

Precision prognostics for cardiovascular disease in Type 2 diabetes: a systematic review and meta-analysis

Abrar Ahmad^{1,200}, Lee-Ling Lim^{2,3,4,200}, Mario Luca Morieri^{5,6,200}, Claudia Ha-ting Tam^{3,7,8,200}, Feifei Cheng⁹, Tinashe Chikowore^{10,11}, Monika Dudenhöffer-Pfeifer¹, Hugo Fitipaldi¹, Chuiguo Huang^{3,7,8}, Sarah Kanbour¹², Sudipa Sarkar¹³, Robert Wilhelm Koivula¹⁴, Ayesha A. Motala¹⁵, Sok Cin Tye^{16,17}, Gechang Yu^{3,7,8}, Yingchai Zhang^{3,7,8}, Michele Provenzano¹⁸, Diana Sherifali¹⁹, Russell J. de Souza^{20,21}, Deirdre Kay Tobias²², ADA/EASD PMDI*, Maria F. Gomez^{1,23,201}, Ronald C. W. Ma^{3,7,8,201} & Nestoras Mathioudakis^{13,201}

Abstract

Background Precision medicine has the potential to improve cardiovascular disease (CVD) risk prediction in individuals with Type 2 diabetes (T2D).

Methods We conducted a systematic review and meta-analysis of longitudinal studies to identify potentially novel prognostic factors that may improve CVD risk prediction in T2D. Out of 9380 studies identified, 416 studies met inclusion criteria. Outcomes were reported for 321 biomarker studies, 48 genetic marker studies, and 47 risk score/model studies.

Results Out of all evaluated biomarkers, only 13 showed improvement in prediction performance. Results of pooled meta-analyses, non-pooled analyses, and assessments of improvement in prediction performance and risk of bias, yielded the highest predictive utility for N-terminal pro b-type natriuretic peptide (NT-proBNP) (high-evidence), troponin-T (TnT) (moderate-evidence), triglyceride-glucose (TyG) index (moderate-evidence), Genetic Risk Score for Coronary Heart Disease (GRS-CHD) (moderate-evidence); moderate predictive utility for coronary computed tomography angiography (low-evidence), single-photon emission computed tomography (low-evidence), pulse wave velocity (moderate-evidence); and low predictive utility for C-reactive protein (moderate-evidence), coronary artery calcium score (low-evidence), galectin-3 (low-evidence), troponin-I (low-evidence), carotid plaque (low-evidence), and growth differentiation factor-15 (low-evidence). Risk scores showed modest discrimination, with lower performance in populations different from the original development cohort.

Conclusions Despite high interest in this topic, very few studies conducted rigorous analyses to demonstrate incremental predictive utility beyond established CVD risk factors for T2D. The most promising markers identified were NT-proBNP, TnT, TyG and GRS-CHD, with the highest strength of evidence for NT-proBNP. Further research is needed to determine their clinical utility in risk stratification and management of CVD in T2D.

Plain language summary

People living with type 2 diabetes (T2D) are more likely to develop problems with their heart or blood circulation, known as cardiovascular disease (CVD), than people who do not have T2D. However, it can be difficult to predict which people with T2D are most likely to develop CVD. This is because current approaches, such as blood tests, do not identify all people with T2D who are at an increased risk of CVD. In this study we reviewed published papers that investigated the differences between people with T2D who experienced CVD compared to those who did not. We found some indicators that could potentially be used to determine which people with T2D are most likely to develop CVD. More studies are needed to determine how useful these are. However, they could potentially be used to enable clinicians to provide targeted advice and treatment to those people with T2D at most risk of developing CVD.

Individuals with type 2 diabetes (T2D) have a 1.5 to 2-fold higher risk of developing cardiovascular disease (CVD) compared to those without T2D^{1,2}. This is particularly concerning given the high global prevalence of diabetes and the aging population. More than 500 million individuals worldwide are affected by this chronic disease, resulting in substantial human and economic costs^{3,4}. However, predicting CVD risk in T2D remains a challenge, and existing risk algorithms, such as the UK Prospective Diabetes Study (UKPDS) Risk Engine and Framingham Risk Score (FRS), have shown only modest predictive value in external validation studies^{5–7}. Thus, it is essential to identify or develop readily available and cost-effective measures that can accurately identify individuals with a higher absolute risk of developing CVD beyond the risk estimated from established risk factors.

Precision medicine provides a promising approach to optimize risk prediction by integrating multidimensional data (i.e., genetic, clinical, sociodemographic), accounting for individual differences⁸. Recognizing the potential value of precision medicine in improving diabetes prevention and care, the Precision Medicine in Diabetes Initiative (PMDI) was established in 2018 by the American Diabetes Association (ADA) in partnership with the European Association for the Study of Diabetes (EASD) and is led by global leaders in precision diabetes medicine⁹. This systematic review is written on behalf of the ADA/EASD PMDI as part of a comprehensive evidence evaluation in support of the 2nd International Consensus Report on Precision Diabetes Medicine¹⁰. As part of this broader initiative, we conducted a systematic review and meta-analyses addressing precision prognosis for CVD outcomes.

While previous systematic reviews of biomarkers for prediction of CVD have been conducted in the general population^{11–25}, this review focused on patients with T2D. We sought to answer two questions: (1) Which novel markers predict CVD in people with T2D? (2) Is there any evidence that these markers enhance risk prediction beyond current practice? Addressing these questions may inform the development of more effective strategies for detecting and predicting CVD in individuals with T2D, ultimately leading to improved management and prevention of this complication.

Therefore, to identify those biomarkers with most promising clinical utility for CV risk assessment, we followed a rigorous stepwise approach, including evaluation of the incremental value of each biomarker beyond traditional risk factors (i.e. with evaluation of improvement in different metrics such as c-statistic and net reclassification improvement – NRI), as recommended by the statement from the American Heart Association for identification of novel markers for CV disease²⁶.

In summary, employing a stringent study selection process, this systematic review and meta-analysis identified four prognostic factors with high predictive utility, supported by moderate to high-strength evidence. Furthermore, three prognostic factors demonstrated moderate predictive utility, backed by low to moderate-strength evidence, and six prognostic factors showed low predictive utility, with evidence levels ranging from low to moderate. Risk scores demonstrated modest discrimination on internal validation, with diminished performance in external validation, particularly in cohorts diverging from the original population.

Methods

As a reporting guidance, we followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement²⁷. Figure 1 presents the PRISMA flow diagram, illustrating the process that led to the final selection of studies for

review. Prior to data collection, the proposed systematic review and meta-analysis was registered on PROSPERO (Registration number: CRD42021262843).

Inclusion and exclusion criteria. This review included longitudinal studies (prospective or retrospective cohorts, including secondary analyses of cohorts from randomized controlled trials) of participants with T2D (youth-onset and adult-onset). Inclusion criteria included observational studies published from 1990–2021 that reported on the association between a prognostic factor or risk score and one or more CVD outcomes among participants with T2D. During the period of our review, the diagnostic criteria for T2D underwent some modifications (e.g. change in fasting glucose threshold, addition of hemoglobin A1C). We accepted studies that reported the inclusion of participants with T2D as defined in each individual study. Exclusion criteria included cross-sectional studies, studies utilizing surrogate endpoints for cardiovascular (CVD) outcomes such as carotid intima-media thickness, endothelial dysfunction, and arterial stiffness, and studies including only participants with pre-diabetes or only participants with type 1 diabetes. Studies with mixed populations of diabetes were included only if results were reported separately for participants with T2D. Supplemental Table 1 summarizes the Participant Intervention Comparison Outcomes and Studies (PICOS) framework.

Outcomes. Only studies reporting outcomes on fatal or non-fatal coronary heart disease (CHD) or cardiovascular mortality (either alone or as individual component of composite outcomes) were included. A broad definition of CHD, including any outcomes defined by terms such as myocardial infarction, ischemic heart events, cardiac events, coronary artery disease, and major cardiovascular events was used.

Search strategy. We conducted a comprehensive search on Medline and Embase of studies published from January 1990 to March 2021 using keywords and MeSH (Medical Subject Headings) terms relevant to T2D and CVD (see Supplemental Note 1). In addition, we searched the reference lists of eligible studies and systematic reviews to identify any further relevant studies. The search strategy was designed by a multi-professional team of researchers with expertise in precision medicine, clinical diabetes, cardiovascular disease, biomarker development and evaluation, genetic markers, and predictive analytics, supported by two librarians with expertise in conducting systematic reviews and meta-analyses. References identified were exported to EndNote (Clarivate Analytics) and imported to Covidence, where studies were assessed for eligibility. After the removal of duplicates, 14 authors participated in screening each title/abstract, and full-text articles were obtained if abstracts were considered eligible by at least one author. Each full-text article was assessed for inclusion independently by two authors (among 12 total authors), and disagreements were resolved by consensus.

Data extraction. All data were extracted and coded by one author and reviewed by a second author to ensure data accuracy. After undergoing training to ensure consistency in the process, thirteen authors participated in the data extraction process (A.A., C.T., L.L., M.F.G., M.L.M., N.M., R.C.W.M., S.K., C.H., G.Y., Y.Z., M.D.P., S.C.T.). To minimize inter-reviewer variability and ensure consistency in data extraction, all authors underwent training sessions via video conferences and participated in mock assessments.

During data extraction, studies were classified into three categories based on the primary type of prognostic factors

reported, namely biomarkers, genetic markers, and risk scores. Biomarkers were broadly defined as non-genetic laboratory tests, clinical conditions, socio-demographics, vital signs, diagnostic procedures, and imaging tests. Genetic markers included specific DNA sequences or variations, such as single nucleotide polymorphisms (SNPs), restriction fragment length polymorphisms (RFLP), or short tandem repeats (STR). Risk scores were defined as predictive models, algorithms, or risk calculation tools that estimated the overall likelihood or category of cardiovascular disease (CVD) based on a set of risk factors. When multiple genetic variants were combined to predict risk (using SNPs), the study was classified as a genetic marker (i.e., genetic risk score) rather than a risk score. Additional details about the included studies can be found in Supplemental Note 2.

The following data were extracted from each article using a standardized data form in Covidence and Excel data tables: study characteristics (country or countries of the study population, study start and end year, study design, inclusion/exclusion criteria, study setting, data sources), participant characteristics (years of follow-up, follow-up duration, total number of participants, race/ethnicity/ancestry, and baseline characteristics), prognostic factor(s) characteristics (name, prognostic factor type, units of measurement, units and cut-offs in regression analyses, transformation methods, effect measures [hazard ratio, odds ratio, c-statistic, net reclassification improvement (NRI), integrated discrimination index (IDI), etc.] and 95% confidence intervals, adjusted covariates), and outcomes (CVD outcome definition, number of events and non-events), and validation methods. For genetic markers, we collected risk variants, risk alleles, and closest gene (locus).

For continuous variables, we collected mean and standard deviation or median and interquartile range as reported in the study. We collected fully adjusted effect measures (HR, RR, OR, c-statistic) and their corresponding 95% CIs reported in the original articles. When studies reported multiple multivariate-adjusted effect measures, we collected the estimate from the most fully adjusted model. We did not contact primary authors to obtain data that were not reported. Furthermore, data were collected to evaluate the risk of biases in each study as summarized in Supplemental Table 2 and described in the quality assessment paragraph.

Quality assessment. We used a modified Newcastle-Ottawa Scale (NOS) to assess quality and risk of biases. The scale assesses studies based on six common domains, including representativeness of the exposed and non-exposed cohorts, ascertainment of exposure and outcome, and adequacy of study follow-up for primary and secondary CVD events, as well as the adequacy of cohort follow-up²⁸. For biomarker studies, we added two additional domains to the NOS to address bias due to confounding by evaluating the number of covariates and established CVD risk factors included in the adjusted models. Each study was given a score for each domain and an overall quality evaluation was determined by adding up these scores. The possible range of scores for non-genetic biomarkers, based on 8 domains, was 2 to 28, while for genetic biomarkers and risk scores, scores ranged from 2 to 18 based on 6 domains. Two authors assessed study quality independently, and a third author resolved any disagreements.

We reported the overall risk of bias based on the distribution of scores in each prognostic factor category, with higher scores representing lower risk of bias. Studies in the top, second, and lowest tertiles (according to the distribution specific for each type of study, i.e. non-genetic biomarkers, genetic biomarkers and risk scores) were considered to have low, medium, and high risk of

bias, respectively. The score of each domain was also classified as low, medium, or high risk of bias for graphical purposes, as clarified in Supplemental Table 2.

Statistical analysis. A random-effects model was used to pool the overall effect estimates in all meta-analyses, only if the heterogeneity test was statistically significant. For studies reporting the same effect measure (e.g. HR), we calculated the pooled effect estimate with 95% CIs for each biomarker or genetic marker and assessed heterogeneity between studies using the Cochran's Q statistic ($p < 0.1$), the I^2 index $>75\%$, and τ^2 . Due to the limited number of studies per prognostic factor, subgroup analyses by population characteristics or outcomes were not performed. We performed sensitivity analyses by excluding studies with high risk of bias. As the number of studies per prognostic factor was always less than 10, we were unable to assess publication bias using funnel plots. We used R, version 4.2.3 (R Project for Statistical Computing), with the "meta", "metafor", and "forestplot" packages for all analyses²⁹. Two-sided statistical tests were used with a significance threshold of <0.05 .

Strength of the evidence. We considered aspects of the GRADE approach³⁰ and the JBI critical appraisal tools³¹ in grading the strength of evidence for individual biomarkers and genetic markers/risk scores. We applied relevant GRADE criteria, including indirectness, inconsistency, and imprecision, throughout the study. Since we only included studies that involved patients with T2D and a "hard" clinical CVD outcome, the evidence is considered direct by definition. We analyzed the results from T2D patients with and without baseline CVD and specified all relevant CVD outcomes to assess the applicability of individual biomarkers in specific populations and outcomes. To ensure robustness and validity of our findings, we established strict eligibility criteria, excluding studies that did not adjust for established CVD risk factors (listed in Supplemental Table 3). Furthermore, we scored studies based on the adequacy of adjustment for covariates, including the total number of covariates and established CVD risk factors, in accordance with the JBI criterion for statistical adjustment of confounders.

We used the American Heart Association scientific consensus report for stepwise evaluation of novel markers for CVD risk²⁶ to identify promising biomarkers and genetic markers based on their strength of evidence progressing from measures of association, discrimination, improvement in discrimination, net reclassification index (NRI) or integrated discrimination index (IDI). This approach is summarized in Supplemental Table 4. For biomarkers and genetic markers, we progressed from those with significant adjusted association in at least one study to those with net positive number of studies showing significant association in a consistent direction. The net positive number of studies was calculated by summing up all studies with positive association and subtracting studies with no association (e.g., three studies showing positive association and two studies with no association yielded a net positive number of one). We identified biomarkers that improved prediction performance when added to established models, based on improvement in at least one of c-statistic, NRI (the probability that a person is appropriately classified into either high- or low-risk), or IDI (quantification of predicted probabilities of events and non-events based on inclusion of the biomarker in the model), and further narrowed down the list to those with improvement in all three indicators.

Accordingly, for each of the prognostic factors that passed our evidence-based screening criteria, predictive utility was classified as high (3 points), moderate (2 points), or low (<2 points) based on three criteria: number of studies with all three performance

indicators satisfied (1 point if >0 studies, 0 points if 0 studies), number of pooled meta-analyses showing significant association (1 point if >0, 0 points if 0 studies), non-pooled analysis showing $\geq 75\%$ of studies had a significant association (1 point if yes, 0 points if no). Strength of Evidence was classified as high (4 points), moderate (2 or 3 points), or low (<2 points) based on four criteria: at least one meta-analysis was conducted regardless of outcome (1 point if yes, 0 points if no), exclusion of high risk of bias studies did not alter inferences from meta-analyses (1 point if unaltered, 0 points if altered), exclusion of high risk of bias studies did not alter inferences from non-pooled analyses (1 point if unaltered, 0 points if altered), and consistencies in the definition of the prognostic marker used in analyses (1 point if yes, 0 points if no).

For the risk scores, we provide a complete assessment of risk of bias and pooled c-statistics; however, we decided not to conduct a corresponding stepwise approach to evidence grading as explained above for biomarkers/genetic markers due to the complexity in verifying specifications of each model over time and across comparisons. Inferences from the risk score results are here meant to guide future work that would permit analyses to handle this complexity.

Inclusion and ethics statement. This research is a part of a broader initiative, Precision Medicine in Diabetes Initiative (PMDI), that was established by the American Diabetes Association (ADA) in partnership with the European Association for the Study of Diabetes (EASD) and is led by global leaders in precision diabetes medicine. Therefore, researchers from multiple countries and continents have contributed to this study. The roles and responsibilities of co-authors were collaboratively agreed upon before the start of the review process. This study is exempt from ethical review due to the use of publicly available data.

Reporting summary. Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Results

Study selection and characteristics. Out of 9380 studies identified from databases/registries ($N=9332$) and other sources ($N=48$), there were 9316 unique studies after removing 64 duplicates. Of these, 615 articles were selected for full-text review, and finally, 416 articles were considered appropriate for inclusion in the analysis^{5,32–446}. Outcomes were reported for 321 biomarker studies, 48 genetic marker studies, and 47 risk score/model studies, as shown in Supplemental Data 1, 2, and 3. Figures 1 and 2 provide an overview of the screening and selection process.

Predominant ancestry in the studied populations were European (57.1%), East Asian (19.7%), South Asian (5.5%) and Hispanic or Latin American (4.2%). Geographically, the United States, United Kingdom, China, Japan, and Italy were the top five represented countries with regards to origin of study participants and author affiliation in the included studies. Figure 3 and online interactive figures (https://hugofitipaldi.shinyapps.io/T2D_prognostic/) offer a detailed breakdown of ethnic and geographic distributions⁴⁴⁷.

CVD outcomes. There was heterogeneity in the CVD outcomes evaluated across the analyzed studies (see Supplemental Fig. 1). The median duration of follow-up reported across studies was 5 years (IQR 3.1 to 7.8 years). The most frequently reported outcomes were coronary heart disease, cardiovascular mortality, and stroke, either individually or combined. The vast majority (87%)

of studies had a clearly defined outcome based on ICD-10 codes, clinical documentation, or adjudication, with 9% relying on registry or record linkage, and 4% using either patient self-report or having an unclear definition. We classified primary prevention as the prediction of CVD in individuals without a history of the disease, secondary prevention as the prediction of recurrent CVD events or CVD progression in those already diagnosed with the disease, and mixed populations as a combination of both primary and secondary prevention.

Biomarkers. Among 416 included studies, 321 (77.2%), 48 (11.5%), and 47 (11.2%) were studies of non-genetic biomarkers, genetic biomarkers, and non-genetic risk scores, respectively. Among the 321 studies of non-genetic biomarkers, 70 (21.8%) evaluated established CVD risk factors and were excluded, while 30 studies (9.3%) were included because they used a novel approach (e.g., variability, setting) for an established risk factor (Fig. 2). Further, three studies did not adjust for any CVD risk factors and were excluded, leaving 218 studies consisting of 195 unique biomarkers in the analysis.

Among these 195 biomarkers analyzed, 134 (69%) had a significant adjusted association for predicting CVD, based on a net positive number of studies (Fig. 4 and Supplemental Data 4). Out of these, 12 (9%) showed improvement in c-statistic, NRI, or IDI in more than one study: N-terminal pro b-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP), troponin T (TnT), coronary artery calcium score (CACs), coronary computed tomography angiography (CCTA), single-photon emission computed tomography (SPECT) scintigraphy, pulse wave velocity (PWV), galectin-3 (Gal-3), troponin I (TnI), carotid plaque, growth differentiation factor-15 (GDF-15), and triglyceride-glucose (TyG) index. The following biomarkers showed prediction performance but in only one study: SPECT, TnI, TyG, 25-hydroxyvitamin D, poly (ADP-ribose) polymerase (PARP), and interleukin-6 (IL-6).

Biomarkers with all three prediction performance indicators satisfied in more than one study were NT-proBNP, TnT, and CCTA, with results summarized in Table 1. For NT-proBNP, 5 studies reported improvement in c-statistics ranging from 0.01 to 0.07, significant increase in NRI ranging from 0.04 to 0.50, and significant rIDI ranging from 0.012 to 0.48 (in four studies). For TnT, 3 studies reported improvement in c-statistics ranging from 0.02 to 0.10, significant NRI ranging from 0.150 to 0.44, and rIDI ranging from 0.03 to 0.05. For CCTA, 3 studies reported improvement in c-statistics ranging from 0.08 to 0.35, with one study reporting statistically significant improvements in NRI of 0.55 and rIDI of 0.046. Of these three biomarkers, NT-proBNP showed the strongest incremental predictive value based on the magnitude of these indicators. Supplemental Data 5 shows the degree of variation in measurement methods used for each of these biomarkers.

Forest plots in Fig. 5a show the HRs for 11 studies evaluating NT-proBNP, conducted in heterogeneous populations (2 primary, 5 mixed, and 4 secondary), outcomes, units in regression analyses (i.e., SD, SD of log), and laboratory units (ng/L, pg/mL). Nonetheless, all studies except one showed a significant association with a CVD outcome. Eight out of 11 (73%) studies were assessed to be at low risk of bias. Figure 6a and Supplemental Figs. 2a, b show the meta-analysis of NT-proBNP as a continuous variable per logarithmic and per 1 SD unit increase, confirming the highly significant association with CVD (pooled HR 1.53, 95% CI 1.26–1.85 per log increase; pooled HR 1.59, 95% CI 1.27–1.99 per SD increase) after accounting for heterogeneity with the random effects models (I^2 90% and I^2 83%, respectively). Interestingly, although our review excluded studies

T2D CVD Prognostics

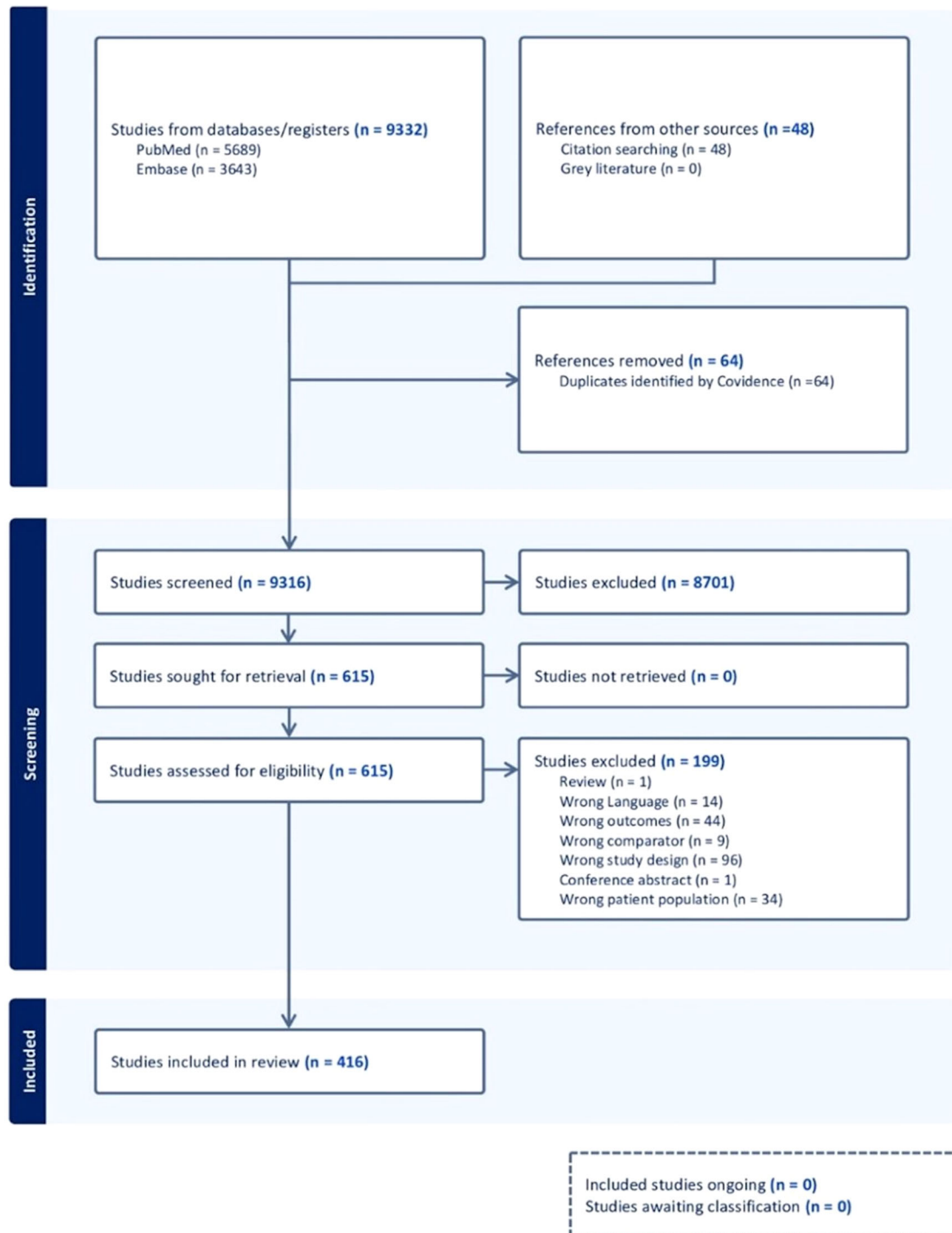


Fig. 1 PRISMA flow diagram detailing the process that led to final study inclusion for review. Flowchart illustrating the screening of studies through title and abstract review, screening, and inclusion. *n* number of studies.

focusing exclusively on heart failure patients, among three studies that incorporated EF as a covariate in their models, NT-proBNP was shown to have predictive value for cardiovascular outcomes independent of EF^{241,326,397} (Supplemental Data 5).

Forest plots in Fig. 5b show the HRs for 8 studies evaluating TnT, conducted primarily for mixed or secondary populations with variable CVD outcomes. Studies differed with respect to cut-offs and categories for TnT, units of measurement (ng/ml, ng/L)

and analysis (per log, per 1 SD log). Among these studies, all but one showed a positive association. Notably, the study by Lepojarvi 2016 was an outlier in its magnitude of effect and confidence intervals. Overall, for TnT, study quality was good with 6 out of 8 (75%) assessed to be at low risk of bias²²⁷. A significant association for TnT was observed in studies where the biomarker was evaluated as a continuous variable per 1 log increase with pooled HR 1.64 (95% CI 1.23, 2.18) and I² 59% (Fig. 6b and

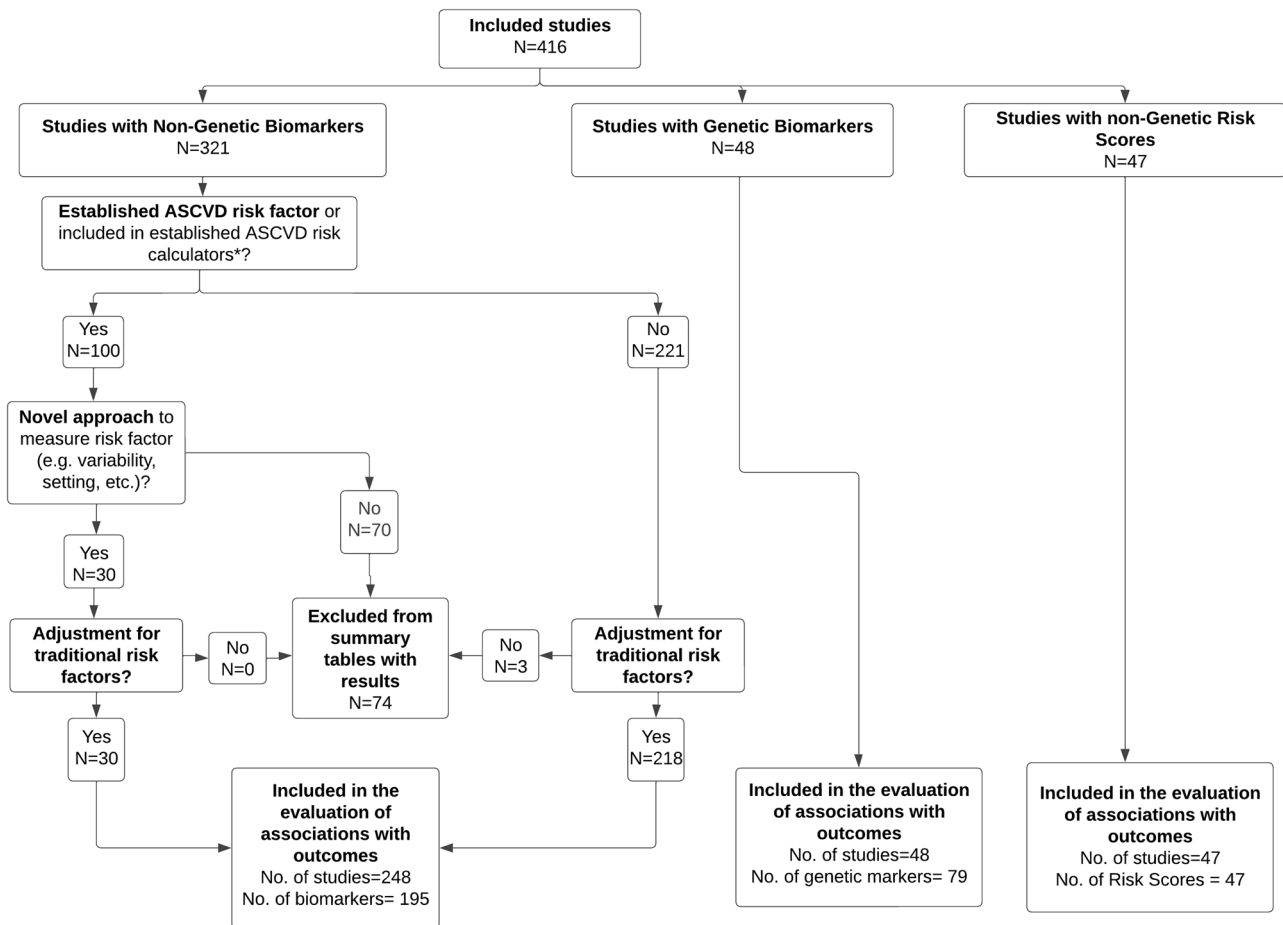


Fig. 2 Selection of studies to be included for evaluating the associations of biomarkers, genetic markers and non-genetic risk scores with cardiovascular outcomes. This figure shows the selection criteria used to identify included biomarkers, genetic biomarkers, and non-genetic risk scores. No. number. *See Supplemental Table 3.

Supplemental Fig. 3a); similarly, when treated as a binary or categorical variable, the pooled HR was 2.64 (95% CI 1.03, 6.72) with $I^2 = 95.9\%$ (Fig. 6b and Supplemental Fig. 3b). However, when treated as a continuous variable per 1 SD, there was no longer a significant association in a random effects model (Fig. 6b and Supplemental Fig. 3c).

Forest plots in Fig. 5c show the HRs for 5 studies evaluating CCTA conducted primarily for primary CVD prevention with variable CVD outcomes. Studies differed significantly with respect to CCTA definition of subclinical or clinical CHD. All 5 studies showed a significant association; however, 2 of the 5 studies (40%) were assessed to be at a high risk of bias.

Apart from these three biomarkers, SPECT, TnI, TyG, 25-hydroxyvitamin D, poly(ADP-ribose) polymerase (PARP), and interleukin-6 (IL-6) showed prediction performance in all three performance indicators but in only one study. Forest plots for the remaining 9 biomarkers that showed improvement in at least one performance indicator in more than one study (CACs, carotid plaque, CRP, gal-3, GDF-15, PWV, SPECT scintigraphy, TnI, and TyG) are shown in Supplemental Figs. 4–6. Again, there was substantial heterogeneity with respect to study populations, outcomes, and units of analysis for these biomarkers. Biomarkers showing positive association in at least 75% of studies included CACs, carotid plaque, gal-3, PWV, SPECT scintigraphy, TnI, and TyG. While CRP did not meet the threshold of 75% of studies showing an association, when meta-analyzed as a binary or categorical variable, it showed a significant pooled association;

PWV and TyG also demonstrated significant association in pooled analysis (Supplemental Fig. 7).

Genetic markers. Among the 48 genetic studies analyzed (Supplemental Data 2), 79 genetic biomarkers were examined for their association with incident CVD events (Supplemental Data 6), mainly in populations of European (65%) or Asian (26%) ancestries, with sparse representation of populations of other ancestries (e.g., African 12% or Hispanic 3%), with 12% of associations being tested in mixed populations. Most of the studies (70 out of 79) used single variants as distinct genetic biomarkers (exposure), while 9 studies used a combination of different SNPs into genetic risk scores (GRS) as the exposure. Remarkably, most of these exposures were tested only in one study, and external validation was performed in only 4 out of 48 studies, with only one study using a longitudinal cohort as a validation set, i.e., GRS for CHD. Overall, among the 79 genetic biomarkers, 33 (41.8%) had at least one study showing significant association, out of which 29 had a net positive number of studies showing significant association. Out of these 29 genetic biomarkers, two were tested in more than one study (rs10911021 on *GLUL*, GRS for CHD [GRS-CHD]), one had improvement in any performance indicator in a single study (isoform e4 in *APOE*), and one had improvement in all three performance indicators in a single study (GRS-CHD) (Fig. 7).

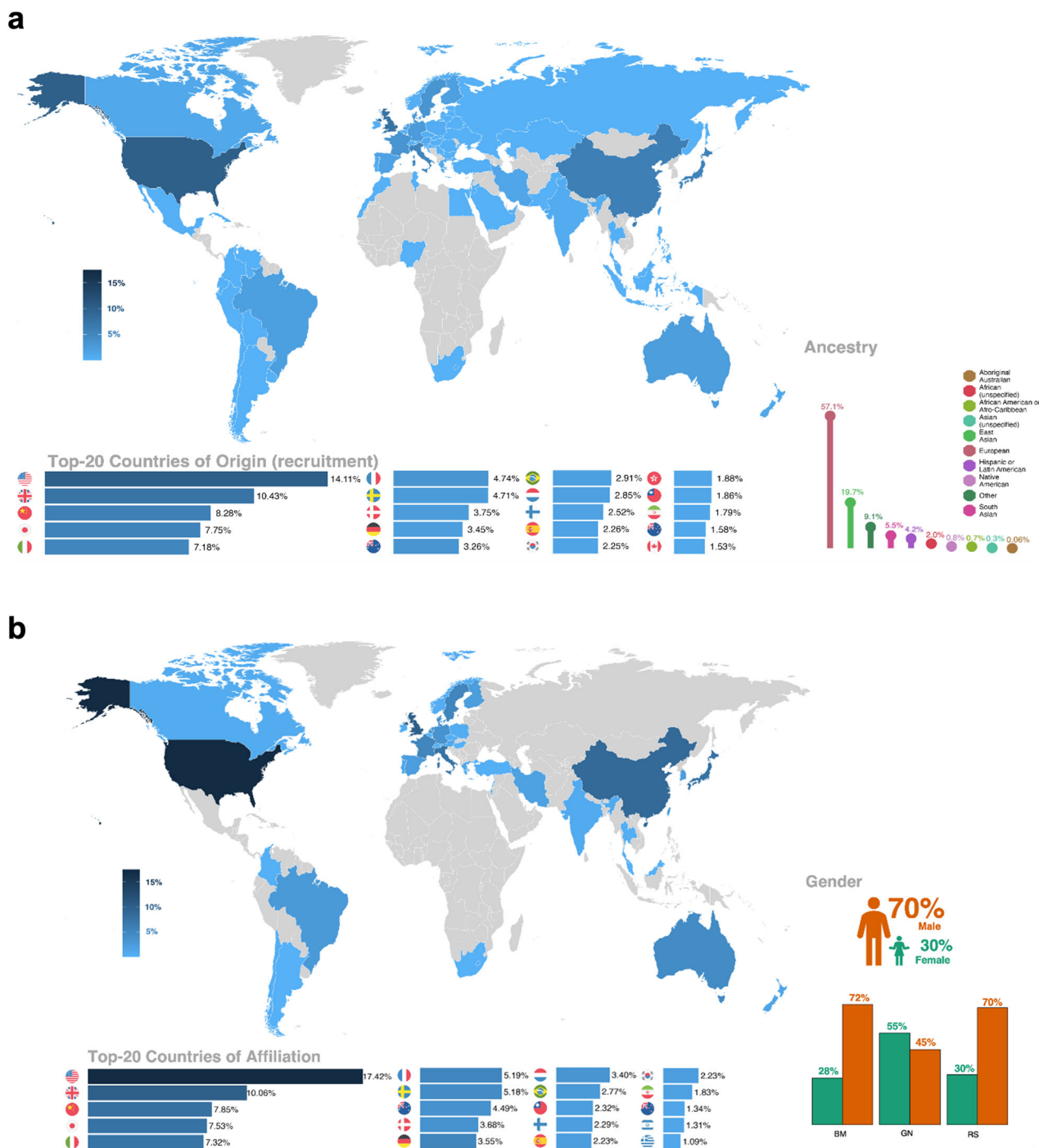


Fig. 3 Global distribution of origin and ancestry of the study populations and countries of affiliation and gender distribution of authors of the included studies. Panel **A** shows the top 20 countries of origin and ancestry of the study populations evaluated in the included studies. Panel **B** shows the top 20 countries of affiliation and gender distribution of authors of the included studies. The data used for this visualization was obtained from PubMed and PubMed Central through manual curation and by applying text mining functions developed using R software version 4.1.2. The final proportions of ancestries were calculated for each unique study and then aggregated as described in detail here⁴⁴⁸.

Notably, the rs10911021 variant in *GLUL* was the only single variant that showed an association with CVD in several studies. This variant was initially identified in T2D patients using a genome-wide approach and subsequently confirmed for its association with CVD in selected populations from two additional studies. For GRS-CHD, four separate studies investigated the combination of up to 204 CHD variants from 160 distinct loci derived from the general population. These studies had distinct but overlapping and increasing numbers of loci and variants

tested in more recent investigations. The most recently performed GRSs were externally validated and demonstrated significant improvements in CVD risk reclassification (cNRI) as well as notable enhancements of 8% in relative IDI (rIDI). However, these findings were identified in subjects of European ancestry and ancestry-specific analyses showed consistency in Asian subjects but not in other ancestral backgrounds. Forest plots for variants located on the GRS-CHD and *GLUL* are shown in Fig. 8, while their meta-analyses can be found in Supplemental Fig. 8.

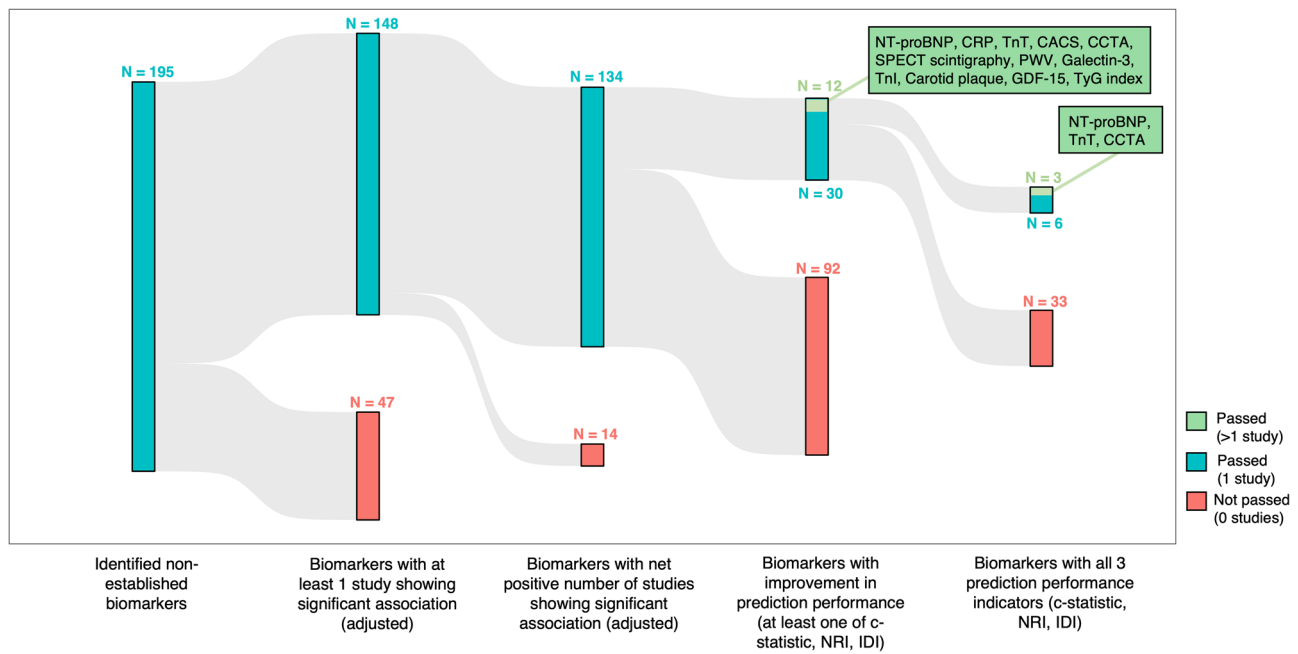


Fig. 4 Sankey diagram showing the funneling of identified non-genetic biomarkers through sequential filtering steps. The number of biomarkers passing or not passing each step (based on the criteria specified at the bottom of the diagram) is depicted at the top of the colored bars, with biomarkers passing all steps having the strongest predictive performance value.

Risk scores/models. Forty-seven studies reported results of 27 unique CVD risk scores (Supplemental Data 3 and 7). Supplemental Figs. 9 and 10 provides the c-statistics from internal and external validation analyses, respectively. On both internal and external validation, discrimination was modest. Most risk scores were developed in the United States, Europe, and East Asia and 61.1% of the internal validation studies were assessed to be at a high risk of bias. Model performance tended to decline when validated in countries that differed from the development cohort (Supplemental Fig. 11). For example, the FDS study achieved high c-statistics (>0.80) when validated in an Australian cohort, but lower ones (0.58–0.69) when tested in European countries. In line with previous studies^{5–7}, discrimination for the UKPDS and FRS was generally poor on external validation. Most prediction models focused on baseline characteristics and did not account for time-varying factors that may modify CVD risk (e.g., statin, SGLT-2i, GLP-1 RA). An exception was the BRAVO risk engine, published in 2020 and validated in trials of SGLT-2i patients, showing that this risk engine effectively predicted CV health benefits through improvements in common clinical measures (e.g., A1C, SBP, and BMI)³⁴³.

Supplemental Figs. 12, 13 provide the pooled c-statistics from external validation studies on those risk scores for which the analysis was possible: ADVANCE, CHS, CVD-EDIC, NDR, NZ DCS and UKPDS risk scores. All risk scores exhibited modest discrimination (pooled c-statistics ranging from 0.63 to 0.68), with no individual risk score substantially outperforming the others.

Supplemental Fig. 14a, b provide a histogram of the total number of adjusted covariates and number of adjusted traditional CVD risk factors in each of the studies, respectively. Supplemental Fig. 15 is a network figure representing the connections of the adjusted covariates in the 416 included studies.

Sensitivity analyses. The results of sensitivity analyses excluding studies with high risk of bias from meta-analyses of biomarkers, genetic risk score, and for risk scores where pooled analyses were possible, respectively, are shown in Supplemental Figs. 16–18.

Synthesis. Table 2 provides a summary of findings of studies assessing the most promising biomarkers and genetic markers/scores for precision prognosis of CVD in T2D, along with our conclusions regarding their predictive utility and strength of evidence. In our synthesis of the evidence, we took into account the results from the sensitivity analyses described in the previous paragraph. The highest predictive utility was observed for NT-proBNP (high-evidence), TnT (moderate-evidence), TyG (high-evidence), and GRS-CHD (moderate-evidence). Prognostic factors with moderate predictive utility were CCTA (low-evidence), SPECT scintigraphy (low-evidence), and PWV (moderate-evidence). Prognostic factors with low predictive utility included CRP (moderate-evidence), CACS (low-evidence), Gal-3 (low-evidence), TnI (low-evidence), carotid plaque (low-evidence), and GDF-15 (low-evidence). Supplemental Figs. 19–22, 23, 24 provide the quality assessment for the included biomarker, genetic marker, and risk score studies, respectively.

Discussion

Our systematic review of prognostic markers for CVD in individuals with T2D has revealed several notable findings. First, among the numerous studies that investigated the prognostic significance of CVD risk markers, only a few have been consistently found to be significantly associated with cardiovascular risk. Namely, NT-proBNP, TnT, TyG, and GRS-CHD demonstrated the highest predictive utility, with NT-proBNP having the strongest evidence. However, most of the remaining markers have not been adequately tested or compared against established CVD risk factors. Finally, even though some markers have demonstrated the capability of predicting cardiovascular events beyond what current risk factor-based models can offer, their application in clinical practice remains limited, as there is inadequate evidence of their contemporary clinical utility.

During the search process, a considerable number of studies were found ineligible for inclusion in our systematic review. Available studies were primarily cross-sectional in design, and only a limited number of them focused specifically on individuals with T2D and examined the early utility of risk factors and

Table 1 Performance of the prediction of 3 biomarkers with the most evidence.

Biomarker	Study	Clinical factors / biomarkers to be compared	Improvement in C-statistics		NRI		IDI	
			Yes /No	Estimate (95% CI) and P-value	NRI (95% CI)	P-value	IDI (95% CI)	P-value
NT-proBNP	Sharma 2020	Age, sex, SBP, history of HF, duration of diabetes, prior MI, hypertension, hyperlipidemia, smoking, eGFR.	Yes	0.05 (NR)	0.39 (0.30-0.47)	NR	0.09 (0.08-0.10)	<0.05
	Wolks 2017	Prior MI, BMI, NSTEMI (index event), heart rate, HbA _{1c} , percutaneous coronary intervention at the index event, cerebrovascular disease, Af, prior HF, sodium concentration, macroalbuminuria, PAD, age, and LDL concentration.	Yes	0.01 (CI NR), P<0.05	0.11 (5.7-16.6)	<0.05	0.08 (0.03-1.6)	<0.05
	Wong 2019	Age ≥ 65 years, Male, T2D, Hypertension	Yes	0.03 (CI NR), P = 0.001	0.35 (0.24-0.45)	<0.001	0.01 (0.01-0.02)	<0.001
	Scirica 2016	Treatment arms, age, SBP, sex, history of HF-, duration of diabetes, prior MI, history of hypertension, history of hyperlipidemia, smoking, and eGFR	Yes	0.07 (CI NR), P<0.001	0.040 (0.03-0.04)	<0.05	0.48 (0.41-0.55)	<0.05
	Van der Leeuw 2016	Female sex, age at diabetes diagnosis, duration of diabetes, HbA _{1c} , square of HbA _{1c} , SBP, square of SBP, TC/HDL ratio, urinary ACR, current smoking status, history of major macrovascular disease	Yes	0.02 (0.00-0.04), P-value NR	0.2 (0.10-0.44)	<0.05	NR	NR
	Van der Leeuw 2016	Female sex, age at diabetes diagnosis, duration of diabetes, HbA _{1c} , systolic blood pressure, TC/HDL ratio, eGFR, current smoking status, history of major macrovascular disease	Yes	0.02 (0.00-0.05), P-value NR	0.50 (0.26-0.73)	<0.05	NR	NR
	Lepojarvi 2016	Age, sex, history of acute MI, BMI, Canadian Cardiovascular Society grading of angina pectoris, left ventricular ejection fraction and mass index, HDL cholesterol, ACR, HbA _{1c} and type of glucose metabolism disorder	Yes	0.10 (CI and P-value NR),	0.231 (0.067-0.394)	<0.01	0.05 (0.03-0.08)	<0.001
	Scirica 2016	Treatment arms, age, SBP, sex, history of HF, duration of diabetes, prior MI, history of hypertension, history of hyperlipidemia, smoking, and eGFR	Yes	0.07 (CI NR), P<0.001	0.440 (0.380-0.510)	<0.05	0.03 (0.02-0.03)	<0.05
	Rørth 2019	Natural logarithm of NT-proBNP, age, sex, treatment effect, ejection fraction, NYHA class, BMI, heart rate, SBP, creatinine, LDL, prior angina pectoris, AF and pacemaker implantation.	Yes	0.02 (CI NR), P = 0.02	0.150 (0.051-0.261)	0.007	0.03 (0.01-0.06)	<0.001

Table 1 (continued)

Biomarker	Study	Clinical factors / biomarkers to be compared	Improvement in C-statistics		NRI		IDI	
			Yes /No	Estimate (95% CI) and P-value	NRI (95% CI)	P-value	IDI (95% CI)	P-value
CCTA	Lee 2017 Halon 2016	Age, male sex, HTN, smokers, hyperlipidemia, eGFR, and HbA _{1c} UKPDS and log CAC Score	Yes Yes	0.07 (CI NR), P = 0.03 0.35 (CI NR), P = 0.021	0.550 (0.343–0.757) 0.63 (CI NR)	<0.0001 NR	0.05 (0.02–0.07) 0.65 (CI NR)	0.0006 NR

Data on improvement in C-statistics was collected from the study, either as reported or derived by comparing the C-statistic obtained from the combination of the reference model and the novel biomarker. NR Not Reported, SBP systolic blood pressure, HF heart failure, MI myocardial infarction, BMI body mass index, AF atrial fibrillation, PAD peripheral artery disease, T2D Type 2 diabetes, eGFR estimated glomerular filtration rate, ACR albumin-creatinine ratio. P-values were extracted from studies as reported, therefore some p-values are given as <0.05 or <0.001 because exact p-values were unavailable.

biomarkers in predicting future cardiovascular events. A major limitation in many studies was inadequate adjustment for established CVD risk factors; and even if studies considered adjustments, only a small fraction evaluated clinical utility beyond the use of established risk factors. These findings emphasize the need for better-designed studies to improve our understanding of the prognostic value of markers for CVD in T2D.

Most studies included in the final analysis were conducted in people of European, East or South Asian ancestry, with the top-5 countries of recruitment being the United States, UK, China, Japan and Italy. African ancestry and countries were under-represented. A skewed geographical distribution was also evident regarding countries of author affiliation, with the same top-5 countries dominating the volume of publications. Although the geographical and ancestral imbalance reported here for biomarker studies is less pronounced than what was recently reported for GWAS studies⁴⁴⁸, it highlights the pressing need to enhance data collection, biomarker discovery and validation, as well as the development of population-specific cardiovascular risk prediction models in underrepresented populations and ancestries to hopefully help reduce healthcare disparities⁴⁴⁹.

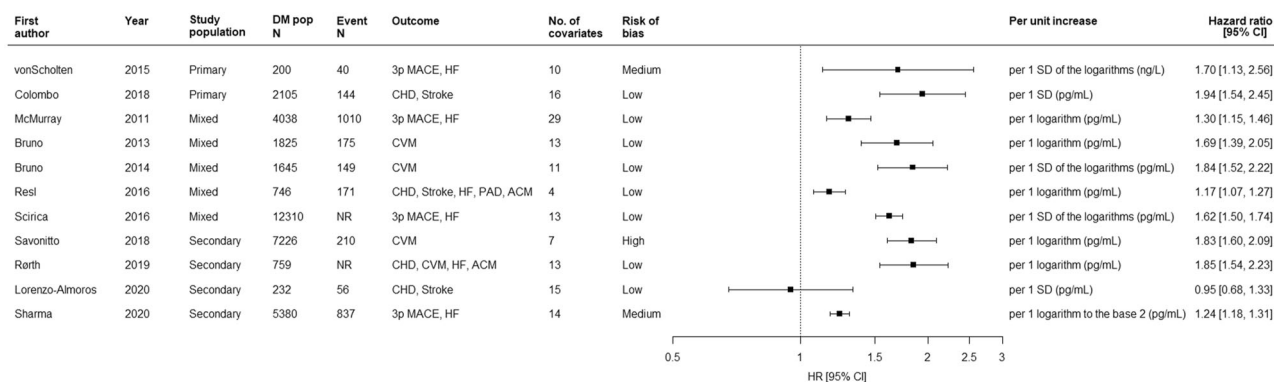
In our analyses, the novel biomarker emerging as the best predictor was NT-proBNP; indeed, it fulfilled all criteria of predictive and clinical utility with multiple studies showing improvement in all prediction performance indicators, with consistency of results across studies and meta-analyses. Notably, this biomarker had also been found to be useful as a prognostic marker for incident CVD in the general population⁴⁵⁰. Our findings suggest that NT-proBNP, beyond its established role in the diagnosis and management of patients with heart failure, might also be used as a marker to predict CVD. Another biomarker found in the general population to improve primary CVD risk prediction among asymptomatic middle-aged adults is high-sensitivity CRP (hs-CRP). In our review, CRP was found to have low predictive utility with moderate strength of evidence, which may be due to variability in cut-offs used for this marker, the relatively small numbers of studies, differential effects in diabetes, or less sensitive to detect low-grade vascular inflammation (compared with hs-CRP).

Despite numerous genetic studies probing the link between polymorphisms and cardiovascular outcomes in diabetes, few genetic markers have been consistently examined in longitudinal studies or reliably found to be associated with these outcomes. Only one study from the systematic review utilized a genome-wide association study (GWAS) approach, identifying the rs10911021 variant near *GLUL* to be associated with CV outcome in diabetes, at genome-wide significance. The variant at *GLUL* was subsequently confirmed in two independent studies¹⁷². A more recent GWAS conducted among Chinese patients with T2D identified a variant at *PDE1A* for CHD in T2D, which was not included in our systematic review as it fell beyond our study inclusion period⁴⁵¹. Polygenic risk scores also appear to emerge as promising tools, and GRS constructed from variants associated with CHD in the general population seem helpful for cardiovascular risk stratification in diabetes²⁵⁷.

Based on these limited findings, it becomes clear that we need a greater number of adequately powered GWAS to identify genetic markers associated with CVD in T2D. Nevertheless, we found several examples of studies that evaluated the utility of applying polygenic risk scores, or genome-wide polygenic risk scores, derived from the general population, for CVD risk stratification in T2D. In general, these have fair performance and a similar ability to stratify as in patients without diabetes. Considering the substantially larger sample sizes in currently published meta-analyses of GWAS for CHD in the general population, this approach will probably be more fruitful for the integration of

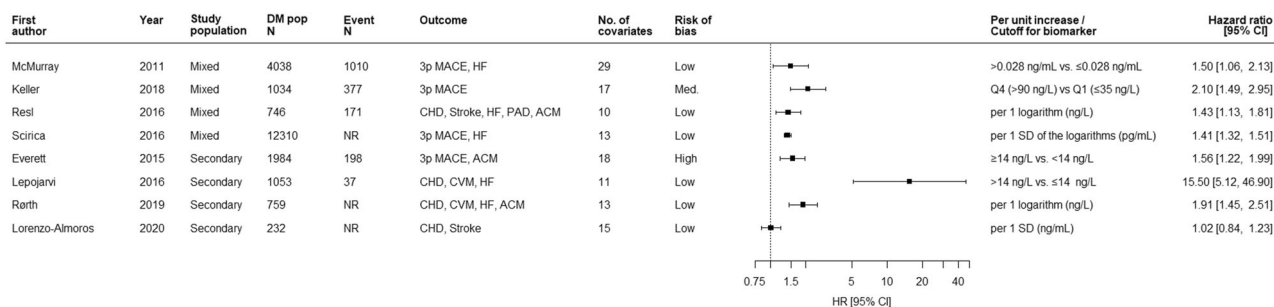
a

N terminal pro B type natriuretic peptide (NT-proBNP)



b

Troponin T (TnT)



c

Coronary computed tomography angiography (CCTA)

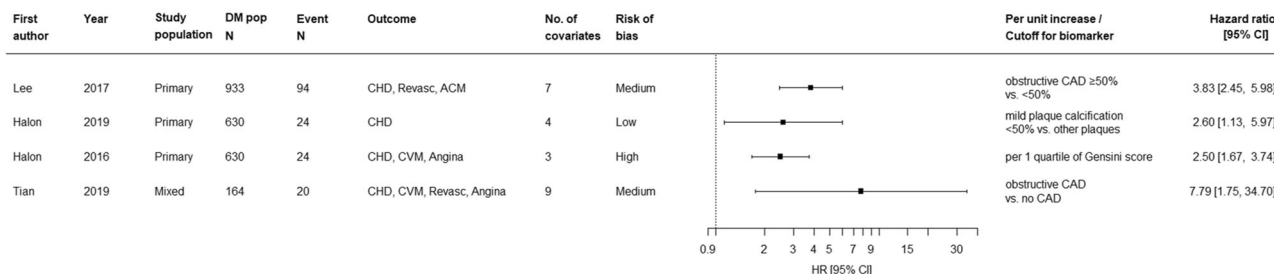


Fig. 5 Forest plots for three biomarkers (NT-proBNP, TnT, and CCTA) with the most evidence for prediction of CVD outcomes. Panel **a** (NT-proBNP); Panel **b** (TnT); Panel **c** (CCTA). HR hazard ratio, CI confidence interval, DM pop N, sample size for diabetes population; Event N, number of individuals developed CVD outcomes; 3p MACE, 3-point major adverse cardiovascular events; HF heart failure, CHD coronary heart disease, CVM cardiovascular mortality, PAD peripheral artery disease, ACM all-cause mortality.

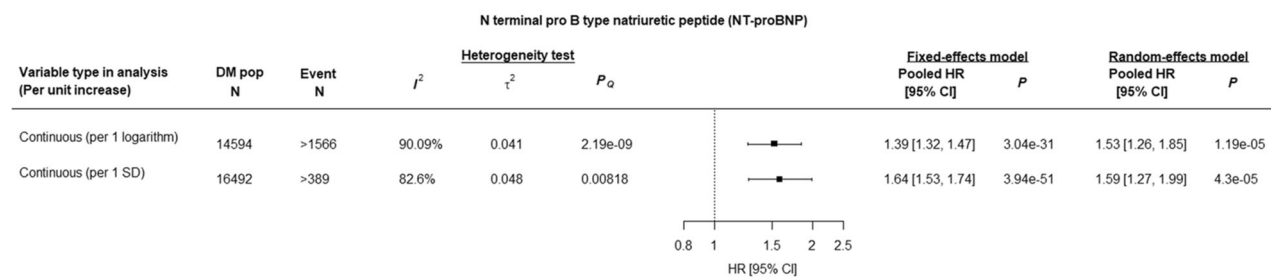
genetic markers into risk stratification of cardiovascular complications. In the limited studies that have evaluated the added benefit of polygenic risk scores above clinical markers, there is, in general, a modest but significant improvement in prediction. Whether polygenic risk scores will become viable options for future risk stratification would partly depend on the availability of these tools, and the cost-effectiveness of adding these measures into clinical practice.

Beyond individual prognostic markers, our review identified several studies that evaluated CVD risk prediction models. While the UKPDS risk engine (developed among subjects with newly diagnosed T2D the UK) and the Framingham risk equation (developed from the general population in the US) were the most widely studied, they do not perform well in contemporary studies of people with T2D. This suggests difficulties in applying certain

risk models to current healthcare settings. Nevertheless, our literature review shows that clinical risk models are perhaps the “readiest” for implementation in clinical practice to improve risk stratification in diabetes. On external validation, newer risk scores generally achieved higher discrimination compared to UKPDS and FRS, with Fremantle Diabetes Study 2 (FDS-2) having the highest c-statistic of 0.81 (developed and validated in different populations in Australia). We found that risk models performed better when validated in cohorts similar to the derivation cohort, with c-statistics of 0.699 ± 0.015 and 0.668 ± 0.006 (95% CI) ($P = 0.018$) for concordant and discordant studies, respectively.

In an era when electronic medical record (EMR)-based prediction models are being increasingly used, our results suggest that researchers should focus on the development of population-specific risk models that are intended to be deployed in the same

a



b

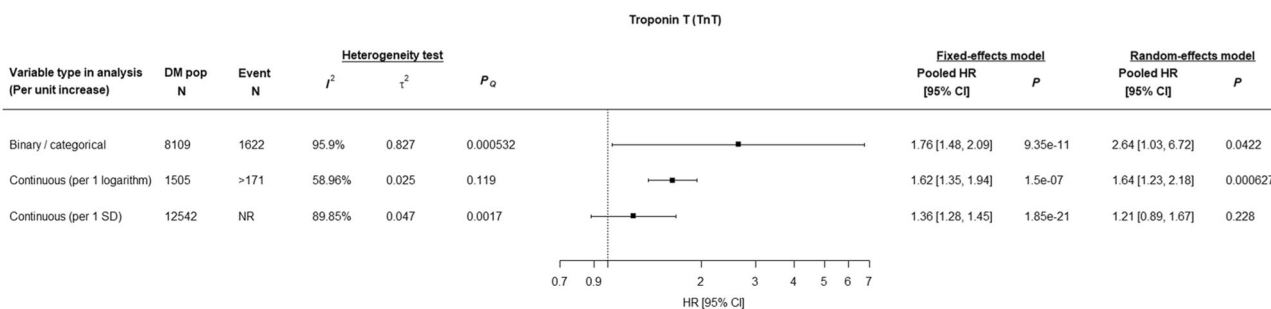


Fig. 6 Meta-analysis of NT-proBNP and TnT for predicting cardiovascular outcomes. Panel **a** (NT-proBNP); Panel **b**: TnT; P_Q is the p -value obtained from the Cochran’s Q test. HR, hazard ratio; CI, confidence interval; DM pop N , sample size for diabetes population; Event N , number of individuals developed CVD outcomes.

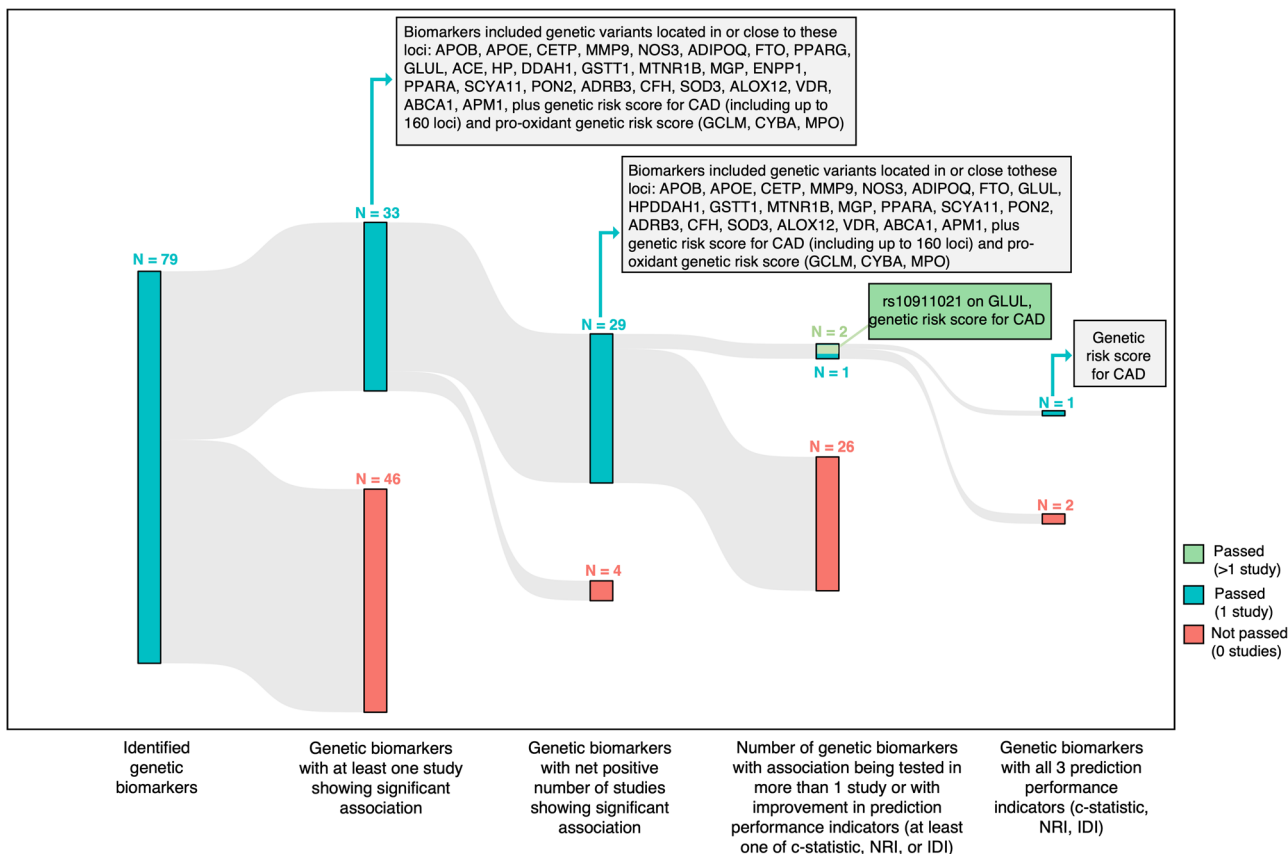
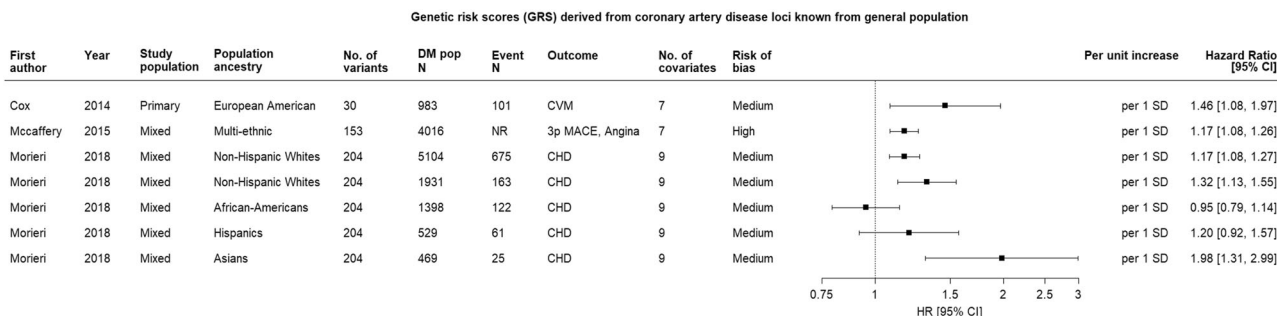


Fig. 7 Sankey diagram showing the funneling of identified genetic biomarkers through sequential filtering steps. The number of biomarkers passing or not passing each step (based on the criteria specified at the bottom of the diagram) is depicted at the top of the colored bars, with biomarkers passing all steps having the strongest predictive performance value.

a



b

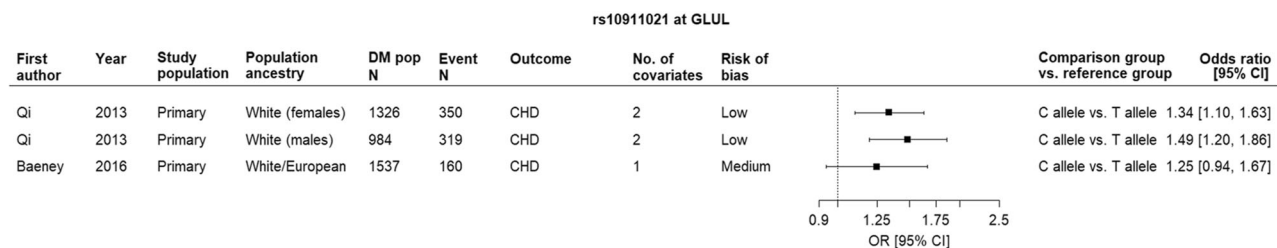


Fig. 8 Forest plots of genetic risk scores and *GLUL* variant rs10911021 for predicting cardiovascular outcomes. Panel **a**: Genetic risk scores; Panel **b**: *GLUL* variant rs10911021; HR, hazard ratio; CI, confidence interval; DM pop N, sample size for diabetes population; Event N, number of individuals developed CVD outcomes; 3p MACE, 3-point major adverse cardiovascular events.

population from which they were developed since the goal should be to achieve the highest predictive accuracy rather than to find a generic model that performs modestly well in all settings. Despite their potential utility and low implementation costs, we found a paucity of evidence showing integration of risk engine calculators into clinical practice. We are aware of several notable exceptions. For example, the Joint Asia Diabetes Evaluation (JADE) program has incorporated several risk prediction algorithms derived from Asian patients with diabetes into a web-based e-health portal, together with a graphical interface and decision support⁴⁵², and has been evaluated in different clinical settings, including in randomized clinical trials^{453–456}. Many EMR systems offer quick calculations of CVD risk using the American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations based on inputs available in the patient’s record, and we recommend that future risk scores found to have high predictive accuracy be made easily accessible to clinicians within their EMR workflow.

Given the limitations and gaps that emerged from this review, we recommend that future studies follow several guidelines to improve the quality and impact of studies on precision prognostics in diabetes. First, studies attempting to identify a risk marker should be conducted in prospective or longitudinal cohorts or trials, to provide more robust and reliable data. Second, studies should have sufficient sample size and duration of follow-up (at least 3 years for primary CVD events and at least 1 year for secondary CVD events) to ensure adequate statistical power. Third, studies must adjust for a minimal set of established clinical cardiovascular risk factors, to ensure that known risk factors do not confound any observed associations. Finally, studies must attempt to explore the added utility of biomarkers by comparing against prediction using established risk factors or models, or available risk engines for cardiovascular events. This would include evaluation of the change in c-statistics after adding risk markers/biomarkers of interest but also consider including additional metrics such as NRI and IDI. We believe that if journals make these requirements mandatory when evaluating such studies, it will help ensure that research funders are made

aware and future studies are best suited for informing advances in this area especially in resource-limited countries. As in any other research field, harmonization of protocols, methods, and analysis pipelines should be encouraged to allow comparisons across studies and for clinical translation.

There are several unique strengths of this work. To our knowledge, this represents one of the most comprehensive overviews of the current status of knowledge about risk stratification of cardiovascular outcomes in T2D. We included studies from 1990 onwards, to capture some of the older studies, as well as more contemporary studies. Our inclusion of “biomarkers” in the broadest term allowed us to provide an objective overview of the different approaches currently being explored for better risk stratification. Limiting the analyses to studies using longitudinal cohorts allowed us to focus on studies that would inform prognostication. Limiting analyses to “hard” cardiovascular endpoints, rather than also including surrogate endpoints such as carotid intima-medial thickness, allowed us to focus on endpoints that would be of greatest clinical relevance. However, while this approach allows us to maximize the translational approach of our analyses, future studies focused on identification of biomarkers associated with early disease-informative endpoints (i.e. sub-clinical markers of atherosclerosis or minor cardiovascular disease) might identify different novel biomarkers for early-stage cardiovascular complications.

Our study does have limitations. We had to omit a considerable number of cross-sectional studies due to the extensive scope of the systematic review and the explained focus on longitudinal studies. We included only English language publications. Our search terms, potentially more sensitive towards detecting studies on clinical risk factors and biomarkers than genetic factors, may have led to fewer genetic studies being identified. However, we managed to supplement this by reintegrating some missing articles using the identified literature and the investigators’ expertise.

In conclusion, our systematic review on prognostic markers for cardiovascular endpoints in T2D identified several findings, which to the best of our knowledge, have not been previously reported, and has revealed some important knowledge gaps. We

Table 2 Conclusion and strength of the evidence.

Prognostic Biomarker	A No. of studies with all 3 performance indicators satisfied	B No. of pooled meta-analyses showing significant association	C No. of pooled meta-analyses showing significant association (excluding high risk of bias)	D Non-pooled analyses showed that >=75% of studies had significant association	E Persistent association on sensitivity analysis for non-pooled analyses (excluding high risk of bias)	F Consistency in definition of prognostic biomarker used in analysis	G Conclusion (predictive utility)	H Strength of Evidence
NT-proBNP	3	2/2	2/2	Yes	Yes	Yes	High	High
CRP	0	1/2	1/2	No	No	No	Low	Moderate
TnT	4	2/3	1/3	Yes	Yes	No	High	Moderate
CACS	0	0	0	Yes	No	No	Low	Low
CCTA	2	0	0	Yes	No	No	Moderate	Low
SPECT	1	0	0	Yes	No	No	Moderate	Low
PWW	0	1/1	1/1	Yes	Yes	No	Moderate	Moderate
Gal-3	0	0	0	Yes	Yes	No	Low	Moderate
TnI	1	0	0	No	No	No	Low	Low
Carotid plaque	0	0	0	Yes	Yes	No	Low	Low
GDF-15	0	0	0	No	No	No	Low	Low
TyG	1	1/1	NA	Yes	No	Yes	High	Moderate
GRS-CHD	1	1/1	1/1	Yes	No	No	High	Moderate

Table includes genetic and non-genetic biomarkers showing improvement in prediction performance (i.e. at least one of c-statistic, NRI, IDI) and in more than 1 study (corresponding to all markers in green boxes in Fig. 4 and Fig. 5). Notes: Predictive utility was classified as high (3 point), moderate (2 points) or low (<2 points) based on the criteria defined in columns A, B and D (Column A: >0 = 1 point; Column B: >0 = 1 point; Column D: "Yes" = 1 point). Strength of Evidence was classified as High (4 points), moderate (2 or 3 points) and low (<2 points) based on criteria defined in columns B, C, E and F (Column B: at least one meta-analysis conducted [regardless of outcome] = 1 point; Column C: exclusion of high risk of bias studies did not alter inferences from meta-analyses [same number as in column B] = 1 point; Column E: exclusion of high risk of bias studies did not alter inferences from non-pooled analyses [YES] = 1 point; Column F: "yes" = 1 point).

found that NT-proBNP, TnT, TyG, and GRS-CHD had high predictive utility beyond traditional CVD risk factors, with the highest strength of evidence for NT-proBNP. Among genetic markers, there was only sufficient evidence for the polygenic risk score for CHD, and among risk scores, predictive utility was modest on external validation. Given the relatively low number of studies analyzing these novel prognostic factors using a rigorous approach, these findings support the need for future studies testing these markers with convincing demonstration of incremental predictive utility. NT-proBNP appears to be the only biomarker ready to be tested prospectively to evaluate its utility in modifying clinical practice for prediction of CVD risk.

Data availability

The protocol for this systematic review and meta-analysis is publicly available through the International Prospective Register of Systematic Reviews (PROSPERO), with the registration number CRD42021262843. Comprehensive search strategies that can be reproduced are outlined in Supplemental Note 1. Any further details required are available from the corresponding author upon reasonable request. Complete lists of the publications where data were extracted for this study are provided as Excel files in Supplemental Data 1 (list of studies on non-genetic biomarkers), Supplemental Data 2 (list of studies on genetic biomarkers), and Supplemental Data 3 (list of studies on non-genetic risk scores). Supplemental Data 4, 6, and 7 provide source data used to generate forest plots and meta-analyses. The data presented in Fig. 3 is also available as online interactive figures (https://hugofitipaldi.shinyapps.io/T2D_prognostic/) and in a data repository (<https://zenodo.org/records/10277173>)⁴⁴⁷.

Received: 12 May 2023; Accepted: 14 December 2023;

Published online: 22 January 2024

References

- Rawshani, A. et al. Mortality and cardiovascular disease in Type 1 and Type 2 diabetes. *Nw Eng. J. Med.* **376**, 1407–1418 (2017).
- Pearson-Stuttard, J. et al. Trends in predominant causes of death in individuals with and without diabetes in England from 2001 to 2018: an epidemiological analysis of linked primary care records. *Lancet Diabetes Endocrin.* **9**, 165–173 (2021).
- Nathan, D. M. et al. Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. *N Engl J Med* **387**, 1063–1074 (2022).
- I. D. F. Diabetes Atlas. *Diabetes around the world in 2021*, <https://diabetesatlas.org/> (2021).
- van Dieren, S. et al. External validation of the UK Prospective Diabetes Study (UKPDS) risk engine in patients with Type 2 diabetes. *Diabetologia* **54**, 264–270 (2011).
- Szymoniak, J. et al. Cardiovascular disease risk prediction for people with type 2 diabetes in a population-based cohort and in electronic health record data. *JAMIA Open* **3**, 583–592 (2020).
- Ho, J. C. et al. Evaluation of available risk scores to predict multiple cardiovascular complications for patients with type 2 diabetes mellitus using electronic health records. *Comp. Methods Prog. Biomed. Update* **3**, 100087 (2023).
- Chung, W. K. et al. Precision medicine in diabetes: a consensus report from the American Diabetes Association (ADA) and the European Association for the study of diabetes (EASD). *Diabetes Care* **43**, 1617–1635 (2020).
- Nolan, J. J. et al. ADA/EASD precision medicine in diabetes initiative: an international perspective and future vision for precision medicine in diabetes. *Diabetes Care* **45**, 261–266 (2022).
- Tobias, D. K. et al. Second international consensus report on gaps and opportunities for the clinical translation of precision diabetes medicine. *Nat. Med.* **29**, 2438–2457 (2023).
- Damen, J. A. et al. Prediction models for cardiovascular disease risk in the general population: systematic review. *BMJ* **353**, i2416 (2016).
- Zhiting, G. et al. Cardiovascular disease risk prediction models in the Chinese population- a systematic review and meta-analysis. *BMC Public Health* **22**, 1608 (2022).
- Damen, J. A. et al. Performance of the Framingham risk models and pooled cohort equations for predicting 10-year risk of cardiovascular disease: a systematic review and meta-analysis. *BMC Med.* **17**, 109 (2019).
- Romero-Cabrera, J. L., Ankeny, J., Fernández-Montero, A., Kales, S. N. & Smith, D. L. A systematic review and meta-analysis of advanced biomarkers for predicting incident cardiovascular disease among asymptomatic middle-aged adults. *Int. J. Mol. Sci.* **23**, 13540 (2022).
- van Holten, T. C. et al. Circulating biomarkers for predicting cardiovascular disease risk: a systematic review and comprehensive overview of meta-analyses. *PLoS One* **8**, e62080 (2013).
- Guasti, L. et al. TMAO as a biomarker of cardiovascular events: a systematic review and meta-analysis. *Intern. Emerg. Med.* **16**, 201–207 (2021).
- Rienks, J., Barbaresco, J. & Nöthlings, U. Association of polyphenol biomarkers with cardiovascular disease and mortality risk: a systematic review and meta-analysis of observational studies. *Nutrients* **9**, 415 (2017).
- Gohel, V., Jones, J. A. & Wehler, C. J. Salivary biomarkers and cardiovascular disease: a systematic review. *Clin. Chem. Lab Med.* **56**, 1432–1442 (2018).
- Kanbay, M. et al. Sclerostin, cardiovascular disease and mortality: a systematic review and meta-analysis. *Int. Urol. Nephrol.* **48**, 2029–2042 (2016).
- Heianza, Y., Ma, W., Manson, J. E., Rexrode, K. M. & Qi, L. Gut microbiota metabolites and risk of major adverse cardiovascular disease events and death: a systematic review and meta-analysis of prospective studies. *J. Am. Heart Assoc.* **6**, e004947 (2017).
- Wallace, T. C., Slavin, M. & Frankenfeld, C. L. Systematic review of anthocyanins and markers of cardiovascular disease. *Nutrients* **8**, 32 (2016).
- Emadian, A., Andrews, R. C., England, C. Y., Wallace, V. & Thompson, J. L. The effect of macronutrients on glycaemic control: a systematic review of dietary randomised controlled trials in overweight and obese adults with type 2 diabetes in which there was no difference in weight loss between treatment groups. *Br. J. Nutr.* **114**, 1656–1666 (2015).
- Yun, H., Noh, N. I. & Lee, E. Y. Genetic risk scores used in cardiovascular disease prediction models: a systematic review. *Rev. Cardiovasc. Med.* **23**, 8 (2022).
- Jeong, E. G. et al. Depth and combined infection is important predictor of lower extremity amputations in hospitalized diabetic foot ulcer patients. *Korean J. Intern Med.* **33**, 952–960 (2018).
- Lin, J. S. et al. Nontraditional risk factors in cardiovascular disease risk assessment: updated evidence report and systematic review for the US preventive services task force. *Jama* **320**, 281–297 (2018).
- Hlatky, M. A. et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. *Circulation* **119**, 2408–2416 (2009).
- Page, M. J. et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* **372**, n71 (2021).
- Wells GA, S. B., et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
- Viechtbauer, W. Conducting meta-analyses in R with the metafor Package. *J. Stat. Soft.* **36**, 1–48 (2010).
- Owens, D. K. et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—agency for healthcare research and quality and the effective health-care program. *J. Clin. Epidemiol.* **63**, 513–523 (2010).
- Aromataris E. et al. *JBI Manual for Evidence Synthesis*. *JBI*, <https://doi.org/10.46658/JBIMES-20-01> (2020).
- Aboyans, V. et al. The prognosis of diabetic patients with high ankle-brachial index depends on the coexistence of occlusive peripheral artery disease. *J. Vasc. Surg.* **53**, 984–991 (2011).
- Abu-Lebdeh, H. S., Hodge, D. O. & Nguyen, T. T. Predictors of macrovascular disease in patients with Type 2 diabetes mellitus. *Mayo Clin. Proc.* **76**, 707–712 (2001).
- Afarideh, M. et al. Complex association of serum alanine aminotransferase with the risk of future cardiovascular disease in Type 2 diabetes. *Atherosclerosis* **254**, 42–51 (2016).
- Afsharian, S. et al. Risk factors for cardiovascular disease and mortality events in adults with Type 2 diabetes- a 10-year follow-up: Tehran lipid and glucose study. *Diabetes Metab. Res. Rev.* **32**, 596–606 (2016).
- Alele, J. D., Luttrell, L. M., Hollis, B. W., Luttrell, D. K. & Hunt, K. J. Relationship between vitamin D status and incidence of vascular events in the Veterans Affairs Diabetes Trial. *Atherosclerosis* **228**, 502–507 (2013).
- Alkhalaf, A. et al. Sex specific association between carnosinase gene CNPD1 and cardiovascular mortality in patients with Type 2 diabetes (ZODIAC-22). *J. Nephrol.* **28**, 201–207 (2015).
- Anand, D. V., Lahiri, A., Lim, E., Hopkins, D. & Corder, R. The relationship between plasma osteoprotegerin levels and coronary artery calcification in uncomplicated Type 2 diabetic subjects. *J. Am. Coll. Cardiol.* **47**, 1850–1857 (2006).
- Anand, D. V. et al. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. *Eur. Heart J.* **27**, 713–721 (2006).
- Anavekar, N. S. et al. Predictors of cardiovascular events in patients with Type 2 diabetic nephropathy and hypertension: a case for albuminuria. *Kidney Int Suppl.* **66** S50–55 (2004).

41. Angiolillo, D. J. et al. Impact of platelet reactivity on cardiovascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease. *J Am Coll Cardiol* **50**, 1541–1547 (2007).
42. Anyanwagu, U., Donnelly, R. & Idris, I. Albuminuria regression and all-cause mortality among insulin-treated patients with Type 2 Diabetes: analysis of a large UK primary care Cohort. *Am. J. Nephrol.* **49**, 146–155 (2019).
43. Apperloo, E. M., Pena, M. J., de Zeeuw, D., Denig, P. & Heerspink, H. J. L. Individual variability in response to renin angiotensin aldosterone system inhibition predicts cardiovascular outcome in patients with Type 2 diabetes: a primary care cohort study. *Diabetes Obes. Metab.* **20**, 1377–1383 (2018).
44. Araki, S. et al. Predictive effects of urinary liver-type fatty acid-binding protein for deteriorating renal function and incidence of cardiovascular disease in type 2 diabetic patients without advanced nephropathy. *Diabetes Care* **36**, 1248–1253 (2013).
45. Avogaro, A. et al. Incidence of coronary heart disease in Type 2 diabetic men and women: impact of microvascular complications, treatment, and geographic location. *Diabetes Care* **30**, 1241–1247 (2007).
46. Azab, B., Chainani, V., Shah, N. & McGinn, J. T. Neutrophil-lymphocyte ratio as a predictor of major adverse cardiac events among diabetic population: a 4-year follow-up study. *Angiology* **64**, 456–465 (2013).
47. Azevedo, M. J. et al. Value of diagnostic tools for myocardial ischemia used in routine clinical practice to predict cardiac events in patients with type 2 diabetes mellitus: a prospective study. *Arq. Bras. Endocrinol. Metab.* **50**, 46–52 (2006).
48. Bacci, S. et al. The ENPP1 Q121 variant predicts major cardiovascular events in high-risk individuals: evidence for interaction with obesity in diabetic patients. *Diabetes* **60**, 1000–1007 (2011).
49. Backhaus, S. J. et al. Cardiac magnetic resonance myocardial feature tracking for optimized risk assessment after acute myocardial infarction in patients with Type 2 Diabetes. *Diabetes* **69**, 1540–1548 (2020).
50. Basu, S. et al. Validation of risk Equations for complications of Type 2 diabetes (RECODE) using individual participant data from diverse longitudinal Cohorts in the U.S. *Diabetes Care* **41**, 586–595 (2018).
51. Basu, S., Sussman, J. B., Berkowitz, S. A., Hayward, R. A. & Yudkin, J. S. Development and validation of risk equations for complications Of Type 2 diabetes (RECODE) using individual participant data from randomised trials. *Lancet Diabetes Endocrinol.* **5**, 788–798 (2017).
52. Bates, R. E. et al. Impact of stress testing for coronary artery disease screening in asymptomatic patients with diabetes mellitus: a community-based study in olmsted county, Minnesota. *Mayo Clin. Proc.* **91**, 1535–1544 (2016).
53. Beaney, K. E. et al. Variant rs10911021 that associates with coronary heart disease in type 2 diabetes, is associated with lower concentrations of circulating HDL cholesterol and large HDL particles but not with amino acids. *Cardiovasc. Diabetol.* **15**, 115 (2016).
54. Beilin, J., Stanton, K. G., McCann, V. J., Knuiaman, M. W. & Divitini, M. L. Microalbuminuria in Type 2 diabetes: an independent predictor of cardiovascular mortality. *Aust. N Z J. Med.* **26**, 519–525 (1996).
55. Bell, K. J. L. et al. Prognostic impact of systolic blood pressure variability in people with diabetes. *PLoS One* **13**, e0194084 (2018).
56. Berkelmans, G. F. N. et al. Prediction of individual life-years gained without cardiovascular events from lipid, blood pressure, glucose, and aspirin treatment based on data of more than 500,000 patients with Type 2 diabetes mellitus. *Eur Heart J* **40**, 2899–2906 (2019).
57. Bernard, S. et al. Relation between XbaI apolipoprotein B gene polymorphism and cardiovascular risk in a Type 2 diabetic cohort. *Atherosclerosis* **175**, 177–181 (2004).
58. Bernard, S. et al. Incremental predictive value of carotid ultrasonography in the assessment of coronary risk in a cohort of asymptomatic Type 2 diabetic subjects. *Diabetes Care* **28**, 1158–1162 (2005).
59. Bianco, H. T. et al. Relevance of target-organ lesions as predictors of mortality in patients with diabetes mellitus. *Arq Bras Cardiol* **103**, 272–281 (2014).
60. Biscetti, F. et al. Association between omentin-1 and major cardiovascular events after lower extremity endovascular revascularization in diabetic patients: a prospective cohort study. *Cardiovasc. Diabetol.* **19**, 170 (2020).
61. Bonito, B., Silva, A. P., Rato, F., Santos, N. & Neves, P. L. Resistin as a predictor of cardiovascular hospital admissions and renal deterioration in diabetic patients with chronic kidney disease. *J. Diabetes Complications* **33**, 107422 (2019).
62. Bosevski, M., Borozanov, V., Tosev, S. & Georgievska-Ismail, L. Is assessment of peripheral endothelial dysfunction useful tool for risk stratification of Type 2 diabetic patients with manifested coronary artery disease? *Int. J. Cardiol.* **131**, 290–292 (2009).
63. Bouchi, R. et al. Fluctuations in HbA1c are associated with a higher incidence of cardiovascular disease in Japanese patients with Type 2 diabetes. *J. Diabetes Invest.* **3**, 148–155 (2012).
64. Brownrigg, J. R. et al. Microvascular disease and risk of cardiovascular events among individuals with Type 2 diabetes: a population-level cohort study. *Lancet Diabetes Endocrinol* **4**, 588–597 (2016).
65. Bruce, D. G., Davis, W. A., Starkstein, S. E. & Davis, T. M. A prospective study of depression and mortality in patients with Type 2 diabetes: the Fremantle Diabetes Study. *Diabetologia* **48**, 2532–2539 (2005).
66. Bruno, G., Barutta, F., Landi, A., Cavallo Perin, P. & Gruden, G. NT-proBNP linking low-moderately impaired renal function and cardiovascular mortality in diabetic patients: the population-based Casale Monferrato Study. *PLoS One* **9**, e114855 (2014).
67. Bruno, G. et al. N-terminal probrain natriuretic peptide is a stronger predictor of cardiovascular mortality than C-reactive protein and albumin excretion rate in elderly patients with type 2 diabetes: the Casale Monferrato population-based study. *Diabetes Care* **36**, 2677–2682 (2013).
68. Bruno, G. et al. Fibrinogen and AER are major independent predictors of 11-year cardiovascular mortality in Type 2 diabetes: the Casale Monferrato Study. *Diabetologia* **48**, 427–434 (2005).
69. Bruno, G. et al. Metabolic syndrome as a predictor of all-cause and cardiovascular mortality in Type 2 diabetes: the Casale Monferrato Study. *Diabetes Care* **27**, 2689–2694 (2004).
70. Burgess, D. C. et al. Incidence and predictors of silent myocardial infarction in Type 2 diabetes and the effect of fenofibrate: an analysis from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Eur. Heart J.* **31**, 92–99 (2010).
71. Busch, M. et al. The advanced glycation end product N(epsilon)-carboxymethyllysine is not a predictor of cardiovascular events and renal outcomes in patients with type 2 diabetic kidney disease and hypertension. *Am. J. Kidney Dis.* **48**, 571–579 (2006).
72. Böger, C. A. et al. RANTES gene polymorphisms predict all-cause and cardiac mortality in Type 2 diabetes mellitus hemodialysis patients. *Atherosclerosis* **183**, 121–129 (2005).
73. Cardona, A. et al. Trimethylamine N-oxide and incident atherosclerotic events in high-risk individuals with diabetes: an ACCORD trial post hoc analysis. *BMJ Open Diabetes Res Care* **7**, e000718 (2019).
74. Cardoso, C. R., Ferreira, M. T., Leite, N. C. & Salles, G. F. Prognostic impact of aortic stiffness in high-risk Type 2 diabetic patients: the Rio de Janeiro Type 2 Diabetes Cohort Study. *Diabetes Care* **36**, 3772–3778 (2013).
75. Cardoso, C. R., Leite, N. C. & Salles, G. F. Prognostic importance of C-Reactive protein in high cardiovascular risk patients with Type 2 diabetes mellitus: the Rio de Janeiro Type 2 diabetes Cohort Study. *J. Am. Heart Assoc.* **5**, e004554 (2016).
76. Cardoso, C. R., Salles, G. F. & Deccache, W. Prognostic value of QT interval parameters in Type 2 diabetes mellitus: results of a long-term follow-up prospective study. *J. Diabetes Complications* **17**, 169–178 (2003).
77. Cardoso, C. R. L., Leite, N. C., Moram, C. B. M. & Salles, G. F. Long-term visit-to-visit glycemic variability as predictor of micro- and macrovascular complications in patients with Type 2 diabetes: The Rio de Janeiro Type 2 Diabetes Cohort Study. *Cardiovasc. Diabetol.* **17**, 33 (2018).
78. Cardoso, C. R. L., Leite, N. C. & Salles, G. F. Prognostic importance of visit-to-visit blood pressure variability for micro- and macrovascular outcomes in patients with type 2 diabetes: The Rio de Janeiro Type 2 Diabetes Cohort Study. *Cardiovasc. Diabetol.* **19**, 50 (2020).
79. Cardoso, C. R. L., Salles, G. C., Leite, N. C. & Salles, G. F. Prognostic impact of carotid intima-media thickness and carotid plaques on the development of micro- and macrovascular complications in individuals with type 2 diabetes: the Rio de Janeiro Type 2 diabetes cohort study. *Cardiovasc. Diabetol.* **18**, 2 (2019).
80. Carlsson, A. C. et al. Growth differentiation factor 15 (GDF-15) is a potential biomarker of both diabetic kidney disease and future cardiovascular events in cohorts of individuals with type 2 diabetes: a proteomics approach. *Ups J. Med. Sci.* **125**, 37–43 (2020).
81. Carlsson, A. C. et al. Association of soluble tumor necrosis factor receptors 1 and 2 with nephropathy, cardiovascular events, and total mortality in Type 2 diabetes. *Cardiovasc. Diabetol.* **15**, 40 (2016).
82. Carnethon, M. R. et al. Association of weight status with mortality in adults with incident diabetes. *JAMA* **308**, 581–590 (2012).
83. Casiglia, E. et al. Cardiovascular mortality in non-insulin-dependent diabetes mellitus. A controlled study among 683 diabetics and 683 age- and sex-matched normal subjects. *Eur. J. Epidemiol.* **16**, 677–684 (2000).
84. Cavalot, F. et al. Postprandial blood glucose predicts cardiovascular events and all-cause mortality in Type 2 diabetes in a 14-year follow-up: lessons from the San Luigi Gonzaga Diabetes Study. *Diabetes Care* **34**, 2237–2243 (2011).
85. Cavalot, F. et al. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in Type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. *J. Clin. Endocrinol. Metab.* **91**, 813–819 (2006).
86. Cea Soriano, L., Johansson, S., Stefansson, B. & Rodriguez, L. A. Cardiovascular events and all-cause mortality in a cohort of 57,946 patients with Type 2 diabetes: associations with renal function and cardiovascular risk factors. *Cardiovasc. Diabetol.* **14**, 38 (2015).

87. Cederholm, J. et al. Risk prediction of cardiovascular disease in Type 2 diabetes: a risk equation from the Swedish National Diabetes Register. *Diabetes Care* **31**, 2038–2043 (2008).
88. Celis-Morales, C. A. et al. Associations between diabetes and both cardiovascular disease and all-cause mortality are modified by grip strength: evidence from UK Biobank, a prospective population-based Cohort study. *Diabetes Care* **40**, 1710–1718 (2017).
89. Ceriello, A. et al. Empagliflozin reduced long-term HbA1c variability and cardiovascular death: insights from the EMPA-REG OUTCOME trial. *Cardiovasc. Diabetol.* **19**, 176 (2020).
90. Cha, S. A. et al. Time- and frequency-domain measures of heart rate variability predict cardiovascular outcome in patients with Type 2 diabetes. *Diabetes Res. Clin. Pract.* **143**, 159–169 (2018).
91. Cha, S. A. et al. Diabetic cardiovascular autonomic neuropathy predicts recurrent cardiovascular diseases in patients with Type 2 Diabetes. *PLoS One* **11**, e0164807 (2016).
92. Chacko, K. M. et al. Heart rate recovery predicts mortality and cardiovascular events in patients with type 2 diabetes. *Med. Sci. Sports Exerc.* **40**, 288–295 (2008).
93. Chan, J. C. et al. Premature mortality and comorbidities in young-onset diabetes: a 7-year prospective analysis. *Am. J. Med.* **127**, 616–624 (2014).
94. Chang, C. W. et al. The first harmonic of radial pulse as an early predictor of silent coronary artery disease and adverse cardiac events in Type 2 diabetic patients. *Cardiol. Res. Pract.* **2018**, 5128626 (2018).
95. Chang, L. H. et al. The ankle brachial index exhibits better association of cardiovascular prognosis than non-high-density lipoprotein cholesterol in Type 2 diabetes. *Am. J. Med. Sci.* **351**, 492–498 (2016).
96. Chang, L. H. et al. Upstroke time per cardiac cycle is associated with cardiovascular prognosis in Type 2 diabetes. *Endocr. Pract.* **25**, 1109–1116 (2019).
97. Charlton-Menys, V. et al. Apolipoproteins, cardiovascular risk and statin response in Type 2 diabetes: the collaborative atorvastatin diabetes study (CARDS). *Diabetologia* **52**, 218–225 (2009).
98. Chen, H. S. et al. Subclinical hypothyroidism is a risk factor for nephropathy and cardiovascular diseases in Type 2 diabetic patients. *Diabet. Med.* **24**, 1336–1344 (2007).
99. Chen, S. et al. The long-term effectiveness of metabolic control on cardiovascular disease in patients with diabetes in a real-world health care setting - A prospective diabetes management study. *Prim. Care Diabetes* **14**, 274–281 (2020).
100. Cheng, F. et al. Shortened relative leukocyte telomere length is associated with prevalent and incident cardiovascular complications in Type 2 diabetes: analysis from the Hong Kong diabetes register. *Diabetes Care* **43**, 2257–2265 (2020).
101. Christensen, P. K. et al. QTc interval length and QT dispersion as predictors of mortality in patients with non-insulin-dependent diabetes. *Scand J. Clin. Lab Invest.* **60**, 323–332 (2000).
102. Christiansen, M. S., Hommel, E., Magid, E. & Feldt-Rasmussen, B. Orosomucoid in urine predicts cardiovascular and over-all mortality in patients with Type II diabetes. *Diabetologia* **45**, 115–120 (2002).
103. Christiansen, M. S., Hommel, E., Magid, E. & Feldt-Rasmussen, B. Orosomucoid in urine is a powerful predictor of cardiovascular mortality in normoalbuminuric patients with Type 2 diabetes at five years of follow-up. *Diabetologia* **48**, 386–393 (2005).
104. Church, E. et al. Relationship between estimated glomerular filtration rate and incident cardiovascular disease in an ethnically diverse primary care cohort. *N Z Med. J.* **132**, 11–26 (2019).
105. Chyun, D. A. et al. Autonomic dysfunction independently predicts poor cardiovascular outcomes in asymptomatic individuals with Type 2 diabetes in the DIAD study. *SAGE Open Med.* **3**, 2050312114568476 (2015).
106. Cioffi, G. et al. Usefulness of subclinical left ventricular midwall dysfunction to predict cardiovascular mortality in patients with Type 2 diabetes mellitus. *Am. J. Cardiol.* **113**, 1409–1414 (2014).
107. Clarke, P. M. et al. A model to estimate the lifetime health outcomes of patients with Type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). *Diabetologia* **47**, 1747–1759 (2004).
108. Clarke, P. M. et al. Using the EQ-5D index score as a predictor of outcomes in patients with Type 2 diabetes. *Med. Care* **47**, 61–68 (2009).
109. Cockcroft, J. R. et al. Pulse pressure predicts cardiovascular risk in patients with type 2 diabetes mellitus. *Am. J. Hypertens.* **18**, 1463–1467 (2005).
110. Colombo, M. et al. Apolipoprotein CIII and N-terminal pro-hormone b-type natriuretic peptide as independent predictors for cardiovascular disease in Type 2 diabetes. *Atherosclerosis* **274**, 182–190 (2018).
111. Cortigiani, L. et al. Prognostic meaning of coronary microvascular disease in type 2 diabetes mellitus: a transthoracic Doppler echocardiographic study. *J. Am. Soc. Echocardiogr.* **27**, 742–748 (2014).
112. Cosson, E. et al. Cardiovascular risk prediction is improved by adding asymptomatic coronary status to routine risk assessment in type 2 diabetic patients. *Diabetes Care* **34**, 2101–2107 (2011).
113. Courmot, M. et al. Circulating concentrations of redox biomarkers do not improve the prediction of adverse cardiovascular events in patients with Type 2 diabetes mellitus. *J Am Heart Assoc* **7**, e007397 (2018).
114. Cox, A. J. et al. Prediction of mortality using a multi-bed vascular calcification score in the Diabetes Heart Study. *Cardiovasc. Diabetol.* **13**, 160 (2014).
115. Cox, A. J. et al. Genetic risk score associations with cardiovascular disease and mortality in the Diabetes Heart Study. *Diabetes Care* **37**, 1157–1164 (2014).
116. Cox, A. J. et al. Usefulness of biventricular volume as a predictor of mortality in patients with diabetes mellitus (from the Diabetes Heart Study). *Am. J. Cardiol.* **111**, 1152–1158 (2013).
117. Cui, N. H., Yang, J. M., Liu, X. & Wang, X. B. Poly(ADP-Ribose) Polymerase activity and coronary artery disease in Type 2 Diabetes mellitus: an observational and bidirectional mendelian randomization study. *Arterioscler Thromb. Vasc. Biol.* **40**, 2516–2526 (2020).
118. Daka, B. et al. Low concentrations of serum testosterone predict acute myocardial infarction in men with Type 2 diabetes mellitus. *BMC Endocr Disord* **15**, 35 (2015).
119. Davis, T. M., Coleman, R. L. & Holman, R. R. Ethnicity and long-term vascular outcomes in Type 2 diabetes: a prospective observational study (UKPDS 83). *Diabet Med* **31**, 200–207 (2014).
120. Davis, W. A., Colagiuri, S. & Davis, T. M. Comparison of the Framingham and United Kingdom Prospective Diabetes Study cardiovascular risk equations in Australian patients with Type 2 diabetes from the Fremantle Diabetes Study. *Med. J. Aust.* **190**, 180–184 (2009).
121. Davis, W. A., Hellbusch, V., Hunter, M. L., Bruce, D. G. & Davis, T. M. E. Contemporary cardiovascular risk assessment for Type 2 diabetes including heart failure as an outcome: The fremantle diabetes study phase ii. *J. Clin. Med.* **9**, 1428 (2020).
122. Davis, W. A., Knuiman, M. W. & Davis, T. M. An Australian cardiovascular risk equation for Type 2 diabetes: the Fremantle Diabetes Study. *Intern. Med.* **40**, 286–292 (2010).
123. Dayan, A. et al. Coronary calcium score, albuminuria and inflammatory markers in Type 2 diabetic patients: associations and prognostic implications. *Diabetes Res. Clin. Pract.* **98**, 98–103 (2012).
124. de Galan, B. E. et al. Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with Type 2 diabetes: the action in diabetes and vascular disease: preterax and diamicron modified release controlled evaluation (ADVANCE) trial. *Diabetologia* **52**, 2328–2336 (2009).
125. De Lorenzo, A., Lima, R. S., Siqueira-Filho, A. G. & Pantoja, M. R. Prevalence and prognostic value of perfusion defects detected by stress technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography in asymptomatic patients with diabetes mellitus and no known coronary artery disease. *Am. J. Cardiol.* **90**, 827–832 (2002).
126. de Santiago, A., Garcia-Lledó, A., Ramos, E. & Santiago, C. Prognostic value of ECGs in patients with Type-2 diabetes mellitus without known cardiovascular disease. *Rev. Esp. Cardiol.* **60**, 1035–1041 (2007).
127. de Vries, T. I. et al. Normal-range thyroid-stimulating hormone levels and cardiovascular events and mortality in Type 2 diabetes. *Diabetes Res. Clin. Pract.* **157**, 107880 (2019).
128. Djaileb, L. et al. Prognostic value of SPECT myocardial perfusion entropy in high-risk Type 2 diabetic patients. *Eur. J. Nucl. Med. Mol. Imaging* **48**, 1813–1821 (2021).
129. Doney, A. S. et al. The FTO gene is associated with an atherogenic lipid profile and myocardial infarction in patients with Type 2 diabetes: a genetics of diabetes audit and research study in Tayside Scotland (Go-DARTS) study. *Circ. Cardiovasc. Genet.* **2**, 255–259 (2009).
130. Doney, A. S., Lee, S., Leese, G. P., Morris, A. D. & Palmer, C. N. Increased cardiovascular morbidity and mortality in Type 2 diabetes is associated with the glutathione S transferase theta-null genotype: a Go-DARTS study. *Circulation* **111**, 2927–2934 (2005).
131. Doney, A. S. F. et al. Association of common variation in the PPARA gene with incident myocardial infarction in individuals with Type 2 diabetes: A Go-DARTS study. *Nuclear Receptor* **3**, 4 (2005).
132. Donnan, P. T., Donnelly, L., New, J. P. & Morris, A. D. Derivation and validation of a prediction score for major coronary heart disease events in a U.K. Type 2 diabetic population. *Diabetes Care* **29**, 1231–1236 (2006).
133. Drinkwater, J. J. et al. Retinopathy predicts stroke but not myocardial infarction in Type 2 diabetes: the Fremantle Diabetes Study Phase II. *Cardiovasc. Diabetol.* **19**, 43 (2020).
134. Drury, P. L. et al. Estimated glomerular filtration rate and albuminuria are independent predictors of cardiovascular events and death in Type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetologia* **54**, 32–43 (2011).

135. Duan, J. G. et al. Long-term risk of cardiovascular disease among Type 2 diabetic patients with asymptomatic intracranial atherosclerosis: a prospective cohort study. *PLoS One* **9**, e106623 (2014).
136. Duan, J. G. et al. Sex differences in epidemiology and risk factors of acute coronary syndrome in Chinese patients with Type 2 diabetes: a long-term prospective cohort study. *PLoS One* **10**, e0122031 (2015).
137. Eguchi, K., Hoshida, S. & Kario, K. Target home morning SBP be below 125 mmHg in Type 2 diabetes patients. *J. Hypertens.* **36**, 1284–1290 (2018).
138. Eguchi, K. et al. Differential impact of left ventricular mass and relative wall thickness on cardiovascular prognosis in diabetic and nondiabetic hypertensive subjects. *Am. Heart J.* **154**, 79.e79–15 (2007).
139. Eguchi, K. et al. Night time blood pressure variability is a strong predictor for cardiovascular events in patients with Type 2 diabetes. *Am. J. Hypertens.* **22**, 46–51 (2009).
140. Eguchi, K. et al. Ambulatory blood pressure is a better marker than clinic blood pressure in predicting cardiovascular events in patients with/without Type 2 diabetes. *Am. J. Hypertens.* **21**, 443–450 (2008).
141. Eguchi, K. et al. Increased heart rate variability during sleep is a predictor for future cardiovascular events in patients with Type 2 diabetes. *Hypertens. Res.* **33**, 737–742 (2010).
142. Eijkkamp, W. B. et al. Renal function and risk for cardiovascular events in Type 2 diabetic patients with hypertension: the RENAAL and LIFE studies. *J. Hypertens.* **25**, 871–876 (2007).
143. Eliasson, B. et al. Clinical usefulness of different lipid measures for prediction of coronary heart disease in Type 2 diabetes: a report from the Swedish National Diabetes Register. *Diabetes Care* **34**, 2095–2100 (2011).
144. Elkeles, R. S. et al. Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with Type 2 diabetes: the PREDICT study. *Eur. Heart J.* **29**, 2244–2251 (2008).
145. Elley, C. R., Kenealy, T., Robinson, E. & Drury, P. L. Glycated haemoglobin and cardiovascular outcomes in people with Type 2 diabetes: a large prospective cohort study. *Diabet Med.* **25**, 1295–1301 (2008).
146. Elley, C. R., Robinson, E., Kenealy, T., Bramley, D. & Drury, P. L. Derivation and validation of a new cardiovascular risk score for people with Type 2 diabetes: the new zealand diabetes cohort study. *Diabetes Care* **33**, 1347–1352 (2010).
147. Estacio, R. O., Dale, R. A., Schrier, R. & Krantz, M. J. Relation of reduction in urinary albumin excretion to ten-year cardiovascular mortality in patients with Type 2 diabetes and systemic hypertension. *Am. J. Cardiol.* **109**, 1743–1748 (2012).
148. Everett, B. M. et al. Troponin and cardiac events in stable ischemic heart disease and diabetes. *N. Engl. J. Med.* **373**, 610–620 (2015).
149. Fadini, G. P. et al. p66Shc gene expression in peripheral blood mononuclear cells and progression of diabetic complications. *Cardiovasc. Diabetol.* **17**, 16 (2018).
150. Fadini, G. P., Rigato, M., Cappellari, R., Bonora, B. M. & Avogaro, A. Long-term prediction of cardiovascular outcomes by circulating CD34+ and CD34+CD133+ stem cells in patients with Type 2 diabetes. *Diabetes Care* **40**, 125–131 (2017).
151. Faghihi-Kashani, S. et al. Fasting hyperinsulinaemia and 2-h glycaemia predict coronary heart disease in patients with Type 2 diabetes. *Diabetes Metab.* **42**, 55–61 (2016).
152. Faglia, E. et al. Cardiac events in 735 type 2 diabetic patients who underwent screening for unknown asymptomatic coronary heart disease: 5-year follow-up report from the Milan Study on Atherosclerosis and Diabetes (MISAD). *Diabetes Care* **25**, 2032–2036 (2002).
153. Ferrarezi, D. A. et al. Allelic variations of the vitamin D receptor (VDR) gene are associated with increased risk of coronary artery disease in Type 2 diabetics: the DIABHYCAR prospective study. *Diabetes Metab.* **39**, 263–270 (2013).
154. Filippella, M. et al. Ankle brachial pressure index usefulness as predictor factor for coronary heart disease in diabetic patients. *J. Endocrinol. Invest.* **30**, 721–725 (2007).
155. Florkowski, C. M., Scott, R. S., Coope, P. A. & Moir, C. L. Predictors of mortality from Type 2 diabetes mellitus in Canterbury, New Zealand; a ten-year cohort study. *Diabetes Res Clin Pract* **53**, 113–120 (2001).
156. Folsom, A. R., Chambless, L. E., Duncan, B. B., Gilbert, A. C. & Pankow, J. S. Prediction of coronary heart disease in middle-aged adults with diabetes. *Diabetes Care* **26**, 2777–2784 (2003).
157. Fox, C. S., Sullivan, L., D'Agostino, R. B. Sr & Wilson, P. W. The significant effect of diabetes duration on coronary heart disease mortality: the Framingham Heart Study. *Diabetes Care* **27**, 704–708 (2004).
158. Fragoso, A., Mendes, F., Silva, A. P. & Neves, P. L. Insulin resistance as a predictor of cardiovascular morbidity and end-stage renal disease. *J. Diabetes Complications* **29**, 1098–1104 (2015).
159. Freemantle, N., Danchin, N., Calvi-Gries, F., Vincent, M. & Home, P. D. Relationship of glycaemic control and hypoglycaemic episodes to 4-year cardiovascular outcomes in people with type 2 diabetes starting insulin. *Diabetes Obes. Metab.* **18**, 152–158 (2016).
160. Friedman, A. N., Hunsicker, L. G., Selhub, J. & Bostom, A. G. Total plasma homocysteine and arteriosclerotic outcomes in Type 2 diabetes with nephropathy. *J. Am. Soc. Nephrol.* **16**, 3397–3402 (2005).
161. Fukushima, H. et al. Prognostic value of remnant-like lipoprotein particle levels in patients with coronary artery disease and type II diabetes mellitus. *J. Am. Coll. Cardiol.* **43**, 2219–2224 (2004).
162. Fuller, J. H., Stevens, L. K. & Wang, S. L. Risk factors for cardiovascular mortality and morbidity: the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* **44**, S54–64 (2001).
163. Fumisawa, Y. et al. Systematic analysis of risk factors for coronary heart disease in Japanese patients with Type 2 diabetes: a matched case-control study. *J. Atheroscler. Thromb.* **19**, 918–923 (2012).
164. Gasior, M. et al. Effect of blood glucose levels on prognosis in acute myocardial infarction in patients with and without diabetes, undergoing percutaneous coronary intervention. *Cardiol. J.* **15**, 422–430 (2008).
165. Gazzaruso, C. et al. Transcutaneous oxygen tension as a potential predictor of cardiovascular events in Type 2 diabetes: comparison with ankle-brachial index. *Diabetes Care* **36**, 1720–1725 (2013).
166. Gazzaruso, C. et al. Lipoprotein(a), apolipoprotein(a) polymorphism and restenosis after intracoronary stent placement in Type 2 diabetic patients. *J. Diabetes Complications* **17**, 135–140 (2003).
167. Gazzaruso, C. et al. Erectile dysfunction as a predictor of cardiovascular events and death in diabetic patients with angiographically proven asymptomatic coronary artery disease: a potential protective role for statins and 5-phosphodiesterase inhibitors. *J. Am. Coll. Cardiol.* **51**, 2040–2044 (2008).
168. Georgoulas, P. et al. Long-term prognostic value of heart-rate recovery after treadmill testing in patients with diabetes mellitus. *Int. J. Cardiol.* **134**, 67–74 (2009).
169. Gimeno-Orna, J. A., Lou-Arnal, L. M., Boned-Juliani, B. & Molinero-Herguedas, E. Mild renal insufficiency as a cardiovascular risk factor in non-proteinuric Type II diabetes. *Diabetes Res. Clin. Pract.* **64**, 191–199 (2004).
170. Giorda, C. B. et al. Recurrence of cardiovascular events in patients with Type 2 diabetes: epidemiology and risk factors. *Diabetes Care* **31**, 2154–2159 (2008).
171. Giovacchini, G. et al. Microalbuminuria predicts silent myocardial ischaemia in Type 2 diabetes patients. *Eur. J. Nucl. Med. Mol. Imaging* **40**, 548–557 (2013).
172. Group, T. L. A. R. Prospective Association of GLUL rs10911021 with cardiovascular morbidity and mortality among individuals with Type 2 diabetes: The Look AHEAD Study. *Diabetes* **65**, 297–302, (2015).
173. Guzder, R. N., Gatling, W., Mullee, M. A. & Byrne, C. D. Impact of metabolic syndrome criteria on cardiovascular disease risk in people with newly diagnosed Type 2 diabetes. *Diabetologia* **49**, 49–55 (2006).
174. Guzder, R. N., Gatling, W., Mullee, M. A., Mehta, R. L. & Byrne, C. D. Prognostic value of the Framingham cardiovascular risk equation and the UKPDS risk engine for coronary heart disease in newly diagnosed Type 2 diabetes: results from a United Kingdom study. *Diabet Med* **22**, 554–562 (2005).
175. Hadaegh, F. et al. Electrocardiography-defined silent CHD and risk of cardiovascular events among diabetic patients in a Middle Eastern population. *Eur. J. Prev. Cardiol.* **19**, 1227–1233 (2012).
176. Hadjadj, S. et al. Prognostic value of the insertion/deletion polymorphism of the ACE gene in Type 2 diabetic subjects: results from the Non-insulin-dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril (DIABHYCAR), Diabetes. *Diabetes Care* **31**, 1847–1852 (2008).
177. Hage, F. G. et al. The heart rate response to adenosine: a simple predictor of adverse cardiac outcomes in asymptomatic patients with type 2 diabetes. *Int. J. Cardiol.* **167**, 2952–2957 (2013).
178. Halon, D. A. et al. Coronary computed tomography (CT) angiography as a predictor of cardiac and noncardiac vascular events in asymptomatic Type 2 diabetics: a 7-year population-based Cohort Study. *J. Am. Heart Assoc.* **5**, e003226 (2016).
179. Halon, D. A. et al. Plaque morphology as predictor of late plaque events in patients with asymptomatic Type 2 diabetes. *A Long-Term Observational Study. JACC Cardiovasc. Imaging* **12**, 1353–1363 (2019).
180. Hamada, S. & Gulliford, M. C. Multiple risk factor control, mortality and cardiovascular events in Type 2 diabetes and chronic kidney disease: a population-based cohort study. *BMJ Open* **8**, e019950 (2018).
181. Hanefeld, M. et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia* **39**, 1577–1583 (1996).
182. Hata, J. et al. Effects of visit-to-visit variability in systolic blood pressure on macrovascular and microvascular complications in patients with Type 2 diabetes mellitus: the ADVANCE trial. *Circulation* **128**, 1325–1334 (2013).
183. Hayashi, T. et al. Metabolic predictors of ischemic heart disease and cerebrovascular attack in elderly diabetic individuals: difference in risk by age. *Cardiovasc Diabetol* **12**, 10 (2013).

184. Hayes, A. J., Leal, J., Gray, A. M., Holman, R. R. & Clarke, P. M. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. *Diabetologia* **56**, 1925–1933 (2013).
185. He, Q., Pan, J., Wang, L., Fang, Y. & Hu, R. Prospective study: Aldehyde dehydrogenase 2 gene is associated with cardio-cerebrovascular complications in Type 2 diabetes patients. *J. Diabetes Investig.* **12**, 1845–1854 (2021).
186. Heidari, B. et al. Assessment of serum 25-hydroxy vitamin D improves coronary heart disease risk stratification in patients with Type 2 diabetes. *Am. Heart J.* **170**, 573–579.e575 (2015).
187. Heijmans, B. T. et al. Common paraoxonase gene variants, mortality risk and fatal cardiovascular events in elderly subjects. *Atherosclerosis* **149**, 91–97 (2000).
188. Ho, J. S. et al. Association of the PPARG Pro12Ala polymorphism with Type 2 diabetes and incident coronary heart disease in a Hong Kong Chinese population. *Diabetes Res. Clin. Pract.* **97**, 483–491 (2012).
189. Hoffmann, M. M., März, W., Genser, B., Drechsler, C. & Wanner, C. Lack of association between the Trp719Arg polymorphism in kinesin-like protein-6 and cardiovascular risk and efficacy of atorvastatin among subjects with diabetes on dialysis: the 4D study. *Atherosclerosis* **219**, 659–662 (2011).
190. Hong, L. F. et al. Predictive value of non-fasting remnant cholesterol for short-term outcome of diabetics with new-onset stable coronary artery disease. *Lipids Health Dis* **16**, 7 (2017).
191. Howard, B. V. et al. LDL cholesterol as a strong predictor of coronary heart disease in diabetic individuals with insulin resistance and low LDL: The Strong Heart Study. *Arterioscler Thromb Vasc. Biol.* **20**, 830–835 (2000).
192. Hsieh, Y. T. et al. Subnormal estimated glomerular filtration rate strongly predict incident cardiovascular events in Type 2 diabetic chinese population with normoalbuminuria. *Medicine (Baltimore)* **95**, e2200 (2016).
193. Hu, C. P. et al. Platelet distribution width on admission predicts in-stent restenosis in patients with coronary artery disease and Type 2 diabetes mellitus treated with percutaneous coronary intervention. *Chin. Med. J. (Engl)* **131**, 757–763 (2018).
194. Huang, X. H. et al. Angiotensin-converting enzyme gene polymorphism is associated with coronary heart disease in non-insulin-dependent diabetic patients evaluated for 9 years. *Metabolism* **47**, 1258–1262 (1998).
195. Hunt, K. J. et al. Plasma connective tissue growth factor (CTGF/CCN2) levels predict myocardial infarction in the veterans affairs diabetes trial (VADT) Cohort. *Diabetes Care* **41**, 840–846 (2018).
196. Iijima, K. et al. Lower physical activity is a strong predictor of cardiovascular events in elderly patients with type 2 diabetes mellitus beyond traditional risk factors: the Japanese Elderly Diabetes Intervention Trial. *Geriatr Gerontol Int* **12**, 77–87 (2012).
197. Ikeda, Y. et al. Low human paraoxonase predicts cardiovascular events in Japanese patients with type 2 diabetes. *Acta Diabetol.* **46**, 239–242 (2009).
198. Irie, Y. et al. The utility of ultrasonic tissue characterization of carotid plaque in the prediction of cardiovascular events in diabetic patients. *Atherosclerosis* **230**, 399–405 (2013).
199. Jeevarethinam, A. et al. Usefulness of carotid plaques as predictors of obstructive coronary artery disease and cardiovascular events in asymptomatic individuals with diabetes mellitus. *Am. J. Cardiol.* **121**, 910–916 (2018).
200. Jha, D. et al. Prognostic role of soluble ST2 in acute coronary syndrome with diabetes. *Eur. J. Clin. Invest.* **48**, e12994 (2018).
201. Jiang, R. et al. Non-HDL cholesterol and apolipoprotein B predict cardiovascular disease events among men with type 2 diabetes. *Diabetes Care* **27**, 1991–1997 (2004).
202. Jimenez-Corona, A. et al. Electrocardiographic abnormalities predict deaths from cardiovascular disease and ischemic heart disease in Pima Indians with Type 2 diabetes. *Am. Heart J.* **151**, 1080–1086 (2006).
203. Jin, J. L. et al. Triglyceride glucose and haemoglobin glycation index for predicting outcomes in diabetes patients with new-onset, stable coronary artery disease: a nested case-control study. *Ann. Med.* **50**, 576–586 (2018).
204. Johnston, S. S. et al. Evidence linking hypoglycemic events to an increased risk of acute cardiovascular events in patients with Type 2 diabetes. *Diabetes Care* **34**, 1164–1170 (2011).
205. Juutilainen, A., Lehto, S., Suhonen, M., Rönnemaa, T. & Laakso, M. Thoracoabdominal calcifications predict cardiovascular disease mortality in Type 2 diabetic and nondiabetic subjects: 18-year follow-up study. *Diabetes Care* **33**, 583–585 (2010).
206. Kamoi, K., Ito, T., Miyakoshi, M. & Minagawa, S. Usefulness of home blood pressure measurement in the morning in patients with type 2 diabetes: long-term results of a prospective longitudinal study. *Clin. Exp. Hypertens.* **32**, 184–192 (2010).
207. Katakami, N. et al. Accumulation of oxidative stress-related gene polymorphisms and the risk of coronary heart disease events in patients with Type 2 diabetes—an 8-year prospective study. *Atherosclerosis* **235**, 408–414 (2014).
208. Katakami, N. et al. Clinical utility of brachial-ankle pulse wave velocity in the prediction of cardiovascular events in diabetic patients. *Cardiovasc. Diabetol.* **13**, 128 (2014).
209. Katakami, N. et al. Ultrasonic tissue characterization of carotid plaque improves the prediction of cardiovascular events in diabetic patients: a pilot study. *Diabetes Care* **35**, 2640–2646 (2012).
210. Kawasaki, R. et al. Risk of cardiovascular diseases is increased even with mild diabetic retinopathy: the Japan diabetes complications study. *Ophthalmology* **120**, 574–582 (2013).
211. Keavney, B. D. et al. UK prospective diabetes study (UKPDS) 14: association of angiotensin-converting enzyme insertion/deletion polymorphism with myocardial infarction in NIDDM. *Diabetologia* **38**, 948–952 (1995).
212. Keller, T. et al. Prognostic value of high-sensitivity versus conventional cardiac Troponin T assays among patients with Type 2 diabetes mellitus undergoing maintenance hemodialysis. *Am. J. Kidney Dis.* **71**, 822–830 (2018).
213. Kenealy, T. et al. An association between ethnicity and cardiovascular outcomes for people with Type 2 diabetes in New Zealand. *Diabet. Med.* **25**, 1302–1308 (2008).
214. Kengne, A. P. et al. The Framingham and UK Prospective Diabetes Study (UKPDS) risk equations do not reliably estimate the probability of cardiovascular events in a large ethnically diverse sample of patients with diabetes: the Action in Diabetes and Vascular Disease: Preterax. *Diabetologia* **53**, 821–831 (2010).
215. Kengne, A. P. et al. Contemporary model for cardiovascular risk prediction in people with Type 2 diabetes. *Eur. J. Cardiovasc. Prev. Rehabil.* **18**, 393–398 (2011).
216. Khalili, S., Hatami, M., Hadaegh, F., Sheikholeslami, F. & Azizi, F. Prediction of cardiovascular events with consideration of general and central obesity measures in diabetic adults: results of the 8.4-year follow-up. *Metab. Syndr. Relat. Disord.* **10**, 218–224 (2012).
217. Kim, M. K. et al. Hemoglobin glycation index predicts cardiovascular disease in people with Type 2 diabetes mellitus: A 10-year longitudinal cohort study. *J. Diabetes Complications* **32**, 906–910 (2018).
218. Koch, M., Kutkuhn, B., Grabensee, B. & Ritz, E. Apolipoprotein A, fibrinogen, age, and history of stroke are predictors of death in dialysed diabetic patients: a prospective study in 412 subjects. *Nephrol Dial Transplant* **12**, 2603–2611 (1997).
219. Koo, B. K., Chung, W. Y. & Moon, M. K. Peripheral arterial endothelial dysfunction predicts future cardiovascular events in diabetic patients with albuminuria: a prospective cohort study. *Cardiovasc. Diabetol.* **19**, 82 (2020).
220. Kuricová, K. et al. NOS3 894G>T polymorphism is associated with progression of kidney disease and cardiovascular morbidity in Type 2 diabetic patients: NOS3 as a modifier gene for diabetic nephropathy? *Kidney Blood Press Res.* **38**, 92–98 (2013).
221. Lagani, V. et al. Development and validation of risk assessment models for diabetes-related complications based on the DCCT/EDIC data. *J. Diabetes Complications* **29**, 479–487 (2015).
222. Lapin, B. R. et al. Pain in patients with Type 2 diabetes-related polyneuropathy is associated with vascular events and mortality. *J. Clin. Endocrinol. Metab.* **105**, dgaa394 (2020).
223. Lau, K. K. et al. Prognostic implications of surrogate markers of atherosclerosis in low to intermediate risk patients with Type 2 diabetes. *Cardiovasc. Diabetol.* **11**, 101 (2012).
224. Le Feuvre, C. L. et al. Stress myocardial scintigraphy and dobutamine echocardiography in the detection of coronary disease in asymptomatic patients with Type 2 diabetes. *Diabetes Metab.* **31**, 135–142 (2005).
225. Lee, K. Y. et al. Computed tomography angiography images of coronary artery stenosis provide a better prediction of risk than traditional risk factors in asymptomatic individuals with Type 2 DIABETES: a long-term study of clinical outcomes. *Diabetes Care* **40**, 1241–1248 (2017).
226. Lehto, S., Niskanen, L., Suhonen, M., Rönnemaa, T. & Laakso, M. Medial artery calcification. A neglected harbinger of cardiovascular complications in non-insulin-dependent diabetes mellitus. *Arterioscler Thromb Vasc. Biol.* **16**, 978–983 (1996).
227. Lepojärvi, E. S. et al. Usefulness of highly sensitive troponin as a predictor of short-term outcome in patients with diabetes mellitus and stable coronary artery disease (from the ARTEMIS Study). *Am. J. Cardiol.* **117**, 515–521 (2016).
228. Levy, A. P. et al. Haptoglobin phenotype is an independent risk factor for cardiovascular disease in individuals with diabetes: The Strong Heart Study. *J. Am. Coll. Cardiol.* **40**, 1984–1990 (2002).
229. Li, P. I., Wang, J. N. & Guo, H. R. A long-term quality-of-care score for predicting the occurrence of macrovascular diseases in patients with Type 2 diabetes mellitus. *Diabetes Res. Clin. Pract.* **139**, 72–80 (2018).
230. Li, W. P. et al. Pregnancy-associated plasma protein-A is a stronger predictor for adverse cardiovascular outcomes after acute coronary syndrome in Type-2 diabetes mellitus. *Cardiovasc. Diabetol.* **16**, 45 (2017).

231. Liao, K. M. et al. Risk assessment of macrovascular and microvascular events in patients with Type 2 diabetes by analyzing the amplitude variation of the fourth harmonic component of radial pulse wave. *Physiol. Rep.* **7**, e14252 (2019).
232. Lièvre, M. M. et al. Detection of silent myocardial ischemia in asymptomatic patients with diabetes: results of a randomized trial and meta-analysis assessing the effectiveness of systematic screening. *Trials* **12**, 23 (2011).
233. Lim, L. L. et al. Sudomotor dysfunction independently predicts incident cardiovascular-renal events and all-cause death in Type 2 diabetes: the Joint Asia Diabetes Evaluation register. *Nephrol. Dial. Transplant* **34**, 1320–1328 (2019).
234. Lim, S. et al. Association of adiponectin and resistin with cardiovascular events in Korean patients with type 2 diabetes: the Korean atherosclerosis study (KAS): a 42-month prospective study. *Atherosclerosis* **196**, 398–404 (2008).
235. Lin, C. H., Li, H. Y., Jiang, Y. D., Chang, T. J. & Chuang, L. M. Plasma YKL-40 predicts 10-year cardiovascular and all-cause mortality in individuals with Type 2 diabetes. *Clin. Endocrinol. (Oxf)* **79**, 185–191 (2013).
236. Lin, E. H. et al. Depression and advanced complications of diabetes: a prospective cohort study. *Diabetes Care* **33**, 264–269 (2010).
237. Lin, L. Y. et al. The ankle brachial index exhibits better association with cardiovascular outcomes than interarm systolic blood pressure difference in patients with type 2 diabetes. *Medicine (Baltimore)* **98**, e15556 (2019).
238. Linnemann, B. & Janka, H. U. Prolonged QTc interval and elevated heart rate identify the Type 2 diabetic patient at high risk for cardiovascular death. The Bremen Diabetes Study. *Exp. Clin. Endocrinol. Diabetes* **111**, 215–222 (2003).
239. Linnemann, B., Voigt, W., Nobel, W. & Janka, H. U. C-reactive protein is a strong independent predictor of death in Type 2 diabetes: association with multiple facets of the metabolic syndrome. *Exp. Clin. Endocrinol. Diabetes* **114**, 127–134 (2006).
240. Lopes-Virella, M. F., Hunt, K. J., Baker, N. L., Virella, G. & Moritz, T. The levels of MDA-LDL in circulating immune complexes predict myocardial infarction in the VADT study. *Atherosclerosis* **224**, 526–531 (2012).
241. Lorenzo-Almorós, A. et al. Galectin-3 is associated with cardiovascular events in post-acute coronary syndrome patients with Type-2 diabetes. *J. Clin. Med.* **9**, 1105 (2020).
242. Lowe, G. et al. Circulating inflammatory markers and the risk of vascular complications and mortality in people with Type 2 diabetes and cardiovascular disease or risk factors: the ADVANCE study. *Diabetes* **63**, 1115–1123 (2014).
243. Lu, T. M., Lin, S. J., Lin, M. W., Hsu, C. P. & Chung, M. Y. The association of dimethylarginine dimethylaminohydrolase 1 gene polymorphism with Type 2 diabetes: a cohort study. *Cardiovasc. Diabetol.* **10**, 16 (2011).
244. Lu, W. et al. Non-HDL cholesterol as a predictor of cardiovascular disease in Type 2 diabetes: the strong heart study. *Diabetes Care* **26**, 16–23 (2003).
245. Lutgers, H. L. et al. Skin autofluorescence provides additional information to the UK Prospective Diabetes Study (UKPDS) risk score for the estimation of cardiovascular prognosis in Type 2 diabetes mellitus. *Diabetologia* **52**, 789–797 (2009). 1308–9.
246. Masi, S. et al. Telomere length, antioxidant status and incidence of ischaemic heart disease in Type 2 diabetes. *Int. J. Cardiol.* **216**, 159–164 (2016).
247. Massardo, T. et al. Factors associated with silent myocardial ischemia, autonomic or peripheral neuropathies, and survival in diabetes mellitus type 2 patients without cardiovascular symptoms. *Int. J. Diabetes Developing Countries* **40**, 80–86 (2020).
248. McEwan, P., Bennett, H., Ward, T. & Bergenheim, K. Refitting of the UKPDS 68 risk equations to contemporary routine clinical practice data in the UK. *Pharmacoeconomics* **33**, 149–161 (2015).
249. McMurray, J. J. et al. Predictors of fatal and nonfatal cardiovascular events in patients with Type 2 diabetes mellitus, chronic kidney disease, and anemia: an analysis of the trial to reduce cardiovascular events with aranesp (darbepoetin-alfa) therapy (TREAT). *Am. Heart J.* **162**, 748–755.e743 (2011).
250. Meerwaldt, R. et al. Skin autofluorescence is a strong predictor of cardiac mortality in diabetes. *Diabetes Care* **30**, 107–112 (2007).
251. Mellbin, L. G. et al. Copeptin, IGFBP-1, and cardiovascular prognosis in patients with Type 2 diabetes and acute myocardial infarction: a report from the DIGAMI 2 trial. *Diabetes Care* **33**, 1604–1606 (2010).
252. Mentz, R. J. et al. Effect of once-weekly exenatide on clinical outcomes according to baseline risk in patients with Type 2 diabetes mellitus: insights from the EXSCEL trial. *J. Am. Heart Assoc.* **7**, e009304 (2018).
253. Mohammadi, K. et al. Plasma extracellular superoxide dismutase concentration, allelic variations in the SOD3 gene and risk of myocardial infarction and all-cause mortality in people with Type 1 and Type 2 diabetes. *Cardiovasc. Diabetol.* **14**, 845 (2015).
254. Mohammadi, K. et al. Absence of peripheral pulses and risk of major vascular outcomes in patients with Type 2 diabetes. *Diabetes Care* **39**, 2270–2277 (2016).
255. Monseu, M. et al. Acute kidney injury predicts major adverse outcomes in diabetes: synergic impact with low glomerular filtration rate and albuminuria. *Diabetes Care* **38**, 2333–2340 (2015).
256. Moosaie, F. et al. Lp(a) and Apo-lipoproteins as predictors for micro- and macrovascular complications of diabetes: A case-cohort study. *Nutr. Metab. Cardiovasc. Dis.* **30**, 1723–1731 (2020).
257. Morieri, M. L. et al. Genetic tools for coronary risk assessment in Type 2 diabetes: a Cohort study from the ACCORD clinical trial. *Diabetes Care* **41**, 2404–2413 (2018).
258. Morrish, N. J., Stevens, L. K., Fuller, J. H., Jarrett, R. J. & Keen, H. Risk factors for macrovascular disease in diabetes mellitus: the London follow-up to the WHO multinational study of vascular disease in diabetics. *Diabetologia* **34**, 590–594 (1991).
259. Mukamal, K. J. et al. Prediction and classification of cardiovascular disease risk in older adults with diabetes. *Diabetologia* **56**, 275–283 (2013).
260. Nag, S. et al. All-cause and cardiovascular mortality in diabetic subjects increases significantly with reduced estimated glomerular filtration rate (eGFR): 10 years' data from the South Tees Diabetes Mortality study. *Diabet Med.* **24**, 10–17 (2007).
261. Nagamachi, S. et al. Prognostic value of cardiac I-123 metaiodobenzylguanidine imaging in patients with non-insulin-dependent diabetes mellitus. *J. Nucl. Cardiol.* **13**, 34–42 (2006).
262. Nakamura, M. et al. Brachial-ankle pulse wave velocity as a risk stratification index for the short-term prognosis of Type 2 diabetic patients with coronary artery disease. *Hypertens Res.* **33**, 1018–1024 (2010).
263. Nam, G. E. et al. Body weight variability and the risk of cardiovascular outcomes and mortality in patients with Type 2 diabetes: a nationwide Cohort Study. *Diabetes Care* **43**, 2234–2241 (2020).
264. Nargesi, A. A. et al. Nonlinear relation between pulse pressure and coronary heart disease in patients with Type 2 diabetes or hypertension. *J. Hypertens.* **34**, 974–980 (2016).
265. Nazimek-Siewniak, B., Moczulski, D. & Grzeszczak, W. Risk of macrovascular and microvascular complications in Type 2 diabetes: results of longitudinal study design. *J. Diabetes Complications* **16**, 271–276 (2002).
266. Ndrepepa, G. et al. Prognostic value of uric acid in patients with Type 2 diabetes mellitus and coronary artery disease. *Clin. Sci. (Lond)* **124**, 259–268 (2013).
267. Nelson, R. G. et al. Low incidence of fatal coronary heart disease in Pima Indians despite high prevalence of non-insulin-dependent diabetes. *Circulation* **81**, 987–995 (1990).
268. Neves, A. L. et al. Allelic variations in superoxide dismutase-1 (SOD1) gene and renal and cardiovascular morbidity and mortality in Type 2 diabetic subjects. *Mol. Genet. Metab.* **106**, 359–365 (2012).
269. Nichols, G. A., Joshua-Gotlib, S. & Parasuraman, S. Independent contribution of A1C, systolic blood pressure, and LDL cholesterol control to risk of cardiovascular disease hospitalizations in type 2 diabetes: an observational cohort study. *J. Gen. Intern. Med.* **28**, 691–697 (2013).
270. Nilsson, P. M. et al. Smoking as an independent risk factor for myocardial infarction or stroke in type 2 diabetes: a report from the Swedish National Diabetes Register. *Eur. J. Cardiovasc. Prev. Rehabil.* **16**, 506–512 (2009).
271. Ningshen, R., Odyuo, Moathung, Arvind, Z., Deba Singh, G. & Devi, T. S. B. A study of QTc interval prolongation as an independent predictor of cardiac mortality in type 2 diabetes mellitus. *JMS - J. Med. Soc.* **26**, 21–25 (2012).
272. Niskanen, L., Turpeinen, A., Penttilä, I. & Uusitupa, M. I. Hyperglycemia and compositional lipoprotein abnormalities as predictors of cardiovascular mortality in type 2 diabetes: a 15-year follow-up from the time of diagnosis. *Diabetes Care* **21**, 1861–1869 (1998).
273. Niskanen, L. K., Penttilä, L., Parviainen, M. & Uusitupa, M. I. Evolution, risk factors, and prognostic implications of albuminuria in NIDDM. *Diabetes Care* **19**, 486–493 (1996).
274. Nitenberg, A. et al. Cardiovascular outcome of patients with abnormal coronary vasomotion and normal coronary arteriography is worse in type 2 diabetes mellitus than in arterial hypertension: a 10 year follow-up study. *Atherosclerosis* **183**, 113–120 (2005).
275. Novo-Rodríguez, C. et al. Circulating levels of sclerostin are associated with cardiovascular mortality. *PLoS One* **13**, e0199504 (2018).
276. Odeberg, J., Larsson, C. A., Råstam, L. & Lindblad, U. The Asp298 allele of endothelial nitric oxide synthase is a risk factor for myocardial infarction among patients with Type 2 diabetes mellitus. *BMC Cardiovasc. Disord.* **8**, 36 (2008).
277. Oellgaard, J. et al. Application of urinary proteomics as possible risk predictor of renal and cardiovascular complications in patients with Type 2-diabetes and microalbuminuria. *J. Diabetes Complications* **32**, 1133–1140 (2018).
278. Oliveira, J. L. et al. Prognostic value of exercise echocardiography in diabetic patients. *Cardiovasc. Ultrasound* **7**, 24 (2009).
279. Ong, K. L. et al. The relationship of fibroblast growth factor 21 with cardiovascular outcome events in the Fenofibrate Intervention and Event Lowering in Diabetes study. *Diabetologia* **58**, 464–473 (2015).
280. Ong, K. L. et al. Relationships of adipocyte-fatty acid binding protein and lipocalin 2 with risk factors and chronic complications in type 2 diabetes and effects of fenofibrate: A fenofibrate Intervention and event lowering in diabetes sub-study. *Diabetes Res. Clin. Pract.* **169**, 108450 (2020).

281. Ortega Moreno, L. et al. Evidence of a causal relationship between high serum adiponectin levels and increased cardiovascular mortality rate in patients with type 2 diabetes. *Cardiovasc. Diabetol.* **15**, 17 (2016).
282. Oshima, M. et al. Early change in albuminuria with canagliflozin predicts kidney and cardiovascular outcomes: a post hoc analysis from the CREDENCE trial. *J. Am. Soc. Nephrol.* **31**, 2925–2936 (2020).
283. Otto, S. et al. Microembolization and myonecrosis during elective percutaneous coronary interventions in diabetic patients: an intracoronary Doppler ultrasound study with 2-year clinical follow-up. *Basic Res. Cardiol.* **107**, 289 (2012).
284. Pagidipati, N. J. et al. Association of obesity with cardiovascular outcomes in patients with Type 2 diabetes and cardiovascular disease: Insights from TECOS. *Am. Heart J.* **219**, 47–57 (2020).
285. Panero, F. et al. Uric acid is not an independent predictor of cardiovascular mortality in Type 2 diabetes: a population-based study. *Atherosclerosis* **221**, 183–188 (2012).
286. Park, G. M. et al. Coronary computed tomographic angiographic findings in asymptomatic patients with Type 2 diabetes mellitus. *Am. J. Cardiol.* **113**, 765–771 (2014).
287. Peng, W. H. et al. Decreased serum esRAGE level is associated with angiographically determined coronary plaque progression in diabetic patients. *Clin. Biochem.* **42**, 1252–1259 (2009).
288. Peters, K. E., Chubb, S. A., Davis, W. A. & Davis, T. M. The relationship between hypomagnesemia, metformin therapy and cardiovascular disease complicating type 2 diabetes: the Fremantle Diabetes Study. *PLoS One* **8**, e74355 (2013).
289. Petretta, M. et al. Transient ischemic dilation in patients with diabetes mellitus: prognostic value and effect on clinical outcome after coronary revascularization. *Circ. Cardiovasc. Imaging* **6**, 908–915 (2013).
290. Pfister, R., Cairns, R., Erdmann, E. & Schneider, C. A. Prognostic impact of electrocardiographic signs in patients with Type 2 diabetes and cardiovascular disease: results from the PROactive study. *Diabet. Med.* **28**, 1206–1212 (2011).
291. Pickup, J. C. & Mattock, M. B. Activation of the innate immune system as a predictor of cardiovascular mortality in Type 2 diabetes mellitus. *Diabet. Med.* **20**, 723–726 (2003).
292. Piniés, J. A. et al. Development of a prediction model for fatal and non-fatal coronary heart disease and cardiovascular disease in patients with newly diagnosed type 2 diabetes mellitus: the Basque Country Prospective Complications and Mortality Study risk engine (BASCORE). *Diabetologia* **57**, 2324–2333 (2014).
293. Pintó, X. et al. [Factors predictive of cardiovascular disease in patients with type-2 diabetes and hypercholesterolemia. ESODIAH study]. *Rev Esp Cardiol* **60**, 251–258 (2007).
294. Poon, P. Y., Szeto, C. C., Kwan, B. C., Chow, K. M. & Li, P. K. Relationship between beta1-adrenergic receptor polymorphisms and cardiovascular disease in patients with diabetic nephropathy. *Nephrology (Carlton)* **15**, 242–247 (2010).
295. Poon, P. Y., Szeto, C. C., Kwan, B. C., Chow, K. M. & Li, P. K. Relationship between HSP70-2 A+1267G polymorphism and cardiovascular events of Chinese peritoneal dialysis patients. *Nephron Clin. Pract.* **128**, 153–158 (2014).
296. Porchay-Baldérelli, I. et al. The CETP TaqIB polymorphism is associated with the risk of sudden death in Type 2 diabetic patients. *Diabetes Care* **30**, 2863–2867 (2007).
297. Porchay-Baldérelli, I. et al. Relationships between common polymorphisms of adenosine triphosphate-binding cassette transporter A1 and high-density lipoprotein cholesterol and coronary heart disease in a population with Type 2 diabetes mellitus. *Metabolism* **58**, 74–79 (2009).
298. Prentice, J. C., Pizer, S. D. & Conlin, P. R. Identifying the independent effect of HbA1c variability on adverse health outcomes in patients with Type 2 diabetes. *Diabetic Med.* **33**, 1640–1648 (2016).
299. Qi, L. et al. The +276 polymorphism of the APM1 gene, plasma adiponectin concentration, and cardiovascular risk in diabetic men. *Diabetes* **54**, 1607–1610 (2005).
300. Qi, L. et al. Genetic susceptibility to coronary heart disease in type 2 diabetes: 3 independent studies. *J. Am. Coll. Cardiol.* **58**, 2675–2682 (2011).
301. Qi, L. et al. Association between a genetic variant related to glutamic acid metabolism and coronary heart disease in individuals with type 2 diabetes. *JAMA* **310**, 821–828 (2013).
302. Qi, Q., Workalemahu, T., Zhang, C., Hu, F. B. & Qi, L. Genetic variants, plasma lipoprotein(a) levels, and risk of cardiovascular morbidity and mortality among two prospective cohorts of Type 2 diabetes. *Eur. Heart J.* **33**, 325–334 (2012).
303. Qin, Z. et al. The atherogenic index of plasma plays an important role in predicting the prognosis of Type 2 diabetic subjects undergoing percutaneous coronary intervention: results from an observational cohort study in China. *Cardiovasc. Diabetol.* **19**, 23 (2020).
304. Quan, J. et al. Risk prediction scores for mortality, cerebrovascular, and heart disease among Chinese people with Type 2 diabetes. *J. Clin. Endocrinol. Metab.* **104**, 5823–5830 (2019).
305. Raghavan, S. et al. Diabetes mellitus-related all-cause and cardiovascular mortality in a National cohort of adults. *J. Am. Heart Assoc.* **8**, e011295 (2019).
306. Ramirez-Prado, D. et al. A four-year cardiovascular risk score for Type 2 diabetic inpatients. *PeerJ* **2015**, e984 (2015).
307. Rana, B. S. et al. QT interval abnormalities are often present at diagnosis in diabetes and are better predictors of cardiac death than ankle brachial pressure index and autonomic function tests. *Heart* **91**, 44–50 (2005).
308. Rasmussen, D. G. K. et al. Higher collagen VI formation is associated with all-cause mortality in patients with Type 2 diabetes and microalbuminuria. *Diabetes Care* **41**, 1493–1500 (2018).
309. Ravassa, S. et al. Association of low GLP-1 with oxidative stress is related to cardiac disease and outcome in patients with Type 2 diabetes mellitus: a pilot study. *Free Radic. Biol. Med.* **81**, 1–12 (2015).
310. Rawshani, A. et al. Risk factors, mortality, and cardiovascular outcomes in patients with Type 2 diabetes. *N. Engl. J. Med.* **379**, 633–644 (2018).
311. Rawshani, A. et al. Association between socioeconomic status and mortality, cardiovascular disease, and cancer in patients with Type 2 diabetes. *JAMA Intern Med* **176**, 1146–1154 (2016).
312. Read, S. H. et al. Performance of cardiovascular disease risk scores in people diagnosed with Type 2 diabetes: external validation using data from the National Scottish diabetes register. *Diabetes Care* **41**, 2010–2018 (2018).
313. Reinhard, H. et al. Osteoprotegerin and mortality in type 2 diabetic patients. *Diabetes Care* **33**, 2561–2566 (2010).
314. Resl, M. et al. Serum uric acid is related to cardiovascular events and correlates with N-terminal pro-B-type natriuretic peptide and albuminuria in patients with diabetes mellitus. *Diabet. Med.* **29**, 721–725 (2012).
315. Resl, M. et al. Targeted multiple biomarker approach in predicting cardiovascular events in patients with diabetes. *Heart* **102**, 1963–1968 (2016).
316. Rossi, M. C. et al. Quality of diabetes care predicts the development of cardiovascular events: results of the AMD-QUASAR study. *Diabetes Care* **34**, 347–352 (2011).
317. Rotbain Curovic, V. et al. Urinary tubular biomarkers as predictors of kidney function decline, cardiovascular events and mortality in microalbuminuric type 2 diabetic patients. *Acta Diabetol.* **55**, 1143–1150 (2018).
318. Roumeliotis, A. et al. Carotid intima-media thickness is an independent predictor of all-cause mortality and cardiovascular morbidity in patients with diabetes mellitus Type 2 and chronic kidney disease. *Ren Fail* **41**, 131–138 (2019).
319. Roumeliotis, A. K. et al. Association of ALOX12 gene polymorphism with all-cause and cardiovascular mortality in diabetic nephropathy. *Int. Urol. Nephrol.* **50**, 321–329 (2018).
320. Roumeliotis, S. et al. Matrix Gla protein T-138C polymorphism is associated with carotid intima media thickness and predicts mortality in patients with diabetic nephropathy. *J. Diabetes Complications* **31**, 1527–1532 (2017).
321. Rozing, M. P. et al. Changes in HbA1c during the first six years after the diagnosis of Type 2 diabetes mellitus predict long-term microvascular outcomes. *PLoS One* **14**, e0225230 (2019).
322. Ruggenenti, P. et al. Measurable urinary albumin predicts cardiovascular risk among normoalbuminuric patients with Type 2 diabetes. *J. Am. Soc. Nephrol.* **23**, 1717–1724 (2012).
323. Russo, G. T. et al. Mild hyperhomocysteinemia, C677T polymorphism on methylenetetrahydrofolate reductase gene and the risk of macroangiopathy in type 2 diabetes: a prospective study. *Acta Diabetol* **48**, 95–101 (2011).
324. Rutter, M. K., Wahid, S. T., McComb, J. M. & Marshall, S. M. Significance of silent ischemia and microalbuminuria in predicting coronary events in asymptomatic patients with Type 2 diabetes. *J. Am. Coll. Cardiol.* **40**, 56–61 (2002).
325. Rådholm, K. et al. The impact of using sagittal abdominal diameter to predict major cardiovascular events in European patients with Type 2 diabetes. *Nutr. Metab. Cardiovasc. Dis.* **27**, 418–422 (2017).
326. Rørth, R. et al. The prognostic value of troponin T and N-terminal pro B-type natriuretic peptide, alone and in combination, in heart failure patients with and without diabetes. *Eur. J. Heart Fail* **21**, 40–49 (2019).
327. Saely, C. H. et al. The metabolic syndrome, insulin resistance, and cardiovascular risk in diabetic and nondiabetic patients. *J. Clin. Endocrinol. Metab.* **90**, 5698–5703 (2005).
328. Saely, C. H. et al. Lipoprotein(a), type 2 diabetes and vascular risk in coronary patients. *Eur. J. Clin. Invest.* **36**, 91–97 (2006).
329. Saito, I. et al. Nontraditional risk factors for coronary heart disease incidence among persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. *Ann. Intern. Med.* **133**, 81–91 (2000).
330. Sakai, K. et al. Small dense low-density lipoprotein cholesterol is a promising biomarker for secondary prevention in older men with stable coronary artery disease. *Geriatr. Gerontol. Int.* **18**, 965–972 (2018).
331. Salles, G. F., Leite, N. C., Pereira, B. B., Nascimento, E. M. & Cardoso, C. R. Prognostic impact of clinic and ambulatory blood pressure components in high-risk Type 2 diabetic patients: the Rio de Janeiro Type 2 Diabetes Cohort Study. *J. Hypertens* **31**, 2176–2186 (2013).

332. Satirapoj, B., Tasanavipap, P. & Supasyndh, O. Role of TCF7L2 and PPARG2 gene polymorphisms in renal and cardiovascular complications among patients with Type 2 diabetes: a Cohort Study. *Kidney Dis.* **5**, 220–227 (2019).
333. Saulnier, P. J. et al. Urinary sodium concentration is an independent predictor of all-cause and cardiovascular mortality in a Type 2 diabetes Cohort Population. *J. Diabetes Res.* **2017**, 5327352 (2017).
334. Savonitto, S. et al. Predictors of mortality in hospital survivors with type 2 diabetes mellitus and acute coronary syndromes. *Diabetes Vasc. Dis. Res.* **15**, 14–23 (2018).
335. Schimke, K., Chubb, S. A. P., Davis, W. A. & Davis, T. M. E. Helicobacter pylori cytotoxin-associated gene-A antibodies do not predict complications or death in Type 2 diabetes: The Fremantle Diabetes Study. *Atherosclerosis* **212**, 321–326 (2010).
336. Schulze, M. B. et al. C-reactive protein and incident cardiovascular events among men with diabetes. *Diabetes Care* **27**, 889–894 (2004).
337. Schulze, M. B. et al. Joint role of non-HDL cholesterol and glycated haemoglobin in predicting future coronary heart disease events among women with Type 2 diabetes. *Diabetologia* **47**, 2129–2136 (2004).
338. Scirica, B. M. et al. Prognostic implications of biomarker assessments in patients with Type 2 diabetes at high cardiovascular risk: A secondary analysis of a randomized clinical trial. *JAMA Cardiol.* **1**, 989–998 (2016).
339. Scirica, B. M. et al. Cardiovascular outcomes according to urinary albumin and kidney disease in patients with Type 2 diabetes at high cardiovascular risk: observations from the SAVOR-TIMI 53 trial. *JAMA Cardiol.* **3**, 155–163 (2018).
340. Seferovic, J. P. et al. Retinopathy, neuropathy, and subsequent cardiovascular events in patients with Type 2 diabetes and acute coronary syndrome in the ELIXA: the importance of disease duration. *J. Diabetes Res.* **2018**, 1631263 (2018).
341. Seyoum, B., Estacio, R. O., Berhanu, P. & Schrier, R. W. Exercise capacity is a predictor of cardiovascular events in patients with Type 2 diabetes mellitus. *Diabetes Vasc. Dis. Res.* **3**, 197–201 (2006).
342. Shao, H., Fonseca, V., Stoecker, C., Liu, S. & Shi, L. Novel risk engine for diabetes progression and mortality in USA: building, relating, assessing, and validating outcomes (BRAVO). *Pharmacoeconomics* **36**, 1125–1134 (2018).
343. Shao, H., Shi, L. & Fonseca, V. A. Using the BRAVO risk engine to predict cardiovascular outcomes in clinical trials with sodium-glucose transporter 2 inhibitors. *Diabetes Care* **43**, 1530–1536 (2020).
344. Sharma, A. et al. Causes of death in a contemporary Cohort of Patients With Type 2 diabetes and atherosclerotic cardiovascular disease: insights from the TECOS trial. *Diabetes Care* **40**, 1763–1770 (2017).
345. Sharma, A. et al. Clinical and biomarker predictors of expanded heart failure outcomes in patients with Type 2 diabetes mellitus after a recent acute coronary syndrome: insights from the EXAMINE Trial. *J. Am. Heart Assoc.* **9**, e012797 (2020).
346. Shin, S. H. et al. Hyperglycaemia, ejection fraction and the risk of heart failure or cardiovascular death in patients with Type 2 diabetes and a recent acute coronary syndrome. *Eur. J. Heart Fail.* **22**, 1133–1143 (2020).
347. Siddique, A. et al. Relationship of mildly increased albuminuria and coronary artery revascularization outcomes in patients with diabetes. *Catheter Cardiovasc. Interv.* **93**, E217–e224 (2019).
348. Sidorenkov, G., Voorham, J., de Zeeuw, D., Haaijer-Ruskamp, F. M. & Denig, P. Do treatment quality indicators predict cardiovascular outcomes in patients with diabetes? *PLoS One* **8**, e78821 (2013).
349. Silva, A. P. et al. Phosphorus as an early marker of morbidity and mortality in Type 2 chronic kidney disease diabetic patients. *J. Diabetes Complications* **27**, 328–332 (2013).
350. Silva, A. P. et al. What is the role of apelin regarding cardiovascular risk and progression of renal disease in Type 2 diabetic patients with diabetic nephropathy? *Biomed. Res. Int.* **2013**, 247649 (2013).
351. Simmons, R. K. et al. Performance of the UK prospective diabetes study risk engine and the Framingham risk equations in estimating cardiovascular disease in the EPIC–Norfolk Cohort. *Diabetes Care* **32**, 708–713 (2009).
352. Smáradóttir, M. I. et al. Copeptin and insulin-like growth factor binding protein-1 during follow-up after an acute myocardial infarction in patients with type 2 diabetes: a report from the diabetes mellitus insulin-glucose infusion in acute myocardial infarction 2 cohort. *Diab. Vasc. Dis. Res.* **16**, 22–27 (2019).
353. So, W. Y. et al. Aldose reductase genotypes and cardiorenal complications: an 8-year prospective analysis of 1074 Type 2 diabetic patients. *Diabetes Care* **31**, 2148–2153 (2008).
354. Soejima, H. et al. Proteinuria is independently associated with the incidence of primary cardiovascular events in diabetic patients. *J. Cardiol.* **75**, 387–393 (2020).
355. Soinio, M., Marniemi, J., Laakso, M., Lehto, S. & Rönnemaa, T. Elevated plasma homocysteine level is an independent predictor of coronary heart disease events in patients with Type 2 diabetes mellitus. *Ann. Intern. Med.* **140**, 94–100, (2004).
356. Sone, H. et al. Waist circumference as a cardiovascular and metabolic risk in Japanese patients with Type 2 diabetes. *Obesity (Silver Spring)* **17**, 585–592 (2009).
357. Sone, H. et al. Comparison of various lipid variables as predictors of coronary heart disease in Japanese men and women with Type 2 diabetes: subanalysis of the Japan Diabetes Complications Study. *Diabetes Care* **35**, 1150–1157 (2012).
358. Sone, H. et al. Serum level of triglycerides is a potent risk factor comparable to LDL cholesterol for coronary heart disease in Japanese patients with Type 2 diabetes: subanalysis of the Japan Diabetes Complications Study (JDCS). *J. Clin. Endocrinol. Metab.* **96**, 3448–3456 (2011).
359. Sone, H. et al. Leisure-time physical activity is a significant predictor of stroke and total mortality in Japanese patients with Type 2 diabetes: analysis from the Japan Diabetes Complications Study (JDCS). *Diabetologia* **56**, 1021–1030 (2013).
360. Spoelstra-de Man, A. M., Brouwer, C. B., Stehouwer, C. D. & Smulders, Y. M. Rapid progression of albumin excretion is an independent predictor of cardiovascular mortality in patients with Type 2 diabetes and microalbuminuria. *Diabetes Care* **24**, 2097–2101 (2001).
361. Standl, E. et al. Predictors of 10-year macrovascular and overall mortality in patients with NIDDM: the Munich General Practitioner Project. *Diabetologia* **39**, 1540–1545 (1996).
362. Stehouwer, C. D., Gall, M. A., Hougaard, P., Jakobs, C. & Parving, H. H. Plasma homocysteine concentration predicts mortality in non-insulin-dependent diabetic patients with and without albuminuria. *Kidney Int* **55**, 308–314 (1999).
363. Stevens, R. J., Kothari, V., Adler, A. I. & Stratton, I. M. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin. Sci. (Lond)* **101**, 671–679 (2001).
364. Strojek, K. et al. Factors associated with cardiovascular events in patients with Type 2 diabetes and acute myocardial infarction. *J. Clin. Endocrinol. Metab.* **101**, 243–253 (2016).
365. Sultan, A. et al. Myocardial perfusion imaging and cardiac events in a cohort of asymptomatic patients with diabetes living in southern France. *Diabet. Med.* **23**, 410–418 (2006).
366. Svendstrup, M., Christiansen, M. S., Magid, E., Hommel, E. & Feldt-Rasmussen, B. Increased orosomucoid in urine is an independent predictor of cardiovascular and all-cause mortality in patients with Type 2 diabetes at 10 years of follow-up. *J. Diabetes Complications* **27**, 570–575 (2013).
367. Svensson, E. et al. Early glycemic control and magnitude of HbA(1c) reduction predict cardiovascular events and mortality: population-based Cohort Study of 24,752 metformin initiators. *Diabetes Care* **40**, 800–807 (2017).
368. Svensson, M. K., Cederholm, J., Eliasson, B., Zethelius, B. & Gudbjörnsdóttir, S. Albuminuria and renal function as predictors of cardiovascular events and mortality in a general population of patients with Type 2 diabetes: a nationwide observational study from the Swedish National Diabetes Register. *Diab. Vasc. Dis. Res.* **10**, 520–529 (2013).
369. Takao, T., Suka, M., Yanagisawa, H. & Iwamoto, Y. Impact of postprandial hyperglycemia at clinic visits on the incidence of cardiovascular events and all-cause mortality in patients with Type 2 diabetes. *J. Diabetes Investig.* **8**, 600–608 (2017).
370. Tan, X. & Benedict, C. Increased risk of myocardial infarction among patients with type 2 diabetes who carry the common rs10830963 variant in the MTNR1B gene. *Diabetes Care* **43**, 2289–2292 (2020).
371. Tanaka, S. et al. Predicting macro- and microvascular complications in Type 2 diabetes: the Japan diabetes complications study/the Japanese elderly diabetes intervention trial risk engine. *Diabetes Care* **36**, 1193–1199 (2013).
372. Thanayasiri, P., Celermajer, D. S. & Adams, M. R. Predictors of long-term outcome following percutaneous coronary intervention in patients with type 2 diabetes mellitus. *Coron Artery Dis* **17**, 131–138 (2006).
373. The Look, A. R. G. Prospective association of a genetic risk score and lifestyle intervention with cardiovascular morbidity and mortality among individuals with type 2 diabetes: the Look AHEAD randomised controlled trial. *Diabetologia* **58**, 1803–1813 (2015).
374. Theilade, S. et al. Pulse pressure is not an independent predictor of outcome in type 2 diabetes patients with chronic kidney disease and anemia—the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT). *J. Hum. Hypertens.* **30**, 46–52 (2016).
375. Thomas, M. C. et al. Relationship Between Plasma 8-OH-Deoxyguanosine and Cardiovascular Disease and Survival in Type 2 Diabetes Mellitus: Results From the ADVANCE Trial. *J. Am. Heart Assoc.* **7**, e008226 (2018).
376. Tian, P., Zheng, X., Li, M., Li, W. & Niu, Q. Long-term prognostic value of coronary computed tomography angiography for asymptomatic patients with cad in type 2 diabetes mellitus. *Exp. Therap. Med.* **18**, 747–754 (2019).
377. Ting, R. Z. et al. Lipid control and use of lipid-regulating drugs for prevention of cardiovascular events in Chinese type 2 diabetic patients: a prospective cohort study. *Cardiovasc. Diabetol.* **9**, 77 (2010).
378. Tobias, D. K. et al. Circulating branched-chain amino acids and incident cardiovascular disease in a prospective Cohort of US women. *Circ. Genom. Precis. Med.* **11**, e002157 (2018).

379. Turner, R. C. et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ* **316**, 823–828 (1998).
380. Twito, O. et al. New-onset diabetes in elderly subjects: association between HbA1c levels, mortality, and coronary revascularization. *Diabetes Care* **36**, 3425–3429 (2013).
381. Umamahesh, K., Vigneswari, A., Surya Thejaswi, G., Satyavani, K. & Viswanathan, V. Incidence of cardiovascular diseases and associated risk factors among subjects with type 2 diabetes - an 11-year follow up study. *Indian Heart J.* **66**, 5–10 (2014).
382. Valmadrid, C. T., Klein, R., Moss, S. E. & Klein, B. E. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. *Arch. Intern. Med.* **160**, 1093–1100 (2000).
383. Valoti, E. et al. Impact of a complement factor H Gene variant on renal dysfunction, cardiovascular events, and response to ACE inhibitor therapy in Type 2 diabetes. *Front Genet* **10**, 681 (2019).
384. van der Heijden, A. A., Ortegon, M. M., Niessen, L. W., Nijpels, G. & Dekker, J. M. Prediction of coronary heart disease risk in a general, pre-diabetic, and diabetic population during 10 years of follow-up: accuracy of the Framingham, SCORE, and UKPDS risk functions: The Hoorn Study. *Diabetes Care* **32**, 2094–2098 (2009).
385. van der Leeuw, J. et al. Novel biomarkers to improve the prediction of cardiovascular event risk in Type 2 diabetes mellitus. *J. Am. Heart Assoc.* **5**, e003048 (2016).
386. van der Leeuw, J. et al. The validation of cardiovascular risk scores for patients with Type 2 diabetes mellitus. *Heart* **101**, 222–229 (2015).
387. Vanzetto, G. et al. Prediction of cardiovascular events in clinically selected high-risk NIDDM patients. Prognostic value of exercise stress test and thallium-201 single-photon emission computed tomography. *Diabetes Care* **22**, 19–26 (1999).
388. Vavruch, C. et al. Using proximity extension proteomics assay to discover novel biomarkers associated with circulating leptin levels in patients with Type 2 diabetes. *Sci. Rep.* **10**, 13097 (2020).
389. Velho, G. et al. Plasma copeptin, kidney disease, and risk for cardiovascular morbidity and mortality in two cohorts of Type 2 diabetes. *Cardiovasc. Diabetol.* **17**, 110 (2018).
390. Vengen, I. T., Dale, A. C., Wiseth, R., Midthjell, K. & Videm, V. Lactoferrin is a novel predictor of fatal ischemic heart disease in diabetes mellitus type 2: long-term follow-up of the HUNT 1 study. *Atherosclerosis* **212**, 614–620 (2010).
391. Venskutonyte, L., Brismar, K., Öhrvik, J., Rydén, L. & Kjellström, B. Self-rated health predicts outcome in patients with Type 2 diabetes and myocardial infarction: a DIGAMI 2 quality of life sub-study. *Diab. Vasc. Dis. Res.* **10**, 361–367 (2013).
392. Venskutonyte, L., Malmberg, K., Norhammar, A., Wedel, H. & Rydén, L. Effect of gender on prognosis in patients with myocardial infarction and type 2 diabetes. *J. Intern. Med.* **268**, 75–82 (2010).
393. Venuraju, S. M. et al. Duration of Type 2 diabetes mellitus and systolic blood pressure as determinants of severity of coronary stenosis and adverse events in an asymptomatic diabetic population: PROCEED study. *Cardiovasc. Diabetol.* **18**, 51 (2019).
394. Venuraju, S. M. et al. Association of epicardial fat volume with the extent of coronary atherosclerosis and cardiovascular adverse events in asymptomatic patients with diabetes. *Angiology* **72**, 442–450 (2021).
395. Venäläinen, M. S., Klén, R., Mahmoudian, M., Raitakari, O. T. & Elo, L. L. Easy-to-use tool for evaluating the elevated acute kidney injury risk against reduced cardiovascular disease risk during intensive blood pressure control. *J. Hypertens.* **38**, 511–518 (2020).
396. Vepsäläinen, T. et al. Proteinuria modifies the effect of systolic blood pressure on total and cardiovascular disease mortality in patients with type 2 diabetes. *J. Intern. Med.* **272**, 611–619 (2012).
397. von Scholten, B. J. et al. Additive prognostic value of plasma N-terminal pro-brain natriuretic peptide and coronary artery calcification for cardiovascular events and mortality in asymptomatic patients with Type 2 diabetes. *Cardiovasc. Diabetol.* **14**, 59 (2015).
398. von Scholten, B. J. et al. Urinary biomarkers are associated with incident cardiovascular disease, all-cause mortality and deterioration of kidney function in Type 2 diabetic patients with microalbuminuria. *Diabetologia* **59**, 1549–1557 (2016).
399. von Scholten, B. J. et al. Markers of inflammation and endothelial dysfunction are associated with incident cardiovascular disease, all-cause mortality, and progression of coronary calcification in type 2 diabetic patients with microalbuminuria. *J. Diabetes Complications* **30**, 248–255 (2016).
400. Wallander, M. et al. IGF binding protein 1 predicts cardiovascular morbidity and mortality in patients with acute myocardial infarction and type 2 diabetes. *Diabetes Care* **30**, 2343–2348 (2007).
401. Wan, E. Y., Fong, D. Y., Fung, C. S. & Lam, C. L. Incidence and predictors for cardiovascular disease in Chinese patients with Type 2 diabetes mellitus - a population-based retrospective cohort study. *J. Diabetes Complications* **30**, 444–450 (2016).
402. Wan, E. Y. F. et al. Development of a cardiovascular diseases risk prediction model and tools for Chinese patients with Type 2 diabetes mellitus: A population-based retrospective cohort study. *Diabetes Obes. Metab.* **20**, 309–318 (2018).
403. Wang, Y. et al. Independent predictive roles of eotaxin Ala23Thr, paraoxonase 2 Ser311Cys and beta-adrenergic receptor Trp64Arg polymorphisms on cardiac disease in Type 2 Diabetes—an 8-year prospective cohort analysis of 1297 patients. *Diabet Med.* **27**, 376–383 (2010).
404. Wang, Y. et al. Prognostic effect of insertion/deletion polymorphism of the ace gene on renal and cardiovascular clinical outcomes in Chinese patients with Type 2 diabetes. *Diabetes Care* **28**, 348–354 (2005).
405. Watson, C. et al. Investigation of association of genetic variant rs3918242 of matrix metalloproteinase-9 with hypertension, myocardial infarction and progression of ventricular dysfunction in Irish Caucasian patients with diabetes: a report from the STOP-HF follow-up prog. *BMC Cardiovasc. Disord.* **21**, 87 (2021).
406. Wei, M., Gaskill, S. P., Haffner, S. M. & Stern, M. P. Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality. The San Antonio Heart Study. *Diabetes Care* **21**, 1167–1172 (1998).
407. Wells, B. J. et al. Prediction of morbidity and mortality in patients with Type 2 diabetes. *PeerJ* **2013**, e87 (2013).
408. Wijkman, M., Länne, T., Östgren, C. J. & Nystrom, F. H. Aortic pulse wave velocity predicts incident cardiovascular events in patients with type 2 diabetes treated in primary care. *J. Diabetes Complications* **30**, 1223–1228 (2016).
409. Wijkman, M., Länne, T., Östgren, C. J. & Nystrom, F. H. Diastolic orthostatic hypertension and cardiovascular prognosis in Type 2 diabetes: a prospective cohort study. *Cardiovasc. Diabetol.* **15**, 83 (2016).
410. Winkler, K. et al. Apolipoprotein E genotype predicts cardiovascular endpoints in dialysis patients with Type 2 diabetes mellitus. *Atherosclerosis* **208**, 197–202 (2010).
411. Wolsk, E. et al. Role of B-Type natriuretic peptide and N-Terminal prohormone BNP as predictors of cardiovascular morbidity and mortality in patients with a recent coronary event and Type 2 diabetes mellitus. *J. Am. Heart Assoc.* **6**, e004743 (2017).
412. Wong, Y. K. et al. High-sensitivity troponin I and B-type natriuretic peptide biomarkers for prediction of cardiovascular events in patients with coronary artery disease with and without diabetes mellitus. *Cardiovasc. Diabetol.* **18**, 171 (2019).
413. Woodward, M. et al. Prediction of 10-year vascular risk in patients with diabetes: the AD-ON risk score. *Diabetes Obes. Metab.* **18**, 289–294 (2016).
414. Yamada, T., Itoi, T., Kiuchi, Y., Nemoto, M. & Yamashita, S. Proliferative diabetic retinopathy is a predictor of coronary artery disease in Japanese patients with type 2 diabetes. *Diabetes Res. Clin. Pract.* **96**, e4–6 (2012).
415. Yamasaki, Y. et al. Carotid intima-media thickness in Japanese Type 2 diabetic subjects: predictors of progression and relationship with incident coronary heart disease. *Diabetes Care* **23**, 1310–1315 (2000).
416. Yang, F., Ye, J., Pomerantz, K. & Stewart, M. Potential modification of the UKPDS risk engine and evaluation of macrovascular event rates in controlled clinical trials. *Diabetes, Metab. Syndrome Obesity: Targets Ther.* **6**, 247–256 (2013).
417. Yang, G. R. et al. Association between neck circumference and the occurrence of cardiovascular events in Type 2 diabetes: Beijing Community Diabetes Study 20 (BCDS-20). *Biomed. Res. Int.* **2019**, 4242304 (2019).
418. Yang, S. H. et al. Triglyceride to high-density lipoprotein cholesterol ratio and cardiovascular events in diabetics with coronary artery disease. *Am. J. Med. Sci.* **354**, 117–124 (2017).
419. Yang, S. H. et al. Serum fibrinogen and cardiovascular events in Chinese patients with Type 2 diabetes and stable coronary artery disease: a prospective observational study. *BMJ Open* **7**, e015041 (2017).
420. Yang, X. et al. Impacts of chronic kidney disease and albuminuria on associations between coronary heart disease and its traditional risk factors in type 2 diabetic patients - the Hong Kong diabetes registry. *Cardiovasc. Diabetol.* **6**, 37 (2007).
421. Yang, X. et al. Development and validation of a total coronary heart disease risk score in Type 2 diabetes mellitus. *Am. J. Cardiol.* **101**, 596–601 (2008).
422. Yang, Z. K. et al. Elevated glycated albumin and reduced endogenous secretory receptor for advanced glycation endproducts levels in serum predict major adverse cardio-cerebral events in patients with Type 2 diabetes and stable coronary artery disease. *Int. J. Cardiol.* **197**, 241–247 (2015).
423. Yeboah, J. et al. Development of a new diabetes risk prediction tool for incident coronary heart disease events: the Multi-Ethnic Study of Atherosclerosis and the Heinz Nixdorf Recall Study. *Atherosclerosis* **236**, 411–417 (2014).

424. Yeboah, P., Hsu, F. C., Bertoni, A. G. & Yeboah, J. Body mass index, change in weight, body weight variability and outcomes in Type 2 diabetes mellitus (from the ACCORD Trial). *Am. J. Cardiol.* **123**, 576–581 (2019).
425. Yiu, K. H. et al. Predictive value of high-sensitivity troponin-I for future adverse cardiovascular outcome in stable patients with type 2 diabetes mellitus. *Cardiovasc. Diabetol.* **13**, 63 (2014).
426. Yoshida, M. et al. Combination of the Framingham risk score and carotid intima-media thickness improves the prediction of cardiovascular events in patients with Type 2 diabetes. *Diabetes Care* **35**, 178–180 (2012).
427. Yoshimura, T. et al. Low blood flow estimates in lower-leg arteries predict cardiovascular events in Japanese patients with Type 2 diabetes with normal ankle-brachial indexes. *Diabetes Care* **29**, 1884–1890 (2006).
428. Young, J. B. et al. Development of predictive risk models for major adverse cardiovascular events among patients with Type 2 diabetes mellitus using health insurance claims data. *Cardiovasc. Diabetol.* **17**, 118 (2018).
429. Yu, D. et al. Development and external validation of risk scores for cardiovascular hospitalization and rehospitalization in patients with diabetes. *J. Clin. Endocrinol. Metab.* **103**, 1122–1129 (2018).
430. Yu, D. et al. Total/high density lipoprotein cholesterol and cardiovascular disease (re)hospitalization nadir in type 2 diabetes. *J. Lipid Res.* **59**, 1745–1750 (2018).
431. Yu, D. et al. Derivation and external validation of a risk prediction algorithm to estimate future risk of cardiovascular death among patients with Type 2 diabetes and incident diabetic nephropathy: prospective cohort study. *BMJ Open Diabetes Res Care* **7**, e000735 (2019).
432. Yu, D. & Simmons, D. Relationship between HbA1c and risk of all-cause hospital admissions among people with Type 2 diabetes. *Diabetic Medicine* **30**, 1407–1411 (2013).
433. Yu, D. & Simmons, D. Association between blood pressure and risk of cardiovascular hospital admissions among people with type 2 diabetes. *Heart* **100**, 1444–1449 (2014).
434. Yun, J. S., Park, Y. M., Cha, S. A., Ahn, Y. B. & Ko, S. H. Progression of cardiovascular autonomic neuropathy and cardiovascular disease in type 2 diabetes. *Cardiovasc. Diabetol.* **17**, 109 (2018).
435. Zafrir, B. et al. Low cardiorespiratory fitness and coronary artery calcification: Complementary cardiovascular risk predictors in asymptomatic Type 2 diabetics. *Atherosclerosis* **241**, 634–640 (2015).
436. Zafrir, B. et al. Resting heart rate and measures of effort-related cardiac autonomic dysfunction predict cardiovascular events in asymptomatic type 2 diabetes. *Eur. J. Prev. Cardiol.* **23**, 1298–1306 (2016).
437. Zethelius, B. et al. A new model for 5-year risk of cardiovascular disease in Type 2 diabetes, from the Swedish National Diabetes Register (NDR). *Diabetes Res. Clin. Pract.* **93**, 276–284 (2011).
438. Zhang, C. et al. Genetic variation in the hepatic lipase gene and the risk of coronary heart disease among US diabetic men: potential interaction with obesity. *Diabetologia* **49**, 1552–1559 (2006).
439. Zhang, X. L. et al. Improved framingham risk scores of patients with Type 2 Diabetes Mellitus in the Beijing Community: A 10-Year prospective study of the effects of multifactorial interventions on cardiovascular risk factors (The Beijing Communities Diabetes Study 22). *Diabetes Therapy* **11**, 885–903 (2020).
440. Zhao, Q. et al. Impacts of triglyceride-glucose index on prognosis of patients with type 2 diabetes mellitus and non-ST-segment elevation acute coronary syndrome: results from an observational cohort study in China. *Cardiovasc. Diabetol.* **19**, 108 (2020).
441. Zhou, J. B. et al. Prediction of proliferative diabetic retinopathy to asymptomatic obstructive coronary artery disease in Chinese Type 2 diabetes individuals: an exploratory study. *Metab. Syndr. Relat. Disord.* **17**, 367–373 (2019).
442. Zimring, M. B., Anderson, R. J., Ge, L. & Moritz, T. E. Increased plasma basic fibroblast growth factor is associated with coronary heart disease in adult type 2 diabetes mellitus. *Metabolism* **60**, 284–291 (2011).
443. Zimring, M. B., Anderson, R. J., Ge, L., Moritz, T. E. & Duckworth, W. C. Basic fibroblast growth factor predicts cardiovascular disease occurrence in participants from the veterans affairs diabetes trial. *Front. Endocrinol.* **4**, 183 (2013).
444. Zobel, E. H. et al. Toe-brachial index as a predictor of cardiovascular disease and all-cause mortality in people with type 2 diabetes and microalbuminuria. *Diabetologia* **60**, 1883–1891 (2017).
445. Zoppini, G. et al. Usefulness of the triglyceride to high-density lipoprotein cholesterol ratio for predicting mortality risk in type 2 diabetes: role of kidney dysfunction. *Atherosclerosis* **212**, 287–291 (2010).
446. Østergaard, H. B. et al. Limited benefit of haemoglobin glycation index as risk factor for cardiovascular disease in type 2 diabetes patients. *Diabetes Metab.* **45**, 254–260 (2019).
447. Fitipaldi, H. *hugofitipaldi/T2DCVD_Prognostics: T2DCVD-Prognostics Shiny app. Zenodo*, <https://doi.org/10.5281/zenodo.10277173> (2023).
448. Fitipaldi, H. & Franks, P. W. Ethnic, gender and other sociodemographic biases in genome-wide association studies for the most burdensome non-communicable diseases: 2005–2022. *Hum. Mol. Genet.* **32**, 520–532 (2023).
449. Misra, S. et al. Temporal trends in emergency admissions for diabetic ketoacidosis in people with diabetes in England before and during the COVID-19 pandemic: a population-based study. *Lancet Diabetes Endocrinol.* **9**, 671–680 (2021).
450. Di Angelantonio, E. et al. B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. *Circulation* **120**, 2177–2187 (2009).
451. Tam, C. H. T. et al. Identification of a common variant for coronary heart disease at PDE1A contributes to individualized treatment goals and risk stratification of cardiovascular complications in Chinese patients with Type 2 diabetes. *Diabetes Care* **46**, 1271–1281 (2023).
452. Chan, J. et al. The Joint Asia Diabetes Evaluation (JADE) Program: a web-based program to translate evidence to clinical practice in Type 2 diabetes. *Diabet Med.* **26**, 693–699 (2009).
453. Chan, J. C. N. et al. Effect of a web-based management guide on risk factors in patients with Type 2 diabetes and diabetic kidney disease: A JADE randomized clinical trial. *JAMA Netw. Open* **5**, e223862 (2022).
454. Lim, L. L. et al. Association of technologically assisted integrated care with clinical outcomes in Hong Kong using the prospective JADE program: a retrospective cohort analysis. *PLoS Med.* **17**, e1003367 (2020).
455. Chan, J. C. et al. Effects of telephone-based peer support in patients with type 2 diabetes mellitus receiving integrated care: a randomized clinical trial. *JAMA Intern Med.* **174**, 972–981 (2014).
456. Lim, L. L. et al. Effects of a technology-assisted integrated diabetes care program on cardiometabolic risk factors among patients with Type 2 Diabetes in the Asia-Pacific Region: the JADE program randomized clinical trial. *JAMA Netw. Open* **4**, e217557 (2021).

Acknowledgements

A.A., M.D.-P., H.F., M.F.G. acknowledge support from the Swedish Heart-Lung Foundation (20190470), Swedish Research Council (EXODIAB, 2009-1039; 2018-02837), Swedish Foundation for Strategic Research (LUDC-IRC, 15-0067), EU H2020-JTI-IM2-2015-05 (Grant agreement number 115974 – BEAT-DKD) to M.F.G. L.-L.L. acknowledge UK Medical Research Council Population and Systems Medicine Board (IF048-2022). M.L.M. is supported by Italian Ministry of Health Grant “Ricerca Finalizzata 2019” – GR-2019-12369702. C.H.T.T., C.H. and R.C.W.M. acknowledge support from the Research Grants Council of the Hong Kong Special Administrative Region (CU R4012-18), the Croucher Foundation Senior Medical Research Fellowship, University Grants Committee Research Grants Matching Scheme and Research Committee Postdoctoral Fellowship Scheme of the Chinese University of Hong Kong. F.F.C. acknowledge the Second Affiliated Hospital of Chongqing Medical University (No. 2022cffiqqdj). T.C. is an international training fellow supported by the Wellcome Trust grant (214205/Z/18/Z). R.W.K. was funded by a Novo Nordisk Foundation (NNF18OC0031650) postdoctoral fellowship. G.Y. and R.C.W.M. acknowledges support from the Provost’s Scheme for PhD scholarship from the Chinese University of Hong Kong. Y.Z. acknowledges a Postgraduate Studentship and Vice-Chancellor’s PhD scholarship from the Chinese University of Hong Kong. The authors wish to acknowledge the support of librarians from Lund University, Maria Björklund and Krister Aronsson for their expert support with the literature search. N.M. is supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK125780, R01DK134955).

Author contributions

Drs. M.F.G., R.C.W.M., and N.M. had full access to all the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: R.C.W.M., N.M., M.F.G., A.A.M., A.A., L.-L.L., R.W.K., S.C.T., C.H.T., M.D.-P., F.C., S.S. Acquisition, analysis, or interpretation of data: R.C.W.M., N.M., A.A., M.F.G., M.D.-P., C.H.T., R.W.K., F.C., S.C.T., L.-L.L., S.S., A.A.M., T.C., M.P., M.L.M., H.F., S.K., G.Y., Y.Z., C.H. Drafting of the manuscript: R.C.W.M., N.M., M.F.G., A.A., M.L.M., L.-L.L., C.H.T., H.F., S.K. Critical revision of the manuscript for important intellectual content: R.C.W.M., N.M., M.F.G., A.A., L.-L.L., M.L.M., C.H.T., F.C., T.C., M.D.-P., H.F., C.H., S.K., S.S., R.W.K., A.A.M., S.C.T., G.Y., Y.Z., M.P., D.S., R.J.dS., D.K.T. Statistical analysis: C.H.T., M.L.M., N.M. A.A., L.-L.L., M.L.M., C.H.T. contributed equally to this work and are considered co-first authors. M.F.G., R.C.W.M., and N.M. supervised all aspects of this work and are considered co-senior authors.

Competing interests

The authors declare the following competing interests: L.-L.L. has served as an advisory committee member for Bayer, Boehringer Ingelheim, Novo Nordisk, Procter & Gamble Health, and Viatrix; and as a speaker for Abbott, AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Novo Nordisk, Roche, Sanofi, Servier, and Zuellig Pharma Therapeutics. She has also received research grants from Abbott, AstraZeneca, and Boehringer Ingelheim. M.L.M. received lecture fees, consultancy, or advisory board fees from Amarin, Amgen, Eli Lilly, Merck Sharp & Dohme, Mylan, Novo Nordisk, Servier, and SlaPharma, all not directly related to this manuscript. R.W.K. has received consulting fees from Novo Nordisk. M.F.G. has received financial and non-financial (in kind)

support from Boehringer Ingelheim Pharma GmbH, JDRF International, Eli Lilly, AbbVie, Sanofi-Aventis, Astellas, Novo Nordisk A/S, Bayer AG within EU grant H2020-JTI-IMI2-2015-05 (Grant agreement number 115974 – BEAT-DKD). She has also received financial and in-kind support from Novo Nordisk, Pfizer, Follicum, Coegin Pharma, Abcentra, Probi, Johnson & Johnson within a project funded by the Swedish Foundation for Strategic Research on precision medicine in diabetes (LUDC-IRC #15-0067). Dr. Gomez has received personal consultancy fees from Lilly and Tribune Therapeutics AB. R.C.W.M. has received research grants from AstraZeneca, Bayer, Novo Nordisk, Pfizer, Roche Diagnostics (HK) Ltd, Tricida Inc, and consultancy/speaker honorarium from AstraZeneca, Boehringer Ingelheim, Bayer, Merck. All proceeds have been donated to the Chinese University of Hong Kong to support diabetes research. R.C.W.M. is a co-founder of GemVCare, a technology start-up initiated with support from the Hong Kong Government Innovation and Technology Commission and its Technology Start-up Support Scheme for Universities (TSSSU). R.J.d.S. has served as an external resource person to the World Health Organization's Nutrition Guidelines Advisory Group on trans fats, saturated fats, and polyunsaturated fats. The WHO paid for his travel and accommodation to attend meetings from 2012-2017 to present and discuss this work. He has presented updates of this work to the WHO in 2022. He has also done contract research for the Canadian Institutes of Health Research's Institute of Nutrition, Metabolism, and Diabetes, Health Canada, and the World Health Organization for which he received remuneration. He has received speaker's fees from the University of Toronto, and McMaster Children's Hospital. He has served as an independent director of the Helderleigh Foundation (Canada). He serves as a member of the Nutrition Science Advisory Committee to Health Canada (Government of Canada), co-chair of the Method working group of the ADA/EASD Precision Medicine in Diabetes group and is a co-opted member of the Scientific Advisory Committee on Nutrition (SACN) Subgroup on the Framework for the Evaluation of Evidence (Public Health England). He has held grants from the Canadian Institutes of Health Research, Canadian Foundation for Dietetic Research, Population Health Research Institute, and Hamilton Health Sciences Corporation as a principal investigator, and is a co-investigator on several funded team grants from the Canadian Institutes of Health Research. All other authors have no competing interests to declare.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s43856-023-00429-z>.

Correspondence and requests for materials should be addressed to Maria F. Gomez, Ronald C. W. Ma or Nestoras Mathioudakis.

Peer review information *Communications Medicine* thanks Xiao Liu, Jairo Arturo Pinzon Cortes and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Reprints and permission information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2024

¹Department of Clinical Sciences, Lund University Diabetes Centre, Lund University, Malmö, Sweden. ²Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia. ³Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China. ⁴Asia Diabetes Foundation, Hong Kong SAR, China. ⁵Metabolic Disease Unit, University Hospital of Padova, Padova, Italy. ⁶Department of Medicine, University of Padova, Padova, Italy. ⁷Laboratory for Molecular Epidemiology in Diabetes, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China. ⁸Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Hong Kong SAR, China. ⁹Health Management Center, The Second Affiliated Hospital of Chongqing Medical University, Chongqing Medical University, Chongqing, China. ¹⁰MRC/Wits Developmental Pathways for Health Research Unit, Department of Paediatrics, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. ¹¹Sydney Brenner Institute for Molecular Bioscience, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. ¹²AMAN Hospital, Doha, Qatar. ¹³Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. ¹⁴Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, United Kingdom. ¹⁵Department of Diabetes and Endocrinology, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa. ¹⁶Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, the Netherlands. ¹⁷Sections on Genetics and Epidemiology, Joslin Diabetes Center, Harvard Medical School, Boston, Massachusetts, USA. ¹⁸Nephrology, Dialysis and Renal Transplant Unit, IRCCS—Azienda Ospedaliero-Universitaria di Bologna, Alma Mater Studiorum University of Bologna, Bologna, Italy. ¹⁹Heather M. Arthur Population Health Research Institute, McMaster University, Ontario, Canada. ²⁰Department of Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada. ²¹Population Health Research Institute, Hamilton Health Sciences Corporation, Hamilton, Ontario, Canada. ²²Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA. ²³Faculty of Health, Aarhus University, Aarhus, Denmark. ²⁰⁰These authors contributed equally: Abrar Ahmad, Lee-Ling Lim, Mario Luca Morieri, Claudia Ha-ting Tam. ²⁰¹These authors jointly supervised this work: Maria F. Gomez, Ronald C.W. Ma, Nestoras Mathioudakis. *A list of authors and their affiliations appears at the end of the paper. ✉email: maria.gomez@med.lu.se; rcwma@cuhk.edu.hk; nmathio1@jh.edu

ADA/EASD PMDI

Deirdre K. Tobias^{24,25}, Jordi Merino^{26,27,28}, Abrar Ahmad^{1,200}, Catherine Aiken^{29,30}, Jamie L. Benham³¹, Dhanasekaran Bodhini³², Amy L. Clark³³, Kevin Colclough³⁴, Rosa Corcoy^{35,36,37}, Sara J. Cromer^{27,38,39}, Daisy Duan⁴⁰, Jamie L. Felton^{41,42,43}, Ellen C. Francis⁴⁴, Pieter Gillard⁴⁵, Véronique Gingras^{46,47}, Romy Gaillard⁴⁸, Eram Haider⁴⁹, Alice Hughes³⁴, Jennifer M. Ikle^{50,51}, Laura M. Jacobsen⁵², Anna R. Kahkoska⁵³, Jarno L. T. Kettunen^{54,55,56}, Raymond J. Kreienkamp^{27,28,38,57}, Lee-Ling Lim^{2,4,58}, Jonna M. E. Männistö^{59,60}, Robert Massey⁴⁹, Niamh-Maire McLennan⁶¹, Rachel G. Miller⁶², Mario Luca Morieri^{5,6,200}, Jasper Most⁶³, Rochelle N. Naylor⁶⁴, Bige Ozkan^{65,66}, Kashyap Amratlal Patel³⁴,

Scott J. Pilla^{67,68}, Katsiaryna Prystupa^{69,70}, Sridharan Raghavan^{71,72}, Mary R. Rooney^{65,73}, Martin Schön^{69,70,74}, Zhila Semnani-Azad²⁵, Magdalena Sevilla-Gonzalez^{38,39,75}, Pernille Svalastoga^{76,77}, Wubet Worku Takele⁷⁸, Claudia Ha-ting Tam^{7,8,58}, Anne Cathrine B. Thuesen²⁶, Mustafa Tosur^{79,80,81}, Amelia S. Wallace^{65,73}, Caroline C. Wang⁷³, Jessie J. Wong⁸², Jennifer M. Yamamoto⁸³, Katherine Young³⁴, Chloé Amouyal^{84,85}, Mette K. Andersen²⁶, Maxine P. Bonham⁸⁶, Mingling Chen⁸⁷, Feifei Cheng⁹, Tinashe Chikowore^{10,11,39,88}, Sian C. Chivers⁸⁹, Christoffer Clemmensen²⁶, Dana Dabelea⁹⁰, Adem Y. Dawed⁴⁹, Aaron J. Deutsch^{28,38,39}, Laura T. Dickens⁹¹, Linda A. DiMeglio^{41,42,43,92}, Monika Dudenhöffer-Pfeifer¹, Carmella Evans-Molina^{41,42,43,93}, María Mercè Fernández-Balsells^{94,95}, Hugo Fitipaldi¹, Stephanie L. Fitzpatrick⁹⁶, Stephen E. Gitelman⁹⁷, Mark O. Goodarzi^{98,99}, Jessica A. Grieger^{100,101}, Marta Guasch-Ferré^{25,102}, Nahal Habibi^{100,101}, Torben Hansen²⁶, Chuiguo Huang^{7,58}, Arianna Harris-Kawano^{41,42,43}, Heba M. Ismail^{41,42,43}, Benjamin Hoag^{103,104}, Randi K. Johnson^{105,106}, Angus G. Jones^{34,107}, Robert W. Koivula¹⁴, Aaron Leong^{27,39,108}, Gloria K. W. Leung⁸⁶, Ingrid M. Libman¹⁰⁹, Kai Liu¹⁰⁰, S. Alice Long¹¹⁰, William L. Lowe Jr.¹¹¹, Robert W. Morton^{112,113,114}, Ayesha A. Motala ¹⁵, Suna Onengut-Gumuscu¹¹⁵, James S. Pankow¹¹⁶, Maleesa Pathirana^{100,101}, Sofia Pazmino¹¹⁷, Dianna Perez^{41,42,43}, John R. Petrie¹¹⁸, Camille E. Powe^{27,38,39,119}, Alejandra Quinteros¹⁰⁰, Rashmi Jain^{120,121}, Debashree Ray^{73,122}, Mathias Ried-Larsen^{123,124}, Zeb Saeed¹²⁵, Vanessa Santhakumar²⁴, Sarah Kanbour^{12,67}, Sudipa Sarkar⁶⁷, Gabriela S. F. Monaco^{41,42,43}, Denise M. Scholtens¹²⁶, Elizabeth Selvin^{65,73}, Wayne Huey-Herng Sheu^{127,128,129}, Cate Speake¹³⁰, Maggie A. Stanislawski¹⁰⁵, Nele Steenackers¹¹⁷, Andrea K. Steck¹³¹, Norbert Stefan^{70,132,133}, Julie Støy¹³⁴, Rachael Taylor¹³⁵, Sok Cin Tye^{16,17}, Gebresilasea Gendisha Ukke⁷⁸, Marzhan Urazbayeva^{80,136}, Bart Van der Schueren^{117,137}, Camille Vatieer^{138,139}, John M. Wentworth^{140,141,142}, Wesley Hannah^{143,144}, Sara L. White^{89,145}, Gechang Yu^{7,58}, Yingchai Zhang^{7,58}, Shao J. Zhou^{101,146}, Jacques Beltrand^{147,148}, Michel Polak^{147,148}, Ingvild Aukrust^{76,149}, Elisa de Franco³⁴, Sarah E. Flanagan³⁴, Kristin A. Maloney¹⁵⁰, Andrew McGovern³⁴, Janne Molnes^{76,149}, Mariam Nakabuye²⁶, Pål Rasmus Njølstad^{76,77}, Hugo Pomares-Millan^{1,151}, Michele Provenzano¹⁸, Cécile Saint-Martin¹⁵², Cuilin Zhang^{153,154}, Yeyi Zhu^{155,156}, Sungyoung Auh¹⁵⁷, Russell de Souza^{20,113}, Andrea J. Fawcett^{158,159}, Chandra Gruber¹⁶⁰, Eskedar Getie Mekonnen^{161,162}, Emily Mixer¹⁶³, Diana Sherifali^{113,164}, Robert H. Eckel¹⁶⁵, John J. Nolan^{166,167}, Louis H. Philipson¹⁶³, Rebecca J. Brown¹⁵⁷, Liana K. Billings^{168,169}, Kristen Boyle⁹⁰, Tina Costacou⁶², John M. Dennis³⁴, Jose C. Florez^{27,28,38,39}, Anna L. Gloyn^{50,51,170}, Maria F. Gomez ^{1,23,201}, Peter A. Gottlieb¹³¹, Siri Atma W. Greeley¹⁷¹, Kurt Griffin^{121,172}, Andrew T. Hattersley^{34,107}, Irl B. Hirsch¹⁷³, Marie-France Hivert^{27,174,175}, Korey K. Hood⁸², Jami L. Josefson¹⁵⁸, Soo Heon Kwak¹⁷⁶, Lori M. Laffel¹⁷⁷, Siew S. Lim⁷⁸, Ruth J. F. Loos^{26,178}, Ronald C. W. Ma^{7,8,58}, Chantal Mathieu⁴⁵, Nestoras Mathioudakis⁶⁷, James B. Meigs^{39,108,179}, Shivani Misra^{180,181}, Viswanathan Mohan¹⁸², Rinki Murphy^{183,184,185}, Richard Oram^{34,107}, Katharine R. Owen^{14,186}, Susan E. Ozanne¹⁸⁷, Ewan R. Pearson⁴⁹, Wei Perng⁹⁰, Toni I. Pollin^{150,188}, Rodica Pop-Busui¹⁸⁹, Richard E. Pratley¹⁹⁰, Leanne M. Redman¹⁹¹, Maria J. Redondo^{79,80}, Rebecca M. Reynolds⁶¹, Robert K. Semple^{61,192}, Jennifer L. Sherr¹⁹³, Emily K. Sims^{41,42,43}, Arianne Sweeting^{194,195}, Tiinamaija Tuomi^{54,56,141}, Miriam S. Udler^{27,28,38,39}, Kimberly K. Vesco¹⁹⁶, Tina Vilsbøll^{197,198}, Robert Wagner^{69,70,199}, Stephen S. Rich¹¹⁵ & Paul W. Franks^{1,14,25,114}

²⁴Division of Preventative Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.

²⁵Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA. ²⁶Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. ²⁷Diabetes Unit, Endocrine Division, Massachusetts General Hospital, Boston, MA, USA. ²⁸Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA.

²⁹Department of Obstetrics and Gynaecology, the Rosie Hospital, Cambridge, UK. ³⁰NIHR Cambridge Biomedical Research Centre, University of Cambridge, Cambridge, UK. ³¹Departments of Medicine and Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada. ³²Department of Molecular Genetics, Madras Diabetes Research Foundation, Chennai, India. ³³Division of Pediatric Endocrinology, Department of Pediatrics, Saint Louis University School of Medicine, SSM Health Cardinal Glennon Children's Hospital, St. Louis, MO, USA. ³⁴Department of Clinical and Biomedical Sciences, University of Exeter Medical School, ExeterDevonUK. ³⁵CIBER-BBN, ISCIII,

Madrid, Spain. ³⁶Institut d'Investigació Biomèdica Sant Pau (IIB SANT PAU), Barcelona, Spain. ³⁷Departament de Medicina, Universitat Autònoma de Barcelona, Bellaterra, Spain. ³⁸Programs in Metabolism and Medical & Population Genetics, Broad Institute, Cambridge, MA, USA. ³⁹Department of Medicine, Harvard Medical School, Boston, MA, USA. ⁴⁰Division of Endocrinology, Diabetes and Metabolism, Johns Hopkins University School of Medicine, Baltimore, MD, USA. ⁴¹Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, USA. ⁴²Herman B Wells Center for Pediatric Research, Indiana University School of Medicine, Indianapolis, IN, USA. ⁴³Center for Diabetes and Metabolic Diseases, Indiana University School of Medicine, Indianapolis, IN, USA. ⁴⁴Department of Biostatistics and Epidemiology, Rutgers School of Public Health, Piscataway, NJ, USA. ⁴⁵University Hospital Leuven, Leuven, Belgium. ⁴⁶Department of Nutrition, Université de Montréal, Montreal, Quebec, Canada. ⁴⁷Research Center, Sainte-Justine University Hospital Center, Montreal, Quebec, Canada. ⁴⁸Department of Pediatrics, Erasmus Medical Center, Rotterdam, The Netherlands. ⁴⁹Division of Population Health & Genomics, School of Medicine, University of Dundee, Dundee, UK. ⁵⁰Department of Pediatrics, Stanford School of Medicine, Stanford University, Stanford, CA, USA. ⁵¹Stanford Diabetes Research Center, Stanford School of Medicine, Stanford University, Stanford, CA, USA. ⁵²University of Florida, Gainesville, FL, USA. ⁵³Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ⁵⁴Helsinki University Hospital, Abdominal Centre/Endocrinology, Helsinki, Finland. ⁵⁵Folkhalsan Research Center, Helsinki, Finland. ⁵⁶Institute for Molecular Medicine Finland FIMM, University of Helsinki, Helsinki, Finland. ⁵⁷Department of Pediatrics, Division of Endocrinology, Boston Children's Hospital, Boston, MA, USA. ⁵⁸Department of Medicine & Therapeutics, Chinese University of Hong Kong, Hong Kong SAR, China. ⁵⁹Departments of Pediatrics and Clinical Genetics, Kuopio University Hospital, Kuopio, Finland. ⁶⁰Department of Medicine, University of Eastern Finland, Kuopio, Finland. ⁶¹Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK. ⁶²Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA, USA. ⁶³Department of Orthopedics, Zuyderland Medical Center, Sittard-Geleen, The Netherlands. ⁶⁴Departments of Pediatrics and Medicine, University of Chicago, Chicago, Illinois, USA. ⁶⁵Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. ⁶⁶Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins School of Medicine, Baltimore, MD, USA. ⁶⁷Department of Medicine, Johns Hopkins University, Baltimore, MD, USA. ⁶⁸Department of Health Policy and Management, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA. ⁶⁹Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Auf'm Hennekamp 65, 40225 Düsseldorf, Germany. ⁷⁰German Center for Diabetes Research (DZD), Ingolstädter Landstraße 1, 85764 Neuherberg, Germany. ⁷¹Section of Academic Primary Care, US Department of Veterans Affairs Eastern Colorado Health Care System, Aurora, CO, USA. ⁷²Department of Medicine, University of Colorado School of Medicine, Aurora, CO, USA. ⁷³Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. ⁷⁴Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia. ⁷⁵Clinical and Translational Epidemiology Unit, Massachusetts General Hospital, Boston, MA, USA. ⁷⁶Mohn Center for Diabetes Precision Medicine, Department of Clinical Science, University of Bergen, Bergen, Norway. ⁷⁷Children and Youth Clinic, Haukeland University Hospital, Bergen, Norway. ⁷⁸Eastern Health Clinical School, Monash University, Melbourne, Victoria, Australia. ⁷⁹Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA. ⁸⁰Division of Pediatric Diabetes and Endocrinology, Texas Children's Hospital, Houston, TX, USA. ⁸¹Children's Nutrition Research Center, USDA/ARS, Houston, TX, USA. ⁸²Stanford University School of Medicine, Stanford, CA, USA. ⁸³Internal Medicine, University of Manitoba, Winnipeg, MB, Canada. ⁸⁴Department of Diabetology, APHP, Paris, France. ⁸⁵Sorbonne Université, INSERM, NutriOmic team, Paris, France. ⁸⁶Department of Nutrition, Dietetics and Food, Monash University, Melbourne, Victoria, Australia. ⁸⁷Monash Centre for Health Research and Implementation, Monash University, Clayton, VIC, Australia. ⁸⁸Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA, USA. ⁸⁹Department of Women and Children's health, King's College London, London, UK. ⁹⁰Lifecourse Epidemiology of Adiposity and Diabetes (LEAD) Center, University of Colorado Anschutz Medical Campus, Aurora, CO, USA. ⁹¹Section of Adult and Pediatric Endocrinology, Diabetes and Metabolism, Kovler Diabetes Center, University of Chicago, Chicago, USA. ⁹²Department of Pediatrics, Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, IN, USA. ⁹³Richard L. Roudebush VAMC, Indianapolis, IN, USA. ⁹⁴Biomedical Research Institute Girona, IdIBGi, Girona, Spain. ⁹⁵Diabetes, Endocrinology and Nutrition Unit Girona, University Hospital Dr Josep Trueta, Girona, Spain. ⁹⁶Institute of Health System Science, Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY, USA. ⁹⁷University of California at San Francisco, Department of Pediatrics, Diabetes Center, San Francisco, CA, USA. ⁹⁸Division of Endocrinology, Diabetes and Metabolism, Cedars-Sinai Medical Center, Los Angeles, CA, USA. ⁹⁹Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA. ¹⁰⁰Adelaide Medical School, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, Australia. ¹⁰¹Robinson Research Institute, The University of Adelaide, Adelaide, Australia. ¹⁰²Department of Public Health and Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, 1014 Copenhagen, Denmark. ¹⁰³Division of Endocrinology and Diabetes, Department of Pediatrics, Sanford Children's Hospital, Sioux Falls, SD, USA. ¹⁰⁴University of South Dakota School of Medicine, E Clark St, Vermillion, SD, USA. ¹⁰⁵Department of Biomedical Informatics, University of Colorado Anschutz Medical Campus, Aurora, CO, USA. ¹⁰⁶Department of Epidemiology, Colorado School of Public Health, Aurora, CO, USA. ¹⁰⁷Royal Devon University Healthcare NHS Foundation Trust, Exeter, UK. ¹⁰⁸Division of General Internal Medicine, Massachusetts General Hospital, Boston, MA, USA. ¹⁰⁹UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA. ¹¹⁰Center for Translational Immunology, Benaroya Research Institute, Seattle, WA, USA. ¹¹¹Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. ¹¹²Department of Pathology & Molecular Medicine, McMaster University, Hamilton, Canada. ¹¹³Population Health Research Institute, Hamilton, Canada. ¹¹⁴Department of Translational Medicine, Medical Science, Novo Nordisk Foundation, Tuborg Havnevej 19, 2900 Hellerup, Denmark. ¹¹⁵Center for Public Health Genomics, Department of Public Health Sciences, University of Virginia, Charlottesville, VA, USA. ¹¹⁶Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA. ¹¹⁷Department of Chronic Diseases and Metabolism, Clinical and Experimental Endocrinology, KU Leuven, Leuven, Belgium. ¹¹⁸School of Health and Wellbeing, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK. ¹¹⁹Department of Obstetrics, Gynecology, and Reproductive Biology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA. ¹²⁰Sanford Children's Specialty Clinic, Sioux Falls, SD, USA. ¹²¹Department of Pediatrics, Sanford School of Medicine, University of South Dakota, Sioux Falls, SD, USA. ¹²²Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. ¹²³Centre for Physical Activity Research, Rigshospitalet, Copenhagen, Denmark. ¹²⁴Institute for Sports and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark. ¹²⁵Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, Indiana University School of Medicine, Indianapolis, IN, USA. ¹²⁶Department of Preventive Medicine, Division of Biostatistics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. ¹²⁷Institute of Molecular and Genomic Medicine, National Health Research Institutes, Taipei City, Taiwan. ¹²⁸Division of Endocrinology and Metabolism, Taichung Veterans General Hospital, Taichung, Taiwan. ¹²⁹Division of Endocrinology and Metabolism, Taipei Veterans General Hospital, Taipei, Taiwan. ¹³⁰Center for Interventional Immunology, Benaroya Research Institute, Seattle, WA, USA. ¹³¹Barbara Davis Center for Diabetes, University of Colorado Anschutz Medical Campus, Aurora, CO, USA. ¹³²University Hospital of Tübingen, Tübingen, Germany. ¹³³Institute of Diabetes Research and Metabolic Diseases (IDM), Helmholtz Center Munich, Neuherberg, Germany. ¹³⁴Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus, Denmark. ¹³⁵University of Newcastle, Newcastle upon Tyne, UK. ¹³⁶Gastroenterology, Baylor College of Medicine, Houston, TX, USA. ¹³⁷Department of Endocrinology, University

Hospitals Leuven, Leuven, Belgium. ¹³⁸Sorbonne University, Inserm U938, Saint-Antoine Research Centre, Institute of Cardiometabolism and Nutrition, Paris 75012, France. ¹³⁹Department of Endocrinology, Diabetology and Reproductive Endocrinology, Assistance Publique-Hôpitaux de Paris, Saint-Antoine University Hospital, National Reference Center for Rare Diseases of Insulin Secretion and Insulin Sensitivity (PRISIS), Paris, France. ¹⁴⁰Royal Melbourne Hospital Department of Diabetes and Endocrinology, Parkville, Vic, Australia. ¹⁴¹Walter and Eliza Hall Institute, Parkville, Vic, Australia. ¹⁴²University of Melbourne Department of Medicine, Parkville, Vic, Australia. ¹⁴³Deakin University, Melbourne, Australia. ¹⁴⁴Department of Epidemiology, Madras Diabetes Research Foundation, Chennai, India. ¹⁴⁵Department of Diabetes and Endocrinology, Guy's and St Thomas' Hospitals NHS Foundation Trust, London, UK. ¹⁴⁶School of Agriculture, Food and Wine, University of Adelaide, Adelaide, Australia. ¹⁴⁷Institut Cochin, Inserm U 10116, Paris, France. ¹⁴⁸Pediatric endocrinology and diabetes, Hopital Necker Enfants Malades, APHP Centre, université de Paris, Paris, France. ¹⁴⁹Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway. ¹⁵⁰Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA. ¹⁵¹Department of Epidemiology, Geisel School of Medicine at Dartmouth, Hanover, NH, USA. ¹⁵²Department of Medical Genetics, AP-HP Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France. ¹⁵³Global Center for Asian Women's Health, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore. ¹⁵⁴Department of Obstetrics and Gynecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore. ¹⁵⁵Kaiser Permanente Northern California Division of Research, Oakland, California, USA. ¹⁵⁶Department of Epidemiology and Biostatistics, University of California San Francisco, California, USA. ¹⁵⁷National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA. ¹⁵⁸Ann & Robert H. Lurie Children's Hospital of Chicago, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. ¹⁵⁹Department of Clinical and Organizational Development, Chicago, IL, USA. ¹⁶⁰American Diabetes Association, Arlington, Virginia, USA. ¹⁶¹College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia. ¹⁶²Global Health Institute, Faculty of Medicine and Health Sciences, University of Antwerp, 2160 Antwerp, Belgium. ¹⁶³Department of Medicine and Kovler Diabetes Center, University of Chicago, Chicago, IL, USA. ¹⁶⁴School of Nursing, Faculty of Health Sciences, McMaster University, Hamilton, Canada. ¹⁶⁵Division of Endocrinology, Metabolism, Diabetes, University of Colorado, Boulder, CO, USA. ¹⁶⁶Department of Clinical Medicine, School of Medicine, Trinity College Dublin, Dublin, Ireland. ¹⁶⁷Department of Endocrinology, Wexford General Hospital, Wexford, Ireland. ¹⁶⁸Division of Endocrinology, NorthShore University HealthSystem, Skokie, IL, USA. ¹⁶⁹Department of Medicine, Pritzker School of Medicine, University of Chicago, Chicago, IL, USA. ¹⁷⁰Department of Genetics, Stanford School of Medicine, Stanford University, Stanford, CA, USA. ¹⁷¹Departments of Pediatrics and Medicine and Kovler Diabetes Center, University of Chicago, Chicago, USA. ¹⁷²Sanford Research, Sioux Falls, SD, USA. ¹⁷³University of Washington School of Medicine, Seattle, WA, USA. ¹⁷⁴Department of Population Medicine, Harvard Medical School, Harvard Pilgrim Health Care Institute, Boston, MA, USA. ¹⁷⁵Department of Medicine, Université de Sherbrooke, Sherbrooke, QC, Canada. ¹⁷⁶Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea. ¹⁷⁷Joslin Diabetes Center, Harvard Medical School, Boston, MA, USA. ¹⁷⁸Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹⁷⁹Broad Institute, Cambridge, MA, USA. ¹⁸⁰Division of Metabolism, Digestion and Reproduction, Imperial College London, London, UK. ¹⁸¹Department of Diabetes & Endocrinology, Imperial College Healthcare NHS Trust, London, UK. ¹⁸²Department of Diabetology, Madras Diabetes Research Foundation & Dr. Mohan's Diabetes Specialities Centre, Chennai, India. ¹⁸³Department of Medicine, Faculty of Medicine and Health Sciences, University of Auckland, Auckland, New Zealand. ¹⁸⁴Auckland Diabetes Centre, Te Whatu Ora Health New Zealand, Auckland, New Zealand. ¹⁸⁵Medical Bariatric Service, Te Whatu Ora Counties, Health New Zealand, Auckland, New Zealand. ¹⁸⁶Oxford NIHR Biomedical Research Centre, University of Oxford, Oxford, UK. ¹⁸⁷University of Cambridge, Metabolic Research Laboratories and MRC Metabolic Diseases Unit, Wellcome-MRC Institute of Metabolic Science, Cambridge, UK. ¹⁸⁸Department of Epidemiology & Public Health, University of Maryland School of Medicine, Baltimore, MD, USA. ¹⁸⁹Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, MI, USA. ¹⁹⁰AdventHealth Translational Research Institute, Orlando, FL, USA. ¹⁹¹Pennington Biomedical Research Center, Baton Rouge, LA, USA. ¹⁹²MRC Human Genetics Unit, Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK. ¹⁹³Yale School of Medicine, New Haven, CT, USA. ¹⁹⁴Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia. ¹⁹⁵Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, NSW, Australia. ¹⁹⁶Kaiser Permanente Northwest, Kaiser Permanente Center for Health Research, Portland, OR, USA. ¹⁹⁷Clinical Research, Steno Diabetes Center Copenhagen, Herlev, Denmark. ¹⁹⁸Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. ¹⁹⁹Department of Endocrinology and Diabetology, University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany.