Wilson, M, Al-Hamid, A, Abbas, I, Birkett, JW, Khan, I, Harper, M, Al-Jumeily, D and Assi, S

Identification of diagnostic biomarkers used in the diagnosis of cardiovascular diseases and diabetes mellitus: A systematic review of quantitative studies

Received: 17 January 2024 | Revised: 15 March 2024 | Accepted: 25 March 2024

DOI: 10.1111/dom.15593

REVIEW ARTICLE

WILEY

Identification of diagnostic biomarkers used in the diagnosis of cardiovascular diseases and diabetes mellitus: A systematic review of quantitative studies

Megan Wilson BSc[1] | Abdullah Al-Hamid PhD[2] | Ismail Abbas PhD[3] | Jason Birkett PhD[1] | Iftikhar Khan PhD[1] | Matthew Harper PhD[4] | Dhiya Al-Jumeily OBE PhD[4] | Sulaf Assi PhD[1]

[1]Faculty of Science, School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK

[2]Pharmacy Practice, College of Clinical Pharmacy, King Faisal University, AlAhsa, Saudi Arabia

[3]Faculty of Science, Lebanese University, Beirut

[4]Faculty of Engineering and Technology, School of Computer Science and Mathematics, Liverpool John Moores University, Liverpool, UK

Correspondence
Megan Wilson, Faculty of Science, School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, L3 5AH, UK.
Email: m.wilson3@2019.ljmu.ac.uk

Abstract

Aims: To perform a systematic review of studies that sought to identify diagnostic biomarkers for the diagnosis of cardiovascular diseases (CVDs) and diabetes mellitus (DM), which could be used in low- and middle-income countries (LMICs) where there is a lack of diagnostic equipment, treatments and training.

Materials and Methods: Papers were sourced from six databases: the British Nursing Index, Google Scholar, PubMed, Sage, Science Direct and Scopus. Articles published between January 2002 and January 2023 were systematically reviewed by three reviewers and appropriate search terms and inclusion/exclusion criteria were applied.

Results: A total of 18 studies were yielded, as well as 234 diagnostic biomarkers (74 for CVD and 160 for DM). Primary biomarkers for the diagnosis of CVDs included growth differentiation factor 15 and neurogenic locus notch homologue protein 1 (Notch1). For the diagnosis of DM, alpha-2-macroglobulin, C-peptides, isoleucine, glucose, tyrosine, linoleic acid and valine were frequently reported across the included studies. Advanced analytical techniques, such as liquid chromatography mass spectrometry, enzyme-linked immunosorbent assays and vibrational spectroscopy, were also repeatedly reported in the included studies and were utilized in combination with traditional and alternative matrices such as fingernails, hair and saliva.

Conclusions: While advanced analytical techniques are expensive, laboratories in LMICs should carry out a cost–benefit analysis of their use. Alternatively, laboratories may want to explore emerging techniques such as infrared, Fourier transform-infrared and near-infrared spectroscopy, which allow sensitive noninvasive analysis.

KEYWORDS
diabetes complications, heart failure, meta-analysis, type 2 diabetes, type 1 diabetes, cardiovascular disease

1 | INTRODUCTION

The ever-growing prevalence of cardiovascular diseases (CVDs) and diabetes mellitus (DM) is made apparent by the World Health's Organization, which states that 17.9 million and 1.5 million lives are lost annually to CVDs and DM, respectively.[1,2] In fact, 80% of people with CVDs/DM are from low- and middle-income countries (LMICs) including Bangladesh, India and some African nations.[3-5] The prevalence of the aforementioned diseases can be attributed to epidemiological transitions and rapid urbanization, which have caused negative changes to the public's diet and lifestyle behaviours.[6] Consequently, the CVD and DM epidemic has created a significant burden on already strained healthcare systems in LMICs. This results in a limited number of resources, treatments and therapies for CVD and/or DM management. Therefore, many patients are likely to develop additional life-threatening complications such as diabetic nephropathy, heart failure and myocardial infarction.[7-11]

The limited funding and resources available in LMICs provides an explanation for the misuse of advanced analytical techniques, such as electrocardiogram (ECG). For the diagnosis of CVDs, ECG interpretation requires advanced user knowledge, a lack of which can create misdiagnosis, mistreatment and further complications. The lack of sufficient equipment also explains the misdiagnosis of DM through the electrochemical method, which was identified in a previous systematic review.[12] While the electrochemical method of glycated haemoglobin (HbA1c) and fasting plasma glucose measurement is deemed the 'gold standard' for DM diagnosis, it is frequently unfeasible for LMICs, where there is a lack of adequate equipment and facilities.[3-5] Hence, it is imperative that cheaper diagnostic approaches are explored. Through the identification of such methods, the number of diagnostic errors is likely to be reduced and disease management/treatment greatly improved. Therefore, the aim of this systematic review was to identify a range of diagnostic techniques and CVD and DM biomarkers.

2 | MATERIALS AND METHODS

2.1 | Study design

A systematic literature search was conducted to identify diagnostic biomarkers and techniques used for the diagnosis of CVDs and DM. The study was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Data S1).[13]

2.2 | Search strategy

For study collection, six databases were selected: the British Nursing Index, Google Scholar, PubMed, Sage, Science Direct and Scopus. The results were filtered to include articles published between January 2002 and January 2023. A set of search terms was applied to all databases, which included key words such as 'analysis', 'biomarkers', 'cardiovascular disease', 'detection', 'diabetes mellitus', 'identification', 'detection' and 'metabolites'. Article titles were first evaluated by two reviewers (M.W. and S.A.) in terms of relevance and, if deemed eligible, underwent full review by a third reviewer (I.A.). The systematic review protocol was registered at PROSPERO (CRD42023483319).[14]

2.3 | Selection criteria

Studies that looked at the identification of biomarkers used in the diagnosis of CVDs and DM were included. To ensure that disease diagnosis occurred during the early prognosis stage, participants in the eligible studies were adults (aged 18–65 years old). Reviews, meta-analyses and editorials were excluded. Studies that looked at diagnosis through genes or microbes were excluded as outside the study's scope.

2.4 | Study selection and data extraction

M.W. and S.A. first screened the titles and abstracts of all retrieved papers. One of three options was selected by the reviewers, those being: include, exclude or unsure. In cases where a disagreement was encountered, or a reviewer could not make a conclusive decision, discussion was carried out with all reviewers. The first and third reviewers (M.W. and I.A.) reviewed the full papers and M.W. collated information from accepted studies related to study design, study setting, population age, sample size, biological matrix and biomarkers (Table 1).

2.5 | Assessment of study quality

The quality of the included studies was determined via the Critical Appraisal Skills Programme, which also determined the relevance of included systematic reviews.[15] An additional tool, the Newcastle-Ottawa Scale quality tool, was employed to judge the quality of case–control and cohort studies.[16]

TABLE 1 Information extracted from included papers.

Sections	Subsections
Title	Aim of study
Study characteristics	Experimental settings, sample size, study design, population and instrumentation
Extraction procedure	Cleaning procedures, sample type/size, storage and storage conditions
Experimental conditions	Diagnostic technique used and parameters
Biomarkers	Type of biomarker, concentration and regulation

2.6 | Data analysis

The median and interquartile range (IQR) were calculated using SPSS and Microsoft Excel. Quantitative data were pooled in a statistical meta-analysis where possible. In cases where high heterogeneity was suspected, findings are shown as a narrative summary; hence, figures and tables have been used to improve presentation.

3 | RESULTS

3.1 | Study extraction

A total of 3 640 260 articles were screened through the selected databases, of which 2764 were assessed in the initial reviewing process (Figure 1). Based on the relevance of titles and application of the inclusion/exclusion criteria, 2574 papers were excluded. The abstracts of the remaining 190 studies were reviewed and 37 excluded. After full-text review, 18 studies were deemed eligible and underwent quality reassurance through quality tools. Each study received a star rating of one to three, three being the highest and one the lowest. Studies with three stars were eligible and included within the review. If a study scored two stars, it was included but reviewed with caution, while studies that scored one or no stars were not eligible for inclusion. After the application of quality assessment tools, 17 studies received a three-star rating[17-27,29-34] and one study a two-star rating.[28] Thus, a total of 18 studies were accepted and included in the review.

3.2 | Study characteristics

The characteristics of the included studies are shown in Appendix 2.1. Articles were filtered between 2002 to 2023, with the earliest included article published in 2008. The included studies' sample size ranged from 23 to 7184, with a median range of 117 (IQR 75–640). With regard to study design, 12 studies were case–control studies,[17,18,20,21,23-27,30,31,33] two were cohort studies,[32,34] three were prospective case–control studies[19,28,29] and one was a prospective cohort study.[22] The aforementioned studies used patients recruited from 12 countries, including: Belgium,[18] Brazil,[26] China,[17,20,22,30,34] India,[23,28] Iraq,[19] Mexico,[33] Netherlands,[29] Pakistan,[31] Spain,[32] Sweden,[24,25] Turkey[27] and the United States.[21] The study settings included hospitals ($n = 7$) and laboratories ($n = 11$). When reported,

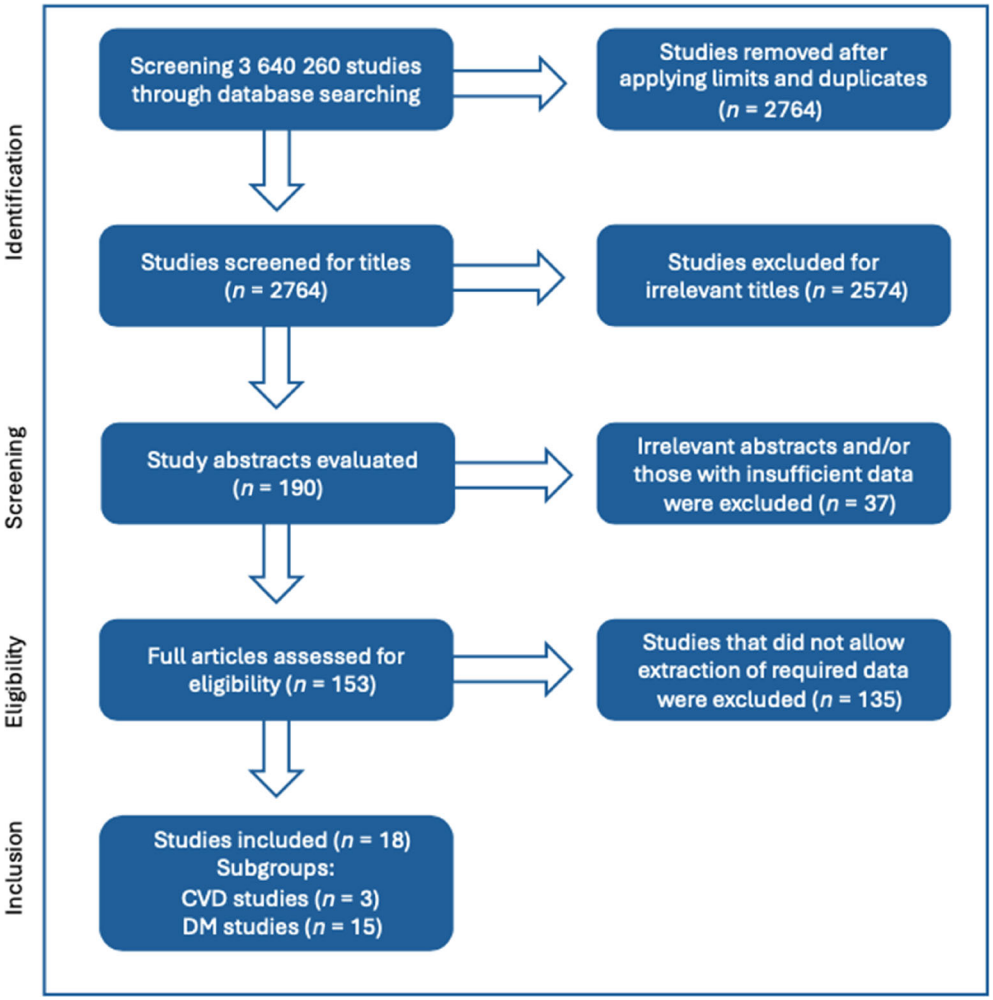

FIGURE 1 Data extraction process and study selection workflow.

TABLE 2 Characteristics of participants in the included studies.

Study number	Age range, years	Male: Female	Population size	Non-disease: disease
1[17]	30–61	67:80 (46:54)	147	53:94 (36:64)
2[18]	28–34	80:79 (51:49)	159	107:52 (67:59)
3[19]	18–34	44:39 (53:47)	83	42:41 (51:49)
4[20]	40–60	84:0 (100:0)	84	42:42 (50:50)
5[21]	30–60	366:274 (57:43)	640	523:117 (82:18)
6[22]	35–63	3289:3895 (46:54)	7184	6737:447 (94:6)
7[23]	30–60	241:188 (56:44)	429	216:213 (50.3:49.7)
8[24]	45–65	1017:1244 (45:55)	2261	1911:350 (85:15)
9[25]	42–58	443:563 (44:56)	1006	503:503 (50:50)
10[26]	18–65	NR	23	2:21 (8:92)
11[27]	30–61	24:38 (39:61)	62	23:39 (37:63)
12[28]	36–62	NR	40	20:20 (50:50)
13[29]	45–65	74:0 (100:0)	86	12:74 (14:86)
14[30]	48–61	81:68 (54:46)	149	48:101 (32:68)
15[31]	20–55	NR	41	20:21 (49:51)
16[32]	24–43	29:46 (39:61)	75	25:50 (33:67)
17[33]	30–50	69:12 (85:15)	81	32:49 (40:60)
18[34]	40–59	NR	767	0:100 (0:100)

the duration of studies was between 2 months and 5 years with a median of 2 years and 6 months (IQR 11 months–3 years and 3 months).

3.3 | Participant characteristics

Details regarding the participants' characteristics, including age, non-disease: disease ratio, male: female ratio and population size, are shown in Table 2. As previously mentioned, the studies included participants aged between 18 and 65 years (median [IQR] 45 [35–53] years). Where reported, the median male: female ratio for participant ages in case–control, cohort and prospective case–control studies were 241:188 (IQR 73.5:404.5–79.5:418.5), 75:29 (IQR 59:9–81.75:51.5) and 59:19.5 (IQR 51.9:9.75–66.5:29.25) years, respectively.

3.4 | Identified biomarkers

Seven biological matrices were used for the diagnosis of CVD and/or DM. These included blood,[17] fingernails,[18,19] hair,[18] plasma,[20-25,29] saliva,[26-28] serum[30,31,33] and urine.[32,34] Plasma and urine were employed in the diagnosis of CVDs, whereas blood, fingernails, hair, plasma, saliva and serum were used for the diagnosis of DM.

In addition, 234 biomarkers (74 CVD and 160 DM biomarkers) were reported for the diagnosis of CVDs and DM (Appendices 2.2 and 2.3). Of the 234 biomarkers, four were used in both CVD and DM participants: alanine, collagen, cystatin-C and leptin.[17,18,21,22,25,26,28-30,33,34] It is worth noting that most of the reported biomarkers were highlighted once across the 18 included studies, and this infrequent identification of the highlighted biomarkers could explain the lack of quantifiable reference and diagnostic ranges.

3.4.1 | CVD biomarkers

A total of 74 CVD biomarkers were identified (Appendix 2.2). Growth differentiation factor 15 (GDF15) was identified in two of the included studies, where it was detected in plasma[22] and urine.[32] In plasma, GDF15 was observed within the range of 1200–1800 pg/mL and was specifically related to the diagnosis of atherosclerosis, atrial fibrillation, coronary artery disease and hypertension.[61,62] Similarly, levels of GDF15 were elevated in urine from the healthy range of 537–931 pg/mL to 1044–2555 pg/mL in CVD patients.[100] GDF15 is a stress-induced transforming growth factor-β superfamily cytokine and has previously been associated with stress and inflammation that causes tissue damage. Elevated levels of GDF15 can provide an indication of disease progression and prognosis and may act as a therapeutic target in future work. Neurogenic locus notch homologue protein 1 (Notch1) was also detected in both plasma[22] and urine.[32] Despite two studies observing Notch1, no quantification of this biomarker occurred.

3.4.2 | DM biomarkers

For the diagnosis of DM, 163 biomarkers were extracted (Appendix 2.3). Several biomarkers, including alpha-2-macroglobulin (A2M), C-peptides, isoleucine, glucose, tyrosine, linoleic acid and

valine, were reported two or more times across the included studies.[19-21,23,25,29,30] Isoleucine was detected in plasma and reported in three studies.[20,21,25] Previously, this biomarker has been observed at elevated levels of 107 ± 32.3 and 143.4 ± 23.6 μmol/L in type 1 (T1DM) and type 2 DM (T2DM) cases, respectively.[123] Similarly, C-peptides offered the advantage of specific diagnostic ranges for T1DM and T2DM and were detected in fingernails ($n = 1$), hair ($n = 1$) and plasma ($n = 1$).[19,21] In fingernails and hair, C-peptides were seen at levels of ~20–45 pg/mg in T1DM cases and ~ 40–145 pg/mg in healthy controls.[19] In plasma, C-peptide levels between 0.3–0.6 nmol/L were deemed as healthy, while downregulated C-peptide levels (<0.03 nmol/L) were specific to T1DM and upregulated levels (>2.0 nmol/L) were characteristic of T2DM.[112,113] C-peptides also offer therapeutic potential for treatment of diabetic complications, particularly in T1DM.[113]

It is important to note the overlap between health reference and diagnostic ranges for biomarkers within the literature. For example, previous work revealed an overlap between healthy (792.19 ± 116.59 μg/mL) and diabetic (845.43 ± 101.10 μg/mL) levels of complement factor B for the diagnosis of T2DM.[31] The overlap between healthy reference and diagnostic ranges may create diagnostic error. Thus, laboratories should look at employing several biomarkers during the diagnosis process to maximize diagnostic potential. Alternatively, laboratories may also choose to employ gold standard biomarkers such as glucose, which offers defined diagnostic ranges and detectability in several biological matrices including blood,[17] plasma[21] and saliva.[28] While blood and saliva provided an indication of DM, glucose detected in plasma was identified at specific levels for T1DM (176.7 ± 82.5 mg/dL) and T2DM (154.1 ± 33.8 mg/dL).[123] The high levels of glucose seen in both T1DM and T2DM are highly specific due to abnormalities seen in insulin production. As a result, glucose is left unmetabolized and builds up in the bloodstream.[18] If left untreated, people with DM are likely to develop hyperglycaemia and further diabetic complications such as diabetic ketoacidosis.

3.5 | Methods of Identification

The techniques employed for the identification of CVD and DM biomarkers varied across the published data. Techniques reported included: ECGs,[29] enzyme-linked immunosorbent assay (ELISA),[21,22,28,32] Fourier-transform infrared spectroscopy (FT-IR),[26] gas chromatography (GC)-flame ionization detector,[23] GC–mass spectrometry (MS),[20,21] infrared (IR) spectroscopy,[27] liquid chromatography (LC)-MS[24,25] LC–tandem MS (LC–MS/MS),[21] nano-LC–MS/MS,[31] near-infrared (NIR) spectroscopy,[17,18] proton magnetic resonance spectroscopy,[29] proton nuclear magnetic resonance spectroscopy,[34] target MS,[32] ultra-high performance liquid chromatography-Q Exactive hybrid quadrupole-orbitrap high-resolution accurate MS,[30] ultrafast GC (e-Nose),[33] (Appendix 2.4).

Five studies used LC–MS methods for the identification of CVD and DM biomarkers in plasma ($n = 3$),[21,24,25] saliva ($n = 1$)[28] and serum ($n = 1$).[31] To validate a metabolic panel for the early diagnosis of T2DM, LC–MS/MS was applied.[21] The application of this technique revealed increased levels of branched-chain amino acids (isoleucine, leucine and valine), tyrosine, mannose and 2-hydroxybutyrate and decreased levels of glycine, lysophosphatidylcholine C18:2 and 1,5-anhydrosorbitol in DM. Untargeted LC–MS was also applied to identify plasma biomarkers.[25] A comparison was made using 187 case–control pairs and identified 46 predictive plasma biomarkers including phosphatidylcholines and 2-hydroxyethanesulphonate.[25]

The use of ELISAs for the detection of CVD and DM biomarkers in plasma ($n = 2$) and urine ($n = 1$) was also reported.[21,22,32] Through the application of a multiplex ELISA, a metabolic panel for the early detection of T2DM was validated.[21] This technique also demonstrated significant differences between concentrations of diagnostic proteins including eosinophil cationic protein, GDF15 and guanine deaminase in cases versus healthy controls.[32] Furthermore, the relationship between biological sex and diagnostic biomarker concentration was identified through a modified ELISA approach.[22] A total of 71 biomarkers were detected, 61 (86%) of which displayed significant differences in male and female participants. From the 61 biomarkers, 37 were higher in females, with leptin, ceruloplasmin and hemopexin showing the largest differences between males and females.[22]

Four studies utilized vibrational spectroscopic techniques including FT-IR ($n = 1$), IR ($n = 1$) and NIR ($n = 2$) spectroscopy for the detection of diagnostic biomarkers in blood ($n = 1$),[17] fingernails ($n = 1$)[18] and saliva ($n = 2$).[26,27] FT-IR spectra suggested that differences between controls and diabetic participants were present in the fingerprint region between 600 and 1300 cm^{-1}. Research also focussed on bands at 1076 cm^{-1} (vibrational mode of skeletal cis conformation of DNA), 1403 cm^{-1} (symmetric CH3 bending modes of protein methyl groups and bending CH_3 of collagen) and 1451 cm^{-1} (asymmetric CH3 bending of protein methyl groups).[26] Scott et al.[27] identified strong bands at 2852 and 2926 cm^{-1}, which originated from symmetric and asymmetric stretching of lipid acyl CH_2 groups, respectively. Furthermore, NIR spectroscopy was applied to fingernails and focused on the region, 4150–6150 cm^{-1} for the detection of DM biomarkers.[18] For example, band 4666 cm^{-1}, attributed to $CONH_2$ stretching band, increased in broadness when glycation increased.[18]

4 | DISCUSSION

The findings of this review suggest the capabilities of a range of diagnostic biomarkers for the diagnosis of CVDs and DM. The studies included in the review frequently reported the detection of GDF15 and Notch1 for the diagnosis of CVDs, and of A2M, C-peptides, isoleucine, linoleic acid, tyrosine and valine for the diagnosis of DM. However, it is worth noting that the lack of a quantified reference range for several of the detected biomarkers suggests that further research within the field of diagnostic biomarker detection and quantification is required. Moreover, this may imply that laboratories are more likely to employ gold standard biomarkers that have set diagnostic ranges such as glucose.

While previous systematic reviews focused on the use of traditional biological matrices (blood, plasma and serum), this review collated a number of biomarkers from traditional and alternative matrices including fingernails, hair and saliva.[18,19,26] The noninvasive nature and simple sampling procedure of alternative matrices are appealing to patients, therefore, are likely to improve compliance rates for diagnostic monitoring and reduce diagnostic errors. Hence, these matrices are highly beneficial for LMICs, where sampling equipment is limited.[3-5] Other reviews focused on a single biological matrix and subsequently limited the number of diagnostic biomarkers identified.[143,144] This review adds to the previous literature and provides important insights for laboratories, healthcare institutions and researchers working with CVDs and DM.

In relation to the concentration of biomarkers, laboratories should consider confounding variables such as biological sex. Previous research made apparent the relationship between biological sex and CVD biomarker concentration.[145] For example, female subjects were found to have a higher concentration of C-reactive protein in comparison to male subjects (2.56 vs. 1.43 mg/L).[146] A previous review also made evident the differences in concentrations of adiponectin and leptin between females and males, with females often showing higher levels.[51] Sex-specific variation can be attributed to differences seen in risk factors and behavioural habits such as high blood pressure, cholesterol, smoking and obesity. This explains why CVDs are often perceived as a 'man's disease' and misdiagnosed in females.[147]

It is worth mentioning that several of the recorded techniques employed in LMICs for the detection of biomarkers are expensive. Nevertheless, their repeated use in both developed and developing countries can be attributed to their high level of accuracy, precision and sensitivity. Therefore, LMICs are likely to invest in expensive techniques to improve diagnostic capabilities/results. Nevertheless, the high costs of techniques mean that the number of laboratories equipped with advanced instrumentation is limited. For example, techniques such as LC–MS/MS may only be offered at private hospitals in the most affluent areas. However, laboratories should carry out cost–benefit analyses and determine the overall benefits of using advanced techniques that offer high levels of accuracy, precision, sensitivity and selectivity for biomarker detection. The employment of such techniques is likely to reduce the number of diagnostic errors and improve patients' treatment/management. In this regard, LC–MS/MS is a highly desirable technique for the diagnosis of CVDs and DM. The addition of tandem MS/MS allows for high sensitivity and the detection of a wide range of biomarkers.[148] LC–MS/MS also offers the advantages of accuracy and specificity, which are key for the prevention of diagnostic errors[148] Likewise, ELISAs are frequently employed for diagnosis based on their ability to sensitively detect a wide range of target analytes.[64] The addition of an ELISA sandwich approach guarantees further sensitivity required for diagnostic biomarker detection. However, in cases of diagnostic biomarkers sharing similar structures, cross-reactivity may occur and cause false-positive or false-negative readouts.[149]

Vibrational spectroscopic techniques such as IR, FT-IR and NIR spectroscopy offer cost-effective, nonintrusive and noninvasive biomarker detection. In comparison to gold standard techniques for CVD and DM diagnosis, which include cardiac catheterization and the electrochemical method, vibrational spectroscopy offers the advantage of working with noninvasive and nonintrusive biological matrices including fingernails and hair. The application of such matrices, reduces sample preparation costs and instrumentation maintenance and improves patient compliance rates. The ability of IR and FT-IR spectroscopy to identify chemical structures is highly beneficial for disease detection. Furthermore, NIR offers additional information regarding a sample's physiochemical structure, hence it can be used in combination as a complementary technique. Unlike the gold standard techniques, which often target one or two biomarkers during analysis, vibrational spectroscopy allows the detection of a wide range of biomarkers.[150] Furthermore, despite the low sensitivity and specificity of many diagnostic biomarkers, vibrational techniques have worked in combination with a range of biological matrices including bile,[151] bladder wash,[152] blood, fingernails, saliva, sputum[153,154] and urine for the diagnosis of bladder cancer, CVDs, DM, oral cancer, oropharyngeal cancer, ovarian cancer and laryngeal cancer.[18,26,27,29]

4.1 | Implications for practice

Many LMICs do not have the facilities, staff and/or expenses to frequently administer diagnostic tools and collect matrices, therefore, several patients develop further disease-related complications. However, through the application of alternative matrices and nontraditional analytical techniques, laboratories can reduce costs and frequencies of diagnostic errors, and improve patients' treatment/experience. Not only will this improve the patient's overall experience, which will in turn improve compliance rates and hospital visit attendance, but it will also improve the overall quality, accuracy and precision of laboratory findings. Moreover, through the analysis of alternative matrices, for example, fingernails, which can be collected in the patient's home and require minimal-to-no sample preparation, funding, previously utilized for diagnostic purposes, can be redistributed to disease management and treatment.

4.2 | Strengths and weaknesses

The studies accepted in this review identified a significant number of diagnostic biomarkers that can be employed by laboratories for the diagnosis of CVDs and DM. Furthermore, some studies included novel diagnostic techniques including vibrational spectroscopy, which offers rapid, noninvasive analysis of a range of biological matrices and biomarkers. Despite the rigorous and systematic reviewing process, limitations have still been encountered. Studies were variable in terms of design, technique and inclusion criteria. Hence, comparative conclusions between the published data are limited. For instance, studies utilized a range of analytical techniques to assess similar clinical outcomes. However, the lack of a standardized technique/approach for the identification of diagnostic biomarkers creates heterogeneity within the results. The variability with regards to sample size (23–7184, median 117, IQR 75–640) further contributed to heterogeneity

among the studies. Additionally, studies with smaller sample sizes (<40) were less likely to see statistically significant outcomes. It is also worth noting that the diagnostic criteria for CVDs and DM in the reviewed papers may vary. Based on the inconsistency of diagnostic criteria, findings could not be generalized.

5 | CONCLUSIONS

This review identifies emerging biomarkers for the diagnosis of CVDs and DM including GDF15, Notch1, isoleucine, tyrosine and valine. Moreover, this review complements previous systematic reviews by highlighting the use of traditional and alternative biological matrices, the latter of which offers noninvasive, nonintrusive sampling for improved diagnostic monitoring compliance rates. To improve disease diagnosis, laboratories should consider carrying out cost–benefit analysis of emerging advanced techniques. Despite their high costs, advanced techniques offer accurate and highly sensitive biomarker detection, which has the potential to reduce the number of diagnostic errors and the misadministration of treatment. Therefore, whilst initial costs may be high, emerging techniques such as LC–MS/MS and ELISA offer cost-effective diagnosis in the long term. The literature also revealed vibrational spectroscopic techniques, that offer cost-effective diagnosis with high sensitivity and selectivity. As an emerging technique, vibrational spectroscopy offers non-invasive, non-intrusive analysis that requires little-to-no sample preparation; thus, it is extremely cost-effective for LMICs. Future work will look at carrying out cost-effective analysis of the highlighted emerging techniques, as well as targeting frequently reported biomarkers in alternative matrices to determine their diagnostic efficacy.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15593.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ORCID

Megan Wilson https://orcid.org/0000-0002-9840-2272

REFERENCES

1. Organisation, W.H.O. Cardiovascular Diseases. 2023. https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1. Accessed 1 May 2023
2. Organisation, W.H.O. Diabetes. 2023. https://www.who.int/health-topics/diabetes#tab=tab_1. Accessed 1 May 2023
3. Ahsan M, Siddique Z. (2021) machine learning-based heart disease diagnosis: a systematic literature review. *Artif Intell Med Imaging*. 2021;128:102289.
4. Lam AA, Lepe A, Wild SH, Jackson C. Diabetes comorbidities in low- and middle-income countries: an umbrella review. *J Glob Health*. 2021;11:04040.
5. Wurie HR, Cappuccio FP. Cardiovascular disease in low- and middle-income countries: an urgent priority. *Ethnicity Health*. 2012;17:543-550.
6. Hu FB. Globalisation of diabetes: the role of diet, lifestyle and genes. *Diabetes Care*. 2011;43:1249-1257.
7. Owolabi M, Miranda JJ, Yaria J, Ovbiagele B. Controlling cardiovascular diseases in low and middle income countries by placing proof in pragmatism. *BMJ Glob Health*. 2016;1:e000105.
8. Flood D, Seiglie JA, Dunn M, et al. The state of diabetes treatment coverage in 55 low-income and middle-income countries: a cross-sectional study of nationally representative, individual-level data in 680 102 adults. *Lancet Healthy Longevity*. 2021;2:e340-e351.
9. Cameron FJ, Scratch SE, Nadebaum C, et al. Neurological consequences of diabetic ketoacidosis at initial presentation of type 1 diabetes in a prospective cohort study of children. *Diabetes Care*. 2014;37:1554-1562.
10. Vanelli M, Chiari G, Lacava S, Iovane B. Campaign for diabetic ketoacidosis prevention still effective 8 years later. *Diabetes Care*. 2007;30:e12.
11. Garibaldi L, Becker D. Is the risk of diabetic ketoacidosis modifiable? *J Pediatr*. 2016;171:10-12.
12. Bennett CM, Guo M, Dharmage SC. HbA(1c) as a screening tool for detection of type 2 diabetes: a systematic review. *Diabet Med*. 2007;24:333-343.
13. PRISMA. Transparent Reporting of Systematic Reviews and Meta-Analyses 2020. http://www.prisma-statement.org/. Accessed 11 December 2023
14. National Institute for Health and Care Research. Prospero. 2023. https://www.crd.york.ac.uk/prospero/ Accessed 11 December 2023
15. Programme CAS. CASP Checklist 2022. https://casp-uk.net/casp-tools-checklists/. Accessed 29 March 2023
16. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2021. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 29 March 2023
17. Li Y, Guo L, Li L, et al. Early diagnosis of type 2 diabetes based on near-infrared spectroscopy combined with machine learning and Aquaphotomics. *Front Chem*. 2020;8:580489.
18. Monteyne T, Coopman R, Kishabongo AS, et al. Analysis of protein glycation in human fingernail clippings with near-infrared (NIR) spectroscopy as an alternative technique for the diagnosis of diabetes mellitus. *Clin Chem Lab Med*. 2018;56:1551-1558.
19. Salih JM, Abdulateef DS. Detection of C-peptide in human hair and nail: a comparison between healthy persons and persons with type 1 diabetes. *BMJ Open Diabetes Res Care*. 2020;8:e001297.
20. Lin W, Wang M, Chen M, et al. Metabolomics and correlation network analyses of core biomarkers in type 2 diabetes. *Amino Acids*. 2020;52:1307-1317.
21. Carter TC, Rein D, Padberg I, et al. Validation of a metabolite panel for early diagnosis of type 2 diabetes. *Metabolism*. 2016;65:1399-1408.
22. Lau ES, Paniagua SM, Guseh JS, et al. Sex differences in circulating biomarkers of cardiovascular disease. *J Am Coll Cardiol*. 2019;74:1543-1553.
23. Shetty SS, Kumari NS, Shetty PK. ω-6/ω-3 fatty acid ratio as an essential predictive biomarker in the management of type 2 diabetes mellitus. *Nutrition*. 2020;79:110968.

24. Wang TJ, Ngo D, Psychogios N, et al. 2-Aminoadipic acid is a biomarker for diabetes risk. *J Clin Invest*. 2013;123:4309-4317.
25. Shi L, Brunius C, Lehtonen M, et al. Plasma metabolites associated with type 2 diabetes in a Swedish population: a case-control study nested in a prospective cohort. *Diabetologia*. 2018;61:849-861.
26. Nogueira MS, Barreto AL, Furukawa M, et al. FTIR spectroscopy as a point of care diagnostic tool for diabetes and periodontitis: a saliva analysis approach. *Photodiagnosis Photodyn Ther*. 2022;40:103036.
27. Scott DA, Renaud DE, Krishnasamy S, et al. Diabetes-related molecular signatures in infrared spectra of human saliva. *Diabetol Metab Syndr*. 2010;2:48.
28. Rao PV, Reddy AP, Lu X, et al. Proteomic identification of salivary biomarkers of type-2 diabetes. *J Proteome Res*. 2009;8:239-245.
29. Rodríguez-Calvo R, Girona J, Rodríguez M, et al. Fatty acid binding protein 4 (FABP4) as a potential biomarker reflecting myocardial lipid storage in type 2 diabetes. *Metabolism*. 2019;96:12-21.
30. Long J, Liu L, Jia Q, et al. Integrated biomarker for type 2 diabetes mellitus and impaired fasting glucose based on metabolomics analysis using ultra-high performance liquid chromatography quadrupole-Orbitrap high-resolution accurate mass spectrometry. *Rapid Commun Mass Spectrom*. 2020;34:e8779.
31. Tariq S, Mirza MR, Choudhary MI, Sultan R, Zafar M. Prediction of type 2 diabetes at pre-diabetes stage by mass spectrometry: a preliminary study. *Int J Pept Res Ther*. 2022;28(4):111.
32. Martínez PJ, Baldán-Martín M, López JA, et al. Identification of six cardiovascular risk biomarkers in the young population: a promising tool for early prevention. *Atherosclerosis*. 2019;282:67-74.
33. Méndez-Rodríguez KB, Figueroa-Vega N, Ilizaliturri-Hernandez CA, et al. Identification of metabolic markers in patients with type 2 diabetes by ultrafast gas chromatography coupled to electronic nose. A pilot study. *Biomed Chromatogr*. 2020;34(12):e4956.
34. Yap IK, Brown IJ, Chan Q, et al. Metabolome-wide association study identifies multiple biomarkers that discriminate north and south Chinese populations at differing risks of cardiovascular disease: INTERMAP study. *J Proteome Res*. 2010;9:6647-6654.
35. Amatruda JG, Estrella MM, Garg AX, et al. Urine Alpha-1-microglobulin Levels and acute kidney injury, mortality, and cardiovascular events following cardiac surgery. *Am J Nephrol*. 2021;52:673-683. doi:10.1159/000518240
36. Dare A, Chen SY. Adipsin in the pathogenesis of cardiovascular diseases. *Vascul Pharmacol*. 2023;154:107270. doi:10.1016/j.vph.2023.107270
37. Jauhiainen R, Vangipurapu J, Laakso A, Kuulasmaa T, Kuusisto J, Laakso M. The association of 9 amino acids with cardiovascular events in Finnish men in a 12-year follow-up study. *J Clin Endocrinol Metab*. 2021;106:3448-3454. doi:10.1210/clinem/dgab562
38. Kraaijenhof JM, Tromp TR, Nurmohamed NS, et al. ANGPTL3 (Angiopoietin-Like 3) preferentially resides on High-density lipoprotein in the human circulation, affecting its activity. *J Am Heart Assoc*. 2023;12:e030476. doi:10.1161/JAHA.123.030476
39. Chen MC, Hsu BG, Lee CJ, Wang JH. High-serum angiopoietin-like protein 3 Levels associated with cardiovascular outcome in patients with coronary artery disease. *Int J Hypertens*. 2020;2020:2980954. doi:10.1155/2020/2980954
40. Siniawski DA, Masson WM, Sorroche P, Scordo W. What should Be the goals of Apolipoprotein A1? Analysis of a healthy population from Argentina. *J Clin Lipidol*. 2012;6:251. doi:10.1016/j.jacl.2012.04.007
41. Dorobanțu M, Halațiu V-B, Gheorghe-Fronea O, et al. The association between Apolipoprotein B, cardiovascular risk factors and subclinical atherosclerosis—findings from the SEPHAR National Registry on hypertension in Romania. *Int J Mol Sci*. 2023;24:2813.
42. Alcântara VM, Chautard-Freire-Maia EA, Scartezini M, Cerci MSJ, Braun-Prado K, Picheth G. Butyrylcholinesterase activity and risk factors for coronary artery disease. *Scand J Clin Lab Invest*. 2002;62:399-404. doi:10.1080/00365510260296564
43. Kocabaş R, Erenler AK, Yetim M, Doğan T, Erdemli HK. Butyrylcholinesterase as an additional marker in the diagnostic network of acute myocardial infarction. *Laboratoriumsmedizin*. 2016;40(2):147-152. doi:10.1515/labmed-2015-0086
44. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart*. 2006;92:843-849. doi:10.1136/hrt.2005.071233
45. Durda P, Raffield LM, Lange EM, et al. Circulating soluble CD163, associations with cardiovascular outcomes and mortality, and identification of genetic variants in older individuals: the cardiovascular health study. *J Am Heart Assoc*. 2022;11:e024374. doi:10.1161/jaha.121.024374
46. Castelblanco E, Sarrias MR, Betriu À, et al. Circulating CD5L is associated with cardiovascular events and all-cause mortality in individuals with chronic kidney disease. *Aging*. 2021;13:22690-22709. doi:10.18632/aging.203615
47. Göçmen AY, Şahin E, Semiz E, Gümüşlü S. Is elevated serum ceruloplasmin level associated with increased risk of coronary artery disease? *Can J Cardiol*. 2008;24:209-212. doi:10.1016/S0828-282X(08)70586-5
48. Nikolov A, Popovski N. Extracellular matrix in heart disease: focus on circulating collagen type I and III derived peptides as biomarkers of myocardial fibrosis and their potential in the prognosis of heart failure: a concise review. *Metabolites*. 2022;12:297. doi:10.3390/metabo12040297
49. Jiménez-Navarro MF, Gómez-Doblas JJ, Cabrera-Bueno F, et al. Collagen synthesis and heart failure. *Rev Esp Cardiol*. 2005;58(8):975-978. doi:10.1016/S1885-5857(06)60381-2
50. Kuzan A, Chwiłkowska A, Pezowicz C, et al. The content of collagen type II in human arteries is correlated with the stage of atherosclerosis and calcification foci. *Cardiovasc Pathol*. 2017;28:21-27. doi:10.1016/j.carpath.2017.02.003
51. Lu X, Wang Z, Ye D, et al. The role of CXC chemokines in cardiovascular diseases. *Front Pharmacol*. 2021;12:765768. doi:10.3389/fphar.2021.765768
52. Wang H, Cao J, Su J-b, et al. Serum fatty acid-binding protein 4 levels and responses of pancreatic islet β-cells and α-cells in patients with type 2 diabetes. *Diabetol Metab Syndr*. 2021;13:70. doi:10.1186/s13098-021-00690-z
53. West M, Kirby A, Stewart RA, et al. Circulating cystatin C is an independent risk marker for cardiovascular outcomes, development of renal impairment, and Long-term mortality in patients with stable coronary heart disease: the LIPID study. *J Am Heart Assoc*. 2022;11:e020745. doi:10.1161/JAHA.121.020745
54. Edinga-Melenge BE, Yakam AT, Nansseu JR, et al. Reference intervals for serum cystatin C and serum creatinine in an adult sub-Saharan African population. *BMC Clin Pathol*. 2019;19:4. doi:10.1186/s12907-019-0086-7
55. Cepeda J, Tranche-Iparraguirre S, Marín-Iranzo R, et al. Cystatin C and cardiovascular risk in the general population. *Rev Esp Cardiol*. 2010;63:415-422. doi:10.1016/S1885-5857(10)70090-6
56. Potjewijd J, Tobal R, Boomars KA, et al. Plasma dephosphorylated-uncarboxylated matrix Gla-protein in systemic sclerosis patients: biomarker potential for vascular calcification and inflammation. *Diagnostics*. 2023;13:3526.
57. Batra J, Buttar RS, Kaur P, Kreimerman J, Melamed ML. FGF-23 and cardiovascular disease: review of literature. *Curr Opin Endocrinol Diabetes Obes*. 2016;23:423-429. doi:10.1097/med.0000000000000294
58. Bouma-de Krijger A, Vervloet MG. Fibroblast growth factor 23: are we ready to use it in clinical practice? *J Nephrol*. 2020;33:509-527. doi:10.1007/s40620-020-00715-2

59. Aalders J, Léger L, Van der Meeren L, et al. Effects of fibrillin mutations on the behavior of heart muscle cells in Marfan syndrome. *Sci Rep*. 2020;10:16756. doi:10.1038/s41598-020-73802-w
60. Hui P, Bai Y, Su X, et al. The value of plasma fibrillin-1 level in patients with spontaneous coronary artery dissection. *Int J Cardiol*. 2020;302:150-156. doi:10.1016/j.ijcard.2019.12.015
61. Kato ET, Morrow DA, Guo J, et al. Growth differentiation factor 15 and cardiovascular risk: individual patient meta-analysis. *Eur Heart J*. 2022;44:293-300. doi:10.1093/eurheartj/ehac577
62. Wiklund FE, Bennet AM, Magnusson PKE, et al. Macrophage inhibitory cytokine-1 (MIC-1/GDF15): a new marker of all-cause mortality. *Aging Cell*. 2010;9:1057-1064. doi:10.1111/j.1474-9726.2010.00629.x
63. Blann AD, Nadar SK, Lip GYH. The adhesion molecule P-selectin and cardiovascular disease. *Eur Heart J*. 2003;24:2166-2179. doi:10.1016/j.ehj.2003.08.021
64. Song C, Wu G, Chang S, Bie L. Plasma P-selectin level is associated with severity of coronary heart disease in Chinese Han population. *J Int Med Res*. 2020;48(6):300060519896437. doi:10.1177/0300060519896437
65. Li Y, Chen R, Wang C, Deng J, Luo S. Double-edged functions of hemopexin in hematological related diseases: from basic mechanisms to clinical application. *Front Immunol*. 2023;14:1-13. doi:10.3389/fimmu.2023.1274333
66. Chou CH, Ueng KC, Liu YF, Wu CH, Yang SF, Wang PH. Impact of intercellular adhesion Molecule-1 genetic polymorphisms on coronary artery disease susceptibility in Taiwanese subjects. *Int J Med Sci*. 2015;12:510-516. doi:10.7150/ijms.12097
67. Othlein R, Mainolfi EA, Czajkowski M, Marlin SD. A form of circulating ICAM-1 in human serum. *J Immunol*. 1991;1(147):3788-3793.
68. Ridker PM, Hennekens CH, Roitman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. *Lancet*. 1998;351:88-92. doi:10.1016/s0140-6736(97)09032-6
69. Lin J, Yang L, Huang J, et al. Insulin-like growth factor 1 and risk of cardiovascular disease: results from the UK biobank cohort study. *J Clin Endocrinol Metabol*. 2023;108:e850-e860. doi:10.1210/clinem/dgad105
70. Macvanin M, Gluvic Z, Radovanovic J, Essack M, Gao X, Isenovic ER. New insights on the cardiovascular effects of IGF-1. *Front Endocrinol*. 2023;14:1142644. doi:10.3389/fendo.2023.1142644
71. Laughlin GA, Barrett-Connor E, Criqui MH, Kritz-Silverstein D. The prospective association of serum insulin-like growth factor I (IGF-I) and IGF-binding protein-1 levels with all cause and cardiovascular disease mortality in older adults: the rancho Bernardo study. *J Clin Endocrinol Metab*. 2004;89:114-120. doi:10.1210/jc.2003-030967
72. Yang J, Griffiths M, Nies MK, et al. Insulin-like growth factor binding protein-2: a new circulating indicator of pulmonary arterial hypertension severity and survival. *BMC Med*. 2020;18:268. doi:10.1186/s12916-020-01734-3
73. Fang Z, Yang S, Zhu L, et al. Association study of IGFBP1 and IGFBP3 polymorphisms with hypertension and cardio-cerebral vascular diseases in a Chinese Han population. *Oncotarget*. 2017;8:77836.
74. Kucukhuseyin o, Toptas B, Timirci-Kahraman O, Isbir S, Karsidag K, Isbir T. The effect of GHR/exon-3 polymorphism and serum GH, IGF-1 and IGFBP-3 Levels in diabetes and coronary heart disease. *In Vivo*. 2015;29:371-378.
75. Lisowska A, Święcki P, Knapp M, et al. Insulin-like growth factor-binding protein 7 (IGFBP 7) as a new biomarker in coronary heart disease. *Adv Med Sci*. 2019;64:195-201. doi:10.1016/j.advms.2018.08.017
76. Wallace AM, McMahon AD, Packard CJ, et al. Plasma leptin and the risk of cardiovascular disease in the West of Scotland coronary prevention study (WOSCOPS). *Circulation*. 2001;104:3052-3056. doi:10.1161/hc5001.101061
77. Banach J, Grochowska M, Gackowska L, et al. Melanoma cell adhesion molecule as an emerging biomarker with prognostic significance in systolic heart failure. *Biomark Med*. 2016;10:733-742. doi:10.2217/bmm-2016-0053
78. Zhang ZY, Zhai C, Yang XY, Li HB, Wu LL, Li L. Knockdown of CD146 promotes endothelial-to-mesenchymal transition via Wnt/β-catenin pathway. *PLoS One*. 2022;17:e0273542. doi:10.1371/journal.pone.0273542
79. Blanco-Colio LM, Méndez-Barbero N, Pello Lázaro AM, et al. MCP-1 predicts recurrent cardiovascular events in patients with persistent inflammation. *J Clin Med*. 2021;10. doi:10.3390/jcm10051137
80. Papazafiropoulou A, Sotiropoulos A, Skliros E, et al. Familial history of diabetes and clinical characteristics in Greek subjects with type 2 diabetes. *BMC Endocr Disord*. 2009;9:12. doi:10.1186/1472-6823-9-12
81. Kalela A, Koivu TA, Sisto T, et al. Serum matrix metalloproteinase-9 concentration in angiographically assessed coronary artery disease. *Scand J Clin Lab Invest*. 2002;62:337-342. doi:10.1080/00365510260296483
82. Baseri M, Heidari R, Mahaki B, Hajizadeh Y, Momenizadeh A, Sadeghi M. Myeloperoxidase levels predicts angiographic severity of coronary artery disease in patients with chronic stable angina. *Adv Biomed Res*. 2014;3:139. doi:10.4103/2277-9175.135155
83. Kottwitz J, Bruno KA, Berg J, et al. Myoglobin for detection of high-risk patients with acute myocarditis. *J Cardiovasc Transl Res*. 2020;13:853-863. doi:10.1007/s12265-020-09957-8
84. Rusanescu G, Weissleder R, Aikawa E. Notch signalling in cardiovascular disease and calcification. *Curr Cardiol Rev*. 2008;4:148-156. doi:10.2174/157340308785160552
85. Tofler GH, Massaro J, O'Donnell CJ, et al. Plasminogen activator inhibitor and the risk of cardiovascular disease: the Framingham heart study. *Thromb Res*. 2016;140:30-35. doi:10.1016/j.thromres.2016.02.002
86. Vélez P, García Á. Platelet proteomics in cardiovascular diseases. *Translational*. *Proteomics*. 2015;7:15-29. doi:10.1016/j.trprot.2014.09.002
87. Zhou C, Cao J, Shang L, et al. Reduced paraoxonase 1 activity as a marker for severe coronary artery disease. *Dis Markers*. 2013;35:97-103. doi:10.1155/2013/816189
88. Li L, Jia D, Graf R, Yang J. Elevated serum level of pancreatic stone protein/regenerating protein (PSP/reg) is observed in diabetic kidney disease. *Oncotarget*. 2017;8:38145-38151. doi:10.18632/oncotarget.16369
89. Jamaluddin MS, Weakley SM, Yao Q, Chen C. Resistin: functional roles and therapeutic considerations for cardiovascular disease. *Br J Pharmacol*. 2012;165:622-632. doi:10.1111/j.1476-5381.2011.01369.x
90. Chang C, Pan Y, Du H, Wang X, Li X. Serum amyloid A1 can be a novel biomarker for evaluating the presence and severity of acute coronary syndrome. *Clin Biochem*. 2020;85:27-32. doi:10.1016/j.clinbiochem.2020.08.005
91. Subramanian S, Liu C, Aviv A, et al. Stromal cell-derived factor 1 as a biomarker of heart failure and mortality risk. *Arterioscler Thromb Vasc Biol*. 2014;34:2100-2105. doi:10.1161/atvbaha.114.303579
92. Ritschel VN, Seljeflot I, Arnesen H, et al. Circulating levels of IL-6 receptor and gp130 and Long-term clinical outcomes in ST-elevation myocardial infarction. *J Am Heart Assoc*. 2016;5:e003014. doi:10.1161/jaha.115.003014
93. Witkowska AM. Soluble ICAM-1: a marker of vascular inflammation and lifestyle. *Cytokine*. 2005;31:127-134. doi:10.1016/j.cyto.2005.04.007
94. Andrýs C, Pozler O, Krejsek J, Derner V, Drahošová M, Kopecký O. Serum soluble adhesion molecules (sICAM-1, sVCAM-1 and sE-

selectin) in healthy school aged children and adults. *Acta Med*. 2000; 43:103-106. doi:10.14712/18059694.2019.121
95. Falcone C, Emanuele E, D'Angelo A, et al. Plasma levels of soluble receptor for advanced glycation end products and coronary artery disease in nondiabetic men. *Arterioscler Thromb Vasc Biol*. 2005;25: 1032-1037. doi:10.1161/01.Atv.0000160342.20342.00
96. Chen Y, Han H, Yan X, et al. Tetranectin as a potential biomarker for stable coronary artery disease. *Sci Rep*. 2015;5(1):17632. doi:10.1038/srep17632
97. Lindsey ML, Yabluchanskiy A, Ma Y. Tissue inhibitor of Metalloproteinase-1: actions beyond matrix metalloproteinase inhibition. *Cardiology*. 2015;132(3):147-150. doi:10.1159/000433419
98. Pudil R, Vasatova M, Fucikova A, et al. Vascular endothelial growth factor is associated with the morphologic and functional parameters in patients with hypertrophic cardiomyopathy. *Biomed Res Int*. 2015; 2015:762950. doi:10.1155/2015/762950
99. Shlipak MG, Stehman-Breen C, Vittinghoff E, et al. Creatinine levels and cardiovascular events in women with heart disease: do small changes matter? *Am J Kidney Dis*. 2004;43:37-44. doi:10.1053/j.ajkd.2003.08.044
100. Moreira GR, Avila DX, Di Candia AM, et al. Relationship between GDF-15, urinary sodium and markers of renal function in patients with chronic heart failure. *Eur Heart J*. 2022;43(Suppl 2):467-473. doi:10.1093/eurheartj/ehac544.1084
101. Yoon HS, Jeong Yang J, Rivera ES, et al. Urinary metabolites and risk of coronary heart disease: a prospective investigation among urban Chinese adults. *Nutr Metab Cardiovasc Dis*. 2020;30:467-473. doi:10.1016/j.numecd.2019.10.011
102. Ussher JR, Elmariah S, Gerszten RE, Dyck JRB. The emerging role of metabolomics in the diagnosis and prognosis of cardiovascular disease. *J Am Coll Cardiol*. 2016;68:2850-2870. doi:10.1016/j.jacc.2016.09.972
103. Lever M, Sizeland PCB, Bason LM, Hayman CM, Chambers ST. Glycine betaine and proline betaine in human blood and urine. *Biochim Biophys Acta, Gen Subj*. 1994;1200:259-264. doi:10.1016/0304-4165(94)90165-1
104. Monnard I, Bénet T, Jenni R, Austin S, Silva-Zolezzi I, Godin JP. Plasma and urinary inositol isomer profiles measured by UHPLC-MS/MS reveal differences in scyllo-inositol levels between non-pregnant and pregnant women. *Anal Bioanal Chem*. 2020;412: 7871-7880. doi:10.1007/s00216-020-02919-8
105. Al Hageh C, Rahy R, Khazen G, et al. Plasma and urine metabolomic analyses in aortic valve stenosis reveal shared and biofluid-specific changes in metabolite levels. *PLoS One*. 2020;15:e0242019. doi:10.1371/journal.pone.0242019
106. Magkos F, Reeds DN, Mittendorfer B. Evolution of the diagnostic value of "the sugar of the blood": hitting the sweet spot to identify alterations in glucose dynamics. *Physiol Rev*. 2023;103:7-30. doi:10.1152/physrev.00015.2022
107. Coopman R, Van de Vyver T, Kishabongo AS, et al. Glycation in human fingernail clippings using ATR-FTIR spectrometry, a new marker for the diagnosis and monitoring of diabetes mellitus. *Clin Biochem*. 2017;50:62-67. doi:10.1016/j.clinbiochem.2016.09.001
108. Wang F, Xu L, Qi M, et al. Metabolomic analysis-identified 2-hydroxybutyric acid might be a key metabolite of severe pre-eclampsia. *Open Life Sci*. 2023;18:20220572. doi:10.1515/biol-2022-0572
109. Hotta K, Funahashi T, Arita Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol*. 2000;20:1595-1599. doi:10.1161/01.atv.20.6.1595
110. McCann A, Melvaer Giil L, Ulvik A, et al. Plasma amino acids and incident type 2 diabetes in patients with coronary artery disease. *Diabetes Care*. 2019;42:1225-1233. doi:10.2337/dc18-2217
111. Mantovani A, Dalbeni A, Peserico D, et al. Plasma bile acid profile in patients with and without type 2 diabetes. *Metabolites*. 2021;11: 453. doi:10.3390/metabo11070453
112. Buzzetti R, Tuomi T, Mauricio D, et al. Management of latent autoimmune diabetes in adults: a consensus statement from an international expert panel. *Diabetes*. 2020;69:2037-2047. doi:10.2337/dbi20-0017
113. Yosten GL, Maric-Bilkan C, Luppi P, Wahren J. Physiological effects and therapeutic potential of proinsulin C-peptide. *Am J Physiol Endocrinol Metab*. 2014;307:E955-E968. doi:10.1152/ajpendo.00130.2014
114. Chang CK, Tso TK, Snook JT, Huang YS, Lozano RA, Zipf WB. Cholesteryl ester transfer and cholesterol esterification in type 1 diabetes: relationships with plasma glucose. *Acta Diabetol*. 2001;38(1): 37-42. doi:10.1007/s005920170027
115. Cao Y-F, Li J, Zhang Z, et al. Plasma Levels of amino acids related to urea cycle and risk of type 2 diabetes mellitus in Chinese adults. *Front Endocrinol*. 2019;10:427858. doi:10.3389/fendo.2019.00050
116. Braeckman RA, Stirtan WG, Soni PN. Pharmacokinetics of Eicosapentaenoic acid in plasma and red blood cells after multiple Oral dosing with Icosapent ethyl in healthy subjects. *Clin Pharmacol Drug Dev*. 2014;3:101-108. doi:10.1002/cpdd.84
117. Abbas E, Ahmed Siddiqui I, Khan MS, Perveen K, Butt A, Fawwad A. Fasting glucagon level in type 2 diabetes and impaired glucose tolerance and its association with diabetes-associated clinical parameters: a study from Karachi, Pakistan. *Cureus*. 2021;13(2):e13430.
118. Persiani S, Roda E, Rovati LC, Locatelli M, Giacovelli G, Roda A. Glucosamine oral bioavailability and plasma pharmacokinetics after increasing doses of crystalline glucosamine sulfate in man. *Osteoarthr Cartil*. 2005;13(12):1041-1049. doi:10.1016/j.joca.2005.07.009
119. Ge P, Dong C, Ren X, et al. The high prevalence of low HDL-cholesterol Levels and dyslipidemia in rural populations in northwestern China. *PLoS One*. 2015;10:e0144104. doi:10.1371/journal.pone.0144104
120. Pickup JC, Chusney GD, Thomas SM, Burt D. Plasma interleukin-6, tumour necrosis factor α and blood cytokine production in type 2 diabetes. *Life Sci*. 2000;67:291-300. doi:10.1016/S0024-3205(00)00622-6
121. Feng QP, Wei W-Q, Chung CP, et al. Relationship between very low low-density lipoprotein cholesterol concentrations not due to statin therapy and risk of type 2 diabetes: a US-based cross-sectional observational study using electronic health records. *PLoS Med*. 2018;15:e1002642.
122. Onyemelukwe OU, Ogoina D, Onyemelukwe GC. Leptin concentrations in type 2 diabetes and non-diabetes Nigerian-Africans. *Am J Cardiovasc Dis*. 2020;10:444-454.
123. Kawamori D, Kageyama Y, Tanaka T, et al. Characteristic changes in plasma glutamate levels and free amino acid profiles in Japanese patients with type 1 diabetes mellitus. *J Diabetes Invest*. 2023;14: 111-121. doi:10.1111/jdi.13911
124. Abdelmagid SA, Clarke SE, Nielsen DE, et al. Comprehensive profiling of plasma fatty acid concentrations in young healthy Canadian adults. *PLoS One*. 2015;10(2):e0116195. doi:10.1371/journal.pone.0116195
125. Barber MN, Risis S, Yang C, et al. Plasma lysophosphatidylcholine levels are reduced in obesity and type 2 diabetes. *PLoS One*. 2012;7: e41456. doi:10.1371/journal.pone.0041456
126. Yoshimura K, Hirano S, Takata H, et al. Plasma mannose level, a putative indicator of glycogenolysis, and glucose tolerance in Japanese individuals. *J Diabetes Invest*. 2017;8:489-495. doi:10.1111/jdi.12622
127. Qureshi W, Santaren ID, Hanley AJ, Watkins SM, Lorenzo C, Wagenknecht LE. Risk of diabetes associated with fatty acids in the de novo lipogenesis pathway is independent of insulin sensitivity and response: the insulin resistance atherosclerosis study (IRAS).

BMJ Open Diabetes Res Care. 2019;7:e000691. doi:10.1136/bmjdrc-2019-000691
128. Li J, Cao YF, Sun XY, et al. Plasma tyrosine and its interaction with low high-density lipoprotein cholesterol and the risk of type 2 diabetes mellitus in Chinese. *J Diabetes Invest*. 2019;10:491-498. doi:10.1111/jdi.12898
129. Liao X, Liu B, Qu H, et al. A high level of circulating valine is a biomarker for type 2 diabetes and associated with the hypoglycemic effect of Sitagliptin. *Mediators Inflamm*. 2019;2019:8247019. doi:10.1155/2019/8247019
130. Rastogi V, Kalra P, Gowda MV. Relationship between salivary Alpha-2 macroglobulin and HbA1c among patients with Type-2 diabetes mellitus: a cross-sectional study. *Indian J Endocrinol Metab*. 2019;23:184-187. doi:10.4103/ijem.IJEM_40_19
131. Ravindran R, Gopinathan DM, Sukumaran S. Estimation of salivary glucose and glycogen content in exfoliated buccal mucosal cells of patients with type II diabetes mellitus. *J Clin Diagn Res*. 2015;9:Zc89-93. doi:10.7860/jcdr/2015/11633.5971
132. Singal AK, Bansal R, Singh A, et al. Concomitant transthyretin amyloidosis and severe aortic stenosis in elderly Indian population: a pilot study. *JACC Cardio Oncol*. 2021;3:565-576. doi:10.1016/j.jaccao.2021.08.008
133. Ahamed F, Karim MR, Haque MA, et al. Study on alanine aminotransferase in patients of type 2 diabetes mellitus. *Mymensingh Med J*. 2021;30:343-350.
134. Erkus E, Aktas G, Kocak MZ, Duman TT, Atak BM. Serum bilirubin level is associated with diabetic control in type 2 diabetes mellitus. *Blood Heart and Circ*. 2018;2:2.
135. Wang W-T, Wu T-C, Tseng W-K, et al. Prognostic indicators for the onset of ischaemic versus haemorrhagic stroke in stable coronary artery disease. *Medicine*. 2021;100:e27973. doi:10.1097/md.0000000000027973
136. Menge BA, Schrader H, Ritter PR, et al. Selective amino acid deficiency in patients with impaired glucose tolerance and type 2 diabetes. *Regul Pept*. 2010;160:75-80. doi:10.1016/j.regpep.2009.08.001
137. Suhail M, Rizvi SI. Red cell phosphoglycerate kinase in insulin-dependent diabetes mellitus. *Indian J Med Res*. 1990;92:21-23.
138. Ebtehaj S, Gruppen EG, Parvizi M, Tietge UJF, Dullaart RPF. The anti-inflammatory function of HDL is impaired in type 2 diabetes: role of hyperglycemia, paraoxonase-1 and low grade inflammation. *Cardiovasc Diabetol*. 2017;16(1):132. doi:10.1186/s12933-017-0613-8
139. Tirosh A, Shai I, Bitzur R, et al. Changes in triglyceride levels over time and risk of type 2 diabetes in young men. *Diabetes Care*. 2008;31:2032-2037. doi:10.2337/dc08-0825
140. Mohorko N, Petelin A, Jurdana M, Biolo G, Jenko-Pražnikar Z. Elevated serum levels of cysteine and tyrosine: early biomarkers in asymptomatic adults at increased risk of developing metabolic syndrome. *Biomed Res Int*. 2015;2015:418681. doi:10.1155/2015/418681
141. Ozgen L, Ozgen G, Dincgez B, Bayram F. Role of increased plasminogen activator inhibitor-1 and vitronectin in gestational diabetes mellitus. *Rev Assoc Med Bras*. 1992;2023(69):e20230563. doi:10.1590/1806-9282.20230563
142. Harita N, Hayashi T, Sato KK, et al. Lower serum creatinine is a new risk factor of type 2 diabetes: the Kansai healthcare study. *Diabetes Care*. 2009;32:424-426. doi:10.2337/dc08-1265
143. Bahbah EI, Noehammer C, Pulverer W, Jung M, Weinhaeusel A. Salivary biomarkers in cardiovascular disease: an insight into the current evidence. *FEBS J*. 2021;288:6392-6405.
144. Kaufman E, Lamster IB. The diagnostic applications of saliva—a review. *Crit Rev Oral Biol Med*. 2002;13:197-212.
145. Lau ES, Binek A, Parker SJ, et al. Sexual dimorphism in cardiovascular biomarkers: clinical and research implications. *Circ Res*. 2022;130:578-592.
146. Salama NAS, Salama G. Do sex hormones impact stress responses by modulating the cellular composition of the myocardium? *Cardiovasc Res*. 2021;117:2140-2142.
147. Lakoski SG, Cushman M, Criqui M, et al. Gender and C-reactive protein: data from the multiethnic study of atherosclerosis (MESA) cohort. *Am Heart J*. 2006;152:593-598.
148. Herath P, Wimalasekera S, Amarasekara T, Fernado M, Turale S. Effect of cigarette smoking on smoking biomarkers, blood pressure and blood lipid levels among Sri Lankan male smokers. *Postgrad Med J*. 2022;98:848-854.
149. Ul-Haq Z, Mackay DF, Pell JP. Association between self-reported general and mental health and adverse outcomes: a retrospective cohort study of 19 625 Scottish adults. *PLoS One*. 2014;9:e93857.
150. Hosseini S, Vázquez-Villegas P, Rito-Palomares M, Martinez-Chapa SO. Advantages, disadvantages and modifications of conventional ELISA. In: Hosseini S, Vázquez-Villegas P, Rito-Palomares M, Martinez-Chapa SO, eds. *Enzyme-Linked Immunosorbent Assay (ELISA): from A to Z*. Springer Singapore; 2018:67-115.
151. Frampton JP, White JB, Simon AB, Tseui M, Paczesny S, Takayama S. Aqueous two-phase system patterning of detection antibody solutions for cross-reaction-free multiplex ELISA. *Sci Rep*. 2014;4:4878.
152. Old OJ, Fullwood LM, Scott R, et al. Vibrational spectroscopy for cancer diagnostics. *Anal Methods*. 2014;6:3901-3917.
153. Untereiner V, Sockalingum GD, Garnotel R, et al. Bile analysis using high-throughput FTIR spectroscopy for the diagnosis of malignant biliary strictures: a pilot study in 57 patients. *J Biophotonics*. 2014;7:241-253.
154. Gok S, Aydin OZ, Sural YS, Zorlu F, Bayol U, Severcan F. Bladder cancer diagnosis from bladder wash by Fourier transform infrared spectroscopy as a novel test for tumour recurrence. *J Biophotonics*. 2016;9:967-975.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wilson M, Al-Hamid A, Abbas I, et al. Identification of diagnostic biomarkers used in the diagnosis of cardiovascular diseases and diabetes mellitus: A systematic review of quantitative studies. *Diabetes Obes Metab*. 2024; 1-11. doi:10.1111/dom.15593