Systematic review and meta-analysis examining the relationship between postprandial hypotension, cardiovascular events, and all-cause mortality

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ABSTRACT

Background: Postprandial hypotension (PPH) has been reported to be associated with syncope, falls, adverse cardiovascular outcomes, and increased all-cause mortality. It has been reported to have an incidence as high as 30% in the elderly and persons with diabetes. We therefore performed a meta-analysis to determine the relation of PPH with cardiovascular disease (CVD) events and all-cause mortality.

Objectives: Our objective was to conduct a systematic review and meta-analysis of cohort and cross-sectional studies to determine the association of PPH with CVD and all-cause mortality.

Methods: We searched the databases MEDLINE, EMBASE, and Cochrane library up to 13 April 2022 for prospective cohort and cross-sectional studies that examined the association of PPH with CVD outcomes and all-cause mortality. Data were analyzed using the generic inverse variance method with a random-effects model. Grading of Recommendations, Assessment, Development, and Evaluation approach assessed the certainty of evidence.

Results: Seven studies that included 2389 participants met our inclusion criteria. PPH was associated with each outcome individually, including increased all-cause mortality, total CVD, CVD mortality, and stroke. CVD outcomes and all-cause mortality combined were also associated with PPH (RR: 1.52; 95% CI: 1.05, 2.18; $P = 0.03$; $I^2 = 77\%$). The certainty of evidence was graded as very low due to significant heterogeneity and the limited number of studies.

Conclusions: This assessment indicates an association of PPH with CVD and all-cause mortality. Further studies are required to improve CVD and mortality estimates, but the potential seriousness of CVD and all-cause mortality as outcomes of PPH justifies more screening, diagnosis, and research. *Am J Clin Nutr* 2022;116:663–671.

Keywords: postprandial hypotension, cardiovascular disease, all-cause mortality, stroke, meta-analysis

Introduction

Postprandial hypotension (PPH) is a well-documented phenomenon but has received little attention clinically as a cause of concern. The disorder appears to be more common with increasing age, diabetes, and autonomic neuropathy (1, 2). It has been associated with syncope and falls (3) and also with cardiovascular events and increased all-cause mortality (4). The incidence has been reported to be on the order of 10–30% of the residents of long-term care homes (4–7). PPH has been defined as a postmeal reduction in systolic blood pressure of >20 mmHg during the first 2 h after the start of a meal (8). It is most commonly seen after the first meal of the day and is thought to be due to the increased mesenteric blood flow to supply the gut, possibly compounded by insulin-induced peripheral

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Data described in the manuscript, code book, and analytic code will be made available upon request pending approval of the principal investigator.

Supplemental Figures 1–3 and Supplemental Tables 1–4 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: CVD, cardiovascular disease; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; JBI, Joanna Briggs Institute; MI, myocardial infarction; NOS, Newcastle–Ottawa Scale; PPH, postprandial hypotension.

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vasodilatation (9–14). This "steal" of blood from the systemic circulation results in a potential fall in systemic blood pressure and a compensatory increase in pulse rate and cardiac output to maintain systematic blood pressure in healthy people. This process is deficient in those who have PPH (9, 15).

PPH appears treatable through lifestyle change by increasing the meal fluid volume, reducing meal content of carbohydrates, and possibly altering the physiologic effect of the carbohydrate pharmacologically by reducing the rate of carbohydrate digestion (12, 16) and gastric emptying (17–19).

The attention paid to PPH as a possible cause of cardiovascular disease (CVD) and all-cause mortality has been based on a relatively few small studies (4, 8, 12, 20–22). However, because of the potential seriousness of these outcomes, we felt it important to undertake a systematic review and meta-analysis to determine the consistency of the data. We have focused on cohort and cross-sectional studies that explored the association of PPH with CVD and all-cause mortality among older community-dwelling and long-term care facility residents. We hypothesized that PPH may be associated with increased CVD and all-cause mortality outcomes. Demonstration of these associations will encourage further research in this area, routine screening, and treatment to reduce adverse events in the future.

Methods

Design

We followed the Cochrane Handbook for Systematic Reviews and Interventions (23) and reported the results according to Meta-analysis of Observational Studies in Epidemiology (24) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The study protocol is registered at https://www.crd.york.ac.uk/PROSPERO/ (PROSPERO identifier, CRD42021262425).

Study selection

We conducted a literature search in Cochrane Library, MEDLINE, and EMBASE up to 13 April 2022 using the search terms "postprandial hypotension" AND ("cardiovascular disease" OR "stroke" OR "myocardial infarction" OR "syncope" OR "heart failure" OR "all-cause mortality") that was supplemented by a manual search (see **Supplemental Table 1** for our full search terms). The search was restricted to human studies without any restrictions on publication date and language. We included prospective, retrospective, cross-sectional, and case-control studies conducted in adult human populations examining the relation between PPH and CVD, CVD mortality, heart failure, stroke, myocardial infarction (MI), syncope, and all-cause mortality, with prospective cohorts followed for ≥6 mo. Excluded were studies conducted in the laboratory and those done with animals, children, pregnant and breastfeeding women, and those with chronic infections (e.g., HIV and hepatitis C).

Data extraction

Full-article review and data extraction were conducted twice by independent reviewers (KK, FL, MK, KSelvaganesh, JW, or MW) with all disagreements reconciled through consensus. Attempts were also made to contact the authors where needed. As with all meta-analyses, the outcomes tend to be exploratory in nature with total CVD, CVD mortality, and all-cause mortality being the outcomes of primary interest and the secondary outcomes of interest being the components of CVD (stroke and MI).

Risk of bias assessment

The quality of the prospective cohort studies included in the meta-analysis was assessed by the Newcastle–Ottawa Scale (NOS) (25). A maximum of 9 points can be given based on cohort selection, comparability of cohorts, and ascertainment of outcome, and studies scoring ≥6 points were considered high-quality studies. The Joanna Briggs Institute (JBI) appraisal checklist for analytical cross-sectional studies was used to assess the quality of the included cross-sectional studies. The overall ratings were "Include," "Exclude," and "Seek further information" (26).

Outcomes

The outcomes were exploratory, with the primary interests being most adjusted RRs for total CVD, CVD mortality, and all-cause mortality and secondary interests being CVD-related outcomes (please see "Data extraction" above).

Data synthesis

Data were analyzed using Review Manager (RevMan) version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration) and STATA software version 16.1 (StataCorp) with between-study variability estimated by τ^2 (DerSimonian-Laird). Pooled analyses were conducted using the generic inverse variance method with random-effects models. Data were expressed as RRs with 95% CIs. Heterogeneity between the studies was assessed through the Cochrane Q statistic at $P < 0.1$ and quantified by I^2. We interpreted $I^2 \geq 50\%$ as substantial heterogeneity with $P < 0.1$ (27). If 10 or more studies were detected, publication bias was assessed by visual inspection of the funnel plots and using the Begg and Egger tests, where $P < 0.05$ was considered evidence of small study effects (28, 29).

Grading of the evidence

The overall certainty of evidence of all studies was assessed using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) (30, 31). By default, prospective cohort studies are graded as low-certainty evidence. Criteria to downgrade included study limitations (as assessed by the NOS), inconsistency (substantial or unexplained interstudy heterogeneity, $I^2 > 50\%$ and $P < 0.10$), indirectness (presence of factors that limit the generalizability of the results), imprecision [the 95% CI for effect estimates crosses a minimally important difference of 5% (RR: 0.95–1.05) from the line of unity], and publication bias (significant evidence of small study effects).

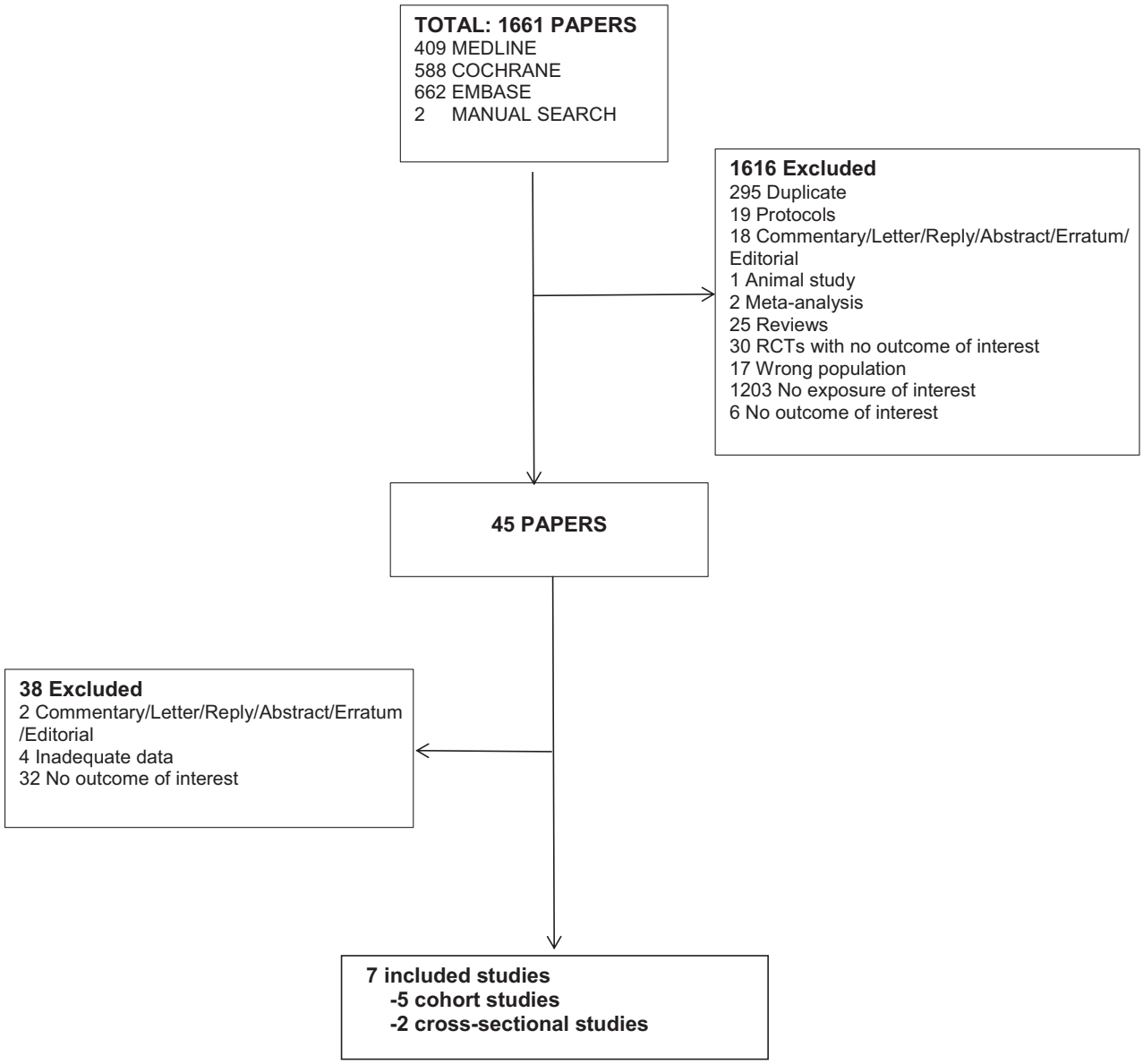

FIGURE 1 Search summary.

Results

Flow of the literature

We identified a total of 7 studies [5 cohorts identified from our comprehensive search (6, 20, 21, 32, 33) and 2 cross-sectional studies identified from our manual search (3, 22)] that included a total of 2389 participants, out of which 3 studies were included for all-cause mortality (n = 516 participants) (6, 32, 33), 1 for total CVD (n = 94 participants) (20), 1 for CVD mortality (n = 401 participants) (21), and 2 for stroke ("silent" lacunar infarcts) (n = 1378 participants) (3, 22) (**Figure 1**).

Study characteristics

From the included studies, 2 were conducted in Australia (6, 33), 1 in the Netherlands (32), 1 in Italy (21), 2 in Japan (3, 22), and 1 in South Korea (34). Three cohorts were identified that reported all-cause mortality (6, 32, 33). The first study was a prospective cohort study of 179 semi-independent residents with a mean age of 83.2 y living in long-term health care facilities in Canberra, Australia, and followed over 4.7 y (6). The second study was a retrospective study of 302 consecutive patients, mean age of 78.7 y, who attended a falls clinic in the Netherlands and were followed for a mean of ~2 y (32). The third was a small study of 35 patients older than 70 y who had been discharged from the intensive care unit 3 mo previously and were followed for a further 9 mo (33). One study was included for total CVD that followed 94 people, aged >70 y, from 3 community centers in B city, South Korea, for 3 y (34). For CVD mortality, again only 1 study was included, and the cohort consisted of 401 patients, mean age 77.8 y, attending a cardiac clinic in Modena, Italy, and followed for a mean of over 4 y (51 mo) (21). Two

cross-sectional studies from Japan on stroke ("silent" lacunar infarcts) were included; 1 study was in 70 hospitalized patients, aged >60 y, with essential hypertension (22) and the other in 1308 older community residents with a mean age of 65.2 y (3) (**Table 1**).

Risk of bias

The quality of the cohort studies was assessed according to the NOS, and all studies were of high quality, receiving a score of 7 or higher (**Supplemental Table 2**). The JBI appraisal checklist for analytical cross-sectional studies was used to assess the quality of the included cross-sectional studies, and the overall appraisal was "Include" (**Supplemental Table 3**).

Association between PPH all-cause mortality, total CVD, CVD mortality, and stroke

Data from these 3 studies including 516 participants (6, 32, 33) demonstrated an association with increased risk of total mortality in those with PPH (RR: 1.48; 95% CI: 1.03, 2.14; $P = 0.03$) with minimal heterogeneity ($I^2 = 8\%$; $P = 0.34$) (**Figure 2**).

Total CVD was only assessed in usable form in 1 study with 94 participants (34). The definition of CVD for this particular study was broad and included new-onset congestive heart failure, angina, and transient ischemic attacks in addition to MI and stroke. A positive association with PPH and CVD was reported with a very large risk ratio and confidence interval (RR: 11.18; 95% CI: 2.43, 51.41; $P = 0.002$). Two deaths were also recorded for MI and 2 from stroke, but their relation to PPH was not reported separately.

Similarly, only 1 study ($n = 401$ participants) was included for cardiovascular mortality (21). The risk ratio for the association of PPH with all cardiovascular mortality was close to unity but significant due to narrow confidence intervals (RR: 1.02; 95% CI: 1.00, 1.04; $P = 0.04$).

The 2 cross-sectional studies determined the association between PPH and stroke ("silent" lacunar infarcts) assessed by MRI in 1378 participants (3, 22). Together, these studies demonstrated an association between PPH and stroke ("silent" lacunar infarcts) (RR: 1.69; 95% CI; 1.21, 2.36; $P = 0.002$; $I^2 = 0\%$).

The association of PPH with the combination of all outcomes ($n = 3289$ participants) was significant (RR: 1.52; 95% CI: 1.05, 2.18; $P = 0.03$; $I^2 = 77\%$) (Figure 2).

Subgroup analyses

Subgroup analyses were undertaken to compare the associations of PPH by geography and culture (Japan and South Korea compared with Australia, the Netherlands, and Italy), by study type (cohort compared with cross-sectional studies), and age (mean cohort age above and below 70 y). The relative risks for all comparisons were similar and no interaction terms were significant (**Supplemental Figures 1–3**).

Grading of the evidence

The certainty of evidence was considered very low for all outcomes, but we believe it noteworthy that PPH was significantly associated with both the combined and each individual component outcome (**Supplemental Table 4**).

Discussion

These data indicate an association between PPH, cardiovascular outcomes, and all-cause mortality. However, the small sample size and high heterogeneity may lower the credibility and utility of the evidence in our meta-analysis. Nevertheless, each outcome lay to the right side of the unity line, and individually, they were significant. Interestingly, despite the apparently common occurrence of PPH, there were few data available on the nature of the foods or the macronutrient profiles of the meals that precipitate PPH. This disorder appears to have a higher prevalence in those with diabetes and in the institutionalized elderly that may be as high as 25–38% (4, 6, 7). Not only is it a potential cause of syncope, falls, and fractures, but our data suggest that PPH may also be significantly associated with CVD and total mortality.

Further studies are essential, but the studies associated with CVD and CVD mortality are also supported by a number of other reports on associations with PPH that were not included in this meta-analysis because the data provided were incomplete. One large study by Aronow and Ahn (4) in this area was not included in our meta-analysis because the data were not provided in the appropriate form. They assessed 499 older nursing home residents with a follow-up of 29 mo for falls, syncope, MI, stroke, and all-cause mortality. In this study, reductions in blood pressure of 17–23 mmHg were all significantly greater in those who had an event compared with the mean systolic blood pressure reductions of 12–15 mmHg in those who did not experience these conditions (4).

The MRI studies of the association with lacunar infarcts are of particular interest (3, 22) as these often asymptomatic events are associated with cognitive decline and are strongly associated with later symptomatic strokes (35). These infarcts occur deep in the white matter of the brain and also in the basal ganglia and pons and result from the occlusion of small perforating arteries. Over time, 30% of patients become dependent, and 25% have a further stroke within 5 y (36).

The mechanism by which PPH precipitates stroke and coronary events has not been clearly defined. Earlier studies indicated that, during exercise testing, hypotension accompanied the onset of angina in patients with coronary artery disease and in whom bypass surgery eliminated the fall in blood pressure, angina, and S-T depression (37). Concerns have been expressed over the effect of hypotension on symptomatic and silent ischemia in patients with ischemic heart disease associated with hypotensive drug therapy (38), particularly in patients with low diastolic blood pressure (39). Furthermore, in patients undergoing noncardiac surgery, intraoperative hypotension was seen to be a risk factor for perioperative MI (40). In relation to stroke, orthostatic hypotension in the 11,707 persons in the Atherosclerosis Risk in Communities cohort, followed over 7.9 y, was associated with an increased risk of stroke (HR: 2.0; 95%

TABLE 1 Characteristics of included cohort and cross-sectional studies[1]

Study, year	Country	Design	Participants		PPH/no PPH	Number of events (cases/controls)	Age, mean ± SD, y	BMI, mean ± SD, kg/m^2	Follow-up	Methods of outcome assessment	Outcomes
			Total	F/M							
Kohara et al., 1999 (22)	Japan	Cross-sectional	70 hospitalized essential hypertensive patients	37 F, 33 M	18 (PPH ≥ 10 mmHg) – PPH	15/3	62.8 ± 8.1	25.6 ± 3.4	NA	MRI report	Stroke ("silent" lacunar infarcts)
					16 (5–10 mmHg PPH) – PPH	11/5	69.2 ± 6.9	23.4 ± 3.8			
					36 (PPH<5 mmHg) – normal	16/20	63.4 ± 6.8	24.3 ± 2.9			
Fisher et al., 2005 (6)	Australia	Prospective cohort	179 ELD (semi-independent residents)	144 F, 35 M	68/111	97/82	83.2 ± 7.0	Not reported	4.7 y (over a period of 4.7 y)	Record linkage	All-cause mortality
Lagro et al., 2012 (32)	The Netherlands	Retrospective cohort	302 ELD (consecutive patients visiting falls outpatient clinic)	191 F, 111 M	175/127	58/244	78.7 ± 8.0	26.2 ± 4.4, PPH group; 26.9 ± 4.5, no PPH group	23 mo (median follow-up)	Record linkage	All-cause mortality
Zanasi et al., 2012 (21)	Italy	Prospective cohort	401 ELD (hypertensive)	214 F, 187 M	292/109	34/333	77.8 ± 11	26.3 ± 3.6	51 mo (median follow-up)	Record linkage and self-report	CVD mortality
Tabara et al., 2014 (3)	Japan	Cross-sectional	1308 ELD	794 F, 514 M	118/1072	15/103	65.2 ± 9.1	23.3 ± 3.1	NA	MRI report	Stroke
Ali Abdelhamid et al., 2020 (33)	Australia	Prospective cohort	35 ELD (post-ICU discharge)	NA	10/25 (at 3 mo)	3/32 (at 9 mo)	74 ± 4.5	28.7 ± 9.8	9 mo	Record linkage and self-report	All-cause mortality
Jang, 2020 (34)	South Korea	Prospective cohort	94 ELD	79 F, 15 M	47/47	30/64	73.1 ± 4.8	23.7 ± 2.5	36 mo (within 36-mo follow-up)	Record linkage and self-report	CVD

[1]CVD, cardiovascular disease; ELD, elderly; ICU, intensive care unit; NA, not applicable; PPH, postprandial hypotension.

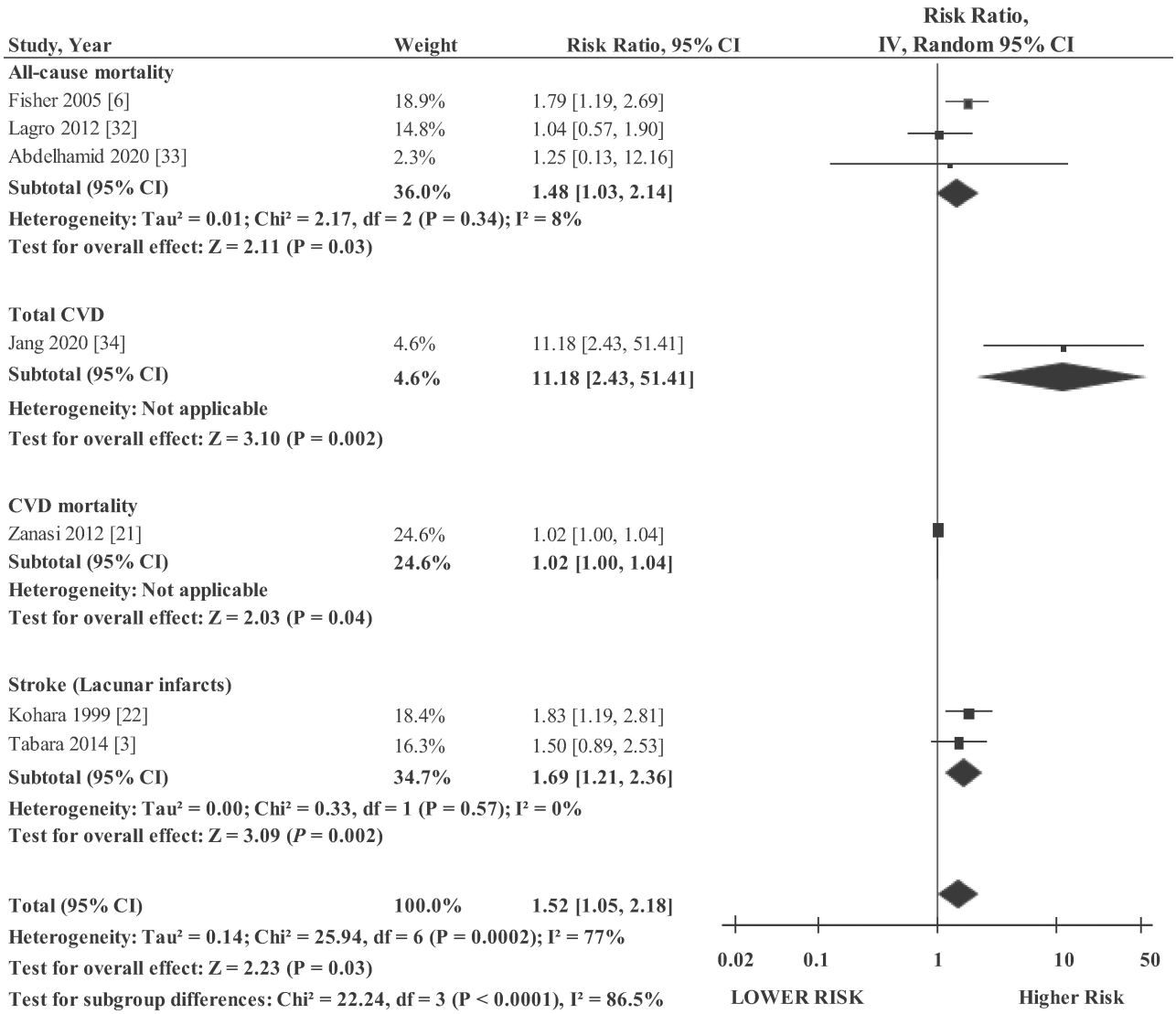

FIGURE 2 Forest plot of studies examining the association between postprandial hypotension , with all-cause mortality, total cardiovascular disease (CVD) risk, CVD mortality, and stroke ("silent" lacunar infarcts). Data are expressed as RR with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane Q statistic (χ^2) at a significance level of $P < 0.10$ and quantified by I^2 statistics.

CI: 1.2, 3.2) (41). These data, although not related to PPH per se, support the hypothesis that repeated episodes of hypotension may have negative effects on the cardiovascular system, especially in those with preexisting CVD.

Both dietary and pharmacologic approaches have been shown to reduce the occurrence of PPH and give insights into the mechanisms of PPH. As pharmacologic treatment, glucagon-like peptide 1 agonists have been shown to reduce PPH by reducing the rate of gastric emptying and decreasing superior mesenteric artery blood flow, although the effect in delaying gastric emptying is reported to be transient (36). Similarly, as expected, dipeptidyl peptidase 4 inhibitors, by preventing incretin degradation, also reduce gastric emptying and therefore PPH (18). The somatostatin analogue octreotide reduces gastric emptying, decreases small intestinal peristalsis, and causes splanchnic vasoconstriction. This combination of actions has been shown to reduce PPH (19). Considerable research has been done on the drug acarbose, the α glycoside hydrolase inhibitor that reduces the rate of carbohydrate digestion and absorption (36). As expected, this change also has been shown to be effective in reducing PPH (42) and to reduce splanchnic blood flow in elderly inpatients diagnosed with PPH (43). As little as 50 mg acarbose taken with meals has been shown to reduce superior mesenteric artery blood flow, the postprandial fall in systolic blood pressure, and the rise in pulse rate (42).

Dietary measures that have been recommended to reduce PPH include eating smaller and more frequent meals, reducing meal carbohydrate content, and consuming more fluid with meals. These measures are aimed at reducing the osmotic activity of

the gastric and small intestinal contents and thereby reducing the requirement for increased mesenteric blood flow and the resulting fall in systemic blood pressure (8, 9, 18).

It is of interest that rapidly digested, high glycemic index foods have also been associated with increased risk of stroke, total CVD, and total mortality in a large cohort study (44). The observation that PPH resulting from ingestion of rapidly absorbed carbohydrates is also associated with CVD and total mortality suggests a possible shared etiology and that dietary carbohydrates selected by those with PPH should also be low glycemic index.

The chief limitations of this analysis are the relatively few and small studies on all-cause mortality and cardiovascular outcomes, which, due to limited statistical power, weaken the validity of our study. The lack of studies may be due to the inconvenience of testing that involves preparing standard fresh breakfasts, establishing a stable baseline, and taking measurements at 15-min intervals over the following 2 h. We included 2 cross-sectional studies for stroke. Their results were consistent. Their elimination resulted in an overall loss of significance (RR: 1.47; 95% CI: 0.90, 2.41; $P = 0.12$), although the risk ratio remains unchanged. There was also evidence of heterogeneity between study estimates. We did not downgrade the evidence for inconsistency as all the point estimates lay to the right side of the unity line. Furthermore, because both the overall and identified outcomes individually showed significant associations with PPH, we consider these associations to be noteworthy, acknowledging that there is an increased risk of type I error that results from analyzing multiple outcomes.

There are several strengths of this synthesis. It is based on a comprehensive systematic search of the available literature and included a GRADE assessment to assess the certainty of the evidence.

Finally, it is of interest that the elderly, those with diabetes, and those with increased CVD risk are the groups with the highest risk for PPH and also for adverse outcomes following coronavirus infection (45, 46). Would adequate treatment of PPH in these groups help to lessen the severity of the consequences of infection?

In conclusion, PPH is associated with higher cardiovascular outcomes and all-cause mortality. Confidence in the available evidence must be limited. More data are obviously required, but given the seriousness of the outcomes, we believe the evidence is sufficiently compelling to warrant more routine assessment of this condition and consideration of hygienic measures and, if necessary, drugs that are used commonly in the treatment of diabetes, as a potential means to reduce the ill effects of PPH (44).

The authors' responsibilities were as follows—DJAJ: conceptualized the meta-analysis, designed the overall research plan, and is the study guarantor; SS-P: conducted the database search, analyzed the data, and revised the manuscript; KK, FL, MK, JW, MW, and KSelvaganesh: screened studies for inclusion, extracted the data, and revised the manuscript; DJAJ and JLS: drafted and revised the manuscript; MP, DP, AJG, KSrichaikul, and CWCK revised the manuscript; and all authors: reviewed and approved the final version of the manuscript.

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He has received funds for dietary studies from Loblaw's, which, during the course of his funding, acquired Shopper's Drugmart, which is a pharmaceutical company that also sells supplements. His wife, Alexandra L Jenkins, is a director and partner of INQUIS Clinical Research for the Food Industry; his 2 daughters, Wendy Jenkins and Amy Jenkins, have published a vegetarian book that promotes the use of the low glycemic index plant foods advocated here, *The Portfolio Diet for Cardiovascular Risk Reduction* (Academic Press/Elsevier 2020); and his sister, Caroline Brydson, received funding through a grant from the St. Michael's Hospital Foundation to develop a cookbook for one of his studies. He is also a vegan. (Please see full conflict of interest declared in J Am Coll Cardiol 2018;71(22):2570–2584 prior to 2018). 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