Moving to an HbA$_{1c}$ based diagnosis of diabetes has a different impact on prevalence in different ethnic groups

Running title: Diabetes prevalence and diagnostic tools

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Objective: To compare screen detected diabetes prevalence and the degree of diagnostic agreement by ethnicity with the current OGTT-based and newly proposed HbA$_{1c}$-based diagnostic criteria.

Research design and methods: Six studies (1999-2009) from Denmark, United Kingdom, Australia, Greenland, Kenya, and India were tested for the probability of an HbA$_{1c}$ ≥ 6.5% among diabetes cases based on an OGTT. The difference in probability between centers was analyzed by logistic regression adjusting for relevant confounders.

Results: Diabetes prevalence was lower with the HbA$_{1c}$-based diagnostic criteria in four out of six studies. The probability of an HbA$_{1c}$ ≥ 6.5% among OGTT-diagnosed cases ranged widely (17.0 to 78.0%) by study center. Differences in diagnostic agreement between ethnic sub-groups in the United Kingdom study were of the same magnitude as between-country comparisons.

Conclusions: A shift to an HbA$_{1c}$-based diagnosis for diabetes will have substantially different consequences for diabetes prevalence across ethnic groups and populations.

Recently an International Expert Committee report recommended a shift in the diagnostic tool for diabetes from the 75-g oral glucose tolerance test (OGTT) to HbA$_{1c}$ (1), thereby proposing replacement of the current World Health Organization (WHO) criteria (2). More specifically, an HbA$_{1c}$ threshold of greater or equal to 6.5% was recommended, as this value has been shown to be strongly related to retinopathy (1). In their report, the International Expert Committee emphasizes that it is premature to establish separate diagnostic thresholds based on race/ethnicity, and that the new diagnostic criterion is likely to identify different individuals than those identified by the WHO criteria (1). Previous studies have shown HbA$_{1c}$ levels in individuals with impaired glucose tolerance or diabetes to differ by race and ethnicity (3-5). We aimed to compare diabetes prevalence and the degree of diagnostic agreement between the OGTT and HbA$_{1c}$ based definitions by race/ethnicity in six different countries. Below, the term diabetes is referring to diabetes assessed by one OGTT or one HbA$_{1c}$ at screening.

RESEARCH DESIGN AND METHODS
Six studies including populations from different ethnic origins were included in the analysis (6-11). Populations from Denmark (Inter99), the United Kingdom (Whitehall II, Phase 7), Australia (The Australian Diabetes, Obesity and Lifestyle Study: AusDiab), Greenland (Inuit Health in Transition), Kenya and India (Chennai Urban Rural Epidemiology Study: CURES) were included.

Data were collected during the period 1999-2009. Participants were excluded if they had missing OGTT or HbA$_{1c}$ measurements or known diabetes (self-reported). In the Inter99 study, 5.6% were not of Danish nationality and were excluded from the analyses. In Whitehall II, Whites were included in the main analysis, whereas South Asian (4.2%) and Black (1.9%) participants were analyzed in a subsidiary analysis. In the AusDiab study, only individuals born in Australia or New Zealand who spoke English at home and were not of Aboriginal/Torres Strait Islander origin were included (76.2%). In the Inuit Health in Transition study, only Inuit participants were included in the analysis (95.5%). The participants in the study from Kenya were all Black and participants in the CURES study were all of Indian origin. A total of 23,094 participants were included in this analysis.

Participants were categorized into four groups based on their OGTT results (diabetes or no diabetes) and HbA$_{1c}$ levels (< 6.5% or ≥ 6.5%). Exact 95% confidence intervals were calculated for proportions (12). The probability of an HbA$_{1c}$ ≥ 6.5% among diabetes cases based on an OGTT was calculated. This probability is effectively the sensitivity of an HbA$_{1c}$ cut-point of 6.5% with the WHO criteria as gold standard. The magnitude of the difference in probability between centers was analyzed using logistic regression analysis adjusted for relevant confounders (age, gender, BMI, waist circumference (WC) and smoking). HbA$_{1c}$ assays were aligned to the Diabetes Control and Complications Trial assay at each study centre according to local laboratory guidelines (assay details in Online Appendix at http://care.diabetesjournals.org).

RESULTS
The prevalence of diabetes was lower in four out of the six studies (Whitehall II, AusDiab, Inuit Health in Transition, Kenya) with the HbA$_{1c}$ diagnostic criterion than with the OGTT, (Table 1). The probability of a person having an HbA$_{1c}$ ≥ 6.5% given the presence of diabetes according to the OGTT differed by study center (range 17.0-78.0%). Overall, the magnitude of this difference between

centers was independent of differences in age and gender distributions. Further adjustment for BMI, WC and smoking reduced the magnitude of the difference between some centers, but the overall difference remained significant (p<0.0001). Pair-wise comparisons between centers on this difference in probability were significant. Exceptions were the contrasts between Whitehall II and Greenland, and the comparisons between Kenya on the one hand and Inter99, Whitehall II, AusDiab and Greenland on the other. These results did not change when adjusting for age, gender, BMI, WC and smoking.

We also performed a subsidiary analysis on the South Asian (N=204) and Black (N=91) minority groups in the Whitehall II study. The differences in agreement between the two diagnostic criteria for diabetes between these ethnic sub-groups within Whitehall matched those observed between populations in the main analysis (Online Appendix). Disregarding differences in study size, the overall prevalence of diabetes was 18% lower with an HbA_{1c}-based diagnostic test for diabetes. The corresponding probability of $HbA_{1c} \geq 6.5\%$ among diabetes cases based on an OGTT was 43.5%.

CONCLUSIONS

The diabetes prevalence was more likely to be lower than higher when replacing the OGTT diagnostic criteria with HbA_{1c}. The rate was 63% higher in the Inter99 study while it was 82% lower in the AusDiab study. These differences are quite substantial, and may in part be due to methodological differences.

There was also a significant discrepancy in the magnitude of the OGTT and HbA_{1c} diabetes diagnosis overlap between study populations of different ethnic origins, even after adjusting for age, gender, BMI, WC, and smoking. However, the differences between the White populations of Inter99, Whitehall II and AusDiab were also significant and of the same magnitude suggesting that part of the discrepancy in overlap can be ascribed to difference in study methodology such as the HbA_{1c} assay method. On the other hand, the subsidiary analysis of the South Asian and Black minorities compared to the White majority group of Whitehall II indicates that discrepancies are at least partly due to ethnic differences.

The lack of a significant difference in the pair-wise comparisons between the Kenyan population and four of the five other studies does not rule out a true difference in the probability of $HbA_{1c} \geq 6.5\%$ among OGTT diagnosed diabetes cases but may be due to the limited number of individuals in the Kenya data.

Although we cannot dismiss the possibility that part of the observed diagnostic inconsistency is due to methodological differences between studies, we can conclude that the proposed shift to HbA_{1c} as the diagnostic tool for diabetes is likely to have a substantially different impact on diabetes prevalence in different populations, partly due to differences in race/ethnicity. However, future analyses on ethnic differences between studies using the same methodology are needed.

Conflict of interest: Borch-Johnsen is head of the Steno Diabetes Center, a hospital integrated in the Danish National Health Care Service, but owned by Novo Nordisk. Borch-Johnsen holds shares in Novo Nordisk Inc. Knut Borch-Johnsen and Jonathan Shaw were on the Expert Committee which published the new diagnostic recommendations. The remaining authors have no relevant conflict of interest to declare.

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Table 1 Background characteristics and diabetes prevalence by OGTT and HbA$_{1c}$ diagnostic criteria in different ethnic groups

	Denmark Inter99	UK Whitehall II (Phase 7)	Australia AusDiab	Greenland Inuit Health in Transition	Kenya	India CURES
Study period	1999-2001	2002-2004	1999-2000	2005-2009	2005-2006	2001-2004
N	5932	4563	7800	2321	296	2182
Age	46.2 (7.9)	60.5 (5.9)	50.9 (14.4)	44.1 (14.6)	37.6 (10.6)	38.8 (12.6)
Males (%)	49.7 (48.4;51.0)	73.9 (72.6;75.2)	44.4 (43.3;45.5)	43.4 (41.4;45.5)	44.6 (38.8;50.5)	46.0 (43.9;48.1)
BMI (kg/m2)	26.2 (4.5)	26.5 (4.2)	26.9 (4.9)	26.4 (5.1)	22.1 (4.6)	23.0 (4.0)
Waist circumference (cm)	86.5 (13.2)	93.2 (12.0)	90.6 (13.8)	91.9 (13.3)	79.9 (12.2)	83.0 (11.4)
Current smoker (%)	36.0 (34.8;37.2)	6.8 (6.1;7.6)	16.3 (15.5;17.2)	66.1 (64.1;68.0)	10.5 (7.3;14.6)	18.6 (17.0;20.3)
FPG (mmol/l)	5.5 (0.8)	5.3 (0.7)	5.4 (0.7)	5.7 (0.8)	4.5 (0.9)	5.1 (1.7)
2hPG (mmol/l)	6.2 (2.1)	6.5 (2.0)	6.2 (2.2)	5.9 (2.4)	5.6 (1.7)	7.0 (3.5)
HbA$_{1c}$ (%)	5.8 (0.5)	5.2 (0.5)	5.1 (0.4)	5.7 (0.4)	5.0 (0.6)	5.9 (1.2)
DM by OGTT (%)	4.2 (3.7;4.8)	3.7 (3.2;4.3)	4.0 (3.6;4.4)	7.0 (6.0;8.1)	3.4 (1.6;6.1)	10.2 (9.0;11.6)
DM by HbA$_{1c}$ (%)	6.7 (6.1;7.3)	1.0 (0.7;1.3)	0.7 (0.5;0.9)	3.9 (3.1;4.7)	1.4 (0.4;3.4)	12.9 (11.5;14.4)
HbA$_{1c}$ ≥ 6.5% given DM by OGTT (%)	42.6 (36.4;49)	25.0 (18.7;32.3)	17.0 (13.0;21.7)	29.6 (22.7;37.3)	20.0 (2.5;55.6)	78.0 (72.0;83.3)
DM by OGTT given HbA$_{1c}$ ≥ 6.5% (%)	27.0 (22.7;31.7)	91.3 (79.2;97.6)	98.1 (90.1;100)	53.3 (42.5;63.9)	50.0 (6.8;93.2)	61.9 (56.0;67.6)

Data are means (SD) and proportions (95%-CI). FPG: fasting plasma glucose. 2hPG: 2-hour plasma glucose. DM: diabetes
DM by OGTT: FPG ≥ 7.0 mmol/l or 2hPG ≥ 11.1 mmol/l. DM by HbA$_{1c}$: HbA$_{1c}$ ≥ 6.5%