

Prevalence, risk factors, and prognosis of orthostatic hypotension in diabetic patients

A systematic review and meta-analysis

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Abstract

Background: Orthostatic hypotension (OH) is a major clinical sign of cardiovascular autonomic dysfunction in diabetic patients. Our aim was to quantitatively evaluate the prevalence and risk factors of OH in patients with diabetes mellitus (DM) and assess its prognosis.

Methods: A comprehensive search of the PubMed, Embase, China National Knowledge Infrastructure, VIP Chinese Journal, Wanfang, and SINOMED databases was conducted for related published work up to September 25, 2016, and manually searched eligible studies from the references in accordance with the inclusion criteria.

Results: We included 21 studies in the analysis, with a total sample size of 13,772. The pooled prevalence of OH in DM was 24% (95% confidence interval [CI]: 19–28%). Potential risk factors, that is, glycosylated hemoglobin A (HbA1c) (odds ratio [OR], 1.13, 95% CI, 1.07–1.20), hypertension (OR, 1.02, 95% CI, 1.01–1.02), and diabetic nephropathy (OR, 2.37, 95% CI, 1.76–3.19), were significantly associated with OH in DM. In addition, the prognosis of OH in DM was associated with higher risk of total mortality and cardiovascular events.

Conclusion: The pooled prevalence of OH in DM appears high. HbA1c, hypertension, and diabetic nephropathy are risk factors for OH in DM. OH indicates poor prognosis in diabetic patients. Attention should be focused on diabetic patients with the stated risk factors to prevent OH.

Abbreviations: CAN = diabetic cardiac autonomic neuropathy, CI = confidence interval, DBP = diastolic blood pressure, DM = diabetes mellitus, HbA1c = glycosylated hemoglobin A, HDL-C = high-density lipoprotein cholesterol, HR = hazard ratio, IMT = intima-media thickness, LVEF = left ventricular ejection fraction, LVET = interventricular septum thickness, NPDR = nonproliferative diabetic retinopathy, OH = orthostatic hypotension, PP = pulse pressure, PWV = pulse wave velocity, RMSSD = square root of the mean of squared differences of successive RR intervals, RR = risks ratio, SBP = systolic blood pressure, Scr = serum creatinine, SDNN = standard deviation of successive RR intervals, TC = total cholesterol, TG = triglyceride, UARE = urinary albumin excretion rate.

Keywords: diabetes mellitus, meta-analysis, orthostatic hypotension, prevalence, risk factors

1. Introduction

Orthostatic hypotension (OH) is a major clinical sign of cardiovascular dysautonomia and affects between 5% and 30% of all individuals in an age-dependent manner.^[1] According to the consensus of the Committee of the American Autonomic

Society and the American Academy of Neurology,^[2] OH is most widely defined as a fall in systolic blood pressure (SBP) of at least 20 mm Hg or a drop in diastolic blood pressure (DBP) of at least 10 mm Hg within 3 minutes of standing. OH is easy to diagnose; however, it is often overlooked in clinical practice because it is asymptomatic in normal conditions. The risk factors associated with OH include older age; use of antihypertensive drugs; and comorbidities such as hypertension, cardiac failure, and kidney disease.^[3,4] OH is associated with increased risk for cardiovascular mortality in different populations.^[5–7] OH also may lead to falls and syncope.^[8,9]

OH and diabetes mellitus (DM) are a dangerous combination. OH prevalence is higher in patients with DM as compared with people without DM.^[10,11] Furthermore, both DM and OH are strong predictors of mortality and cardiovascular events.^[12] In patients with DM, OH may indicate the increased risk of developing severe complications, and reduces quality of life.^[13] Hypertension occurs in >50% of adults with DM. Although the incident rate of OH is not related to aggressive (SBP < 120 mm Hg) versus standard (SBP < 140 mm Hg) blood pressure target assignment,^[14] some antihypertensive medications, including diuretics, α -blockers, and vasodilators tend to cause OH.^[15] Currently, there is no satisfactory drug for treating OH. Many studies have reported the prevalence, risk factors, and prognosis

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of OH in patients with DM, but quantitative estimation of OH in such patients is scarce. We, therefore, conducted a systematic review and meta-analysis in patients with DM with OH to estimate its prevalence, identify the risk factors, and evaluate the prognosis. The pooled estimates could lead to insights for better prevention strategies of OH and alert clinicians to pay closer attention to the use of antihypertensive medications.

2. Methods

2.1. Ethics statement

As all analyses are based on previously published studies, ethical approval was not necessary for this review.

2.2. Search strategy

Two investigators independently searched the PubMed, Embase, China National Knowledge Infrastructure, VIP Chinese Journal, Wanfang, and SINOMED databases for published related work up to September 25, 2016, and manually searched eligible studies from the references in accordance with the inclusion criteria. The search terms were “orthostatic hypotension,” “postural hypotension,” “diabetes mellitus,” and their corresponding keywords in Chinese. Discrepancies were resolved by additional assessment by a third investigator. The corresponding authors of the selected articles were contacted for information missing from the published articles.

2.3. Inclusion and exclusion criteria

Studies potentially eligible for inclusion had to meet the following criteria: (1) written in English or Chinese; (2) investigated subjects with OH in a sample of patients with DM, with original data being derived from cross-section, case-control, and a certain phase in a longitudinal study; (3) reported estimates of prevalence or odds ratio (OR) with corresponding 95% confidence interval (CI) or reported sufficient data to calculate them; (4) for studies with overlapping data sets, the study with the most complete data was selected. We excluded: (1) case reports, conference abstracts, and drug trials (as drugs might induce OH or cause hypotension); and (2) studies that did not meet ≥ 1 inclusion criteria.

2.4. Data extraction and methodological quality score

Two researchers extracted the literature independently. For all included studies, we extracted the following information: first author and publication year, type of DM, quality score, sample size, country, setting, and definition of OH and prevalence. Table 1 lists the characteristics of the 21 studies included in this meta-analysis.^[8,9,11,14,16–32]

We assessed the quality of the eligible literature according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.^[33] If a study fulfilled the item, 1 point was awarded. If it did not, 0 points were awarded. All items were assumed to be of equal importance and were not weighted. Quality was graded according to the score: a higher score indicated a higher quality study.

2.5. Statistical analysis

We quantitatively evaluated the prevalence and potential risk factors of OH in DM by meta-analysis. The correlation between risk factors and OH was examined based on the OR for

case-control studies, and risk ratio (RR) or hazard ratio (HR) for cohort studies. We assumed that these effect measures would yield a similar effect estimate in the overall effect estimate^[34] and would be referred to as OR. When both crude and adjusted OR were provided, the fully adjusted value for potential confounding variables was selected. When this was not possible, a qualitative descriptive analysis was performed.

Heterogeneity between studies was estimated using the Q test and I^2 statistic, which show the percentage of variation between studies that is due to heterogeneity rather than chance. $I^2 < 25\%$, $25\text{--}50\%$, and $> 50\%$ is considered low, moderate, and high-level heterogeneity, respectively.^[11,35] Where there was high inter-study heterogeneity ($I^2 > 50\%$), the random effects model was used to combine results. Otherwise, the fixed effects model was used. We used the DerSimonian and Laird method in the random effects models for the pooled estimation of prevalence. Subgroup analysis was conducted to investigate the source of heterogeneity (type of DM, methodological quality score, sample size, country, and definition of OH).

Sensitivity analyses were performed by excluding the studies performed in community. Begg's and Egger's tests were used to test publication bias. A P -value of $< .05$ was considered statistically significant. All statistical calculations were made using STATA 12.0 (StataCorp, College Station, TX).

3. Results

3.1. Search results

A total 3679 potentially relevant studies were retrieved, of which only 21 were eventually included in the meta-analysis. Figure 1 shows the detailed flowchart of study selection. A total 28 full-text articles were selected for further review. Of these, 21 fulfilled our selection criteria. We excluded the remaining articles because of overlapping data ($n=3$), article was not in English ($n=2$), article was not full-text ($n=2$).

3.2. Prevalence of OH in DM

The included studies documented sample sizes ranging from 26 to 4266 subjects, with a total sample size of 13,772. The prevalence of OH in patients with DM ranged between 7.0% and 64.4%, and pooled prevalence was 24% (95% CI: 19%–28%, Fig. 2). The diabetic patient population was subgrouped according to type of DM, methodological quality score, sample size, country, and definition of OH. Table 2 presents the pooled prevalence of these subgroups, and information on the data heterogeneity and the publication bias. The pooled prevalence in the subgroups ranged from 19% to 29%, and heterogeneity was high; the I^2 ranged from 78.7% to 98.4%. No significant bias in the included studies were revealed by Begg's test ($P = .291$) and Egger's test ($P = .897$). Sensitivity analysis was conducted by excluding the 2 studies performed in community, and the results of the pooled prevalence remained the same.

3.3. Risk factors of OH in DM

Table 3 summarizes the risk factors of statistical testing ($P < .05$) of the major risk factors in univariate analysis, and unadjusted and adjusted multivariable regression analysis. Of the various risk factors, only 7 risk factors from 9 studies were eligible for the exploratory meta-analysis: age, sex, HbA1c (glycosylated hemoglobin A), BMI (body mass index), supine SBP, hypertension, and diabetic nephropathy.

Table 1**Characteristics of the 21 studies included in this meta-analysis.**

No.	Study	Type of DM	Quality score	Sample size	Country	Setting	Definition of OH	Event-prevalence
1	Tsutsu et al, 1990	2	13	886	Japan	Clinic based	A fall of 30 mm Hg or more in SBP when the subject arose from the supine position	62–7.0%
2	Delcourt et al, 1998	2	16	427	France	Clinic based	Fall in SBP greater than 20 mm Hg, 1–5 min after standing	35–8.2%
3	Chen et al, 2001	2	15	612	China	Clinic based	Not stated	195–31.9%
4	Kempler et al, 2002	1	19	3010	Europe	Clinic based	A fall in SBP > 20 mm Hg on standing	542–18.0%
5	Fan and Zheng, 2004	Not stated	16	101	China	Clinic based	A fall in SBP > 20 mm Hg on standing	65–64.4%
6	Zhang and Yu, 2005	2	13	102	China	Clinic based	A fall of 30 mm Hg or more in SBP and 15 mm Hg or more in DBP when the subject arose from the supine position	8–7.8%
7	Hirai et al, 2009	1	17	440	America	Community based	Standing decrease in SBP or DBP of at least 20 mm Hg or 10 mm Hg	71–16.1%
8	Wu et al, 2009	Not stated	16	157	China	Community based	A decline in SBP of at least 20 mm Hg and/or a decline in DBP of at least 10 mm Hg after either 1 or 3 min of standing after an individual changed from a supine to a standing position	40–25.5%
9	Peng et al, 2010	2	17	187	China	Clinic based	A fall in blood pressure of at least 20 mm Hg systolic or 10 mm Hg diastolic after at least 2 min in an upright position	55–32.7%
10	Van Haterenet al, 2012	2	22	352	Netherland	Clinic based	A fall in SBP of at least 20 mm Hg or 10 mm Hg DBP after either 1 or 3 min in an upright position	99–28.0%
11	Azidah et al, 2012	2	17	288	Malaysia	Clinic based	A reduction of SBP of at least 20 mm Hg, or DBP of at least 10 mm Hg with a transition from supine to standing position	35–12.2%
12	Eze et al, 2013	2	13	70	Nigeria	Clinic based	A fall in blood pressure (≥ 20 mm Hg for SBP or/and ≥ 10 mm Hg for DBP) in response to change from supine to erect posture	16–23.3%
13	Jiang et al, 2013	2	18	256	China	Clinic based	A decrease in SBP ≥ 20 mm Hg and/or decrease in DBP ≥ 10 mm Hg within 3 min of standing, or, in addition, as standing systolic BP < 90 mm Hg.	80–31.3%
14	Oduwole et al, 2014	1	17	26	Nigeria	Clinic based	A decrease in SBP ≥ 20 mm Hg and/or a decrease in DBP ≥ 10 mm Hg	12–46.2%
15	Refaie, 2014	2	14	100	Egypt	Clinic based	Fall in SBP > 20 mm Hg and > 10 mm Hg in DBP during 3 minutes of standing and resolving with sitting or lying down	34–34.0%
16	Bouhanick et al, 2014	2	17	987	France	Clinic based	A decrease in SBP of at least 20 mm Hg and/or a decrease in DBP of at least 10 mm Hg at any of the measurements while standing	301–30.5%
17	Wijkman, 2016	2	22	749	Sweden	Clinic based	Fall in SBP ≥ 20 mm Hg and ≥ 10 mm Hg in DBP during 2 min of standing and resolving with sitting	55–7.3%
18	Gaspar et al, 2016	1+2	22	247	Slovakia	Clinic based	A fall in SBP of at least 20 mm Hg and/or DBP of at least 10 mm Hg within 3 min of active orthostasis compared to blood pressure in supine position.	60–24.3%
19	Kobayashi et al, 2016	Not stated	18	159	Japan	Clinic based	A decline in SBP and/or DBP of at least 20 mm Hg or 10 mm Hg, respectively	42–26.4%
20	Budyono et al, 2016	Not stated	18	350	Indonesia	Clinic based	A decrease of SBP ≥ 20 mm Hg and/or DBP ≥ 10 mm Hg in 3 min after changing of position from lying to standing.	96–27.4%
21	Fleg et al, 2016	2	22	4266	United States and Canada	Clinic based	A decline in SBP ≥ 20 mm Hg or a decline in DBP ≥ 10 mm Hg from sitting to standing	852–20.0%

DM = diabetes mellitus, DBP = diastolic blood pressure, Event = Sample size* Prevalence, OH = orthostatic hypotension, SBP = systolic blood pressure.

3.3.1. Age. Seven studies reported the age effect size.^[11,14,20–22,29,31] The overall estimate of age as a risk factor was 1.01 (95% CI, 1.00–1.02, $Z = 1.84$, $P = .066$), suggesting no significant difference. There was low heterogeneity ($I^2 = 0.00\%$, $P = .594$; Fig. 3) and no publication bias as per Begg's test ($P = .368$) and Egger's test ($P = .260$).

3.3.2. Sex. Three studies assessed the effects of sex.^[11,20,21] Compared with female patients, male patients did not have significantly higher risk for OH in DM (OR, 0.96, 95% CI, 0.58–1.60, $Z = 0.15$, $P = .881$). There was low heterogeneity ($I^2 = 0.00\%$, $P = .537$; Fig. 4) and no publication bias as per Begg's test ($P = 1.000$) and Egger's test ($P = .911$).

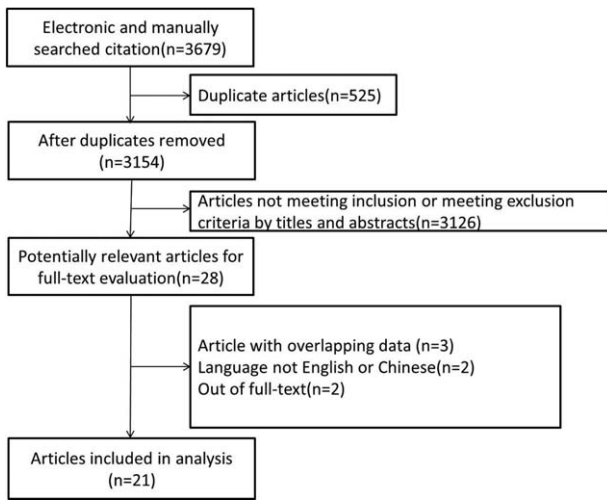


Figure 1. Flow diagram of study selection.

3.3.3. HbA1c. Seven studies evaluated the influence of HbA1c on OH in DM.^[11,14,20,22,29,31,32] The pooled OR was 1.13 (95% CI, 1.07–1.20, $Z=4.34$, $P<.001$), which indicated that high HbA1c increased the risk of OH in DM. There was low heterogeneity ($I^2=38.9%$, $P=.133$; Fig. 5) and no publication bias as per Begg’s test ($P=.368$) and Egger’s test ($P=.224$).

3.3.4. BMI. Three studies reported the effect size of BMI.^[14,20,22] The pooled OR was 1.00 (95% CI, 0.98–1.01, $Z=0.07$, $P=.948$), revealing that BMI and OH in DM were not correlated. There was low heterogeneity ($I^2=9.7%$, $P=.330$; Fig. 6) and no publication bias as per Begg’s test ($P=1.000$) and Egger’s test ($P=.530$).

3.3.5. Supine SBP. Four studies reported the supine SBP effect size.^[14,20,31,32] The pooled OR was 1.39 (95% CI, 0.95–2.03, $Z=1.68$, $P=.093$), indicating that supine SBP and OH in DM were not correlated. There was high heterogeneity ($I^2=71.2%$, $P=.008$; Fig. 7) but no publication bias as per Begg’s test ($P=1.000$) and Egger’s test ($P=.834$).

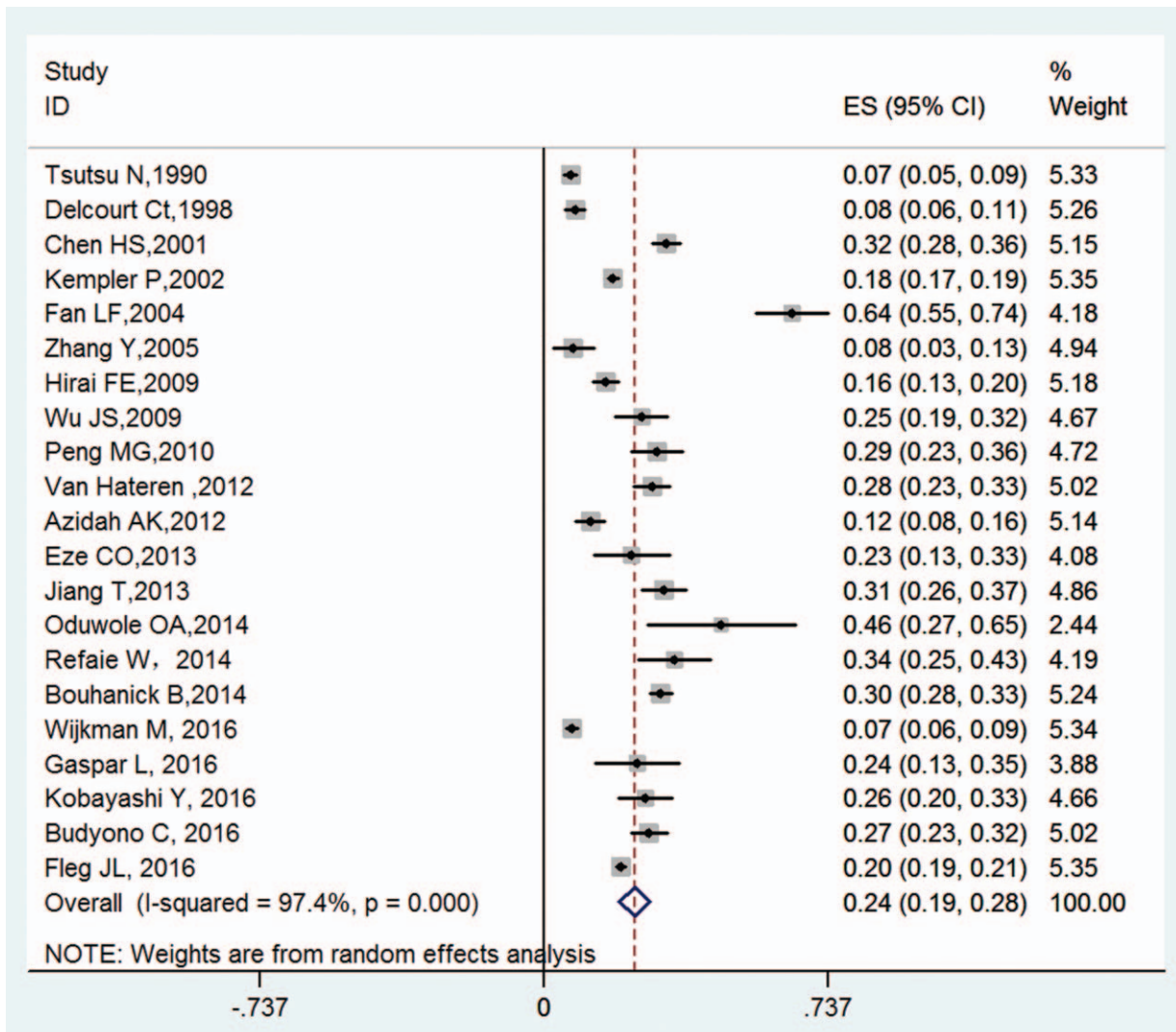


Figure 2. Prevalence of OH in DM and the pooled prevalence rate per study (with the corresponding 95% CI). CI = confidence interval, DM = diabetes mellitus, ES = estimated statistics, OH = orthostatic hypotension.

Table 2

Subgroup analyses of prevalence rates of orthostatic hypotension in diabetes mellitus.

	Subgroup	Number of studies	Sample size	Estimated prevalence			Publication Bias test	
				95 CI	I ² -value, %	P	P, Begg's test	P, Egger's test
	Total	21	13,772	0.24 (0.19, 0.28)	97.4%	<.0001	0.291	0.897
Type of DM	1	3	3476	0.19 (0.14, 0.24)	78.7%	<.0001	1.000	0.562
	2	13	9282	0.20 (0.15, 0.26)	98.0%	<.0001	0.200	0.384
Methodological quality score	≤16	8	2455	0.25 (0.15, 0.34)	97.8%	<.0001	0.386	0.174
	>16	13	11,317	0.23 (0.19, 0.28)	96.9%	<.0001	0.855	0.733
Sample size	<300	11	1693	0.29 (0.20, 0.37)	93.9%	<.0001	0.213	0.027
	>300	10	12,079	0.19 (0.14, 0.24)	98.4%	<.0001	0.107	0.327
Country	Asian	10	3098	0.26 (0.17, 0.35)	97.6%	<.0001	0.020	0.088
	Non-Asian	11	10,674	0.21 (0.16, 0.26)	97.3%	<.0001	1.000	0.898
Definition of OH	Definition A	14	8194	0.25 (0.20, 0.31)	96.8%	<.0001	0.443	0.649
	Other	7	5578	0.21 (0.13, 0.28)	98.2%	<.0001	1.000	0.616

Definition A: A decrease of SBP ≥20 mm Hg and/or DBP ≥10 mm Hg.

CI = confidence interval, DM = diabetes mellitus, DBP = diastolic blood pressure, OH = orthostatic hypotension, SBP = systolic blood pressure.

3.3.6. Hypertension. Five studies analyzed the impact of hypertension on OH in DM.^[11,20,21,29,31] Compared to non-hypertensive patients, patients with hypertension showed the increased risk for OH in DM (OR, 1.02, 95% CI, 1.01–1.02, Z = 6.13, P < .001). There was high heterogeneity (I² = 77.5%, P = .004; Fig. 8) and no publication bias as per Begg's test (P = .734). However, Egger's test revealed publication bias (P = .038).

3.3.7. Diabetic nephropathy. Five studies reported the diabetic nephropathy effect size.^[20,21,27,29,32] The pooled OR was 2.37 (95% CI, 1.76–3.19, Z = 5.69, P < .001), revealing a correlation between diabetic nephropathy and OH in DM. There was high

heterogeneity (I² = 75.5%, P < .001; Fig. 9) and significant publication bias as per Begg's test (P = .009) and Egger's test (P = .002).

3.4. Prognosis of OH in DM

Four cohort studies reported the prognosis of OH in DM.^[14,25–27] Bouhanick et al^[25] showed that, during a 5-year follow-up, OH was associated with severe hypertension and amputations in patients with type 2 DM. Fleg et al^[14] demonstrated that the occurrence of OH was an independent marker of total mortality and heart failure death or hospitalization but not for nonfatal myocardial infarction (MI), stroke,

Table 3

Risk factors of orthostatic hypotension in diabetes mellitus.

Study	Risk factors in univariate analysis, P < .05	Risk factors in unadjusted or adjusted multivariable regression analysis, P < .05
Tsutsu et al, 1990	Gender, insulin therapy, HbA1c, combined with polyneuropathy	NA
Hirai et al, 2009	Age, diabetes duration, QT index, RMSSD, SDNN, supine SBP, standing SBP, supine DBP, standing DBP, smoking, alcohol consumption, diuretics use	QT index, RMSSD, SDNN, SBP, DBP, smoking, alcohol consumption, proliferative NPDR, diuretics use
Wu et al, 2009	NA	Age, gender, HbA1c, combined with hypertension
Peng et al, 2010	Age, supine SBP, HbA1c, combined with hypertension	Age, supine SBP, HbA1c, combined with hypertension
Eze et al, 2013	NA	Combined with hypertension retinopathy, proteinuria, peripheral neuropathy
Jiang et al, 2013	HbA1c, TC, TG, HDL-C, Scr, UARE, supine SBP, supine heart rate, left atrial systolic diameter, LVET, LVEF, combined with diabetic nephropathy	HbA1c, supine SBP, LVET, combined with diabetic nephropathy
Oduwole et al, 2014	Duration of DM, supine SBP, standing SBP,	NA
Bouhanick et al, 2014	Combined with hypertension, supine SBP, standing SBP, supine SBP, combined with hypertension peripheral vascular disease	NA
Wijkman et al, 2016	Supine SBP, standing SBP, supine DBP, standing DBP, aortic PWV, carotid IMT	NA
Gaspar et al, 2016	NA	Combined with nephropathy, retinopathy, peripheral polyneuropathy
Kobayashi et al, 2016	SBP, DBP, heart rate, Scr,	NA
Budyono et al, 2016	NA	HbA1c
Fleg et al, 2016	Gender, ethnicity, previous myocardial infarction, SBP, DBP, antihypertensive (β-Blockers), insulin therapy, sulfonyleureas therapy	Gender, HbA1c, ethnicity (Black vs non-Hispanic white), SBP, smoking (current vs never smokers), antihypertensive (α-blockers and β-blockers), insulin therapy

DBP = diastolic blood pressure, HbA1c = glycosylated hemoglobin A, HDL-C = high-density lipoproteincholesterol, IMT = intima-media thickness, LVEF = left ventricular ejection fraction, LVET = interventricular septum thickness, NPDR = nonproliferative diabetic retinopathy, PP = pulse pressure, PWV = pulse wave velocity, RMSSD = square root of the mean of squared differences of successive RR intervals, SBP = Systolic blood pressure, Scr = serum creatinine, SDNN = standard deviation of successive RR intervals, TC = total cholesterol, TG = triglyceride, UARE = urinary albumin excretion rate.

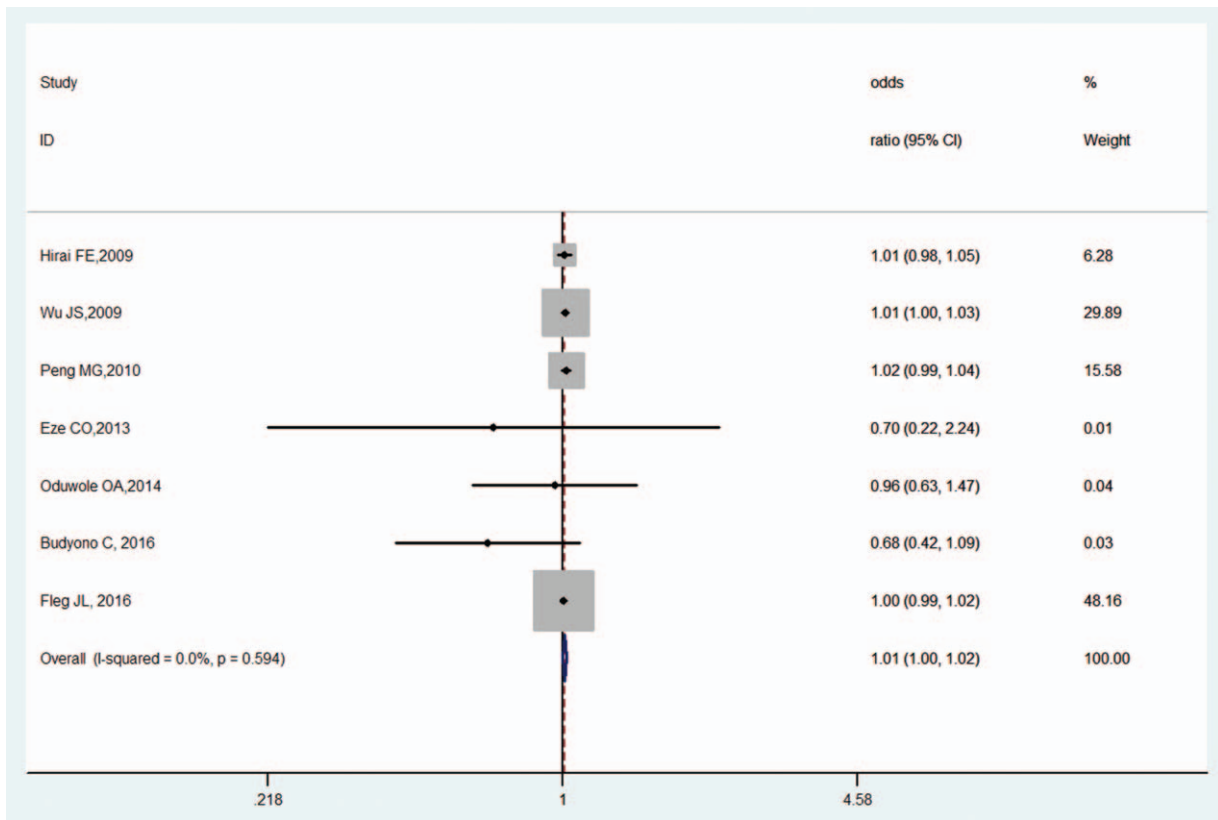


Figure 3. Forest plot of age and OH in DM. DM = diabetes mellitus, OH = orthostatic hypotension.

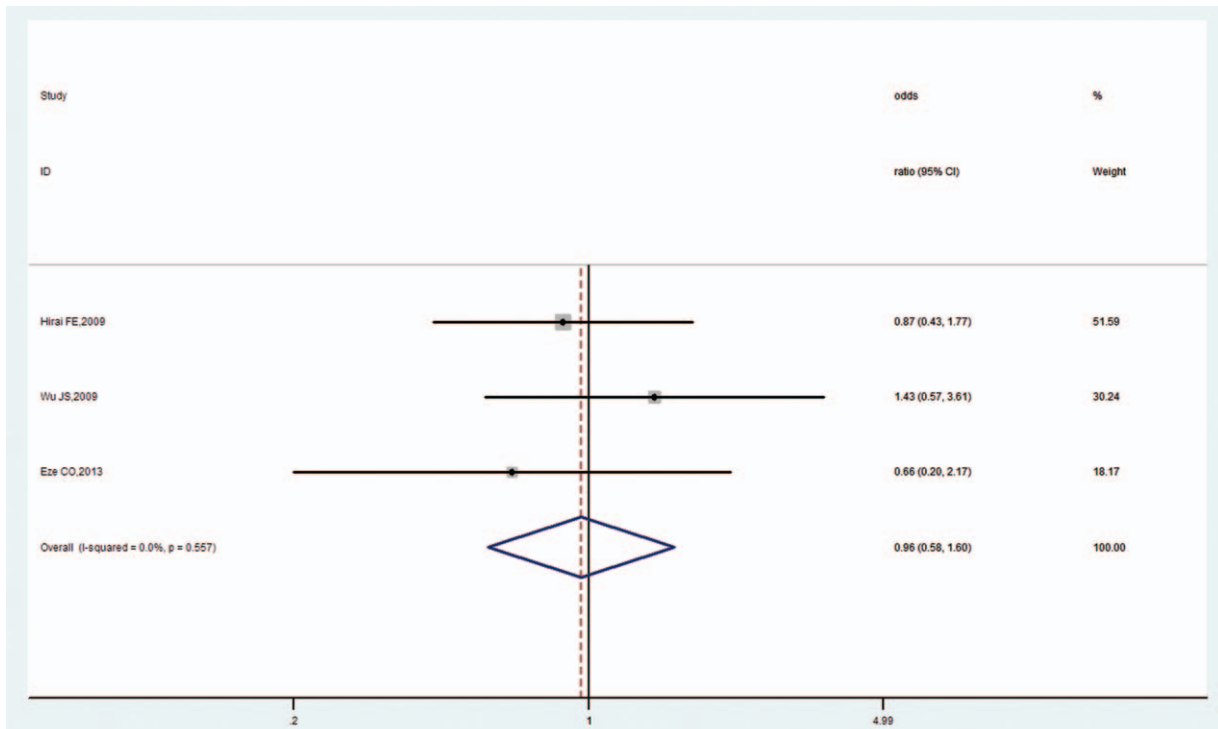


Figure 4. Forest plot of sex and OH in DM. DM = diabetes mellitus, OH = orthostatic hypotension.

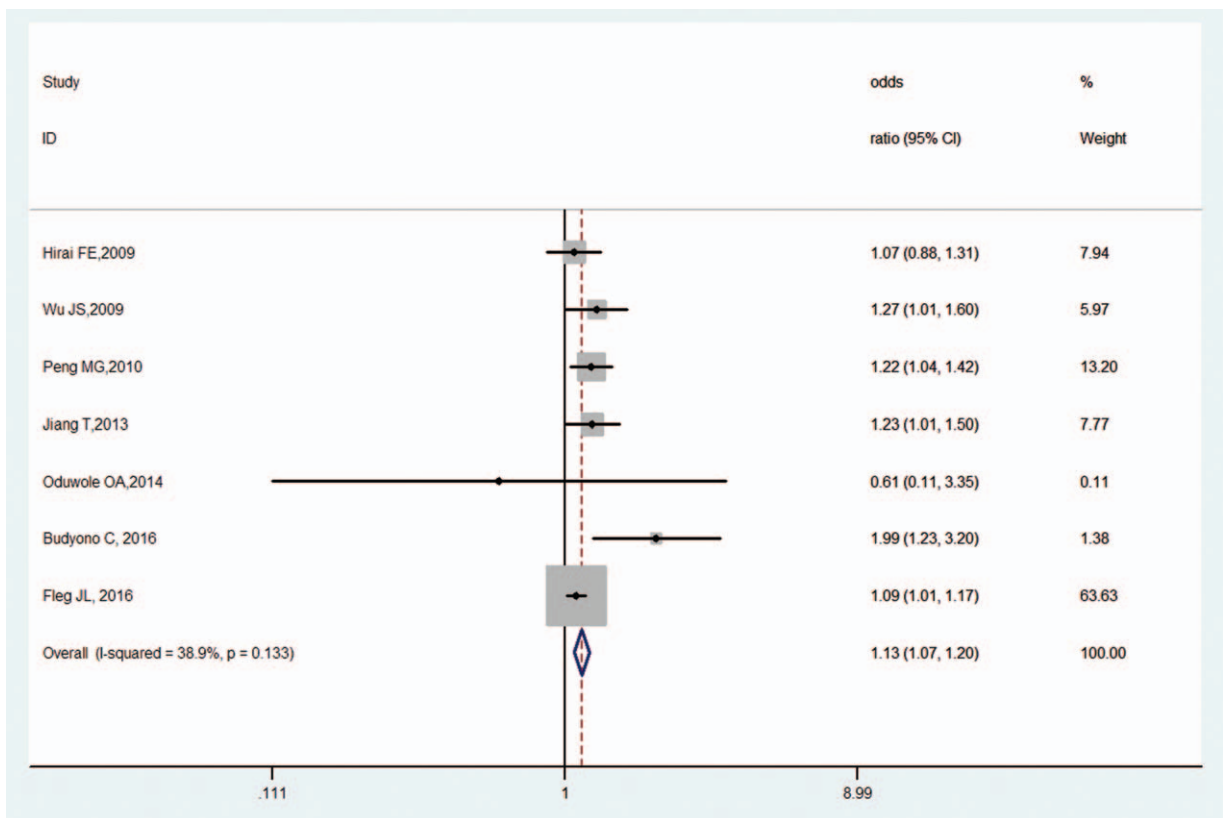


Figure 5. Forest plot of HbA1c and OH in DM. DM = diabetes mellitus, OH = orthostatic hypotension.

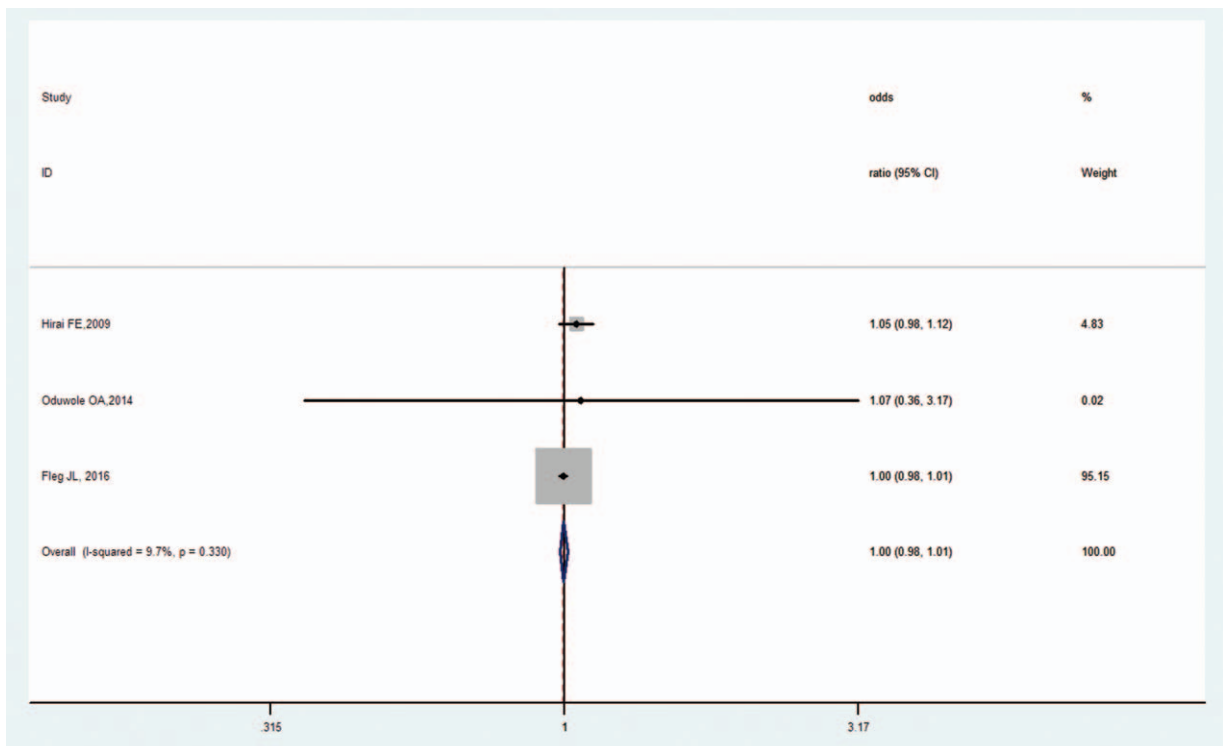


Figure 6. Forest plot of BMI and OH in DM. BMI = body mass index, DM = diabetes mellitus, OH = orthostatic hypotension.

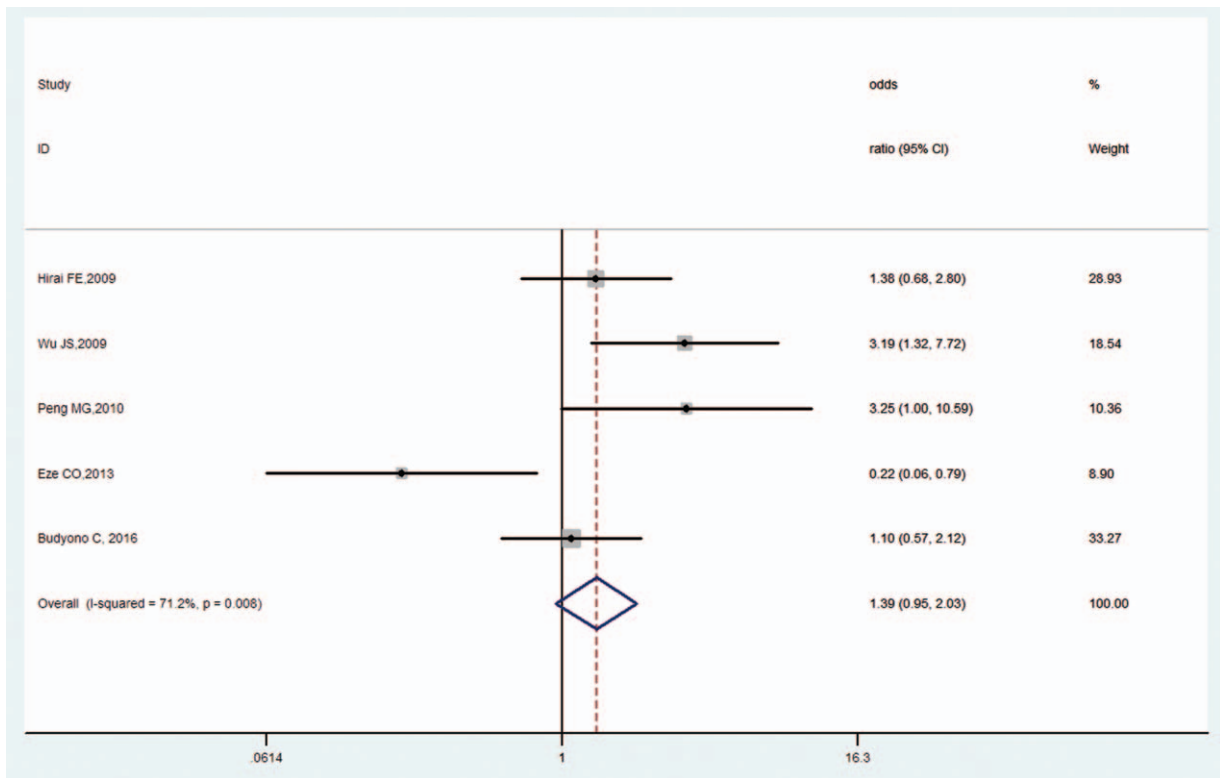


Figure 7. Forest plot of supine SBP and OH in DM. DM = diabetes mellitus, OH = orthostatic hypotension, SBP = systolic blood pressure.

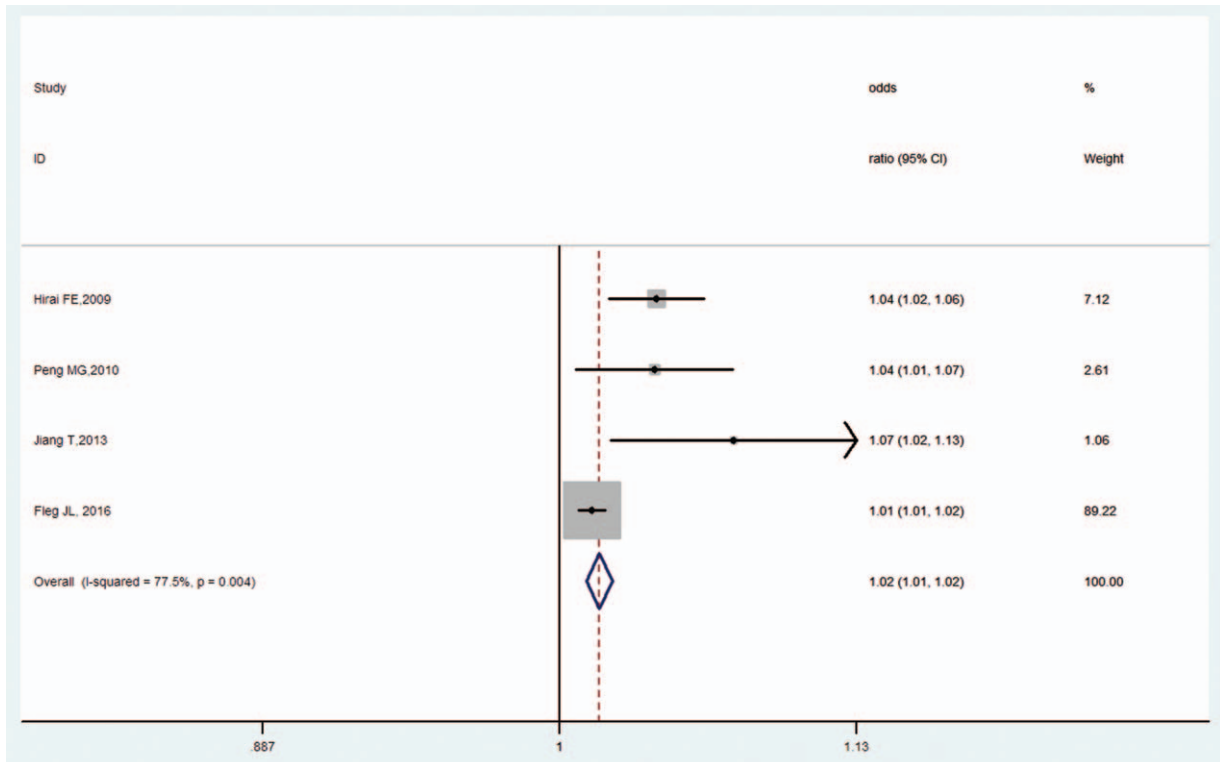


Figure 8. Forest plot of hypertension and OH in DM. DM = diabetes mellitus, OH = orthostatic hypotension.

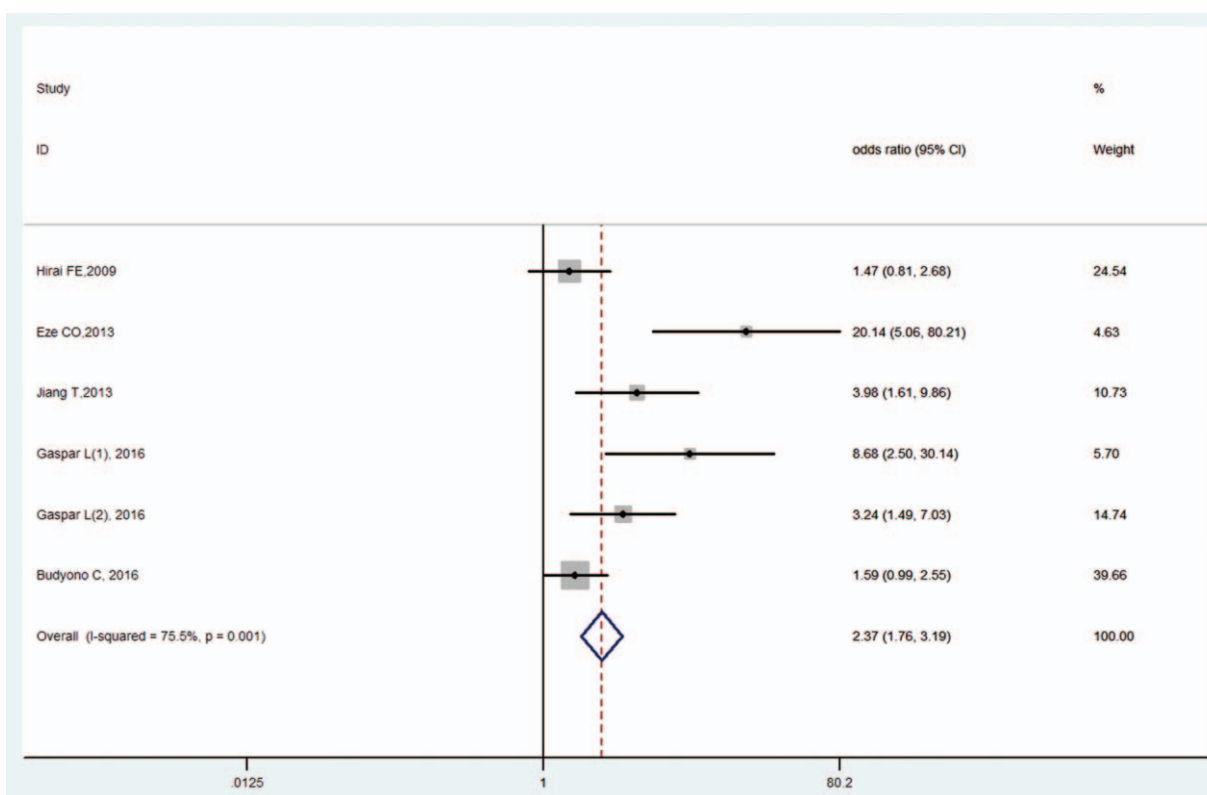


Figure 9. Forest plot of diabetic nephropathy and OH in DM. DM = diabetes mellitus, OH = orthostatic hypotension.

cardiovascular death, or their composite over a median follow-up of 46.9 months. In a 10-year follow-up retrospective study, Gaspar et al^[27] reported that the 10-year mortality rate was higher in diabetic patients with OH. However, a prospective cohort study by Wijkman et al^[26] showed that OH in DM was not significantly associated with risk of combined end-point (the first nonfatal or fatal event of hospitalization for acute MI, stroke, or cardiovascular mortality).

4. Discussion

This is the first meta-analysis to date to investigate the prevalence of OH in DM. We also evaluated the risk factors and prognosis of OH in DM. The OH prevalence we detected is within the range reported in previous nonsystematic reviews on the subject. Although our meta-analysis revealed much inter-study variation, most studies had large sample sizes (>100) that could produce precise estimates.

The prevalence of OH in DM varied widely across studies. It is worth noting that 2 important factors can influence the results. First, the definition of OH in the studies differed slightly from the criteria in the consensus statement. For example, Bouhanick et al^[25] defined OH as a decrease in SBP of at least 20 mm Hg and/or a decrease in DBP of at least 10 mm Hg at any of the measurements while standing. If the consensus definition had been adopted, the prevalence of OH in DM would have been 26.8% instead of 30.5%. Second, elderly patients with DM are often unable to stand up; therefore, the sitting BP is measured instead of standing BP. Chen et al^[18] reported that standing tests did not yield reliable data for 60 patients (9.8%), which is considered an underestimation for OH. These factors led to the

inconsistent prevalence of OH in DM. In our study, meta-analysis determined that the pooled prevalence of OH in DM was 24% (95% CI: 19%–28%) after the above comprehensive factors had been considered. The pooled prevalence in the subgroups ranged from 19% to 29%. This indicates high OH prevalence, which warrants further study.

In the diabetic population, OH is associated with conventional diabetes risk factors, such as age, duration of DM, hypertension, smoking, hyperlipidemia, and obesity.^[36,37] However, the risk factors in each study were not uniform. In the meta-analysis, we quantitatively evaluated 7 potential risk factors of OH in DM derived from 9 included studies, which were free from the variation of a single study sample. Among the 7 factors, we found that HbA1c, hypertension, and diabetic nephropathy were significantly associated with the increased risk of OH in DM.

OH occurs because of impaired sympathetic response to postural change secondary to poor norepinephrine response and abnormalities in baroreceptor sensitivity, resulting in the inadequate heart rate response and peripheral vasoconstriction.^[36,37] HbA1c levels can reflect the general condition of blood sugar within 2 to 3 months. Poor glycemic control, as shown by high HbA1c levels, can affect vascular elasticity and reduce extravascular volume due to osmotic diuresis, eventually inducing OH.^[38] Furthermore, poor glycemic control may cause decreased vasodilatation, leading to diminished blood flow in nerve fibers by reducing myo-inositol content. Autonomic denervation causes endothelial dysfunction and reduces neuropeptide responses, volume depletion caused by nephropathy, and osmotic diuresis, which may induce OH.^[39,40] Hypertension can decrease carotid sinus baroreflex and β -adrenergic sensitivity and impair arterial elasticity and myocardial compliance. These physiopathological

changes are closely associated with OH.^[13] Here, we observed a higher prevalence of diabetic nephropathy in patients with OH. OH is a common feature of diabetic cardiac autonomic neuropathy (CAN). The impact of CAN in the pathogenesis of diabetic nephropathy is that it alters kidney glomeruli hemodynamics mainly through endothelial dysfunction, albuminuria, and erythropoietin insufficiency-induced anemia.^[41] Therefore, it is vital to control the blood glucose and BP and delay the progression of diabetic nephropathy in diabetic patients.

We also determined that the prognosis of OH in DM is associated with higher risk of total mortality and cardiovascular events. These results were not surprising and mainly confirm that OH is an expression of an advanced CAN correlated with MI, stroke, and macrovascular and microvascular complications. A recent review has indicated that the presence of OH may complicate the treatment of hypertension, heart failure, and coronary heart disease.^[42] Therefore, orthostatic evaluation should also be a part of the diagnostic workup in diabetic patients. However, randomized trials have shown that only a few pharmacological agents, including droxidopa^[43] and midodrine,^[44] demonstrate a moderate effect as compared to the placebo group. We do not know if these OH therapies will in any way alter mortality rates. More studies on the potential mechanisms of OH are needed.

Although this meta-analysis includes more studies with larger sample sizes than individual studies, there are some limitations. First, the meta-analysis of OH prevalence in DM showed large inter-study heterogeneity. The subgroup and sensitivity analyses were not much different from the meta-analysis results. Moreover, we did not perform specific statistical comparisons with the previous results in all subgroups owing to data limitations, different grouping methods, and nonspecific analysis of the previous data. We also believe that drug factors may have influenced heterogeneity. Many medications commonly used by patients with DM, such as diuretics, vasodilators, tricyclic antidepressants, and insulin, can aggravate OH.^[45] However, we did not acquire sufficient information about these aspects for subsequent analysis. Second, the OR, RR, and HR were treated in the same way in our systematic review. Generally, it is reasonable to combine the OR with RR (or HR) when the incidence is very low (<10%).^[46] With a higher incidence, combining OR and RR is more likely to generate bias. Third, not all the studies reported estimates of risk factors (OR, RR, or HR value).

In conclusion, this meta-analysis reveals that the pooled prevalence of OH in DM is high and that HbA1c, hypertension, and diabetic nephropathy are risk factors for OH in DM. More attention should be paid to diabetic patients with these risk factors in order to prevent OH, and more studies on the potential mechanisms of OH are needed.

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