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**Impact of diabetes definition on global surveillance of diabetes prevalence and diagnosis:
pooled analysis of 96 population-based studies with 331,000 participants**

NCD Risk Factor Collaboration (NCD-RisC)

Summary

Background: Over time, diabetes has been defined based on different biomarkers, including fasting plasma glucose (FPG) or 2-hour plasma glucose in an oral glucose tolerance test (2hOGTT) and, more recently, haemoglobin A1c (HbA1c). We examined the influence of diagnostic definitions on both the population prevalence of diabetes and the classification of previously-undiagnosed individuals as with vs. without diabetes in a pooled analysis of data from population-based health examination surveys in different world regions.

Methods: We used data from 96 population-based health examination surveys that had measured at least two of the biomarkers used for defining diabetes. We calculated diabetes prevalence taking into account complex survey design and survey sample weights. We compared the prevalences of diabetes using different definitions graphically and in regression analyses. We calculated sensitivity and specificity of diabetes diagnosis, among previously-undiagnosed individuals, using HbA1c against either FPG or FPG-or-2hOGTT definitions. Sensitivity and specificity were calculated in each survey, and then pooled across surveys using a random-effects model. We examined the sources of heterogeneity of sensitivity and specificity using meta-regressions and a set of *a-priori*-selected study characteristics.

Results: Population prevalence of diabetes based on FPG-or-2hOGTT (FPG \geq 7.0 mmol/L or 2hOGTT \geq 11.1 mmol/L or history of diabetes or using insulin or oral hypoglycaemic agents) was correlated with prevalence based on FPG alone ($r = 0.98$), but was higher by 2 to 6 percentage points at different prevalence levels. Prevalence based on HbA1c (HbA1c \geq 6.5% or history of diagnosis with diabetes or using insulin or oral hypoglycaemic agents) was lower than prevalence based on FPG in 42.8% of data and higher in another 41.6%; in the other 15.6%, the two definitions led to similar prevalence estimates. The variation across studies in the relationship between glucose-based and HbA1c-based prevalences was partly related to participants' age, followed by natural logarithm of per-capita gross domestic product, the year of survey, mean BMI, and whether the survey population was national, subnational, or from specific communities. Diabetes defined as HbA1c \geq 6.5% had a pooled sensitivity of 52.8% (95% confidence interval 51.3-54.3%) and a pooled specificity of 99.74% (99.71-99.78%) compared with FPG \geq 7.0 mmol/L in diagnosing previously-undiagnosed participants; sensitivity compared with diabetes defined based on FPG-or-2hOGTT was 30.5% (28.7-32.3 %). None of the pre-selected study-level characteristics explained the heterogeneity in the sensitivity of HbA1c versus blood glucose.

Conclusions: Different biomarkers and definitions for diabetes can provide different estimates of population prevalence of diabetes, and differentially identify people without prior diagnosis as having diabetes. Using HbA1c alone in health surveys will not identify a substantial proportion of previously-undiagnosed people who would be considered as having diabetes using a glucose-based test and, inversely, using a glucose-based test alone will not identify some persons who would be considered as having diabetes with an HbA1c test.

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Introduction

Diabetes prevalence and diabetes-related deaths are rising in most parts of the world, at least partially fuelled by the worldwide rise in excess weight and adiposity.¹⁻⁵ This rising trend has created concerns about the health and functioning consequences for people, and costs for health systems.⁶⁻⁸ Tracking the epidemic and the progress of programmes aimed at reducing diabetes and its complications requires consistent and comparable measurement of the prevalence of diabetes and the coverage of pharmacological and lifestyle interventions that slowdown diabetes progression and the risk of complications.

Over time, definitions of diabetes have used different biomarkers, including fasting plasma glucose (FPG), 2-hour plasma glucose in an oral glucose tolerance test (2hOGTT), and more recently, haemoglobin A1c (HbA1c).⁹⁻¹⁵ Population-based health surveys in different countries and years also have used, and continue to use, different biomarkers for glycaemia and diabetes, and hence define diabetes differently. This multiplicity of biomarkers and definitions creates a challenge in consistently analysing diabetes prevalence across countries and over time, and in measuring what proportion of people with diabetes are diagnosed and receive effective treatments for diabetes and its complications.^{1,16,17} Therefore, there is a need to understand how the use of different biomarkers and definitions affects the identification of diabetes cases and the resulting population prevalence estimates. This need is particularly pressing as two of the nine global targets for noncommunicable diseases (NCDs) set after the 2011 United Nations high level meeting on NCDs require estimates of diabetes prevalence: to halt the rise in the prevalence of diabetes, and to achieve a 50% coverage of drug therapy and counselling, including glycaemic control, to prevent coronary heart disease and stroke in people at high risk of cardiovascular

disease.^{4,18} Diabetes is also one of the four main NCDs for which there is a global target of 25% reduction in premature mortality by 2025 compared to 2010 levels.^{4,18}

Some studies have analysed the classification of individuals as having diabetes or compared prevalence estimates based on different definitions in specific cohorts, especially for HbA1c compared to either FPG or 2hOGTT.¹⁹⁻⁶¹ Most of these analyses were based on a single cohort and very few cover different world regions. Two pooled analyses of Asian and European cohorts, and a study in the Pacific and Indian Ocean islands, assessed how the prevalence of diabetes and the classification of individuals as with or without diabetes changed depending on whether diabetes was defined based on FPG vs. 2hOGTT.⁶²⁻⁶⁶ There is no pooling study for HbA1c, which can be measured easily in population-based surveys without the need to fast overnight and has recently been approved by the American Diabetes Association (ADA) and the World Health Organization (WHO) as a diagnostic test for diabetes.^{11,14} However, an overview of data from six countries found that the sensitivity of diabetes diagnosis based on HbA1c compared to FPG ranged between 17% and 78%,⁶⁷ raising concerns about ethnic variation of HbA1c-based definition.¹⁷

Our aim was to examine the influence of diagnostic definitions both on the identification of diabetes in previously-undiagnosed individuals and on population prevalence estimates for diabetes in a pooled analysis of data from a large number of population-based health examination surveys in different world regions.

Methods

Study design

We aimed to answer the following questions:

First, how does the estimated prevalence of diabetes in a population change when the new definition of diabetes based on HbA1c (HbA1c \geq 6.5% or history of diagnosis with diabetes or using insulin or oral hypoglycaemic agents)¹¹ is used compared with earlier definitions based on blood glucose, e.g., the ADA definition of FPG \geq 7.0 mmol/L or history of diagnosis with diabetes or using insulin or oral hypoglycaemic agents (which is also used in the global monitoring framework for prevention and control of NCDs),^{12,18} or the WHO definition of FPG \geq 7.0 mmol/L or 2hOGTT \geq 11.1 mmol/L or history of diabetes or using insulin or oral hypoglycaemic agents?^{9,10}

Second, how does the new definition of diabetes based on HbA1c compare with the earlier definitions endorsed by ADA and WHO in identifying previously undiagnosed people with diabetes, as measured by the sensitivity and specificity of the new definition with respect to the prior ones? We further assessed whether sensitivity varies by the characteristics of the study population, because this possible variation seems to be a source of concern regarding the generalizability of HbA1c as a diagnostic and surveillance tool.^{17,67-70}

Data sources

We used population-based data collated by the NCD Risk Factor Collaboration (NCD-RisC). NCD-RisC is a worldwide network of health researchers and practitioners who, together with WHO, have collated a large database of population-based health surveys and epidemiological

studies on cardio-metabolic risk factors. All data sources were carefully checked by at least two independent reviewers for being representative of a national or subnational population, and for study quality indicators such as fasting duration and the protocol for OGTT. We excluded surveys that had not used a standard glucose load for OGTT. Within each survey, we included participants aged 18 years and older who were not pregnant and had fasted at least for 6 hours prior to measurement as a part of the survey instructions. We excluded HbA1c data prior to the year 2000 to minimize the use of non-standard assays.⁷¹ Further, we excluded surveys that had measured a biomarker only among participants with a high value of another, e.g., studies in which FPG was only measured in participants with HbA1c above a pre-specified value, because the relationship between the two measurements may be different in this pre-screened group compared with the whole sample.

We restricted the analysis of sensitivity and specificity to people without a previous history of diabetes diagnosis, because prior diagnosis and the use of medication are likely to affect the levels of different biomarkers used to diagnose diabetes. History of diabetes diagnosis was established using survey-specific questions, often worded such as “have you ever been told by a doctor or other health professional that you have diabetes?” or the combination of “do you now have, or have you ever had diabetes?” and “were you told by a doctor that you had diabetes?”. We also excluded follow-up surveys of closed cohorts from the analysis of sensitivity and specificity because active surveillance within a cohort shifts subjects from undiagnosed to diagnosed status at each follow-up, hence affecting the composition of undiagnosed cases which are used for sensitivity/specificity analysis. The flowchart for selecting surveys is shown in Figure 1 and details on individual surveys are provided in Webtables 1 and 2.

Statistical methods

We calculated diabetes prevalence by sex and age group, taking into account complex survey designs and survey sample weights where relevant. We excluded age-sex groups with fewer than 25 participants when calculating prevalence estimates because the sampling error of estimated prevalence can bias the associations between prevalences based on different definitions. Some surveys had measured HbA1c or FPG in all participants, but had not measured 2hOGTT among people with diagnosed diabetes. These previously-diagnosed subjects were included in calculation of diabetes prevalence because their exclusion would underestimate diabetes prevalence. Further, some of these surveys had measured 2hOGTT in only a subset of people without history of diabetes diagnosis, generally for logistical or cost reasons. Simply combining these subjects with previously-diagnosed subjects might overestimate diabetes prevalence based on 2hOGTT. To account for these missing measurements, and to avoid overestimation of diabetes prevalence, we re-calculated the survey sample weights for these subjects – as the original sample weight divided by weighted proportion of non-diabetic subjects with data. This approach is similar to the use of 2hOGTT sample weights in the US National Health and Nutrition Examination Survey.⁷² A similar approach was taken in a few surveys that had measured HbA1c in all participants, but had not measured FPG among people with diagnosed diabetes.

We compared the prevalences of diabetes using different definitions graphically. We also analysed the relationship between diabetes defined (i) based on FPG-or-2hOGTT and based on FPG and (ii) based on HbA1c and based on FPG in regression analyses. We did not do a

regression for diabetes prevalence based on HbA1c vs. prevalence based on FPG-or-2hOGTT because very few surveys had data on both 2hOGTT and HbA1c, leading to unstable regression coefficients. Diabetes prevalence was probit-transformed because this transformation provided better fit to the data and because it avoids predicting prevalences that are less than zero or greater than one. We considered alternative regression models in terms of covariates and specification, and chose the best model using the Bayesian Information Criterion (BIC) – BIC measures the relative goodness of fit of a model; it rewards how well the model fits the data but discourages overfitting.⁷³ The regressions included age (mean age of each age-sex group); the year(s) over which each survey collected data (as the mid-year of the period of data collection as shown in Webtables 1 and 2); national income (natural logarithm of per-capita gross domestic product, GDP) in the survey country and year; whether the study was representative of a national, subnational, or community population; and mean BMI for each age-sex group. Sex was excluded from the regressions based on the BIC. The regression of diabetes prevalence based on HbA1c on diabetes prevalence based on FPG, for which there were more data, also included terms for geographical region as random effects based on the BIC; these random effects account for differences in the relationship by region. Two of the regions consisted of high-income countries, as done in previous global analyses^{5,74} – these were high-income Asia-Pacific (consisting of Japan, Singapore, and South Korea) and high-income Western countries (consisting of Australasia, North America, and Western Europe). The other countries were divided based on their geography into Central and Eastern Europe; Central Asia, North Africa, and Middle East; East and South East Asia; South Asia; Latin America and the Caribbean; and sub-Saharan Africa.

We plotted the residuals of the regression models against the main independent variable (probit-transformed FPG-based prevalence), and found no evidence of heteroscedasticity in the residuals. We also report the univariate and semi-partial R^2 for each of the variables in the regression model. Univariate R^2 measures how much of the variance is explained by each independent variable. Semi-partial correlation measures the contribution of each variable to the total explained variance, conditional on the presence of the other model variables.⁷⁵

We calculated sensitivity and specificity of diagnosis using HbA1c against either FPG or FPG-or-2hOGTT definitions separately in each survey, and then pooled the sensitivities and specificities across surveys using a random-effects model.⁷⁶ We examined the sources of heterogeneity of sensitivity and specificity using meta-regressions and *a-priori*-selected study characteristics which were: mean age of participants, proportion of male participants, mid-year of study data collection period; survey sample size; prevalence of undiagnosed diabetes in the survey; whether the survey was representative of a national, subnational, or community population; survey country's geographical region; national income in the survey country and year; and mean haemoglobin levels in the survey country and year(s).

All analyses were done in Stata (version 12.2) and R (version 3.0.3).

Role of the funding source

The sponsors of the study had no role in study design, data collection and analysis, interpretation, or writing of the report. SF, YL, and BZ together had full access to all data used in this study. ME was responsible for submitting the article for publication.

Results

After exclusions, the data for our analyses came from 96 population-based health examination surveys with 331,288 participants. Of these, 46 surveys were from Australia, USA, and Western Europe; 18 from East and Southeast Asia; 10 from Latin America and the Caribbean; 7 from Oceania; 6 from Sub-Saharan Africa; 5 from South Asia; 3 from the Middle East and North Africa; and 1 from Central and Eastern Europe. All but three of the studies used for analysing the relationship between prevalence based on FPG vs. FPG-or-2hOGTT measured glucose in a laboratory; two of the remaining studies used a portable unit; we did not have information for the last study. All but one study used for analysing the relationship between glucose-based and HbA1c-based prevalences measured glucose in a laboratory; the remaining study had used a portable unit for glucose measurement. Glucose measurements in the laboratory for 65 of the studies were based on an enzymatic method, but there was no information for the remaining 27 studies. All studies measured HbA1c in a laboratory; in 40 of these, the measurements were done by chromatography or immunoassay; no information was available for the remaining 24. Such a dominance of laboratory-based measurements does not allow an examination of the role of measurement method as a source of variation because laboratory-based methods are equally acceptable, especially for glucose.⁷⁷

Impact of diabetes definition on population prevalence

Figure 2 shows the relationship between prevalence of diabetes defined based on FPG vs. based on FPG-or-2hOGTT in survey-age-sex groups; Figure 3 shows the relationship between prevalence estimates for diabetes based on HbA1c and on the two glucose-based definitions.

Diabetes prevalences ranged from 0% in people younger than 40 years of age in some surveys to about 70% in middle-aged and older adults in Nauru (Figure 2). Prevalence of diabetes based on FPG alone was lower than that based on FPG-or-2hOGTT, by 2 to 6 percentage points at different prevalence levels, although prevalences estimated using these two glucose-based metrics were highly correlated ($r = 0.98$) (Figure 2). The regression analyses of these are shown in Tables 1 and 2. After accounting for prevalence based on FPG, prevalence based on FPG-or-2hOGTT increased with age, i.e. a sharper rise in FPG-or-2hOGTT-based prevalence than FPG-based prevalence with age.^{65,78,79}

HbA1c-based prevalences were lower than those based on FPG in 42.8% of data and higher in another 41.6%; in the other 15.6%, the two definitions gave similar prevalences (Figure 3). In the regression analysis, prevalence based on HbA1c was on average slightly lower than prevalence based on FPG (Table 2). The most important determinant of variation between these two prevalences was age, with also some roles for national income, mean BMI, the year of survey, and whether the survey was representative of a national, subnational, or community population. After accounting for prevalence based on FPG, prevalence based on HbA1c increased with age, national income, mean BMI, and the year of survey. After accounting for prevalence based on FPG, HbA1c-based prevalence was higher in South Asia than in other regions, and was lower in high-income regions than in other regions (Webfigure 1).

Impact of diabetes definition on diabetes diagnosis in people without history of diagnosis

Diabetes defined as $\text{HbA1c} \geq 6.5\%$ had a pooled sensitivity of 52.8% (51.3-54.3) compared with $\text{FPG} \geq 7.0 \text{ mmol/L}$ in diagnosing participants without a previous diagnosis of diabetes. This

indicates that 47.2% of those *without a previous diagnosis of diabetes* who would be considered to have diabetes based on their FPG level would not be considered to have diabetes with an HbA1c test (Table 3). The sensitivity of HbA1c varied substantially across studies (I-squared of 97.6%), ranging from 13.0% to 93.2% (Webfigure 2). HbA1c had even lower sensitivity when compared with defining diabetes based on FPG-or-2hOGTT (30.5%; 28.7-32.3). None of the pre-selected study-level characteristics explained the heterogeneity in the sensitivity of HbA1c versus FPG (Table 4). Pooled specificity of HbA1c was 99.74% (99.71, 99.78) relative to FPG and 99.69% (99.63, 99.76) relative to FPG-or-2hOGTT, indicating few apparent “false positives” relative to glucose-based definitions.

Lowering the threshold for HbA1c from 6.5% to 6.3%, a cut-off value suggested by some studies,^{49,50} would increase sensitivity compared with the FPG-based definition from 52.8% to 64.3% while maintaining a high specificity at 99.53%. Lowering it further to 6.1% would increase sensitivity to 72.8% but the specificity would drop to 99.08%, resulting in higher apparent false positives – however, the significance of these cut-offs for how they predict complications and sequelae in newly diagnosed diabetes requires follow-up studies.^{80,81}

Discussion

In this large multi-country pooled analysis of population-based health examination surveys, we found that the use of different biomarkers and definitions for diabetes can lead to different estimates of population prevalence of diabetes, with prevalence being highest when diabetes is defined based on FPG-or-2hOGTT and lowest when it is defined based on HbA1c alone. For example, at an FPG-based prevalence of 10%, similar to the age-standardised global prevalence

of diabetes in adults aged 25 years and older in 2008,¹ prevalence based on FPG-or-2hOGTT would be about 13% using the relationship in Figure 2. The variation across studies in the relationship between glucose-based and HbA1c-based prevalences was partly related to participants' age, followed by national income, mean BMI, the year of survey, and whether the survey population was national, subnational, or from specific communities. The reasons for additional regional effects – higher prevalence of HbA1c-based prevalence in South Asia and lower prevalence in high-income regions than in other regions after accounting for prevalence based on FPG – are not known, but they may reflect true physiological differences, e.g., related to red cell turnover (itself related to anaemia and iron status) which affects HbA1c or to glucose dysregulation at the fasting and non-fasting time periods which are captured by HbA1c.⁸² Establishing these reasons requires multi-centre studies with consistent methods and protocols and data on phenotypical factors that may affect glucose-HbA1c relationship. For the time being, they remain unexplained empirical results that should be taken into account when using surveys from different regions.

Similarly, different definitions identified different people without prior diagnosis as having diabetes. Specifically, HbA1c-based definition did not identify almost half of the undiagnosed cases that could be detected using an FPG test, and over three quarters of undiagnosed cases that would be detected by FPG and 2hOGTT combined, but it led to few “false positives” relative to glucose-based definitions. Inversely, using a glucose-based test alone will not identify some persons who would be considered as having diabetes with HbA1c.

Our results, based on a large number of surveys from different world regions, are consistent with previous smaller studies that compared different diabetes definitions (panel). Notably, analyses of 13 European cohorts and 11 Asian cohorts found that diabetes prevalence based on FPG-or-2hOGTT was higher than prevalence based on FPG alone, by 18% and 6% in the two studies, respectively.^{63,64} A previous comparison of diabetes prevalence across 6 studies (including 2 analysed here) found diagnostic sensitivities for HbA1c compared with 2hOGTT ranging from 17% to 78%,⁶⁷ which is consistent with the range of sensitivities in our analysis. However, this study also found surprisingly low specificities for HbA1c compared with our results.⁶⁷ Other single-cohort studies also generally found low but variable sensitivities and high specificities for HbA1c relative to blood glucose. A few studies evaluated the optimal cut-off level for HbA1c in different populations and all reported values lower than 6.5% which is consistent with our finding that lowering the threshold would increase sensitivity while preserving high specificity.⁸³⁻⁸⁶ One small study examined the impact of anaemia on diagnostic accuracy of HbA1c and reported higher sensitivity (in comparison with FPG) in anaemic patients,⁸⁷ which is consistent with our meta-regression results.

Our analysis, which focused on questions that are relevant for population-based surveillance of diabetes and monitoring treatment coverage, has several strengths. We pooled data from a large number of population-based surveys from different world regions, thereby increasing both the precision of our estimates and their generalizability compared with analyses of one or a small number of cohorts. We used consistent eligibility and inclusion criteria across surveys, and rigorously assessed whether the surveys meet these criteria. In particular, we only used surveys that had rigorous protocols for fasting duration and for OGTT. Further, the great majority of

surveys had measured glucose and HbA1c in a laboratory. We also examined the sources of heterogeneity in how diagnostic criteria compare across surveys, an examination that could not be done in previous analyses because they had included few surveys.

Our results should be interpreted with some limitations in mind. We had few studies from some regions including Sub-Saharan Africa, South Asia, Middle East and North Africa, and Central and Eastern Europe. We analysed the surveys using consistent methods but surveys may have differed in details such as the exact limit for fasting duration beyond the 6-hour limit imposed by us. Because HbA1c measurement has evolved over time,⁸⁸⁻⁹⁶ and to minimise the use of non-standard assays, the NCD-RisC databases do not include any HbA1c data prior to 2000.⁷¹ Despite this exclusion, and the fact that all of our surveys had measured HbA1c in a laboratory, measurements may vary between laboratories and instruments,⁹⁷ factors on which we did not have complete data. For the same reason, we could not standardize the HbA1c data to account for different assays and instruments used in measurement. Nutritional status especially iron deficiency and anaemia, malaria and other parasitic diseases, living at high altitudes, and high prevalence of haemoglobinopathies can affect HbA1c, but could not be assessed here as a source of heterogeneity beyond their effects through mean haemoglobin levels.⁹⁸ Similarly, data on glucose can be affected by unobserved factors like inaccurate information about fasting, fluctuations in diet and physical activity in days prior to measurement, and how samples are handled. Although we assessed the role of geographical region, we did not have data on the ethnic composition of participants in each survey. By their nature, health examination surveys used for population-based surveillance use a single measurement in each subject whereas diagnosis in clinical application may repeat the measurements based on the first test. The use of a

single test is affected by within-individual and even within-laboratory variation, and may lead to misclassification of some individuals.⁹⁶ Finally, it would have been ideal to have longitudinal follow-up data on the participants, to assess sensitivity and specificity not only for diagnosis using one definition (or one cut-off value of HbA1c) compared to another, but also for development of diabetes complications and sequelae that contribute the bulk of the public health burden of diabetes. Such data are not available in population surveys because they are typically cross-sectional.

There is no “gold standard” definition which captures the phenotypic complexity of diabetes and the risk of its micro- and macro-vascular complications, although 2hOGTT is often treated as the most reliable test.^{15,99,100} In clinical practice, physicians follow an analytical process for the diabetes diagnosis, in which different sequences of glucose biomarkers are used depending on factors such as a patient’s age and symptoms; those with high levels of one biomarker (e.g., HbA1c) may be requested to have additional measurements, of the same or a different biomarker, and be monitored over a period of time to decide on the best course of treatment. The process may vary from patient to patient to reflect their unique characteristics, and may further vary from physician to physician based on available infrastructure and medical resources. In surveillance using population-based surveys, which provides evidence for policies and programmes related to whole populations, repeated measurements are virtually impossible. Therefore, considerations about diabetes definition and diagnosis are different from those of clinical practice, and the emphasis is on comparability of definitions over time and across populations. Our results provide much needed empirical evidence for planning global surveillance of diabetes and coverage of its interventions. Specifically, despite its ease of use,

using HbA1c alone in health surveys may miss some previously-undiagnosed people who would be considered as having diabetes using a glucose-based test, and hence could benefit from lifestyle and treatment interventions. At the same time, 2hOGTT is difficult to measure even in a clinical setting, let alone in population-based surveys. In fact, of 458 worldwide population-based data sources between 1975 and 2014 in the NCD-RisC databases, 414 had measured FPG but only 46 had measured 2hOGTT; the share of surveys with 2hOGTT was 38% before 1990 and only 9% after 1990. Therefore, a strategy for consistent and comparable surveillance is to use FPG in population-based surveys, be it national ones or multi-country survey programmes such as the WHO STEPS (STEPwise approach to Surveillance) surveys, and define diabetes based on FPG. Data such as those in Figure 2 and Table 1 can then be used to relate prevalences based on FPG to those based on FPG-or-2hOGTT. The use of HbA1c in surveillance requires further consideration in terms of how it predicts, and helps prevent, the burden of diabetes complications and sequelae. When HbA1c is used, it would be valuable to also measure FPG in a sub-sample of participants in order to provide information on how the two tests relate.

NCD Risk Factor Collaboration (NCD-RisC)

Pooled Analysis and Writing (* equal contribution; listed alphabetically)

Goodarz Danaei (Harvard T.H. Chan School of Public Health, USA)*; Saman Fahimi (Harvard T.H. Chan School of Public Health, USA)*; Yuan Lu (Harvard T.H. Chan School of Public Health, USA)*; Bin Zhou (Imperial College London, UK)*; Kaveh Hajifathalian (Harvard T.H. Chan School of Public Health, USA); Mariachiara Di Cesare (Imperial College London, UK); Wei-Cheng Lo (National Taiwan University, Taiwan); Barbara Reis-Santos (Universidade Federal de Pelotas, Brazil); Melanie J Cowan (World Health Organization, Switzerland); Jonathan E Shaw (Baker IDI Heart and Diabetes Institute, Australia); James Bentham (Imperial College London, UK); John K Lin (University of California San Francisco, USA); Honor Bixby (Imperial College London, UK); Dianna Magliano (Baker IDI Heart and Diabetes Institute, Australia); Pascal Bovet (University of Lausanne, Switzerland; Ministry of Health, Republic of Seychelles); J Jaime Miranda (Universidad Peruana Cayetano Heredia, Peru); Young-Ho Khang (Seoul National University, Republic of Korea); Gretchen A Stevens (World Health Organization, Switzerland); Leanne M Riley (World Health Organization, Switzerland); Mohammed K Ali (Emory University, USA); Majid Ezzati (Imperial College London, UK)

Country and Regional Data (* equal contribution; listed alphabetically)

Ziad A Abdeen (Al-Quds University, Palestine)*; Khalid Abdul Kadir (Monash University Malaysia, Malaysia)*; Niveen M Abu-Rmeileh (Birzeit University, Palestine)*; Benjamin Acosta-Cazares (Instituto Mexicano del Seguro Social, Mexico)*; Wichai Aekplakorn (Mahidol University, Thailand)*; Carlos A Aguilar-Salinas (Instituto Nacional de Ciencias Médicas y Nutrición, Mexico)*; Alireza Ahmadvand (Tehran University of Medical Sciences, Iran)*;

Mohannad AA Al-Nsour (Eastern Mediterranean Public Health Network, Jordan)*; Ala'a Alkerwi (Luxembourg Health Institute, Luxembourg)*; Philippe Amouyel (Lille University and Hospital, France)*; Lars Bo Andersen (University of Southern Denmark, Denmark)*; Sigmund A Anderssen (Norwegian School of Sport Sciences, Norway)*; Dolores S Andrade (Universidad de Cuenca, Ecuador)*; Ranjit Mohan Anjana (Madras Diabetes Research Foundation, India)*; Hajer Aounallah-Skhiri (National Institute of Public Health, Tunisia)*; Tahir Aris (Ministry of Health Malaysia, Malaysia)*; Nimmathota Arlappa (Indian Council of Medical Research, India)*; Dominique Arveiler (University of Strasbourg, France)*; Felix K Assah (Health of Populations in Transition Research Group, Cameroon)*; Mária Avdicová (Regional Authority of Public Health, Banská Bystrica, Slovakia)*; Nagalla Balakrishna (Indian Council of Medical Research, India)*; Piotr Bandosz (Medical University of Gdansk, Poland)*; Carlo M Barbagallo (University of Palermo, Italy)*; Alberto Barceló (Pan American Health Organization, USA)*; Anwar M Batieha (Jordan University of Science & Technology, Jordan)*; Louise A Baur (University of Sydney, Australia)*; Habiba Ben Romdhane (University Tunis El Manar, Tunisia)*; Antonio Bernabe-Ortiz (Universidad Peruana Cayetano Heredia, Peru)*; Santosh K Bhargava (Sunder Lal Jain Hospital, India)*; Yufang Bi (Shanghai Jiao-Tong University School of Medicine, China)*; Peter Bjerregaard (University of Southern Denmark, Denmark; University of Greenland, Greenland)*; Cecilia Björkelund (University of Gothenburg, Sweden)*; Margaret Blake (NatCen Social Research, UK)*; Anneke Blokstra (National Institute for Public Health and the Environment, The Netherlands)*; Simona Bo (University of Turin, Italy)*; Bernhard O Boehm (Nanyang Technological University, Singapore)*; Carlos P Boissonnet (Centro de Educación Médica e Investigaciones Clínicas, Argentina)*; Pascal Bovet (University of Lausanne, Switzerland; Ministry of Health, Republic of Seychelles)*; Imperia Brajkovich

(Universidad Central de Venezuela, Venezuela)*; Juergen Breckenkamp (Bielefeld University, Germany)*; Lizzy M Brewster (University of Amsterdam, The Netherlands)*; Garry R Brian (The Fred Hollows Foundation New Zealand, New Zealand)*; Graziella Bruno (University of Turin, Italy)*; Anna Bugge (University of Southern Denmark, Denmark)*; Antonio Cabrera de León (Canarian Health Service, Spain)*; Gunay Can (Istanbul University, Turkey)*; Ana Paula C Cândido (Universidade Federal de Juiz de Fora, Brazil)*; Vincenzo Capuano (Reparto di Cardiologia ed UTIC di Mercato S., Italy)*; Maria J Carvalho (University of Porto, Portugal)*; Felipe F Casanueva (Santiago de Compostela University, Spain)*; Carmelo A Caserta (Associazione Calabrese di Epatologia, Italy)*; Katia Castetbon (French Institute for Health Surveillance, France)*; Snehalatha Chamukuttan (India Diabetes Research Foundation, India)*; Nishi Chaturvedi (University College London, UK)*; Chien-Jen Chen (Academia Sinica, Taiwan)*; Fangfang Chen (Capital Institute of Pediatrics, China)*; Shuohua Chen (Kailuan General Hospital, China)*; Ching-Yu Cheng (Duke-NUS Graduate Medical School, Singapore)*; Angela Chetrit (The Gertner Institute for Epidemiology and Health Policy Research, Israel)*; Shu-Ti Chiou (Ministry of Health and Welfare, Taiwan)*; Yumi Cho (Korea Centers for Disease Control & Prevention, Republic of Korea)*; Jerzy Chudek (Medical University of Silesia, Poland)*; Renata Cifkova (Charles University in Prague, Czech Republic)*; Frank Claessens (Katholieke Universiteit Leuven, Belgium)*; Hans Concin (Agency for Preventive and Social Medicine, Austria)*; Cyrus Cooper (University of Southampton, UK)*; Rachel Cooper (University College London, UK)*; Simona Costanzo (IRCCS Istituto Neurologico Mediterraneo Neuromed, Italy)*; Dominique Cotel (Institut Pasteur de Lille, France)*; Chris Cowell (Westmead University of Sydney, Australia)*; Ana B Crujeiras (CIBERobn, Spain)*; Graziella D'Arrigo (National Council Research, Italy)*; Jean Dallongeville

(Institut Pasteur de Lille, France)*; Rachel Dankner (The Gertner Institute for Epidemiology and Health Policy Research, Israel)*; Luc Dauchet (Lille University Hospital, France)*; Giovanni de Gaetano (IRCCS Istituto Neurologico Mediterraneo Neuromed, Italy)*; Stefaan De Henauw (Ghent University, Belgium)*; Abbas Dehghan (University Medical Center Rotterdam, The Netherlands)*; Klodian Dhana (University Medical Center Rotterdam, The Netherlands)*; Augusto F Di Castelnuovo (IRCCS Istituto Neurologico Mediterraneo Neuromed, Italy)*; Shirin Djalalinia (Tehran University of Medical Sciences, Iran)*; Kouamelan Doua (Ministère de la Santé et de la Lutte contre le Sida, Cote d'Ivoire)*; Wojciech Drygas (The Cardinal Wyszyński Institute of Cardiology, Poland)*; Yong Du (Robert Koch Institute, Germany)*; Eruke E Egbagbe (University of Benin College of Medical Sciences, Nigeria)*; Robert Eggertsen (University of Gothenburg, Sweden)*; Jalila El Ati (National Institute of Nutrition & Food Technology, Tunisia)*; Roberto Elosua (Institut Hospital del Mar d'Investigacions Mèdiques, Spain)*; Rajiv T Erasmus (University of Stellenbosch, South Africa)*; Cihangir Erem (Karadeniz Technical University, Turkey)*; Gul Ergor (Dokuz Eylül University, Turkey)*; Louise Eriksen (University of Southern Denmark, Denmark)*; Jorge Escobedo-de la Peña (Instituto Mexicano del Seguro Social, Mexico)*; Caroline H Fall (MRC Lifecourse Epidemiology Unit, UK)*; Farshad Farzadfar (Tehran University of Medical Sciences, Iran)*; Francisco J Felix-Redondo (Centro de Salud Villanueva Norte, Spain)*; Trevor S Ferguson (The University of the West Indies, Jamaica)*; Daniel Fernández-Bergés (Hospital Don Benito-Villanueva de la Serena, Spain)*; Marika Ferrari (Agricultural Research Council - Research Center on Food and Nutrition, Italy)*; Catterina Ferreccio (Pontificia Universidad Católica de Chile, Chile)*; Joseph D Finn (University of Manchester, UK)*; Bernhard Föger (Agency for Preventive and Social Medicine, Austria)*; Leng Huat Foo (Universiti Sains Malaysia,

Malaysia)*; Heba M Fouad (World Health Organization Regional Office for the Eastern Mediterranean, Egypt)*; Damian K Francis (The University of the West Indies, Jamaica)*; Maria do Carmo Franco (Federal University of São Paulo, Brazil)*; Oscar H Franco (University Medical Center Rotterdam, The Netherlands)*; Guillermo Frontera (Hospital Universitario Son Espases, Spain)*; Takuro Furusawa (Kyoto University, Japan)*; Zbigniew Gaciong (Medical University of Warsaw, Poland)*; Andrzej Galbarczyk (Jagiellonian University Medical College, Poland)*; Sarah P Garnett (University of Sydney, Australia)*; Jean-Michel Gaspoz (Geneva University Hospitals, Switzerland)*; Magda Gasull (CIBER en Epidemiología y Salud Pública (CIBERESP), Spain)*; Louise Gates (Australian Bureau of Statistics, Australia)*; Johanna M Geleijnse (Wageningen University, The Netherlands)*; Simona Giampaoli (Istituto Superiore di Sanita, Italy)*; Francesco Gianfagna (University of Insubria, Italy)*; Jonathan Giovannelli (Lille University Hospital, France)*; Marcela Gonzalez Gross (Universidad Politécnica de Madrid, Spain)*; Juan P González Rivas (The Andes Clinic of Cardio-Metabolic Studies, Venezuela)*; Mariano Bonet Gorbea (National Institute of Hygiene, Epidemiology and Microbiology, Cuba)*; Frederic Gottrand (Université de Lille 2, France)*; Janet F Grant (The University of Adelaide, Australia)*; Tomasz Grodzicki (Jagiellonian University Medical College, Poland)*; Anders Grøntved (University of Southern Denmark, Denmark)*; Gabriella Gruden (University of Turin, Italy)*; Dongfeng Gu (National Center of Cardiovascular Diseases, China)*; Ong Peng Guan (Singapore Eye Research Institute, Singapore)*; Ramiro Guerrero (Univesridad Icesi, Colombia)*; Idris Guessous (Geneva University Hospitals, Switzerland)*; Andre L Guimaraes (State University of Montes Claros, Brazil)*; Laura Gutierrez (Institute for Clinical Effectiveness and Health Policy, Argentina)*; Rebecca Hardy (University College London, UK)*; Rachakulla Hari kumar (Indian Council of Medical Research, India)*; Jiang He (Tulane University, USA)*;

Christin Heidemann (Robert Koch Institute, Germany)*; Ilpo Tapani Hihtaniemi (Imperial College London, UK)*; Sai Yin Ho (University of Hong Kong, China)*; Suzanne C Ho (The Chinese University of Hong Kong, China)*; Albert Hofman (University Medical Center Rotterdam, The Netherlands)*; Andrea R V Ruso Horimoto (Heart Institute (InCor), Brazil)*; Claudia M Hormiga (Fundación Oftalmológica de Santander, Colombia)*; Bernardo L Horta (Universidade Federal de Pelotas, Brazil)*; Leila Houti (University of Oran, Algeria)*; Abdullatif S Hussieni (Birzeit University, Palestine)*; Inge Huybrechts (International Agency for Research on Cancer, France)*; Nahla Hwalla (American University of Beirut, Lebanon)*; Licia Iacoviello (IRCCS Istituto Neurologico Mediterraneo Neuromed, Italy)*; Anna G Iannone (Reparto di Cardiologia ed UTIC di Mercato S., Italy)*; Mohsen M Ibrahim (Cairo University, Egypt)*; Nayu Ikeda (National Institute of Health and Nutrition, Japan)*; M Arfan Ikram (University Medical Center Rotterdam, The Netherlands)*; Vilma E Irazola (Institute for Clinical Effectiveness and Health Policy, Argentina)*; Muhammad Islam (Aga Khan University, Pakistan)*; Masanori Iwasaki (Niigata University, Japan)*; Jeremy M Jacobs (Hadassah University Medical Center, Israel)*; Tazeen Jafar (Duke-NUS Graduate Medical School Singapore, Singapore)*; Grazyna Jasienska (Jagiellonian University Medical College, Poland)*; Chao Qiang Jiang (University of Hong Kong, China)*; Jost B Jonas (Ruprecht-Karls-University of Heidelberg, Germany)*; Pradeep Joshi (World Health Organization Country Office, India)*; Anthony Kafatos (University of Crete, Greece)*; Ofra Kalter-Leibovici (The Gertner Institute for Epidemiology and Health Policy Research, Israel)*; Amir Kasaeian (Tehran University of Medical Sciences, Iran)*; Joanne Katz (Johns Hopkins Bloomberg School of Public Health, USA)*; Prabhdeep Kaur (National Institute of Epidemiology, India)*; Maryam Kavousi (University Medical Center Rotterdam, The Netherlands)*; Roya Kelishadi (Isfahan University

of Medical Sciences, Iran)*; Andre P Kengne (South African Medical Research Council, South Africa)*; Mathilde Kersting (Research Institute of Child Nutrition (FKE), Germany)*; Yousef Saleh Khader (Jordan University of Science & Technology, Jordan)*; Young-Ho Khang (Seoul National University, Republic of Korea)*; Stefan Kiechl (Medical University Innsbruck, Austria)*; Jeongseon Kim (National Cancer Center, Republic of Korea)*; Yutaka Kiyohara (Kyushu University, Japan)*; Patrick Kolsteren (Institute of Tropical Medicine, Belgium)*; Paul Korrovits (Tartu University Clinics, Estonia)*; Seppo Koskinen (National Institute for Health and Welfare, Finland)*; Wolfgang Kratzer (University Hospital Ulm, Germany)*; Daan Kromhout (Wageningen University, The Netherlands)*; Krzysztof Kula (Medical University of Łódź, Poland)*; Pawel Kurjata (The Cardinal Wyszyński Institute of Cardiology, Poland)*; Catherine Kyobutungi (African Population and Health Research Center, Kenya)*; Carl Lachat (Ghent University, Belgium)*; Youcef Laid (National Institute of Public Health, Algeria)*; Tai Hing Lam (University of Hong Kong, China)*; Orlando Landrove (Ministerio de Salud Pública, Cuba)*; Vera Lanska (Institute for Clinical and Experimental Medicine Prague, Czech Republic)*; Georg Lappas (Sahlgrenska Academy, Sweden)*; Avula Laxmaiah (Indian Council of Medical Research, India)*; Catherine Leclercq (Food and Agriculture Organization, Italy)*; Jeannette Lee (National University of Singapore, Singapore)*; Jeonghee Lee (National Cancer Center, Republic of Korea)*; Terho Lehtimäki (Tampere University Hospital, Finland)*; Rampal Lekhraj (Universiti Putra Malaysia, Malaysia)*; Luz M León-Muñoz (Universidad Autónoma de Madrid, Spain)*; Yanping Li (Harvard T.H. Chan School of Public Health, USA)*; Wei-Yen Lim (National University of Singapore, Singapore)*; M Fernanda Lima-Costa (Oswaldo Cruz Foundation Rene Rachou Research Institute, Brazil)*; Hsien-Ho Lin (National Taiwan University, Taiwan)*; Xu Lin (University of Chinese Academy of Sciences, China)*; Lauren

Lissner (University of Gothenburg, Sweden)*; Roberto Lorbeer (University Medicine Greifswald, Germany)*; José Eugenio Lozano (Consejería de Sanidad Junta de Castilla y León, Spain)*; Per Lytsy (University of Uppsala, Sweden)*; Guansheng Ma (Peking University, China)*; George LL Machado-Coelho (Universidade Federal de Ouro Preto, Brazil)*; Suka Machi (The Jikei University School of Medicine, Japan)*; Stefania Maggi (National Research Council (CNR), Italy)*; Dianna Magliano (Baker IDI Heart and Diabetes Institute, Australia)*; Marcia Makdisse (Hospital Israelita Albert Einstein, Brazil)*; Kodavanti Mallikharjuna Rao (Indian Council of Medical Research, India)*; Yannis Manios (Harokopio University of Athens, Greece)*; Enzo Manzato (University of Padova, Italy)*; Paula Margozzini (Pontificia Universidad Católica de Chile, Chile)*; Pedro Marques-Vidal (Lausanne University Hospital, Switzerland)*; Reynaldo Martorell (Emory University, USA)*; Shariq Masoodi (Sher-i-Kashmir Institute of Medical Sciences, India)*; Tandi E Matsha (Cape Peninsula University of Technology, South Africa)*; Jean Claude N Mbanya (University of Yaoundé 1, Cameroon)*; Shelly R McFarlane (The University of the West Indies, Jamaica)*; Stephen T McGarvey (Brown University, USA)*; Stela McLachlan (University of Edinburgh, UK)*; Breige A McNulty (University College Dublin, Ireland)*; Sounnia Mediene-Benchekor (University of Oran, Algeria)*; Aline Meirhaeghe (INSERM, France)*; Ana Maria B Menezes (Universidade Federal de Pelotas, Brazil)*; Shahin Merat (Tehran University of Medical Sciences, Iran)*; Indrapal I Meshram (Indian Council of Medical Research, India)*; Jie Mi (Capital Institute of Pediatrics, China)*; Juan Francisco Miquel (Pontificia Universidad Católica de Chile, Chile)*; Jaime Miranda (Universidad Peruana Cayetano Heredia, Peru)*; Mostafa K Mohamed (Ain Shams University, Egypt)*; Kazem Mohammad (Tehran University of Medical Sciences, Iran)*; Deepa Mohan (Madras Diabetes Research Foundation, India)*; Muhammad Fadhli Mohd Yusoff

(Ministry of Health Malaysia, Malaysia)*; Niels C Møller (University of Southern Denmark, Denmark)*; Denes Molnar (University of Pécs, Hungary)*; Charles K Mondo (Mulago Hospital, Uganda)*; Luis A Moreno (Universidad de Zaragoza, Spain)*; Karen Morgan (PU-RCSI School of Medicine, Malaysia)*; George Moschonis (Harokopio University of Athens, Greece)*; Malgorzata Mossakowska (International Institute of Molecular and Cell Biology, Poland)*; Aya Mostafa (Ain Shams University, Egypt)*; Jorge Mota (University of Porto, Portugal)*; Maria L Muiesan (University of Brescia, Italy)*; Martina Müller-Nurasyid (Helmholtz Zentrum München, Germany)*; Jaakko Mursu (University of Eastern Finland, Finland)*; Gabriele Nagel (University of Ulm, Germany)*; Jana Námešná (Regional Authority of Public Health, Banska Bystrica, Slovakia)*; Ei Ei K Nang (National University of Singapore, Singapore)*; Vinay B Nangia (Suraj Eye Institute, India)*; Eva Maria Navarrete-Muñoz (CIBER de Epidemiología y Salud Pública (CIBERESP), Spain)*; Ndeye Coumba Ndiaye (INSERM, France)*; Flavio Nervi (Pontificia Universidad Católica de Chile, Chile)*; Nguyen D Nguyen (The University of Pharmacy and Medicine of Ho Chi Minh City, Viet Nam)*; Ramfis E Nieto-Martínez (Universidad Centro-Occidental Lisandro Alvarado, Venezuela)*; Guang Ning (Shanghai Jiao-Tong University School of Medicine, China)*; Toshiharu Ninomiya (Kyushu University, Japan)*; Marianna Noale (National Research Council (CNR), Italy)*; Davide Noto (University of Palermo, Italy)*; Angelica M Ochoa-Avilés (Universidad de Cuenca, Ecuador)*; Kyungwon Oh (Korea Centers for Disease Control & Prevention, Republic of Korea)*; Altan Onat (Istanbul University, Turkey)*; Clive Osmond (MRC Lifecourse Epidemiology Unit, UK)*; Johanna A Otero (Fundación Oftalmológica de Santander, Colombia)*; Luigi Palmieri (Istituto Superiore di Sanita, Italy)*; Songhomitra Panda-Jonas (Ruprecht-Karls-University of Heidelberg, Germany)*; Francesco Panza (University of Bari, Italy)*; Mahboubeh Parsaeian (Tehran

University of Medical Sciences, Iran)*; Sergio Viana Peixoto (Oswaldo Cruz Foundation Rene Rachou Research Institute, Brazil)*; Alexandre C Pereira (Heart Institute (InCor), Brazil)*; Annette Peters (Helmholtz Zentrum München, Germany)*; Niloofar Peykari (Tehran University of Medical Sciences, Iran)*; Aida Pilav (Federal Ministry of Health, Bosnia and Herzegovina)*; Freda Pitakaka (University of New South Wales, Australia)*; Aleksandra Piwonska (The Cardinal Wyszynski Institute of Cardiology, Poland)*; Pedro Plans-Rubio (Public Health Agency of Catalonia, Spain)*; Miquel Porta (Hospital del Mar Medical Research Institute-IMIM, Spain)*; Marileen LP Portegies (University Medical Center Rotterdam, The Netherlands)*; Hossein Poustchi (Tehran University of Medical Sciences, Iran)*; Jacqueline F Price (University of Edinburgh, UK)*; Margus Punab (Tartu University Clinics, Estonia)*; Radwan F Qasrawi (Al-Quds University, Palestine)*; Mostafa Qorbani (Alborz University of Medical Sciences, Iran)*; Olli Raitakari (University of Turku, Finland)*; Pradeepa Rajendra (Madras Diabetes Research Foundation, India)*; Sudha Ramachandra Rao (National Institute of Epidemiology, India)*; Ambady Ramachandran (India Diabetes Research Foundation, India)*; Rafel Ramos (Institut Universitari d'Investigació en Atenció Primària Jordi Gol, Spain)*; Sanjay Rampal (University of Malaya, Malaysia)*; Wolfgang Rathmann (German Diabetes Center, Germany)*; Josep Redon (Universitat de València, Spain)*; Paul Ferdinand M Reganit (University of the Philippines, Philippines)*; Fernando Rigo (Health Center San Agustin, Spain)*; Sian M Robinson (University of Southampton, UK)*; Cynthia Robitaille (Public Health Agency of Canada, Canada)*; Laura A Rodríguez (Universidad Industrial de Santander, Colombia)*; Fernando Rodríguez-Artalejo (Universidad Autónoma de Madrid, Spain)*; María del Cristo Rodríguez-Perez (Canarian Health Service, Spain)*; Rosalba Rojas-Martinez (Instituto Nacional de Salud Pública, Mexico)*; Dora Romaguera (Centre for Research in Environmental

Epidemiology, Spain)*; Annika Rosengren (Sahlgrenska Academy, Sweden)*; Adolfo Rubinstein (Institute for Clinical Effectiveness and Health Policy, Argentina)*; Ornelas Rui (University of Madeira, Portugal)*; Blanca Sandra Ruiz-Betancourt (Instituto Mexicano del Seguro Social, Mexico)*; Marcin Rutkowski (Medical University of Gdansk, Poland)*; Charumathi Sabanayagam (Singapore Eye Research Institute, Singapore)*; Harshpal S Sachdev (Sitaram Bhartia Institute of Science and Research, India)*; Olfa Saidi (University Tunis El Manar, Tunisia)*; Sibel Sakarya (Marmara University, Turkey)*; Benoit Salanave (French Institute for Health Surveillance, France)*; Jukka T Salonen (University of Helsinki, Finland)*; Massimo Salvetti (University of Brescia, Italy)*; Jose Sánchez-Abanto (Institute National of Health Lima, Peru)*; Renata Nunes dos Santos (University of São Paulo, Brazil)*; Rute Santos (University of Porto, Portugal)*; Luis B Sardinha (Universidade de Lisboa, Portugal)*; Marcia Scazufca (University of São Paulo, Brazil)*; Herman Schargrodsky (Hospital Italiano de Buenos Aires, Argentina)*; Christa Scheidt-Nave (Robert Koch Institute, Germany)*; Jonathan E Shaw (Baker IDI Heart and Diabetes Institute, Australia)*; Kenji Shibuya (The University of Tokyo, Japan)*; Youchan Shin (Singapore Eye Research Institute, Singapore)*; Rahman Shiri (Finnish Institute of Occupational Health, Finland)*; Rosalynn Siantar (Singapore Eye Research Institute, Singapore)*; Abla M Sibai (American University of Beirut, Lebanon)*; Mary Simon (India Diabetes Research Foundation, India)*; Judith Simons (St Vincent's Hospital, Australia)*; Leon A Simons (University of New South Wales, Australia)*; Michael Sjoström (Karolinska Institute, Sweden)*; Jolanta Slowikowska-Hilczer (Medical University of Łódź, Poland)*; Przemysław Słusarczyk (International Institute of Molecular and Cell Biology, Poland)*; Liam Smeeth (London School of Hygiene and Tropical Medicine, UK)*; Marieke B Snijder (The University of Amsterdam, The Netherlands)*; Vincenzo Solfrizzi (University of Bari, Italy)*; Emily Sonestedt

(Lund University, Sweden)*; Aicha Soumare (University of Bordeaux, France)*; Jan A Staessen (University of Leuven, Belgium)*; Jostein Steene-Johannessen (Norwegian School of Sport Sciences, Norway)*; Peter Stehle (Bonn University, Germany)*; Aryeh D Stein (Emory University, USA)*; Jochanan Stessman (Hadassah University Medical Center, Israel)*; Doris Stöckl (Helmholtz Zentrum München, Germany)*; Jakub Stokwiszewski (National Institute of Hygiene, Poland)*; Maria Wany Strufaldi (Federal University of São Paulo, Brazil)*; Chien-An Sun (Fu Jen Catholic University, Taiwan)*; Johan Sundström (Uppsala University, Sweden)*; Paibul Suriyawongpaisal (Mahidol University, Thailand)*; Rody G Sy (University of the Philippines, Philippines)*; E Shyong Tai (National University of Singapore, Singapore)*; Mohammed Tarawneh (Ministry of Health, Jordan)*; Carolina B Tarqui-Mamani (Institute National of Health, Peru)*; Lutgarde Thijs (University of Leuven, Belgium)*; Janne S Tolstrup (University of Southern Denmark, Denmark)*; Murat Topbas (Karadeniz Technical University, Turkey)*; Maties Torrent (Area de Salut de Menorca (ib Salut), Spain)*; Pierre Traissac (Institut de Recherche pour le Développement, France)*; Oanh TH Trinh (The University of Pharmacy and Medicine of Ho Chi Minh City, Viet Nam)*; Marshall K Tulloch-Reid (The University of the West Indies, Jamaica)*; Tomi-Pekka Tuomainen (University of Eastern Finland, Finland)*; Maria L Turley (Ministry of Health, New Zealand)*; Christophe Tzourio (University of Bordeaux, France)*; Peter Ueda (Harvard T.H. Chan School of Public Health, USA)*; Flora M Ukoli (Meharry Medical College, USA)*; Hanno Ulmer (Medical University of Innsbruck, Austria)*; Gonzalo Valdivia (Pontificia Universidad Católica de Chile, Chile)*; Irene GM van Valkengoed (Academic Medical Center of the University of Amsterdam, The Netherlands)*; Dirk Vanderschueren (Katholieke Universiteit Leuven, Belgium)*; Diego Vanuzzo (Centro di Prevenzione Cardiovascolare, Italy)*; Tomas Vega (Consejería de Sanidad, Junta de Castilla y

León, Spain)*; Gustavo Velasquez-Melendez (Universidade Federal de Minas Gerais, Brazil)*; Giovanni Veronesi (University of Insubria, Italy)*; Monique Verschuren (National Institute for Public Health and the Environment, The Netherlands)*; Jesus Vioque (Universidad Miguel Hernandez, Spain)*; Jyrki Virtanen (University of Eastern Finland, Finland)*; Sophie Visvikis-Siest (INSERM, France)*; Bharathi Viswanathan (Ministry of Health, Republic of Seychelles)*; Mohan Viswanathan (Madras Diabetes Research Foundation, India)*; Peter Vollenweider (Lausanne University Hospital, Switzerland)*; Sari Voutilainen (University of Eastern Finland, Finland)*; Alisha N Wade (University of the Witwatersrand, South Africa)*; Aline Wagner (University of Strasbourg, France)*; Janette Walton (University College Cork, Ireland)*; Wan Nazaimoon Wan Mohamud (Institute for Medical Research, Malaysia)*; Ming-Dong Wang (Public Health Agency of Canada, Canada)*; Ya Xing Wang (Beijing Tongren Hospital, China)*; S Goya Wannamethee (University College London, UK)*; Deepa Weerasekera (Ministry of Health, New Zealand)*; Peter H Whincup (University of London, UK)*; Kurt Widhalm (Medical University of Vienna, Austria)*; Andrzej Wiecek (Medical University of Silesia, Poland)*; Rainford J Wilks (The University of the West Indies, Jamaica)*; Johann Willeit (Medical University Innsbruck, Austria)*; Bogdan Wojtyniak (National Institute of Hygiene, Poland)*; Tien Yin Wong (Duke-NUS Graduate Medical School, Singapore)*; Jean Woo (The Chinese University of Hong Kong, China)*; Mark Woodward (University of Sydney, Australia; University of Oxford, UK)*; Aleksander Giwercman Wu (Lund University, Sweden)*; Frederick C Wu (University of Manchester, UK)*; Shou Ling Wu (Kailuan General Hospital, China)*; Haiquan Xu (Institute of Food and Nutrition Development of Ministry of Agriculture, China)*; Xiaoguang Yang (Chinese Center for Disease Control and Prevention, China)*; Xingwang Ye (University of Chinese Academy of Sciences, China)*; Akihiro

Yoshihara (Niigata University, Japan)*; Novie O Younger-Coleman (The University of the West Indies, Jamaica)*; Sabina Zambon (University of Padova, Italy)*; Abdul Hamid Zargar (Center for Diabetes & Endocrine Care, India)*; Tomasz Zdrojewski (Medical University of Gdansk, Poland)*; Wenhua Zhao (Chinese Center for Disease Control and Prevention, China)*; Yingfeng Zheng (Singapore Eye Research Institute, Singapore)*

Contributions

GD and ME developed study concept and oversaw research. Members of Country and Regional Data Group collected and re-analysed data, and checked pooled data for accuracy of information about their study. Members of Pooled Analysis and Writing Group collated data, checked all data sources in consultation with Country and Regional Data Group, analysed pooled data, and prepared results. GD and ME wrote the first draft of the paper with input from other members of Pooled Analysis and Writing Group. Members of Country and Regional Data Group commented on draft manuscript.

Conflict of interest

JJM reports funding from Medtronic Foundation outside the submitted work. DM reports grants to her institution from Novartis Pharmaceutical (Aust) Pty Ltd, Novo Nordisk Pharmaceutical Pty Ltd, Pharmacia and Upjohn Pty Ltd, Pfizer Pty Ltd, Sanofi Synthelabo, and Servier Laboratories (Aust) Pty Ltd. JES reports grants to his institution from Abbott Australasia Pty Ltd, Alphapharm Pty Ltd, AstraZeneca, Aventis Pharmaceutical, Eli Lilly (Aust) Pty Ltd, GlaxoSmithKline, Janssen-Cilag (Aust) Pty Ltd, Merck Lipha SA, Merck Sharp & Dohme (Aust), from Novartis Pharmaceutical (Aust) Pty Ltd, Novo Nordisk Pharmaceutical Pty Ltd,

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The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Research in context

Evidence before this study

We reviewed studies included in the NCD-RisC databases for comparisons of various diabetes definitions. In addition, we searched PubMed using ((A1c[Title/Abstract]) AND Sensitivity[Title/Abstract]) AND Specificity[Title/Abstract]) on 13/04/2015. We also searched the references of recent reviews and guidelines.^{11-14,17} We found some studies on the classification of individuals as having diabetes or on comparison of prevalence estimates based on different definitions in specific cohorts, especially for HbA1c compared to either FPG or 2hOGTT.¹⁹⁻⁶¹ Most of these analyses were based on a single cohort and very few cover different world regions. Two pooled analyses of Asian and European cohorts, and a study in the Pacific and Indian Ocean islands, assessed how the prevalence of diabetes and the classification of individuals as with or without diabetes changed depending whether diabetes was defined based on FPG vs. 2hOGTT.⁶²⁻⁶⁶ There is no pooling study for HbA1c and we identified only one overview of data from six countries.⁶⁷ Other studies, not cited here due to space restrictions, compared different diabetes definitions among people with specific pre-existing diseases, e.g., heart disease and tuberculosis. We also found some prospective studies that examined how HbA1c predicts future incidence of diabetes or cardiovascular diseases with mixed results.

Added value of this study

This study is the first pooling of a large number of population-based data from different world regions that addresses how different definitions of diabetes affect both the total prevalence, and the identification of previously undiagnosed individuals. By pooling a large number of data sources, the overall meta-analytical finding overcomes between-study variation which can itself

be probed in meta-regressions. Furthermore, by having a large number of studies, and age-sex groups within each study, we are able to develop regressions to convert or “cross-walk” across different diabetes definitions, which is essential for enhancing comparability over time and across countries in surveillance.

Implications of all the available evidence

The use of HbA1c in surveillance requires further consideration in terms of how it predicts, and helps prevent, the burden of diabetes complications and sequelae. As such studies are conducted, and in order to maximize comparability of results across surveys, the most optimal approach in population-based health surveys is to measure FPG and define diabetes as $FPG \geq 7.0$ mmol/L or history of diagnosis with diabetes or using insulin or oral hypoglycaemic agents, as used in the global monitoring framework for prevention and control of NCDs. When HbA1c is used, it would be valuable to also measure FPG in a sub-sample of participants in order to provide information on how the two tests relate. The conversion regressions developed here can be used to convert prevalence based on FPG to that based on FPG-or-2hOGTT.

Table 1: Regression coefficients for the relationship between probit-transformed prevalence of diabetes defined based on FPG-or-2hOGTT (FPG \geq 7.0 mmol/L or 2hOGTT \geq 11.1 mmol/L or history of diabetes or using insulin or oral hypoglycaemic agents) and probit-transformed prevalence of diabetes defined based on FPG alone (FPG \geq 7.0 mmol/L or history of diabetes or using insulin or oral hypoglycaemic agents).

Variable	Coefficient (95% CI)	p-value	Univariate R ² ^a	Semi-partial R ² ^b
Intercept	0.135 (-0.020, 0.290)	0.0872	NA	NA
Probit-transformed prevalence (FPG \geq 7.0 mmol/L or history of diabetes or using insulin or oral hypoglycaemic agents)	0.903 (0.880, 0.927)	< 0.0001	0.963	0.368
Mean age of age group (per 10 years older)	0.048 (0.039, 0.056)	< 0.0001	0.444	0.008
Study mid-year (per one more recent year since 1976)	-0.001 (-0.002, 0.000)	0.1643	0.003	< 0.001
Natural logarithm of per-capita gross domestic product (GDP)	-0.033 (-0.046, -0.019)	< 0.0001	0.004	0.001
Mean BMI	0.000 (-0.004, 0.004)	0.9057	0.092	< 0.001
Study representativeness				
National	Reference			
Subnational	-0.031 (-0.070, 0.008)	0.1141	0.021	0.001
Community	-0.070 (-0.101, -0.039)	< 0.0001		

^a Univariate R² is from regressing against each independent variable alone. It equals the square of the correlation coefficient.

^b Semi-partial R² shows how much the R² decreases if that independent variable is removed from the full model. The overall R² for the model was 0.973.

Table 2: Regression coefficients for the association between probit-transformed prevalence of diabetes defined based on HbA1c (HbA1c \geq 6.5% or history of diabetes or using insulin or oral hypoglycaemic agents) and probit-transformed prevalence of diabetes defined based on FPG (FPG \geq 7.0 mmol/L or history of diabetes or using insulin or oral hypoglycaemic agents). Regional random effects are shown in Webfigure 1.

Variable	Coefficient (95% CI)	p-value ^a	Univariate R ² ^b	Semi-partial R ² ^c
Intercept	-1.761 (-2.229, -1.266)	< 0.0001	NA	NA
Probit-transformed prevalence (FPG \geq 7.0 mmol/L or history of diabetes or using insulin or oral hypoglycaemic agents)	0.799 (0.763, 0.835)	< 0.0001	0.915	0.075
Mean age of age group (per 10 years older)	0.052 (0.042, 0.062)	< 0.0001	0.601	0.011
Study mid-year (per one more recent year since 2000)	0.012 (0.009, 0.015)	< 0.0001	0.014	0.006
Natural logarithm of per-capita gross domestic product (GDP)	0.076 (0.035, 0.114)	0.0001	0.052	0.003
Mean BMI	0.018 (0.010, 0.027)	< 0.0001	0.022	0.002
Study representativeness				
National	Reference			
Subnational	-0.004 (-0.047, 0.040)	0.8758	0.013	0.004
Community	0.090 (0.060, 0.119)	< 0.0001		

^a Traditional p-values are not clearly defined for mixed-effect models. We have reported p-values using likelihood ratio test which compares the likelihood of the models with and without the variable of interest.¹⁰¹

^b Univariate R² is from regressing against each independent variable alone, without the regional random effects. It equals the square of the correlation coefficient.

^c Semi-partial R² is the decrease of R² if one of the independent variables is removed from the full model. However, traditional R² is not clearly defined for mixed-effect models. We have used the conditional R² that describes the proportion of variance explained by both fixed and random factors.¹⁰² The overall conditional R² for the model was 0.949.

Table 3: Pooled sensitivity and specificity of diabetes diagnosis using different definitions among participants without prior diagnosis of diabetes. See Webfigures 2-9 for detailed results of these meta-analyses.

Test vs. reference test(s) ^a	Number of surveys	Sensitivity (percentage points) (95% CI)	I-squared (%)	Specificity (percentage points) (95% CI)	I-squared (%)
HbA1c vs. FPG	27	52.82 (51.33, 54.30)	97.6	99.74 (99.71, 99.78)	98.2
HbA1c vs. 2hOGTT	9	37.16 (35.05, 39.28)	97.6	99.84 (99.79, 99.89)	97.3
HbA1c vs. FPG or 2hOGTT	9	30.46 (28.66, 32.25)	97.9	99.69 (99.63, 99.76)	98.0
FPG vs. 2hOGTT	33	54.42 (53.26, 55.57)	96.9	98.90 (98.83, 98.97)	94.4

^aDiabetes was defined as HbA1c \geq 6.5%, FPG \geq 7.0 mmol/L, and 2hOGTT \geq 11.1 mmol/L in different comparisons.

Table 4: Univariate meta-regression coefficients for sensitivity of HbA1c \geq 6.5% vs. FPG \geq 7.0 mmol/L in participants without diagnosed diabetes.

Variable	Mean difference in sensitivity (percentage points) (95% CI)	p-value
Mean age (per ten years)	-4.1 (-12.7, 4.5)	0.3361
Per cent male participants (per 10% more male)	4.6 (-9.0, 18.2)	0.4901
Study mid-year (per one more recent year)	1.2 (-0.9, 3.2)	0.2566
Region		
High-income Western countries	Reference group	
East, South, and Southeast Asia	21.0 (-0.3, 42.2)	0.2097
Latin America and the Caribbean	8.5 (-17.9, 34.9)	
Sub-Saharan Africa	17.6 (-14.1, 49.2)	
Study representativeness		
National	Reference group	0.0915
Subnational	1.7 (-28.6, 31.9)	
Community	21.4 (2.1, 40.8)	
Prevalence of undiagnosed diabetes (percentage point higher undiagnosed diabetes)	-0.7 (-4.0, 2.6)	0.6780
Sample size (per 1,000 participants without a history of diabetes)	-1.6 (-4.6, 1.4)	0.2730
Natural logarithm of per-capita gross domestic product	-6.5 (-17.6, 4.6)	0.2410
Mean haemoglobin (per g/L) ^a	-2.0 (-4.1, 0.2)	0.0677

^a Reliable mean haemoglobin data were available only for women of child-bearing age.¹⁰³ In the results in the table, the national mean for each country-year was used for both men and women. Restricting the analysis to women led to similar results, with a mean difference of -2.1 (-4.5, 0.3) and a p-value of 0.0929.

Figure 1: Flowchart of data inclusion.

Figure 2: Prevalence of diabetes defined based on FPG-or-2hOGTT (FPG \geq 7.0 mmol/L or 2hOGTT \geq 11.1 mmol/L or history of diabetes or using insulin or oral hypoglycaemic agents) vs. based on FPG (FPG \geq 7.0 mmol/L or history of diabetes or using insulin or oral hypoglycaemic agents).

Each point shows one age-sex group in one survey. See Table 1 for the relationship summarised as regression coefficients.

Figure 3: Prevalence of diabetes defined based on HbA1c ($\text{HbA1c} \geq 6.5\%$ or history of diabetes or using insulin or oral hypoglycaemic agents) vs. prevalence of diabetes as defined based on (A) FPG ($\text{FPG} \geq 7.0 \text{ mmol/L}$ or history of diabetes or using insulin or oral hypoglycaemic agents) and (B) FPG-or-2hOGTT ($\text{FPG} \geq 7.0 \text{ mmol/L}$ or $2\text{hOGTT} \geq 11.1 \text{ mmol/L}$ or history of diabetes or using insulin or oral hypoglycaemic agents). Each point shows one age-sex group in one survey. See Table 2 for the relationships summarised as regression coefficients.

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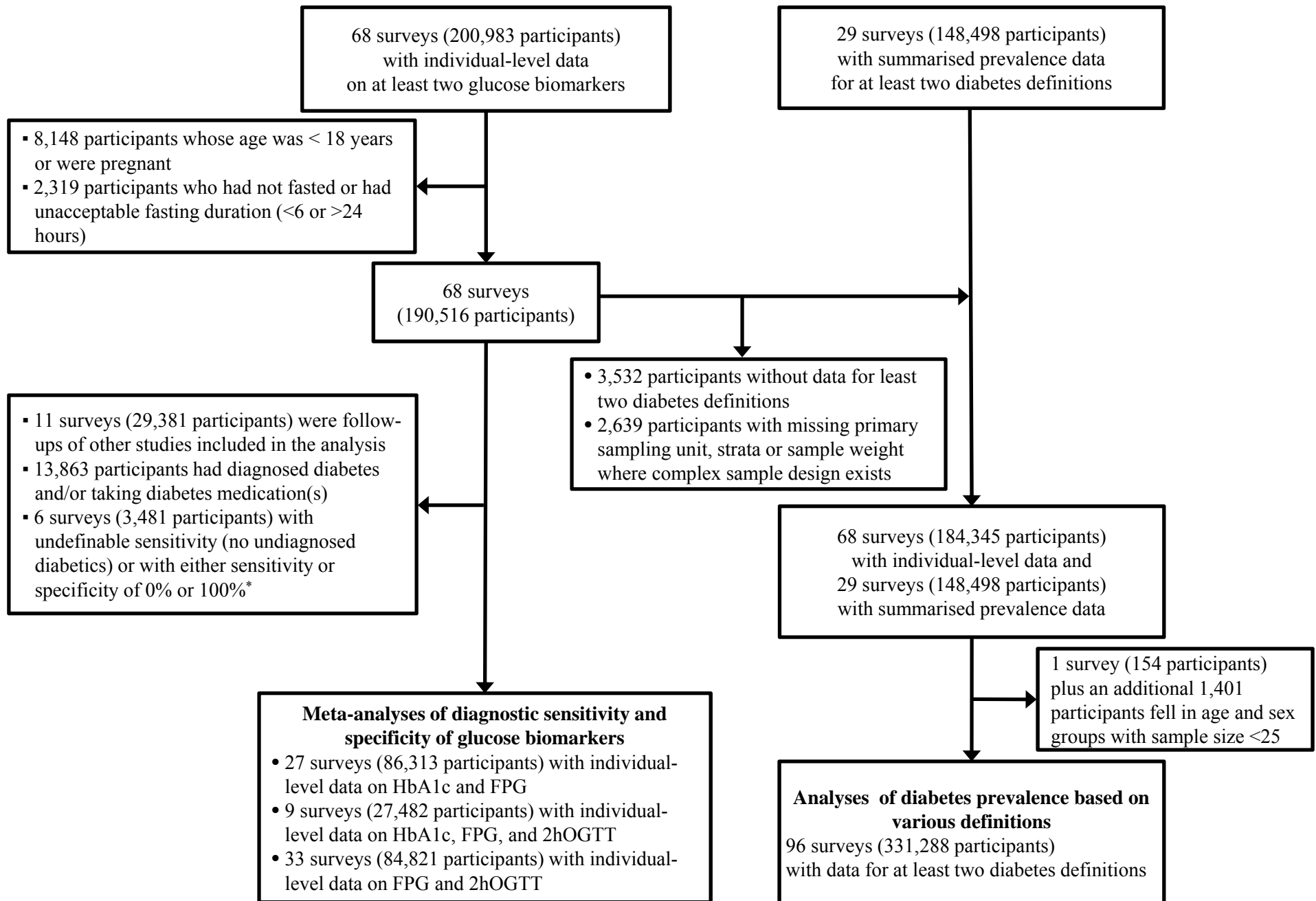
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* The meta-analyses used inverse of variance as survey weights; with values for either sensitivity or specificity being 0% or 100%, the corresponding variance would be zero leading to inverse of variance becoming infinite and therefore were excluded.

