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Fasting plasma glucose variability levels and risk of adverse outcomes among patients with type 2 diabetes: A systematic review and meta-analysis

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ABSTRACT

Aim: This systematic review and meta-analysis assessed the association between fasting plasma glucose (FPG) variability levels and the risk of retinopathy and all-cause mortality in patients with type 2 diabetes.

Methods: PubMed and EMBASE were searched to identify studies that evaluated the association between FPG variability and retinopathy and all-cause mortality in patients with type 2 diabetes mellitus. The hazard ratios (HRs) and 95% confidence intervals (CIs) were pooled with the random-effects model.

Results: Eight studies were included in our meta-analysis. Five studies evaluated the impact of FPG variability on all-cause mortality and showed that high FPG variability was associated with the risk of all-cause mortality (HR 1.28, 95% CI 1.12–1.46; three studies). For median or mean FPG variability levels under 20%, the relationship between all-cause mortality and FPG variability was not significant. Three studies evaluated FPG variability and the risk of diabetic retinopathy and showed that high FPG variability was strongly associated with the risk of retinopathy (odds ratio (OR) = 3.68; 95% CI 1.01–13.4).

Conclusion: High FPG variability levels were positively associated with the risk of retinopathy and all-cause mortality in patients with type 2 diabetes.

Contents

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1. Introduction

Intermittent hyperglycaemia has been associated with impairment of endothelial function [1] and increased risk of vascular complications and all-cause mortality [2] in patients with type 2 diabetes mellitus. Moreover, some studies have demonstrated that people with excessive high [3,4] or low [5,6] glucose levels have a high risk of vascular diseases and all-cause mortality. In recent years, glycaemic variability (GV) has emerged as an independent risk factor for long-term complications of diabetes [7]. Hence, glycaemic variability is a sensitive indicator for assessing low and high blood glucose levels.

There have been quite a few studies exploring the relationship between FPG variability and adverse outcomes in type 2 diabetes mellitus [8–15]. For example, the Verona Diabetes Study [12] and a dynamic cohort study in China [14] suggested that FPG variability was not associated with the development of retinopathy or risk for all-cause mortality, respectively, in type 2 diabetic patients after adjusting for potential confounders. Nevertheless, some studies found that high FPG variability was significantly correlated with the incidence of retinopathy [13] and all-cause mortality [15] in type 2 diabetic patients. Therefore, whether high FPG variability levels is related to adverse outcomes in type 2 diabetes mellitus is under debate. We conducted this meta-analysis and systematic review to assess the relationship between FPG variability levels and the risk of retinopathy and all-cause mortality in patients with type 2 diabetes.

2. Materials and methods

2.1. *Publication search*

We conducted a detailed search (through 14 June 2018) on PubMed and EMBASE to identify literature that evaluated the association between FPG variability and the risk of retinopathy or all-cause mortality in type 2 diabetes mellitus. The main search terms were fasting plasma glucose variability, glucose variability, glycaemic variability, visit-to-visit glycaemic variability, type 2 diabetes mellitus, type 2 diabetes, T2DM, diabetes, retinopathy, and death. To identify additional eligible studies, we also searched the grey literature sources. The article search was conducted by two reviewers (F.Z. and Q.Z.), and discrepancies were resolved by conference.

2.2. *Eligibility criteria*

The study inclusion criteria were as follows: (1) all participants were patients with type 2 diabetes; (2) the exposure variable was variability of FPG, and FPG variability was assessed by standard deviation (SD) or the coefficient of variation (CV); and (3) we could extract comparison categories and corresponding effect sizes from the study. The effect sizes were obtained from hazard ratios (HRs), odds ratios (ORs), or relative risks (RRs), which were expressed in 95% confidence intervals (CIs). We excluded animal studies, reviews, case reports, letters, duplicates and studies for which we could not obtain the full text.

2.3. *Data collection and quality assessment*

Two authors (F.Z., Q.Z.) extracted data independently according to the selection criteria. The data that were collected included the authors, publication year, participant characteristics, follow-up duration, effect sizes for all categories of level of variability, outcomes evaluated and so on. Discrepancies were resolved by conference or by consultation with the senior investigator.

Study quality was assessed by the Newcastle–Ottawa Quality Assessment Scale (NOS), which is a nine-point system [16]. Studies with fewer than five, five to seven, and more than seven points were considered to be of low, moderate and high quality, respectively. To analyse the relationship between FPG variability levels and adverse outcomes, we extracted the median or mean FPG variability, which are midpoints of the lower and upper boundaries of each category. When the upper boundaries were open-ended, we assigned that the open-ended interval length, which was high FPG variability. Low FPG variability was defined as the open-ended lower boundaries.

2.4. *Statistical analysis*

Initially, a fixed-effects model was used for the pooled analyses, while a random-effects model was applied when heterogeneity was found. We calculated the pooled hazard ratio (HR) for CV of FPG. However, other effect sizes were not combined on account of a lack of adequate studies, so we performed

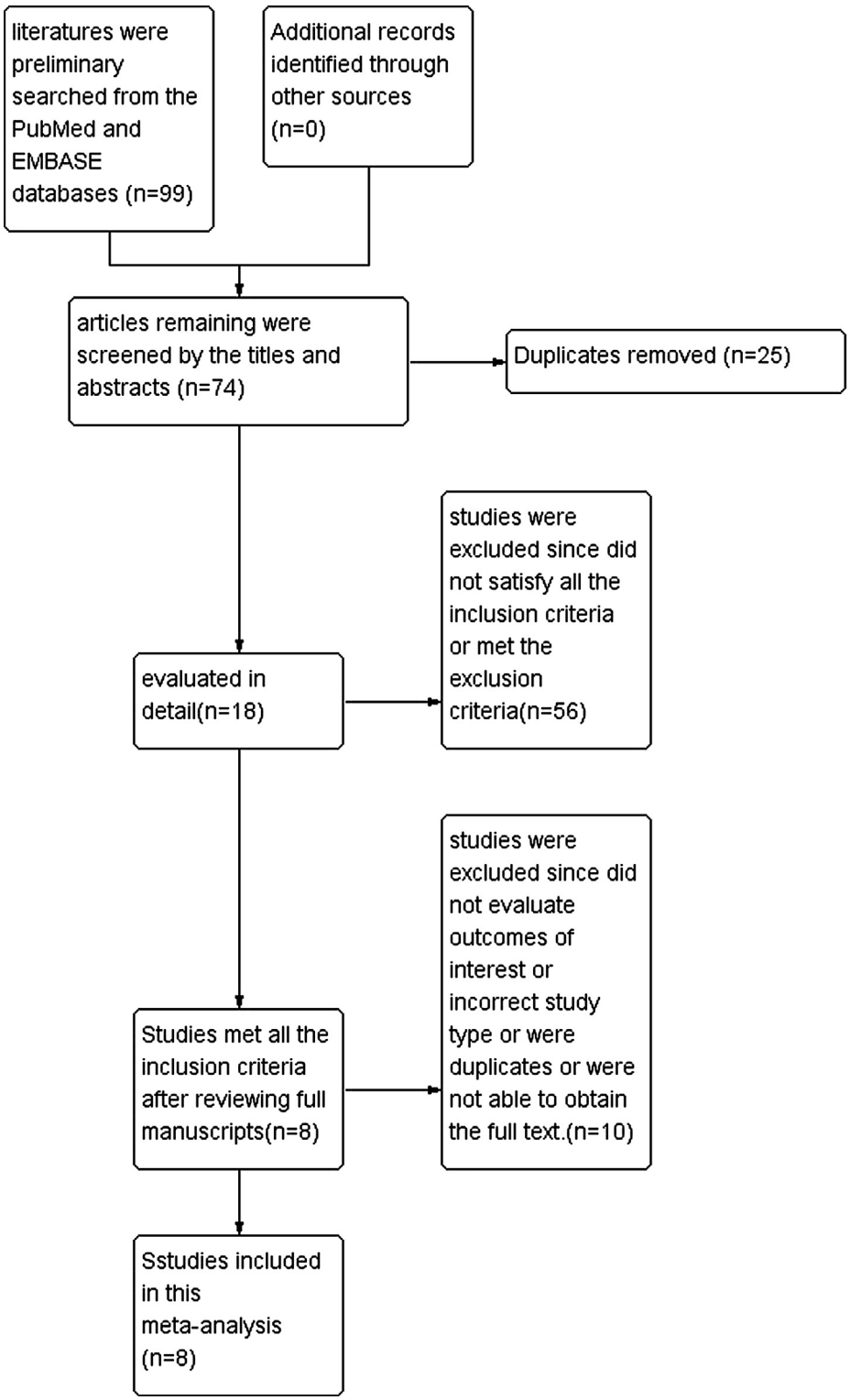

Fig. 1 – Flow chart of the studies selection process. Legend: Solid lines with arrows stand for the process of study selection.

narrative synthesis instead. FPG-CV or FPG-SD could be calculated or acquired from the primary study.

Heterogeneity among the studies was assessed using the Cochran Q test ($P \leq 0.10$) and I^2 statistic, and I^2 values under 25%, from 25 to 50%, and above 50% were considered small, medium, and high degrees of heterogeneity, respectively [17]. The possibility of publication bias was estimated using funnel plots if more than ten studies included meta-analyses. Meta-analyses and statistical analyses were conducted using STATA software (Version 12.0 College Station, TX, USA). Statistical significance was set as two-tailed P values <0.05.

Table 1 – Characteristics of 8 studies included in this meta-analysis.

Study	Sample (male%)	Mean age (Follow-up)	Mean-FPG (mmol/L)	Mean HbAlc (%)	Diabetes duration (years)	FPG variability	Number of FPG measurements
Muggeo 2000	1409 (46.3)	66.4 (10.0)	8.9	NR	12.3	aCV	Number of FPG measurements per patient was at least 3
Gimeno-Orna 2003	130 (32.3)	62.5 (5.2)	NR	8.2	NR	aCV	NR
Zoppini 2009	1019 (54.4)	69.0 (4.0)	NR	NR	NR	aCV	The number of measurements was at least 3 FPG determinations
Takao 2010	170 (66.5)	44.2 (32.8)	8.1	6.9	2.5	aSD	During the entire observation period, FPG was measured 18–423 times
Yang 2015	31,841 (46.5)	60.9 (8.2)	9.6	8.2	4.5	aCV	Patients were followed up every 3 to 6 months and received blood tests during follow-up visits
Xu 2016	8871 (44.06)	71.9 (8.0)	7.1	NR	13	aCV	NR
Wang 2017	53,607 (76.4)	49.10 (4.9)	5.6	NR	NR	aCV	NR
Lee 2018	3569 (54.9)	68.57 (4.4)	8.3	7.7	NR	aCV	FPG was measured every 3 months

Study	Comparison categories and corresponding effect size	Outcome (number)	Adjustments for potential confounders	Design	NOS Score
Muggeo 2000	<11.7, RR:1 11.7–18.7, RR: 1.67 (1.30–2.14) >18.7, RR: 1.68 (1.29–2.18)	All-cause mortality (468)	1, 2, 3, 5, 6, 7, 8, 16, 17	Observational study	9
Gimeno-Orna 2003	<16, OR:1 16–22, OR: 2.91 (0.83–10.1) 22–29, OR: 2.29 (0.62–8.4) >29, OR: 3.68 (1.01–13.4)	Retinopathy (47)	1, 5, 16, 19, 24	Retrospective cohort study	8
Zoppini 2009	NR, OR:1.26 (0.99–1.49)	The development/progression of retinopathy (124)	1, 2, 5, 6, 7, 8, 16, 17, 19	Prospective cohort study	5
Takao 2010	<26.1, HR: 1 ≥26.1, HR: 3.01 (1.11–8.14)	Retinopathy (131)	1, 2, 5, 14	Retrospective cohort study	7
Yang 2015	<11.8, HR:1 11.8–20.5, HR: 0.94 (0.86–1.03) 20.5–30.9, HR: 1.07 (0.98–1.17) 30.9–48.6, HR:1.21 (1.11–1.31) >48.6, HR:1.29 (1.18–1.40)	All-cause mortality (NR)	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19	Retrospective cohort study	9
Xu 2016	<4.25, HR: 1 4.25–7.75, HR: 0.86 (0.73–1.02). 7.75–13.45, HR:0.92 (0.78–1.09) >13.45, HR:1.10 (0.93–1.31)	All-cause mortality (1136)	1, 2, 3, 5, 6, 7, 8, 16, 22, 23	Retrospective cohort study	8
Wang 2017	<5.27, HR: 1 5.27–8.49, HR: 1.18 (1–1.39) 8.49–13.11, HR:1.20 (1.02–1.40) >13.11, HR:1.46 (1.25–1.70)	All-cause mortality (1545)	1, 2, 3, 4, 5, 6, 7, 8, 12, 17, 20, 21, 22	Prospective cohort study	6

Lee 2018	Low, HR: 1 Increasing HR: 2.05 (0.83–5.02) Fluctuating HR: 2.63 (1.40–4.93) Decreasing HR: 2.78 (1.33–5.80) High HR: 4.44 (1.80–11.06)	All-cause mortality (159)	1, 2, 6, 7, 12, 13, 16, 19	Retrospective cohort study	6

FPG: fasting plasma glucose, NOS: the Newcastle-Ottawa Quality Assessment Scale, aSD: adjusted SD, aCV: adjusted CV, 1: age, 2: gender, 3: tobacco, 4: alcohol, 5: duration of diabetes, 6: type of hypoglycemic drugs, 7: hypertension, 8: obesity or body mass index at baseline, 9: cardiovascular disease, 10: chronic hepatitis, 11: chronic obstructive pulmonary disease, 12: estimated glomerular filtration rate (eGFR), 13: chronic kidney disease, 14: hypoglycemia, 15: stroke, 16: baseline fasting glucose, 17: dyslipidemia, 18: tumor, 19: baseline HbA1c, 20: education, 21: income, 22: physical activity, 23: family history, 24: length of follow-up

3. Results

3.1. *Literature search and baseline characteristics*

The process of the selection of the studies is shown in Fig. 1. A total of 99 studies were obtained from the preliminary search of the PubMed and EMBASE databases. Of these 99 studies, 8 studies [12–15,18–21] were included in our meta-analysis, which ultimately involved 100,616 patients with T2DM.

The characteristics of the included studies are presented in Table 1. All studies were analysed for potential risk factors using multivariate Cox proportional hazards models. The mean follow-up durations ranged from 4.0 to 32.8 years. The mean FPG was between 5.6 and 9.6 mmol/L, and the duration of diabetes diagnoses ranged from 2.5 to 12.3 years. The mean NOS score was 7.25 (Table 2), indicating that the studies were of high quality. The outcomes of three studies was retinopathy, and five studies assessed all-cause mortality.

3.2. *Adverse outcomes*

3.2.1. *All-cause mortality*

Five studies [14,15,18,20,21] evaluated all-cause mortality by considering the impact of FPG CV. All studies except one showed that FPG CV was significantly associated with all-cause mortality in the high FPG variability group. Nevertheless, only three studies were combined due to different effect sizes. Fig. 2 shows the pooled HR results, which revealed that high FPG CV was associated with the risk of all-cause mortality (HR 1.28, 95% CI 1.12–1.46; $P = 0.000$) with strong evidence of heterogeneity ($I^2 = 65.6\%$, $P = 0.055$).

One study evaluated the FPG variability trajectory and showed that a high FPG variability trajectory versus a low FPG variability trajectory was also significantly related to the risk of mortality (HR: 4.44, 95% CI: 1.80–11.06; $P = 0.001$, one study). However, incremental increases in the FPG variability trajectory were not associated with the risk of mortality (HR: 2.05, 95% CI: 0.834–5.019; $P = 0.118$).

For a median or mean FPG CV range from 10 to 20%, the relationship between all-cause mortality and FPG CV was not significant (HR 1.01, 95% CI 0.86–1.18; $P = 0.929$; three studies, Fig. 3). In addition, no significant association was found between all-cause mortality and FPG CV when mean or median FPG CV was under 10% (HR 1.01, 95% CI 0.74–1.37; $P = 0.961$, two studies, Fig. 4).

3.2.2. *Retinopathy*

Three studies [12,13,19] reporting retinopathy as an outcome were not pooled owing to the high levels of heterogeneity. Two of the studies showed that high FPG fluctuations are related to the risk of diabetic retinopathy (OR = 3.68; 95% CI 1.01–13.4; $P = 0.049$). Nevertheless, for elderly patients with type 2 diabetes, FPG fluctuations do not increase the development/progression of diabetic retinopathy (OR: 1.26, 95% CI 0.99–1.49, one study).

3.3. *Publication bias*

Given that the number of included studies was fewer than 10, we could not conduct funnel plots to assess the publication bias.

Table 2 – Quality assessment of the studies included in the meta-analysis by Newcastle–Ottawa Scale.

Study	Selection (maximum 4)				Comparability (maximum 2)		Outcome (maximum 3)			Total scores
	A	B	C	D	A1	B1	A2	B2	C2	
Muggeo 2000	1	1	1	1	1	1	1	1	1	9
Gimeno-Orna 2003	1	1	1	1	1	1	1	0	1	8
Zoppini 2009	0	1	1	1	1	0	1	0	0	5
Takao 2010	0	1	1	1	1	0	1	1	1	7
Yang 2015	1	1	1	1	1	1	1	1	1	9
Xu 2016	0	1	1	1	1	1	1	1	1	8
Wang 2017	0	1	0	1	1	1	1	0	1	6
Lee 2018	1	1	1	1	0	0	1	0	1	6

A: Representativeness of exposed cohort.
B: Representativeness of unexposed cohort.
C: Ascertainment of exposure (If the exposure data was obtained from prescription database or medical record).
D: Outcome was not present at start.
A1: Important factor (If adjusted for the duration of diabetes or type of hypoglycemic drugs, a point was assigned.)
B1: Additional factor (If adjusted for lifestyle (e.g. cigarette smoking, or alcohol consumption and any other additional factors.)
A2: Assessment of outcome.
B2: Exposure Follow-up for outcomes (If follow-up period is ≥6 years).
C2: Rate of follow-up (If the rate of lost to follow-up was 20% or less).

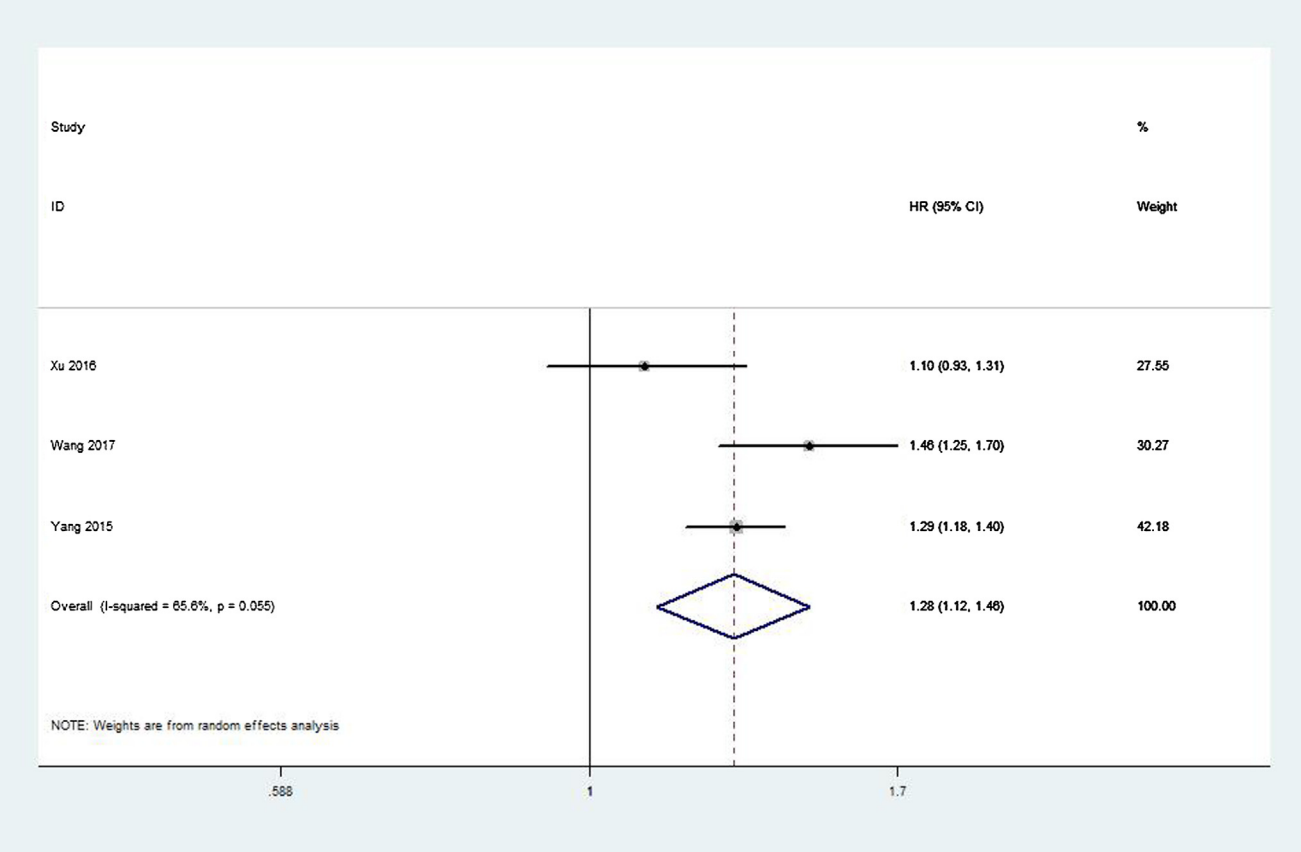

Fig. 2 – Forest plot of the relationship between high FPG CV and All-cause Mortality. Legend: FPG: fasting plasma glucose; CV: the coefficient of variation; HR: hazard ratio; CI: confidence interval. The pooled HR results revealed that high FPG CV was associated with the risk of all-cause mortality (HR 1.28, 95%CI 1.12–1.46; *P* = 0.000), with high evidence of heterogeneity (I^2 = 65.6%, *P* = 0.055).

4. Discussion

The main finding of our meta-analysis and systematic review indicated that a high level of FPG variability was correlated with the risk of all-cause mortality and retinopathy in type 2 diabetes mellitus. The former was supported by four studies [15,18,20,21]. Only one retrospective study [14] did not report this strong association after adjusting for other risk factors.

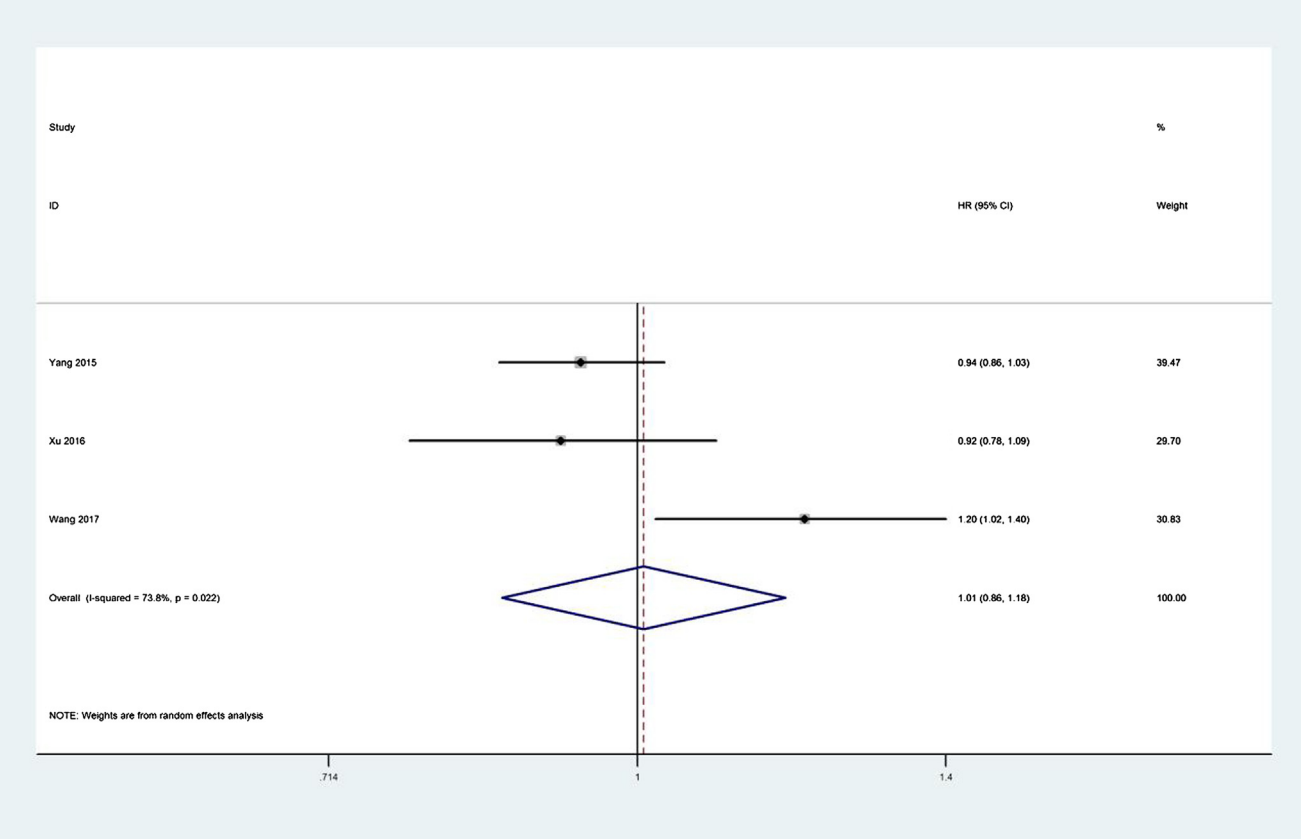

Fig. 3 – Forest plot of the relationship between FPG CV from 10 to 20% and All-cause Mortality. Legend: FPG: fasting plasma glucose; CV: the coefficient of variation; HR: hazard ratio; CI: confidence interval. The pooled HR results revealed that median or mean FPG CV range from 10 to 20% was not associated with the risk of all-cause mortality (HR 1.01, 95%CI 0.86–1.18; *P* = 0.929).

However, its stratified analysis found that FPG CV was closely correlated with all-cause mortality in patients whose glucose control was poor. The association between FPG variability and retinopathy was supported by two studies [13,19]. A cohort study with a 4-year follow-up period [12] did not report this association; compared with that in the two previous studies [13,19], the age of the participants was high (69 ± 11 years), which may explain the lack of association.

The present study also suggested that, for median or mean FPG CV levels under or equal to 20%, FPG CV and all-cause mortality were not significantly correlated. This relationship was supported by the pooled HR of FPG CV in the present meta-analysis, and the results were particularly notable in patients with type 2 diabetes. Nevertheless, the present study did not have enough evidence to prove that FPG CV levels under 20% and retinopathy were not significantly correlated. The study by Gimeno-Orna et al. [13] suggested that there was no significant increase in the OR of progression to retinopathy in median FPG CV levels under 29%. In addition, a longitudinal study over 27 years [9] revealed that the cut-off values of FPG variability for detecting the presence of retinopathy and advanced retinopathy in type 2 diabetes were 1.4 mmol/L and 1.9 mmol/L, respectively, for the SD of FPG, which were roughly equivalent to 18% and 25% for the CV of FPG. Therefore, more research is needed to assess the relationship between FPG CV levels under 20% and retinopathy in type 2 diabetes mellitus.

Many previous studies found that high FPG variability was associated with an increased risk of micro-vascular complications and mortality in diabetic patients [2,20,22–24]. However, the relationship between the level of FPG variability level and the risk of micro-vascular complications and mortality has been debated. One possible explanation is that categories of FPG variability differed across studies. For example, the definitions of high FPG CV ranged from >13.11 to >48.6%. Moreover, through stratified analysis, our study found that for median or mean FPG CV levels under or equal to 20%, FPG CV and all-cause mortality may not be correlated, which offers insight into previous studies reporting the relationships between FPG variability and mortality.

The accurate mechanisms that mediate the connection between glycaemic variability and the risk of vascular diseases and all-cause mortality are unknown. Glycaemic variability has been shown to be connected with an increased release of inflammatory cytokines [25] and endothelial dysfunction [26], both of which are connected with diabetes complications and further resulted in the increased mortality. In addition, previous studies have found an evident correlation between glycaemic variability and increased risk of hypoglycaemia [24,27,28]. Moreover, hypoglycaemia, in turn,

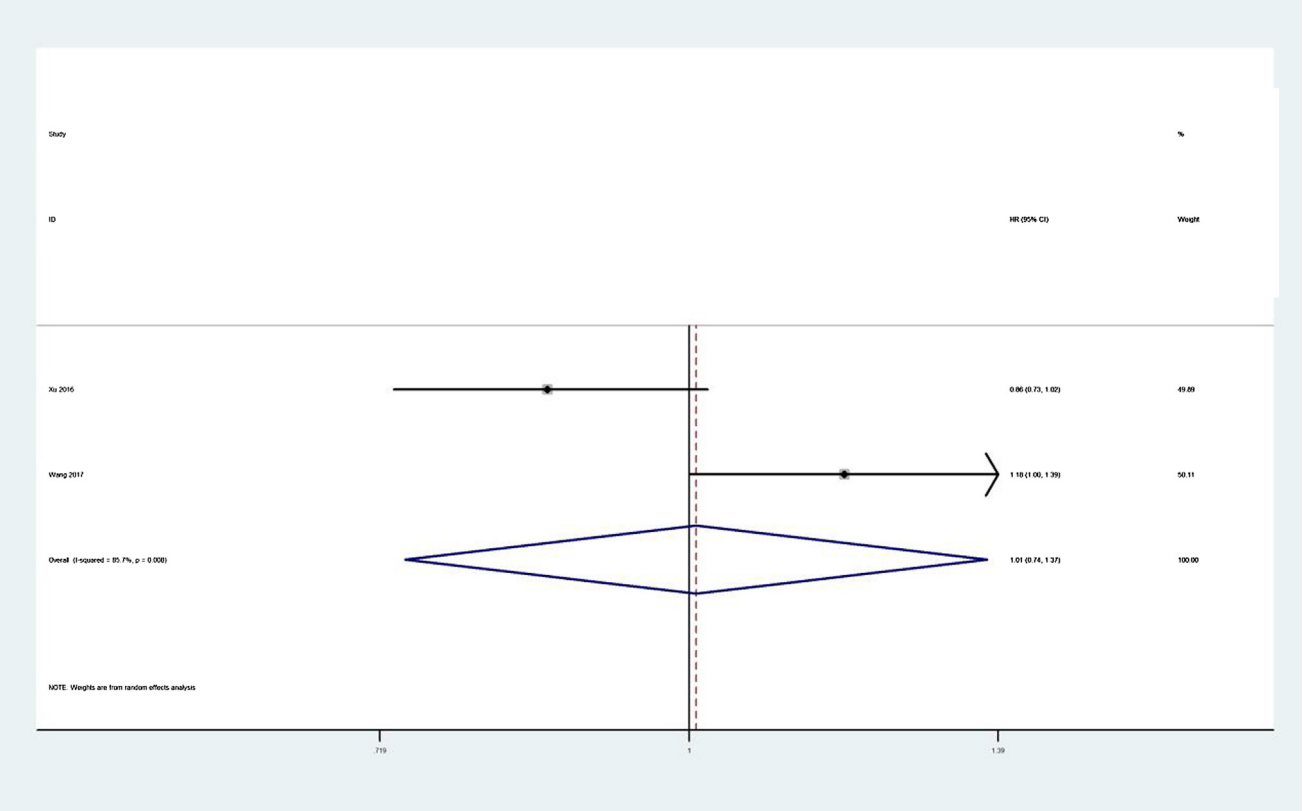

Fig. 4 – Forest plot of the relationship between FPG CV under or equal to10% and All-cause Mortality. Legend: FPG: fasting plasma glucose; CV: the coefficient of variation; HR: hazard ratio; CI: confidence interval. The pooled HR results revealed that median or mean FPG CV under or equal to 10% was not associated with the risk of all-cause mortality (HR 1.01, 95%CI 0.74–1.37; P = 0.961).

increased the risk of micro-vascular complications and death. Glycaemic variability has also been shown to cause loss of pancreatic B-cells because of increased apoptotic cell death [29], which may result in glycaemic deterioration and subsequent vascular complications or even death.

To our knowledge, this meta-analysis is the first report of FPG variability levels in diabetes and risk of diabetic retinopathy and all-cause mortality. The mean NOS score was above 7, indicating that all studies were of high quality. Several limitations of the current study should also be acknowledged. First, we searched 'Google Scholar Search' and other related search engines and found some related literature. However, because the NOS scores were low, the studies were not suitable for inclusion in our study. In addition, the majority of the included studies were retrospective cohort studies, and a minority were prospective cohort studies. Moreover, the included studies have some differences in the methods used for FPG measurement, and the frequency of testing and the time between tests for FPG were not consistent. Second, research focused on retinopathy is rare and lacks conviction. Hence, additional research is needed to explore this relationship. Third, FPG variability was related to some risk factors for diabetes-related diseases, such as diet, exercise, unhealthy lifestyle behaviours, poor physical health, undiagnosed medical diseases, and stress response. Nevertheless, this relationship persisted after adjusting for potential confounders. Additionally, additional research is needed to explore the accurate mechanism of FPG variability and the associated adverse outcomes.

5. Conclusion

This meta-analysis shows that high FPG variability is significantly associated with an increased risk of retinopathy and all-cause mortality in patients with type 2 diabetes. However, for median or mean FPG CV levels under or equal to 20%, FPG CV and all-cause mortality are not significantly correlated. These relationships suggest that FPG variability is vital in the prevention of retinopathy and the reduction of all-cause mortality in patients with type 2 diabetes.

Duality of interest

No potential conflicts of interest relevant to this article were reported.

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