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Original Article

Visit-to-visit variability of blood pressure and risk of diabetic retinopathy: a systematic review and meta-analysis

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Abstract: Background: Diabetes mellitus (DM), a worldwide disease affecting more than 400 million people, is associated with high blood pressure (BP). In addition to macrovascular complications, high BP in DM patients is potentially linked to microvascular complications. More than 70% of DM patients have retinopathy. To our knowledge, no systematic review and meta-analysis has been conducted on the relationship between visit-to-visit variability in blood pressure and diabetic retinopathy risk. Methods: This systematic review and meta-analysis study was performed on the related articles. The search strategy, screening, and data selection were all checklist-based. A comprehensive search was done in three databases, including PubMed, Google Scholar, and Scopus. The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) were followed. English clinical studies published up to January 2023 contained diabetic patients as the population, retinopathy as the outcome, and visit-to-visit blood pressure as the intervention. Using the QUIPS technique, two authors independently quantify the risk of bias in included publications. The meta-analysis was conducted using R version 4.4.1. We calculated relative risk (RR) as the effect size, applying the random effect model. Standard deviation (SD) and coefficient of variation (CV), were used as measures of BP variability. Results: A total number of 8 studies with 743,315 participants were covered in this systematic review. After meta-analysis, we concluded that the group with higher SD of BP variability had 2 percent higher risk than the control group (RR = 1.02, 95% CI = 1.01-1.03, I-squared = 41%); however, results of our analysis for CV of BP variability showed no significant contrast with control group thus no increased risk was reported (RR = 1.04, 95% CI = 0.94-1.15, I-squared = 32%, *P*-value = 0.23). Conclusion: In conclusion, an increased SD of BP variability significantly increased the relative risk for the development of retinopathy.

Keywords: Diabetes mellitus, retinopathy, visit-to-visit variability, blood pressure, risk factor

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Introduction

Diabetes mellitus is a global epidemic that afflicts 415 million people, which will rise to 642 million by 2040 [1]. Among the significant risk factors of macrovascular diseases such as coronary heart disease in diabetics is high blood pressure (BP), and there is also an association with microvascular complications, especially retinopathy and nephropathy [2].

Diabetes patients frequently experience diabetic retinopathy (DR), a microvascular condition that is a significant contributor to vision loss and blindness [3-5]. Elevated BP can cause damage to the delicate microvessels in the retina, leading to increased permeability and leakage, which manifests as microaneurysms, hemorrhages, and exudates [6]. This microvascular damage is further exacerbated by the high blood glucose levels in diabetic patients, resulting in a synergistic effect that accelerates retinal degeneration. Recent studies have suggested that fluctuations in BP may contribute to endothelial dysfunction and further compromise retinal microcirculation [7].

A known risk factor for diabetic retinopathy is hypertension, namely high SBP [8] and high PP [9]. However, novel studies have revealed that BPV is also connected to diabetic retinopathy in people with diabetes [10, 11]. Systolic BPV was an independent risk factor for diabetic retinopathy in people with type 2 diabetes mellitus, according to multicenter research by Hata et al. in Europe [9].

Globally, the leading cause of adult blindness is DR [10]. There is some degree of retinal damage in 98% of people with type 1 diabetes and 78% of those with type 2 after 15 years of suffering from diabetes [11]. A well-known microvascular consequence of diabetes mellitus that poses a hazard to vision is diabetic retinopathy. Ninety-three million individuals across the world suffer from diabetic retinopathy at this time [12]. Numerous studies have consistently demonstrated that high blood pressure fluctuations in diabetic individuals are an unequivocal predictor of nephropathy and its precursors, such as microalbuminuria [13]. There have been many studies on the control of blood pressure on microvascular complications, especially retinopathy.

Certain studies have suggested that managing retinopathy may be accomplished by using visit-to-visit variability in blood pressure [14]. However, other studies have not concluded clearly about the effect of blood pressure change on retinopathy [15-17].

This study aims to consider the controversy that has existed in previous studies. For the first time, a systematic review has been written on the role of blood pressure variability on the risk of diabetic retinopathy.

Methods

Search strategy

This research was prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. From inception to January 2023, we searched the three central databases (PubMed et al.).

Search terms included keywords of “Diabetes mellitus, Retinopathy, Visit-to-visit variability, Blood pressure, Risk factor” and the search strategy of (“Diabetic Retinopathy” OR “Diabetic Retinopathies” OR “micro” OR “microvascular”) AND (“Blood Pressure” OR “Arterial Pressure” OR “Pulmonary Wedge Pressure” OR “Venous Pressure” OR “Central Venous Pressure” OR “Portal Pressure” OR “blood pressure” OR “Diastolic Pressure” OR “Systolic Pressure”) AND (“variability”) were searched. **Table 1** represents the total search strategy words. The systematic review protocol was submitted to OSF (https://doi.org/10.17605/OSF.IO/AEHJZ).

Study eligibility

If the following criteria were met, a study was included: (1) A cohort experiment including a retrospective or prospective cohort of people with diabetes; (2) A follow-up investigation of a randomized controlled trial with BPV as the exposure of interest; (3) The outcome was diabetic retinopathy; and (4) Quantitative assessments for the modified comparative risk (RR) and 95% confidence interval (95% CI) for BPV-related retinopathy were presented. The research was excluded if it did not meet the following standards: (1) There were no clear or logical criteria for inclusion or exclusion; (2) The data obtained from that study were not suffi-

Table 1. Search strategy of databases

Database	Search terms	Results (Search date: 3 January, 2023)
PubMed	("Diabetic Retinopathy"[Mesh] OR "Diabetic Retinopathy" OR "Diabetic Retinopathies" OR "micro" OR "microvascular") AND ("Blood Pressure"[Mesh] OR "Arterial Pressure"[Mesh] OR "Pulmonary Wedge Pressure"[Mesh] OR "Venous Pressure"[Mesh] OR "Central Venous Pressure"[Mesh] OR "Portal Pressure"[Mesh] OR "blood pressure" OR "Diastolic Pressure" OR "Systolic Pressure") AND ("variability")	195
Scopus		
1	(TITLE-ABS-KEY (blood AND pressure) OR TITLE-ABS-KEY (systolic AND pressure) AND TITLE-ABS-KEY (diastolic AND pressure) AND TITLE-ABS-KEY (pulse AND pressure))	15,871
2	(TITLE-ABS KEY (diabetic AND retinopath*) OR TITLE-ABS-KEY (diabetic AND retinopathy) OR TITLE-ABS-KEY (micro) OR TITLE-ABS-KEY (microvascular) OR TITLE-ABS-KEY (diabetic AND eye AND disease))	1,039,787
3	(TITLE-ABS-KEY (variability) OR TITLE-ABS-KEY (variabl*) OR TITLE-ABS-KEY (variable))	3,658,521
4	#1 AND #2 AND #3	44

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P and Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71.

cient; (3) The study was reviewed, abstract only, supplement, grey literature, editorial, or commentary article. If the information in the two articles were similar, we would have selected an article and entered it into a study that examines a more prominent target population.

Data extraction

All included two independent review writers' adapted studies. A third investigator resolved discussions or disagreements on data rupture. The following figures extracted from included studies: first author, publication year, region of study conduct and the source database; design of each trial with its sample size for treatment groups in intervention periods; follow-up period duration measurements being conducted either open or blinded (≥ 3 months); mean age ± standard deviation (SD) of patients analyzed (i.e., number males); results measure outcomes definitions.

Quality assessment

The quality in prognosis studies (QUIPS) tool is recommended for evaluating quality in prognostic factor reviews. Using the QUIPS technique, two authors independently quantify the risk of bias in included publications [16]. This tool evaluates six elements of the research question for bias and acceptability: participation in the study, prognostic factor measurement, attrition study, study confounding, result measurement, and statistical analysis and reporting. "High", "moderate", or "low" risk of bias is assigned to each domain. Discourses solved disagreements.

Statistical analysis

The Ln of HRs, ORs, and relative risk (RR) (and also 95% CIs) were first calculated for the calculation of effect size (ES). To calculate the summary ES as a tool for comparing the highest versus the lowest groups of blood pressure variability, we used a random-effects model to take study heterogeneity into account. Calculations of two indicators of heterogeneity, including I^2 values and Q-statistic, were conducted. In significant cases of between-study heterogeneity, subgroup analysis is based on sample size, participants' gender, location, methods, follow-up duration, and adjustment for confounding variables. The Egger regression asymmetry test was utilized to examine publication bias. A trim-and-fill method was utilized to detect probable missing studies on the overall effect. A sensitivity analysis using a random-effects model was also performed, and each of the studies was excluded to examine the effect of that study on the overall estimate.

Results

Study selection

The current study was carried out based on the PRISMA checklist. Based on the keyword combination search, we identified 195 studies in PubMed, 12 articles in Google Scholar, and 44

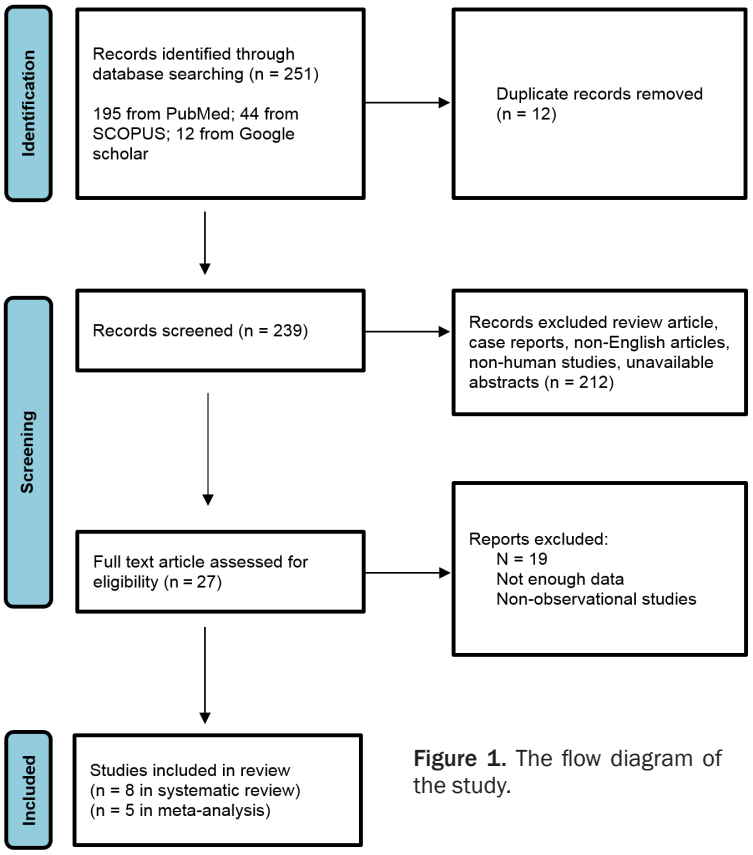

Figure 1. The flow diagram of the study.

studies in Scopus. After removing duplicates, screening the titles and abstracts, and reading the full texts of articles, eight articles were eventually included in our study (**Figure 1**). All included stated posts were published to January 23, four of which could be meta-analyzed. Systematic review: 8 studies included **Table 2** results of included articles.

Study characteristics

The systematic review included a total of 743,315 participants. The average follow-up duration for the eight included publications varied from 2 to 17 years, while the average patient age varied from 46.3 to 67.5 years. Two of these studies were conducted in Brazil, two in Japan, one in Taiwan, one in Singapore, and one in the United States of America. One of the studies recruited individuals from 20 countries, such as Australia, Asia, North America, and Europe [15].

Five of the studies were retrospective, and three of them were prospective. The quality scores of our included studies were above 8.11.

Systematic review of the included studies

Standard deviation (SD), and Coefficient variant (CV) were employed as measures of visit-to-visit systolic BPV (SBPV). SD and CV are considered the traditional measures of BP variability [18, 19].

One of the studies indicated that, in type 2 diabetes, SBP and maximal SBP were independent risk factors for retinopathy (Hazard ratio: 1.24 [1.10-1.39], for SBP and 1.26 [1.13-1.42] for MAX-SBP) [15]. In contrast, three studies indicated that CV and SD of SBP were not significant predictors of retinopathy in type 2 diabetes [17, 20, 21]. It is crucial to acknowledge that the study [13], which indicated SBP as an independent risk factor for retinopathy, had a more significant included population (8811 individuals) then the combined population of the other three studies (3376 individuals) [17, 20, 21].

Additionally, a study conducted by Lou et al. compared the hazard ratio of four groups with different SBP and SDs and found that group 4 (mean SBP ≥ 130 mmHg, SD ≥ 11.16 mmHg) with more SBP had the highest risk of diabetic retinopathy (hazard ratio (HR) = 1.980, 95% CI: 1.716-2.285, P < 0.01) and patients of group 1 group (mean SBP < 130 mmHg, SD of SBP < 11.16 mmHg) with the lowest amounts of SBP were in the lowest risk [22]. In another study, Foo et al. declared that iM-HbA1c (Intrapersonal mean for HbA1c) and iM-SBP (Intrapersonal mean for Systolic Blood Pressure) were significantly related to moderate diabetic retinopathy (odds ratio 1.80, 95% confidence interval [15] 1.37-2.36; and OR 1.03, 95% CI 1.01-1.05, respectively) [23]. After adjusting for demographic, mean SBP, and clinical factors, one of the studies on non-elderly diabetes revealed that individuals with the highest SBP variability had a 17% (OR = 1.17; 95% CI, 1.13-1.21) higher retinopathy incidence than those with the lowest SBP variability [14].

Table 2. Data extraction of the included articles

Reference	Publication year	Country	Database	Study design	Population	No of subjects	Duration of follow-up (year)	Duration between BP measurements	Mean age (year)	Males (%)	Outcome	Definition	Results	Quality score
Hata et al. [15]	2013	20 countries from Asia, Australasia, Europe, and North America	ADVANCE	Retrospective	Type 2 Diabetes	8,811	2	At 3, 4, 6, 12, 18, and 24 months	66	58	Retinopathy	Development of proliferative retinopathy, macular edema, diabetes mellitus-related blindness, or retinal photocoagulation-Therapy.	SBP and maximum SBP were independent risk factors. Hazard ratio: 1.24 [1.10-1.39], 1.26 [1.13-1.42].	11/13
Takao et al. [21]	2017	Japan	JDS	Retrospective	Type 2 Diabetes	832	8.2	816 patients were followed for more than 1 year, of whom 649 visited the clinic at least once a year	54.5	82.2	Non-proliferative retinopathy	The endpoint of retinopathy was defined as the development of Mild to moderate non-proliferative diabetic retinopathy by fundoscopy.	Mean SBP, SBPCV, and SBPVIM were not significant predictors of mild to moderate non-proliferative retinopathy.	10/11
Cardoso et al. [37]	2020	Brazil	Rio de Janeiro Type 2 Diabetes (RIOT2D) Cohort Study	Prospective	Type 2 Diabetes	632	11.3	At least 3-4 times a year	60.0	38.6	Diabetic retinopathy	Retinopathy development or worsening was determined annually. Progression of retinopathy was described as mild non-proliferative retinopathy at baseline and severe non-proliferative retinopathy, proliferative retinopathy or laser photocoagulation or moderate/severe non-proliferative retinopathy at baseline and proliferative retinopathy at any subsequent examination.	SBP-SD did not predict diabetic retinopathy (HR = 1.06, 95% CI 0.89-1.26, P = 0.49).	11/11
Cardoso et al. [20]	2021	Brazil	RIO-T2D Cohort Study	pro-spective study	Type2 diabetes	525	11.2	At least 3-4 times a year	60.2	38.8	Retinopathy (development or worsening)	Retinopathy outcomes were evaluated by annual examinations.	No BPV parameter predicted any microvascular outcome.	8/11
Takao et al. [17]	2014	Japan	JDS and NGSP	Retrospective	Type 2 Diabetes	1912	11.5	At least 4 times and at least once a year	55.7 ± 9.4	82	No severe NPDR	Development of retinopathy was defined as the development of mild-moderate NPDR, and progression of retinopathy was defined as progression to severe NPDR.	Both the SD and coefficient of variation (CV) of SBP were significant predictors of development and progression of nephropathy, but not retinopathy, independently of mean SBP. (*P*-value > 0.01 for both mild-to-moderate and severe NDPR).	10/13

Lou et al. [22]	2022	Taiwan	Diabetes patients who visited Taiwan Lee's united clinics	prospective	Type 2 Diabetes	3275	3-10	4 times a year	DR = 67.5 NDR = 65.2	DR = 54.1 NDR = 50.3	Diabetic retinopathy	Direct ophthalmoscopy after mydriasis was performed by an ophthalmologist. The presence of microaneurysm, cotton wool spots, intracavitary microvascular abnormalities, bleeding.hard exudate, venous aneurysm, or new retinal blood vessels was defined as DR.	The mean and SD of SBP, pulse pressure, and their SDs were risk factors for the DRG4 group (mean SBP ≥ 130 mmHg, SD ≥ 11.16 mmHg) had the highest risk of DR (hazard ratio HR = 1:980, 95% CI: 1.716-2.285, P < 0:01). G1 group (mean SBP < 130 mmHg, SD of SBP < 11.16 mmHg) had the lowest risk.	9/11
Sohn et al. [14]	2017	USA	US Department of Veterans Affairs healthcare system	Retrospective	Non-elderly Diabetic (aged 60 years old and younger)	726,930	3.5	3-12 times a year	53.7	95.4	Retinopathy	identified using ICD-9-CM codes: 250.5x, 366.41: Diabetes with ocular manifestations and Diabetic cataract.	Compared to individuals with the least SBP variability (Quartile 1), those with most variability (Quartile 4) had 81% (OR = 1.81; 95% CI, 1.72-1.91), 17% (OR = 1.17; 95% CI, 1.13-1.21), 30% (OR = 1.30; 95% CI, 1.25-1.35), and 19% (OR = 1.19; 95% CI, 1.15-1.23) higher incidence of nephropathy, retinopathy, neuropathy, and any complication, respectively, after adjusting for mean SBP, demographic and clinical factors.	8/11
Foo et al. [23]	2016	Singapore	Public primary care clinic (polyclinic) in the Outram district in southern Singapore	Retrospective	Type 2 Diabetes	398	2	3-6 times every 4-month	DR = 59.7 ± 11.5 NDR = 62.0 ± 10.6	DR = 62.2 NDR = 87.7	Retinopathy	Subjects were considered to have DR if any of the following lesions were present in any eye: microaneurysms, hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, venous beading, and new vessels. For each eye, the retinopathy severity score was assigned according to the modified Airlie House Classification System.24 Based on the severity score of the worse eye, any-DR was defined as a severity score of level 15 and above, whereas moderate or worse DR was defined as a severity score of level 43 and above.	Moderate DR had higher iM-HbA1c [8.2% vs 7.3 %; P = 0.001], iSD-HbA1c [1.22 vs 0.64; P = 0.001], iM-SBP [136.8 vs 129.6 mmHg; P = 0.001] and iSD-SBP [13.3 vs 11.1; P = 0.002] than controls the multivariate regression model adjusted for age, gender, ethnicity, duration of diabetes, SBP, and HbA1c, iM-HbA1c and iM-SBP were significantly associated with moderate DR (odds ratio [OR] 1.80, 95% confidence interval [CI] 1.37-2.36; and OR 1.03, 95% CI 1.01-1.05, respectively).	9/11

Abbreviations: ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; SBP, Systolic Blood Pressure; JDS, Japan Diabetes Society; SBPCV, Systolic Blood Pressure Coefficient of Variation; SBPVIM, Systolic Blood Pressure Variation Independent of Mean; SBP-SD, systolic blood pressure standard deviation; HR, hazard ratio; BPV, blood pressure variability; DBP-SD, standard deviation of diastolic blood pressure; NGSP, National Glycohemoglobin Standardization Program; DR, Diabetic Retinopathy; NDR, Not (having) Diabetic Retinopathy; NPDR, Non-proliferative diabetic retinopathy; iM-HbA1c, Intrapersonal mean for HbA1c; iSD-HbA1c: SD values for HbA1c; iM-SBP, Intrapersonal mean for Systolic Blood Pressure; iSD-SBP, SD values for Systolic Blood Pressure; CI, Confidence Interval.

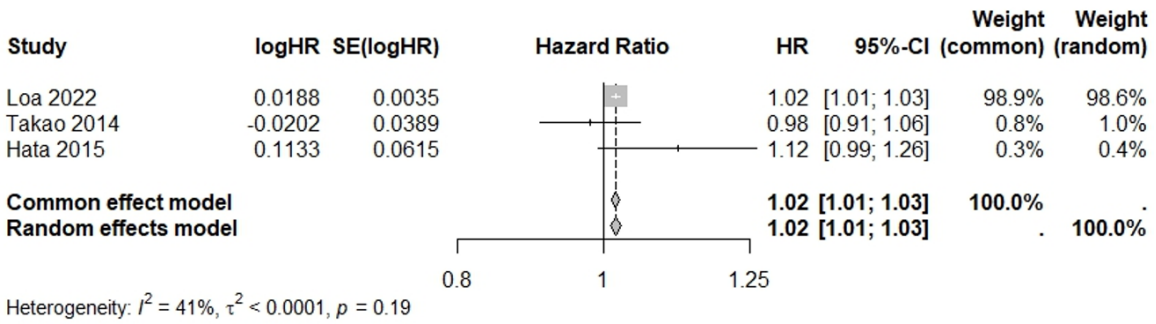

Figure 2. Forest plot of the meta-analysis of the SD of visit-to-visit variability of blood pressure and risk of diabetic retinopathy.

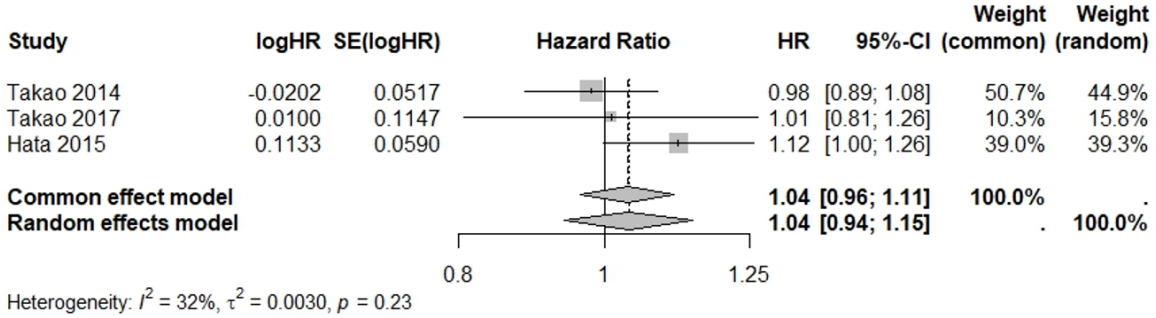

Figure 3. Forest plot of the meta-analysis of the CV of visit-to-visit variability of blood pressure and risk of diabetic retinopathy.

SD was used to determine visit-to-visit diastolic BPV (DBPV). According to Cardoso and associates' research, no BPV parameter predicted any microvascular outcome. There were no variations in the prevalence of microvascular outcomes between DBP-SD subgroups [20].

Meta-analysis results

Based on the indexed BP-SD, the group with higher blood pressure variability has an 2 percent higher risk than the control group (95% CI = 1.01-1.03, I-squared = 41%) (**Figure 2**); however, results of our analysis for BP-CV showed no significant contrast with control group thus no increased risk is reported (RR = 1.04, 95% CI = 0.94-1.15, I-squared = 32%, *P*-value = 0.23) (**Figure 3**).

Publication bias

We conducted a funnel plot of the SD to detect publication bias in meta-analysis; it is relatively symmetric, with studies scattered evenly on both sides, which means there is little to no conspicuous publication bias (**Figure 4**). However, the funnel plot of the SD to detect publication bias in meta-analysis, including studies from Takao 2014, Takao 2017, and Hata 2015, showed that among them, the most significant standard error belonged to Takao 2017, which represents the smaller sample size or less precise estimate, while Hata 2015 had its place with lower standard error, which indicates an exact result. The distribution of points is generally symmetric, indicating no significant publication bias in the set of studies. This symmetry implies that both small and large studies contribute equally to the meta-analysis, reducing many of the concerns about bias (**Figure 5**).

The sensitivity analysis is also added as Supplementary Figures 1 and 2. No studies were removed due to the results of sensitivity analysis.

Discussion

To the best of our knowledge, our systematic review and meta-analysis was the first study

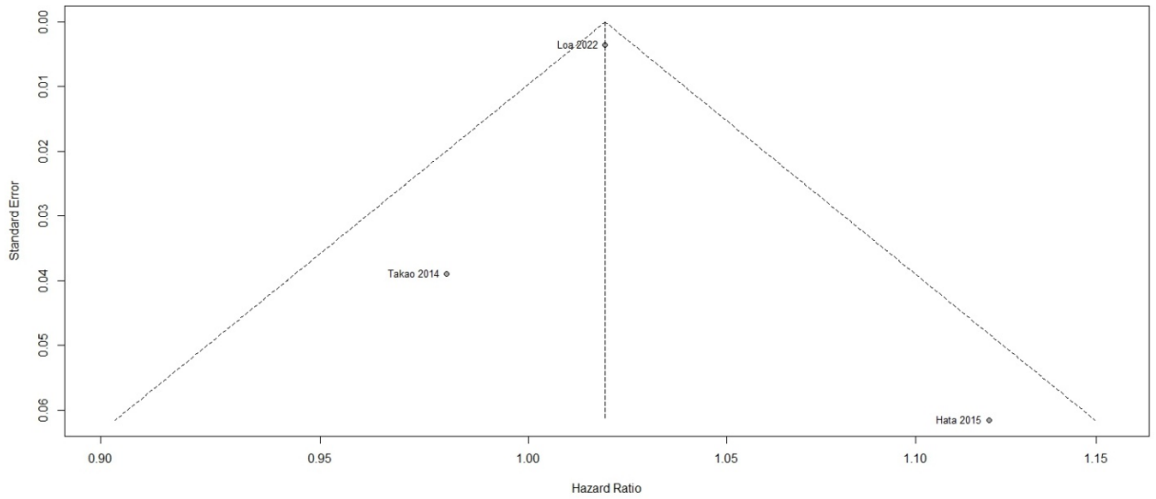

Figure 4. Funnel plot of the meta-analysis of the SD of visit-to-visit variability of blood pressure and risk of diabetic retinopathy.

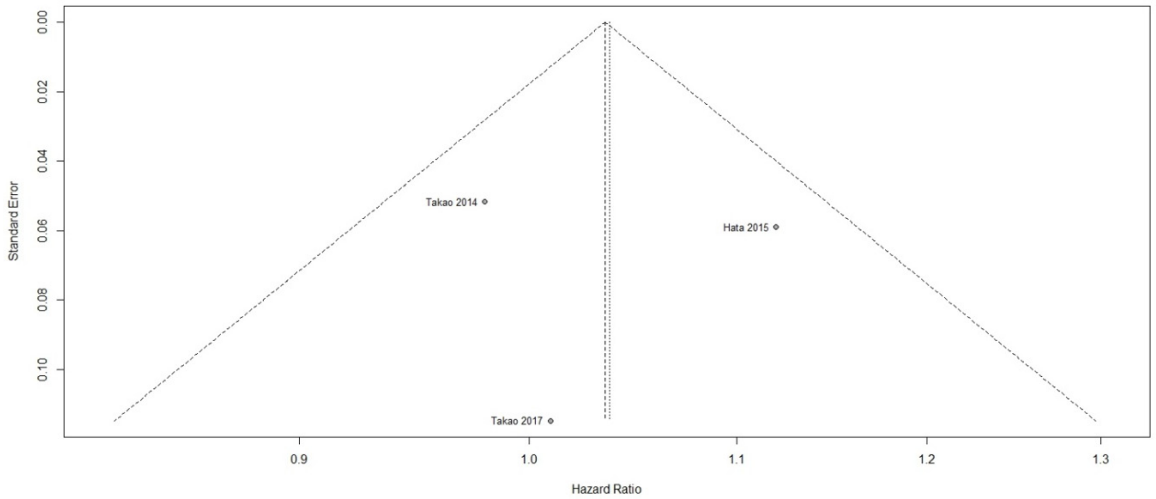

Figure 5. Funnel plot of the meta-analysis of the CV of visit-to-visit variability of blood pressure and risk of diabetic retinopathy.

that explored the potential relationship between diabetic retinopathy and visit-to-visit BP variability for the first time. Based on the indexed BP-SD, our analysis of the topic showed that the group with higher blood pressure variability has an 2 percent higher risk of developing the outcome than the control group. Although indexed BP-CV were not associated with a significant risk of developing the outcome in our study, results from different investigations were controversial, as discussed in the following paragraphs.

A study revealed that patients with maximum variability were more likely (17%) to experience incident retinopathy than those with minimum variability. Compared to the lowest variability group, the maximum variability group had a higher risk (19%) for any microvascular complication. It was indicated that augmenting hypertension treatment with therapy may be required to reduce SBP variability. According to this research, clinicians may need to start therapy for SBP variation as low as 4 mm Hg in standard deviation [20]; however, in our study, indexed SD showed no significant difference in risk of developed outcomes between the groups.

The study focused on short-term ambulatory blood pressure variability, whereas our research examined long-term visit-to-visit BP vari-

ability. This difference in measurement periods can influence the variability observed and its impact on microvascular outcomes. Moreover, the methods used to adjust for confounding variables and the specific definitions of outcomes might have varied between the studies, further influencing the results.

Blood pressure is a physiological parameter reflecting the hemodynamic status while having specific features and dynamic changes. We initially hypothesized that the magnitude of BP fluctuation could skew each patient's BPlow and BHBP assessments. However, increasing evidence supports BPV as a critical pathogenetic mechanism in the full-size table [24]. It is presumed that visit-to-visit BPV reflects various mechanisms, including fluctuations to activate the central sympathetic nervous system overactivity, renin-angiotensin-aldosterone system, increased arterial stiffness, incremented vasoactive compound secretion, psychological and environmental circumstances such as alterations in BP-lowering treatment regimen during the measurement period and variable adherence to anti-hypertensive treatment [25]. According to animal studies, the increased BP variability leads to direct endothelial damage, cardiomyocyte apoptosis augmentation, and inflammation, resulting in cardiac remodeling and end-organ damage [26]. Furthermore, visit-to-visit BP variability can be associated with different methodological factors such as the BP measurement method (automatic or manual), the number of visits, the time interval between visits, the adjustment level for other risk factors, and the duration of follow-up [27].

Some possible descriptions can clarify such a disparity between long-term and short-term BPV. Short-term BPV is a complex phenomenon determined by physiological factors (baroreflex regulation and cardiovascular autonomic control), hemodynamic reactions to medium stimuli, and behavior factors (daily activities), mainly during the awake daytime period [28].

Furthermore, serial clinic (office) BP measurements orient the long-term visit-to-visit BP variability over time. Within various health professionals, it is significantly less standardized than 24-h ABPM. Besides, visit-to-visit BPV is dependent strongly on the adherence of the people to anti-hypertensive medication over time, while short-term 24-h BPV is less oriented by treatment adherence [20].

Hata et al. revealed that BP fluctuation can significantly predict microvascular problems in type 2 diabetes patients. However, they could not provide equivalent definitive evidence regarding the impacts of SBP variation on each microvascular outcome component (retinopathy and nephropathy). Sohn et al. revealed a robust and significant graded association between SBP variability and retinopathy [14, 15].

The findings from Hata et al. and Sohn et al. align with our observations that blood pressure (BP) fluctuation can significantly predict microvascular problems, including retinopathy, in type 2 diabetes patients. However, our study provides a nuanced perspective by differentiating the impacts of various BP variability indices. While Hata et al. and Sohn et al. reported significant associations with systolic BP variability (SBP), our study found that only the Standard Deviation (SD) was significantly associated with an increased risk of diabetic retinopathy. In contrast, the Coefficient of Variation (CV) of BP did not show significant differences in risk between the groups. These discrepancies highlight the importance of considering different BP variability measures when assessing the risk of microvascular complications.

According to Takao et al., visit-to-visit SBP variability can significantly indicate the progression and development of diabetic nephropathy. However, the progression or development of diabetic retinopathy was not predicted in T2DM patients, self-reliantly on the mean SBP. They present a difference in the variability predictive ability in SBP between retinopathy and nephropathy. Such a differing risk prediction may be associated with the structural difference in the vessel wall of the retina and kidney. It is considered that the vessel wall in the retina is simpler compared to the kidney. Thus, retinopathy is likely less susceptible to arteriosclerosis than nephropathy. The discrepancy in the effects of SBP variability on retinopathy and nephropathy may be responsible for other differences in the contributions of two mechanisms of episodic fluctuations in SBP and continuing hypertension. Moreover, such a discrepancy may be caused by a possible time-to-

effect association between diabetic microangiopathy and SBP status [17, 21]. As seen in studies, there has yet to be a unified consensus on the relationship between the two variables; hence, before any change in clinical practice, more research is required to understand pathophysiology and underlying causality better.

Lou et al. (2022), represented that such results may be owing to the small used sample, shorter duration of diabetes, and lower overall mean SBP SD [22].

Cardoso et al. (2020, 2021), Could not predict any microvascular outcomes by the short-term and long-term BP-VVV parameters. Different determinants may come about from macrovascular and microvascular damage. Microvascular problems may rely more on glycemic management and less on BP levels, or BP levels may be more crucial than BPV for developing microvascular complications [20].

According to Foo et al., Moderate DR cases had a more considerable mean SBP and HbA1c rather than SBP and HbA1c variability. Extensive variability of SBP was related to moderate DR in individuals with satisfactory glycemic control. Poor glycemic condition plays a substantial role in developing DR. In this case, the effects of SBP fluctuation were not apparent in individuals with poor glycemic conditions. Lou et al. (2022), indicated that this difference might be caused by the short follow-up time, smaller sample size, the short duration of diabetes, and the non-homogeneous population of the study [22, 23].

Lou et al. revealed variability in PP and SBP as the risk factors for DR in T2DM patients. This variability may be more significant in the DR development than the mean SBP and PP. Hypothetically, a BP increase may damage the retinal capillary endothelial cells. Studies conducted on retinal physiology demonstrated that blood pressure contributes to the pathological alterations of DR and plays a role in the local renin-angiotensin system [29]. Hyper-perfusion can be avoided by controlling blood pressure to reduce the possibility of hypertension-caused blood vessel shear injury. Thus, DR can be prevented by decreasing the high perfusion damage to the endothelial cells, blood vessels, and surrounding tissues. Since the data were only gathered from DR cases, it is not possible to determine whether DR is due to diabetes or hypertension [22].

Sohn et al. (2017), revealed a considerable association between the incidence of microvascular complications and SBP variability for non-elderly diabetic patients. Such relationships were observed in patients with BP ≥ 130/80 mm Hg and those with BP < 130/80 mm Hg with anti-hypertensive agents [14].

The study by Liu et al. (2020), examined the correlation between hypertension, blood pressure management, and diabetic retinopathy. The study revealed a substantial association between inadequately managed and untreated hypertension and the development of diabetic retinopathy. The researchers also noted a positive correlation between elevated systolic blood pressure (SBP) and pulse pressure (PP) levels and any diabetic retinopathy and vision-threatening diabetic retinopathy [30].

The findings of Zhang et al. (2023), have contributed significant empirical support to the advantages of using aggressive measures for blood pressure management. Furthermore, the blind evaluation conducted by a professional reading center has significantly mitigated the potential bias associated with the misdiagnosis of diabetic retinopathy (DR) in fundus pictures. The development of prediction techniques for diabetic retinopathy (DR) and proliferative diabetic retinopathy (PDR) has been accomplished. Nomogram models are practical visualization tools for quantitatively predicting and assessing diabetic retinopathy (DR) in clinical and public health settings [31].

In a study conducted by Ji Hyun Lee (2020), it was observed that there is a correlation between the difference in blood pressure between the arms and the occurrence of diabetic retinopathy. This correlation existed even when the difference in systolic blood pressure between the arms was equal to or more than five mmHg, and the overall systolic blood pressure level did not influence it. A discrepancy in systolic blood pressure between the arms should indicate potential vascular complications in individuals diagnosed with type 2 diabetes [32].

In a study conducted by Li (2021), systolic blood pressure (BP) levels consistently rose

across all categories of diabetic retinopathy (DR) severity, regardless of the presence of concurrent hypertension. The ordinal logistic regression analysis results indicated a statistically significant and independent association between elevated systolic blood pressure and diabetic retinopathy. This association remained significant even after controlling for confounding factors such as diabetes duration, sex, lifestyles, and hemoglobin A1c levels [33].

A study by Jian-Bo Zhou (2018), showed that intensive blood pressure management resulted in a 17% reduction in the relative risk of developing diabetic retinopathy (DR). Insufficient evidence was provided to establish or disprove a relative risk reduction of 15% for the development of diabetic retinopathy (DR) or the occurrence of proliferative diabetic retinopathy (PDR) and macular edema (ME) [34].

Considering various studies, our results reveal that different indices of blood pressure (BP) variability have distinct impacts on diabetic retinopathy. Takao et al. indicated that visit-to-visit systolic blood pressure (SBP) variability significantly predicts the progression of diabetic nephropathy but not retinopathy, possibly due to the structural differences between the retinal and kidney vessel walls. Similarly, Lou et al. and Foo et al. emphasized that SBP variability, especially variation independent of the mean (VIM), is crucial in developing diabetic retinopathy, although the effects might be less pronounced in patients with poor glycemic control.

In contrast, Cardoso et al. could not find significant predictive value in short-term or long-term BP variability parameters for microvascular outcomes, suggesting that factors such as glycemic management might play a more critical role. Our study aligns with these findings by showing that while SD was significantly associated with an increased risk of diabetic retinopathy and CV did not showes significant differences. These discrepancies underscore the importance of considering various BP variability indices and highlight the need for further research to understand the underlying mechanisms better [30-35].

In a population with type 2 diabetes, the potential impact of BPV on microvascular damage may be mediated by several physio-pathological pathways. Increased arterial stiffness caused by increased BPV may facilitate the passage of excessive pulsatile energy to the microvascular beds. This might result in barotrauma on the wall of small vessels, which would cause vascular remodeling and reduced tissue perfusion, causing damage to target organs to begin and progress [36]. Additionally, in diabetic patients, an altered microvascular response to BP changes brought on by altered autonomic nervous system function may induce microvascular damage [37].

Despite SD, our analysis of CV showed no significant relation between BPV and the risk of DR. A justification could be that VIM is a transformation of SD, which is not correlated with mean BP and is calculated by dividing SD by mean BP [17]. Also, the number of studies assessing VIM was lower than those reporting CV or SD; this could be effective in obtaining results.

Our search strategy was very detailed. Statistical tests showed no evidence of publication bias in the analyses. On the other hand, this systematic review and meta-analysis also have several limitations: as reported above, many studies have considered various visit-to-visit BP variables that we should have considered; also, there was substantial heterogeneity between eligible studies. Because that research included adopting a different disease coding system, such as ICD-9-CM, this cannot definitively diagnose diabetic microvascular complications and may have influenced the results. Interpretation of findings: Autious interpretation is warranted because the present study has several limitations.

Conclusion

The present systematic review revealed controversial associations between the risk of diabetic retinopathy and visit-to-visit BPV. Future prospective studies are necessary for this area to assess the relationship between BPV and diabetic retinopathy. Current results indicate that abnormal fluctuations of BP must be prevented to restore regular BP rhythm. More clinical research is necessary to evaluate the visit-to-visit BPV average reference values for clinical practice and identify more efficient treatment approaches for BPV reduction.

Disclosure of conflict of interest

None.

Abbreviations

DM, Diabetes Mellitus; BP, blood pressure; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis; RR, relative risk; SD, Standard deviation; CV, coefficient of variation; VIM, variation independent of the mean; DR, diabetic retinopathy; QUIPS, quality in prognosis studies; ES, effect size; SBPV, systolic BPV; iM-HbA1c, Intrapersonal mean for HbA1c; in-SBP, Intrapersonal mean for Systolic Blood Pressure; DBPV, diastolic BPV; SBP, systolic blood pressure; PP, pulse pressure; PDR, proliferative diabetic retinopathy.

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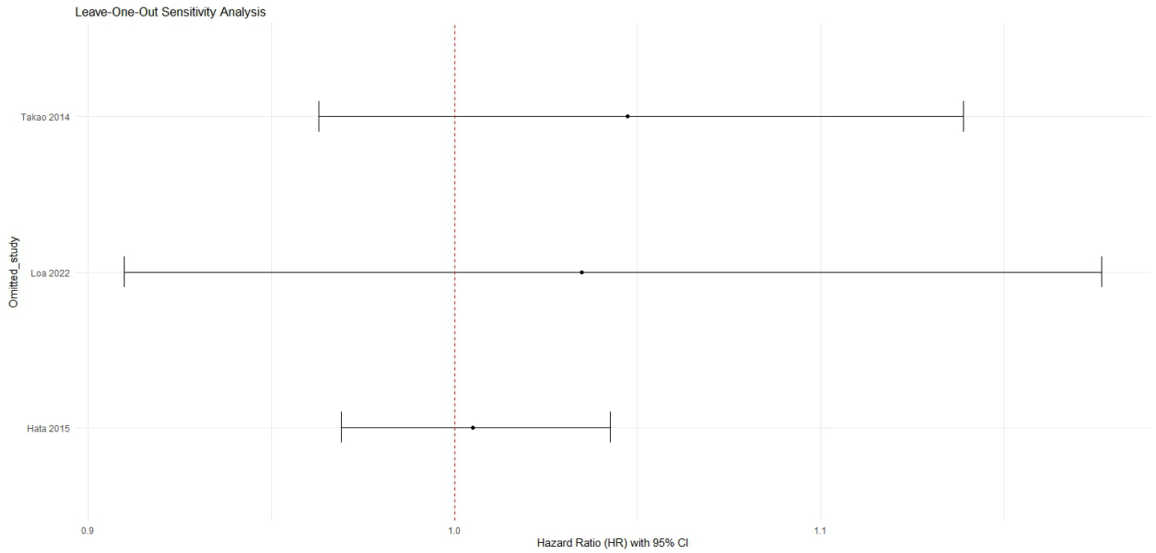
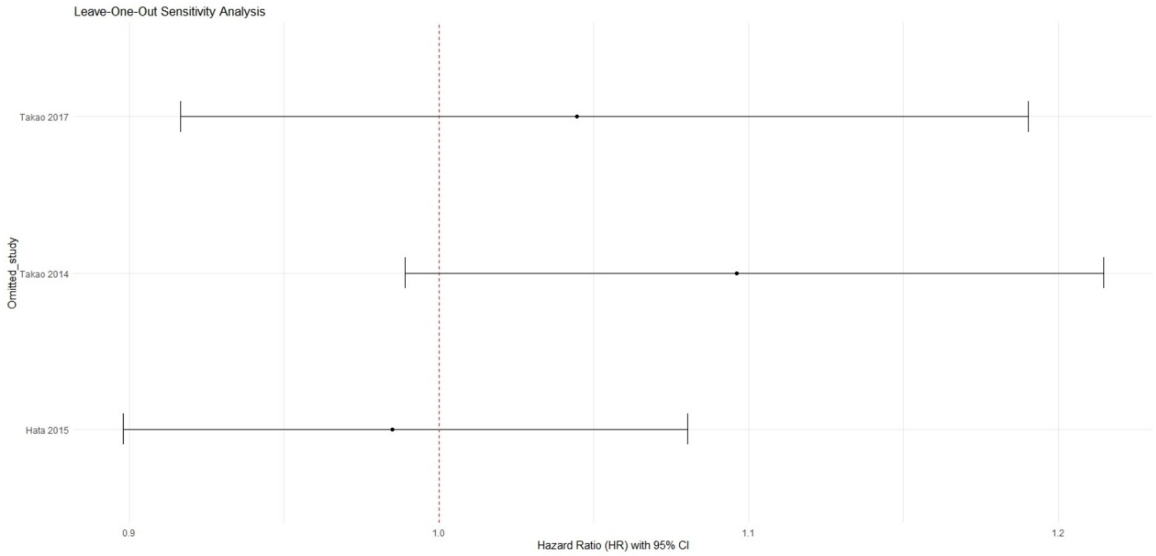


Supplementary Figure 1. Sensitivity analysis of the meta-analysis of the SD of visit-to-visit variability of blood pressure and risk of diabetic retinopathy.



Supplementary Figure 2. Sensitivity analysis of the meta-analysis of the CV of visit-to-visit variability of blood pressure and risk of diabetic retinopathy.