediately after standing (27). The prevalence of OH was 19% in the SGASS study (22), 18.6% in the Netherlands (25) 18.3% in Italy (24) 16.6% in Singapore (6), 13% in the 3-City study (27) 5.1% in the USA and 2.1% in the Malmö study (23). The Rotterdam study further reported a prevalence of OH at 30.6% in those aged 75 and over (25), the 3-City study reported 32% as having mild OH and 4.5% severe OH (27) and the Swedish SGASS study classified Orthostatic Intolerance (OI) as those with a BP (BP) fall less than that required for OH but with the presence of relevant symptoms e.g. unsteadiness (22).

Four studies used the Mini-Mental State Exam (MMSE) to assess cognitive function (6, 22, 24, 25). The ARIC study used a neuropsychological battery (26). The SGASS and 3-City studies used the Diagnostic Statistical Manual (DSM) IV and the Rotterdam study the DSMIIIR (22, 25, 27), for diagnosis of dementia, with additional standard criteria for dementia type (25, 27) and the Malmö study validated dementia diagnoses from a national registry using the DSMIIIR (23). See supplemental table 2.

Principal summary measures were OR and HR. All studies except the ARIC study reported data from populations that were specified as cognitively intact at baseline. The Malmö, SGASS, the Rotterdam and the 3-City studies reported that the presence of OH was likely to be associated with an increased risk of dementia (22, 23, 25, 27). For the SGASS this was a 93% increased risk OR 1.93 (1.19:3.14) (22); for the Rotterdam study, HR1.15 (1.00:1.34) (25). The Malmö study found a HR of 1.18 (0.73:1.89) for incident dementia, a HR of 1.02 (0.89:1.15) per 10mmHg fall in systolic BP and HR 1.22 (1.01:1.44) for diastolic BP (23). The 3-City study reported a 26% increased risk of dementia, HR1.26 (1.03:1.53) using a competing risk model taking illness and death into account and a HR of 1.19 (0.98:1.46) using a Cox proportional hazard regression model (27). The 3-City study also found statistically significant increases in risk of dementia when using the definitions of both mild and severe OH for both competing risk and Cox regression models, see supplemental table 2 for details (27). The SGASS further reported that OI may increase risk, particularly when subjective memory loss

was taken into account (22). The ARIC study found no relationship between baseline OH and the quintile showing greatest cognitive decline for each cognitive test (26). Similarly the SLASC found no association between OH and risk of a fall in MMSE score (OR0.87 (0.61:1.23) (6). The PVA study reported similar results OR 0.78 (0.69:1.05) for cognitive decline (a drop of >=3 MMSE points over follow-up) and OR1.01 (0.90:1.15) for cognitive impairment (MMSE <=24) (24). There were no obvious relationships between length of follow up or study gender balance and outcome.

Overall study quality was adequate although full study details were often lacking, see supplemental table 3 for details. Studies used relatively standard but varying assessments of BP and cognitive outcomes and due to attrition all reported results for potentially selective populations (6, 22, 24,25, 26, 27). In particular, the SLASC, the ARIC and two Swedish studies reported high attrition rates (6, 22, 23, 26) and for the SLASC study the follow up was too short to exclude reverse causality (6). There was insufficient information across the studies to allow meaningful comment on dementia type.

Conclusion

Overall, therefore, there is evidence to suggest that a diagnosis of OH may be associated with a subsequent increased risk of dementia and cognitive decline, however, there are no data available on the oldest old, that is those at highest risk of hypertension, OH and cognitive decline or dementia. Furthermore, few studies have investigated the relationship between the magnitude of the orthostatic fall and the degree of risk (i.e. the potential dose response), or the possible influence of 'sub-clinical' orthostatic fall and symptoms potentially associated with orthostatic fall. A greater understanding of relationships between orthostatic fall and cognitive outcome in older adults is essential to be able to identify those at risk of cognitive decline or dementia and to provide appropriate clinical support.

Supplementary text 2 search strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>26 July 2017

Search Strategy:

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1 hypotension.mp. or exp Hypotension, Orthostatic/ or exp Hypotension/

2 exp Alzheimer Disease/ or alzheimer*.mp.

3 exp Dementia/ or Dementia, Multi-Infarct/ or exp Frontotemporal Dementia/ or Dementia, Vascular/ or dementia.mp.

4 exp Cognition Disorders/ or exp Cognition/ or cognit*.mp.

5 2 or 3 or 4

6 1 and 5

7 limit 6 to (english language and humans and yr="1997 -Current")

Database: Embase Classic+Embase <1947 to 2017 July 26

Search Strategy:

---

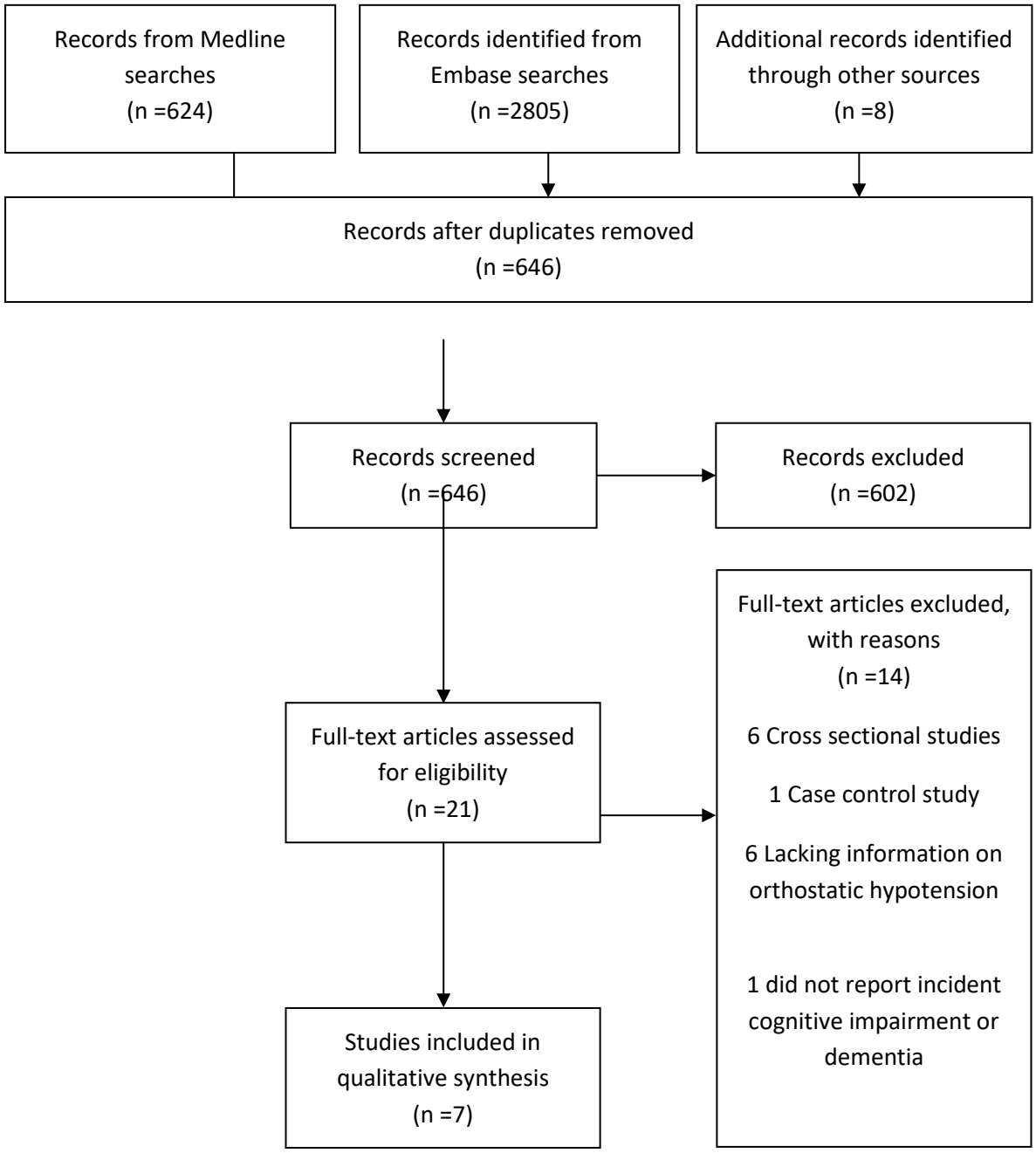
1 orthostatic hypotension.af.

2 (dementia or multi-infarct dementia or vascular dementia or alzheimer* or cognit*).af.

3 1 and 2

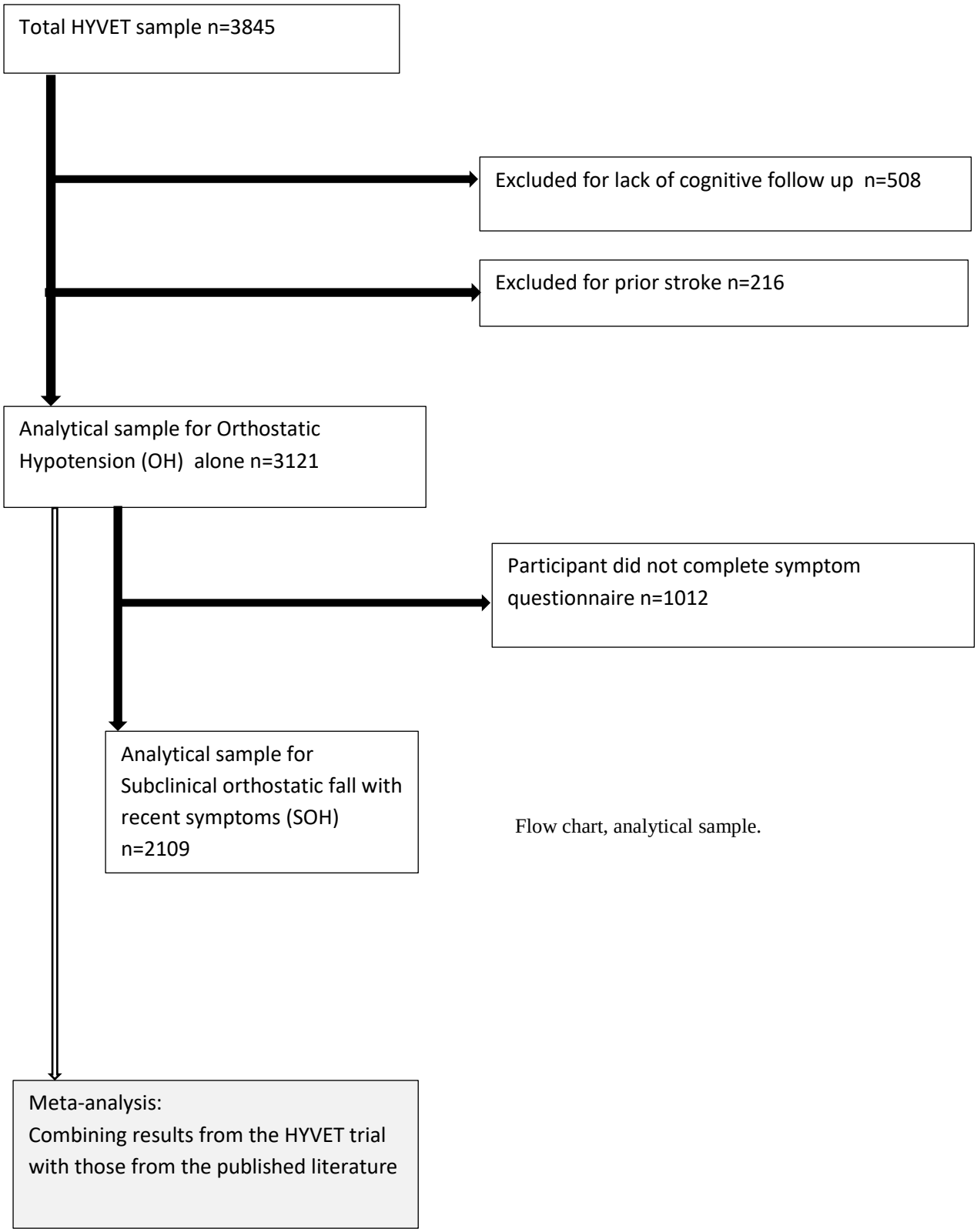
4 limit 3 to (human and english language and yr="1997 -Current")

Supplementary figure 1



Flow chart, systematic review.

Supplementary figure 2



Flow chart, analytical sample.

Supplemental table 1 - Characteristics of the longitudinal study populations reporting on orthostatic hypotension and cognitive outcomes in those without prior cognitive impairment

Study	Population	Age (years)	Percent female	Follow up
Swedish Good Aging in Skåne Study. Elmståhl et al 2014	Longitudinal general population study. This sample excluded those with baseline Mini-Mental State Exam (MMSE) <24 or with a diagnosis of Mild cognitive Impairment (MCI) or dementia or prior stroke, myocardial infarction, angina pectoris and those unable to be tested for orthostatic hypotension. Baseline n=2931, 1832 were re-examined, 710 died or left the study, 23 had missing data. The final analytic sample was 1480	68 (Standard Deviation (SD) 8.5. From 9 age cohorts, aged 60,66, 72, 78, 81, 84, 87, 90, 93	54%	6 years (assessments at baseline and 6 years)
Rotterdam Study. Wolters et al 2016	Population based study recruited from an area of Rotterdam. This sample included those who attended centre baseline visit, were without dementia or stroke and where exam data was available for the assessment of OH. Baseline n=7983, 6626 were eligible or whom 6303 had appropriate OH data.	68.5 (8.6) All aged >=55 at baseline.	59.70%	Median 15.3 years (InterQuartile Range (IQR) 8.3:20.8). OH assessed in 1089-93, follow up until 2014.
Singapore Longitudinal Aging Studies Cohort Yap et al 2008	Community living population of Chinese adults. Study included 2321 free of stroke or cardiovascular disease at baseline. 1485 attended the follow up visit (24 died, 785 were lost to follow up, 441 refused, 339 could not be contacted).	65.5 (7.4) All aged >=55 years at baseline.	65.8% (in the full sample)	One/two year follow up. Baseline was 2004/5 and follow up 2005/6
Atherosclerosis Risk in Communities (ARIC) Study, Rose et al 2009	12,702 middle-aged African American and White men and women living in 4 communities: Maryland, Mississippi, Minnesota and North Carolina. At follow-up, 10,572, after exclusion of 1461 (no visit 4, death etc), 337 (no cognition test), and 332 (incident stroke).	No OH 53.9 (53.8-54.0), with OH (57.3 (56.8-57.7)	No OH 54.9 with OH 55.8	Baseline (1987-89) plus 3 triennial visits (last one 1996-99).

Malmö Preventive Project. Holm et al 2017.	33,346 individuals living in Malmö. At follow up 18,204 were available. Missing data stated to range from 3 to 365 cases for different variables and these cases were not included in the respective analyses.	45 (7)	37%	time from baseline to follow-up visit 23 years (4), mean time from baseline to follow up for incident dementia 28 (4) years. Baseline 1974-1992, follow up 2002-2006. Mean
Progetto Veneto Anziani Study. Curreri et al 2016	3099 community dwelling participants enrolled. 1408 with data at follow up and without cognitive impairment (defined as an MMSE score <=24)	71.4 (5.2) range 65-96	59.40%	Mean follow-up 4.4 years. Baseline 1995-1997.
Three-City Study. Cremer et al 2017	7425 recruited from the electoral roll in three French cities. Excluding those without prevalent dementia and with BP measures	73.4 (4.9) all aged 65 or over at baseline	60.50%	Mean follow up 7.5 years Baseline 1999-2001, visits every 2/3 years.

Supplemental table 2 Results from longitudinal studies reporting on orthostatic hypotension and cognitive outcomes in those without prior cognitive impairment.

Study	Assessment of OH	Cognitive outcomes	Analysis methods	Result
Swedish Good Aging in Skåne Study. Elmståhl et al 2014	Orthostatic hypotension was defined as a fall of >20mmHg SYSTOLIC BP or >10mmHg DIASTOLIC BP from supine pressure, after standing for 1-10 minutes or a fall of >40mmHg SYSTOLIC BP or >20 mmHg DIASTOLIC BP immediately after standing. Comprehensive examination by a physician including questions about symptoms such as unsteadiness, blackouts SGASS study also classified Orthostatic Intolerance (OI) as those with a BP (BP) fall less than that required for OH but with the presence of relevant symptoms e.g. unsteadiness (22). BP measured by a mercury sphygmomanometer.	Dementia Incident dementia diagnosed in accordance with the Diagnostic Statistical Manual (DSM)IV. Objective memory loss was defined as a follow up score of 0 or 1 on the 3 word recall sub-score of the MMSE in the absence of subjective memory loss. Subjective memory loss was also collected. MCI was defined as either subjective or objective memory loss at follow up.	Logistic regression comparing those who developed each outcome against those that developed none of the outcomes	19% had OH, 28% had past or present OI. 64% had hypertension Adjusted for age Controls vs objective memory loss OH OR 0.95 (0.68:1.33) OI OR 1.10 (0.83:1.47) Controls vs subjective memory loss OH OR 1.07 (0.68:1.69) OI OR 1.55 (1.06:2.27) Controls vs MCI OH OR1.23 (0.75:2.00) OI OR2.01 (1.33:3.05) Controls vs dementia OH OR1.93 (1.19:3.14) OI OR0.90 (0.55:1.50)
Rotterdam Study. Wolters et al 2016	OH was based on change from supine to standing at 1, 2 and 3 minutes after standing and a fall of >=20mmHg SYSTOLIC BP or >=10mmHg DIASTOLIC BP within 3 minutes. Also categorised OH as >=20/10 but <30/15, >=30/15 but <40/20 and >=40/20 BP was recorded by an automated machine, a Dinamap Critikan.	Dementia Screening at baseline and follow up used the Mini-Mental State Exam (MMSE) and Geriatric Mental State Schedule (GMS). An MMSE <26 or a GMS >0 triggered a more comprehensive exam with CAMDEX. Record linkage was also used to identify case of dementia.	Proportional hazards regression to examine the relationship between OH and later dementia or death.	18.6% with OH, 30.6% in those >=75 years Adjusted for age, sex, SYSTOLIC BP, DIASTOLIC BP, antihypertensive use, diabetes, ratio of total cholesterol to High Density Lipoprotein (HDL) cholesterol, lipid lowering medication, smoking status, alcohol intake, anticholinergic medication, Body Mass Index (BMI) and apoe genotype. For dementia HR 1.15 (1.00:1.34) For Alzheimers disease HR 1.17 (0.99:1.37) For vascular dementia HR 1.20 (0.73:1.96)

		Diagnosis of dementia was made using the DSMIIIR and the NINCDS ADRDA for Alzheimer's Disease and NINDS AIREN for Vascular dementia.		Also state that antihypertensive treatment had no effect.
Singapore Longitudinal Aging Studies Cohort Yap et al 2008	OH was defined as a fall in SYSTOLIC BP of >=20mmHg or a fall of >=10mmHg in DIASTOLIC BP after 3 minutes standing from supine. BP measured by a mercury sphygmomanometer.	Cognitive change Assessment was using the MMSE. An MMSE <24 was categorised as cognitive impairment, a fall of >=1 point was categorised as cognitive decline. An additional analysis was carried out using >= 2 point fall to indicated cognitive decline.	Logistic regression was used to examine the relationship between baseline OH and cognitive decline.	16.6% had OH. Adjusted for age, sex, education, vascular risk factors (dyslipidaemia, diabetes, smoking) anaemia, apoeE4, BMI, depression, BP level, use of BP altering medication, duration of self reported hypertension, baseline MMSE and length of follow up. For the whole sample the results for cognitive decline were OR0.87 (0.61:1.23) For those with hypertension OR0.84 (0.51:1.38)
Atherosclerosis Risk in Communities (ARIC) Study, Rose et al 2009	Orthostatic fall calculated as difference between average standing and supine BP following 20 minutes supine rest, BP taken every 2 seconds for 2 minutes, followed by repeat procedure with subject standing. OH was defined as decrease in systolic BP (BP) by >= 20 mm Hg or diastolic BP by >=10 mm Hg upon standing. BP measured with Dinamap 18465X oscillometric device	Cognitive change At visit 2 and 4, subjects completed a Delayed Word Recall Test (DWRT), a Digit Symbol Substitution Test (DSST) (subtest of Wechsler Adult Intelligence Scale -Revised, and The Controlled Oral Word Association Test (Word Fluency Test WFT) of the Multilingual Asphasic Examination.	Quintiles of change in cognitive performance between visit 2 and 4 calculated. Logistic regression analysis with lowest quintile compared with rest) to estimate association between OH and change in cognition, adjusted for various covariates.	5.1% with OH. Association between baseline OH and cognitive decline over approx. 6 years (visit 2 to 4) Delayed word recall OR1.15 (0.94:1.42) Digit symbol substitution 1.13 (0.90:1.4); Word fluency 1.03 (0.82:1.28), each adjusted for age, race/centre, gender, education, Systolic BP, antihypertensive medication. Delayed word recall 1.08(0.86:1.35); Digit symbol substitution 1.05(0.83: 1.35); Word Fluency 1.03(0.80:1.31) each adjusted for covariates listed above plus current smoking and drinking, diabetes, carotid intima media thickness, low ankle brachial index, low density

				lipoprotein cholesterol, resting heart rate, prevalent CHD, cancer, fair/poor self-reported health
Malmö Preventive Project. Holm et al 2017.	OH defined as a fall of >=20mmHg systolic BP and or a fall of >=10mmHg diastolic BP after supine rest for 10 minutes and standing for one minute. Article specifies that all BP values were rounded up to nearest 5 mmHg and the man value of two measures taken at each position was used. BP measured by a mercury sphygmomanometer.	Dementia Dementia diagnosis taken from the Swedish National Patient Register (SNPR) from baseline until Dec 2009. Dementia diagnoses were validated through review of medical records with physician input.	Cox regression	2.1% had OH. OH HR 1.18 (0.73:1.89) Per 10mmHg fall; Systolic BP fall HR 1.02 (0.89:1.15) Diastolic BP fall HR 1.22 (1.01:1.44) Adjusted for age, gender, antihypertensive treatment, smoking, diabetes, prevalent cardiovascular disease, plasma cholesterol.
Progetto Veneto Anziani Study. Curreri et al 2016	OH defined as a fall of >=20mmHg systolic BP and or a fall of >=10mmHg diastolic BP in BP measures taken after 1 or 3 minutes of standing and after supine rest for 5 minutes. BP measured by a mercury sphygnometer.	Cognitive change Mini Mental State Exam (MMSE) A drop in MMSE of >=3 points classified as cognitive decline and a score of <=24 as cognitive impairment	States that Odds ratios were used.	18.3% with OH. Cognitive decline OR0.78 (0.69:1.05) adjusted for age and formal education using coefficients recommended for the Italian population

Three-City Study. Cremer et al 2017	OH defined as a fall of >=20mmHg systolic BP and or a fall of >=10mmHg diastolic BP in BP measures taken immediately after standing and after supine rest for 5 minutes. Analyses also carried out with mild OH defined as a fall of >=10mmHg systolic BP and or a fall of >=5mmHg diastolic BP and severe OH defined as a fall of >=30mmHg systolic BP and or a fall of >=15mmHg diastolic BP BP measured by an automatic oscillometric device (OMRON CP750).	Diagnosis of dementia using a three step procedure. Trained psychologists assessed cognitive function, at risk participants were seen by a neurologist at the Dijon site and all participants saw a neurologist at the Bordeaux and Montpelier sites. Final diagnosis made by an independent panel of experts based on DSMIV	Cox proportional Hazard Regression models with delayed entry. Date of dementia was defined as midpoint between the visit without a diagnosis and the date the diagnosis was made. Also used an illness death semiparametric multistate model designed to take into account the competitive risk of death.	13% with OH. For OH and dementia Cox model HR1.19 (0.98:1.46) Illness Death model HR 1.26 (1.03:1.53) For mild OH and dementia Cox model HR1.20 (1.04:1.40) Illness death model 1.23 (1.06:1.43) For severe OH and dementia Cox model HR1.54 (1.15:2.08) Illness death model HR1.51 (1.11:2.04) For OH and Alzheimer's Disease Cox model HR1.19 (0.91:1.57) For OH and vascular dementia Cox model HR1.42 (0.92:2.15)

Supplemental table 3 - Study quality

Study	Recruitment bias?	Exposure bias (assessments of risk factor exposure)	Outcome bias (assessment tool, blinded assessors?)	Follow up bias (attrition, length?)	Overview, risk of bias
Swedish Good Aging in Skåne Study. Elmståhl et al 2014	Moderate Longitudinal population study but selected population.	Low. Standard assessment of BP and OH	Low. Standard assessment of cognitive function administered by trained assessors	High. High attrition after baseline, some reasons given for attrition but no analyses to account for it.	Moderate
Rotterdam Study. Wolters et al 2016	Moderate Longitudinal population study but selected population.	Low. Standard assessment of BP and OH. Used the American Autonomic Society and American Academy of Neurology Consensus Committee definition of OH.	Moderate. Standard assessment of cognitive function using a multistage process. Medical record based diagnosis likely to be more open to bias than face to face assessment.	Low. State that assessment was 94% complete by the end of data collection. Imputed missing data in covariate and state that rerunning the analyses omitting the first 5 years or follow up to try to exclude reverse causality did not materially change the results.	Low-Moderate
Singapore Longitudinal Aging Studies Cohort Yap et al 2008	Moderate. Selected population	Low. Standard measurement of BP and definition of OH	Moderate. Standard assessment for cognitive function but limited to a screening instrument. Fall of 1 point to indicate impairment was not well justified.	High. High attrition after baseline, some reasons given for attrition but no analyses to account for it. Missing data was excluded.	Moderate
Atherosclerosis Risk in Communities (ARIC) Study, Rose et al 2009	Moderate. Participants sampled from 4 areas, but ethnic density varied between the 4 communities, so possible bias in overall sample	Low. Standard measurement of BP and definition of OH	Low. Standard tests for assessment of cognitive function	High. 17% lost for follow-up, some reasons given, mainly non-attendance at 4th visit.	Moderate
Malmö Preventive Project. Holm et al 2017.	Moderate. Not clear whether population was representative.	Moderate. Standard criteria for OH but not clear whether rounding of BP values took place before or after calculation of OH.	High. Standard criteria used by research team to validate dementia diagnoses, however, diagnoses taken from medical registries may underestimate incidence and may be more subject to changing diagnostic patterns over time than	High.. No details of reasons for attrition or adjustment. States that prevalence of OH lower, 2.1% in those with follow up compared to 6.1% in the full baseline sample.	Moderate-high

			use of standard research protocols with direct participant assessment.		
Progetto Veneto Anziani Study. Curreri et al 2016	Moderate, population was sampled to ensure male to female ratio of 2:3 and older adults were over sampled.	Low. Standard criteria for OH.	Moderate . Standard assessment for cognitive function but limited to a screening instrument	Moderate, however, details are provided regarding attrition or exclusion from analytical sample.	Moderate
Three-City Study. Cremer et al 2017	Moderate, although sampled from the electoral role.	Low. Standard criteria for OH.	Low, standard criteria for diagnosis and regular visits.	Moderate, however, details are provided regarding exclusion from analytical sample. Those in the study sample were younger and have fewer cardiovascular risk factors than those excluded.	Low-Moderate

Supplemental table 4 - Characteristics of those with Subclinical orthostatic fall with recent symptoms and Orthostatic Hypotension in the subset with symptom data.

Population characteristics mean (Standard Deviation) or n (%)	Neither N=1623	Orthostatic Subclinical orthostatic fall with recent symptoms N=105	Orthostatic hypotension N=381	P-values[a]
Age	83.45 (3.12)	83.13 (2.72)	83.83 (3.26)	0.05[b]
Female	60.4 (980)	74.3 (78)	63.8 (243)	0.01[g]
Sitting systolic BP – baseline	173.4 (9.8)	174.7 (10.0)	175.2 (10.0)	<0.01[c]
Sitting diastolic BP- baseline	89.7 (9.6)	91.9 (9.3)	90.5 (8.9)	0.07[b]
Standing systolic BP- baseline	169.7 (11.1)	168.4 (11.3)	161.5 (11.4)	<0.0001[d]
Standing diastolic BP- baseline	89.3 (9.5)	89.6 (9.3)	82.2 (9.3)	<0.0001[d]
Systolic orthostatic fall- baseline	3.7 (6.2)	6.3 (5.3)	13.7 (8.0)	<0.0001[e,f]
Diastolic orthostatic fall- baseline	0.5 (4.8)	2.3 (4.6)	8.3 (5.2)	<0.0001[f]
Mini Mental State Exam (MMSE) score baseline	25.2 (3.9)	25.1 (3.4)	24.5 (3.8)	<0.01[c]
Incident dementia	132 (8.1)	13 (12.4)	35 (9.2)	0.28
Incident cognitive decline (Protocol definition: MMSE fall)	462 (28.5)	40 (38.1)	139 (36.5)	<0.01[h]
Incident cardiovascular event (stroke, myocardial infarction, heart failure)	97 (6.0)	13 (12.4)	26 (6.8)	0.03[g]
Death	596 (5.9)	18 (17.1)	22 (5.8)	P<0.0001[i]
Follow up (baseline to last available data)	2.4 (1.5)	2.3 (1.3)	2.1 (1.5)	P<0.001
Participants reporting light-headedness and or unsteadiness and or faintness as having bothered them 'a lot' or 'extremely' during the preceding week.	7 (0.43)	105 (100)	4 (1.1)	N/A

[a] global p-values from one-way analysis of variance;

[b] There were no significant pairwise differences between the groups (Tukey-Kramer test, 5% level)

[c] There was a significant pairwise difference between the "Neither" and "Orthostatic hypotension" groups (Tukey-Kramer test, 5% level)

[d] There was a significant pairwise difference between the "Neither" and "Orthostatic hypotension" groups and between the "Orthostatic Subclinical orthostatic fall with recent symptoms" and "Orthostatic hypotension" groups (Tukey-Kramer test, 5% level)

[e] global p-value from W test (similar to F-test for one-way analysis of variance but more robust when there are unequal variances).

[f] All the pairwise comparisons between the groups were significant (Tukey-Kramer test, 5%)

[g] Examination of the adjusted Chi-squared residuals suggests there are no unusually high or low counts in any of the cells.

[h] Examination of the adjusted Chi-squared residuals suggests a difference is between the "Neither" and "Orthostatic Subclinical orthostatic fall with recent symptoms"/"Orthostatic hypotension" groups.

[i] Examination of the adjusted Chi-squared residuals suggests a difference is between the “Neither” and “Orthostatic hypotension” groups and the “Orthostatic Subclinical orthostatic fall with recent symptoms” group.

Supplemental table 5 - Results of proportional hazard regression analyses for systolic and diastolic OH separately.

Stratified by age (80-84, >=85 years), sex and education. Adjusted for baseline sitting systolic and diastolic BP, trial treatment and presence of diabetes.

	Cognitive decline	Dementia	Cognitive decline and cardiovascular events	Dementia and cardiovascular events
	Hazard Ratio (95% Confidence Intervals (CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Systolic OH	1.17 (0.91:1.50)	0.86 (0.50:1.49)	1.22 (0.97:1.54)	1.11 (0.75:1.62)
Diastolic OH	1.47 (1.23:1.75)	1.69 (1.22:2.34)	1.49 (1.26:1.75)	1.54 (1.18:2.00)

Supplemental table 6 - Results of proportional regression analyses using a more severe definition Orthostatic Hypotension*.

Stratified by age (80-84, >=85 years), sex and education. Adjusted for baseline sitting systolic and diastolic BP, trial treatment and presence of diabetes.

	Cognitive decline		Dementia		Cognitive decline and cardiovascular events		Dementia and cardiovascular events	
	Number of events	Hazard Ratio (95% Confidence Intervals (CI)	Number of events	HR (95% CI)	Number of events	HR (95% CI)	Number of events	HR (95% CI)
Orthostatic Hypotension (OH)	906	1.49 (1.16:1.90)	241	1.40 (0.90:2.27)	1021	1.51 (1.19:1.90)	498	1.35 (0.92:1.98)

*Defined as a fall of >20mmHg systolic BP ad or a fall of >10mmHg diastolic BP.

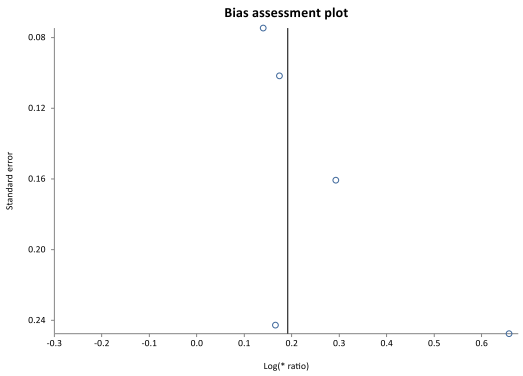
Supplementary analyses 1

Summary meta-analysis

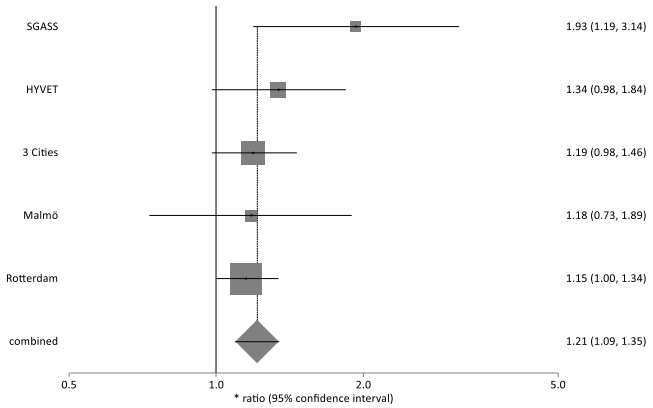
Study	* Ratio	SE	Approximate 95% CI		
1	1.93	0.247522	1.19	3.14	SGASS
2	1.34	0.160709	0.98	1.84	HYVET
3	1.19	0.101696	0.98	1.46	3 Cities
4	1.18	0.24268	0.73	1.89	Malmö
5	1.15	0.074662	1	1.34	Rotterdam

Stratum	Standardized Effect	Standard Error	% Weights (fixed, random)		
1	1.93	0.247522	4.688799	5.652385	SGASS
2	1.34	0.160709	11.122669	12.8318	HYVET
3	1.19	0.101696	27.777073	28.835204	3 Cities
4	1.18	0.24268	4.877786	5.872458	Malmö
5	1.15	0.074662	51.533673	46.808153	Rotterdam

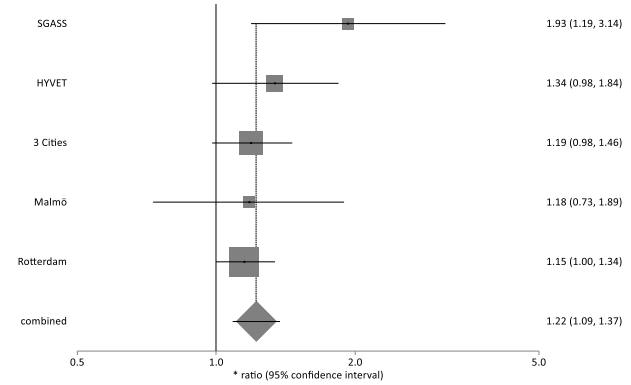
Fixed effects (inverse variance)
Pooled * ratio = 1.211428 (95% CI = 1.090624 to 1.345612)
Z (test test * Ratio differs from 1) = 3.578511 P = 0.0003
Non-combinability of studies
Cochran Q = 4.462408 (df = 4) P = 0.347
Moment-based estimate of between studies variance = 0.002075
I_2 (inconsistency) = 10.4% (95% CI = 0% to 67.7%)
Random effects (DerSimonian-Laird)
Pooled * ratio = 1.221427 (95% CI = 1.086264 to 1.373409)
Z (test * Ratio) = 3.342813 P = 0.0008
Bias indicators
Begg-Mazumdar: Kendall's tau = 0.8 P = 0.0833 (low power)
Egger: bias = 1.632025 (95% CI = -1.031496 to 4.295546) P = 0.1463



Summary meta-analysis plot [fixed effects]



Summary meta-analysis plot [random effects]



Appendix 1

Abbreviations

Blood Pressure	BP
Diagnostic Statistical Manual	DSM
Hazard Ratio	HR
Hypertension in the Very Elderly Trial	HYVET
Mini-Mental State Exam	MMSE
Orthostatic Hypotension	OH
Subclinical Orthostatic Hypotension	SOH