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Research

Systematic review of the biological variation data for diabetes related analytes

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ABSTRACT

Background: Objective interpretation of laboratory test results used to diagnose and monitor diabetes mellitus in part requires the application of biological variation data (BVD). The quality of published BVD has been questioned. The aim of this study was to quality assess publications reporting BVD for diabetes-related analytes using the Biological Variation Data Critical Appraisal Checklist (BIVAC); to assess whether published BVD are fit for purpose and whether the study design and population attributes influence BVD estimates and to undertake a meta-analysis of the BVD from BIVAC-assessed publications.

Methods: Publications reporting data for glucose, HbA_{1c}, adiponectin, C-peptide, fructosamine, insulin like growth factor 1 (IGF-1), insulin like growth factor binding protein 3 (IGFBP-3), insulin, lactate and pyruvate were identified using a systematic literature search. These publications were assessed using the BIVAC, receiving grades A, B, C or D, where A is of highest quality. A meta-analysis of the BVD from the assessed studies utilised weightings based upon BIVAC grades and the width of the data confidence intervals to generate global BVD estimates.

Results: BIVAC assessment of 47 publications delivered 1 A, 3 B, 39C and 4 D gradings. Publications relating to adiponectin, C-peptide, IGF-1, IGFBP-3, lactate and pyruvate were all assessed as grade C. Meta-analysis enabled global BV estimates for all analytes except pyruvate, lactate and fructosamine.

Conclusions: This study delivers updated and evidence-based BV estimates for diabetes-related analytes. There remains a need for delivery of new high-quality BV studies for several clinically important analytes.

Abbreviations: DM, diabetes mellitus; HbA1c, glycated haemoglobin; IGF-1, insulin like growth factor 1; IGFBP-3, insulin like growth factor binding protein 3; BV, biological variation; CVG, between-subject biological variation; CVI, within-subject biological variation; APS, analytical performance specifications; SEQCML, Spanish Society of Laboratory Medicine; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; CLSI, Clinical Laboratory Standards Institute; EFLM, European Federation of Clinical Chemistry and Laboratory Medicine; TFG, Task and Finish Group; WGBV, Working Group Biological Variation; BIVAC, Biological Variation Data Critical Appraisal Checklist; QI, quality item; CVA, analytical coefficient of variation; CV, coefficient of variation

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1. Introduction

Diabetes mellitus (DM) is a major public health problem affecting > 300 million people worldwide, with a projected global prevalence predicted to double by 2030. The risk of vascular complications of DM is associated with hyperglycaemia and raised glycated haemoglobin (HbA_{1c}) levels [1]. Effective early diagnosis and management strategies are vital to prevent and reduce diabetes-related complications. Other biochemical markers such as adiponectin, C-peptide, fructosamine, insulin like growth factor 1(IGF-1), insulin like growth factor binding protein 3 (IGFBP-3), insulin, pyruvate and lactate also play a role in diagnosing and monitoring DM [2,3].

Random Biological Variation (BV) can be defined as the inherent variation of a measurand around a homeostatic set point. The variation among the homeostatic set points of individuals determines defines the between-subject biological variation (CV_G). The variation within each individual around their homeostatic set point denotes the within-subject biological variation (CV_I) [4]. Biological variation data describing the magnitude of biological variation have many applications; those include the definition of reference change value to enable assessment of the significance of changes in serial results within an individual and the assessment of the utility of population-based reference intervals through the application of the index of individuality [5,6]. Both of these applications are important in the context clinical result interpretation. In addition, they can be used to set analytical performance specifications (APS) [7]. This application impacts on decision making around the suitability of assays for clinical laboratory use; originally proposed in the 1999 Stockholm Consensus Conference [8] and further identified the application of BV as one of three models to set APS in the 2014 Milan Strategic Conference [9]. This delivers a demand for high quality and well characterised BV.

There is a significant volume of published work describing BV for different analytes [10,11]. The online BV database [12], compiled by the Analytical Quality Commission of the Spanish Society of Laboratory Medicine ($SEQC^{ML}$) has provided an important collated source of BV data that has been widely used. Since its presentation at the Stockholm Conference in 1999 [13], the database has been updated every two years, the last review taking place in 2014 [12]. Recently, some concerns have been raised about the veracity and utility of the data available even the variation in methodological approaches to delivery of the datasets [14,15], and the fact that some data may no longer fit for purpose having been derived using analytical methods now considered obsolete [16].This is problematic as the need for reliable BV data is becoming increasingly recognized as its various important applications become more widely adopted. IVD companies make extensive use of APS derived from BV data to evaluate their products [17]; the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Working Group on Allowable Error for Traceable Results has identified BV data as required reference data [18]; the Clinical Laboratory Standards Institute (CLSI) propose the use of BV data for setting acceptance criteria for patients' results obtained from multiple instruments within a single organization [19]. These important applications of BV deliver a clear need for BV data of known and appropriate quality. This was highlighted at the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) 1st Strategic Conference in Milan which led to an expert Task and Finish Group (TFG) being established to perform a review of the quality of existing data with a further aim to make available a new online BV database to make available quality assessed estimates of BV [20].

To enable their work the TFG in collaboration with the EFLM Working Group on Biological Variation (WGBV) developed the Biological Variation Critical Appraisal Checklist (BIVAC) [21–23] for biological variation studies and a meta-analysis tool to enable derivation global estimates of BV from studies of acceptable quality as assessed against the BIVAC. This has led to a number of collaborative studies targeting groups of analytes of clinical importance.

The study presented here aimed to 1) critically assess existing publications reporting BV for analytes used in the diagnosis, management and study of DM: glucose, HbA_{1c}, adiponectin, C-peptide, fructosamine, IGF-1, IGFBP-3, insulin, lactate and pyruvate, 2) assess whether aspects of the study population and study design influence the BV estimates and 3) to use results from BIVAC-compliant studies to deliver global BV estimates for diabetes related analytes by meta-analysis for inclusion in the BV database.

2. Material and methods

2.1. Bibliographic search

Publications cited in the 2014 BV database for the analytes of interest were identified for grading. Further studies were identified from review of the references included in the cited publications. Thereafter, a systematic literature search was performed using an approach previously described [23]. Publications identified in the online 2014 BV database [12] are identified in this study by the article number assigned in that database.

2.2. Analysis of data

Each of the identified studies were assessed and graded against using 14 quality items (QI) forming the BIVAC checklist, with alternative scores A, B, C and/or D to verify whether the essential elements required to deliver a valid study of BV were present and documented [23]. Attainment of a grade A indicates compliance with all the checklist QIs and D indicates non-compliance. The overall grade of the study corresponds to the lowest score for any QI; if a study scores an A for all QIs then it receives an overall grade of A, if however, there is a single B score for any of the QIs then the study receives an overall B grade. An additional 30 descriptive items were registered for each publication, describing the analytical method (principle, instrument, reagents), number of subjects studied, state of well-being, number of samples per subject, sampling time, sampling interval, study duration, CV_I and CV_G with confident intervals (CIs), estimates of analytical variation (CV_A), concentration value and measurement unit. When estimates from different populations or sampling intervals were included for the same measurand, BIVAC assessment and data extraction were performed for each subgroup as appropriate according to the following criteria:

- age and gender group,
- health status/state of well-being,
- sampling interval,
- duration of study,
- analytical method.

Two different assessors independently scored each publication. If assessors disagreed, a third assessor reviewed the publication, followed by discussion with the initial assessors or a larger panel to achieve a consensus.

95% CIs for BV estimates were calculated as described by Burdick [24] if the required information on the mean number of subjects and samples and CV_A were provided. Lack of overlap of the 95% CI of the individual subgroup estimates was used to indicate significant differences between subgroups. Meta-analysis was performed using the weighted mean as previously described [25] to provide global estimates of CV_I and CV_G with measures of uncertainty. Only studies considered BIVAC-compliant (overall grade A, B or C), performed in healthy adults (between 18 and 75 years), with sampling intervals from once per week

to once per month, with ≥3 samples per subject, samples tested in duplicate and where 95% CI were presented (or could be calculated, were included in the meta-analysis) to deliver BV point estimates. For the meta-analysis the BIVAC grades were arbitrarily given weights A = 4, B = 3 and C = 1. Percentile bootstrap with the weighted median performed on each of the resampled data sets were used for calculating the CI [25].

3. Results

The literature review identified 47 individual articles (Supplemental Table 1) in total delivering 69 BV estimates for the 10 analytes. The number of publications available for the different analytes was variable: only one paper reported BV estimates for pyruvate, while 23 papers reported for glucose (Table 1). Based on these publications, 119 data subsets were identified for the different subgroups (age, gender, health status and sampling intervals).

A single publication delivered two of the 69 datasets classified as coming from a grade A paper (Table 1). Three publications were classified as grade B as a consequence of issues related to analysis of outliers and the normality of distribution. The majority of publications were graded as C due to lack of variance homogeneity testing, or failure to report the required detail to enable calculation of CI around CV_I estimates (Table 1). Four HbA_{1c} publications scored a D as the measurement included other haemoglobins. BIVAC scoring was consistent among assessors and few discrepancies needed to be resolved by a third assessor.

BV estimates for the same analytes for multiple subgroups within a single publication were usually assigned the same grade. The one exception to this was paper 27; the subgroup where weekly sampling was performed scored A for QI 2, whereas the subgroup where sampling was daily received a C score (the age of included subjects was not described in the latter group). Estimates of CV_I with 95% CI for the analytes studied are presented in Figs. 1–4 and Supplemental Figs. 1–10.

Studies of glucose in serum/plasma, reported variable estimates of CV_I. The highest estimates were reported in patients with DM (Fig. 1). A smaller number of publications reported CV_G estimates (9 papers) (Fig. 2). Published studies for glucose varied in terms of duration and sampling intervals, with estimates being based on daily (n = 3), weekly (n = 8) and monthly samplings (n = 1); one paper reporting within-day BV estimates (Supplemental Fig. 1).

Twenty-one out of the 32 studies delivering BV for HbA_{1c} were performed on healthy adults. They delivered CV_I estimates ranging from 0.7% to 2.3%. CV_I estimates obtained from DM subjects (n = 10) were generally higher, ranging from 1% to 9% (Fig. 3). On visual inspection of the compiled data, CV_I estimates derived from healthy individuals reported in publications graded as A, B and C were similar. If stratified according to the units used to report the results (Fig. 4), global CV_I estimates for non-IFCC units (%), achieved by meta-analysis of studies in healthy adult individuals with weekly or monthly samplings, were significantly lower than the overall estimates available in the online 2014 BV database (Table 2) [12].

Seven publications were identified for insulin and fructosamine, describing a range of study formats and populations (Table 1, Supplemental Figs. 3 and 10, respectively). C-peptide, lactate, pyruvate, IGF-1, IGFBP-3 and adiponectin data were available from < 5 publications (Table 1, Supplemental Figs. 4–9).

For pyruvate, lactate, adiponectin and fructosamine only one study each fulfilled the criteria to be included in meta-analysis (Table 2).

4. Discussion

Early diagnosis and appropriate management strategies of DM that incorporate laboratory testing are vital to prevent and reduce diabetic complications. Availability and applications of robust BV estimates will aide delivery of tests and test interpretation to enable the required optimal diagnosis and monitoring of DM. The veracity of the available BV data does however appear to be an issue. Quality of reported BV estimates are for example compromised by variations in study design and the methods applied to. Application of the BIVAC to the many studies of glucose and HbA1c, identifies only a small number with the highest quality and scored as A or B (Table 1). For the other analytes reviewed smaller numbers of publications were identified for application of the BIVAC; all of those were scored and received a grade C. The most frequent cause for BIVAC C score is related to the QIs applying to outlier analysis and testing for variance homogeneity [22].

To enable valid global estimates of BV from meta-analysis, it is essential that data from studies included have been adequately described and performed in similar populations and settings; that the applied analytical method are comparable to contemporary methods and that the statistical approach is appropriate. Here, only studies from healthy adults with sampling intervals from once per week to once per month, with ≥3 samples per subject tested in duplicate and BV presented with 95% CI (or calculable from data provided) have been included in the meta-analysis to provide global BV estimates. When few estimates are included in the meta-analysis (small n) the percentile bootstrap will be equal to the range of estimates. When using BV data for the many different applications such as setting APS; different approaches may be chosen, e.g. depending on whether the most stringent APSs are warranted. However, it is essential that the BV data used to set APS have been obtained using an optimal study design. In the following, a detailed review of BV data published for the different DM- related analytes is provided.

4.1. Glucose

Our literature review identified 23 publications reporting glucose biological variation collectively delivering 46 different estimates of BV. Only 11 of these estimates were considered as having been derived from BIVAC-compliant studies performed in relevant study populations and therefore suitable for inclusion in the meta-analysis (Fig. 1, Table 2). Main causes for exclusion were that data were derived from non-healthy or elderly subjects and sampling intervals were other than required.

A comparison of the global BV estimates obtained from meta-analysis and those listed in the online 2014 BV database [12] shows that the new point estimate for glucose BVD are quite similar CV_I: 5.6% vs. 4.8% and CV_G: 7.5% vs. 7.9%. The small differences might be explained by the facts that 1) a completely new method has been applied to

Table 1
Number of papers (N) in the different groups after categorization for diabetes-related analytes by review of the Biological Variation Data Critical Appraisal Checklist (BIVAC).

Analytes	BIVAC grade				N	n[a]
	A	B	C	D		
Glucose, serum & plasma (mmol/L)	2	1	20	0	23	46
HbA_{1c}, whole blood (mmol/mol)	1	2	10	4	17	32
C-peptide, serum & plasma (nmol/L)	0	0	4	0	4	4
Insulin, serum & plasma (mIU/L)	0	0	7	0	7	13
Lactate, whole blood & plasma (mmol/L)	0	0	3	0	3	7
Pyruvate, whole blood (nmol/L)	0	0	1	0	1	1
IGF-1, serum (μg/L)	0	0	3	0	3	3
IGFBP-3, serum (μg/mL)	0	0	2	0	2	2
Adiponectin, serum & plasma(μg/mL)	0	0	2	0	2	3
Fructosamine, serum & plasma (mmol/L)	0	0	7	0	7	9

[a] Number of biological variation estimates for included subgroups. As an example: for glucose; paper 27 has two subgroups with different sampling intervals (daily and weekly) and paper 165 has 7 stratified by subject age and sex (18–35 years men, 18–35 years women,35–55 years men, 35-55 years women, > 65 men, > 65 years women, all together).

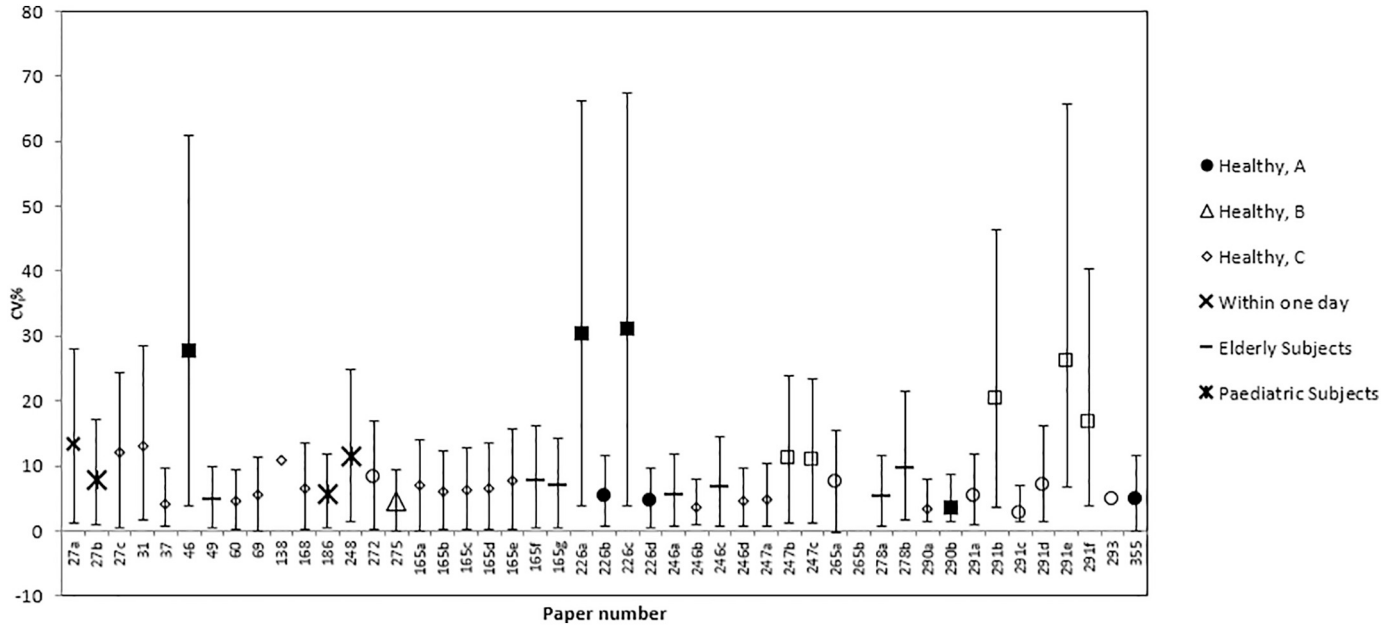

Fig. 1. Estimates of within-subject biological variation with 95% CI for glucose.
The points depicted are derived from 1) healthy adults from BIVAC A, B and C publications, 2) elderly and paediatric subjects, 3) non-healthy and 4) non-classifiable, due to lack of information on subjects' age, or to the insufficient number of samples included per subject (< 2). Publications (X axis) are identified according to the article numbers given in the online 2014 BV database and letters indicate subset of data derived from the same publication.

critically assess the studies identifying valid and appropriately weighted component data for delivery of the point estimates, 2) more studies have been included in the present review than in the online 2014 BV database. As illustrated in Fig. 1, studies of patients with DM demonstrated higher CV_I values than those observed in studies of healthy subjects. Within-one day studies and oral glucose tolerance test studies also demonstrated higher CV_I values than studies performed in healthy subjects with weekly/monthly sampling intervals. Except for within-day studies, there appears to be little influence of the duration of the study or sampling interval upon CV_I estimates observed in healthy adults (Supplemental Fig. 1). Oral glucose testing represents an activation of a complex dynamic physiological response system to the glucose load and it is therefore to be expected that the CV_I is higher in this setting.

Based on the studies included in our review, the age of subjects seems not to be relevant to the CV_I estimate for glucose; visual

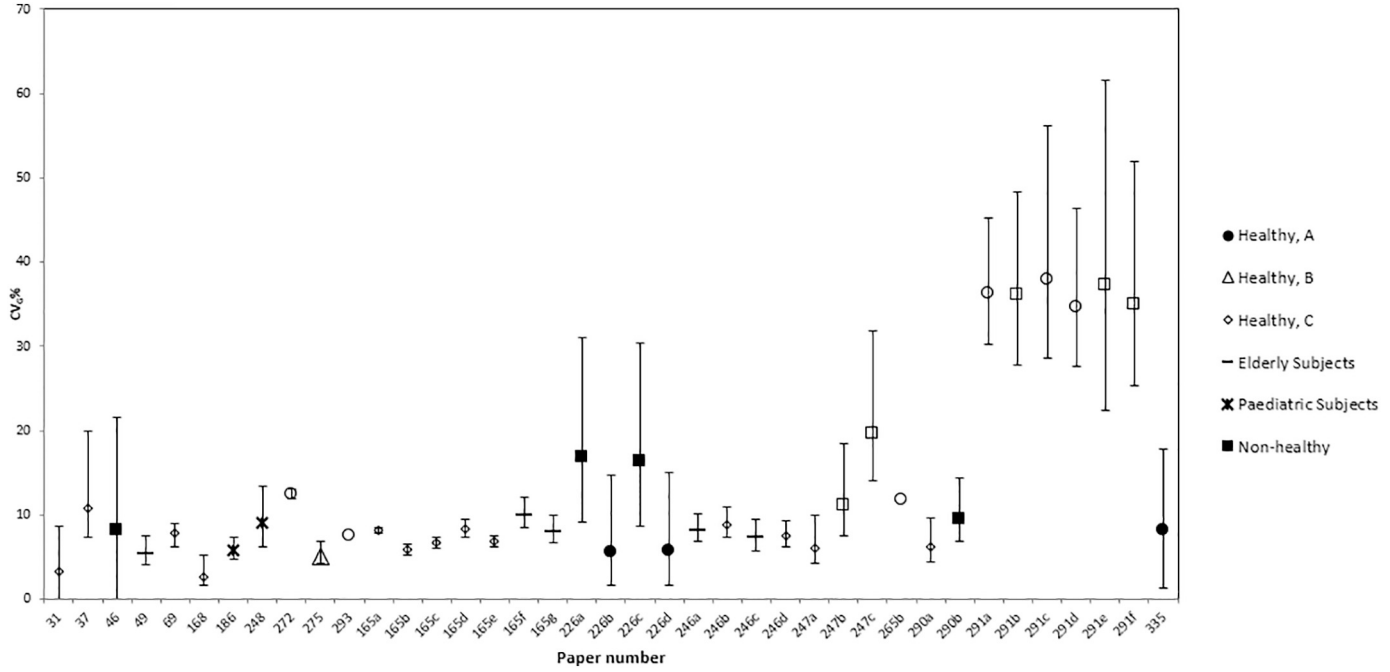

Fig. 2. Estimates of between-subject biological variation with 95% CI for glucose.
The points depicted are derived from 1) healthy adults from BIVAC A, B and C publications, 2) elderly and paediatric subjects, 3) non-healthy and 4) non-classifiable, due to lack of information on subjects' age, or to the insufficient number of samples included per subject (< 2). Publications (X axis) are identified according to the article numbers given in the online 2014 BV database and letters indicate subset of data derived from the same publication.

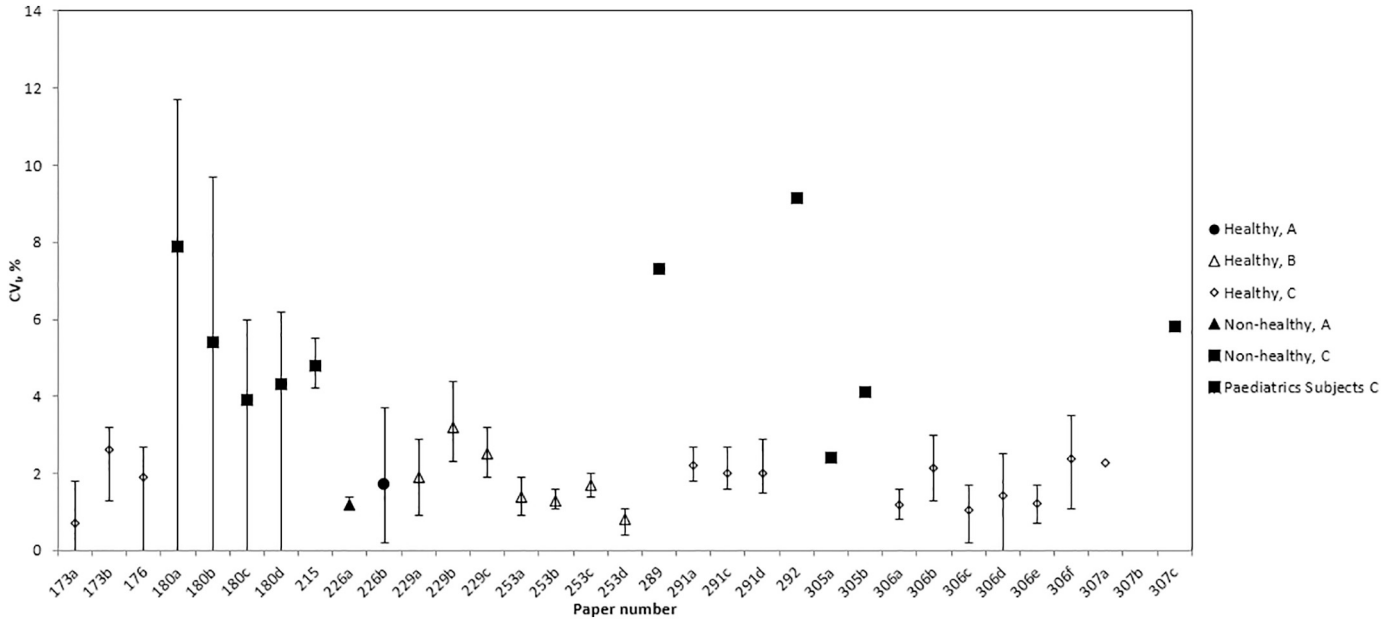

Fig. 3. Estimates of within-subject biological variation with 95% CI for HbA_{1c}.
The points depicted are derived from 1) healthy adults from BIVAC A, B and C publications, 2) elderly and paediatric subjects, 3) non-healthy. Publications (X axis) are identified according to the article numbers given in the online 2014 BV database and letters indicate subset of data derived from the same publication.

inspection of the data did not identify overt differences between CV_I estimates for glucose in children (3 papers, ages from 4 to 18 years old) or in elderly subjects (4 papers, > 75 years) when compared to that obtained in healthy general population (11 papers) (Fig. 1).

4.2. HbA_{1C}

Seventeen publications on HbA1c were identified, delivering 32 BV estimates, out of which only 16 fulfilled the criteria to be included in the meta-analysis. CV_I results, stratified according to the reported units: IFCC (mmol/mol) vs non-IFCC (%), appear slightly lower than those of the online 2014 BV database (Table 2).

As with glucose measurements, patients with DM showed slightly higher CV_I than healthy subjects, this has been seen in previous studies [26]. However, in the only A graded study that included both healthy individuals and stable DM patients, CV_I estimates were comparable (paper 226-Carlsen, see Supplemental Table 1).

The meta-analysis of BV studies stratified in terms of IFCC vs non-

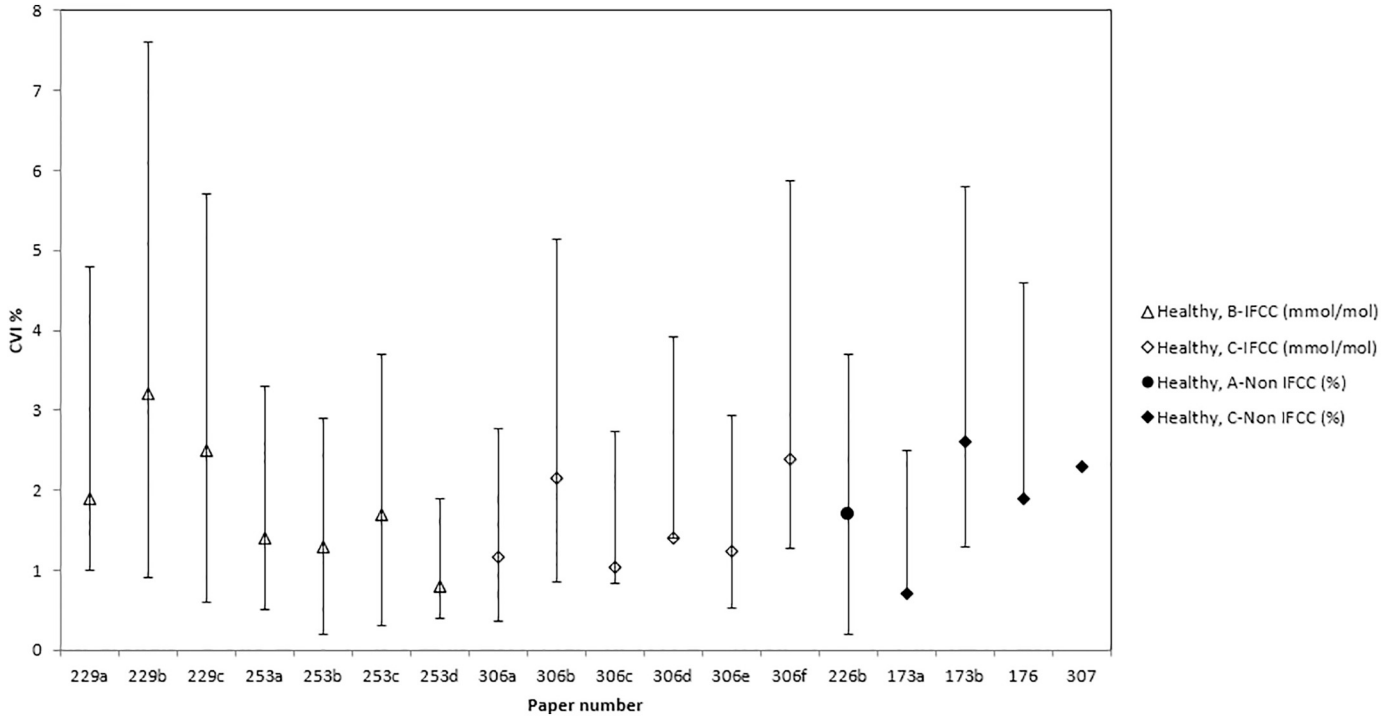

Fig. 4. CV_I for healthy adults obtained from studies according to the reported units: IFCC (mmol/mol) vs non-IFCC (%).
The points depicted are derived from 1) healthy adults from BIVAC A, B and C publications. Publications (X axis) are identified according to the article numbers given in the online 2014 BV database and letters indicate subset of data derived from the same publication.

Table 2
Global biological variation point estimates with 95% CI derived from Biological Variation Data Critical Assessment Checklist compliant studies performed in healthy adults and fulfilling the meta-analysis criteria, compared with estimates from the online 2014 BV database.

Analytes	Meta-analysis			Online 2014 BV database	
	n	CV_I	CV_G	CV_I	CV_G
Glucose	12	4.8 (4.7–6.8)	7.9 (5.5–8.1)	5.6	7.5
HbA_{1c}	3	1.3 (1.2–2.5)[a]	6.7 (5.6–7.5)[a]	1.9	5.7
	4	1.3 (1.2–2.1)[b]	5.0 (3.2–6.8)[b]		
C-peptide	3	19.5 (9.3–24.0)	20.8 (13.3–33.1)	16.6	23.2
Insulin	5	19.1 (15.2–37.1)	22.6 (4.3–45.4)	21.1	58.3
Lactate	1	31.0	29.0	27.2	16.7
Pyruvate	1	15.2	13.0	15.2	13
IGF-1	2	17.5 (9.4–19.8)	26.2 (26.1–27)	14.6	45.4
IGFBP-3	2	10.1	15	10.1	63.9
Adiponectin	1	1.4[c]	4.3[c]	18.8	51.2
	1	18.8[d]	51.2[d]		
Fructosamine	1	2.3	6.3	3.4	5.9

Note: CI is based on the percentile bootstrap. For $n < 5$ the observed range is used.
n: number of biological variation estimates included in the meta-analysis.
[a] Results reported in IFCC units (mmol/mol).
[b] Results reported in non IFCC units (%).
[c] TF-IFMA time resolved fluorescence method.
[d] RIA (radio immunoassay); concentration mean = 6 μg/mL.

IFCC units separately delivered similar estimates (Table 2). This observation is surprising since the two methods measure different analytes [27]. Papers reporting HbA1c in mmol/mol of haemoglobin should be expected to report higher coefficients of variation (CVs) compared to studies reporting HbA1c in %, as has been described by Weykamp et al. [28]. It should be noted that only a limited number of studies were included in our meta-analysis (Fig. 4), and there are a number of other factors related to study design and statistical handling that may have influenced these observations.

The literature review did not identify studies including HbA1c BV for healthy children or healthy elderly. The effect of age upon the estimates of BV components for HbA_{1c} requires further study.

As observed for glucose, study duration and sampling frequency did not seem to influence the CV_I values for HbA_{1c} in healthy adults (Supplemental Fig. 2). (CV_I values do not increase with time sampling interval nor study duration). However, this observation is not in agreement with a previous study from Braga et al. [24], indicating the need for further evaluation of the evidence or delivery of confirmatory data.

4.3. C peptide and insulin

BV estimates for CV_I and CV_G obtained in this study for C peptide are in agreement with estimates in the online 2014 BV database.

A high degree of variability in reported values for CV_I for insulin (Supplemental Fig. 3). The reason for this may be multi-factorial delivering a complex interplay of factors such as study duration and state of health.

4.4. Lactate and pyruvate

The lactate BV estimate were found to be lower than that in the online 2014 BV database [12] (Table 2). Only one of the two studies in healthy subjects included in the 2014 BV database fulfilled the stringent criteria to be met for inclusion in the meta-analysis (Supplemental Fig. 5). Only one publication, graded as a C, was identified for pyruvate (Supplemental Fig. 6). Clearly users of data from single studies that have some quality issues, need to assess the risk associated with their clinical application.

4.5. IGF-1 and IGFBP-3

BV estimates in healthy adults for IGF-1 and IGFBP-3, were reported in 3 and 2 papers respectively, (Supplemental Figs. 7 and 8). The CV_I estimates reported in paper 287 (Belobrajdic, see Supplemental Table 1) were very low (0.1% and 0.003% for both analytes, respectively) and were thus excluded from the meta-analysis.

4.6. Adiponectin and fructosamine

Two papers addressed adiponectin in healthy subjects, one in plasma (paper 199-Shand, $CV_I = 1.4\%$) and the second in serum (paper 287-Belobrajdic, $CV_I = 18.8\%$, see Supplemental Table 1). The highly discrepant CV_I (and CV_G) estimates observed for adiponectin are difficult to explain given the similarities of the experimental protocols (similar number of subjects, sampling intervals, study duration and concentration of the analyte); the reason for differences might be due to the performance characteristics of the two analytical methods used (TR-IFMA and RIA, mean: 9.7 and 6.3 μg/mL; CV_I:1.4% (CI:0–4) and 18.8% (CI:15–26) respectively), and a failure to apply outliers detection and homogeneity of variances analysis as part of the data analysis (Supplemental Fig. 9).

One report of fructosamine BV in healthy adults (Table 2) delivered similar CV_I estimates to those found in two studies in the elderly (> 75 years) delivered.

As with the other analytes included in this review, DM appears to impact on BV of fructosamine: two papers studying diabetic adults reported higher CV_I, than in the healthy (Supplemental Fig. 10), though the set of data for comparison is limited.

5. Conclusions

This study provides updated and evidence-based estimates of CV_I and CV_G values for DM-related analytes. Many studies have been published addressing BV of glucose and HbA_{1c}, but few attained the highest BIVAC A or B grade. A systematic literature search and application of the BIVAC to the papers relating to other DM-related analytes identified only a limited number of publications, all of which received a C grade. This indicates that there is a quality deficit in the BV data available for adiponectin, C-peptide, IGF-1, IGFBP-3, lactate and pyruvate that sets a requirement for delivery of new higher quality BV studies. In our study, we have applied a meta-analysis approach of the collated data sets to enable delivery of global estimates of BV with CI. This systematic review and quality assessment of published data will deliver BV data sets to be made available on the EFLM BV website with metadata that enable to be objectively assessed by users prior to clinical application.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2018.10.031.

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