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REVIEW

Orthostatic hypotension and health outcomes: an umbrella review of observational studies

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Key summary points

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

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

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

Abstract

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

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

Results From 975 abstracts, seven meta-analyses of 12 outcomes were included. For each outcome, the median number of studies was four, and the median number of participants was 46,493, with a median of 3630 incident cases. There was suggestive (class III) evidence that OH was associated with significantly higher risk of coronary heart disease (HR = 1.32, 95% CI 1.12–1.56), stroke (HR = 1.22, 95% CI 1.08–1.38), congestive heart failure (HR = 1.30, 95% CI 1.09–1.55), all-cause mortality (RR = 1.50, 95% CI 1.24–1.81), falls (OR = 1.84, 95% CI 1.39–2.44), and dementia (HR = 1.22, 95% CI 1.11–1.35).

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

Keywords Orthostatic hypotension · Umbrella review · Meta-analysis · Mortality · Fall · Heart failure · Heart disease · Stroke

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Extended author information available on the last page of the article

Introduction

Orthostatic hypotension (OH) diagnosis is often defined as a drop of at least 20 mmHg in systolic BP (SBP) and/or 10 mmHg in diastolic BP (DBP) upon the change in position (from sitting to standing) [1]. The prevalence of OH increases with age and is estimated to be 10–30% in older adults. It is

important to note that different methods used to measure OH have produced different prevalence estimates [2–4]. Reasons for the increase in prevalence of OH with age include an age-related decrease in renin–angiotensin aldosterone level, cardiac hypertrophy, and deficiency in arterial baroreflex sensitivity and vasomotor control, all of which make the management of postural blood pressure increasingly difficult with age [5].

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

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

Materials and methods

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

Data sources and searches

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

Study selection

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

Data extraction

Two independent investigators (PS, JD) extracted the following information for each article: (1) first author name; (2) year of publication; (3) journal; (4) the number of included studies and the total number of the people included in the review; (5) the inclusion criteria for studied population; (6) the definition used for OH; (7) the effect size used in the review; (8) study design (case–control, longitudinal); (9) number of cases (i.e., people having the event of interest, e.g., falls) and controls (i.e., people without events) for each study; and (10) setting. Disagreements were resolved through consensus with another independent reviewer (NV). We then extracted the study-specific estimated relative risk for each health outcome (risk ratio [RR], odds ratio [OR], hazard ratio [HR], mean difference [MDs]), along with the associated 95% confidence interval (CI). If two meta-analyses were available for the same outcome, we included the largest in terms of studies.

Outcomes

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

Methodological quality of systematic reviews

The methodological quality of the included meta-analyses was assessed using ROBIS. The ROBIS is completed in three phases: (1) assess relevance (optional), (2) identify concerns with the review process, and (3) judge risk of bias. Phase 2 covers four domains through which bias may be introduced into an each systematic review of the umbrella review: study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis and findings. Phase 3 assesses the overall risk of bias in the interpretation of review findings and whether this considered limitations identified in any of the phase 2 domains. Signaling questions are included to help judge concerns with the review process (phase 2) and the overall risk of bias in the review (phase 3);

these questions flag aspects of review design related to the potential for bias and aim to help assessors judge risk of bias in the review process, results, and conclusions. Each item can be scored from low to high risk of bias [13].

Statistical analysis

For each meta-analysis, we re-calculated the summary effect size and its 95% CI, using random-effects models [14]. Next, the 95% prediction interval was estimated which further accounts for between-study effects and estimates the certainty of the association if a new study addresses that same association [15]. For the largest study of each meta-analysis, we evaluated whether this was statistically significant. Heterogeneity was estimated using the I^2 metric, with values ≥ 50% indicative of high heterogeneity, and values ≥ 75% suggesting very high heterogeneity [16, 17]. In addition, we calculated the evidence of small study effects. In this regard, we used the regression asymmetry test [18], using a p value < 0.10 [19]. Finally, we applied the excess of significance test [20] which evaluates whether the number of studies with nominally significant results (i.e., with $p < 0.05$) among those included in a meta-analysis is too large based on the power that these data sets have to detect effects at $\alpha = 0.05$. The number of expected 'positive' (E), i.e., statistically significant studies, was compared with the observed (O) number of statistically significant studies through a χ^2-based test [20]. A p value < 0.10 was considered indicating of excess statistical significance.

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

Grading the evidence

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

Results

Literature search

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

Meta-analyses of included studies

Table 1 summarizes the main findings of our umbrella review. For each outcome, the median number of studies was four, and the median number of participants was 46,493, with a median of 3630 incident cases.

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

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

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

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

Discussion

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

Cardiovascular disease (CVD)

While we identified significant associations between OH and several cardiovascular outcomes (coronary heart disease,

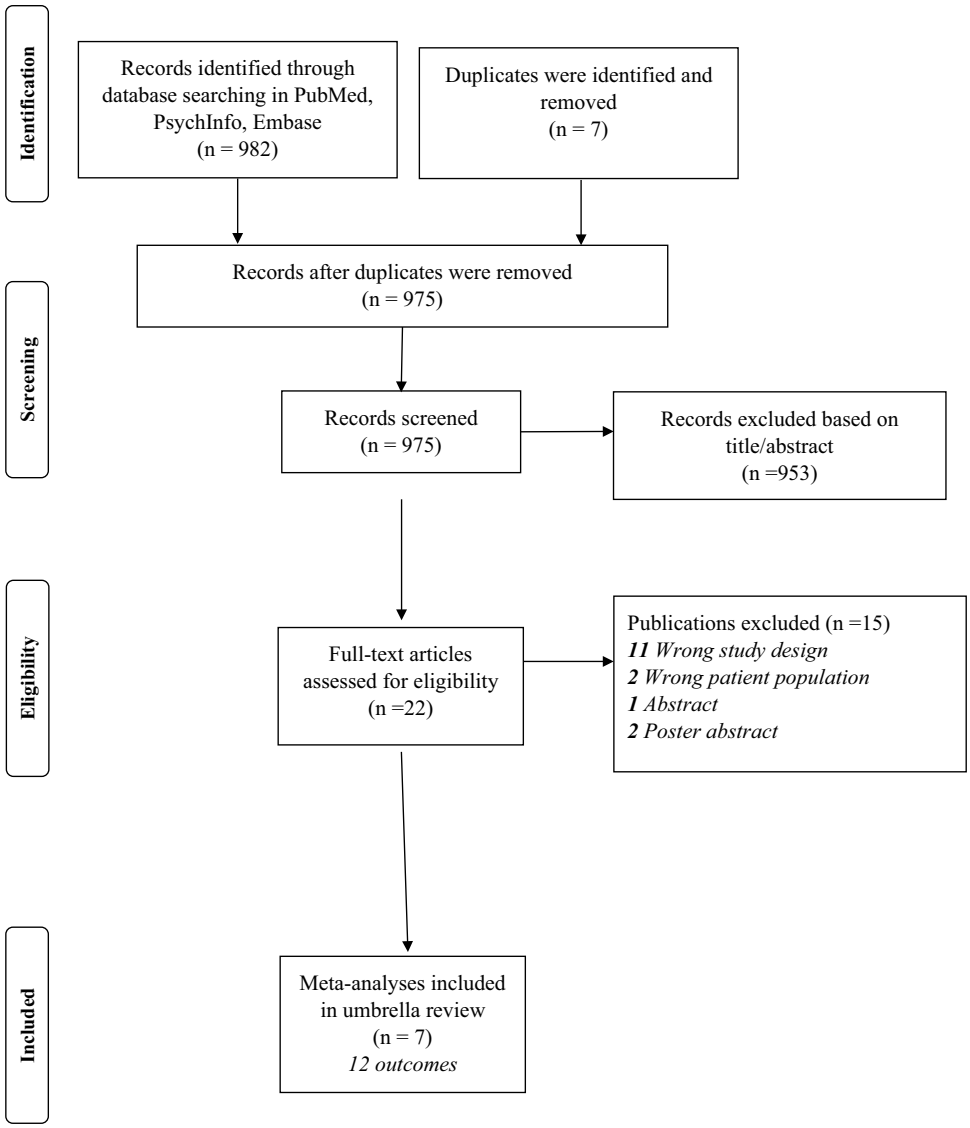

Fig. 1 Prisma flow diagram

stroke, congestive heart failure), none reached the cutoff for class I or II evidence.

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

Falls

Despite some studies failing to find a consistent association between OH and falls, the present review found suggestive evidence for this association meaning that this association

Table 1 Evidence of the association between orthostatic hypotension

Outcome [reference]	No. of studies	Cases	Sample size	Type of metric	Mean effect size (95% CI)	*p*	I^2	Small study effect	Excess significance bias	Largest study significant	95% Prediction intervals	Level of evidence
CHD [40]	7	5719	158,446	HR	1.32 (1.12–1.56)	0.001	65.4	No	Yes	No	0.81–2.15	III
Stroke [40]	7	3657	158,446	HR	1.22 (1.08–1.38)	0.002	20.2	No	Yes	Yes	0.95–1.57	III
Congestive HF [38]	4	3603	51,270	HR	1.30 (1.09–1.55)	0.004	56.5	No	No	Yes	0.66–2.56	III
All-cause mortality [39]	10	NA	65,174	RR	1.50 (1.24–1.81)	0.00004	93.4	No	NA	Yes	0.75–3.00	III
Falls [36]	15	2185	6323	OR	1.84 (1.39–2.44)	0.00002	73.2	Yes	Yes	No	0.68–5.01	III
Dementia [34]	4	NA	41,972	HR	1.22 (1.11–1.35)	0.00009	0	No	NA	No	0.98–1.53	III
Alzheimer [34]	2	NA	12,977	HR	1.18 (1.02–1.35)	0.02	0	NA	NA	No	NA	IV
Vascular dementia [34]	3	NA	30,469	HR	1.40 (1.04–1.89)	0.03	0	No	NA	No	0.20–9.66	IV
MMSE [34]	4	NA	3966	MD	−0.347 (−0.560 to −0.134)	0.001	23	No	NA	Yes	−1.01–0.31	IV
MCI [34]	5	NA	12,969	OR	1.20 (1.001–1.43)	0.048	58.9	No	NA	No	0.71–2.01	IV
CV mortality [37]	3	NA	51,013	RR	1.20 (0.73–2.00)	0.47	91.7	No	NA	No	0–655.7	NS
Non CV mortality [37]	3	NA	51,013	RR	1.20 (0.96–1.50)	0.11	38.6	No	NA	Yes	0.14–9.93	NS

CHD congenital heart disease, *CV* cardiovascular, *HF* heart failure, *HR* hazard ratio, *MCI* mild cognitive impairment, *MD* mean difference, *MMSE* mini-mental state examination, *NA* not applicable, *OR* odd ratios, *RR* relative risk

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

Dementia

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

The most frequently proposed mechanism linking OH to dementia is the recurrent transient brain hypoperfusion hypothesis [50]. Previous research has shown that cerebral blood flow is decreased in OH by electroencephalography [50], besides decreased brain perfusion during orthostatic pressure was demonstrated by the method of single-photon emission computed tomography [51]. Cerebral hypoperfusion may lead to leukoaraiosis underlying the neurodegeneration process in dementia [52]. OH was traditionally thought to be detrimental only if compensatory mechanisms are inadequate. When cerebral autoregulation is impaired, it reacts less efficiently to compensate for a drop in cerebral perfusion pressure and fails to maintain adequate cerebral blood flow which may cause ischemic cerebral damage [53]. However, one recent study reported no relationship between OH and cognitive impairment related with leukoaraiosis, subtle brain microstructural damage, or cerebral blood flow [54]. OH and cognitive function are complicated and affected by multiple factors. The autonomous nervous system has been reported to be essential for orthostatic reflex and dysfunction of this system usually results in OH [55]. Some pathologies such as diabetes, alpha-synucleinopathies, and sarcoidosis are common causes for autonomic neuropathy, and OH is prevalent among these diseases [56, 57]. On the other hand, in a recent study, it was demonstrated that the prevalence of OH, in older patients with Alzheimer's disease, was similar to those with dementia of Lewy body, an alpha-synucleinopathy [58].

All-cause mortality

OH represents a condition of impaired hemodynamic homeostasis, where compensatory neuroendocrine mechanisms

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

Limitations

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

Conclusions

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

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval It was not requested being a revision of already published literature. This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No patients were included in this review.

Sponsor's role None.

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