Bimodal Distribution of Glucose Is Not Universally Useful for Diagnosing Diabetes

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OBJECTIVE — Bimodality in the distribution of glucose has been used to define the cut point for the diagnosis of diabetes. Previous studies on bimodality have primarily been in populations with a high prevalence of type 2 diabetes, including one study in a white Caucasian population. All studies included participants with known diabetes. The aim of this study was to assess whether a bimodal structure is a general phenomenon in fasting plasma glucose (FPG) and 2-h plasma glucose that is useful for deriving a common cut point for diabetes in populations of different origin, both including and excluding known diabetes.

RESEARCH DESIGN AND METHODS — The Evaluation of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance (DETECT-2) project is an international collaboration pooling surveys from all continents. These studies include surveys in which plasma glucose was measured during an oral glucose tolerance test; in total, 43 studies (135,383 participants) from 27 countries were included. A mixture of two normal distributions was fitted to plasma glucose levels, and a cut point for normal glycemia was estimated as their intersection. In populations with a biologically meaningful cut point, bimodality was tested for significance.

RESULTS — Distributions of FPG and 2-h plasma glucose did not, in general, produce bimodal structures useful for deriving cut points for diabetes. When present, the cut points produced were inconsistent over geographical regions.

CONCLUSIONS — Deriving cut points for normal glycemia from distributions of FPG and 2-h plasma glucose does not appear to be suitable for defining diagnostic cut points for diabetes.

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Bimodality in glucose distribution has been reported in a number of populations with a high prevalence of diabetes, including the American Pima Indians (1) and the Micronesian population of Nauru (2). This observation was an important component in defining the 1980 World Health Organization (WHO) diagnostic criteria for diabetes together with thresholds for diabetes-specific microvascular complications such as retinopathy. Subsequent studies of bimodality in Egypt (3,4) and in Mexican Americans (5) rendered further support for the WHO 1980 and 1985 diagnostic criteria for diabetes (6,7).

Later, the presence of bimodality in glucose was also found in the high-diabetes-prevalence populations in Papua New Guinea (8) and in South African Indians (9). Few studies on bimodality have been conducted in populations with low diabetes prevalence (10–12). Here, bimodality was shown in 2-h plasma glucose values but with differing cut points for normal glycemia. Only one study has demonstrated bimodality in white Caucasians (13).

These findings in diverse populations suggest that bimodality in glucose is universal. However, all of these studies included participants with known diabetes. Patients with diabetes are treated (lifestyle and medication) to lower glycemic levels. Including these patients in the analysis introduces a systematic treatment bias, something that could either enhance or diminish the bimodal structure of data.

The aim of this study was to assess whether distributions of plasma glucose (fasting and 2 h), in general, give rise to a bimodal structure, which is useful for deriving a cut point for diabetes in populations of different origin, both including and excluding participants with known diabetes and, if present, to assess whether the cut point for normal glycemia derived from such a bimodal structure varied between populations from different geographic regions.

RESEARCH DESIGN AND METHODS

— This study is based on the Evaluation of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance (DETECT-2) database, a worldwide collaborative study based on original data from population-based surveys of ≥500 participants (14). The individual studies have been described precisely (supplemental data, available in an online appendix at http://dx.doi.org/10.2337/dc08-0867). In this analysis, only studies in which plasma glucose was measured during a 75-g oral glucose tolerance test were included.

Participants who had been told by a doctor they had diabetes or who were receiving antidiabetes treatment (diet or medication) were defined as having known diabetes. All others were classified according to the WHO 1999 diagnostic criteria (15). Participants with one glucose value in the nondiabetic range and missing data for the other glucose value could not be classified according to the WHO criteria and were excluded. All analyses were performed first excluding and then including participants with known diabetes. In all surveys, participants gave their consent for participation in accordance with the Declaration of Helsinki.

Statistical methods

Analyses were performed using R version 2.8.0. All analyses were stratified by country.

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Table 1—*Characteristics of the study populations*

Region	Country	Center	*n*	Known diabetes (%)	SDM (%)	Age range	Study period
Greenland	Greenland	B99*	1,142	1.1	9.1	27–86	1998–2002
North Europe	U.K.	Ely*	1,156	—	7.0	40–69	1990–1992
		NHP*	800	2.6	7.6	30–76	1992–1994
		Whitehall II	10,270	0.8	1.5	39–63	1991–1993
	Finland	East-West Finland*	461	12.4	10.8	70–89	1989
		FIN–MONICA92	1,929	4.6	3.9	40–64	1992
		Vantaa*	613	11.3	6.4	64–66	1990–1991
		FINRISK02*	3,767	3.3	8.8	44–75	2002
	Sweden	NSW–MONICA	3,561	6.8	2.8	25–75	1986–2004
		ULSAM*†	1,221	5.7	10.3	69–74	1991–1995
	Denmark	Glostrup*	695	5.6	3.7	59–62	1996–1997
		Inter99*	6,784	2.0	3.9	30–60	1999–2001
	Germany	KORA*	1,485	8.8	8.0	55–74	1999–2001
Central Europe	Holland	Hoorn*	2,484	3.5	6.6	49–77	1989–1991
		Zutphen*	484	8.1	9.7	70–90	1990
	France	Paris Prospective*	7,176	2.0	4.3	44–55	1968–1974
	Poland	PMSDE*	2,838	6.3	7.8	35–77	1998–2000
South Europe	Spain	Guia*	693	8.9	9.7	30–93	1994–1997
	Israel	GOH*†	1,291	1.9	7.3	35–69	1976–1982
Eastern Mediterranean and Middle East	Egypt	Egypt*†	1,451	28.5	9.3	20–89	1992–1993
Africa	Mauritius	Mauritius*	4,908	6.1	8.4	25–75	1987
	Cameroon	Cameroon*	1,804	0.4	0.7	24–74	1996
India	India	CUPS*†	1,259	7.1	4.8	20–87	1996–1998
		Dombivli	550	5.5	8.5	31–80	1998–1999
		Chennai†	2,182	7.5	6.4	18–94	1993–1995
		CURES*	2,350	6.1	9.7	20+	2001–2004
Japan	Japan	Funagata*†	2,154	5.1	3.5	35–89	1992–1997
Asia remaining	China	Harbin†	1,376	1.5	2.0	40–85	1998
		Qingdao	2,061	4.7	9.3	30–74	2002
	Indonesia	Jakarta*†	1,019	3.5	4.3	14–87	1992–1993
	Taiwan	Kinmen*	1,456	—	12.6	30–88	1991–1994
	Singapore	NHS92*	3,568	4.4	6.0	17–69	1992
	Korea	Korea	10,044	5.7	7.3	37–71	2001–2003
	Vietnam	Vietnam*	9,122	1.2	2.3	30–65	2002
Australia and New Zealand	Australia	AusDiab*	11,144	5.1	4.2	25–95	1999–2000
Pacific Islands	Nauru	Nauru*	868	19.1	14.7	19–81	1987
	Tonga	Tonga*	472	—	15.0	15–85	1998–2000
		Tonga04*	1,016	—	9.3	15–87	2001–2004
	Samoa	Samoa*	3,285	3.8	7.5	20–90	1978–1991
North America	U.S.	NHANES III*†	3,105	7.1	9.9	40–74	1988–1994
		NHANES II*†	3,814	2.6	5.6	20–74	1976–1980
		ARIC, U.S.*	11,596	11.8	10.0	52–70	1996–1999
		NHANES99*	5,929	4.8	2.6	12–85	1999–2001

*Centers with measured fasting plasma glucose in individuals with known diabetes. †Centers with measured 2-h plasma glucose in individuals with known diabetes. ‡In NHANES99, SDM is based on fasting values only. ARIC, Atherosclerosis Risk in Communities; AusDiab, Australian Diabetes, Obesity and Lifestyle Study; CUPS, Chennai Urban Population Study; CURES, Chennai Urban Rural Epidemiology Study; FIN-MONICA, Finland Monitoring of Trends and Determinants in Cardiovascular Disease; GOH, Glucose Intolerance Obesity and Hypertension; FINRISK02, FINRISK 2002; KORA, Cooperative Health Research in the Region of Augsburg; NHANES, National Health and Nutrition Examination Survey; NHS92, 1992 National Health Survey; NHP, Newcastle Heart Project; NSW-MONICA, New South Wales Monitoring of Trends and Determinants in Cardiovascular Disease; PMSDE, Polish Multicenter Study on Diabetes Epidemiology; ULSAM, Longitudinal Study of Adult Men.

The distributions of both fasting plasma glucose (FPG) and 2-h plasma glucose are skewed to the right. To reduce skewness, glucose values were log transformed before model fitting. A normal distribution and a mixture of two normal distributions were fitted to the log-transformed glucose data. The probability density function for the normal distribution is as follows:

$$f(x;\ \mu,\ \sigma) = \frac{1}{\sigma\sqrt{2\pi}}\exp\left(\frac{-(x-\mu)^2}{2\sigma^2}\right).$$

Here, μ and σ are the mean and SD of x. We fitted the normal distribution to data using the maximum likelihood method. The probability density function for the mixture model of two normal components is as follows:

$$f(x) = \alpha f(x; \mu_1, \sigma_1) + (1 - \alpha) f(x; \mu_2, \sigma_2).$$

Here, α and $1 - \alpha$ are the mixture proportions with α between zero and unity. The mixture model was fitted using a combination of a Newton-type method and the expectation-maximization (EM) algorithm (16) (the normalmixEM2comp function from the Mixtools package in R).

To assess the presence of bimodality, the mixture model was compared with the unimodal distribution. The variance of the two components in the mixture model may differ. In that case, simulation results have shown that the limiting function for the likelihood ratio test is bounded by χ^2 distributions with 4 and 6 degrees of freedom (d.f.) (17). In this study, *P* values for significance of the mixture model were based on a χ^2 distribution with 4 d.f. A significance level of 5% was used.

A cut point for normal glycemia was calculated as the crossing point of the two normal distributions in the mixture model. Approximate CIs for the cut points were estimated by bootstrapping (1,000 bootstraps) (18).

The aim of this study was to detect whether distributions of FPG and 2-h plasma glucose give two distinct entities that may be used to separate individuals into two groups: those having normal or abnormal glycemia. For this separation to be biologically meaningful, the cut point separating these two entities should be between their modes (μ_1, μ_2). If not, the estimated cut point would not be useful because more than half of the individuals in the upper entity would have a glucose level below the cut point, which, consequently, would identify them as having normal glycemia.

Mixture models were fitted to the glucose values in each country to derive cut points for normal glycemia. In countries in which this cut point was biologically meaningful, the presence of bimodality was tested. As described in an earlier study on bimodality (10), the ability of a fitted mixture model to be statistically superior to a unimodal model depends on the sample size, the prevalence of diabetes, and the difference between the means of the two underlying distributions in units of SDs. In small samples, a lack of power may prohibit significance of the mixture model even when bimodality is truly present. To not be limited by lack of power, all biologically meaningful cut points for normal glycemia are reported

Table 2—*Results of the mixture model for countries where the cut point is biologically meaningful*

			Fasting plasma glucose										2-h plasma glucose									
			Excluding known diabetes						Including known diabetes						Excluding known diabetes						Including known diabetes			
							Cut					Cut					Cut					Cut	
Region	Country	SDM	μ_1	σ_1	μ_2	σ_2	point	*P* value	μ_1	σ_1	μ_2	σ_2	point	*P* value	μ_1	σ_1	μ_2	σ_2	point	*P* value	μ_1	σ_1	μ_2	σ_2	point	*P* value
North Europe	Sweden	225	5.1	0.7	9.7	4.1	6.9	<0.01	5.1	0.7	11.8	4.9	6.7	<0.01	5.7	1.3	10.3	6.8	8.5	<0.01	6.0	1.7	18.4	6.1	10.2	<0.01
	Germany	119	5.4	0.7	9.3	3.5	7.2	0.027	5.5	0.8	11.8	4.8	7.4	0.017	5.9	1.7	12.0	3.8	9.7	0.048						
Central Europe	Holland	212	5.2	0.6	8.2	3.1	6.8	<0.01	5.2	0.6	9.0	3.5	6.8	<0.01	5.6	2.0	14.0	4.2	9.5	<0.01						
South Europe	Spain	67	5.4	0.6	6.9	2.4	6.6	<0.01	6.7	1.9	14.0	1.7	12.0	0.078												
Eastern Mediterranean and Middle East	Egypt	135	5.1	0.7	9.7	4.1	6.9	<0.01	5.1	0.7	11.8	4.9	6.7	<0.01	5.7	1.3	10.3	6.8	8.5	<0.01	6.0	1.7	18.4	6.1	10.2	<0.01
Africa	Mauritius	410	5.2	0.6	8.2	3.1	6.8	<0.01	5.2	0.6	9.0	3.5	6.8	<0.01	5.6	2.0	14.0	4.2	9.5	<0.01						
India	India	474							4.6	0.7	7.7	4.2	6.4	<0.01	5.6	1.5	12.6	5.3	9.4	<0.01	5.1	1.2	12.5	6.7	8.2	<0.01
Japan	Japan	75																			6.1	1.9	15.1	3.1	11.7	0.090
Asia remaining	Taiwan	183													6.9	2.3	14.9	4.7	12.7	0.031						
	Singapore	214	5.4	0.4	7.8	2.7	6.7	0.075	5.4	0.4	8.8	3.3	6.7	0.055												
	Korea	738	4.9	0.4	6.7	1.9	6.1	<0.01																		
Australia and New Zealand	Australia	464							5.4	0.5	8.0	2.7	6.8	<0.01												
Pacific Islands	Nauru	128	5.4	0.7	9.3	3.5	7.2	0.027	5.5	0.8	11.8	4.8	7.4	0.017	5.9	1.7	12.0	3.8	9.7	0.048						
	Tonga	165													6.5	1.6	13.3	3.1	10.5	0.053						
North America	U.S.	1,826							5.4	0.5	8.6	3.4	6.9	<0.01							6.2	1.9	15.1	6.0	11.2	<0.01
Total			5.1	0.5	8.0	2.9	6.7	<0.01	5.3	0.6	8.3	3.7	6.8	<0.01	6.1	1.8	14.1	5.1	11.0	<0.01	6.1	1.8	15.8	6.0	10.9	<0.01

Data for means, SD, and cut points are in mmol/l. The *P* value is the level of significance of the mixture model over the unimodal normal distribution. The χ^2 distribution with 4 d.f. is used.

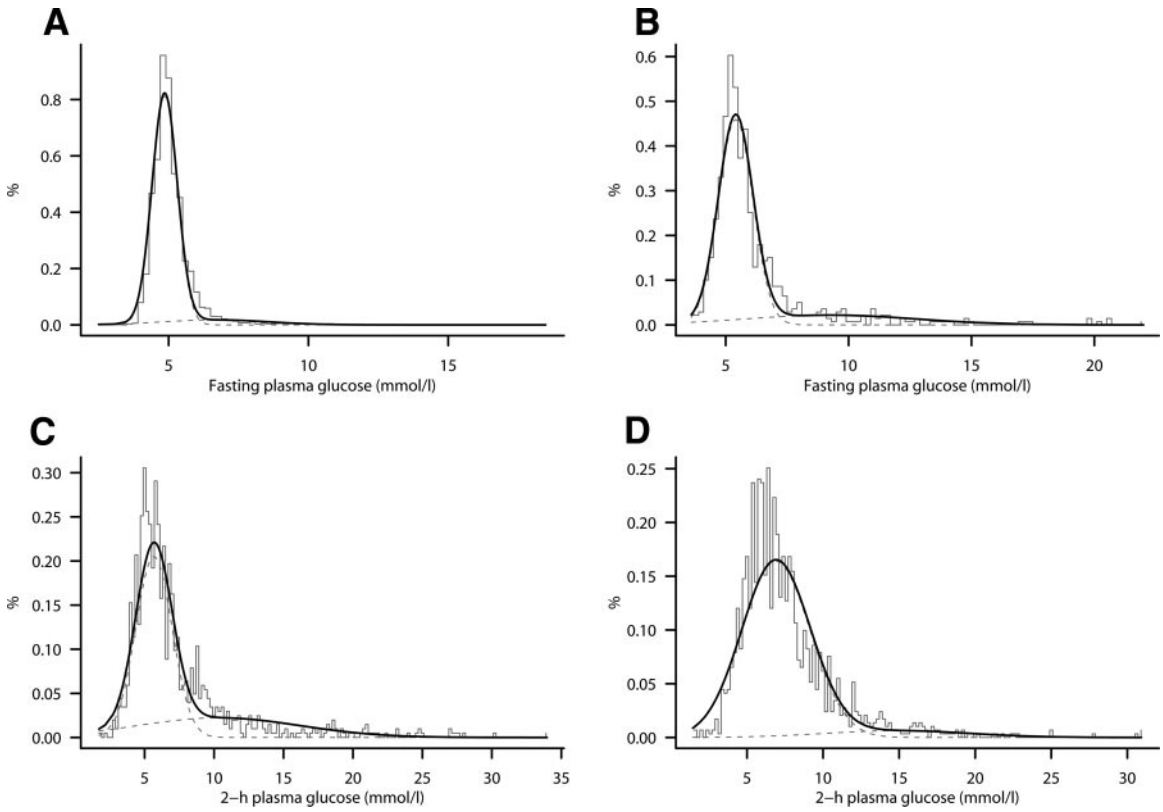

Figure 1—*Distribution of FPG in Korea* (A) *and Nauru* (B) *and 2-h plasma glucose in Egypt* (C) *and Taiwan* (D). *Patients with known diabetes are excluded. The histograms represent data (intervals of 0.2 mmol/l). The superimposed solid curve is the fitted mixture model, and the dotted curves are the two underlying distributions.*

in this article irrespective of the statistical significance of the mixture model.

RESULTS — This study included 135,383 participants with measurements of FPG and/or 2-h plasma glucose from 43 studies in 27 different countries covering 12 different geographic regions. Table 1 lists the characteristics of the study populations.

The prevalence of screen-detected diabetes (SDM) ranged from 0.7% in Cameroon to 14.7% in Nauru. Analysis was done by country, pooling the individual studies within a country. Because the individual studies varied in both sex and age distribution, the pooled data for a country do not necessarily reflect the age and sex distribution in that country. Individual records have not been weighted in the analyses.

The proportion of men and the age range varied among the countries. In studies including both sexes, men seemed slightly underrepresented. The Dutch and German studies were the oldest (49–89 and 55–74 years, respectively), whereas the French study was restricted to the middle-aged (44–55 years) population. In the remaining countries, age range was well represented. In all countries, prevalence of diabetes increased with age, with the only exception being Samoa, where a small decrease was observed.

Analyses excluding patients with known diabetes

For FPG, the mixture model resulted in a biologically meaningful cut point for normal glycemia in 5 of 27 countries (19%). Except for Singapore, the mixture model was also statistically superior to the unimodal model; i.e., bimodality was present (Table 2). The estimated cut points ranged from 6.1 mmol/l (95% CI 6.0–6.3) in Korea to 7.2 mmol/l (6.8–7.6) in Nauru (Fig. 1). Pooling the five meaningful cut points, the overall cut point for normal glycemia was estimated to be 6.7 mmol/l (6.5–6.9) (Fig. 2). This result is somewhat lower than the WHO diabetes diagnostic cut point for fasting plasma glucose of 7.0 mmol/l. Removing Singapore (where bimodality was not significant) from the pooled analysis decreased the overall estimated cut point by 0.2 mmol/l.

For 2-h plasma glucose, 8 of 26 countries (30%) produced a meaningful cut point. Except for Sweden, Spain, and Tonga, the mixture model was statistically superior (Table 2). The estimated cut points ranged from 8.5 mmol/l (95% CI 7.6–9.5) in Egypt to 12.7 mmol/l (7.6–14.9) in Taiwan (Fig. 1). The overall cut point was 11.0 mmol/l (10.6–11.4) (Fig. 2). This result corresponds to the WHO diabetes diagnostic cut point for 2-h plasma glucose of 11.1 mmol/l. Removing Sweden, Spain, and Tonga from the pooled analysis decreased the overall estimated cut point by 0.2 mmol/l.

Analyses including patients with known diabetes

All countries except two had measurements of FPG in participants with known diabetes (n = 103,410). Repeating the analyses for FPG including patients with known diabetes, 11 of 25 countries (44%) now produced a meaningful cut point. In only one of these 11 countries (Singapore) was the mixture model not statistically superior to the unimodal model (Table 2). The pooled cut point was 6.8 mmol/l (95% CI 6.7–6.8) both with and

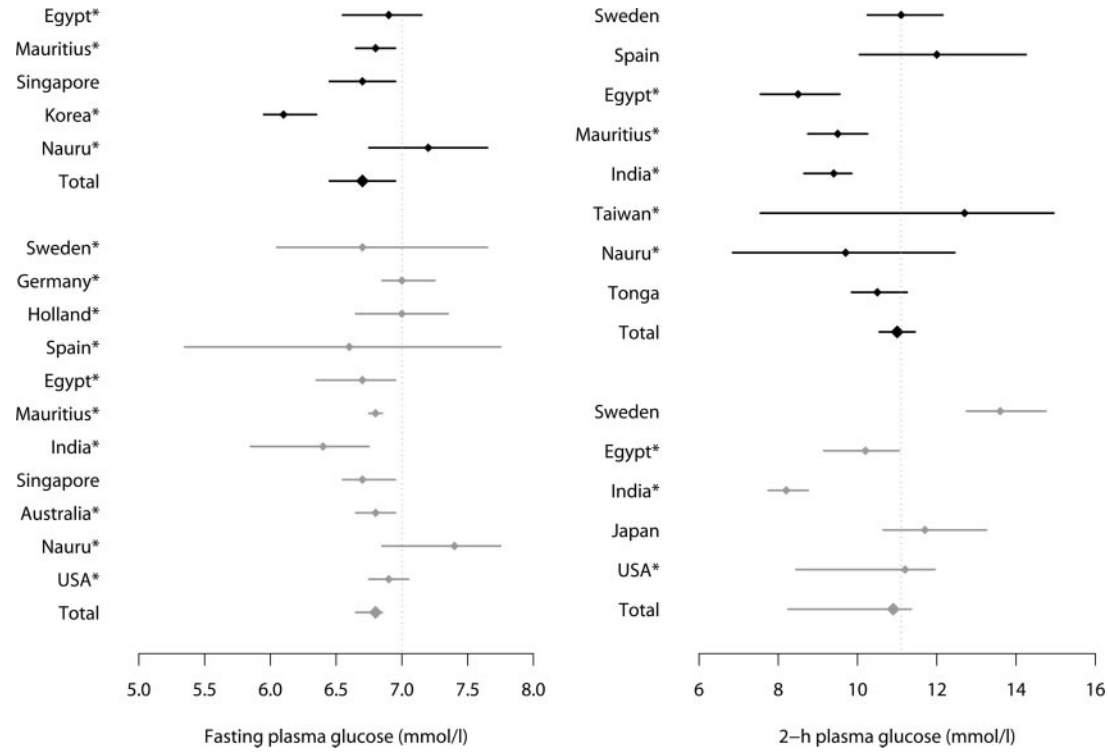

Figure 2—*Cut points (95% CI) for normal glycemia in glucose. The gray and black lines represent analyses with and without individuals with known diabetes. The dotted vertical line is the WHO 1999 cut point for diabetes. *Statistically significant mixture model.*

without Singapore, which is consistent with the result found when patients with known diabetes were excluded. In addition, the range in cut points was comparable: from 6.4 mmol/l (5.9–6.7) in India to 7.4 mmol/l (6.9–7.7) in Nauru.

Ten studies from eight different countries had measurements of 2-h plasma glucose in participants with known diabetes (n = 18,872). Of these, five (63%) produced a meaningful cut point for normal glycemia, and, in addition, the mixture model was significantly superior in Egypt, India, and the U.S. (Table 2). The corresponding pooled cut point was 10.9 mmol/l (95% CI 8.3–11.3), which was reduced by 0.6 mmol/l when Sweden and Japan, which had nonsignificant mixture models, were removed from the analysis. This result is also consistent with the result found when patients with known diabetes were excluded but with a greater range in the individual cut points from 8.2 mmol/l (7.8–8.7) in India to 13.6 mmol/l (12.8–14.7) in Sweden.

CONCLUSIONS — When known diabetes was excluded from the analysis, results from less than one-third of the countries were useful for deriving a cut point for normal glycemia in FPG and 2-h plasma glucose. Consequently, when known diabetes is removed, distributions of plasma glucose do not commonly give rise to a bimodal structure that is useful for deriving a cut point for diabetes. Inclusion of participants with known diabetes, although not universally present, more than doubled this proportion to 44% for FPG and 63% for 2-h plasma glucose. In most countries with a meaningful cut point, the mixture model was significantly superior to the unimodal normal model. This test was, however, based on a χ^2 distribution with 4 d.f. to err on the side of rejecting unimodality in favor of bimodality. These results indicate that the presence of a biologically meaningful bimodal structure in glucose seems to be driven by patients with known diabetes.

The overall pooled cut points for normal glycemia were almost invariant to whether or not participants with known diabetes were included. However, the estimated cut points were inconsistent between countries, especially for 2-h plasma glucose when participants with known diabetes were included. Comparing these results with those of earlier studies, we found that the overall cut point for FPG was somewhat lower (2,3,8,9), whereas the cut point for 2-h plasma glucose was well in line (1–3,5,8,10,11,13), except for the studies of South African Indians (9) and Western Samoans (12), which produced lower cut points for 2-h plasma glucose.

Earlier studies reported that bimodal structure in glucose distribution is more pronounced in the older age-groups, in whom the prevalence of diabetes is higher (1,2,5,8,9,11,12). We addressed the possible effect of age by considering the subpopulation aged ≥60 years (data not shown). In general, our main results were reproduced in this age-group. Only very few additional countries produced a biologically meaningful cut point, but again, including patients with known diabetes increased the proportion of meaningful bimodal structures. This finding is in line with an earlier study showing the mean of the upper normal component to be similar in different age-groups (4).

To increase sample size, we also pooled populations that were geographically in the same ethnic area: Caucasians, Africans, Asians, and Pacific Islanders (data not shown). A meaningful bimodal structure of data was only detected in half of the ethnic areas.

Excluding participants with known diabetes from the analyses reduces the prevalence of diabetes in the population by ~50%, which may prohibit a significant fit of the mixture model. In addition,

the mean of the second component is likely to be lower when patients with known diabetes that is more advanced are excluded. This exclusion potentially makes the two components less distinct and thereby decreases the probability of a meaningful cut point separating them. However, as acknowledged in previous studies (3,10,13), including patients with known diabetes in the analyses will induce a treatment bias for the following reasons. In accordance with existing treatment guidelines, patients with diabetes are treated with the aim of lowering their glucose to a near-normal range. This implies that diabetic patients with higher glucose values are treated relatively more aggressively than patients with only slightly raised glucose values. It seems reasonable to assume that aggressively treated patients have a larger absolute decrease in glucose values than patients who are treated less aggressively (19). Therefore, the effect of treatment is not an equal shift to the left in the glucose distribution of the entire diagnosed population but, rather, a shift that increases with glucose values at diagnosis (20). Hence, the glucose values of the subgroup with the highest values is shifted toward the glucose values of the rest of the diagnosed population. This means that patients with diagnosed diabetes are bunched together, thereby potentially creating an artificial bimodal structure in the glucose data.

How do we overcome this problem? The ideal setting for studying bimodality in glucose distribution is a treatment-naive population (including diabetes treatment) in whom diabetes is undiagnosed. This is not the case in any of the studies in this analysis. A theoretical solution to the problem is to adjust the measured glucose value of a treated patient to its untreated level. This would require knowledge of the exact effect of treatment for each patient. However, different doctors may prescribe different treatments to patients with the same glucose levels. In addition, even if the same treatment is administered, its effect will vary among patients because of differences in phenotype as well as in adherence to treatment. Hence, adjusted glucose values are highly uncertain. A study from Malaysia (10) suggested imputing glucose values for the patients with known diabetes using the measured glucose values of the participants with SDM in the same population and taking into account age, sex, ethnicity, and medical history of diabetes status. The model does not account for diabetes duration. However, glucose is known to increase with diabetes duration despite increasing treatment (21). Participants with SDM have, by definition, newly diagnosed diabetes, whereas patients with known diabetes may have had the diagnosis several years previously, which questions the validity of imputing their glucose values based on those of participants with SDM.

In summary, this study has shown that distributions of FPG and 2-h plasma glucose, in general, do not give rise to a bimodal structure that is useful for deriving a cut point for diabetes in populations of different origin. Including patients with known diabetes increases the possibility of deriving a meaningful cut point, but the bimodal structure in data may be a treatment artifact. In addition, cut points produced for normal glycemia were inconsistent over geographical regions. Thus, bimodality is not a suitable method for defining diagnostic cut points for diabetes. Instead, it seems more relevant to base the diagnostic criteria on thresholds for diabetes-specific micro- and macrovascular complications. However, further analyses are needed in this area.

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No potential conflicts of interest relevant to this article were reported.

APPENDIX

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