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Meta-analyses

Glycemic variability assessed using continuous glucose monitoring in individuals without diabetes and associations with cardiometabolic risk markers: A systematic review and meta-analysis

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SUMMARY

Background & aims: Continuous glucose monitoring (CGM) provides data on short-term glycemic variability (GV). GV is associated with adverse outcomes in individuals with diabetes. Whether GV is associated with cardiometabolic risk in individuals without diabetes is unclear. We systematically reviewed the literature to assess whether GV is associated with cardiometabolic risk markers or outcomes in individuals without diabetes.

Methods: Searches were performed in PubMed/Medline, Embase and Cochrane from inception through April 2022. Two researchers were involved in study selection, data extraction and quality assessment. Studies evaluating GV using CGM for ≥24 h were included. Studies in populations with acute and/or critical illness were excluded. Both narrative synthesis and meta-analyzes were performed, depending on outcome.

Results: Seventy-one studies were included; the majority were cross-sectional. Multiple measures of GV are higher in individuals with compared to without prediabetes and GV appears to be inversely associated with beta cell function. In contrast, GV is not clearly associated with insulin sensitivity, fatty liver disease, adiposity, blood lipids, blood pressure or oxidative stress. However, GV may be positively associated with the degree of atherosclerosis and cardiovascular events in individuals with coronary disease.

Conclusion: GV is elevated in prediabetes, potentially related to beta cell dysfunction, but less clearly associated with obesity or traditional risk factors. GV is associated with coronary atherosclerosis development and may predict cardiovascular events and type 2 diabetes. Prospective studies are warranted, investigating the predictive power of GV in relation to incident disease. GV may be an important risk measure also in individuals without diabetes.

1. Introduction

Chronic hyperglycemia, assessed by HbA1c, is a risk factor for complications in individuals with diabetes [1]. However, HbA1c does not reflect short-term fluctuations in blood glucose, which can vary a lot between individuals despite similar HbA1c [2]. Glycemic variability (GV) is a term used to describe such fluctuations, reflecting both hypoglycemic events and postprandial spikes as well as fluctuations that are repeated the same time on different days [2].

The role of GV in the development of diabetic complications and vascular health [3] is receiving increased attention. Studies in type 2 diabetes indicate that a large GV can be a greater trigger of oxidative stress than chronic hyperglycemia and is therefore thought to be a major mechanism behind diabetic complications [4]. However, GV has not yet been confirmed as an independent risk factor due to lack of studies designed to address this [3,5,6]. In diabetes, GV is associated with development of microvascular

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Abbreviations

ABI	ankle-brachial index
ACS	acute coronary artery syndrome
AGT	abnormal glucose tolerance
ALT	alanine transaminase
AST	aspartate transaminase
CAD	coronary artery disease
carDC	carotid distensibility coefficient
CF	cystic fibrosis
CFRD	cystic fibrosis-related diabetes
CGM	continuous glucose monitoring
C-IMT	carotid intima-media thickness
CONGA	continuous overlapping net glycemic action
CRP	C-reactive protein
CWS	circumferential wall stress
DBP	diastolic blood pressure
DI	disposition index
DP	dawn phenomenon
FMD	flow mediated dilation
fsOGTT	frequently sampled oral glucose tolerance test
GDM	gestational diabetes mellitus
GGT	gamma-glutamyltransferase
GRADE	glycemic risk assessment in diabetes equation
GSH	reduced glutathione
GSSG	oxidized glutathione
GTN	glyceryl trinibrate dilation
GV	glycemic variability
GVC	glycemic variability coefficient
GVP	glycemic variability percentage
ICAM1	intercellular adhesion molecule 1
IFG	impaired fasting glucose
IGC	index of glycemic control
IGM	impaired glucose metabolism
IGR	impaired glucose regulation
IGT	impaired glucose tolerance
8-iso-PGF2a	8-iso prostaglandin F2a
ISSI-2	insulin secretion-sensitivity index-2
IQR	interquartile range
LAGE	largest amplitude of glucose excursion
L-index	lability index
M	male
MACE	major adverse cardiovascular events
MAG	mean absolute glucose
MAGE	mean amplitude of glucose excursions
MetS	metabolic syndrome
MI	myocardial infarction
MODD	mean of daily differences
MPPGE	mean postprandial glucose excursion
MRS	magnetic resonance spectroscopy
NAFLD	non-alcoholic fatty liver disease
NGM	normal glucose metabolism
NGR	normal glucose regulation
NGR-Elev	NGR with elevated (>8.6) 1h glucose
NGT	normal glucose tolerance
NGT-Elev	normal glucose tolerance with elevated 1h glucose
OGIS	oral glucose insulin sensitivity index
8-OH-dG	8-hydroxydeoxyguanosine
oxLDL	oxidized low-density lipoprotein cholesterol
PAI-1	plasminogen activator inhibitor-1
PCOS	polycystic ovary syndrome
PWV	pulse wave velocity
QUICKI	quantitative insulin sensitivity check index
RHI	reactive hyperemia index
SBP	systolic blood pressure
sRAGE	soluble receptor of advanced glycation end-products
T3	triiodothyronine
T4	thyroxine
TBARS	hiobarbituric acid-reactive substances
TC	total cholesterol
TCF7L2 CC	carrier of TCF7L2 CC genotype
TCF7L2 CT/TT	carrier of TCF7L2 CT/TT genotype
TG	triglycerides
V-DBP	ambulatory (24 h) variability in diastolic blood pressure
V-SBP	ambulatory (24 h) variability in systolic blood pressure
WC	waist circumference

complications [7], coronary artery disease [7], heart failure [8], cardiovascular events [9] and increased mortality [10–12]. Increased GV also leads to increased risk for hypoglycemia, which is associated with increased risk for cardiovascular events and mortality in diabetes [13]. In the early stages of type 2 diabetes, about half of the GV is driven by postprandial glucose excursions [14]. Thus, reducing postprandial glucose excursions is likely a main target to improve GV [3,6].

Due to the importance of detecting markers of type 2 diabetes and cardiovascular disease at earlier stages, it is of great interest to scrutinize the potential impact of GV also in populations without diabetes. Borg et al. [15] showed that a majority of participants with normoglycemia reached glucose levels above the threshold for impaired glucose tolerance several times daily. In ten percent of participants, this occurred more than 2 h per day. Nine percent of participants also reached glucose levels above the threshold for diabetes. Recent studies have also suggested that there is a large variability in postprandial response between individuals, despite consuming identical meals, promoting the interest for personalized nutrition [16,17].

Different metrics to assess short-term GV (within- and between-day variation) are used, which are mainly based on the amplitude or frequency of glucose excursions [18]. However, a gold standard measure of short-term GV is still lacking, although the coefficient of variation (CV) has been suggested as the most appropriate as it is not dependent on the mean [3,6,19–21] A CV of 27% has been suggested as the upper limit of normality and may thus be used as a threshold for individuals without diabetes [21].

Continuous glucose monitoring (CGM) devices to measure short-term GV are now easily accessible, also outside the healthcare system. However, little is known about the role and importance of GV in individuals without diabetes, despite bold claims from multiple commercial private companies. Furthermore, there is high interest from both within and outside academia for CGM as a potential tool in the development of precision medicine. Thus, we aimed to systematically review the literature on short-term GV in individuals without diabetes to investigate if there are associations between GV and cardiometabolic risk markers and outcomes.

2. Methods

We followed the PRISMA-guidelines [22]. The search strategy (Electronic Supplementary Material, ESM) was developed after a

scoping search and according to guidelines from the Swedish Agency for Health Technology Assessment and Assessment of Social Services [23]. Since we assumed the number of studies in individuals without diabetes would be limited, and to provide a comprehensive overview of the available evidence to inform future studies, a broad search was made to find all relevant studies examining associations between GV and cardiometabolic risk markers and outcomes. A protocol was published in PROSPERO (CRD42021237873) [24] before searches were conducted.

2.1. Eligibility criteria

A PECO-framework was used to delimit the research question. As *population*, individuals (all ages) without diabetes or with prediabetes (defined by impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or by HbA1c) were included. Exclusion criteria were all types of diabetes, pregnancy, lactation or stress-induced GV (e.g. critical illness, acute events, recent surgery). As *exposure* and *control*, levels or categories of all measures addressing short-term GV measured with CGM for at least 24 h were included, e.g. standard deviation (SD), coefficient of variation (CV), mean amplitude of glycemic excursions (MAGE), mean of daily differences (MODD), continuous overlapping net glycemic action (CONGA), M-value, lability index (L-index), J-index or glycemic risk assessment in diabetes equation (GRADE). Measures addressing long-term GV (variation in HbA1c, FPG or PPG) or short-term GV measured with SMBG were excluded. As *outcomes*, all potential cardiometabolic risk markers and outcomes were included. Outcomes related to sleep apnea *per se* were not included.

2.2. Study selection and data extraction

Searches were conducted in PubMed/Medline, Embase and Cochrane on February 24, 2021, and updated on April 30, 2022. Language was restricted to English and only articles available in full text were included. No restrictions were made for publication date, study type or in terms of ethical approval. Search results from the databases were combined and duplicates removed. Two researchers (A.H., F.R.) independently screened titles and abstracts (full-texts when necessary) for eligibility. When a full-text could not be obtained from the database, a Google-search was made on the study title. Similar titles with matching content from the same authors that were found through the Google search were also included (e.g. a later publication of a poster).

Consensus was reached by discussions. Results were independently extracted by two authors (F.R., A.H.) for a subset of studies (n = 19), using standardized forms including author, year, study type, population characteristics (number of participants, age, sex, BMI), GV measures and duration, cardiometabolic risk markers and outcomes, results, country, funding, and ethical approval. Data was converted from mg/dL to mmol/L by dividing by 18. Data extraction was similar (in good agreement) between the two authors and the remaining studies (n = 52) were therefore extracted by one author (F.R.) and cross-checked for accuracy by a second author (D.I.). Reference lists of included studies were not screened.

2.3. Quality assessment

To evaluate quality and risk of bias a tool from the National Heart, Lung and Blood Institute [25] was used for all study types. The tool consists of fourteen questions, with quality rated as good, fair, or poor. Quality assessment was performed independently by two authors (A.H., F.R.) for a subset of studies (n = 19) whereas the remainder of studies (n = 52) were assessed by one author (F.R.) due to good agreement.

2.4. Data synthesis

Due to the type of studies included and the variation in both GV measures and outcomes, a narrative synthesis was considered most appropriate and performed for all outcomes except for differences in GV between individuals with and without prediabetes, which could also be combined in meta-analyses in adults for the outcomes SD, CV and MAGE using Review Manager 5.3. Random-effects models (DerSimonian and Laird method) were preferred, based on *a priori* assumptions. In studies with more than one prediabetes study arm, these were combined by calculating weighted averages of means and standard deviations.

3. Results

Seventy-one studies were included (Fig. 1), which were highly diverse in terms of population, sample size, outcomes and number of GV measures assessed (ESM Table S1). The majority of studies had a cross-sectional design. Only four studies were rated as 'Good' quality; the majority were rated as 'Fair' (n = 44), or 'Poor' (n = 23) quality. Many different measures of GV were used, the most common being MAGE (n = 52 studies), SD (n = 48 studies) and CV (n = 28 studies). Most studies were performed in China (n = 16), followed by USA (n = 13), Japan (n = 8), Italy (n = 8), The Netherlands (n = 7), Bulgaria (n = 4), Spain (n = 4), Turkey (n = 2), Belgium (n = 1), Greece (n = 1), Germany (n = 1), France (n = 1), India (n = 1), UK (n = 1), Russia (n = 1); two studies were performed at multiple sites (ESM Table S1). Separate tables sorted on outcome variables are presented in ESM Tables S2–S7. Excluded studies are presented in ESM Table S8, with reasons.

3.1. Impaired vs normal glucose regulation

3.1.1. Adults

The majority of studies report that multiple GV measures are higher in individuals with impaired glucose regulation/prediabetes compared to individuals with normal glucose regulation [26–34], differences that appear to persist also when considering age and/or BMI [35–39]. Furthermore, in age- and BMI-matched women with NGT with or without previous gestational diabetes, SD, MODD and MAGE were higher in NGT women with compared to without previous gestational diabetes [40]. However, some contrasting evidence exist as not all studies have observed differences in GV measures between categories of glucose regulation [41–47], which may be influenced, at least partly, by how impaired glucose regulation is defined [48].

When studies performed on adults were meta-analyzed, it was evident that individuals with prediabetes had higher SD (0.29 mmol/L (0.19–0.39), $p < 0.0001$), CV (2.74% (0.71–4.76), $p = 0.008$), and MAGE (0.71 mmol/L (0.41–1.01), $p < 0.0001$) compared to individuals without prediabetes (Fig. 2A-C).

3.1.2. Children and adolescents

When prediabetes was defined by HbA1c, SD was similar in prediabetes compared to normoglycemia [49]. However, when defined by 2-h glucose from OGTT, SD was higher in those with compared to without prediabetes.

CONGA was similar in adolescents with and without insulin resistance (HOMA-IR>/<2.5) [50].

Another study grouped children with cystic fibrosis (CF) into normal- (n = 24), indeterminate- (n = 40) and impaired glucose homeostasis (n = 30) [51]. Although no statistical test was presented, glucose interquartile range (IQR) appeared higher in those with indeterminate (1.0–1.4 mmol/L) and impaired (1.4–1.8 mmol/L) compared to normal (0.83–1.10 mmol/L) glucose homeostasis.

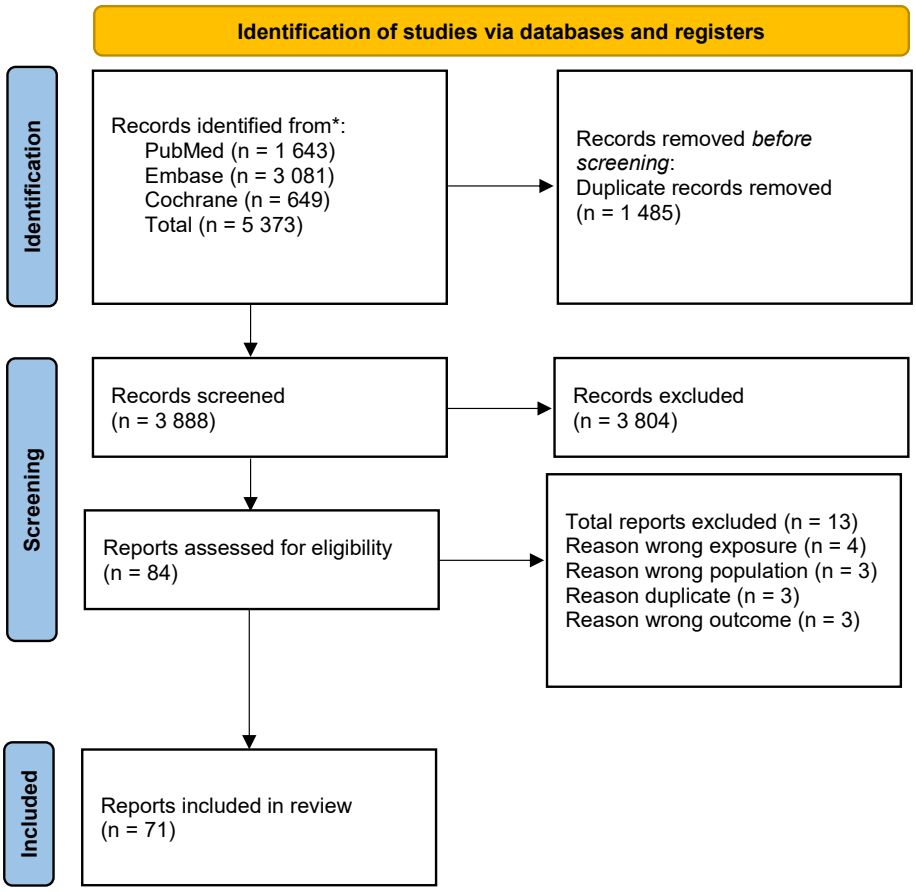

Fig. 1. The PRISMA flow diagram for the systematic review.

However, in a subgroup with repeated assessments, IQR at first assessment did not differ between those who did and did not develop CF-related diabetes.

Also in CF, SD, CV and MAGE were similar in those having abnormal compared to normal glycemic tolerance (defined by FPG and OGTT) [52]. Comparing healthy adolescents with adolescents with CF having normal- or abnormal (defined by FPG and OGTT) glucose tolerance showed that SD and CV were higher in both groups with CF compared to healthy adolescents, whereas MAGE was similar in all groups [53].

3.2. Overweight and obesity vs normal weight

3.2.1. Adults

3.2.1.1. Comparison between groups. Several studies, including one based on a large population-based sample, reported no differences in most GV measures between participants with overweight/obesity and normal weight [54–56], and no difference in BMI or waist circumference between participants having high or low GV [57]. However, there are some exceptions [58], and one large study found that MODD was higher in the highest compared to the lowest category of BMI and waist circumference, whereas both SD and MAGE were similar across categories of BMI and waist circumference [59].

3.2.1.2. Associations. One study found a positive association between GV and BMI [60], whereas three other studies found no association [45,58,61]; however one found positive associations between SD and MAGE and waist circumference [58].

Two studies found no associations between any GV measure and lean body mass, and inconsistent associations for fat mass and regional fat depots [45,56].

Although no formal meta-analysis was considered possible, results from these studies overall do not indicate any important difference in GV measures between obese and normal-weight individuals, nor any strong correlations with body composition.

3.2.2. Children and adolescents

CONGA was positively associated with waist circumference in one study [50], but other studies found no association between multiple GV measures and fat mass, waist circumference, body weight or BMI [62,63] and no difference in MAGE between adolescents with normal weight or obesity [64].

Change in body weight was associated with change in CONGA in one study [65], but not with SD or MAGE in another study [66].

3.3. Metabolic syndrome

One study found that multiple GV measures were higher in individuals with compared to without metabolic syndrome [67], but four other studies found no differences [62,68–70].

3.4. Incidence of type 2 diabetes

In a prospective cohort study of n = 209 patients with essential hypertension with a median follow-up of 32 months, MAGE was positively associated with incidence of type 2 diabetes (n = 17, p = 0.02) in a univariate Cox proportional hazard model [71].

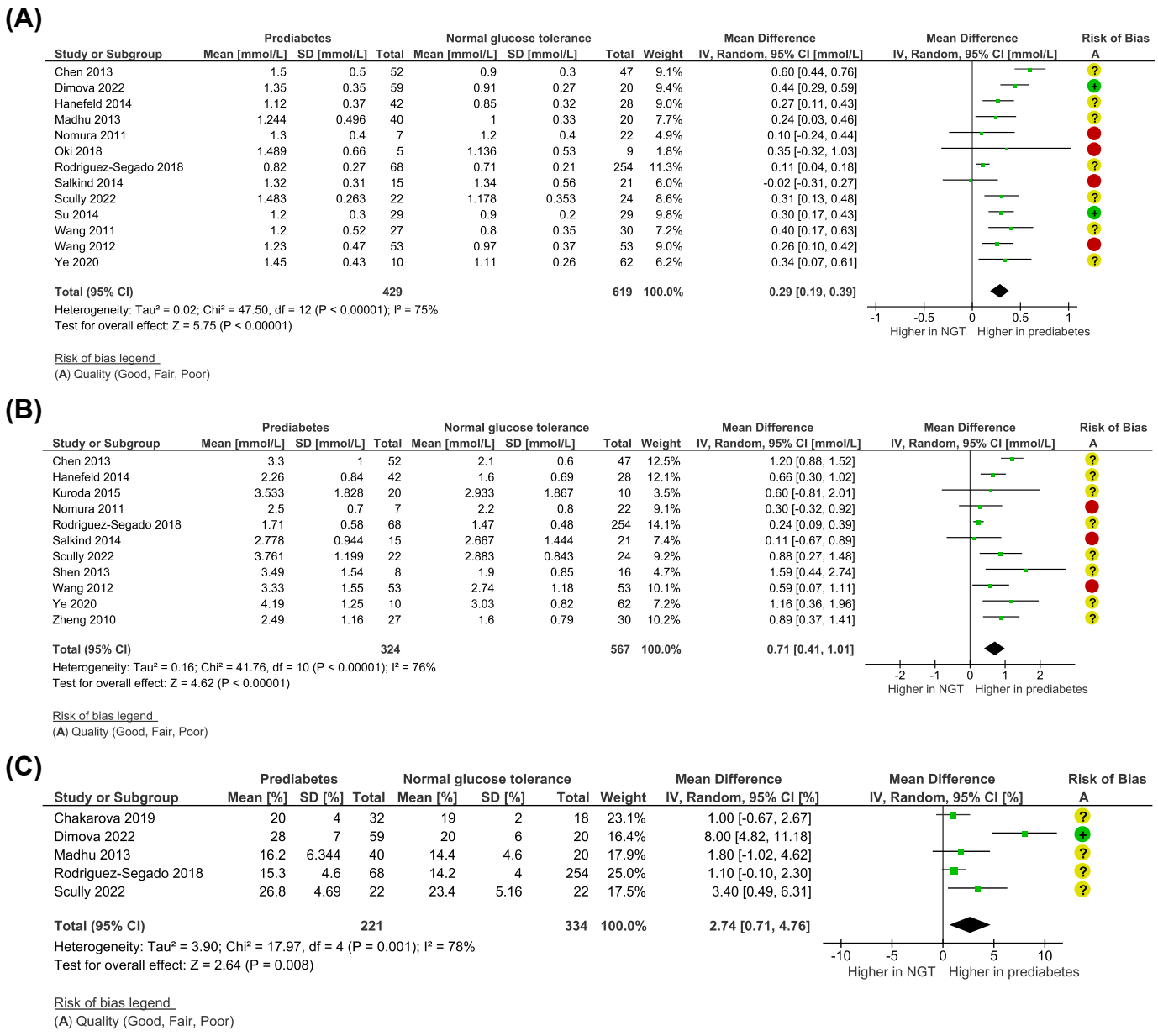

Fig. 2. Meta-analyses comparing GV in adult individuals with and without prediabetes. A: SD, B: MAGE, C: CV.

3.5. Glycemic markers

3.5.1. Adults

3.5.1.1. HbA1c. Positive associations between various GV measures and HbA1c were observed in some [35,60,61,63,72], but not all [57,69,73,74], studies.

3.5.1.2. Fasting glucose. Several studies, including one based on a large population-based sample, report positive associations between multiple GV measures and fasting glucose [35,55,60,63], but there are also contrasting evidence reporting no associations [57,58,61,75].

3.5.1.3. Fasting insulin. Two studies found no associations between GV measures and fasting insulin [58,60]. Surprisingly, in individuals with prediabetes, Dimova et al. (2019) observed inverse associations between both CV and M-value, but not multiple other GV measures, and fasting insulin [76].

3.5.1.4. HOMA. Three studies reported positive associations between GV measures and HOMA-IR [61,77], also when adjusted for multiple confounders [78], however, three other studies found no associations [57,58,63]. Unexpectedly, Dimova et al. (2019) observed inverse associations between both CV and M-value, but not multiple other GV measures, and HOMA-IR in individuals with prediabetes [76].

There were no associations between GV measures and HOMA-B [57,58,63].

3.5.1.5. OGTT-derived measures. One study reported a positive association between GV and 2-h glucose [60], but three other studies found no associations [35,57,58]. However, one study reported positive associations between SD and MAGE and 30-min glucose

change and 30-min insulin change, but not with 2-h insulin [58] whereas another study found higher 1-h glucose in age- and BMI-matched patients with high compared to low MAGE [57]. In response to a standardized meal, MAGE was not associated with overall postprandial glucose [75].

No measure of GV was associated with QUICKI [63].

Two studies found no clear associations between SD and MAGE and insulinogenic index [57,58] whereas another study found that multiple GV measures were inversely associated with insulinogenic index [38].

Two studies found that multiple GV measures were inversely associated with ISSI-2 [38,40].

Two studies reported inverse associations between multiple GV measures and disposition index, also after adjustment for multiple confounders [36,39] whereas another study found that only one out of four GV measures was inversely associated with disposition index [79].

In all, results from six studies [36,38–40,53,79] indicate that measures of beta cell function (disposition index, ISSI-2 and insulinogenic index) are inversely associated with GV, however borderline [57] and null [58] findings are also reported.

van der Kroef et al. found that SD, CONGA4 and MODD were all similar in n = 112 CT/TT carriers of the TCF7L2 rs7903146 allele (associated with increased risk of type 2 diabetes) compared to n = 123 age-matched CC carriers [80].

3.5.2. Adolescents

3.5.2.1. HbA1c. Weak positive associations (r = 0.21–0.25) between GV measures and HbA1c have been observed in some [49,50], but not all [62,81] studies. Furthermore, changes in GV measures were not associated with changes in HbA1c prospectively [65].

3.5.2.2. Fasting glucose. Fasting glucose was positively associated with SD and CV, but not MAGE, in one study [53] whereas three other studies found no associations between any GV measure and fasting glucose [49,50,62]. Similarly, changes in GV measures were not associated with changes in fasting glucose prospectively [65].

3.5.2.3. Fasting insulin. Weak positive associations (r = 0.19–0.30) between GV measures and fasting insulin were observed in two studies [50,62] but changes in GV measures were not associated with changes in fasting insulin prospectively [65].

3.5.2.4. HOMA. SD/mean was positively associated (r = 0.30) with HOMA-IR in one study [62], but CONGA was not associated with HOMA-IR in another study [50] and changes in GV measures were not associated with changes in HOMA-IR prospectively [65].

3.5.2.5. OGTT-derived measures. Three studies (of which two included a few participants with CF-related diabetes) found positive associations between several GV measures and 2-h glucose [49,53,62], but changes in GV measures were not associated with changes in 2-h glucose prospectively [65].

One study found that SD/mean was positively associated with 2-h insulin (r = 0.32), peak insulin (r = 0.28), total insulin (r = 0.29) [62] whereas another study found that CONGA was positively associated with glucose AUC [50].

In a population consisting primarily of patients with CF (including ~11% with CF-related diabetes), SD, CV and MAGE were inversely associated with the insulinogenic index (r = −0.41 to −0.49) and the disposition index (r = −0.43 to −0.51), but not with the Matsuda index [53].

3.6. Cardiovascular risk factors, atherosclerosis development and CVD incidence

In patients with coronary artery disease (CAD), MAGE was positively associated (r = 0.48–0.54, p < 0.02) with the number of $CD14^{++}CD16^{+}$ monocytes, a marker of coronary plaque vulnerability [82,83]. Furthermore, MAGE was positively associated (r = 0.51, p < 0.001) with the percentage of necrotic core within plaques and this association was equally strong in patients with normal- and impaired glucose tolerance and persisted when adjusted for age, sex, HbA1c, fasting- and 120-min glucose [46]. During 12 months of follow-up in patients with stable angina, patients with high MAGE had higher cardiovascular event rate than patients with low MAGE (26.4% vs 11.8%, p = 0.038) and MAGE was a strong risk factor for cardiovascular events (HR 5.63 (1.72–18.4), p = 0.004). Consistently, MAGE was positively associated with, and the only significant predictor of, the severity and extent of atherosclerosis (assessed using the Gensini score (r = 0.74) and SYNTAX score (r = 0.78)) [84]. A meta-analysis of four datasets found that higher MAGE was associated with higher incidence of major cardiovascular events (RR 2.39 (1.62–3.54)), also in subgroup analyses based on CAD/acute coronary syndrome (RR 1.61 (1.25–2.08) for stable CAD, n = 2 datasets), follow-up duration and adjustment for HbA1c [85].

For reactive hyperemia index (RHI), a coronary stenosis index, one study found that no GV measure was associated [86] whereas another reported that patients with angina having high MAGE had lower RHI than patients with low MAGE [57].

For carotid intima-media thickness (C-IMT), no robust association with GV measures was observed [43,58,86,87], and individuals with low and high CV had similar C-IMT [69].

SD was positively associated with pulse wave velocity in univariate analyses but not when adjusted for age, sex and education [87]. Furthermore, SD was not associated with carotid distensibility coefficient, ankle-brachial index or circumferential wall stress [87]. Consistently, individuals with low and high CV had similar endothelium-dependent (flow-mediated dilation, FMD) and −independent (glyceryl-trinitrate dilation, GTN) vasodilation [69]. However, during weight loss, change in CV was inversely associated (r = −0.45, p < 0.05) with change in FMD [88]. Weight loss *per se* was also inversely associated with change in FMD, although not as strongly (r = −0.35, p < 0.05). Pulse pressure was positively associated with L-index, MAG, MAGE and CV and sympatho-vagal balance index was positively associated with M-value [86]. Reduced cerebral vasomotor reactivity (a measure of endothelial function in the cerebral region) induced by acute hyperglycemia was positively associated with MAGE (r = 0.55, p = 0.02), however no association was observed in the basal state [67].

Regarding cardiac autonomic function, CONGA1 and J-index were inversely associated with both sympathetic and parasympathetic activity (r~0.25) whereas M-value was positively associated with sympathetic and parasympathetic activity [31]. Furthermore, 48h ambulatory variability in systolic, but not diastolic, blood pressure was positively associated with CV (r = 0.38), MAGE (r = 0.49), MODD (r = 0.46), and SD (r = 0.52) [89] and SD was associated with 24h mean systolic- and diastolic blood pressure [90]. One study observed that patients with high MAGE had higher prevalence of hypertension than patients with low MAGE [57], but most studies found no association between GV measures and blood pressure [50,58,61,62,65].

The majority of studies report no association between GV measures and blood lipids [57,58,60–62,65], with some exceptions reporting positive associations with triglycerides [50,77].

3.7. Liver enzymes, liver fibrosis and liver fat

In a meta-analysis of three cohorts (n = 436 in total), mean glycemia was positively associated with liver enzymes, but MAGE, SD and MODD were not [91]. Consistently, MAGE was similar in age- and sex-matched individuals with (n = 14) and without (n = 33) NAFLD and MAGE was not associated with liver fat content [92].

In children with NAFLD (n = 30), SD was similar across stages of liver fibrosis assessed by liver biopsy, however the majority had mild-moderate fibrosis and only six children had advanced fibrosis, limiting statistical power [93].

3.8. Inflammation and oxidative stress

Adult patients with high MAGE had higher CRP compared to age- and BMI-matched individuals with low MAGE [57]. Furthermore, MAGE was positively associated with levels of PAI-1 ($r = 0.35$, $p < 0.001$) [75].

In adolescents, MAGE and SD were not associated with ICAM, E-selectin or sRAGE, except for MAGE showing an inverse association with sRAGE specifically in adolescents with normal body weight ($n = 10$; $r = -0.38$, $p < 0.05$) [64]. Similarly, GV (SD/mean) was not associated with IL-6 [62].

Data on oxidative stress are inconsistent but mostly negative. In adults, no GV measure was associated with 3-nitrotyrosine in the fasting state [76,79], nor with isoprostanes, TBARS or GSH/GSSG [79]. In adults, MAGE was associated with 8-iso-PGF2a ($r = 0.61$, $p = 0.001$) and MPPGE with 8-OH-dG ($r = 0.58$, $p < 0.01$) [33], but MAGE was not associated with 8-iso-PGF2a in children [94].

3.9. Miscellaneous

Compared to healthy controls, patients with Graves' disease had higher MAGE, SD and CV, despite having NGT (defined by OGTT) [95]. Circulating free T3 and T4 were positively associated (r~0.4–0.5) with SD, MAGE and CV.

SD and MAGE were similar in women with and without polycystic ovary syndrome [96].

MAGE was inversely associated with estrogen levels ($r = -0.17$, $p < 0.03$) [75].

In adolescents, GV was not associated with adiponectin [62].

MAGE and SD were positively associated serum uric acid in patients with gout [77].

4. Discussion

We performed a systematic review to address whether GV is associated with cardiometabolic risk markers and/or clinical outcomes in individuals without diabetes. Since CGM technology has become more widely available, one important goal has been to find measures, such as GV, that could facilitate earlier identification of disease (e.g. diabetes/prediabetes). We found a large number of studies (n = 71) reporting associations between CGM-derived GV and cardiometabolic risk markers in diverse populations. GV is higher in individuals with impaired compared to normal glucose regulation and appears to be inversely associated with measures of beta cell function. In contrast, GV does not appear to be clearly associated with insulin sensitivity, fatty liver disease, adiposity, blood lipid profile, blood pressure or oxidative stress. However, GV may be positively associated with degree of atherosclerosis and cardiovascular events in individuals with coronary artery disease. However, most studies are cross-sectional and whether or not measures of GV brings additional benefit in terms of diagnostic power over conventional metrics cannot be concluded based on the available evidence. We found only two prospective studies, with limited sample size and measuring different outcomes. Although these studies indicated that GV is positively associated with incidence of cardiovascular events and type 2 diabetes, more prospective studies in healthy individuals are warranted. Furthermore, multiple measures used to assess GV are strongly influenced by or associated with mean glucose levels. Thus, future studies should focus on measures that more specifically assess GV (i.e. measures not being driven by the mean), such as CV, to avoid bias and simplify comparisons between studies, populations and contexts.

In relation to categories of glucose regulation in adults, the majority of studies support the notion that GV is higher in individuals with impaired-compared to normal glucose regulation [26–41], but there are also contrasting evidence reporting no difference between groups [42–48]. However, when meta-analyzed, it was clear that GV was higher in adults with compared to without prediabetes. This finding is not surprising considering that postprandial glucose excursions are higher in individuals with compared to without prediabetes and that postprandial glucose excursions are a strong determinant of GV [14]. For children and adolescents, the evidence is scarce and contrasting [49,51,53,66]. Considering that GV is higher in individuals with impaired glucose regulation, it is somewhat surprising that most studies found no difference in GV between groups with and without metabolic syndrome [62,68–70], however this may be influenced by different definitions of metabolic syndrome as well as by different constellations of components of metabolic syndrome between different individuals. Regarding the association to glycemic markers, the evidence is mixed and difficult to reconcile. This is further aggravated by the divergent associations among different glycemic markers also within studies. However, multiple studies have observed positive associations between GV and HbA1c, both in adults [35,60,61,63,72] and adolescents [49,50], but this finding is not unanimous [57,62,65,69,73,74,81]. The situation is similar for HOMA-IR where some studies report positive associations [61,62,77,78] whereas others report lack of association [50,57,58,63,65]. Surprisingly, Dimova et al. observed inverse associations between some GV measures and HOMA-IR in individuals with prediabetes, but not in individuals with normal glucose tolerance [76]. As HOMA-IR is driven primarily by insulin levels rather than glucose, the finding by Dimova et al. may, speculatively, reflect reduced insulin secretion capacity in prediabetes rather than a true inverse association between GV and HOMA-IR. In relation to glucose, a large population-based study found that all investigated GV measures were positively associated with fasting plasma glucose [55]. This finding has been replicated in multiple studies [35,53,60,63], but is not unanimous [49,50,58,61,65]. Few studies reported associations between GV and insulin metrics (except HOMA-IR) and the overall conclusion from these studies are that there are no clear associations for either fasting or postprandial insulin metrics [50,58,60,65,76]. However, multiple studies have found associations between GV and various indices derived from glucose tolerance tests. For example, the insulinogenic index, reflecting early-phase insulin secretion and thus a marker of beta cell function, has been inversely associated with multiple GV measures in both adults [38] and adolescents [53], although not unanimously [58]. Similarly, other markers of beta cell function, the disposition index and ISSI-2, have been inversely associated with multiple GV measures in both adolescents [53] and adults [36,38–40,79]. However, and similar to the results for fasting and postprandial insulin, there does not appear to be any associations between GV measures and insulin sensitivity indices such as QUICKI [63] and Matsuda index [53]. Overall, the association between GV and measures of insulin sensitivity/resistance derived from equations using insulin will likely differ depending on the

degree of beta cell function. Thus, careful consideration of the study population is required to avoid spurious conclusions.

In concordance with the overall lack of association between GV and insulin sensitivity, multiple studies have found null associations between GV and liver enzymes [91], liver fat content [92], NAFLD status [92] and liver fibrosis [93], suggesting that measures of GV are not useful in distinguishing groups with various stages of liver disease. These results further suggest that the liver does not play a major role in explaining variation in GV between individuals without diabetes. In contrast to our findings, a recent cross-sectional study by Keshet et al. in a large number of individuals without diabetes observed weak positive associations between some measures of GV and liver enzymes and ultrasound-derived liver attenuation [97].

Regarding cardiovascular risk markers, higher GV was positively associated with markers of coronary plaque vulnerability [82,83], as well as size of the necrotic core within plaques [46], in patients with coronary artery disease. Furthermore, GV was a strong risk factor for cardiovascular events during follow-up in patients with stable angina [57], as well as a significant determinant of the extent and severity of atherosclerosis [84]. This is in line with findings from patients with type 2 diabetes and acute myocardial infarction, were large glucose fluctuations (but not HbA1c) was associated with increased incidence of CVD events during follow-up [98,99]. However, whether GV is associated with incidence of CVD in patients with type 2 diabetes but without history of CVD is unclear but currently addressed [100].

Cross-sectional analyses generally do not support associations between GV and carotid intima-media thickness [43,58,86] or vasodilation/vascular function [69,87], but one study found that a decrease in GV during weight loss was associated with increased flow-mediated dilation [88]. Most cross-sectional studies did not report any associations between GV and the blood lipid profile or blood pressure [58,60–62], but some studies reported positive associations between GV and triglycerides [50,77] and with ambulatory variability [89] and mean blood pressure [90]. Similarly, the recent cross-sectional study by Keshet et al. observed weak positive associations between some, but not all, GV measures and blood pressure and triglycerides [97]. Surprisingly, weak inverse associations were observed between some, but not all, GV measures and carotid intima-media thickness.

Increased GV is associated with increased oxidative stress in type 2 diabetes [4,101], which may trigger inflammation [102]. The suggested link between GV and oxidative stress has been demonstrated in experimental settings in humans, in both type 2 diabetes and healthy controls, and shown to be abolished (healthy controls) or attenuated (type 2 diabetes) by concomitant exposure to vitamin C [103]. However, the association between GV and oxidative stress could not be demonstrated in patients with type 1 diabetes [104], and not induced experimentally in healthy controls in another study [105]. In our review, we found little evidence that measures of GV are associated with oxidative stress in individuals without diabetes. Only one study, with limited sample size, found a positive association [33] whereas other studies observed no association [76,79,94]. This may, speculatively, be due to that glucose levels do not fluctuate as much or as rapidly in individuals without compared to with diabetes, but requires further investigation. Alternatively, the association between GV and oxidative stress suggested in individuals with diabetes may be due to confounding factors not present in individuals without diabetes, thus more research is needed to understand potential modifying factors. With regard to inflammation, findings are sparse and inconsistent with some positive findings among adults [57,75] and some null associations among adolescents [62,64], precluding any conclusions on the association between GV and inflammation.

With some exceptions [58–60], the majority of studies report no difference in GV measures between individuals with normal body weight and individuals with overweight or obesity and no association between GV and BMI in adults [45,54–57,61]. Findings are more inconsistent in adolescents but generally in line with findings in adults. Overall, this suggests that neither body weight, nor body composition [56], are major determinants of GV. In contrast to our findings, the recent cross-sectional study by Keshet et al. observed weak positive associations between some measures of GV (e.g. J-index and MODD) and BMI and regional fat depots, and, surprisingly, inverse associations between CV and BMI and regional fat depots [97].

The role of diet as a determinant of GV is an important outstanding question, not being addressed in the current systematic review. Considering the established role of dietary carbohydrate quality on postprandial glucose excursions, part of the variation in GV is likely explained by variation in diet. As dietary composition may influence the risk of various diseases, including type 2 diabetes and CVD, through multiple mechanisms, standardizing or adjusting for diet is an important consideration in future studies investigating the role of GV in the development of cardiometabolic disease.

Strengths of the current work include the broad literature search in three databases, as well as the stringent methodology according to a predetermined protocol. However, multiple limitations need to be acknowledged. The majority of included studies were cross-sectional, precluding temporal resolution of the association between GV and development of cardiometabolic disease. Furthermore, the majority of studies had a different primary purpose, resulting in that data on subpopulations using CGM, as well as the association between GV and outcome measures, were not always satisfactorily described. Additionally, many studies report univariate (and thus potentially confounded) associations and studies reporting adjusted associations have used different variables in the models. Furthermore, multiple measures of GV in the included studies are influenced by the mean glucose value, thus it is difficult to disentangle the specific role of GV. Finally, various populations have been investigated (e.g. with or without cystic fibrosis, prediabetes, cardiovascular disease and among different age groups) and thus a cautious interpretation is advised as the association between GV and outcome measures does not necessarily be similar in these different populations.

In conclusion, GV is higher in individuals with impaired compared to normal glucose regulation and appears to be inversely associated with measures of beta cell function. In contrast, GV does not appear to be clearly associated with insulin sensitivity, fatty liver disease, adiposity, blood lipid profile, blood pressure or oxidative stress. Also, GV may be positively associated with the degree of atherosclerosis and cardiovascular events. Whether GV brings additional benefit in terms of risk prediction over conventional metrics cannot be concluded with any certainty based on the available evidence. Very few prospective studies, with limited sample size, are available and thus more prospective studies in healthy individuals are warranted, investigating the predictive power of GV in relation incident prediabetes and diabetes, as well as cardiovascular disease. To avoid bias and simplify comparisons, future studies may choose to focus on measures of GV (such as the CV) which are less dependent on the mean glucose level.

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Conflict of interest

F.R. and D.I. have no conflict of interest to disclose. A.H. is offering CGM based services through her own practice as nutritionist. A.H. has also received consultancy fees from Mäta Health and OneTwo Analytics, two companies that are offering CGM based services.

Data availability

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Deviations from protocol

The meta-analyses were not pre-specified in the protocol but were performed for outcomes for which the number and homogeneity of retrieved studies allowed.

The protocol specify that all CGM-derived measures should be included, however as our aim was to focus on glycemic variability we removed some CGM-derived measures not clearly reflecting this (e.g. time in range).

The protocol specify that the ROBINS-I tool should be used for quality assessment, however we changed tool as the vast majority of included studies had a cross-sectional design. Furthermore, the protocol specify that two researchers should perform quality assessment and data extraction. This was performed for a subset of the included studies, but the remainder were extracted and assessed by one researcher due to good agreement between the two researchers for the subset.

Contribution statement

A.H., D.I. and F.R. contributed to conception and design. A.H. and F.R. screened titles and abstracts. A.H. and F.R. extracted data. A.H. and F.R. performed quality assessment. D.I. performed meta-analyses. A.H. and F.R. drafted the manuscript. All authors critically revised the manuscript and accepted the final version. F.R. is the guarantor and accepts full responsibility for the work, had access to the data, and controlled the decision to publish.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.02.014.

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