# Diagnostic Strategies to Detect Glucose Intolerance in a Multiethnic Population

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**OBJECTIVE** — Identifying individuals who have elevated glucose concentrations is important for clinicians so that preventive strategies can be invoked, and it is useful for researchers who study associations between elevated glucose and adverse health outcomes. These methods should be applicable worldwide across different ethnic groups. Therefore, the objective of our analysis was to determine whether using the fasting glucose and $HbA_{1c}$ together could improve the classification of individuals with impaired glucose tolerance and diabetes in a multiethnic cohort randomly assembled in Canada.

**RESEARCH DESIGN AND METHODS** — We determined the optimum diagnostic criteria to identify people with abnormal glucose tolerance using fasting plasma glucose, 2-h post–glucose load plasma glucose, and $HbA_{1c}$ in 936 Canadians of South Asian, Chinese, and European descent.

**RESULTS** — The sensitivity of the American Diabetes Association (ADA) criteria to diagnose diabetes compared with the World Health Organization definitions was poor at 48.3% (95% confidence interval [CI] 35.7–61.0). Using a receiver operator characteristic curve, the optimum combined cut-point using fasting glucose and $HbA_{1c}$ to diagnose diabetes was a fasting glucose ≥5.7 mmol/l and an $HbA_{1c}$ ≥5.9%. These cut-points were associated with a sensitivity and specificity of 71.7% (60.3–83.1) and 95.0% (93.5–96.4), respectively, a positive likelihood ratio (LR) of 14.3 (9.6–19.0), and a negative LR of 0.3 (0.2–0.4). Significant ethnic variation in the sensitivity and specificity of this approach was observed: 47.4% (24.9–69.8) and 97.6% (95.9–99.4) among Europeans, 78.6% (57.1–100) and 95.9% (93.6–98.2) among Chinese, and 85.2% (71.8–98.6) and 91.3% (88.1–94.6) among South Asians, respectively. Participants with impaired glucose tolerance could not be identified reliably using the fasting glucose or $HbA_{1c}$ alone or in combination.

**CONCLUSIONS** — The sensitivity of the ADA criteria to diagnose diabetes is low, and there is substantial variation between ethnic groups. Fasting glucose and $HbA_{1c}$ may be used together to improve the identification of individuals who have diabetes, allowing clinicians to streamline the use of the oral glucose tolerance test.

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Individuals with diabetes have an increased risk of developing significant end-organ damage, such as retinopathy, cataracts, nephropathy, neuropathy, and cardiovascular disease (CVD) (1,2). Tight glucose control has been demonstrated to attenuate many of these complications in patients with both type 1 and type 2 diabetes. Individuals with dysglycemia (i.e., elevated glucose levels below the diabetic cut-offs) also have an increased risk of diabetes, CVD, and death (3,4). Although there are no proven pharmacological therapies indicated for this group, some are being evaluated, and diet and lifestyle changes such as weight loss and exercise are effective (5,6). Nevertheless, identifying individuals who have dysglycemia (from normal glucose tolerance to frank diabetes) is important for clinicians so that preventive strategies for the associated clinical consequences can be applied. This information is also necessary for researchers who study the epidemiological association between dysglycemia and adverse health outcomes.

Traditionally, the World Health Organization (WHO) criteria were used to classify nondiabetic people as having either normal or impaired glucose tolerance (IGT) (7). In 1997, an expert committee of the American Diabetes Association (ADA) recommended that glucose tolerance testing not be routinely done in either clinical practice or for epidemiological studies and that fasting glucose levels ≥7.0 mmol/l be used to classify an indi-

**Table 1—*Comparison of the 1998 WHO and 1997 ADA criteria for the diagnosis of abnormalities in glucose metabolism in 936 subjects***

| | WHO | | | |
|---|---|---|---|---|
| | Normal | IGT | DM | Total |
| ADA | | | | |
| Normal | 716 | 124 | 18 | 858 |
| IFG | 18 | 18 | 13 | 49 |
| DM | | | 29 | 29 |
| Total | 734 | 142 | 60 | 936 |

Data are *n*. IFG, impaired fasting glucose; DM, type 2 diabetes.

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**Abbreviations:** ADA, American Diabetes Association; CI, confidence interval; CV, coefficient of variation; CVD, cardiovascular disease; IGT, impaired glucose tolerance; LR, likelihood ratio; OGTT, oral glucose tolerance test; OR, odds ratio; ROC, receiver operator characteristic; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

**Table 2—*Sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of type 2 diabetes using a cut-off of fasting plasma glucose ≥5.7 mmol/l or $HbA_{1c}$ ≥5.9%***

| | Sensitivity | Specificity | PLR | NLR |
|---|---|---|---|---|
| FPG ≥5.7 mmol/l | | | | |
| Overall | 83.3 (73.9–92.8) | 88.0 (85.9–90.2) | 7.0 (5.5–8.4) | 0.2 (0.1–0.3) |
| South Asian | 92.6 (82.7–100) | 84.4 (80.2–88.6) | 5.9 (4.2–7.6) | 0.1 (0–0.1) |
| Chinese | 85.7 (67.4–100) | 91.5 (88.3–94.7) | 10.1 (5.7–14.4) | 0.2 (0–0.4) |
| European | 68.4 (47.5–89.3) | 88.1 (84.4–91.8) | 5.8 (3.3–8.3) | 0.4 (0.1–0.6) |
| $HbA_{1c}$ ≥5.9% | | | | |
| Overall | 75.0 (64.0–86.0) | 79.1 (76.4–81.8) | 3.6 (2.9–4.3) | 0.3 (0.2–0.5) |
| South Asian | 88.9 (77.0–100) | 70.8 (65.6–76.1) | 3.1 (2.4–3.7) | 0.2 (0–0.3) |
| Chinese | 85.7 (67.4–100) | 79.9 (75.3–84.5) | 4.3 (2.9–5.6) | 0.2 (0–0.4) |
| European | 47.4 (24.9–69.8) | 86.4 (82.5–90.3) | 3.5 (1.6–5.4) | 0.6 (0.4–0.9) |

Data are value (95% CI). FPG, fasting plasma glucose; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

vidual as diabetic (8). The ADA also defined a new diagnostic category called impaired fasting glucose when an individual's fasting glucose was 6.1–6.9 mmol/l. They acknowledged that their approach would lead to slightly lower estimates of prevalence of abnormal glycemic status when compared with the WHO criteria. Indeed, this has been observed in numerous reports indicating that use of the ADA criteria does not consistently classify people with abnormal glucose tolerance (9–14).

Neither the WHO criteria nor the ADA criteria use $HbA_{1c}$ in their diagnostic algorithms. $HbA_{1c}$ is a marker of long-term blood glucose control and is used clinically to inform physicians of an individual's glycemic control over the past 3 months (15). Although researchers have proposed using $HbA_{1c}$ to diagnose diabetes, the variability in the assays used throughout the world had previously precluded its validation for this purpose (16,17). The results of the National Glycohemoglobin Standardization Program (NGSP) have now made the measurement of $HbA_{1c}$ precise enough to allow its use in large population studies or clinical practice (18). We hypothesize that the combination of fasting glucose and $HbA_{1c}$ measurements will improve the classification of patients with glucose intolerance compared with using fasting glucose alone.

## RESEARCH DESIGN AND METHODS

— Between December 1996 and October 1998, individuals of South Asian, Chinese, and European origin were randomly recruited from three cities in Canada to undergo a cardiovascular health assessment (19). All participants were required to have fasted for at least 8 h. All nondiabetic participants had fasting glucose and $HbA_{1c}$ measurements taken, and the glucose measurement was repeated 2 h after ingestion of 75 g oral glucose. Immediately after being drawn, all samples were placed on ice and centrifuged and aliquots prepared within 1 h of collection. All serum and plasma aliquots were transferred on dry ice to the core laboratory in Hamilton, Canada, for central core laboratory analysis using standard methodology. Aliquots were frozen at −70°C, and all analyses were conducted within 3 days after arrival at the core lab. Blood for glucose measurement was gathered in serum separator tubes and measured using enzymatic methods with a hexokinase reference. The stated precision was a coefficient of variation (CV) <1% and observed precision was a CV <3.4%. $HbA_{1c}$ was collected in EDTA tubes and analyzed using a 765 Glycomat machine, which uses low-pressure cation exchange chromatography in conjunction with gradient elution to separate human hemoglobin subtypes (20,21). This method is associated with a CV <4%, and at the time of study set-up, this method was not certified by the NGSP. The 1998 WHO diagnostic criteria was used as the "gold standard" and participants were classified as *1*) normal: fasting glucose <7.0 mmol/l and a 2-h glucose <7.8 mmol/l; *2*) IGT: fasting glucose <7.0 mmol/l and a 2-h glucose (post–75 g glucose load) 7.8–11.0 mmol/l; or *3*) diabetic: a fasting glucose ≥7.0 or a 2-h (post–75 g glucose load) glucose ≥11.1 mmol/l. The 1997 ADA criteria were also applied to classify individuals as *1*) normal: fasting glucose <6.1 mmol/l; *2*) impaired fasting glucose: fasting glucose 6.1–6.9 mmol/l; or *3*) diabetic: fasting glucose ≥7.0 mmol/l.

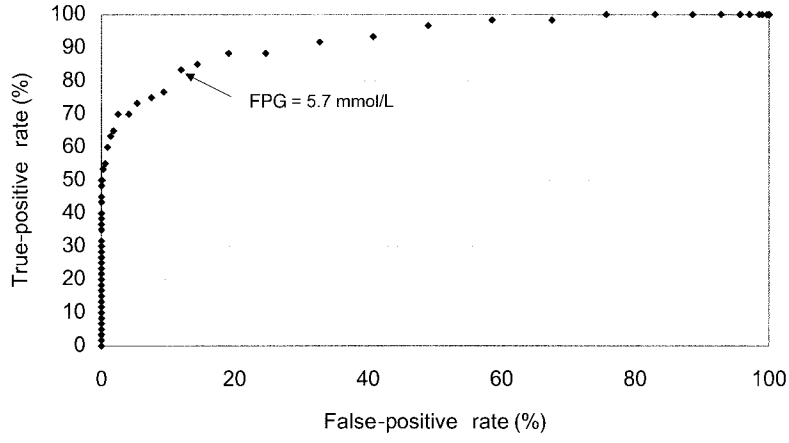


**Figure 1—*ROC for the diagnosis of type 2 diabetes using fasting plasma glucose (FPG). Area under the curve is 0.91 for FPG.***

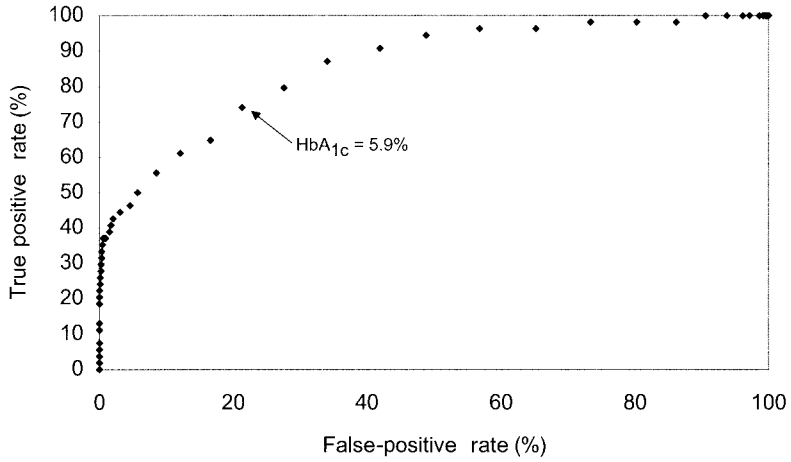


**Figure 2**—*ROC for the diagnosis of type 2 diabetes using $HbA_{1c}$. Area under the curve is 0.86 for $HbA_{1c}$.*

### Statistical methods

To determine the optimal fasting plasma glucose value for the diagnosis of diabetes, we calculated receiver operator characteristic (ROC) curves by plotting the sensitivity (true positive rate) of a range of fasting plasma glucose values versus the false positive rate (1 specificity). The ROC curve is a graphic means of assessing the ability of a screening test to discriminate between healthy and diseased people and allows precise determination of an optimal cut-point, which maximizes the true-positive rate and minimizes the false-positive rate (22). For each cut-point, positive and negative likelihood ratios were calculated. The positive likelihood is the ratio of true-positive rate to false-positive rate, and the negative likelihood ratio is the ratio of true-negative rate to false-negative rate. Unlike the positive and negative predictive values, likelihood ratios are not altered by changes in the prevalence of the target disorder, in this case diabetes, which occurs when the screening test is applied to heterogeneous populations (e.g., geographically or ethnically distinct groups). Likelihood ratios can also be used together with pretest probability estimates to generate the post-test probability of disease, thereby indicating by how much a given diagnostic test result can raise or lower the pretest probability of a disease. Likelihood ratios >1 increase the probability that the target disorder is present, and likelihood ratios <1 decrease the probability that the target disorder is present (23).

**Table 3**—*Ethnic variations in the ROC curve cut-points for the diagnosis of diabetes using fasting plasma glucose (FPG) or $HbA_{1c}$*

| | FPG (mmol/l) | $HbA_{1c}$ (%) |
|---|---|---|
| South Asian | 5.7 | 6.2 |
| Chinese | 5.6 | 6 |
| European | 5.5 | 5.6 |

## RESULTS

### Comparison of the ADA and WHO diagnostic criteria overall and between ethnic groups

Of the 985 participants who were recruited, 37 (3.8%) had established diabetes at entry and were excluded, and of the remaining 948 people, 936 had both fasting and 2-h plasma glucose samples measured. Of these, 315 were South Asian, 307 were Chinese, and 314 were European. Using the ADA criteria, 91.7% of subjects were classified as normal, 5.2% had impaired fasting glucose, and 3.1% had diabetes. Using the WHO criteria, only 78.4% were classified as normal, 15.2% had IGT, and 6.4% had diabetes (Table 1).

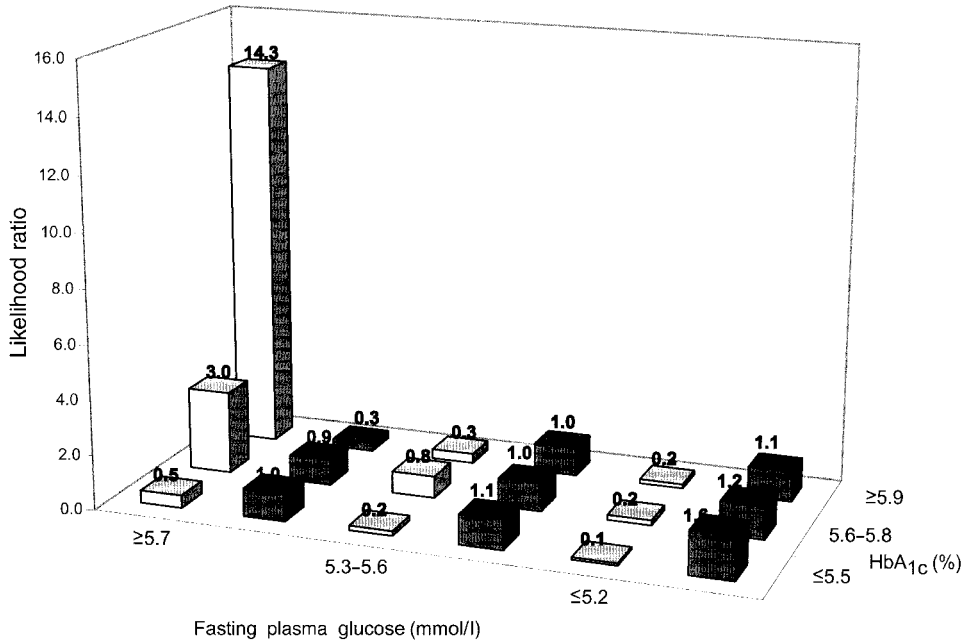


**Figure 3**—*Likelihood ratios for type 2 diabetes using fasting plasma glucose and $HbA_{1c}$. □, positive likelihood; ■, negative likelihood.*

**Table 4—*Sensitivity, specificity, positive likelihood, and negative likelihood of type 2 diabetes using the dual cut-off of fasting plasma glucose ≥5.7 mmol/l and $HbA_{1c}$ ≥5.9%***

| | Sensitivity | Specificity | PLR | NLR |
|---|---|---|---|---|
| Overall | 71.7 (60.3–83.1) | 95.0 (93.5–96.4) | 14.3 (9.6–19.0) | 0.3 (0.2–0.4) |
| South Asian | 85.2 (71.8–98.6) | 91.3 (88.1–94.6) | 9.8 (5.8–13.8) | 0.2 (0–0.3) |
| Chinese | 78.6 (57.1–100) | 95.9 (93.6–98.2) | 19.2 (7.3–31.0) | 0.2 (0–0.5) |
| European | 47.4 (24.9–69.8) | 97.6 (95.9–99.4) | 20.0 (2.6–37.4) | 0.5 (0.3–0.8) |

Data are value (95% CI). PLR, positive likelihood ratio; NLR, negative likelihood ratio.

A substantial proportion (14.5%) of the individuals who were classified as "normal" by the ADA criteria had IGT, and 2.1% had diabetes. Conversely, of those classified as normal by the WHO criteria, only 2.5% had impaired fasting glucose. The sensitivity of the ADA criteria to diagnose diabetes using the WHO criteria as the gold standard was 48.3% (95% CI 35.7–61.0) overall and was 31.6% (10.7–52.5) among Europeans, 28.6% (4.9–52.2) among Chinese, and 70.4% (53.1–87.6) among South Asians.

### Fasting plasma glucose and $HbA_{1c}$ to diagnose diabetes

By constructing an ROC curve, the optimum cut-point using fasting plasma glucose to diagnose diabetes was 5.7 mmol/l. This was associated with a sensitivity and specificity of 83.3 and 88.0%, respectively, a positive LR of 7.0 (95% CI: 5.5–8.4), and a negative LR of 0.2 (0.1–0.3) (Table 2, Fig. 1). The diagnostic ability varied substantially between ethnic groups, although using a 5.7 mmol/l cut-point significantly improved the sensitivity and slightly lowered the specificity of the fasting glucose to diagnose diabetes (Table 2). Using an ROC curve, the optimal cut-off for $HbA_{1c}$ of 5.9% was associated with a specificity and sensitivity of 75.0 and 79.1%, respectively, for diabetes overall, with substantial variation between ethnic groups. (Table 2, Fig. 2).

Using ROC curve analysis, the cut-points for fasting glucose or $HbA_{1c}$ to diagnose diabetes in each ethnic group were determined, and substantial variation was observed (Table 3)

To improve the diagnostic precision for diabetes, a combination of the optimal fasting glucose and $HbA_{1c}$ values was identified. The paired dual optimal cut-point for fasting glucose and $HbA_{1c}$ was obtained by multiple ROC analysis (24). The combined optimal cut-off occurs when a subject simultaneously has a fasting glucose ≥5.7 mmol/l and an $HbA_{1c}$ ≥5.9%, identical to the pairing of the single optimal cut-offs obtained for each marker independently. The highest probability of diabetes was found among people who had a fasting glucose ≥5.7 mmol/l and an $HbA_{1c}$ ≥5.9%. This was associated with a sensitivity of 71.7%, a specificity of 95.0% overall, a positive LR of 14.3 (95% CI 9.6–19.0), and a negative LR of 0.3 (0.2–0.4). Using this cut-point, the sensitivity of this method was highest among South Asians and lowest among European-origin Canadians (Fig. 3, Table 4).

### Fasting plasma glucose and $HbA_{1c}$ to diagnose IGT

A similar procedure was used to identify the optimal cut-point for the determination of IGT using both fasting glucose and $HbA_{1c}$ independently and in combination. However, cut-points were not easy to identify, and a fasting plasma glucose cut-point ≥5.3 mmol/l was associated with a false-positive rate of 32.4% (95% CI 29.1–35.7%) (Fig. 4). A nearly linear ROC curve for IGT was observed. This indicates that for every increase in test sensitivity there is a nearly equal increase in false-positive rate (or a proportional decrease in specificity). For $HbA_{1c}$, a cut-point ≥5.6% was also associated with a high false-positive rate of 42% (38.5–45.4%) (Fig. 5).

The combination of fasting plasma glucose and $HbA_{1c}$ did not improve the precision of classifying people with IGT (Fig. 6).

### Potential use of the fasting plasma glucose and $HbA_{1c}$

Applying the dual cut-point of fasting glucose ≥5.7 mmol/l and $HbA_{1c}$ ≥5.9% in our study cohort, 9.8% (95% CI 8.7–9.9) of people would be classified as diabetic and would not require an oral glucose tolerance test (OGTT). $HbA_{1c}$ was found to correlate with stages of glucose tolerance as defined by the WHO. Subjects classified as normal had a mean $HbA_{1c}$ of 5.4%, as IGT had a mean $HbA_{1c}$ of 5.7%, and as type 2 diabetic had a mean $HbA_{1c}$ of

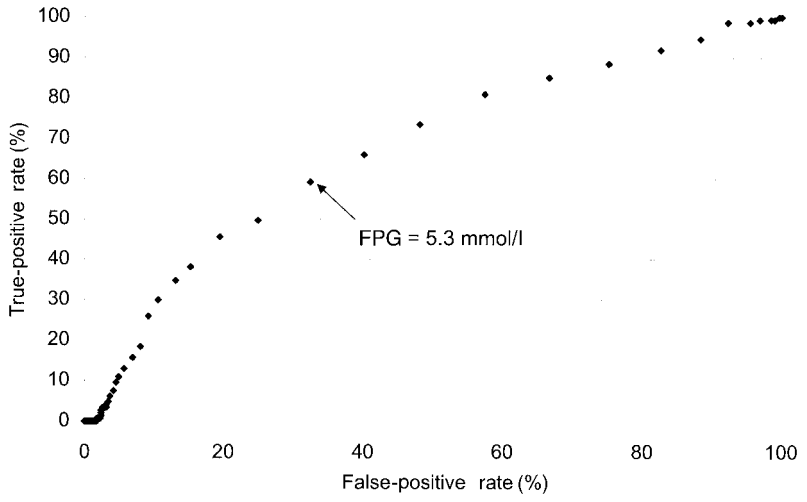


**Figure 4—*ROC for the diagnosis of IGT using fasting plasma glucose (FPG). Area under the curve is 0.77 for FPG.***

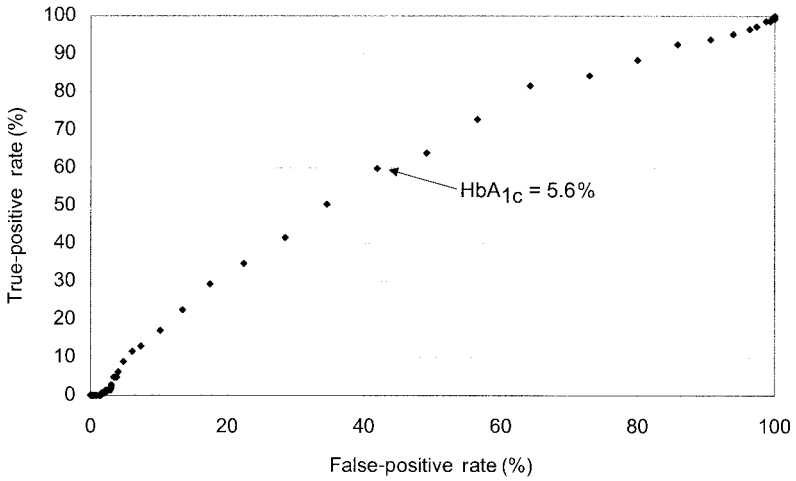


**Figure 5—***ROC for the diagnosis of IGT using $HbA_{1c}$. Area under the curve is 0.67 for $HbA_{1c}$.*

7.0%, and these differences were significant at $P < 0.001$ (Table 5).

## CONCLUSIONS

### Clinical implications

The ADA cut-point of a fasting plasma glucose ≥7.0 mmol/l to diagnose diabetes is not sensitive and results in an unacceptably high number of false negatives. Therefore, relying on a fasting glucose alone to exclude diabetes will falsely reassure approximately one-fifth of the general population that they do not have diabetes or IGT, when they in fact suffer an important abnormality in their glucose metabolism. This is consistent with the observations of other comparisons of the ADA to WHO criteria. For example, the 10 most recent studies we identified in which the ADA criteria were compared with other criteria, the sensitivity ranged from as low as 31% in a an obese French population to as high as 79% in Canarian Caucasians (13,14,25–32) (Table 6). We identified two cut-off values (fasting plasma glucose ≥5.7 mmol/l and an $HbA_{1c}$ ≥5.9%) that minimize the number of false positives and false negatives. The corresponding likelihood ratios for these cut-points may be used together with the patient's pretest probability of diabetes to generate a post-test probability of diabetes. The advantage of using likelihood ratios is their stability in the face of changing disease prevalence, which is important to consider given the tremendous variation in the prevalence of diabetes observed among people of various ethnic origin. Fasting glucose and $HbA_{1c}$ measurements in combination and the accompanying likelihood ratios improve the diagnostic classification of people as being at low risk for having diabetes versus moderate to high risk for having diabetes and therefore allow for the selective use of the OGTT. Unfortunately, neither fasting glucose nor $HbA_{1c}$ alone or in combination can reliably classify which people have IGT, and if classification of this state is desired for clinical or epidemiological purposes, an OGTT test remains necessary.

**Table 5—*Mean $HbA_{1c}$ by WHO category***

| WHO category | Mean $HbA_{1c}$ (%) |
|---|---|
| Normal | 5.4 (5.4–5.5) |
| IGT | 5.7 (5.6–5.8) |
| Type 2 diabetes | 7.0 (6.6–7.5) |

Data are value (95% CI). Overall and all pair-wise comparisons were significant at $P < 0.001$ by Tukey's honestly significant difference (HSD).

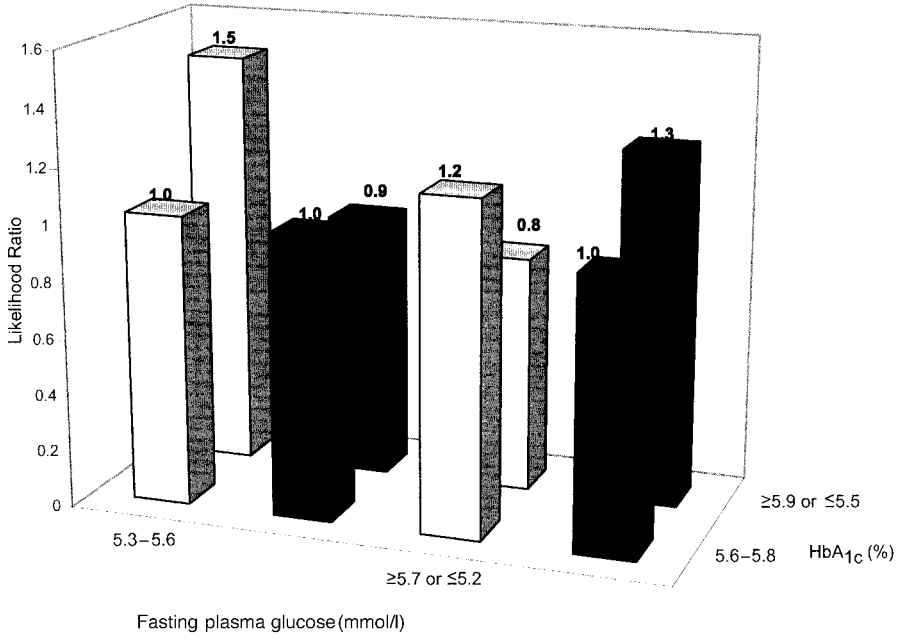


**Figure 6—***Likelihood ratios of IGT using $HbA_{1c}$ and fasting plasma glucose (excluding type 2 diabetes by ADA criteria). □, positive likelihood; ■, negative likelihood.*

### Ethnic variations

When comparing ethnic groups, the sensitivity of the ADA criteria versus the WHO standard to diagnose type 2 diabetes was highest among people of South Asian origin and lowest among people of European origin. The difference in the ROC curve cut-point between South Asians and Europeans is especially large for $HbA_{1c}$ (6.2 vs. 5.6%, Table 3), which is consistent with the large body of evidence that demonstrates that people of South Asian origin have a greater burden of glucose intolerance than Europeans (33,34). Given the differences in the sensitivity and specificity (and hence positive and negative predictive values) of the fasting glucose and $HbA_{1c}$ to diagnose diabetes between ethnic groups, using likelihood ratios can help clinicians more reliably estimate the post-test probability of diabetes. The pretest estimation of diabetes should be influenced by knowledge that diabetes is more prevalent in certain ethnic groups. In our study population

**Table 6—*Recent studies of the sensitivity of the 1997 ADA criteria for the diagnosis of diabetes***

| Sensitivity | Criteria for diabetes | Population | Author(s)[ref. no.] | Publication date |
|---|---|---|---|---|
| 0.31 | WHO 1985 | Obese (BMI ≥30) general French population | Richard JL, et al.[27] | April 2002 |
| 0.34 | WHO 1998 | Elderly (71–93 years old) Japanese-American men | Rodriguez BL, et al.[13] | June 2002 |
| 0.52 | WHO 1998 | General Australian population | Hilton DJ, et al.[14] | February 2002 |
| 0.52 | WHO 1985 | Urban South Indian | Deepa R, et al.[32] | December 2000 |
| 0.53 | WHO 1998 | Caucasian | Melchionda N, et al.[29] | January 2002 |
| 0.55 | WHO 1998 | Elderly (70–79 years old) African-American and Caucasian | Resnick HE, et al.[30] | September 2001 |
| 0.57 | OGTT alone | Ghanaian | Amoah AG[26] | April 2002 |
| 0.71 | WHO 1998 | Singaporean | Chen YT, et al.[28] | March 2002 |
| 0.78 | WHO 1998 | Caucasian | Herdzik E, et al.[25] | April 2002 |
| 0.79 | OGTT alone | Canarian Caucasian | De Pablos-Velasco PL, et al.[31] | March 2001 |

Criteria for diabetes: WHO 1985 (fasting glucose ≥7.8 mmol/l or 2-h glucose ≥11.1 mmol/l); WHO 1998 (fasting glucose ≥7.0 mmol/l or 2-h glucose ≥11.1 mmol/l); OGTT alone (2-h glucose ≥11.1 mmol/l).

the odds ratios (ORs) for diabetes included South Asian ethnicity OR 1.87 (95% CI 1.3–2.6), age per year 1.05 (1.0–1.1), BMI ≥30 2.75 (1.73–4.35), abdominal obesity (WHR ≥0.85) 3.17 (1.9–5.2), HDL cholesterol (<0.9 mmol/l) 2.58 (1.54–4.32), and elevated triglycerides (>2.26 mmol/l) 4.15 (3.0–5.8) (34).

## Epidemiological implications

Based on our results and the results of other investigators (13,14), using a fasting glucose measurement alone inconsistently identifies people who have an abnormal 2-h glucose concentration after an oral glucose challenge. On the other hand, $HbA_{1c}$, which can be taken in the non–fasting state, as we have shown, correlates with the stages of glucose tolerance as defined by WHO criteria. Therefore, the $HbA_{1c}$ is a useful and potentially more feasible method of classifying individuals with glucose intolerance than the OGTT in epidemiological studies.

The principal message from this report is that the potential gain in specificity using only a fasting glucose measurement to diagnose diabetes, while eliminating false positives, is associated with a large number of "false-negative" results. Furthermore, our study population included a large representation of people of Chinese and South Asian origin, people who have repeatedly been observed to develop glucose intolerance upon adoption of Western lifestyles (35,36). Therefore, the application of a uniform set of fasting glucose cut-points is associated with a large variation in the confidence with which we can exclude the presence of diabetes in these groups. Therefore, using a lower fasting plasma glucose cut-off together with the $HbA_{1c}$ decreases the chance of falsely excluding people who have diabetes and leads to a more selective use of the OGTT, a test that is associated with unnecessary cost and inconvenience for patients.

In conclusion, the sensitivity of the ADA criteria to diagnose diabetes is low, and there is substantial variation between ethnic groups. However, use of fasting glucose and $HbA_{1c}$ together, compared with using fasting glucose alone, reduces the number of people who are falsely classified as having normal glucose tolerance. To identify people with IGT, the OGTT remains necessary.

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