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Visit-to-visit glycated hemoglobin A1c variability in adults with type 2 diabetes: a systematic review and meta-analysis

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Abstract

Background: Current practice uses the latest measure of glycated hemoglobin (HbAlc) to facilitate clinical decision-making. Studies have demonstrated that HbAlc variability links the risk of death and complications of diabetes. However, the role of HbAlc variability is unclear in clinical practice. This systematic review summarized the evidence of visit-to-visit HbAlc variability regarding different metrics in micro- and macro-vascular complications and death in people with type 2 diabetes.

Methods: We searched PubMed, EMBASE (via OVID), and Cochrane Central Register (CENTRAL, via OVID) for studies investigating the association between HbAlc variability and adverse outcomes in patients with type 2 diabetes and performed random-effects meta-analysis stratified by HbAlc variability metrics in terms of standard deviation (SD), coefficient of variation (CV), and HbAlc variability score (HVS).

Results: In people with type 2 diabetes, the highest quantile of all three HbAlc variability metrics (HbAlc-standard deviation [HbAlc-SD], HbAlc-coefficient of variance [HbAlc-CV], and HVS) is associated with increased risks of all-cause mortality, cardiovascular events, progression to chronic kidney disease, amputation, and peripheral neuropathy. For example, the hazard ratio of HbAlc-SD on all-cause mortality was l.89 with 95% confidence interval (95% CI) l.46–2.45 (HbAlc-CV l.47, 95% CI l.26–l.72; HVS l.67, 95% CI l.34–2.09).

Conclusions: High HbAlc variability leads to micro- and macro-vascular complications of type 2 diabetes and related death. People with type 2 diabetes and high HbAlc variability need additional attention and care for the potential adverse outcomes.

Keywords: Visit-to-visit HbAlc variability; Type 2 diabetes; Macrovascular complications; All-cause mortality; Glycated hemoglobin

Introduction

Current management of type 2 diabetes requires a periodic measure of glycated hemoglobin (HbAlc) and blood glucose, when the last read facilitates clinical decision-making at the target of preventing death and diabetic complications.[1,2] However, growing evidence shows that getting HbAlc to target is no longer sufficient for people with type 2 diabetes.[3-5] Recently, considerable evidence has accumulated that increased visit-to-visit change of HbAlc links the risk of death and complications of type 2 diabetes independent of a mean elevation of HbAlc.[6-9].

Most studies have evaluated visit-to-visit HbAlc variability using standard deviation (SD) and coefficient of variation (CV) of HbAlc values in one individual during the follow-up duration.[10,11] Recent studies have introduced the HbAlc variability score (HVS), which is calculated as the proportion of HbAlc change (>0.5%) from the last visit to the next.[12,13] For example, in an adult with type 2 diabetes and six reads of HbAlc being successively 7.4%, 6.2%, 6.5%, 7.8%, 6.6%, and 6.4%, three among the five changes surpass 0.5%. The HVS is 3 divided by 5, equaling 60%. A person with HVS being 60% or higher is facing additional risks of multiple diabetic complications and death than his/her peers.[12,13] A systematic review in 20l5 summarized early studies of HbAlc

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variability in people with type 2 diabetes, but the former literature did not support comprehensive analyses.[11] Furthermore, the role of glycemic variability has been still unclear in clinical practice up to now.[14] With greatly increased publications in the last few years, our systematic review pooled the cohort studies and *post-hoc* analyses of randomized trials using meta-analysis to evaluate the association between HbAlc variability and long-term adverse events, including all-cause mortality, cardiovascular, and microvascular complications of diabetes.

Methods

We followed the Meta-analyses of Observational Studies in Epidemiology to guide the synthesis process and report the results.[15] This study was registered in PROSPERO with CRD42021230288.

Data sources and searches

We searched PubMed, EMBASE (via OVID), and Cochrane Central Register of Controlled Trials (CENTRAL, via OVID) from inception to January 2021, using the key search terms of HbA1c variability and visit-to-visit glycemic variability (the full searching strategy is included in the Supplementary file, http://links.lww.com/CM9/A997). The reference lists of all identified studies were cross-checked. All literature management was performed using Endnote X9 (Clarivate, Philadelphia, Pennsylvania, USA).

Study selection

We included cohort studies and *post-hoc* analyses of randomized-controlled trials that enrolled adults with type 2 diabetes and compared the risks of adverse outcomes across people with different HbA1c variability. Any study with a mixed population for type 1 diabetes and type 2 diabetes was excluded. We restricted the variability metrics to within-individual visit-to-visit HbA1c-standard deviation (HbA1c-SD), HbA1c-coefficient of variance (HbA1c-CV), and HVS. The outcomes of interest included all-cause mortality, composite cardiovascular events, fatal or nonfatal stroke, fatal or nonfatal myocardial infarction, heart failure events, coronary artery disease, progression to albuminuria, progression to chronic kidney disease (CKD), kidney failure, retinopathy, amputation, diabetic foot ulcer, and peripheral neuropathy. We followed the study-specific definition of the outcomes, with the details of each included study provided in Appendix 3, http://links.lww.com/CM9/A997.

One researcher (FQ) screened the titles and abstracts and screened the full text with cross-checking by another researcher (QS). The third author (SL) resolves the discrepancy on the final inclusion if any.

Data extraction and quality assessment

One researcher (FQ) extracted the following data with verification by another researcher (QS): (1) study characteristics including the first author's name, publication year, data source, number of participants, study design, and follow-up duration; (2) baseline characteristics of the participants including age, male proportion, baseline HbA1c, baseline duration of diabetes; and definitions of HbA1c variability metrics; (3) point estimate and corresponding confidence interval (CI) of outcomes of interests. Any discrepancy was discussed with an expert (SL). We used the Newcastle-Ottawa quality assessment scale (NOS) to assess the risk of bias of the included studies. One reviewer (FQ) rated the NOS score, which was cross-checked by another reviewer (QS). Disagreement about the NOS score was assessed by a third expert (SL).

Data synthesis and analysis

We used the hazard ratios (HRs) to measure and pool the time-to-event outcomes. We converted the odds ratios (ORs) and risk ratios (RRs) to HRs for the studies that did not report the HRs using established methods[16,17] (details in Appendix 3, http://links.lww.com/CM9/A997).

Given the heterogeneity of the categorization of HbA1c variability metrics across studies, we pooled the HRs of the highest quantile of HbA1c variability metrics vs. the lowest quantile which was derived from the fully adjusted estimates in the article. We used a random-effects model with a generalized inverse variance method[18] to estimate the pooled HRs. The between-study variance was estimated by the DerSimonian–Laird estimator. If provided, we pooled the HRs of per 1-SD increment of HbA1c-SD, -CV, or HVS. We assessed the statistical heterogeneity using Cochran's Q-test, which was quantified by I^2-statistic.

We performed a meta-regression based on the baseline duration of diabetes for the outcomes involving at least five studies and undertook a subgroup analysis based on the study type (cohort study *vs.* *post-hoc* analysis of randomized trials, hypothesizing larger effects in the *post-hoc* analysis of randomized trials). We explored publication bias using funnel plots and Begg's and Egger's tests for the outcomes with at least ten studies. We performed six sensitivity analyses by: (1) excluding the studies that divided people into more than five categories; (2) excluding the studies where we converted the ORs or RRs to HRs; (3) excluding the studies that did not adjust mean HbA1c and/ or the number of HbA1c measurements in the regression analyses; (4) using leave-one-out analyses to detect the influence from a single study; (5) using trim-and-fill analyses when there was a significant publication bias; and (6) performing meta-regressions by either the baseline HbA1c or mean HbA1c during follow-up.

Results

Characteristics of included studies and participants

Among 27,703 relevant records from electronic databases, the systematic review included 43 cohort studies and 6 *post-hoc* analyses of randomized-controlled trials with 634,667 participants [Figure 1]. As shown in Table 1, the included studies reported HbA1c-SD (36 studies), HbA1c-CV (33 studies), and HVS (5 studies) as HbA1c variability metrics with a median follow-up duration of 5.9 years (interquartile range [IQR], 4.2–7.3 years). The median number of the HbA1c measurements per patient was 10

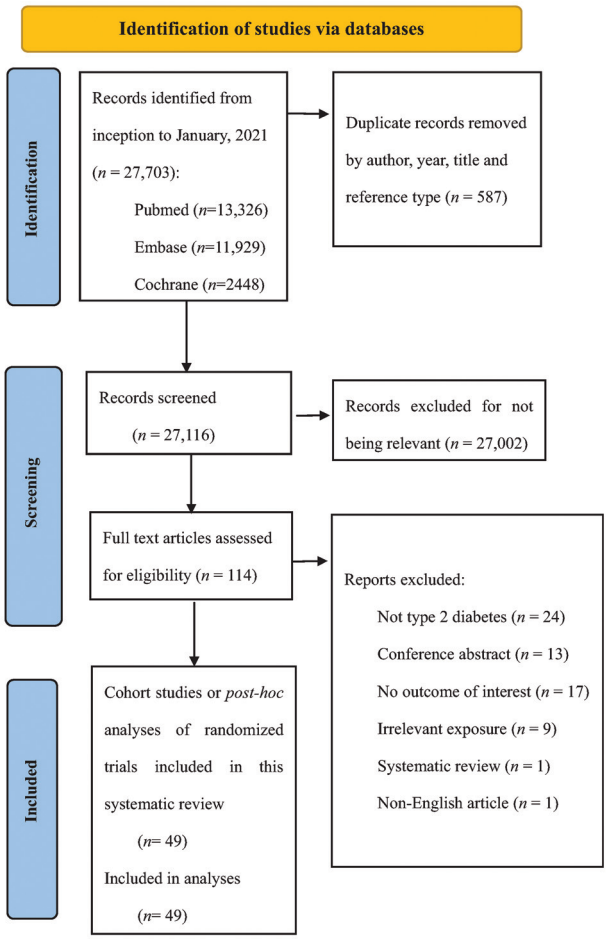

Figure 1: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

(IQR, 7.5–22.5), and the median baseline HbA1c was 7.7% (IQR, 7.4%–8.1%).

Forty out of 49 studies used Cox proportional hazard model to estimate the association between HbA1c variability metrics and outcomes, whereas the rest used Logistic regression. The multivariate models varied across studies. All studies were adjusted for age and sex. Eight of them did not adjust the mean HbA1c, and 13 adjusted the number of HbA1c measurements. Other adjusted covariates were different from study to study, including body mass index, lipid profile, duration of diabetes at baseline, baseline HbA1c, mean fasting plasma glucose, systolic or diastolic blood pressure, hypoglycemia events, statins/aspirin, and anti-diabetic drugs. The median score of NOS among included studies was 8 (IQR, 7–8). Appendix 7, http://links.lww.com/CM9/A997 shows the details of the NOS assessment for each included study.

All-cause mortality and cardiovascular outcomes

As shown in Figure 2, compared to people with the lowest quantile of HbA1c variability in all metrics, those with the highest quantile have increased risks of all-cause mortality, composite cardiovascular events, coronary artery disease, stroke, and heart failure. Taking all-cause mortality as an example, the HR of HbA1c-SD was 1.89 (95% CI, 1.462.45); the HR of HbA1c-CV was 1.47 (95% CI, 1.261.72); and the HR of HVS was 1.67 (95% CI, 1.34–2.09). As shown in Appendix 7, http://links.lww.com/CM9/A997, per 1-SD increment of HbA1c-SD is associated with increased risks of all-cause mortality, composite cardiovascular events, coronary artery disease, and stroke. Per 1-SD increment of HbA1c-CV is associated with increased risks of all-cause mortality, composite cardiovascular events, and heart failure events.

Microvascular complications

As shown in Figure 3, compared to people with the lowest quality of HbA1c-SD, those with the highest quantile were associated with increased risks of progression to CKD, progression to albuminuria, amputation, peripheral neuropathy, and retinopathy. People with the highest quantile of HbA1c-CV were associated with increased risks of kidney failure, progression to CKD, amputation, diabetic foot ulcer, and peripheral neuropathy. People with the highest HVS showed elevated risks of progression to CKD, amputation, diabetic foot ulcer, peripheral neuropathy, and retinopathy. As shown in Appendix 7, http://links.lww.com/CM9/A997, per 1-SD increment of HbA1c-SD was associated with increased risks of kidney failure, progression to CKD, and progression to albuminuria. Per 1-SD increment of HbA1c-CV was associated with increased risks of kidney failure and peripheral neuropathy.

Subgroup/regression analysis, sensitivity analysis, and publication bias

The meta-regression showed a stronger association between both HbA1c-SD and HbA1c-CV and composite cardiovascular events in people with longer diabetes duration (HbA1c-SD: beta, 0.096; $P \leq 0.0001$; HbA1c-CV: beta, 0.105; $P = 0.0227$). We did not identify other regression or subgroup effects in this systematic review [Appendix 8, http://links.lww.com/CM9/A997]. Only one meta-analysis involved more than ten studies when testing the association between HbA1c-CV quantiles and all-cause mortality. The funnel plot identified a potential publication bias with statistical significance using Egger's test ($t = 3.22$, df = 8, $P = 0.012$) but not Begg's test ($z = 0.80$, $P = 0.42$, Appendix 6, http://links.lww.com/CM9/A997). However, the trim and fill analysis suggested that the publication bias did not change the study results [Appendix 9, http://links.lww.com/CM9/A997]. All other sensitivity analyses confirmed the robustness of the findings [Appendix 9, http://links.lww.com/CM9/A997].

Discussion

Our systematic review summarized over 0.6 million people with type 2 diabetes from 49 included studies on visit-to-visit HbA1c variability and its potential impact on the long-term outcomes. The results showed that people with type 2 diabetes among the highest quantile of all three HbA1c variability metrics (HbA1c-SD, HbA1c-CV, and HVS) are associated with increased risks of all-cause mortality, cardiovascular events, progression to CKD, amputation, and peripheral neuropathy. People with type

Table 1: Summary of characteristics of included studies.

Study characteristics	Results	IQR	Range
Eligible studies			
Total number of trials, *n*	49		
Total number of participants, *n*	634,667		
Number of HbAlc measurement*, *n*	10.0	7.5–22.5	3.2–84.0
Least required HbAlc measurement*, *n*	3	3–4	2–5
Follow-up duration*, years	5.9	4.2–7.3	2.0–15.9
Metrics of HbAlc measurement			
HbAlc-SD, *n* (%)	36 (73)		
HbAlc-CV, *n* (%)	33 (67)		
HVS, *n* (%)	5 (10)		
Adjusted covariates			
Age, *n* (%)	49 (100)		
Sex, *n* (%)	49 (100)		
Body mass index, *n* (%)	34 (69)		
Lipid profiles, *n* (%)	31 (63)		
Duration of diabetes at baseline, *n* (%)	36 (73)		
Mean HbAlc during follow-up, *n* (%)	41 (84)		
Baseline HbAlc, *n* (%)	8 (16)		
Number of HbAlc measurements, *n* (%)	13 (27)		
Hypoglycemia events during follow-up, *n* (%)	11 (22)		
Mean fasting glucose during follow-up, *n* (%)	9 (18)		
Systolic/diastolic blood pressure, *n* (%)	35 (71)		
Baseline anti-diabetic drugs, *n* (%)	30 (61)		
Baseline statins/aspirin, *n* (%)	16 (33)		
Regression model			
Cox proportional hazard model, *n* (%)	40 (82)		
Logistic regression model, *n* (%)	9 (18)		
NOS score	8	7–8	6–10
Region			
Europe, *n* (%)	15 (31)		
Asia, *n* (%)	31 (63)		
South America, *n* (%)	1 (2)		
Oceania, *n* (%)	2 (4)		
Characteristics of participants*			
Age, years	62.5	59.2–65.3	51.2–78.0
Male (%)	53.8	48.0–61.2	37.9–97.1
Diabetes duration at baseline, years	7.4	5.6–10.0	2.9–16.0
Baseline HbAlc (%)	7.7	7.4–8.1	6.7–9.4
Insulin (%)	18.5	6.9–26.6	0.7–80.6

* Represents the corresponding number is median value across the included studies. HbAlc: Glycated hemoglobin; HbAlc-CV: Coefficient of variation of glycated hemoglobin; HbAlc-SD: Standard deviation of glycated hemoglobin; HVS: HbAlc variability score; IQR: Interquartile range; NOS: Newcastle–Ottawa quality assessment scale.

2 diabetes among the highest quantile of at least one HbAlc variability metric are associated with increased risks of kidney failure, progression to albuminuria, diabetic foot ulcer, and retinopathy. The risks of all outcomes of interest except for amputation and retinopathy showed elevation along with the per SD increment of HbAlc variability metrics.

Our findings are consistent with previous systematic reviews,[11,19] but we include three HbAlc variability metrics with more comprehensive studies and adverse outcomes. Since the visit-to-visit measure of HbAlc illustrates the variability, a comprehensive review of historical HbAlc reads provides additional information to identify people with type 2 diabetes at high risk of death and complications of diabetes. To facilitate real-world practice, an easy and clinically relevant approach to evaluate HbAlc variability becomes important.

Among the three HbAlc variability metrics in this systematic review, HVS shows the closest relationship with the outcomes of interest, despite the relatively small studies and sample size. In contrast with HbAlc-SD and -CV, the patient categorization of HVS was based on its absolute value rather than its percentage quantile. Only ~1% of people with type 2 diabetes falls in the highest quantile of HVS (usually >80, meaning that most HbAlc measures significantly changed from the last measure),[12] representing those with the highest risks of death and diabetic complications and thus needing additional care. Clinicians, with this knowledge, could look back at the last few measures of the HbAlc during their visits. If all or

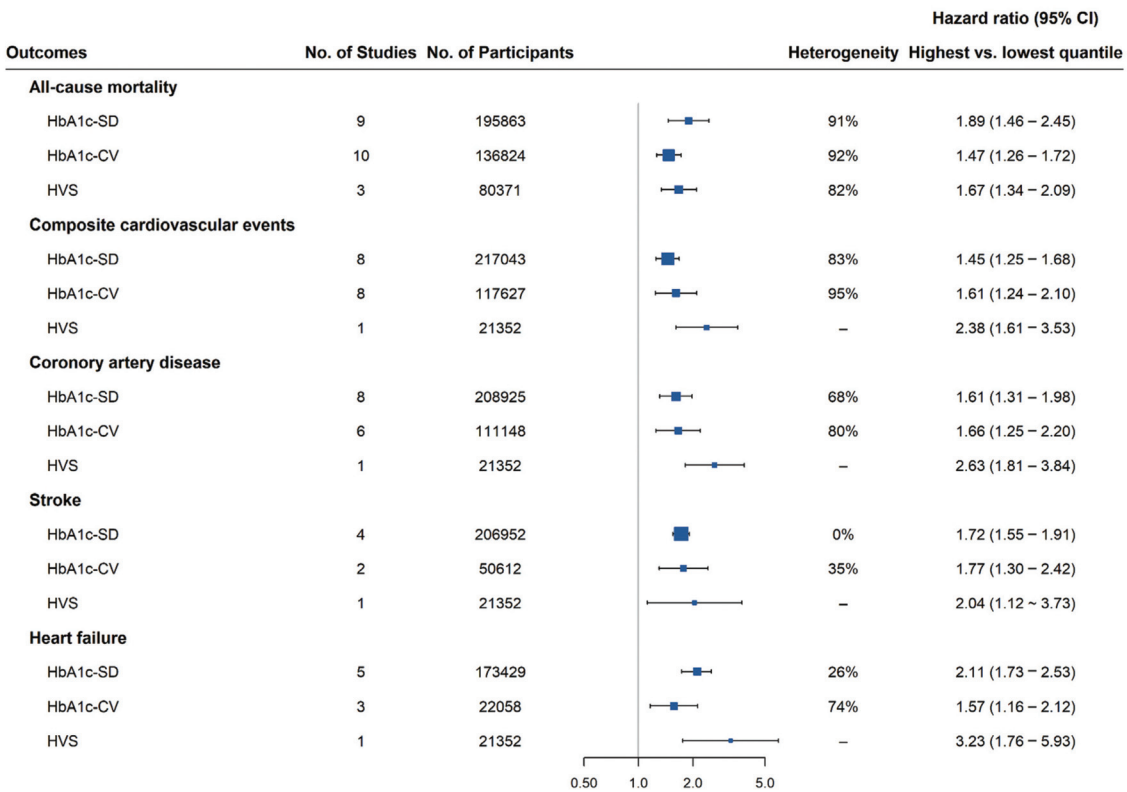

Figure 2: The association between HbA1c variability metrics and macrovascular complications based on quantile contrast. HRs are regarding the comparison between the highest quantile of HbA1c variability metrics vs. lowest. Heterogeneity was quantified by I^2-statistic. CI: confidence interval; HbA1c-SD: Standard deviation of visit-to-visit HbA1c; HbA1c-CV: Variation coefficient of visit-to-visit HbA1c; HVS: HbA1c variability score.

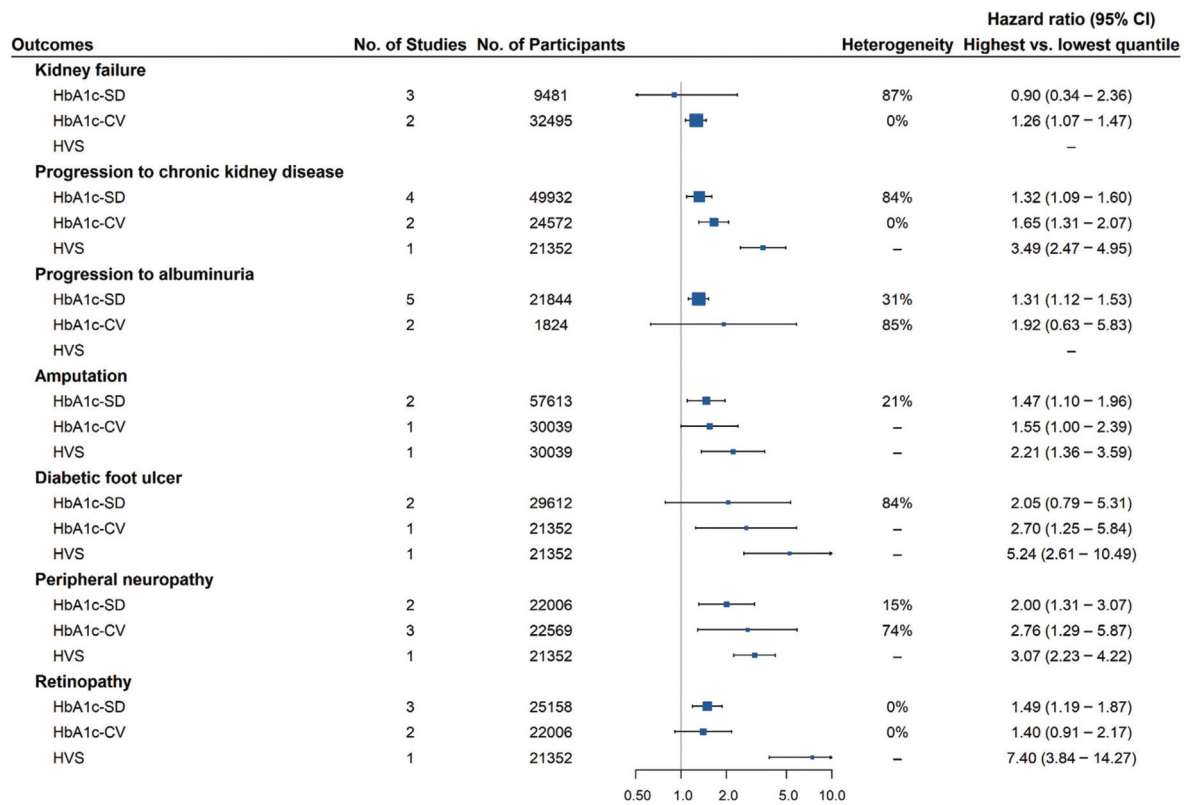

Figure 3: The association between HbA1c variability metrics and microvascular complications based on quantile contrast. HRs are regarding the comparison between the highest quantile of HbA1c variability metrics vs. lowest. Heterogeneity was quantified by I^2-statistic. CI: confidence interval; HbA1c-SD: Standard deviation of visit-to-visit HbA1c; HbA1c-CV: Coefficient of variation of visit-to-visit HbA1c; HVS: HbA1c variability score.

most HbA1c levels go up or down >0.5% from their lasttime reads, the patient is very likely to be among those at the highest risks of death and complication and may need more critical care.

The biological mechanism for variability in HbA1c measures among people with type 2 diabetes remains under investigation. High HbA1c variability may represent a lower quality of care in the practice,[20] which is associated with erratic lifestyle changes and irregular use of medication.[21,22] Personal behavior, drug response, and comorbidities may also contribute to HbA1c fluctuation, and warrant clinicians' attention. Given the risky characteristics that accompany high HbA1c variability at baseline, a causal conclusion remains early between HbA1c variability and adverse outcomes.[12,23] Hypoglycemia is common in people with type 2 diabetes.[24] Research links it to frequent hospitalization with severe hypoglycemia to high HbA1c variability in British people with type 1 and type 2 diabetes.[22] Hypoglycemia itself may increase glycemic variability and also contribute to the development and progression of cardiovascular diseases.[25-27] People who experienced severe hypoglycemia may lose their confidence in the treatment and struggle with regular drug-taking that may lead to the fluctuation of glucose control. Researchers hypothesized that HbA1c variability might increase cardiovascular and microvascular complications of diabetes by increasing oxidative stress and epigenetic modification.[10,28,29] Nevertheless, the hypotheses need support from stringent evidence before further clinical interpretation.

Our study has some limitations. First, the included studies are heterogeneous in population, study design, and statistical methods. Nevertheless, a series of sensitivity analyses confirmed the robustness of our findings. Consistent results in heterogeneous situations further suggest the generalizability of the association between HbAlc variability and adverse outcomes. Second, our primary analyses were largely based on the comparison between the people with the highest and lowest HbAlc variability. The clinically meaningful cutoff for HbAlc metrics may need further exploration in future studies. Third, as a study-level study without individual-level data, we are unable to detect residual confounding factors or keep statistical models consistent in each included study.

Conclusions

Our systematic review demonstrates the associations between visit-to-visit HbAlc variability and multiple adverse outcomes in people with type 2 diabetes. It calls for increased attention for people with type 2 diabetes and high HbAlc variability. A careful review of historical HbAlc measures may facilitate clinicians to identify patients at high risks. However, also it remains necessary to explore potential clinical implementation strategies for these HbAlc variability parameters in people with type 2 diabetes.

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Conflicts of interest

None.

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