Biological variation of capillary blood glucose: A systematic review

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Abstract. Biological variation (BV) refers to changes in biochemical constituents in the blood or other biological fluids, indicative of body regulation via homeostatic processes. Intra- and interindividual BV data are essential for establishing analytical performance specifications and evaluating the significance between consecutive measurements of an analyte. Given this context, the present study conducted a systematic review of the intra- and interindividual BV of capillary blood glucose. Out of 461 initial studies identified, only 4 met the inclusion criteria for detailed analysis after excluding 419 for title irrelevance, 10 for duplication, 21 based on abstract content and 7 based on article content. Notably, none of the studies primarily focused on the intra- and interindividual BV of capillary blood glucose; rather, they reported it as a secondary outcome. Regarding fasting, data analyses revealed intra-individual BVs of 4.5 and 31.1% for healthy and diabetic individuals, respectively, and interindividual coefficient of variations of 4.7-5.8 and 12.9-16.3% for healthy and diabetic individuals, respectively. Only one study provided the analytical coefficient of variation, corroborating the recommended practices. Additionally, the fasting duration, meal standardization before sampling, and number and interval between collections varied among the studies. Hence, the results suggest that there are no reliable data on intra- and interindividual BVs for capillary blood glucose in the literature.

Introduction

Biological variation (BV) refers to changes in the levels of biochemical constituents in blood or other biological fluids, which reflect the body's regulation through homeostatic processes (1). In an equilibrium state, most measurands exhibit random variations around a homeostatic set point, while others may also be influenced by factors such as different life stages or predictable cyclic variation (2). Moreover, BV has two main components: Coefficient of intra-individual BV (CV_I) and coefficient of interindividual BV, also called group coefficient BV (CV_G); the former refers to the random fluctuation around the homeostatic set point of an analyte within an individual, while the latter represents the variation between the homeostatic set points of an analyte among different individuals (3).

Intra-individual variation can occur in either cyclical or random patterns. Cyclical variation occurs predictably (e.g., variations in diurnal cortisol levels, monthly hormonal changes during the female reproductive cycle and seasonal fluctuations in vitamin D levels). Conversely, random variation is unpredictable and occurs naturally around a subject's homeostatic set point (4).

Currently, BV data are estimated by repeatedly measuring biomarkers or analytes in a healthy population under normal physiological conditions (5). Population-based studies have revealed that healthy individuals' BV estimates remain constant (6). The impact of a specific disease on the BV of an analyte can vary, and it may or may not remain unchanged. Therefore, although a disease may alter the homeostatic set point for an analyte, the intra-individual variability may not necessarily change (4).

Data on BV are also available for populations with different diagnoses, including diabetes or chronic kidney disease, as individuals may be stable despite their pathological condition (7). Research has also revealed that pregnancy and prolonged high-intensity physical exercise can influence individuals' BV (8,9). Moreover, these data are extensively utilized in laboratory medicine for various purposes. These include establishing analytical performance specifications for measurement systems (3,10), calculating the reference change value (RCV) to assess the significance of changes between consecutive measurements, using the individuality index (II) to evaluate the utility of population-based reference intervals and determining personalized reference intervals (2,10). In general, utilizing BV estimates in an individual's test results can provide evidence of pathological conditions or response to therapy (11).

According to Fraser (2001) (4), once the pre-analytical phase is properly managed, the total variation of laboratory results, also known as the total coefficient of variation (CV_T), can be calculated by adding the analytical coefficient of

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Abbreviations: BIVAC, biological variation data critical appraisal checklist; BV, biological variation; CV_A, analytical coefficient of variation; CV_G, coefficient of interindividual biological variation; CV_I, coefficient of intra-individual biological variation; II, individuality index; RCV, reference change value

Key words: capillary blood glucose, intra-individual coefficient of biological variation, fasting capillary blood glucose, glucometers

variation (CV_A) and the CV_I. The CV_A can be determined by analyzing control samples with known results (12,13).

At present, the most comprehensive BV database for a wide range of analytes only provides the CV_I and CV_G for plasma (4.5 and 5.8%, respectively) and serum glucose (5.6 and 7.5%, respectively) (14). However, this database does not include the intra- and interindividual BV of capillary blood glucose.

Blood glucose levels can be measured in plasma, serum, whole blood, capillary blood and more recently in interstitial fluid, using laboratory equipment and portable meters called glucometers (15-17).

Plasma glucose testing is used as the gold standard for screening diabetes; however, numerous challenges exist with regard to its widespread use, including low availability in low-resource settings, where capillary glucose testing is suggested as an alternative screening method (18).

Glucometers were first designed to analyze blood samples from capillary sources and are capable of reporting blood glucose levels within seconds (19). These devices are used for monitoring blood glucose (MBG) and can be used by patients and healthcare teams (20).

MBG is recommended for insulin-treated individuals with diabetes in any age group. MBG brings great benefits, by reducing the risk of acute complications, such as ketoacidosis and hypoglycemia, and by allowing the patient to understand the determinants of their blood glucose levels by correlating real-time glycemic results with food intake or physical activity, for example (21,22).

How often an individual with diabetes should check their glucose levels each day can vary from 1 to 10 times, depending on their type of diabetes, treatment plan and individual needs. In hospitalized diabetic patients who can eat, point-of-care (POC) MBG should be performed prior to meals, while in those not eating, MBG is recommended every 4-6 h. POC MBG occurring at a more frequent interval, ranging from every 30 min to every 2 h, is the required standard for safe intravenous insulin therapy (23).

Given the significance of capillary blood glucose monitoring (22), it is crucial to ascertain the intra- and inter-individual BV data for this parameter, which is the primary objective of the present study.

Materials and methods

Study aim. The present study aimed to ascertain the coefficient of BV in capillary blood glucose levels, as measured by a glucometer. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 criteria were adhered in order to maintain methodological rigor. This included utilizing the related checklist and flowchart, as provided by Galvao *et al* (24).

Data sources. The search was conducted between January and March 2023 through the PubMed (https://pubmed.ncbi.nlm.nih.gov/), Scielo (https://scielo.org/en/), Scopus (https://www.scopus.com/) and Google Scholar (https://scholar.google.com/) databases for articles without a defined publication date range. PubMed was selected as it is the largest indexer of medical journals globally. Scopus was chosen for its expansive database of article abstracts and citations. Scielo, an open-access electronic library featuring scientific periodicals in various languages from countries such as those in Latin America, South Africa, Spain, India and Portugal, was also utilized. Lastly, Google Scholar, which is a freely accessible virtual search engine that indexes full-text academic literature in a diverse range of publication formats, was included in the search. Studies were retrieved using a combination of keywords in English, utilizing the AND operator to pair the following descriptors: 'glucometer AND capillary glucose', 'capillary glucose AND biological variation' and 'within subject AND biological variation AND capillary glucose'.

To select appropriate studies, the inclusion criteria of the present study were original articles presenting the object of the present study either in the title, abstract or text, which contained the coefficient of intra-individual or BVs of capillary blood glucose. The exclusion criteria were literature review articles, dissertations, case studies, book chapters and editorials. Articles that simply reiterated the BV of capillary glycemia found in other studies were also omitted. No limitations were imposed regarding publication dates, participant characteristics or funding in order to maximize the potential for data recovery. A single reviewer conducted the research up to this point. The literature review and article selection processes are illustrated in Fig. 1.

BV data critical appraisal checklist (BIVAC). The quality of the studies and the BV data generated by the articles incorporated in the present review were evaluated using the BIVAC. The BIVAC tool is composed of 14 quality items (QI) (25), which were assessed in the present study in terms of whether articles met the criteria or not, without evaluating the degree of compliance. The quality items of the BIVAC tool, as described by Aarsand *et al* (25) are listed as follows:

QI 1: Ratio scale. This item explores whether the measurand is reported on a ratio scale. The importance of this rests on the fact that only ratio scales possess a meaningful zero. Therefore, any estimation of the coefficient of intra-individual variation for measurands on non-ratio scales demands careful consideration.

QI 2, 3 and 4: Subjects, samples and measurands. These items pertain to the subjects (QI 2) and samples (QI 3), and are critical for ensuring the reliability of the assessed BV results. Full characterization and precise reporting of the population attributes wherein the BV was assessed are vital for BV studies. The measurand and analytical method (QI 4) are also essential as earlier-generation analytical procedures might produce different estimations of the measurand.

QI 5, 6 and 7: Pre-analytical procedures, estimation of analytical variation and steady state. Standardized and appropriate pre-analytical procedures are necessary for obtaining reliable BV data (QI 5). A lack of compliance with this requirement may result in an overestimation of the coefficient of intra-individual variation and the coefficient of glucose variation. The accurate estimation of the coefficient of analytical variation (QI 6) should be conducted through replicate analyses within the same analytical run. In addition, there should be no systematic fluctuation in the concentration of the measurand throughout the study period (QI 7: steady state). If such modifications are detected, the data should be properly adjusted.

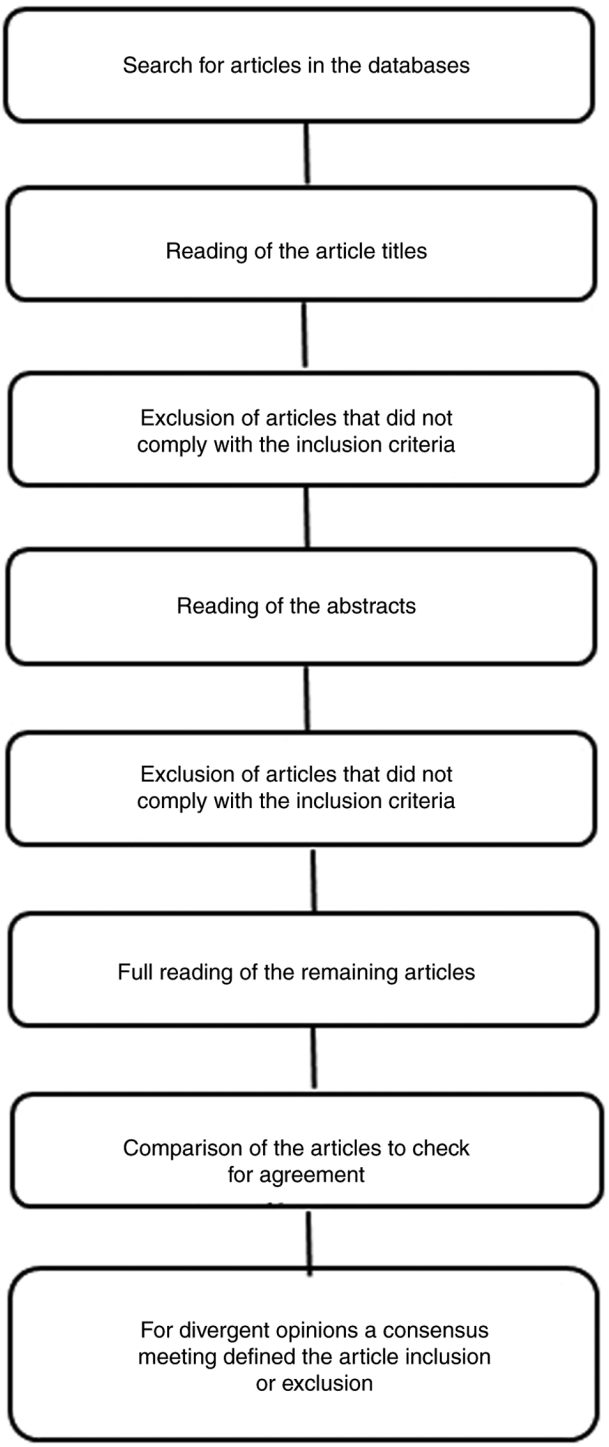

Figure 1. Literature review and article selection process. Flowchart of the steps taken to research and select the articles to be reviewed.

QI 8, 9 and 10: Outliers, normality, and homogeneity of variance. Outliers must be recognized and excluded from the replicates, each individual's samples and the individuals themselves (QI 8). Any failure to address outliers could lead to an overestimation or underestimation of the CV_I. Each individual's data distribution must be examined for normality, and should a departure from normality be observed, the data must undergo transformation (QI 9). Assessment of variance homogeneity is also necessary, for any variance heterogeneity would render the estimates inapplicable to a broader population (QI 10).

QI 11 and 12: Statistical method and confidence intervals (CIs). The statistical method deployed for BV estimation must be explicitly stated and suitable for the research (QI 11). Until recently, BV estimates rarely included reports of measurement uncertainty (QI 12). In the context of the BIVAC, if the study does not report the IC, at least the required data for its calculation must be present.

QI 13 and 14: Number of results and concentrations studied. It is imperative to reveal the number of results included (QI 13) and the average concentrations of the studied analytes (QI 14) in evaluating the correlation between the CV_I and concentration. Importantly, this requirement does not affect the reliability of BV estimates.

Results

A review of the four databases produced 461 articles for consideration. The articles were selected based on specific inclusion and exclusion criteria, which eliminated 419 studies after scrutinizing their titles, and with 10 articles dismissed due to duplication. The abstracts of the remaining 32 articles were then read. A further 21 articles were excluded for failing to meet the inclusion criteria. In the end, 11 articles were selected for a full reading, of which only 4 were included in the final review (7,26-28). Fig. 2 presents the article selection process structured according to the PRISMA protocol.

Out of the 11 articles selected for full reading, six were excluded as they solely focused on evaluating the performance and accuracy of glucometers, while 1 article was excluded as one of its objectives was to calculate glycemic variability after consuming certain foods. These studies used data on BV and CV_I from other articles but did not perform an analysis of them.

Table I summarizes the information obtained from the four reviewed articles (7,26-28). All articles had as one of their objectives the investigation of BV or the assessment of glycemic variability, which indirectly provides data on BV. However, various methodologies were employed to determine BV or glycemic variability, directly impacting the results. The articles under review had a range of 3 to 11 authors and were published in English between 2010 and 2019.

Among the four studies, only one aimed specifically to assess individuals' between-visit BV of capillary blood glucose levels (7). This was the study that most complied with the BIVAC criteria, and reported the CV_I values of 4.5% for healthy individuals and 31.1% for diabetic patients (7) (Table II). On the other hand, all four articles presented the CV_I of fasting capillary blood glucose. However, as the studies were conducted on different populations, and the analyses were performed differently among the four articles, it was not possible to estimate an average CV_I.

As demonstrated in Table II, three articles analyzed capillary blood glucose during fasting (7,26,27), while one examined capillary blood glucose throughout the day or after food intake (28). Table III evaluates the four studies based on the 14 BIVAC quality criteria.

Discussion

The primary objective of the present systematic review was to comprehensively analyze the current state of knowledge

Table I. Studies, objectives and methods of the selected articles.

First author, year	Title	BV CBG-related research objective	Equipment and manufacturer	Formula used to calculate the CV	(Refs.)
Mu *et al,* 2011	Comparison of fasting capillary glucose variability between insulin glargine and NPH	Investigate glycemic variability in individuals using insulin glargine and NPH	Glucometer, OneTouch Ultra 1 (Lifescan Inc.)	CV=SD/mean	(26)
Carlsen *et al*, 2011	Within-subject BV of glucose and HbA1c in healthy persons and DM1 patients	Estimate the BV of capillary glucose and HbA1c in healthy individuals and patients with DM1	HK Gluco-quant Glucose Modular Analyzer (Roche Diagnostics)	CV=SD/mean; analytical and inter-subject CVs were estimated separately via analysis of variance	(7)
Allsop *et al*, 2016	The between-day reproducibility of fasting, satiety-related analytes, in 8- to 11-year-old boys	To evaluate the reproducibility, between days, of plasma GLP-1, glucagon, leptin, insulin and capillary glucose in boys aged 8 to 11 years, who were fasting, lean and overweight/obese	Automated point-of-care glucose (glucose oxidase) analyzer (BiosenC_line, EKF Diagnostics Holdings plc.)	NA	(27)
Colomo *et al*, 2019	Relationship between glucose control, glycemic variability and oxidative stress in children with DM1	To evaluate the relationship between glycemic control, glycemic variability and oxidative stress in children with DM1	One Touch Verio iQ, (Lifescan Inc.)	CV=SD/mean	(28)

BV, biological variation; CBG, capillary blood glucose; CV, coefficient of variation; NPH, Hagedorn standard neutral protamine insulin; SD, standard deviation; DM1, type 1 diabetes mellitus; HbA1C, haemoglobin A1C; NA, data not available.

regarding the BV of capillary glycemia, as measured by glucometers. The analysis of the present study aimed to establish specifications for analytical quality, II and RCV. Specific protocols were employed to guarantee the reliability of the BV studies (29,30).

Mu *et al* (26) conducted a study where fasting capillary blood glucose was measured daily for three months. However, the study lacked standardization in terms of fasting time and the food consumed in the previous meal. Additionally, the present study did not provide data on the CV_A of the glucometer used, indicating that it was not considered when calculating the CV_I.

Carlsen *et al* (7) estimated the BV of capillary blood plasma glucose and venous hemoglobin A1C in healthy individuals and those with diabetes, as presented in Table II. Weekly collections were performed over 10 weeks, with participants required to fast overnight before each collection. However, the specific fasting time was not disclosed. Duplicate samples were analyzed to assess the CV_A, and two-level control samples were utilized to monitor the analytical accuracy of the equipment. The CV_I and CV_G results obtained for plasma glycemia from capillary blood were included in the mean estimate published by the European Federation of Clinical Chemistry and Laboratory Medicine (2023) (14), although they do not represent the capillary glycemia normally analyzed by a glucometer.

The study by Allsop *et al* (27) implemented a standardized 12-h overnight fast, with each participant recording the food consumed the night before the first collection, which they were then instructed to repeat before the second collection. Nevertheless, the participants did not standardize food intake or quantity consumed. In terms of sample collection, the study only conducted two collections with a 1-week interval between them. According to current literature protocols, this number is considered low, and a minimum of five collections is recommended (31). Although a glucometer was employed, the capillary blood sample was placed in a heparinized tube and mixed with hemolysis solution prior to glucose analysis. This sample treatment does not reflect the routine use of glucometers for capillary blood glucose analysis. Furthermore, the method did not consider the analytical variation when calculating VB.

In the study by Colomo *et al* (28), there was no report on the standardization of food intake before sample collection. Additionally, fasting samples were not collected in the study. Furthermore, the analysis did not include information on the accuracy and precision of the equipment used in the tests (i.e., the CV_A was not provided). Considering that this study was

Table II. Research characteristics of selected articles.

First author, year	Participants (age)	Inclusion/exclusion criteria	Samples and collection frequency	CV (%)		Method analytical performance	Does it answer the guiding question of the systematic review?	(Refs.)
Mu *et al*, 2011	130 diabetic individuals using insulin glargine (31-49 years)	Participants with diabetes using oral antidiabetics, without changing medication for at least 3 months; fasting CBG >7.0 mmol/l and HbA1c >7.5%; no serious chronic or acute diabetic complications, nor serious intercurrent illness; female patients were not pregnant and did not plan to become pregnant within 6 months.	Fasting capillary blood (daily collections for 3 months)	Pre-treatment: CV_I BG fasting = 13.4% (±3.6)	Post-treatment: CV_I BG fasting = 10.2% (±4.2)	NA	Yes	(26)
	130 diabetic individuals using NPH insulin (32-49 years)			Pre-treatment: CV_I BG fasting = 12.9% (±4.0)	Post-treatment: CV_I BG fasting = 19.6% (±6.1)	NA		
Carlsen *et al*, 2011	15 diabetic individuals (26-61 years)	Stable diabetic patients with HbA1c between 6-8% and ≤1% change in HbA1c concentration in the last 18 months, no changes in basal insulin dose in the last 2 months and stable body weight (≤10% change in total body weight in the last year)	Venous blood and fasting capillary blood plasma (weekly collections for 10 weeks)	CV_I Fasting capillary blood plasma glucose =31.1% (27.3-36.3) CV_I venous Blood = 30.5% (26.7-35.5)	CV_G plasma glycemia of capillary blood fast = 16.3% (7.4-29.2) CV_G venous blood = 16.8% (8.2-29.8)	CV_A fasting capillary blood plasma glucose = 0.9% (0.8-1.0) CV_A venous blood = 1.0% (0.9-1.0)	No	(7)
	15 healthy individuals (27-59 years)	Self-declared healthy non-obese individuals		CV_I Fasting capillary blood plasma glucose = 4.5% (3.9-5.1) CV_I venous blood = 5.4% (4.7-6.0)	CV_G Fasting capillary blood plasma glucose = 5.8% (4.1-9.3) CV_G venous blood = 5.6% (3.9-9.0)	CV_A fasting capillary blood plasma glucose = 1.4% (1.2-1.6) CV_Avenous blood = 1.4% (1.3-1.6)		

Table II. Continued.

First author, year	Participants (age)	Inclusion/exclusion criteria	Samples and collection frequency	CV (%)		Method analytical performance	Does it answer the guiding question of the systematic review?	(Refs.)
Allsop *et al*, 2016	23 healthy individuals (8-11 years)	Exclusion: Diabetics or taking any medication known to affect taste, smell or appetite	Fasting capillary blood plasma (2 collections with an interval of 1 week between collections)	Skinny boys CV_G = 5.2%	Overweight boys CV_G = 4.7%	Not shown	No	(27)
Colomo *et al*, 2019	25 diabetic individuals (8-15 years)	Inclusion: Children and adolescents with type 1 diabetes mellitus	Capillary blood without fasting [6 daily collections (before meals and 2 h after meals) for 5 days in summer camp and in the home routine]	1st phase (holiday camp for children with diabetes) CV = 0.41% (+/- 0.10)	CV_G plasma glycemia of capillary blood fast = 16.3% (7.4-29.2)	Not shown	No	(28)

CV, coefficient of variation; NPH, Hagedorn standard neutral protamine insulin; CBG, capillary blood glucose; HbA1C, glycated hemoglobin SD, standard deviation; CV_I, within individual coefficient of variation; CV_G, between individual coefficient of variation; CV_A, analytical coefficient of variation; NPH, NPH, Hagedorn standard neutral protamine insulin.

conducted after the publication of BV verification protocols, such as BIVAC, the analysis of glycemic BV should have followed the criteria established by these protocols.

The reviewed articles presented varying CV_I values of capillary blood glucose. This discrepancy could be attributed to differences in verification protocols and the evaluation of different populations, reflecting varying study objectives. Specifically, one study focused on CV_I in healthy individuals (27), while two other studies examined it solely in people with diabetes (26,28). Lastly, one study explored the variation between healthy individuals and those with diabetes (7). Two studies were conducted with children (27,28), while the remaining two involved adult populations (7,26).

The number of data collections varied across studies, and the samples analyzed also differed. Carlsen *et al* (7) and Allsop *et al* (27) assessed glycemia in capillary blood plasma. There were also variations in the timing of blood glucose sample collection, with three studies monitoring fasting blood glucose levels and one study evaluating glucose levels before meals, without specifying the fasting duration, and 2 h after meals (7,26-28). In the study conducted by Allsop *et al* (27), food standardization prior to fasting was performed.

Specifically, in capillary blood glucose testing, the variation in glycemic index from food consumed immediately before sample collection could introduce bias into the results, thereby necessitating standardization (22). The choice of blood glucose measurement equipment also varied across studies, with Carlsen *et al* (7) and Allsop *et al* (27) utilizing biochemical analyzers while the others used glucometers. Moreover, concerning BV, the study by Allsop *et al* (27) solely

Table III. Assessment of articles regarding whether or not they fulfilled each of the 14 QI of BIVAC.

BIVAC QI	Panwei *et al*, 2010	Carlsen *et al*, 2011	Allsop *et al*, 2016	Colomo *et al*, 2019
QI 1 - ratio scale	Yes	Yes	Yes	Yes
QI 2 - participants	Yes	Yes	Yes	Yes
QI 3 - samples	Yes	Yes	Yes	Yes
QI 4 - measuring	Yes	Yes	Yes	Yes
QI 5 - pre-analytic	Yes	Yes	Yes	No
QI 6 - estimation of analytical variation	No	Yes	Yes	No
QI 7 - steady state	No	Yes	Yes	Yes
QI 8 - outliers	No	Yes	No	No
QI 9 - normality	Yes	No	No	No
QI 10 - homogeneity of variance	Yes	Yes	Yes	NA
QI 11 - statistical method	Yes	Yes	Yes	Yes
QI 12 - confidence interval	No	Yes	Yes	Yes
QI 13 - number of results	Yes	Yes	Yes	Yes
QI 14 - concentrations studied	Yes	Yes	Yes	Yes

BIVAC, biological variation data critical appraisal checklist; QI, quality item; NA, does not apply.

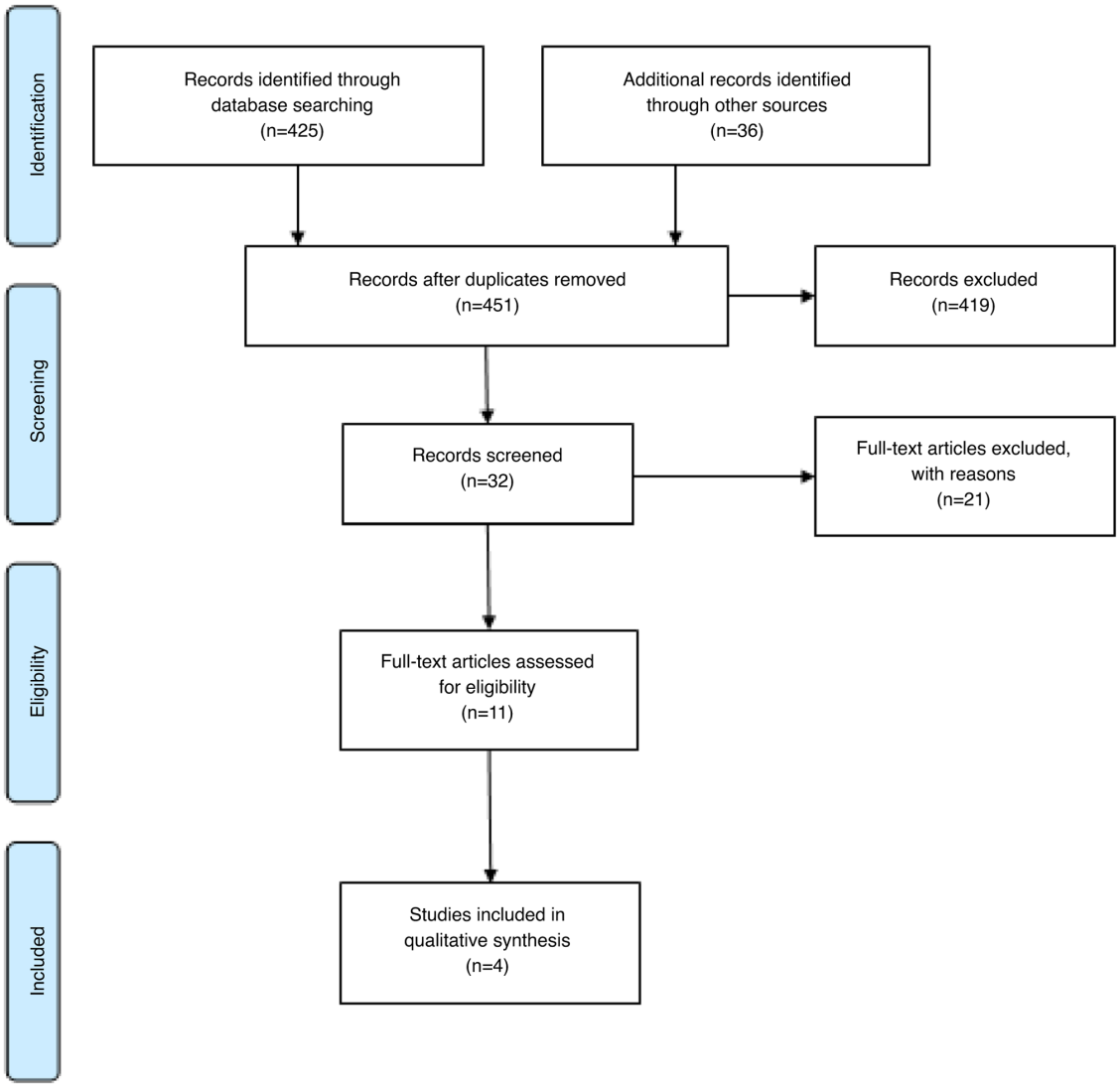

Figure 2. Results of each stage of the literature review and article selection process. Representation of the results of each stage of the literature review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (24).

evaluated CV_G, while the study by Colomo *et al* (28) did not present either CV_I or CV_G, instead solely calculating the coefficient of variation for capillary blood glucose between fasting and post-meal collections.

The difference in study protocols can be justified by the fact that three of the analyzed articles predate the initiative to harmonize the generation and reporting of BV data with the publication of BIVAC (7,13,25-27), which brings weaknesses and uncertainties in the results found. However, even the subsequent article did not use the BIVAC protocol, demonstrating the need for reliable studies to estimate the BV of capillary blood glucose measured by glucometers (28). Moreover, BIVAC allows for the critically evaluation and classification of BV studies concerning study design, pre-analytical handling, analytical methods and statistical analysis (24). The data from applying BIVAC indicate that studies either omitted or did not address essential details related to BIVAC quality indicators. Currently, BIVAC allows for a retrospective assessment of published studies and serves as a guide for future studies.

The evaluated studies found that Mu *et al* (26) did not meet BIVAC QI 7, which refers to the steady state of the sample. The research evaluated the results both with and without the use of insulin. Both Mu *et al* (26) and Colomo *et al* (28) did not meet QI 6, which requires estimating the analytical variation of the method for estimating BV.

Allsop *et al* (27) and Colomo *et al* (28) did not meet QI 14 regarding the presentation of the concentration of the measurand among participants. Corroborating the theory of systematic reviews described by Gurevitch *et al* (32), the review results allowed the identification of future research priorities that would otherwise not have been noticed. For example, the reviewed studies were conducted primarily in Europe and Asia, suggesting the need to conduct them in other regions to consider each continent's eating habits and lifestyle.

Lastly, considering that the present review did not limit the publication period of the studies, it is understood that these are the current state-of-the-art findings. The reported capillary glycemia BV results were intended to answer the specific questions of their respective studies but cannot be used as a reference for BV and CV_I or CV_G for calculating analytical quality specifications, II or RCV. The present systematic review revealed a lack of specific studies that adhere to standardized criteria to assess the BV of intra-individual and interindividual capillary blood glucose levels as measured by glucometers. Consequently, as reported in the current literature, the existing data on BV cannot be considered reliable for establishing analytical quality specifications, II and reference change values for capillary blood glucose measurement using glucometers. Nevertheless, these findings have significant implications for managing patients who monitor their capillary blood glucose levels, as they can contribute to more effective treatment strategies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

Data collection and writing was carried out by KDZ. KDZ and FM were involved in the analysis of data and confirm the authenticity of all the raw data. Supervision and reviewing was carried out by FM. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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