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FULL RESEARCH PAPER
Cardiovascular disease

Orthostatic hypertension and major adverse events: a systematic review and meta-analysis

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Aims The role of orthostatic hypertension (OHT) in cardiovascular disease (CVD) and mortality is unclear. We aimed to determine if this association exists through a systematic review and meta-analysis.

Methods and results Study inclusion criteria included: (i) any observational/interventional studies of participants aged ≥18 years (ii) that assessed the relationship between OHT and (iii) at least one outcome measure—all-cause mortality (primary outcome), coronary heart disease, heart failure, stroke/cerebrovascular disease, or neurocognitive decline. MEDLINE, EMBASE, Cochrane, clinicaltrials.gov, and PubMed were independently searched by two reviewers (inception—19 April 2022). Critical appraisals were conducted using the Newcastle–Ottawa Scale. Random-effects meta-analysis was performed using a generic inverse variance method, and narrative synthesis or pooled results were presented as an odds or hazards ratio (OR/HR), with 95% confidence interval. Twenty studies ($n = 61\,669$; 47.3% women) were eligible, of which 13 were included in the meta-analysis ($n = 55\,456$; 47.3% women). Median interquartile range (IQR) follow-up for prospective studies was 7.85 (4.12, 10.83) years. Eleven studies were of good quality, eight fair, and one poor. Relative to orthostatic normotension (ONT), systolic OHT (SOHT) was associated with a significant 21% greater risk of all-cause mortality (HR: 1.21, 1.05–1.40), 39% increased risk of CVD mortality based on two studies (HR: 1.39, 1.05–1.84), and near doubled odds of stroke/cerebrovascular disease (OR: 1.94, 1.52–2.48). The lack of association with other outcomes may be due to weak evidence or low statistical power.

Conclusion Patients with SOHT may have higher mortality risk relative to those with ONT and increased odds of stroke/cerebrovascular disease. Whether interventions can reduce OHT and improve outcomes should be explored.

Lay summary Orthostatic hypertension (OHT) is defined as an arbitrary rise in upper (systolic) and/or lower (diastolic) blood pressure readings on standing. We performed a thorough literature search and combined the evidence of impact of OHT on future adverse events, including death, heart attack, heart failure, stroke, falls, and impaired cognition. We found the following:

- Twenty studies that investigated the association between OHT and future adverse events. Of these, 13 were eligible to be included in the combined evidence (meta-analysis). This formed a total sample of 61 669 participants (47.3% women), of which 55 456 (47.3% women) were included in the meta-analysis.
- Systolic OHT (SOHT) was associated with a significant 21% increased risk for death from any cause, a 39% greater risk of death due to heart and blood vessel disease and near doubled odds of stroke or brain vessel disease. Furthermore, three of four studies found a significant association between SOHT and impaired cognition. Diastolic OHT was not found to be associated with these outcomes. The lack of association with other outcomes investigated may be due to weak evidence.

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• Eleven studies were of good quality, eight fair, and one poor. Differences in study design, study criteria, and study populations mean that the results need interpreting with caution. Future robust studies can build on this evidence to assess if treatment to reduce OHT would improve future outcomes.

Keywords Orthostatic hypertension • Mortality • Cardiovascular disease • Systematic review • Meta-analysis

Introduction

Orthostatic hypertension (OHT) constitutes an understudied condition with no agreed diagnostic criteria to date.[1] Despite differences in defining OHT,[1,2] most studies use similar systolic and diastolic cut-off values used to define orthostatic hypotension (OH), that is, an increase in systolic blood pressure (SBP) of ≥20 mmHg or ≥10 mmHg for diastolic blood pressure (DBP) on standing. Given diagnostic ambiguity and lack of research associated with OHT, it is likely that its true prevalence is underestimated. Studies have reported a prevalence ranging from 4–28% in the elderly population or suspected transient ischaemic attack population.[3,4]

Emerging evidence for OHT as a potential novel cardiovascular risk factor is hard to ignore. Several prospective and cross-sectional studies have investigated the effects of OHT on adverse events including mortality, stroke, cardiovascular disease (CVD), and cognitive health among others.[3,5] Some earlier studies have looked at increases in orthostatic SBP or DBP and adverse events, however, they did not explicitly define these as OHT *per se*. Over the years, studies found increased risks, rates or odds of mortality, stroke, or CVD.[6–11] Whereas one study found a decreased risk for cardiovascular events,[12] and others were inconclusive.[5,12–14]

Consequently, elucidating the true effect of OHT on future health outcomes is imperative as it may influence patient risk prediction and management, like OH. This is significant in the context of an ageing population, as age appears to be a major risk factor for OHT.[15]

We aimed to investigate the association between OHT and future major adverse events. Our primary outcome was mortality. Secondary outcomes were incident heart failure (HF), coronary heart disease (CHD), stroke/cerebrovascular disease, falls, or conditions of neurocognitive decline.

Materials and methods

Protocol and registration

This review was registered with PROSPERO (registration number: CRD42022302460 https://www.crd.york.ac.uk/prospero).

Eligibility criteria

The following inclusion criteria were applied: (i) cohort, case–control, cross-sectional, interventional, or randomized studies; (ii) participants aged ≥18 years; (iii) assessing the effect of orthostatic systolic and/or diastolic hypertension; and (iv) outcomes including at least one of all-cause mortality (primary outcome), incident CHD, heart failure (HF), stroke, falls, or conditions of neurocognitive decline (any condition or disease resulting in reduced mental function due to organic disease, such as vascular dementia and etc.). Exclusion criteria were if the study did not meet any of the four criteria outlined above.

Information sources

Literature search was conducted in duplicate by two independent reviewers (L.D.P. and Z.P.) across the following databases: Medline (Ovid), EMBASE (Ovid), Cochrane, clinicaltrials.gov, and PubMed. A combination of MeSH and key/text words was employed to identify studies and the search strategy modified to suit each database, as outlined in Supplementary material online, *Tables S1–S4*. Reference lists of included articles were searched manually to identify further studies.

Study selection

Database searches were conducted on 31 October 2021, and an updated manual search was performed on 19 April 2022. Search results were limited to the English language. Search results were then transferred to the Rayyan review software[16] to streamline the study selection process. For eligibility criteria, two reviewers (L.D.P. and Z.P.) independently screened the studies by title, abstract, and then full-text. Consensus between reviewers' decisions were checked within the Rayyan system, and discrepancies discussed. In case of disagreement between decisions, a final decision was reached by consulting a third independent reviewer (T.A.P.). Study reporting was in accordance with the PRISMA checklist (see Supplementary material online, *Tables S5* and *S6*).[17]

Data collection process

A data extraction form (see Supplementary material online, *Table S7*) was designed to ensure consistency among reviewers. Data were extracted using the following headings: study and subject characteristics, study eligibility criteria, definition of OHT, details of exposure and comparator groups, outcomes, confounders, and effect sizes. Following completion of data collection, consensus between reviewers was checked through discussion, and any disagreement was adjudicated by a third reviewer (T.A.P.).

Assessment of study quality

Two reviewers (L.D.P. and Z.P.) independently assessed study quality according to the Newcastle–Ottawa Scale (NOS), which employs a 'star-system' according to three broad perspectives as follows: (i) selection of study groups; (ii) comparability of groups based on study design or analysis; and (iii) ascertainment of either the exposure/outcome of interest for case–control or cohort studies.[18] An adapted version was employed to assess the quality of cross-sectional studies.[19] Studies were evaluated to be of good, fair, or poor quality.[20]

For the domain of 'comparability', reviewers identified age as the most important confounder of interest. If a study was observed to adjust for age only, it was awarded a single star for this domain, whilst if a study adjusted for other confounders in addition to age, it was awarded two stars. Conversely, if a study did not adjust at least for age, then no stars were awarded. The NOS checklist and completed critical appraisals are displayed in Supplementary material online, *Table S8*.

Outcomes

The primary outcome of interest was mortality measured using adjusted and/or unadjusted hazard ratios (HRs) for time-to-event data. Secondary outcomes of interest were incident CHD, HF, stroke/cerebrovascular disease, falls, and conditions of neurocognitive decline that were determined using validated assessment tools or by clinical diagnosis. Where possible, adjusted and/or unadjusted HRs for secondary

outcomes were extracted. Where time-to-event data was unavailable for pooling, unadjusted odds ratios (ORs) were extracted for these secondary outcomes. The populations under study were those of community-dwelling subjects, hospitalized patients, outpatients, or those residing in care homes or residential facilities.

Data synthesis

Only studies considered clinically homogeneous in terms of study design, population, outcome, and context were considered for pooling.[21] Where studies reported data from two arms of a trial, data from both arms were considered in separate analyses.

Time-to-event data (i.e. mortality and HF) and binary outcome data (i.e. incident stroke/cerebrovascular disease) were pooled and summarized as HRs and/or ORs with 95% confidence intervals (CIs). In studies that only provided the raw outcome without presenting a suitable risk estimate for secondary outcomes under investigation, unadjusted OR and 95% CIs were calculated based on raw event data. Thus, studies that only reported a between group comparison and not individual group summaries (i.e. using unadjusted and/or adjusted HRs and unadjusted ORs) were included using a generic inverse variance method and a random-effects model, due to expected differences between studies.[22] Meta-analyses with forest plots of eligible studies were performed in the Cochrane Collaboration statistical software package RevMan (Version 5.4.1 for Windows 10[23]).

The importance of adjustment for confounders was acknowledged, to ensure that risk estimates extracted would be reflective of the true risk estimate of interest. As it would have not been possible for all studies to adjust for the same confounders, it was deemed necessary to identify the most important factor to adjust for, as outlined in the NOS checklist. Age was determined to represent the minimum common adjusting variable required to deem estimates as 'adjusted'. Studies not eligible for statistical pooling have been presented narratively.

Heterogeneity and subgroup analysis

Statistical heterogeneity was identified using the I^2 statistic, where an I^2 of 0%, 25%, 50%, and 75% corresponded to no, low, moderate, and high level of heterogeneity.[24] Instances where $I^2 > 50\%$ were deemed to have substantial heterogeneity and explored using pre-determined subgroups to explain the heterogeneity. These subgroups were evaluated based on the presence of significant comorbidities e.g. presence of chronic disease, subjects residing in nursing homes, or SBP ≥160 mmHg. Where no evidence of significant study design or population heterogeneity was encountered, a pooled meta-analysis was performed. Where applicable, we also preformed additional analyses including only results from studies that adjusted for baseline hypertension, blood pressure, or anti-hypertensive medication use.

Where ≥5 studies were pooled, publication bias was assessed using a funnel plot (see Supplementary material online, *Figure S1*).

Results

Study selection

The study selection process is summarized in a PRISMA flow diagram (*Figure 1*). Following duplicate removal, a total of 378 studies were identified from database searches. After title, abstract and full-text screening, 20 articles were eligible for inclusion.

Study characteristics

Characteristics of all included studies are summarized in *Table 1*. Respective risk estimates are displayed in Supplementary material online, *Table S9*. The full list of confounders adjusted for in each study is documented in Supplementary material online, *Table S10*.

Among 20 studies that met eligibility criteria, the following outcomes were examined: nine assessed the relationship between SOHT and all-cause mortality,[5–11,13,14] two between diastolic orthostatic hypertension (DOHT) and all-cause mortality,[9,11] two between SOHT and CVD-related mortality,[10,11] three between SOHT and incident HF,[11,14,25] two between DOHT and incident HF,[11,25] six between SOHT and incident stroke/cerebrovascular disease,[11,14,26–29] two between DOHT and incident myocardial infarction (MI),[11,30] four between SOHT and cognitive impairment and decline[3,31–33], and four between both SOHT and DOHT or OHT and a composite end-point consisting of either CVD, death, or hospitalization.[6,11,12,14]

A total of 61,669 participants (47.3% women) were included. Mean follow-up time ranged from 2–18.7 years. Seven studies were conducted in USA,[7,8,11,14,29,30,32] three in Japan,[26,28,33] two in Italy,[10,31] one in each of China,[27] France,[3] Israel,[5] Netherlands,[13] Spain,[9] Sweden[12], and UK,[25] and one in France and Italy.[6]

Details on orthostatic blood pressure (BP) measurements and baseline supine, sitting and standing BP readings have been reported in full for each study in Supplementary material online, *Table S11*.

Among 20 studies, five were conducted in hypertensive patients.[7,8,26–28] In the remaining studies, six had data on the percentage of participants with hypertension in OHT, and this ranged from 30.3–76.3%.[3,9,10,25,31,32] Three studies reported hypertension prevalence in their total cohort, and this ranged from 61.7–86%.[12–14] Whilst direct data on hypertension prevalence was unavailable for four studies, and the percentage of antihypertensive users in those with OHT ranged from 35–90%.[5,11,29,33] Of note, one study comprised of a cohort where individuals with SBP >140 mmHg or DBP >90 mmHg were excluded[30] and another reported hypertension to be similarly present in ONT, OHT, and OH groups.[6]

Assessment of study quality

The results of the quality assessment of included studies are summarized in *Table 2*. Eleven were of good quality,[5,9,10,14,25,27–29,31–33] eight of fair quality[3,6,8,11–13,26,30], and one of poor quality.[7]

Primary outcome: orthostatic hypertension and all-cause mortality

Systolic orthostatic hypertension and all-cause mortality

Nine studies ($n = 34242$, women 46.9%) assessed the relationship between SOHT and all-cause mortality.[5–11,13,14] In eight included studies, SOHT was defined as an increase in standing SBP ≥20 mmHg. Seven studies reported their effect using HRs[5,8–11,13,14] and one using risk ratios.[6]

Of these, four reported an association between SOHT and mortality. Five reported time-to-mortality with unadjusted HR estimates and were pooled (HR: 1.44, 1.01–2.06; $P = 0.05$, $I^2 = 86\%$), (*Figure 2A*). To assess the effect after accounting for heterogeneity, we pooled a subgroup that comprised of suspected highly comorbid populations (detailed as part of Supplementary material online, *Figure S2*). Subgroup analysis (see Supplementary material online, *Figure S2*) revealed a non-significant increase in risk of mortality in relation to SOHT (HR 1.25; 95% CI 0.91–1.70, $P = 0.16$) and heterogeneity decreased, although remained high ($I^2 = 64\%$). Thus, caution is required when interpreting these results.

Seven studies reported time-to-mortality using adjusted HRs. Two separate analyses were conducted to determine the pooled adjusted HR estimates; one including data from the standard BP treatment arm of the *post hoc* analyses from the SPRINT trial (data presented) that revealed a 21% greater risk in mortality (aHR: 1.21, 1.05–1.40; $P = 0.007$; $I^2 = 23\%$; *Figure 2B*). The second included data from the intensive BP treatment arm of the *post hoc* analyses from the SPRINT trial that also demonstrated a significant 23% greater risk in all-cause

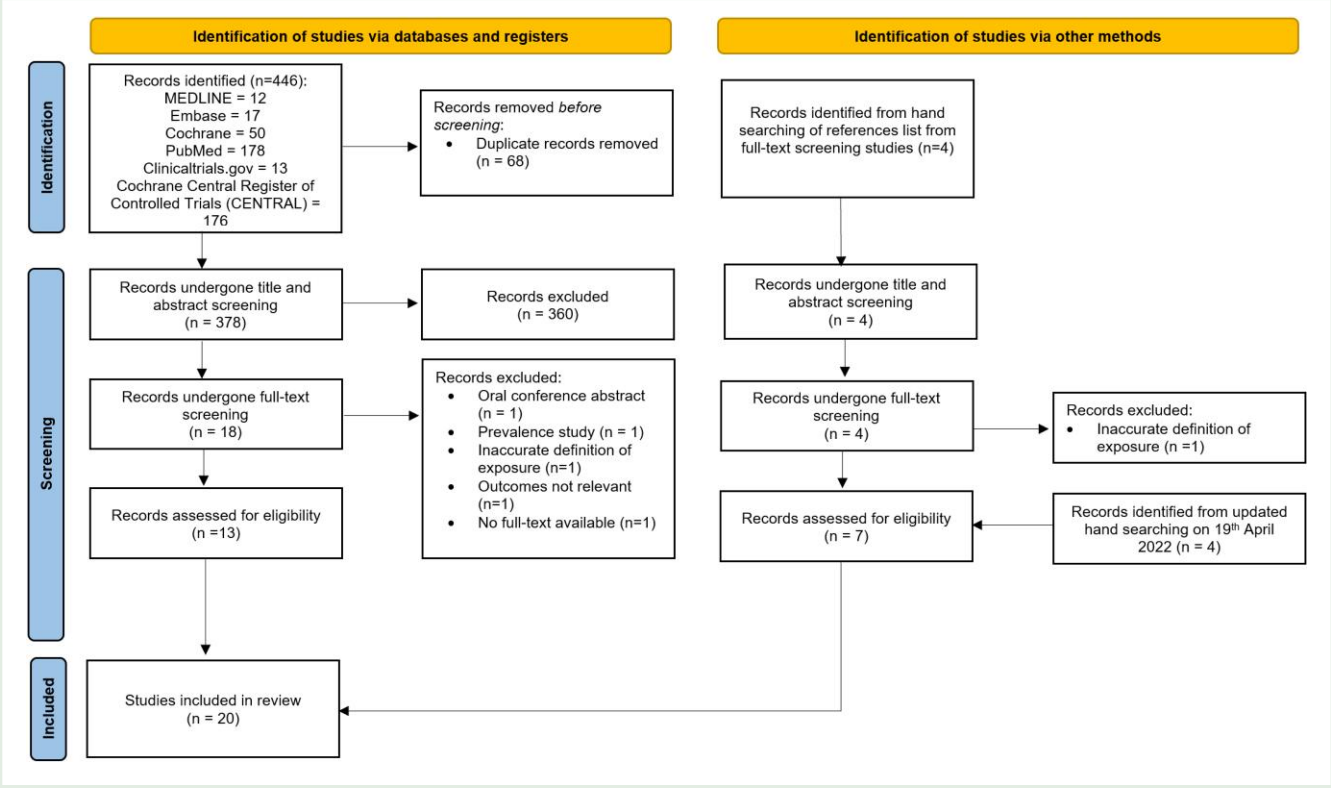

Figure 1 PRISMA 2020 flow diagram for new systematic reviews that included searches of databases, registers, and other sources.

mortality in association with SOHT (see Supplementary material online, *Figure S3*). Moreover, in additional analyses including only studies adjusting for hypertension, blood pressure or anti-hypertensive use, adjusted HRs only slightly increased, and statistical significance remained in both treatment groups (see Supplementary material online, *Figures S4 and S5*). In the standard BP treatment group, this slightly increased to aHR 1.23 (95% CI 1.09–1.38); $I^2 = 0\%$ and 1.24 (95% CI 1.11–1.40; $I^2 = 0\%$) in the intensive BP treatment group.

Diastolic orthostatic hypertension and all-cause mortality

Two studies ($n = 10\,505$; women 37.6%) assessed the relationship between DOHT and all-cause mortality.[9,11] Diastolic orthostatic hypertension was defined as $\Delta DBP \geq 10$ mmHg in both studies, and effect sizes were reported using adjusted HRs. Pooled adjusted HRs for DOHT and all-cause mortality were not statistically significant, and heterogeneity was low to moderate between analyses including standard and intensive BP treatment arms of the SPRINT trial (see Supplementary material online, *Figures S6 and S7*, respectively).

Systolic orthostatic hypertension and/or diastolic orthostatic hypertension and all-cause mortality

Likewise, two studies ($n = 10\,505$; women 37.6%) investigated the association between OHT and all-cause mortality.[9,11] Orthostatic hypertension was defined as $\Delta SBP \geq 20$ mmHg and/or $\Delta DBP \geq 10$ mmHg in both studies. Effect sizes were reported using adjusted HRs, and pooled adjusted HRs showed no statistically significant association between OHT and all-cause mortality (see Supplementary material online, *Figures S8 and S9*). Heterogeneity was low to high between two separate analyses from the standard and intensive BP treatment arms of the SPRINT trial.

Systolic orthostatic hypertension and cardiovascular disease mortality

Two studies ($n = 12115$, women 40.9%) investigated the effect of SOHT on CVD mortality.[10,11] Results were reported using adjusted HRs. Systolic orthostatic hypertension was associated with 39% increase in risk of CVD mortality in data comprising of the standard BP treatment arm from the SPRINT trial (aHR: 1.39, 1.05–1.84; $P = 0.02$; $I^2 = 0\%$; *Figure 3*). Notably, results were mainly driven by one study[10] weighted as 92.7% in the meta-analysis. In the pooled analysis consisting of data from the intensive BP treatment arm from the SPRINT trial, a non-significant 25% increase in risk for CVD mortality was observed (aHR: 1.25, 0.64–2.46; $P = 0.51$; $I^2 = 18\%$; Supplementary material online, *Figure S10*).

Orthostatic hypertension and incident heart failure

Three studies ($n = 16707$, women 30.3%) evaluated the relationship between SOHT and incident HF.[11,14,25] All studies defined SOHT as $\Delta SBP \geq 20$ mmHg and reported their effect using adjusted HRs.

Pooling of adjusted HR estimates displayed a non-significant 31% increase in risk of HF associated with SOHT and moderate statistical heterogeneity (aHR: 1.31, 0.81–2.11; $P = 0.26$; $I^2 = 65\%$; Supplementary material online, *Figure S11*) from data including the standard BP arm of the SPRINT trial. Pooled adjusted HR estimates using data from the intensive BP arm of the SPRINT trial showed a non-significant 50% increase in risk of HF in those with SOHT and moderate statistical heterogeneity (aHR: 1.50, 0.99–2.28; $P = 0.06$; $I^2 = 69\%$; Supplementary material online, *Figure S12*).

Two of these studies also assessed the relationship between DOHT and HF.[11,25] The association between DOHT and HF using data from either of the treatment arms of the SPRINT trial was not statistically

Table 1 Characteristics of included studies

Study	Country of origin	Study design	Sample characteristics	Age range (years) of sample	Mean follow-up (years)	Total population included	Females/ males	Exposure/ definition of OHT	Comparison	Outcomes assessed
Agnoletti *et al.* 2016	France and Italy	Prospective	Participants living in nursing homes	≥80	2	972	748/224	ΔSBP ≥ 20 mmHg	ONT	Cardiovascular morbidity and mortality
Bursztyn *et al.* 2016	Israel	Prospective	Community-dwelling residents born in 1920–1921	85–95	10 years	1004	542/462	ΔSBP ≥ 20 mmHg	ONT	All-cause mortality
Curreri *et al.* 2016	Italy	Prospective	Community dwelling subjects	65–96	4.4	1408	836/572	ΔSBP ≥ 20 mmHg	ONT	Cognitive Impairment and decline
Davis *et al.* 1987	USA	Prospective	Hypertensive individuals	30–69	5	10 536	4826/5710	ΔSBP ≥ 20 mmHg	ΔSBP −19 to 0 mmHg	Mortality
Eguchi *et al.* 2004	Japan	Cross-sectional	Hypertensive individuals and age-matched normotensive	48–86	NA	86	66/20	ΔSBP ≥ 10 mmHg	ONT	Silent Cerebrovascular disease
Fan *et al.* 2010	China	Cross-sectional	Rural community residents	40–75	NA	5437	3649/1788	ΔSBP ≥ 20 mmHg	ONT	Coronary artery disease, stroke, left ventricular hypertrophy, peripheral arterial disease
Gilani *et al.* 2021	UK	Prospective	Males from age-sex register	40–59	13.3	3505	0/3505	ΔSBP ≥ 20 mmHg, ΔDBP ≥ 10 mmHg	ONT	Incident Heart Failure
Hartog *et al.* 2016	Netherlands	Prospective	Participants from 3 departments of a nursing home facility	Not stated.	2.7	290	206/84	ΔSBP ≥ 20 mmHg	ONT	All-cause mortality
Kario *et al.* 2002	Japan	Cross-sectional	Elderly hypertensive outpatients	≥60	NA	241	139/102	ΔSBP ≥ 20 mmHg	ONT	Silent Cerebrovascular disease
Kostis *et al.* 2019	USA	Prospective	Participants with isolated systolic hypertension (SBP ≥ 160 mm Hg) randomized to chlorthalidone-based active treatment or matching placebo	≥60	17	4276	2417/1859	ΔSBP ≥ 15 mmHg	ONT	All-cause mortality
Matsubayashi *et al.* 1997	Japan	Cross-sectional	Subjects with definite neurological diseases, such as Parkinsonism and stroke, and those who were too severely ill to stand without help were excluded. Subjects with definite dementia were also excluded.	≥75	NA	334	182/152	ΔSBP ≥ 20 mmHg	ONT	Cognitive impairment
Rahman *et al.* 2021	USA	*Post hoc* analysis of randomized controlled trial	Participants had age of at least 50 years, systolic BP of 130 to 180 mm Hg, and high risk of cardiovascular disease defined as presence of one or more of the following: clinical or subclinical cardiovascular disease, chronic kidney disease, a 10-year risk of cardiovascular disease ≥15% estimated by the Framingham risk score or age ≥75 years.	≥50	3.26[a]	9329	3317/6012	ΔSBP ≥ 20 mmHg	ONT	All-cause mortality, CVD mortality, HF, MI, injurious falls, composite CVD

Continued

Table 1 *Continued*

Study	Country of origin	Study design	Sample characteristics	Age range (years) of sample	Mean follow-up (years)	Total population included	Females/ males	Exposure/ definition of OHT	Comparison	Outcomes assessed
Roca *et al*. 2022	France	Cross- sectional	All outpatients addressed in a day-hospital unit from a geriatric department	≥80	NA	530	351/179	ΔSBP ≥ 20 mmHg	ONT	Cognitive Impairment
Rouabhi *et al.* 2021	USA	Prospective	Participants with chronic kidney disease	21–74	7.9	3873	1743/2130	ΔSBP ≥ 20 mmHg	No OHT	Cardiovascular events (myocardial infarction, heart failure, stroke, peripheral arterial disease)
Sparrow *et al.* 1984	USA	Prospective	White males	21–80	8.7	1359	0/1359	ΔDBP ≥ 10 mmHg	ΔDBP 1 to 9 mmHg	Incidence of MI
Torres *et al.* 2017	USA	Cross-sectional	Participants living independently in the central New York area surrounding Syracuse at the time of recruitment	≤80	NA	961	569/392	ΔSBP ≥ 20 mmHg	ONT	Cognitive function
Velilla-Zancada *et al*. 2017	Spain	Ambispective	Adults living in Cantabria	≥18	9.4	1176	632/544	ΔSBP ≥ 20 mmHg, ΔDBP ≥ 10 mmHg	No OHT	All-cause mortality
Veronese *et al.* 2015	Italy	Prospective	Caucasian participants	65–103	4.4	2786	1643/1143	ΔSBP ≥ 20 mmHg	ONT	All-cause mortality, cardiovascular disease mortality, non-cardiovascular disease mortality
Wijkman *et al*. 2016	Sweden	Prospective	Type 2 diabetes patients treated in primary care	55–65	7.8	749	257/492	ΔSBP ≥ 20 mmHg, ΔDBP ≥ 10 mmHg	ONT, no SOHT, normal systolic response	Cardiovascular disease hospitalisation or mortality
Yatsuya *et al.* 2011	USA	Prospective	Black and White participants at visit 1 of cohort	45–64	18.7	12 817	7049/5768	ΔSBP ≥ 20 mmHg, ΔDBP ≥ 10 mmHg	ΔSBP −10 to +10 mmHg	Ischaemic stroke subtypes

[a]Median follow-up year.

Table 2 Summary of study quality assessment according to the Newcastle–Ottawa scale (NOS) tool

	Selection (S)				Comparability (C)		Outcome (O)			Subtotal assessment			Conclusion
	1	2	3	4	1a	1b	1	2	3	S[a]	C[b]	O[c]	
Cohort studies													
Agnoletti *et al.* 2016	0	★	★	0	★	★	★	0	★	Fair	Good	Good	Fair
Bursztyn *et al.* 2016	★	★	★	0	★	★	★	★	★	Good	Good	Good	Good
Curreri *et al.* 2016	★	★	★	★	★	★	★	0	★	Good	Good	Good	Good
Davis *et al.* 1987	0	★	★	0	★	0	0	0	★	Fair	Fair	Poor	Poor
Gilani *et al.* 2021	0	★	★	★	★	★	★	0	★	Good	Good	Good	Good
Hartog *et al.* 2016	0	★	★	0	★	★	★	0	★	Fair	Good	Good	Fair
Kostis *et al.* 2019	0	★	★	0	★	★	★	★	★	Fair	Good	Good	Fair
Rahman *et al.* 2021	0	★	★	0	★	★	★	0	★	Fair	Good	Good	Fair
Rouabhi *et al.* 2021	0	★	★	★	★	★	★	0	★	Good	Good	Good	Good
Sparrow *et al.* 1984	0	★	★	0	★	0	★	0	★	Fair	Fair	Good	Fair
Velilla-Zancada *et al.* 2017	★	★	★	0	★	★	★	0	★	Good	Good	Good	Good
Veronese *et al.* 2015	★	★	★	0	★	★	★	★	★	Good	Good	Good	Good
Wijkman *et al.* 2016	0	★	★	0	★	★	★	0	★	Fair	Good	Good	Fair
Yatsuya *et al.* 2012	0	★	★	★	★	★	★	0	★	Good	Good	Good	Good

	Selection (S)				Comparability (C)		Outcome		Subtotal assessment			Conclusion
	1	2	3	4	1a	1b	1	2	S[c]	C[b]	O[b]	
Cross-sectional studies												
Eguchi *et al.* 2004	0	0	★	★★	0	0	★★	★	Fair	Poor	Good	Fair
Fan *et al.* 2010	★	★	0	★★	★	★	★★	★	Good	Good	Good	Good
Kario *et al.* 2002	0	★	★	★★	★	★	★★	★	Good	Good	Good	Good
Matsubayashi *et al.* 1997	★	★	0	★★	★	★	★★	★	Good	Good	Good	Good
Roca *et al.* 2022	0	0	0	★★	★	★	★★	★	Fair	Good	Good	Fair
Torres *et al.* 2017	★	★	0	★★	★	★	★★	★	Good	Good	Good	Good

[a]Domain scored: 0–1 (poor); 2 (fair); 3+ (good).
[b]Domain scored: 0 (poor); 1 (fair); 2+ (good).
[c]Domain scored: 0–1 (poor); 2–3 (fair); 4+ (good).

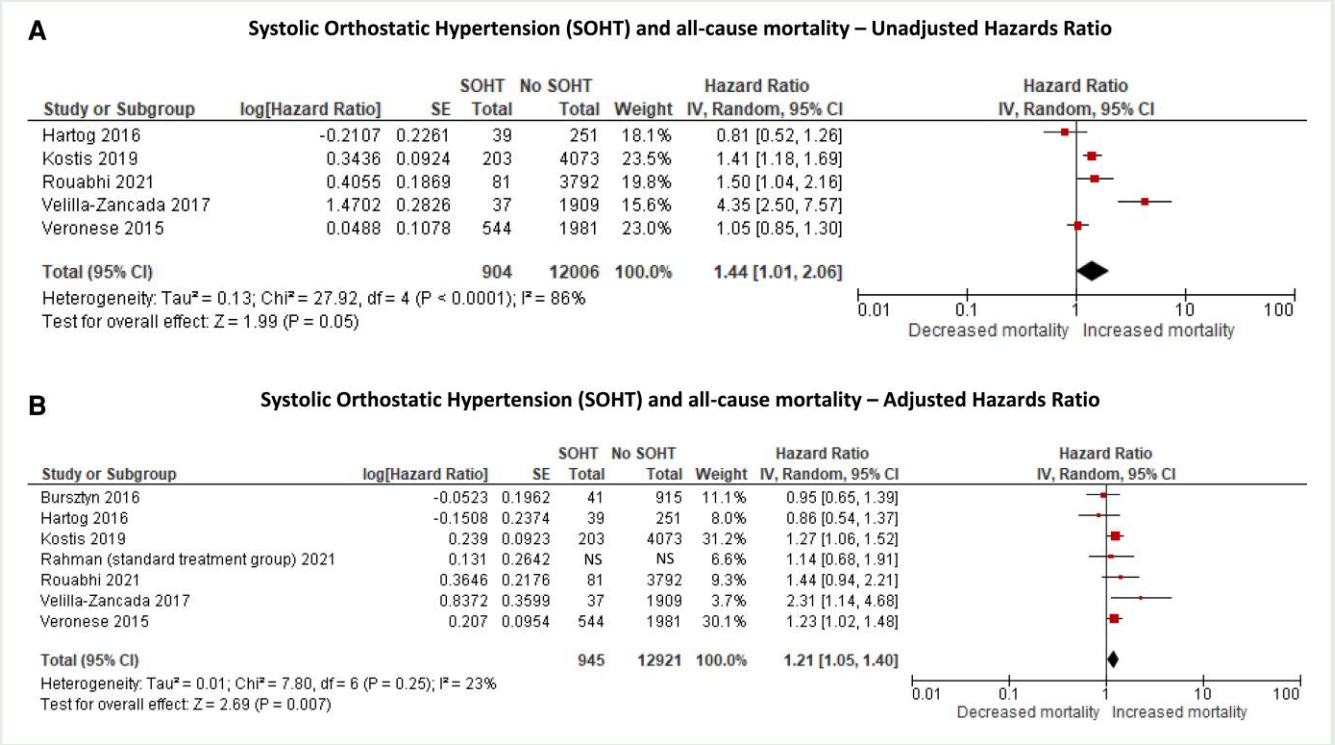

Figure 2 Forest plots displaying the risk of mortality in patients with systolic orthostatic hypertension relative to patients with no systolic orthostatic hypertension for the studies using (*A*) unadjusted hazard ratio and (*B*) adjusted hazard ratio. NS, not stated; SOHT, systolic orthostatic hypertension.

significant and heterogeneity was low to high (see Supplementary material online, *Figures S13* and *S14*).

Systolic orthostatic hypertension and incident myocardial infarction (MI)

Further, two studies ($n = 13\,202$, women 38.3%) investigated the relationship between SOHT and incident MI.[11,14] Pooled adjusted HRs showed a non-significant 25% increase in risk of MI in the analysis including the standard BP treatment group and non-significant 13% increase in risk of MI in the intensive BP treatment group (see Supplementary material online, *Figures S15* and *S16*).

Systolic orthostatic hypertension and incident stroke/cerebrovascular disease

Six studies ($n = 31\,883$, women 50.1%) assessed the association between SOHT and incident all-type stroke or cerebrovascular disease.[11,14,26–29] Five studies defined SOHT as ΔSBP ≥20 mmHg[11,14,26,27,29] and one defined SOHT as ΔSBP ≥ 10 mmHg.[26] In five studies, the overall effect was reported using unadjusted OR.[14,26–29]

The pooled unadjusted OR showed an overall higher odds of incident stroke/cerebrovascular disease (OR: 1.94, 1.52–2.48; $P < 0.0001$) (*Figure 4*), and statistical heterogeneity was low ($I^2 = 12\%$).

Narrative review of studies not eligible for pooling

Orthostatic hypertension and composite cardiovascular disease

Three studies investigated the association between SOHT and composite CVD endpoints.[6,12,14] Two found no significant association between SOHT and composite CVD endpoint,[12,14] and one study found a significant 51% increased risk between SOHT and CVD-related morbidity and mortality.[6]

Rouabhi *et al.*[14] defined composite CVD endpoint as the first occurrence of HF, MI, stroke, or peripheral arterial disease (PAD). Wijkman *et al.*[12] defined composite CVD endpoint as the first fatal or non-fatal event or hospitalization for acute MI, stroke, or CVD mortality. Both studies had a lower percentage of participants with SOHT; 4.6%[14] and 6%,[12] compared to 28.3% in the study by Agnoletti *et al.*[6] Of note, Wijkman *et al.*[12] found a decreased risk of composite CVD in association with DOHT (HR: 0.335, 0.133–0.839), and 18.7% had DOHT in their sample.

Orthostatic hypertension and other secondary outcomes

A summary of the effects of OHT on secondary outcomes including myocardial infarction, coronary artery disease, acute coronary syndromes, left ventricular hypertrophy, PAD, cognitive function, and injurious falls has been reported in Supplementary material online, *Table S12*. Overall, most studies did not find an association between OHT and independent secondary outcomes, apart from one that found a significant association between SOHT and PAD[27] and three studies that found significant associations between SOHT and cognitive functioning or health.[3,31,33]

Discussion

Our searches highlighted 20 eligible studies; 13 were cohort studies, one *post hoc* analysis of a randomized controlled trial, and six cross-sectional studies with typically good risk of bias. Our analyses displayed that SOHT was associated with increased risk of all-cause mortality,

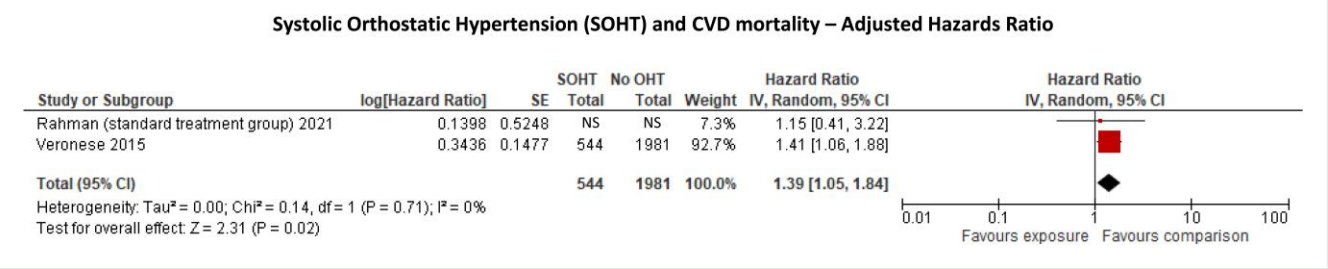

Figure 3 Forest plots displaying the risk of cardiovascular disease mortality in patients with systolic orthostatic hypertension (ΔSBP ≥20 mmHg) relative to patients with no SOHT for the studies using adjusted hazard ratios. NS, not stated; CVD, cardiovascular disease; SOHT, systolic orthostatic hypertension.

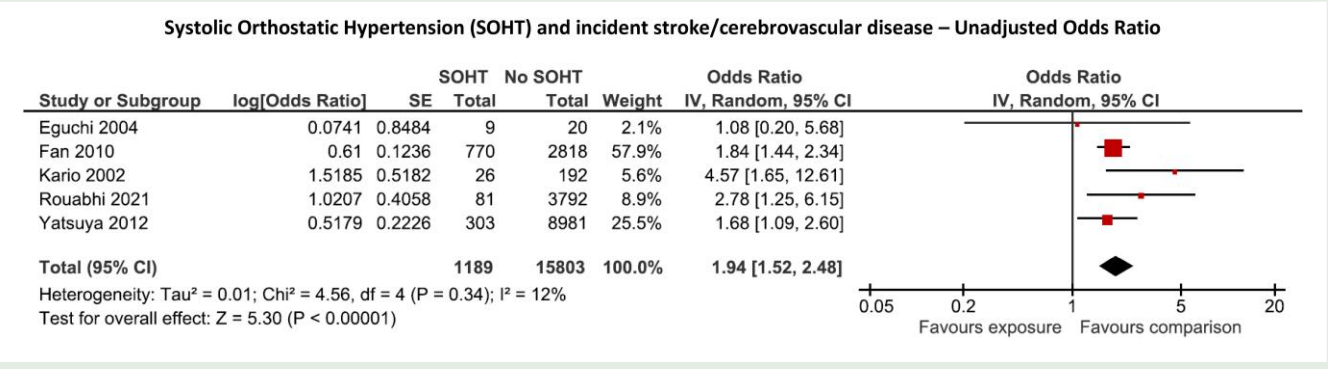

Figure 4 Forest plots displaying the odds of incident stroke/cerebrovascular disease in patients with systolic orthostatic hypertension relative to patients with no systolic orthostatic hypertension for the studies using unadjusted odds ratio. SOHT, systolic orthostatic hypertension.

CVD mortality, and increased odds of stroke/cerebrovascular disease. Of note, the meta-analysis on CVD mortality was based on two studies, for which its pooled estimate was mainly driven by one study, and the association between stroke/cerebrovascular disease was based on unadjusted analyses. Furthermore, narrative synthesis on three of four studies investigating cognitive outcomes found significant associations between SOHT and severe cognitive impairment, neurobehavioral functions, and cognitive decline. Importantly, five studies were conducted among hypertensive patients,[7,8,26–28] and among six that reported the prevalence of hypertension in those with OHT, four had a prevalence >50%.[3,10,25,31] Similarly, the percentage of hypertension reported in studies with data available only for the total cohort was high (>60%) for all three studies.[12–14] Orthostatic hypertension is thought to arise from autonomic instability[1] and is commonly associated with conditions associated with altered cardiovascular adrenergic control mechanisms.[1] Examples include postural tachycardia syndrome, essential hypertension, cardiac hypertrophy, and chronic HF.[1,34,35] Previous research has established the association between impaired autonomic function and increased risk of mortality.[36] In our analysis accounting for adjusted estimates for SOHT and all-cause mortality and CVD mortality, the strength of association was sizeable, with low heterogeneity. Whether this excess risk in mortality is attributable directly to OHT as a risk factor *per se* or due to such autonomic dysfunction being present in already high-risk patient groups or is just a marker is uncertain. Further studies are required in different patient populations to explore this association.

In our adjusted analysis with SOHT and all-cause mortality, Kostis *et al.* defined SOHT as ΔSBP ≥ 15 mmHg. As a 5 mmHg difference is a relatively small disparity in blood pressure, we suspected that the clinical implications of such a small difference are not likely to be very high. However, given the weight of this analysis is mainly driven by Veronese *et al.* (61%) and Kostis *et al.* (31%), we performed a *post hoc* sensitivity analysis to test the statistical impact of this slight disparity. We found that upon removal of the findings from Kostis *et al.* in the adjusted analysis, the pooled adjusted hazards ratio slightly decreased, and the result was borderline significant (aHR: 1.19, 95% CI 0.97–1.45; $I^2 = 33\%$). However, the results maintained the same direction of effect (see Supplementary material online, *Figure S17*). This may be due to a type II error, as notably the study by Kostis *et al.* had a substantial weighting within the meta-analysis, consisting of a total of 4207 patients, of which ~5% had SOHT. Thus, it is difficult to disentangle whether the change in result could be due to an underpowered analysis, or due to a true difference attributable to a slight difference of 5 mmHg in defining SOHT. If the difference in statistical result was due to the latter, then it would stand that even smaller increases in standing systolic BP are indeed significant and should be considered. A similar loss of significance was found when excluding Kostis *et al.* from the unadjusted analysis for SOHT and all-cause mortality (see Supplementary material online, *Figure S18*).

Moreover, we found that DOHT was not associated with adverse events. This may be due to lower reliability in DOHT definition, as DBP is known to typically elevate by 5 to 10 mmHg on orthostatism due to peripheral vasoconstriction and decreased cardiac stroke volume.[1] Additionally, differentiating between phases of Korotkoff sounds for measuring DBP may be more subtle, and inaccuracies in measurement may reflect this result.

There was a strong consistency in the association between SOHT and stroke/cerebrovascular disease among four of five included studies investigating this outcome. Of note, two of these studies consisted of hypertensive patients[27,28] that may account for the association rather

than OHT. Previous research has found that subjects with postural ΔSBP >10 mmHg 3 minutes after orthostatism were likely to have masked hypertension, regardless of antihypertensive treatment status.[37] Since OHT may occur as a result of a hyperactive pressor response mediated through excessive adrenergic sympathetic nervous system activation, the resulting endothelial dysfunction may play a role in the pathogenesis of stroke.[29,38] One study found that OHT emerges as a risk factor for CVD-related mortality only in participants free from CVD at baseline.[10] They hypothesized that the effect of OHT in patients with CVD may be underestimated, given the already high risk of death apparent in those with CVD.[10] Moreover, it has been previously postulated that OHT could be considered a form of pre-hypertension,[28] and thus it may be that OHT is a manifestation of CVD along a continuum. Whilst three studies pooled in this analysis were in hypertensive patients,[26–28] the other two studies consisted of patients with chronic kidney disease (CKD) of which 86% had hypertension,[14] and one study performed a subgroup analysis excluding individuals with baseline congestive heart disease, HF and those on antihypertensive, and other medications potentially associated with orthostatic BP dysfunction.[29] The subgroup analysis found that orthostatic SBP increase (≥20 mmHg) appeared to be associated with increased risk of lacunar stroke only (HR: 1.88, 95% CI 0.94–3.75, $P = 0.075$).[29] Furthermore, whilst three studies[26–28] were cross-sectional, where reverse causality may be a major factor, the remaining studies were prospective and found similar increased odds of stroke/cerebrovascular disease, reinforcing the temporality of the association.

Likewise, this potential mechanistic link between OHT and cerebrovascular disease could also explain its association with severe cognitive impairment[3] and cognitive decline.[31] Such patients who may be at increased risk of cerebrovascular accidents may acquire ischaemic cerebrovascular changes and disruption of the blood–brain barrier. As a result, oxidative stress and the entry or faulty clearance of circulating neurotoxic molecules from brain to blood, along with improper nutrient delivery and expression of various molecular factors critical to brain health, may lead to neuronal dysfunction.[39]

The null association found between SOHT and HF may be due to inadequate sample sizes of included studies. In one of the two studies investigating HF, only 81 (2.1%) participants had SOHT.[14] They did not find a statistically significant association between SOHT and HF, compared to another study with 243 participants with SOHT (6.9% from the total cohort and 12.4% compared to ONT reference category) who found significant increase in risk (aHR: 1.88; 95% CI 1.30–2.73).[25] Further robust large prospective cohort studies are required to establish this association. Of note, given that HF is a continuum, and HF types were not independently explored in these studies, future research should investigate the association between OHT and HF type.

In the clinical setting, postural BP, despite being an important component of the cardiovascular exam, is infrequently performed. Further, in clinical practice, the procedure used to detect this condition may be variable. Since postural BP changes are common, and there is evidence that the presence of this condition along with postural hypotension is associated with significantly increased risk of major adverse events in patients,[40] clinicians should give further attention to this simple bedside test. Whilst resting BP may provide important information regarding patient's CVD risk, OHT as a separate condition with possible different pathophysiology may provide an alternative picture to a patient's CVD status and their autonomic functioning. Further research comparing the predictive potential of OHT compared to resting SBP as a marker of adverse events is warranted to guide clinical assessments. As the first study of its kind to examine the cumulative evidence of the association between OHT and major adverse events, this meta-analysis brings new insights and fills a critical literature gap. Furthermore, two independent reviewers performed database searches, data extractions, and screening to ensure accuracy of the review process and eliminate potential bias. Additionally, only one of the included studies was deemed to be of poor quality, and there was visible symmetry in the funnel plot for the outcome of mortality, thus indicating low chance of publication bias. Whilst most populations included were of Western or European origin, there is little reason to believe that the mechanistic link between OHT and major adverse events would differ among varying ethnic groups.

However, there are several limitations worth acknowledging, some of which are inherent to the research of an understudied condition with lack of formal diagnostic criteria. Whilst most studies had a consistent definition for OHT, one study[26] defined SOHT as ΔSBP ≥ 10 mmHg and another as ΔSBP ≥ 15 mmHg,[8] thus, allowing potential for misclassification bias. Yet, the effect of this is likely insignificant, given its very small deviance from the threshold of the most widely accepted definition (i.e. ΔSBP ≥ 20 mmHg). Further, if the severity of OHT is directly correlated with risk of mortality, then such deviance from the accepted norm would more likely bring the estimate closer to the null effect, than overestimate any effect. Moreover, Eguchi *et al.*[26] found a correlation between OHT patients classified with SBP rises in subsequent head-up tilts. Of 13 OHT patients who had an orthostatic ΔSBP ≥ 20 mmHg in the first head-up tilt, 10 (77%) had orthostatic ΔSBP ≥ 10 mmHg in the second head-up tilt. Of note, some studies slightly differed in their measurement methods for determining OHT, and a full account of this has been presented in Supplementary material online, *Table S11*. A total of 50% of studies determined OHT from supine-standing positions,[3,10,13,26,28–33] and the other half from sitting–standing.[5–9,11,12,14,25,27] Further, most studies recorded standing BP following a similar length of orthostatism. Nine studies measured this between 1 and 3 min of orthostatism[3,6–10,13,31,32] and five between 1 and 2 min[12,14,25,29,33] of orthostatism. One study measured standing BP at 30 s as well as 2 min[27] and two at 1 min standing.[5,11] Only one study evaluated standing BP only 30 s following standing,[30] however, this study was not included in the meta-analyses. Moreover, two studies utilized the head-up tilt test.[26,28] Given reports of standardized protocols for measuring orthostatic BP change carried out by trained nurses, it is unlikely that the accuracy of measurements is at stake. Nevertheless, it is important to acknowledge that direct measures of intra-arterial pressure provide the most accurate measure, and sphygmomanometers may underestimate postural blood pressure under the influence of a hyperactive pressor response.[2]

Conclusions

Systolic orthostatic hypertension was associated with adverse events including all-cause and CVD mortality as well as stroke/cerebrovascular disease. Further large prospective studies with an agreed definition of OHT are required to establish the association between OHT and its individual SOHT and DOHT components on important outcomes such as HF and neurocognitive decline. These patients may potentially benefit from strategies aimed towards mitigating their risk, and targeted trials based on the management of postural hypertension are needed.

Supplementary material

Supplementary material online, *Tables S1–12* and Supplementary material online, *Figures S1–S18* are available as part of the online supplementary material.

Supplementary material is available at European *Journal of Preventive Cardiology* online.

Author contributions

J.F.P. and P.K.M. conceived the study. L.D.P. and Z.P. drafted the study protocol under supervision of P.K.M., B.C., and J.F.P. L.D.P. and Z.P.

performed searches, extracted data, critically appraised included studies, and analysed the data under supervision of T.A.P., B.C., J.F.P., and P.K.M. L.D.P. and Z.P. drafted the paper. B.C. provided expert statistical advice and supervised statistical analysis and data presentation. All authors contributed to data interpretation and writing of the paper. P.K.M. is the guarantor.

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Conflict of interest: None declared.

Data availability

The data underlying this article are available as part of the online supplementary material.

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