"Global variations in diabetes mellitus based on fasting glucose and haemoglobin A1c"

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Fasting plasma glucose (FPG) and haemoglobin A1c (HbA1c) are both used to diagnose diabetes, but may identify different people as having diabetes. We used data from 117 population-based studies and quantified, in different world regions, the prevalence of diagnosed diabetes, and whether those who were previously undiagnosed and detected as having diabetes in survey screening had elevated FPG, HbA1c, or both. We developed prediction equations for estimating the probability that a person without previously diagnosed diabetes, and at a specific level of FPG, had elevated HbA1c, and vice versa. The age-standardised proportion of diabetes that was previously undiagnosed, and detected in survey screening, ranged from 30% in the high-income western region to 66% in south Asia. Among those with screen-detected diabetes with either test, the age-standardised proportion who had elevated levels of both FPG and HbA1c was 29-39% across regions; the remainder had discordant elevation of FPG or HbA1c. In most low- and middle-income regions, isolated elevated HbA1c more common than isolated elevated FPG. In these regions, the use of FPG alone may delay diabetes diagnosis and underestimate diabetes prevalence. Our prediction equations help allocate finite resources for measuring HbA1c to reduce the global gap in diabetes diagnosis and surveillance.

Introduction

Diabetes mellitus is associated with debilitating complications like amputation, vision loss and renal failure, and with increased risk of cardiovascular events, dementia, some cancers, and infections like tuberculosis and severe COVID-19[1-6]. The diagnostic criteria for diabetes have evolved over time to incorporate haemoglobin A1c (HbA1c), which is a measure of long-term glycaemic status and more convenient to measure for patients than is fasting glucose or the 2-hour oral glucose tolerance test (OGTT)[7-10]. In contemporary guidelines, any one or the combination of fasting plasma glucose (FPG), OGTT and HbA1c may be used to diagnose

diabetes[10-14]. OGTT is now rarely used in clinical practice or population surveillance because of the inconvenience related to the glucose load, 2-hour time frame and the two blood draws required for the test[15,16]. FPG and HbA1c, which are both used in clinical practice and epidemiological research and surveillance, measure different glycaemic features, namely basal glucose level (FPG) and average glucose level in the previous 2-3 months (HbA1c)[17]. Therefore, individuals may have elevated levels of one or both biomarkers, and FPG and HbA1c may classify different people as having diabetes[9,10]. Diabetes also has a long subclinical period defined by hyperglycaemia, and may remain undiagnosed without screening or other mechanisms for early identification[18].

Some studies have assessed sensitivity and specificity of diabetes diagnosis using either FPG or HbA1c relative to the OGTT, or have compared diabetes prevalence based on these different glycaemic biomarkers, but most did not provide a direct comparison of HbA1c and FPG[19-21]. Most population-based studies on the concordance and discordance of diabetes diagnosis using FPG versus HbA1c have been conducted in a single country or region[14,22-42], and the only multi-country study[43] used data largely from high-income western countries. Therefore, there are scant data on how the concordance and discordance of FPG and HbA1c in classifying diabetes vary across regions in the world, and on the factors associated with this variation. The lack of data on the regional variation in diabetes identified based on FPG versus HbA1c means that we cannot quantify the full extent of the diabetes epidemic, and its regional variation, because diabetes prevalence is measured and reported using a single glycaemic biomarker in most population-based surveys and analyses[44-46]. For example, in the latest global analysis[44], only ~15% of surveys had measured both FPG and HbA1c.

We assembled a global database of population-based studies that had measured both FPG and HbA1c. Using these data, we quantified the regional variation in the extent of diabetes diagnosis.

We also quantified, among those who were previously undiagnosed and were detected as having diabetes through screening in the survey, the concordance and discordance of having FPG and HbA1c above common diagnostic thresholds (7.0 mmol/L for FPG and 6.5% for HbA1c). We refer to this group as screen-detected diabetes, which is an epidemiological definition, because many clinical guidelines recommend two measurements for diabetes diagnosis[10-13]. We discuss the reasons and implications of this apparent difference between clinical and epidemiological approaches in the Discussion section. We then used regression analysis to examine what individual and study level factors were associated with whether participants with screen-detected diabetes were identified by elevated FPG, elevated HbA1c or elevated levels of both. It has been shown that having elevated levels of both biomarkers has high positive predictive value for subsequent clinical diagnosis and risk of complications[14,47], and hence this group is similar to clinically-diagnosed diabetes.

Finally, we leveraged the global coverage of the dataset and its large sample size to develop prediction equations that estimate, for any given FPG level, the probability that a person without previously diagnosed diabetes would have HbA1c above the clinical threshold for diabetes had it been measured, and vice versa. Our purpose was to develop and validate global and generalisable predictions equations that account for both personal characteristics and regional differences. These equations serve three purposes. First, they allow more efficient use of finite diagnostic resources, by identifying some people with below- or near-threshold level for one biomarker (e.g., FPG) for measurement of another (e.g., HbA1c). Second, they allow the estimation of the probability that a person with screen-detected elevated level of one biomarker would also have elevated level of the other, as a confirmation of diabetes status[14,47]. Finally, the prediction equations can improve diabetes surveillance by allowing estimation of prevalence of diabetes based on both FPG and HbA1c in health surveys that have measured only one of these biomarkers.

Results

Data

After exclusions (Fig. 1), we used data on 601,307 participants aged 18 years and older with information on whether they had been previously diagnosed with diabetes, of whom 364,825 participants also had measured FPG and HbA1c. The difference between the number of participants with data on previous diagnosis and with biomarker data is mostly because many studies do blood tests on a subsample of those with questionnaire data. These participants were from 117 studies whose mid-year was from 2000 to 2021 in 45 countries from seven of eight world regions (Extended Data Table 1). We had no study that measured both FPG and HbA1c from the region of Oceania, which consists of Pacific island nations. The number of studies in other regions ranged from seven in sub-Saharan Africa to 48 in the high-income western region (Table 1). The mean age of study participants was 50 years, and 56% of participants were women. Of the 117 studies with data on glycaemic variables, 113 (97%) with 351,270 participants (96% of all participants) also had data on BMI; the remaining four studies either did not collect anthropometric information or only had self-reported height and weight data.

Extent and composition of screen-detected diabetes by FPG and HbA1c levels

Across all studies, 16% of participants had diagnosed or previously-undiagnosed screen-detected diabetes. Diagnosed diabetes was calculated based on reporting a prior diagnosis and screen-detected diabetes as having FPG and/or HbA1c levels at or above the thresholds of 7.0 mmol/L and 6.5%[10-13] (Fig. 2). After age-standardisation, the total prevalence of diabetes became 12%. The age-standardised prevalence of diagnosed and screen-detected diabetes were 7% and 5%, respectively. Those without a prior diabetes diagnosis had a lower BMI than those with a prior diagnosis in every region, by an average of 2.9 kg/m^2 across all studies (Table 1). Among those without a prior diagnosis, participants with screen-detected diabetes (i.e., whose FPG ≥7.0

mmol/L and HbA1c ≥6.5%) had a mean BMI that was higher than those who did not have diabetes (i.e., whose FPG <7.0 mmol/L and HbA1c <6.5%) by an average of 2.4 kg/m^2.

In most regions, age-standardised diabetes prevalence was slightly lower than crude prevalence, except south Asia where the participants were on average younger than in other regions (Table 1). Regionally, the age-standardised total diabetes prevalence (i.e., the combination of diagnosed and screen-detected diabetes) ranged from ~9% in the high-income western region to ~21% in south Asia and sub-Saharan Africa. The age-standardised proportion of diabetes that was previously undiagnosed, and was detected in the screening via the survey, was highest (66%) in studies from south Asia, and lowest (<35%) in studies from the high-income western region, central and eastern Europe, and the region of central Asia, Middle East and north Africa. Two studies in sub-Saharan Africa were from Mauritius, a country that is different demographically and economically from most other countries in the region. When these studies were removed, total age-standardised diabetes prevalence declined from 21% to 13% and the proportion who were previously undiagnosed increased from 46% to 53% (Extended Data Fig. 2).

Across all studies together, 29% of participants with screen-detected diabetes had isolated elevated FPG, 37% had isolated elevated HbA1c and 34% had elevated levels of both. Regionally, there was substantial heterogeneity in the composition of screen-detected diabetes across these three groups (Fig. 2). The proportions changed little after age-standardisation. The age-standardised proportion of those with screen-detected diabetes who had elevated levels of both FPG and HbA1c ranged from 29% to 39% across regions. The remaining 61-71% of participants with screen-detected diabetes had discordant FPG and HbA1c elevations, with substantial regional heterogeneity. After age-standardisation, isolated elevated HbA1c made up 54% of participants with screen-detected diabetes in sub-Saharan Africa, and 47% in the region of central Asia, Middle East and north Africa. In these regions, isolated elevated FPG accounted

for <17% of all screen-detected diabetes. In contrast, 55% of participants with screen-detected diabetes in central and eastern Europe, and 46% in high-income western region, had isolated elevated FPG. The correlation coefficient between FPG and HbA1c among participants without prior diagnosis of diabetes ranged from 0.51 in central and eastern Europe to 0.76 in sub-Saharan Africa (Extended Data Fig. 3).

Predictors of heterogeneity in FPG and HbA1c status

Some participant and study level characteristics were predictors of whether screen-detected diabetes was manifested as elevated levels of FPG, HbA1c or both (Table 2). Among those with screen-detected diabetes, male sex was associated with a higher probability of having elevated FPG, either alone (prevalence ratio (PR) =1.10; 95% credible interval (CrI): 1.07-1.14) or together with elevated HbA1c (1.07; 1.03-1.11), and with a lower probability of having isolated elevated HbA1c (0.86; 0.83-0.89). Older age was associated with a lower probability of having elevated FPG, alone (PR=0.97 per decade of age; 0.96-0.98) or together with elevated HbA1c (PR=0.97; 0.96-0.99), and a higher probability of having isolated elevated HbA1c (1.05; 1.04-1.06). Higher BMI was associated with a higher probability of having concordant elevation of FPG and HbA1c (PR=1.07 per 5 units; 1.06-1.08) and a lower probability of having isolated elevated FPG (PR=0.92; 0.90-0.93).

At the study level, in studies that used a portable device to measure HbA1c, the composition of screen-detected diabetes was shifted towards more isolated elevated HbA1c but the estimates for this association had wide confidence intervals because the great majority of studies in our analysis had measured glucose and HbA1c in a laboratory. Neither the year of study nor the percentage of participants with diabetes who had reported prior diagnosis were associated with the composition of screen-detected diabetes.

After adjustment for participant and study characteristics, regional heterogeneity remained in the composition of screen-detected diabetes (Table 2). After adjustment for these factors, the composition of screen-detected diabetes, in terms of having elevated FPG and HbA1c in isolation or together, was statistically indistinguishable among high-income western region and central and eastern Europe. In other regions, elevated HbA1c was a more common form of screen-detected diabetes than in the high-income western region, in isolation (PR ranging 1.42-2.20 across these regions) or together with elevated FPG (PR ranging 1.31-1.52 in east and southeast Asia and the Pacific; south Asia; sub-Saharan Africa). In all regions, isolated elevated FPG was less common than in the high-income western region (PR ranging 0.24-0.51).

Prediction equations

Most of the prediction equations had acceptable performance for estimating the probability that a person without diagnosed diabetes at a specific level of one glycaemic biomarker (i.e., FPG or HbA1c) was above the clinical threshold for the other (Extended Data Table 3 and Extended Data Table 4). Specifically, the C-statistic ranged from 0.85 to 0.90 for models that used either biomarker to predict the elevated level of the other. The mean errors were between -0.18 and -0.65 percentage points, and the mean absolute errors were between 2.32 and 3.30 percentage points. The best-performing models for predicting whether participants had HbA1c ≥6.5% using FPG measurement included BMI and region-specific terms for FPG, referred to as Models 5 and 8 in Extended Data Table 2 and Extended Data Table 3. These two models had similar C-statistic. Model 5 had the smallest deviation and Model 8 the smallest bias. The addition of sex interaction terms did not improve model performance. The best models for predicting whether participants had FPG ≥7.0 mmol/L using HbA1c measurement were also Models 5 and 8 (Extended Data Table 2 and Extended Data Table 4). The coefficients of these models are shown in Extended Data Table 5 and Extended Data Table 6.

In Fig. 3, the coefficients from Model 8 were used to calculate the probability that a person without a history of diabetes diagnosis, based on measurement of a single glycaemic biomarker that is below the clinical threshold, would have elevated level of the other – i.e., elevated HbA1c at a specific FPG and BMI level (Fig. 3A), or elevated FPG at a specific HbA1c and BMI level (Fig. 3B). For example, in south Asia, people aged 55 years and older, without a previous diabetes diagnosis, with obesity (BMI ≥30kg/m^2), whose FPG is 6.5-6.9 mmol/L have a ~29-63% probability of having elevated HbA1c. In contrast, the probability of having elevated HbA1c remained no higher than 17% for men and women of the same age and FPG level in the high-income western region and central and eastern Europe, which means that screen-detected diabetes that is manifested as isolated elevated HbA1c is relatively rare in these two regions. For those whose HbA1c was measured, the probability of having elevated FPG was below 30% in every region except central and eastern Europe; the probability surpassed 20% only in those with high BMI and HbA1c levels.

In Fig. 4, the coefficients from Model 8 were used to calculate the probability that a person without a history of diabetes diagnosis, based on measurement of a single glycaemic biomarker that is above the clinical threshold, would have elevated level of the other – i.e., elevated HbA1c at a specific FPG and BMI level (Fig. 4A), or elevated FPG at a specific HbA1c and BMI level (Fig. 4B). These results show that, people without a prior diagnosis who had an elevated level of one diabetes biomarker had varying probabilities of also being elevated for the other depending on region, age, sex and BMI. In particular, those with screen-detected elevated HbA1c, the probability of also having FPG ≥7.0 mmol/L surpassed 90% in some region-age-BMI combinations. The exceptions were south Asia and Latin America and the Caribbean, where isolated elevated HbA1c and isolated elevated FPG are both common and hence only partially predict one another.

Discussion

Our analysis of pooled global data showed that the use of either FPG or HbA1c alone might substantially underestimate the burden of diabetes relative to the number of people who would have elevated levels of either glycaemic measure, especially in low- and middle-income countries where diagnosis rates are currently low. We also presented prediction equations to help allocate finite resources for measurement of HbA1c in settings where FPG (but not HbA1c) is routinely measured due to logistic or cost constraints. The prediction equations can also be used to enhance diabetes surveillance, to adjust the estimated prevalence in the great majority of population-based health surveys which measure only one biomarker.

Our results, based on a large number of studies from different regions of the world, are consistent with a previous smaller study with data from mostly high-income western countries[43] and with the collective results from studies done in individual countries[22-42] in identifying substantial variation in diabetes classified by FPG versus HbA1c across regions. None of the previous studies had sufficient geographical coverage or participants to robustly quantify regional differences in how those with previously-undiagnosed diabetes that were detected in the study process were identified based on elevation of FPG and HbA1c, in isolation or together, as we did. A study using baseline data from the ORIGIN trial[48], which covered people with diabetes or prediabetes from 40 countries, did not quantify the concordance and discordance of diabetes based on different biomarkers but its graphical results indicated smaller differences in FPG-HbA1c relationship between Europe and north America than between these regions and Asia or south America. We found that sex, age and BMI were predictors of having concordant versus discordant elevated FPG and elevated HbA1c, which is consistent with results from individual countries[22,32,34,40,49]. Finally, to our knowledge, our prediction equations are the only global and generalisable tool for predicting the probability of being classified as having diabetes based on one glycaemic biomarker, based on measurement of another. A previous regression related HbA1c to average

glucose[50] (but not fasting glucose). This relationship is currently used by the American Diabetes Association (ADA) for assessing glycaemic control[51] and not for inferring new diagnosis of diabetes. It used data from only 507 individuals, 422 of whom were non-Hispanic White. The data came from 10 centres, of which 9 were in the USA and Europe. Over half (268) had type 1 diabetes, which is the less common form of diabetes in adults. The conversions did not account for other traits like body-mass index (BMI) and age, nor was the performance of model validated in data that were not used in its derivation.

The strengths of our study include the amount, quality and geographical diversity of data, with studies from seven of eight major world regions. We carefully checked that data on biomarkers of diabetes and prior diagnosis were of high quality and consistent across studies. The scale, quality and consistency of data allowed the characterisation of the relationship between these glycaemic biomarkers and the development of prediction equations which can inform the allocation of resources towards closing the global diagnosis and monitoring gaps.

Our study is also affected by limitations that apply to data pooling analyses, especially those that use data collected in different countries and time periods. Despite our extensive efforts to identify and access data, we had limited data in some regions, and none from Pacific island nations in Oceania region. We did not analyse concordance and discordance with OGTT because few studies, mostly from high-income countries, had data on all three glycaemic biomarkers and because it is no longer widely used in clinical practice or population surveillance. The use of OGTT would identify additional people as having diabetes above and beyond those identified with FPG and HbA1c[25,28]. We did not model time trends of diagnosed and screen-detected diabetes, which should be the subject of future work, as done for hypertension[52]. Although we checked all data sources and their characteristics thoroughly, and accounted for whether a study had measured FPG and HbA1c in a laboratory or using a portable device, other unobserved differences might

remain due to differing methods, including differences in assays used for measuring FPG and HbA1c. We attempted to mitigate these differences by limiting our data to studies with mid-year of 2000 and later, a period over which HbA1c assays were more likely to be standardised, and by including the study-level random effects in our models, which remove the influence of unobserved differences across studies. Furthermore, the majority of the studies in our analysis measured FPG and HbA1c in a laboratory, and our results were not sensitive to exclusion of studies that had used a portable device (Extended Data Table 7). Further, studies that have tested different devices on the same set of samples have found high correlations (>0.97) among their measurements, and between these devices and reference laboratory methods[53,54]. We did not have consistent data from all studies on other predictors of concordant versus discordant elevated levels of FPG and HbA1c, such as genetics, fasting duration, time between puncture and centrifuge, measures of insulin resistance, and pre-existing disease status and comorbidities (e.g., liver disease, haemoglobinopathies and anaemia), that might have differential influence on FPG and HbA1c. These predictors should ideally be the subject of coordinated multi-centre studies with consistent data collection methods in different regions and populations. However, such studies would be very costly especially as the number of outcomes and predictors increases. There is intraindividual variation in FPG, and to a lesser extent HbA1c[55], which could reduce the concordance between FPG and HbA1c, and repeated measurements of FPG may improve its concordance with HbA1c[39]. Finally, while the studies that were used to define the diagnostic cut-points were all based on single measurements of glycaemia[8,56], as are epidemiological and surveillance studies[44,57-59], many clinical guidelines recommend using a second confirmatory test for diabetes diagnosis and initiating treatment[10-13] (we note that there is variation in this guidance – for example while the ADA requires two above-threshold tests for diagnosing diabetes in most cases[10], the European Association for the Study of Diabetes only advises doing so[11], the World Health Organization (WHO) only recommends repeated testing for asymptomatic patients[13], and the International Diabetes Federation further limits to when the first measurement is close to the

threshold for diagnosis[12]). A key reason for clinical guidelines recommending a confirmatory test is to minimize risks of erroneous results, e.g., due mis-recording of laboratory results or large intraindividual variability (which is more relevant for FPG than HbA1c), potentially leading to a lifelong (mis-)diagnosis for an individual patient. This is not a relevant issue in prevalence studies, as measurement error and fluctuations in one direction are approximately balanced by those in the opposite direction. Reflecting the difference between the clinical and epidemiological approaches to diabetes definition, we referred to those without a prior diagnosis and biomarker levels above the clinical thresholds as screen detected diagnosis, and our prediction equations should be considered a tool for triaging some people at specific levels of FPG for measurement of HbA1c, and possible vice versa, rather than a tool for conferring a diagnosis.

The observed variation in the composition of screen-detected diabetes across regions may be due to a number of factors. Some genetic and phenotypic factors that affect fasting glucose and glucose metabolism through their effects on beta-cell function and insulin sensitivity may be more common in some regions or ethnic groups[60-64]. Other non-glycaemic factors, including anaemia due to iron deficiency or malaria, certain haemoglobin variants (e.g., HbS and HbF), other haemoglobinopathies, polycythaemia due to living in high altitude, liver and kidney diseases, HIV and certain drugs, can also affect HbA1c and FPG differently[65-77]. Some of these factors, including malaria-induced and iron deficiency anaemia, haemoglobinopathies such as sickle cell disease and thalassemia, and antiretroviral therapy for HIV, are more prevalent in parts of Asia and Africa[78-80], and may have shifted the population distribution of HbA1c or affected its measurement[77]. Guidelines recommend the use of a glucose test for diabetes diagnosis in those with such conditions[10]. Smoking and alcohol use, which vary geographically, may differentially affect HbA1c and FPG[81,82]. Finally, the composition of diabetes that was detected through screening in the survey depends on whether those with prior diagnosis were identified based on FPG or HbA1c. For example, with increasing use of HbA1c in clinical settings in high-income

countries[83], a smaller proportion of people with screen-detected diabetes would have elevated HbA1c.

Although both FPG and HbA1c are associated with increased risk of microvascular and macrovascular complications[2,84,85], the current evidence on the health implications of having discordant versus concordant elevation of FPG and HbA1c is limited. The few available studies found worse outcomes on the health risks associated with concordant elevation of FPG and HbA1c than discordant elevation, but had mixed findings about how isolated elevation of the two biomarkers compare[39,86,87]. To the extent that both FPG or HbA1c are predictors of risk, reliance on a single biomarker may miss or delay diagnosis of diabetes in some people and hence increase their risk of complications. This issue is especially relevant in low- and middle-income countries where resource constraints make FPG the more common approach to diagnosis, possibly because the measurement of HbA1c requires equipment or reagents that are more costly, or because standardisation of the HbA1c laboratory process requires specialist training that is not as widely available[88-92]. With finite resources, our prediction equations can help triage some people for measurement of a second biomarker, often HbA1c, and enhance early detection of diabetes and close the global diagnosis gap[14]. For surveillance, the use of a single biomarker, so far largely FPG[44-46], underestimates the burden of diabetes, and does so to a larger extent in low- and middle-income countries where a larger share of conditions like diabetes (and hypertension[52]) remains undiagnosed. Our prediction equations can help provide a more complete picture of the burden of diabetes in different regions.

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Author contributions

B.Z., K.S. and R.S. led the data collection and management. B.Z., J.E.B., A.M., C.J.P, S.V.H. and M.E. developed the statistical method. B.Z. coded the statistical method, conducted analyses and prepared results. The other authors contributed to study design; and collected, reanalysed, checked and pooled data. B.Z. and M.E. wrote the first draft of the report. All other authors reviewed and commented on the draft report.

Competing interests statement

A.W. reports an honorarium from Sanofi for serving as a panel member at an educational event on thyroid cancer. 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.

Additional Information

Supplementary Information is available for this paper.

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Fig. 1. Flowchart of data cleaning and use.

[a] Excluded because glucose metabolism changes during pregnancy.

[b] Data from the first available measurement were used for these participants.

[c] Some surveys only measured glycaemic biomarker on a subset of participants for logistic or budget reasons.

[d] Excluded because glycaemic measurements in these participants were systematically different from the rest from the same study, possibly because the specific area had high prevalence of thalassemia[93].

[e] Excluded because such values are more likely to be due to data recording error than values within the range.

[f] We removed participants for implausible pairs of FPG and HbA1c using the method of local outlier factor (LOF)[94]. This approach detects data combinations that are extremes in the joint density of the variable pairs (e.g., a participant with FPG of 5 mmol/L and HbA1c of 17%, or with FPG of 28 mmol/L and HbA1c of 5%). We identified extremes as those measurements whose measure of local density by LOF method is less than half of the average of their 100 nearest neighbours.

[g] Including all 2,436 participants from four studies that did not measure BMI.

[h] Including all 3,455 participants from four studies in which all individuals without previously diagnosed diabetes had FPG <7.0 mmol/L and HbA1c <6.5%.

Fig. 2. Extent and composition of diagnosed and screen-detected diabetes by region.

(A) Crude and age-standardised proportion of participants with diagnosed or screen-detected diabetes, and, for those without prior diagnosis, whether they had isolated elevated FPG (FPG ≥7.0 mmol/L and HbA1c <6.5%), isolated elevated HbA1c (HbA1c ≥6.5% and FPG <7.0 mmol/L) or elevated levels of both, and (B) crude and age-standardised proportion of participants with screen-detected diabetes who had isolated elevated FPG, isolated elevated HbA1c or elevated levels of both, by region. Its contents are the same as the segment of Panel A that is below the zero line, scaled to 100% so that the composition of screen-detected diabetes can be compared across regions, regardless of its total prevalence. Having elevated levels of both biomarkers has high positive predictive value for subsequent clinical diagnosis and risk of complications[14,47], and hence this group is similar to clinically-diagnosed diabetes.

In panel A, regions are ordered by the total proportion of participants who had diagnosed and screen-detected diabetes. In panel B, regions are ordered by the crude proportion of participants with screen-detected diabetes who had elevated levels of both FPG and HbA1c. See Extended Data Fig. 1 for sex-specific results.

Fig. 3. The predicted probability of having screen-detected diabetes with isolated elevated HbA1c or FPG.

The figure shows the probability, by sex, age and region, of participants who did not have prior diagnosis of diabetes of having (A) elevated HbA1c (≥6.5%) at different FPG and BMI levels, and (B) elevated FPG (≥7.0 mmol/L) at different HbA1c and BMI levels. The probabilities were calculated using coefficients of prediction equation Model 8, with measurement method set to laboratory for prediction. These results show the probability of having screen-detected diabetes if the second biomarker had been measured, for a person whose first biomarker was below the clinical threshold for diabetes diagnosis.

Fig. 4. The predicted probability of having screen-detected diabetes with elevated levels of both FPG and HbA1c.

The figure shows the probability, by sex, age and region, of participants who did not have prior diagnosis of diabetes of having (A) elevated HbA1c (≥6.5%) at different FPG and BMI levels, and (B) elevated FPG (≥7.0 mmol/L) at different HbA1c and BMI levels. The probabilities were calculated using coefficients of prediction equation Model 8, with measurement method set to laboratory for prediction. These results show the probability that the second biomarker, had it been measured, would be above the clinical threshold for diabetes diagnosis, for a person whose first biomarker was already above the clinical threshold for diabetes diagnosis. Having elevated levels of both biomarkers has high positive predictive value for subsequent clinical diagnosis and risk of complications[14,47].

Table 1. Characteristics of studies and participants included in the analysis: all participants, participants without diagnosed diabetes, and participants without diagnosed diabetes who had FPG ≥7.0 mmol/L and/or HbA1c ≥6.5%.

	Number of studies*	Number of countries (% of all countries in the region or world)	Median year of studies	Number of participants*	Percent female (%)	Mean (SD) age (years)	Mean FPG (mmol/L)	Mean HbA1c (%)	Mean BMI (kg/m^2)
				All participants					
Central and eastern Europe	8	4 (20%)	2012	51,352	55.6	55 (11)	5.8	5.5	28.2
Central Asia, Middle East and north Africa	10	5 (18%)	2015	73,109	54.4	47 (15)	5.7	5.9	27.7
High-income western	48	11 (41%)	2010	190,276	53.2	53 (18)	5.6	5.5	27.8
Latin America and the Caribbean	17	11 (31%)	2016	75,257	62.3	48 (18)	5.7	5.7	28.3
South Asia	8	2 (29%)	2012	87,404	54.4	42 (14)	5.9	6.0	23.1
East and southeast Asia and the Pacific	19	7 (41%)	2012	112,854	56.2	52 (16)	5.6	5.7	24.0
Sub-Saharan Africa	7	5 (10%)	2014	11,055	62.6	49 (14)	6.1	6.2	26.3
All studies	**117**	**45 (22%)**	**2012**	**601,307**	**55.6**	**50 (17)**	**5.7**	**5.7**	**26.4**
				Participants without diagnosed diabetes					
Central and eastern Europe	8	4 (20%)	2012	12,086	52.2	49 (14)	5.4	5.4	27.4
Central Asia, Middle East and north Africa	10	5 (18%)	2015	46,886	55.1	46 (14)	5.3	5.6	27.5
High-income western	48	11 (41%)	2010	100,140	53.9	52 (16)	5.4	5.3	27.4
Latin America and the Caribbean	17	11 (31%)	2016	38,524	60.8	48 (17)	5.3	5.4	28.0
South Asia	8	2 (29%)	2012	28,554	52.7	41 (14)	5.6	5.7	24.0
East and southeast Asia and the Pacific	19	7 (41%)	2012	92,900	56.6	51 (16)	5.4	5.6	23.9
Sub-Saharan Africa	7	5 (10%)	2014	8,464	62.2	48 (14)	5.6	5.8	26.2
All studies	**117**	**45 (22%)**	**2012**	**327,554**	**55.7**	**49 (16)**	**5.4**	**5.5**	**26.2**
				Participants without diagnosed diabetes who had FPG ≥7.0 mmol/L and/or HbA1c ≥6.5%					
Central and eastern Europe	8	4 (20%)	2012	551	41.7	58 (11)	8.0	6.4	31.3

Central Asia, Middle East and north Africa	10	5 (18%)	2015	3,328	52	55 (13)	7.7	7.3	30.2
High-income western	44	11 (41%)	2009	4,422	43.1	62 (13)	7.9	6.7	31.0
Latin America and the Caribbean	17	11 (31%)	2016	2,718	63	55 (15)	8.4	7.3	30.4
South Asia	8	2 (29%)	2012	4,612	51.7	47 (13)	8.0	7.4	26.0
East and southeast Asia and the Pacific	19	7 (41%)	2012	6,157	52	58 (13)	8.1	7.0	26.1
Sub-Saharan Africa	7	5 (10%)	2014	1,257	60.5	55 (11)	7.5	7.2	28.7
All studies	**113**	**45 (22%)**	**2013**	**23,045**	**51.7**	**56 (14)**	**8.0**	**7.1**	**28.4**

SD: standard deviation; FPG: fasting plasma glucose; BMI: body-mass index.

Table 2. Predictors of whether screen-detected diabetes is manifested as isolated elevated FPG, isolated elevated HbA1c or elevated levels of both. The association with each predictor is reported as prevalence ratios, adjusted for all other variables in the table, in the regression models described in Methods in which data from individual participants with screen-detected diabetes were used. See Extended Data Table 7 for results excluding studies that had measured FPG in capillary whole blood using a portable device.

	Isolated elevated FPG			Isolated elevated HbA1c			Elevated levels of both		
	prevalence ratio	credible interval	posterior probability	prevalence ratio	credible interval	posterior probability	prevalence ratio	credible interval	posterior probability
Region									
High-income western	Reference			Reference			Reference		
Central and eastern Europe	1.16	0.73-1.86	0.259	0.62	0.35-1.09	0.049	0.83	0.61-1.12	0.115
Latin America and the Caribbean	0.48	0.32-0.72	<0.001	1.42	0.93-2.16	0.053	1.16	0.91-1.46	0.109
East and southeast Asia and the Pacific	0.51	0.35-0.73	<0.001	1.53	1.04-2.25	0.015	1.35	1.10-1.67	0.002
South Asia	0.24	0.13-0.44	<0.001	1.65	0.89-3.10	0.056	1.52	1.08-2.15	0.009
Central Asia, Middle East and north Africa	0.33	0.20-0.54	<0.001	2.20	1.31-3.67	0.001	1.06	0.80-1.40	0.342
Sub-Saharan Africa	0.33	0.19-0.57	<0.001	1.65	0.92-2.94	0.045	1.31	0.96-1.79	0.045
Sex									
Women	Reference			Reference			Reference		
Men	1.10	1.07-1.14	<0.001	0.86	0.83-0.89	<0.001	1.07	1.03-1.11	<0.001
Age (per 10 years of age)	0.97	0.96-0.98	<0.001	1.05	1.04-1.06	<0.001	0.97	0.96-0.99	<0.001
Body-mass index (per 5 kg/m^2)	0.92	0.90-0.93	<0.001	0.99	0.98-1.01	0.137	1.07	1.06-1.08	<0.001
Study year (per 5 years of time)	1.01	0.89-1.14	0.447	1.05	0.92-1.20	0.240	1.06	0.99-1.14	0.048
Percent people with diabetes who had been diagnosed before (per 10 percentage points)	0.98	0.89-1.09	0.380	0.98	0.88-1.09	0.354	1.05	0.99-1.11	0.046
Measurement of FPG									
Laboratory	Reference			Reference			Reference		
Portable device	1.71	1.00-2.91	0.025	0.89	0.51-1.56	0.338	0.87	0.64-1.16	0.169
Measurement of HbA1c									
Laboratory	Reference			Reference			Reference		
Portable device	0.33	0.16-0.68	0.001	2.13	1.05-4.20	0.018	0.54	0.35-0.81	0.002

Methods

Data

We used data collated by the NCD Risk Factor Collaboration (NCD-RisC). The data sources included national and multi-country measurement surveys that were either publicly available or identified and accessed through contacts with relevant government or academic partners. Additionally, we searched and reviewed published studies as detailed previously[44] and invited eligible studies to join NCD-RisC, as did we with participating studies in a previous pooled analyses of cardiometabolic risk factors[95-98]. The NCD-RisC database is continuously updated through the above routes and through periodic requests to NCD-RisC members to suggest additional sources in their countries.

The inclusion criteria were: (1) data were collected using a probabilistic sampling method with a defined sampling frame; (2) data were from population samples at the national, subnational (defined as covering one or more subnational regions, more than three urban communities or more than five rural communities), or community level (defined as having up to three urban communities or up to five rural communities); and (3) both FPG and HbA1c were measured. Studies were excluded if they had (1) enrolled participants based on health status or cardiovascular risk; (2) were conducted only among ethnic minorities or specific educational, occupational, or other socioeconomic subgroups; (3) recruited participants through health facilities, except studies based on primary care system in high-income and central European countries with universal insurance; (4) had not measured either FPG or HbA1c; (5) had not instructed participants to fast at least for 6 hours prior to FPG measurement; (6) had only measured FPG or HbA1c in the subset of participants who had known diabetes; (7) had measured HbA1c only in a subset of participants selected based on their levels of FPG, and vice versa; (8) had not collected information on prior diagnosis of diabetes; and (9) their mid-year was prior to 2000, before HbA1c assays were widely standardised[99].

At least two independent persons ascertained that each data source met the inclusion criteria. All NCD-RisC members were asked to review the list of data sources from their country, to verify that the included data met the inclusion criteria and were not duplicates. When FPG and/or HbA1c data were missing for more than 10% of participants in a survey, we checked study design documentation to verify missingness at random so that the above inclusion criteria were met. Questions and clarifications were discussed with NCD-RisC members and resolved before data were incorporated in the database. For each data source, we recorded the study population, sampling approach, years of measurement, and measurement methods, including whether FPG and HbA1c were measured in a laboratory or using a portable point-of-care device. In 11 studies, fasting glucose was measured in capillary whole blood; six of these used equipment that reported plasma-equivalent values. We converted the measurements from the other seven studies to plasma-equivalent using the relationship in a study that compared different types of specimens[100]. In a sensitivity analysis, we excluded these 11 studies from the analysis.

We established whether a participant had diagnosed diabetes using questions worded as variations of “Have you ever been told by a doctor or other health professional that you had diabetes, also called high blood sugar?” In some surveys, the question on previous diabetes diagnosis was asked only if a participant had answered “yes” to an earlier question, usually worded as “Have you ever been screened for diabetes?” or “Have you ever had your blood glucose measured?”. In these cases, participants who answered “no” to the first question were coded as not having been diagnosed with diabetes. We also considered participants who used diabetes medication such as metformin or insulin as having diabetes.

The data cleaning and use process is summarised in Fig. 1, and the list of data sources and their characteristics are stated in Supplementary Table 1.

The pooled analysis was approved by Imperial College London Research Ethics Committee. The participating studies followed their corresponding institutional approval process at the time of data collection.

Statistical analysis

We divided the participants into those who had a prior diagnosis of diabetes (hereafter referred to as diagnosed diabetes), those without a prior diagnosis of diabetes who had elevated FPG (FPG ≥7.0 mmol/L) and/or elevated HbA1c (HbA1c ≥6.5%) (referred to as screen-detected diabetes), and the remainder who did not have a prior diagnosis, elevated FPG, or elevated HbA1c. We conducted the following three analyses.

Composition of screen-detected diabetes by FPG and HbA1c levels: We graphically presented how total diabetes is divided into diagnosed and screen-detected diabetes, and how screen-detected diabetes is further divided into those manifested as only elevated FPG (FPG ≥7.0 mmol/L and HbA1c <6.5%, referred to as isolated elevated FPG), only elevated HbA1c (HbA1c ≥6.5% and FPG <7.0 mmol/L, referred to as isolated elevated HbA1c), or elevated levels of both FPG and HbA1c. We report crude and age-standardised prevalence. We calculated crude prevalence using data from all participants regardless of age. We calculated age-standardised prevalence as the weighted mean of the age-specific values using the WHO standard population[101]. We also graphically described the relationship of FPG and HbA1c among people without diagnosed diabetes.

Predictors of heterogeneity in FPG and HbA1c status: We fitted regression models to examine what individual and study level factors were associated with whether participants with screen-detected diabetes were identified by elevated FPG, elevated HbA1c or elevated levels of both.

We fitted three separate log-binomial regression models, with each of the three outcomes, i.e., isolated elevated FPG, isolated elevated HbA1c, and elevated levels of both, as a distinct dependent variable. Log-binomial regression estimates the association of each independent variable with the probability of a participant falling in each of the three categories as prevalence ratio (PR). The individual level explanatory variables were sex, age, BMI; the study level variables were region, study year, whether FPG and HbA1c were measured in a laboratory or using a portable device (to account for differences in measurement between them[53,54]) and percentage of participants with diabetes who had been diagnosed before in each study. The regressions also included a study-level random effect to account for unobserved factors that lead to systematic differences in each study compared to others[102,103].

We fitted the log-binomial regression models using Bayesian model fitting implemented in MultiBUGS (version 2.0)[104]. Bayesian model fitting has better estimation performance for log-binomial model than a frequentist approach[105]. We used normal distribution with mean of zero and standard deviation of 0.01 as the prior for the regression coefficients and a uniform distribution on 0.01-2.00 as the prior for the standard deviation of study-level random effects. We ran four chains and assessed convergence visually using trace plots. After burn-in and thinning, we kept 50,000 draws to represent the posterior distributions of the PRs. We report PRs and their 95% credible intervals (CrI) as the mean and the 2.5th and 97.5th percentiles of their posterior distributions. We report the posterior probability that a PR with posterior mean estimate >1.0 is less than one, and vice versa for PRs <1.0; the posterior probabilities are analogous to p-values in a frequentist analysis.

Prediction equations: We tested nine logistic regression models for estimating the probability that a person without diagnosed diabetes at a specific level of FPG had an HbA1c over the clinical threshold for diabetes (HbA1c ≥6.5%). The predictors in the models were selected based on

clinical and epidemiological relevance and data availability. The predictors included FPG as well as sex, age, BMI, glycaemic measurement method (laboratory based or via a portable device) and region. The nine models (Extended Data Table 2) differed by the predictors included and whether the coefficient of the FPG term was allowed to vary by sex and region. In all models, we included a study-level random effect to account for unobserved factors that lead to systematic differences in each study compared to others[102,103]. We also tested the inclusion of nonlinear (square and cubic) terms of FPG, year of data collection and other interaction terms; these models performed worse than those without the additional terms as evaluated by the metrics below and are not presented. We did not interact age, which is a continuous variable, with FPG and other terms, to avoid overfitting. We fitted and evaluated all prediction models in R (version 4.2.1)[106].

We assessed the performance of the models in predicting (i) individual participants' status of having HbA1c ≥6.5% based on their FPG and (ii) the prevalence of HbA1c ≥6.5% for an entire study. The performance at individual level reflects how well the model works for triaging patients for further measurement for diabetes, and the performance at study (or population) level assesses how well the model works for diabetes surveillance. We used the C-statistic to assess individual-level performance, and mean error and mean absolute error between the predicted and observed prevalence for population-level performance. The C-statistic measures how well a model distinguishes individuals with higher risk from those with lower risk. Mean error assesses whether there is systematic difference (i.e., bias) in the predicted prevalence compared to the observed one, and mean absolute error assesses any deviation of the predicted prevalence from the observed prevalence. We calculated error by study, sex and age group (18-39 years; 40-59 years; 60 years and older).

We evaluated the performance of the models in 20 rounds of 10-fold cross-validation[107]. In each fold of each round, we held out all data from a random 10% of studies, fitted the model to the data

from the remaining 90% of studies and made estimates for the held-out observations. We repeated this process 10 times, each time holding out a different 10% of studies so that each study was held out exactly once. We calculated the above individual-level and population-level performance metrics for all held-out observations. We repeated the 10-fold cross-validation 20 times and report the means and ranges of the performance metrics from all 20 rounds.

We repeated the same process for predicting the probability of having FPG ≥7.0 mmol/L based on HbA1c.

Data availability statement

Data used in this research are governed by data sharing protocols of participating studies. Contact information for data providers can be obtained from www.ncdrisc.org and https://doi.org/10.5281/zenodo.8169146.

Code availability statement

The computer code for the log-binomial regression model in this work is available at www.ncdrisc.org and https://doi.org/10.5281/zenodo.8169146.

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Extended Data Fig. 1. Extent and composition of diagnosed and screen-detected diabetes by region and sex.

(A) Crude and age-standardised proportion of participants with diagnosed or screen-detected diabetes, and, for those without prior diagnosis, whether they had isolated elevated FPG (FPG ≥7.0 mmol/L and HbA1c <6.5%), isolated elevated HbA1c (HbA1c ≥6.5% and FPG <7.0 mmol/L) or elevated levels of both, and (B) crude and age-standardised proportion of participants with screen-detected diabetes who had isolated elevated FPG, isolated elevated HbA1c or elevated levels of both, by region and sex. Its contents are the same as the segment of Panel A that is below the zero line, scaled to 100% so that the composition of screen-detected diabetes can be compared across regions, regardless of its total prevalence. Having elevated levels of both biomarkers has high positive predictive value for subsequent clinical diagnosis and risk of complications[14,47], and hence this group is similar to clinically-diagnosed diabetes.

In panel A, regions are ordered by the total proportion of participants who had diagnosed and screen-detected diabetes. In panel B, regions are ordered by the crude proportion of participants with screen-detected diabetes who had elevated levels of both FPG and HbA1c.

Extended Data Fig. 2. Extent and composition of diagnosed and screen-detected diabetes by region, after removing two studies in Mauritius from sub-Saharan Africa.

(A) Crude and age-standardised proportion of participants with diagnosed or screen-detected diabetes, and, for those without prior diagnosis, whether they had isolated elevated FPG (FPG ≥7.0 mmol/L and HbA1c <6.5%), isolated elevated HbA1c (HbA1c ≥6.5% and FPG <7.0 mmol/L) or elevated levels of both, and (B) crude and age-standardised proportion of participants with screen-detected diabetes who had isolated elevated FPG, isolated elevated HbA1c or elevated levels of both, by region. Its contents are the same as the segment of Panel A that is below the zero line, scaled to 100% so that the composition of screen-detected diabetes can be compared across regions, regardless of its total prevalence. Having elevated levels of both biomarkers has high positive predictive value for subsequent clinical diagnosis and risk of complications[14,47], and hence this group is similar to clinically-diagnosed diabetes.

In panel A, regions are ordered by the total proportion of participants who had diagnosed and screen-detected diabetes. In panel B, regions are ordered by the crude proportion of participants with screen-detected diabetes who had elevated levels of both FPG and HbA1c. Regions are in the same order as in Fig. 2.

Extended Data Fig. 3. Relationship between FPG and HbA1c, among participants who had not been previously diagnosed with diabetes, by region.

The shading indicates the density of participants in each region, with darker shades corresponding to more participants and vice versa. The dotted lines are placed at FPG of 7.0 mmol/L and HbA1c of 6.5%, which are common clinical thresholds for diabetes[10-13]. The numbers on the panels indicate the Pearson correlation coefficient between FPG and HbA1c in each region. A total of 623 (0.2%) participants with FPG of 19-28 mmol/L and/or HbA1c of 12-17% are not shown in the figure so that the axes have sufficient resolution in ranges where the great majority of participants were.

Extended Data Table 1. List of analysis regions and countries in each region. The data used in the analysis came from countries shown in bold.

Extended Data Table 2. Specification of models tested to predict whether a participant has HbA1c ≥6.5% based on FPG levels, and to predict whether a participant has FPG ≥7.0 mmol/L based on HbA1c levels.

* denotes statistical interaction.

Age, FPG, HbA1c and BMI were normalised using the following values (approximately equal to mean and standard deviation across all participants):

Age: centred at 50 years, divided by 15 years

FPG: centred at 5.5 mmol/L, divided by 1.0 mmol/L

HbA1c: centred at 5.5%, divided by 0.7 mmol/L

BMI: centred at 26.5 kg/m^2, divided by 5.0 kg/m^2

FPG: fasting plasma glucose; BMI: body-mass index; RE: random effect.

Extended Data Table 3. Performance of models for predicting whether a participant whose FPG was measured had HbA1c ≥6.5%.

The reported values are the means and ranges over 20 rounds of 10-fold cross-validation. See Extended Data Table 2 for details of model specifications.

Extended Data Table 4. Performance of models for predicting whether a participant whose HbA1c was measured had FPG ≥7.0 mmol/L.

The reported values are the means and ranges over 20 rounds of 10-fold cross-validation. See Extended Data Table 2 for details of model specifications.

Extended Data Table 5. Coefficients of the best-performing prediction models for whether a participant whose FPG was measured had HbA1c ≥6.5%.

The reported coefficients are the means and 95% confidence intervals.

Extended Data Table 6. Coefficients of the best-performing prediction models for whether a participant whose HbA1c was measured had FPG ≥7.0 mmol/L.

The reported coefficients are the means and 95% confidence intervals.

Extended Data Table 7. Predictors of whether screen-detected diabetes is presented as isolated elevated FPG, isolated elevated HbA1c or elevated levels of both, excluding studies that had measured FPG using a portable device.

The association with each predictor is reported as prevalence ratios, adjusted for all other variables in the table, in the regression models described in Methods in which data from individual participants with screen-detected diabetes were used.