Prevalence of Prediabetes and Undiagnosed Diabetes in Canada (2007–2011) According to Fasting Plasma Glucose and HbA_{1c} Screening Criteria

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OBJECTIVE

To provide the first population-based estimates of prediabetes and undiagnosed type 2 diabetes prevalence in Canada.

RESEARCH DESIGN AND METHODS

We combined two fasting subsamples of the Canadian Health Measures Survey, which were restricted to nonpregnant adults ≥20 years of age (*N* = 3,494). Undiagnosed diabetes was defined as not having self-reported type 2 diabetes but having blood glucose measures that met Canadian guidelines (i.e., fasting plasma glucose [FPG] level of ≥7.0 mmol/L or hemoglobin A_{1c} [HbA_{1c}] level of ≥6.5% [≥48 mmol/mol]). Prediabetes was defined as an FPG level of ≥6.1 and <7.0 mmol/L or an HbA_{1c} level of ≥6.0% and <6.5% (≥42 and <48 mmol/mol). All estimates were weighted using survey sampling weights. CIs were calculated with the bootstrap method.

RESULTS

According to FPG levels, the prevalence of undiagnosed type 2 diabetes in Canadian adults was 1.13% (95% CI 0.79, 1.62), contributing to ∼20% of total type 2 diabetes prevalence (5.62 [95% CI 4.52, 6.95]). Compared with FPG levels, the undiagnosed prevalence was greater using HbA_{1c} level as a criterion (3.09% [95% CI 1.97, 4.81]), ∼41% of the total number of cases of diabetes (7.55 [95% CI 5.98, 9.49]). The HbA_{1c}-only criterion resulted in a threefold increase in prediabetes prevalence overall and a sixfold increase among females (FPG 2.22%, HbA_{1c} 13.31%). Screening based on FPG only identified older undiagnosed case patients, with a mean age of 58.7 years (95% CI 59.9, 63.4). Similarly, using HbA_{1c} identified younger individuals with prediabetes, with reduced BMI and waist circumference compared with FPG levels.

CONCLUSIONS

In this first study of a nationally representative sample with biospecimen measures, we found that the prevalence of undiagnosed type 2 diabetes and prediabetes was significantly higher using HbA_{1c} levels compared with FPG levels. Further evaluation is needed to fully assess the impact of using the HbA_{1c} criterion.

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Type 2 diabetes is one of the most prevalent chronic conditions in Canada. It is estimated that approximately one in four Canadians are living with type 2 diabetes, either diagnosed or undiagnosed, or its precursor, which is known as prediabetes; this number is expected to rise to one in three by 2020 (1). The excess costs due to diabetes are large, resulting in a substantial burden on the health care system, largely the result of serious microvascular and macrovascular complications (e.g., blindness, cardiovascular disease, myocardial infarction, and stroke) (2,3). The total costs of diabetes, both direct and indirect, were estimated at $2.4 billion in 2010 (1). The financial burdens associated with type 2 diabetes in Canada are expected to continue rising and are projected to reach $3.8 billion by 2020 (1).

In order to minimize the risk of these complications and associated health care costs, the early detection and management of diabetes and prediabetes is imperative (4–11). Further, diabetes has an asymptomatic preclinical phase, which may last more than a decade (4–7,12–15); however, at the time of diagnosis, diabetic microvascular complications have already developed in as many as 20–30% of patients (3–7). Undiagnosed diabetes, therefore, is neither a benign nor a quiescent state, but represents a serious clinical and public health concern. Treating hyperglycemia to prevent complications would be preferable to and more effective than treating these complications after they arise. Indeed, results from the Diabetes Control and Complications Trial (8) have shown that diabetic microvascular complications were more greatly reduced among patients with no evidence of complications at baseline compared with those in whom complications had already developed.

From a population health perspective, reliable surveillance data are crucial for the identification, surveillance, and characterization of high-risk populations, which is necessary for the planning of interventions and assessing the effectiveness of diabetes prevention strategies (4). The Diabetes Population Risk Tool (DPoRT) (16) is one example of how diabetes surveillance data are used to inform policies and interventions focused on diabetes prevention; it was developed and validated to estimate the 10-year incidence of type 2 diabetes using routinely collected self-reported survey data to forecast the future risk and number of incident cases at the regional, provincial, and national level (16).

The burden of undiagnosed diabetes received considerable attention in the early 2000s after a change in diagnostic cutoff points for fasting plasma glucose (FPG) levels, which were lowered from ≥7.8 to ≥7.0 mmol/L (11). Changes in diagnostic and screening criteria may have important ramifications on the number and characteristics of patients in whom diabetes is diagnosed, on the populations identified as being at high risk for diabetes, and, subsequently, on population prevalence estimates and allocation of resources. For example, the new FPG criterion was found to increase the prevalence of undiagnosed diabetes in Canada by as much as 50% (4). Given recent additions to diagnostic guidelines (16) to include hemoglobin A_{1c} (HbA_{1c}) levels, assessing the hidden burden of undiagnosed diabetes has again become particularly important. Where the measurement of FPG level is relatively simple and inexpensive to perform, HbA_{1c} measurement is a more convenient diagnostic technique that does not require the patient to fast and displays less day-to-day variability (14,17–25). HbA_{1c} measurement is also attractive for opportunistic screening as it can be performed at any time of the day without prior fasting. However, research has been inconsistent as to which test performs better and the utility of each as a screening technique. Currently, estimates of type 2 diabetes, including undiagnosed and total type 2 diabetes, and prediabetes in Canada based on the recently revised HbA_{1c} diagnostic criterion are lacking. It is not known whether and how the demographic and anthropometric characteristics identified according to these various diagnostic criteria differ. Further, there is little evidence on how these changes to screening/diagnostic criteria will affect the predictive ability of risk screening tools.

Until recently, it was not possible to accurately estimate the proportion of Canadians with undiagnosed diabetes given the lack of representative population health data with physical or laboratory measures. The Canadian Health Measures Survey (CHMS) (26) is a recently initiated population-based survey with physical and laboratory data, including FPG and HbA_{1c} measures. The primary objective of this study was to use this new representative data source to provide population-based estimates of the prevalence of prediabetes, undiagnosed diabetes, and total diabetes (undiagnosed plus diagnosed diabetes) in Canada, and to compare and contrast these estimates under different clinical diagnostic guidelines. Our secondary objective was to examine the impact of new diagnostic criteria on population diabetes risk tools, such as DPoRT, by assessing their predictive ability under various diagnostic guidelines.

RESEARCH DESIGN AND METHODS

Data Sources

We used cross-sectional data from two cycles of the CHMS conducted in 2007–2009 (Cycle 1) and 2009–2011 (Cycle 2). The CHMS has been described in detail elsewhere (26). Briefly, the CHMS is a nationally representative health survey, which uses a complex sampling design to survey Canadians aged 3–79 years (Cycle 1 sampled Canadians aged 6–79 years) who were living in private dwellings, but excludes Canadians living in reserves or on Crown lands, residing within institutions, those from certain remote geographical regions, and full-time members of the Canadian Forces (26). In addition to collecting self-reported health data through household interviews, the CHMS also collects physical and biospecimen measures using a mobile examination center (26). High response rates were demonstrated for both Cycle 1 (88% and 85%, respectively, for the household and mobile clinic components) and Cycle 2 (90% and 82%, respectively) (26).

Analytical Sample

For the purposes of this study, we restricted our sample to nonpregnant adults who were ≥20 years of age, provided a blood sample, and had fasted for a minimum of 10 h, a group that is referred to as the "fasted subsample." At the national level, the response rates for the fasting subsample were 46.3% and 48.4%, respectively, for Cycles 1 and 2. We then combined the fasting subsamples for Cycles 1 and 2 to create a combined fasting subsample

for the years 2007–2011. We further excluded any participant for whom neither HbA_{1c} nor FPG measures were obtained, individuals not eligible for phlebotomy, and participants who did not respond to the survey questions pertaining to self-reported type 2 diabetes diagnosis or type of diabetes diagnosis. Individuals were asked to provide the Drug Identification Number for all prescription medications they were taking; from this, we identified all respondents who took a prescription medication for diabetes in the month before the clinic visit using the Anatomical Therapeutic Chemical classification system code A10 for "Drugs used in diabetes." Any individual who reported taking diabetes medication but did not report having diabetes was excluded.

Outcomes

Undiagnosed diabetes was defined as not having self-reported type 2 diabetes, but having blood glucose measures that met current Canadian diagnostic guidelines for type 2 diabetes. Among individuals who reported physician-diagnosed diabetes, the following three criteria were used to calculate diabetes prevalence: *1*) FPG level ≥7.0 mmol/L (11); *2*) HbA_{1c} level ≥6.5% (or equivalently ≥48 mmol/mol) (17); and *3*) either an FPG level of ≥7.0 mmol/L or an HbA_{1c} level of ≥6.5% (or equivalently ≥48 mmol/mol). Total diabetes prevalence was calculated as the combined prevalence of self-reported physician-diagnosed diabetes and undiagnosed diabetes, with the latter being dependent upon diagnostic criteria. Prediabetes was defined as having abnormal glucose levels that were not sufficient to meet the criteria for diabetes diagnosis, e.g., FPG level ≥6.1 but <7.0 mmol/L, HbA_{1c} level ≥6.0% but <6.5% (or equivalently ≥42 but <48 mmol/mol), or an FPG level between 6.1 and 7.0 mmol/L or an HbA_{1c} between 6.0% and 6.5% (≥42 and <48 mmol/mol) (17). Given the lack of comparative data in Canada, particularly regarding HbA_{1c}-based estimates of prediabetes prevalence, we additionally defined prediabetes according to the lower American Diabetes Association (ADA) cut point guidelines, i.e., FPG 5.6–6.9 mmol/L and HbA_{1c} 5.7–6.4% (or 39–48 mmol/mol) (11), so that we could compare any potential differences between criteria to those observed in other countries, such as the U.S.

Statistical Analysis

We estimated the sex-specific prevalence of total diabetes, undiagnosed diabetes, and prediabetes according to FPG-only, HbA_{1c}-only, or the combined FPG-or-HbA_{1c} diagnostic criteria. The total prevalence of type 2 diabetes was calculated by combining the sex-specific prevalence of self-reported diagnosis and sex-specific estimates of undiagnosed diabetes prevalence. We estimated the sex-specific proportion of total type 2 diabetes cases that were undiagnosed by examining the prevalence of the current undiagnosed diabetes among total diabetes prevalence (self-reported or undiagnosed diabetes). Because of the small number of individuals who met the criteria of undiagnosed diabetes, we restricted our analysis to differences in means for age, measured BMI, measured waist circumference (WC), and diabetes risk (as measured by DPoRT). We were unable to further stratify by age, BMI, or WC, or to investigate differences in other variables of interest, such as ethnicity or geographic region.

We further explored how different diagnostic criteria impacted the predictive ability of DPoRT, which uses various self-reported sociodemographic and behavior variables to generate 10-year sex-specific population estimates of physician-diagnosed diabetes. This risk tool has been validated for use within the Canadian population, and has demonstrated excellent calibration and good discrimination for predicting physician-diagnosed type 2 diabetes (16). We examined the diabetes risk across each definition of undiagnosed diabetes and prediabetes. Using logistic regression, we quantified the ability of DPoRT to identify undiagnosed diabetes and prediabetes considering "FPG-only," "HbA_{1c}-only," or "FPG-or-HbA_{1c}" diagnostic criteria. This was assessed with the use of the concordance statistic (C-statistic), where a measure of ≥0.7 suggests a model that discriminates reasonably between those individuals with and without the condition of interest, and the Hosmer-Lemeshow goodness-of-fit χ^2 statistic (HL-χ^2), where a *P* value >0.05 suggests that the model accurately predicts observed precursor conditions (27–29).

To account for the complex survey design of the CHMS and to produce estimates representative of the entire adult Canadian population, all analyses were weighted using sampling weights. Further, fasted subsample weights were applied to adjust for nonresponse at both the questionnaire and medical examination center level; these weights adjust for fasting nonresponse (i.e., among persons who were selected to fast but had not fasted or opted to not provide blood) (30). SEs, CIs, and coefficients of variation were calculated using the bootstrap weights provided by Statistics Canada. Given the limited number of collection sites, we specified 24 df in accordance with the Statistics Canada CHMS user guide (26). Ethics approval for conducting this analysis was obtained from the University of Toronto Research Ethics Board.

All analyses were conducted using SAS version 9.3 survey procedures (SAS Institute Inc., Cary, NC).

RESULTS

After all exclusion criteria were applied, the final sample consisted of 3,494 individuals who were ≥20 years of age. According to the CHMS self-report, the prevalence of physician-diagnosed diabetes was 4.5% (95% CI 3.6, 5.8); the prevalence was higher among males (5.2% [95% CI 3.5, 7.5]) compared with females (3.9% [95% CI 2.8, 5.4]). The estimated total diabetes prevalence (i.e., diagnosed plus undiagnosed diabetes) among Canadian adults was 5.62%, 7.55%, and 7.74%, respectively, according to FPG-only, HbA_{1c}-only, and FPG-or-HbA_{1c} criteria. Specifically, under the FPG diagnostic criterion (FPG ≥7.0 mmol/L), the estimated prevalence of undiagnosed diabetes was 1.13% (95% CI 0.79, 1.62), contributing to ~20% of total diabetes (undiagnosed and diagnosed diabetes) prevalence (Table 1). However, under the HbA_{1c} criterion the prevalence of undiagnosed diabetes rose to 3.09% (95% CI 1.97, 4.81), ~41% of total prevalence. Similarly, the use of HbA_{1c} resulted in higher sex-specific estimates of undiagnosed diabetes prevalence compared with screening criteria based on FPG alone. According to the FPG-only criterion, the proportion of undiagnosed diabetes prevalence was higher for males compared with females (22% vs. 18%), whereas under the

Table 1—Weighted estimates of overall and sex-specific prevalence of undiagnosed and total type 2 diabetes among adult Canadians (20+ years of age) according to different diagnostic criteria

	Total diabetes (diagnosed and undiagnosed) (%)			Undiagnosed diabetes (%)		
Diagnostic criteria	Overall	Males	Females	Overall	Males	Females
FPG (≥7.0 mmol/L)	5.62 (4.52, 6.95)	6.49 (4.80, 8.73)	4.74 (3.46, 6.47)	1.13 (0.79, 1.62)	1.40 (0.87, 2.24)	0.87 (0.41, 1.85)
HbA_{1c} (≥6.5% and ≥48 mmol/mol)	7.55 (5.98, 9.49)	8.04 (5.63, 11.35)	7.07 (5.31, 9.34)	3.09 (1.97, 4.81)*	2.94 (1.48, 5.79)	3.24 (1.98, 5.24)*
FPG or HbA_{1c}	7.74 (6.19, 9.64)	–	–	3.38 (2.26, 5.04)*	–	–

Data are reported as prevalence (95% CI). –, not provided due to small cell size. Note: The undiagnosed diabetes prevalence denominator excludes individuals with self-reported diabetes. Therefore, the difference between the total diabetes prevalence and the undiagnosed diabetes prevalence does not equal the diagnosed diabetes prevalence (i.e., the diagnosed diabetes prevalence is the number of diabetes cases divided by the total sample population, whereas the undiagnosed diabetes prevalence is the number of undiagnosed diabetes cases divided by the total sample minus the number of self-reported diabetes cases. Scaled prediabetes estimates (i.e., estimates using the same denominator) are available in Supplementary Table 1. *Significantly different ($P < 0.05$) compared with the FPG-only criterion; no statistically significant differences in sex-specific prevalence estimates were observed.

HbA_{1c}-only criterion, the proportion of undiagnosed diabetes prevalence was lower for males compared with females (37% vs. 46%).

The prevalence of prediabetes was estimated to be 4.3% according to the FPG-only diagnostic criterion, and was significantly higher for males compared with females (Table 2). Compared with FPG-only criterion, the HbA_{1c}-only criterion resulted in a threefold increase in prediabetes prevalence; for females, a sixfold increase was noted (FPG 2.2%, HbA_{1c} 13.3%). Using the lower criteria in the ADA guidelines (FPG 5.6–7.0%, HbA_{1c} 5.7–6.5%), prediabetes prevalence was 2.5–3 times greater than under the criteria of the Canadian guidelines; however, similar patterns were seen across sex and diagnostic criteria. The overall prevalence of prediabetes was 13.3% according to the FPG-only criterion, and was significantly greater for males compared with females. Similarly, compared with FPG-only criterion, prediabetes prevalence was drastically increased under the HbA_{1c}-only (33.1%) and combined FPG-or-HbA_{1c} criteria (38.3%).

Compared with the HbA_{1c}-only or the combined FPG-or-HbA_{1c} criteria, screening based on the FPG-only criterion identified a slightly, yet significantly, older group of undiagnosed case patients, with a mean age of 58.67 years (95% CI 59.93, 63.40) (Table 3). Mean BMI and WC measures of undiagnosed case patients were not significantly different across diagnostic criteria; however, the mean WC of undiagnosed case patients that was identified using FPG levels was notably higher than that of case patients identified with HbA_{1c} levels (110 vs. 107 cm). The DPoRT-predicted risk was nonsignificantly higher for those undiagnosed individuals identified using the HbA_{1c}-alone or the combined FPG-or-HbA_{1c} diagnostic criteria. Similarly, using HbA_{1c} criterion identified a slightly younger group of individuals with prediabetes, with reduced BMI and WC measures. Compared with the undiagnosed diabetes population, individuals classified as having prediabetes were noticeably younger, with lower values of DPoRT-predicted risk, and smaller BMI and WC measures.

Table 4 provides the odds ratios (95% CIs) for the association between DPoRT risk score (lowest risk score vs. highest risk score) for undiagnosed diabetes and the DPoRT model validation statistics according to each diabetes diagnostic criterion model. The models had comparable C-statistics, ranging from 0.77 (FPG only) to 0.79 (HbA_{1c} only), suggesting good discriminatory ability. The discriminatory ability of the prediabetes model was fairly strong under the FPG-only criterion, but was substantially reduced when HbA_{1c} was used. For both undiagnosed and prediabetes, HL-χ^2 values were significant ($P < 0.05$) under the HbA_{1c} criterion, suggesting that the model does not satisfactorily fit the data when HbA_{1c} is used to identify case patients.

Table 2—Weighted estimates of overall and sex-specific prevalence of prediabetes among adult Canadians (20+ years of age) according to FPG-only, HbA_{1c}-only, and FPG-or-HbA_{1c} diagnostic criteria

		Sex-specific prevalence (%)	
Diagnostic criteria	Overall prevalence (%)	Males	Females
FPG (6.1–6.9 mmol/L)	4.3 (3.4, 5.3)	6.4 (4.6, 8.8)*	2.22 (1.7, 3.0)*
HbA_{1c} (6.0–6.4%; 42–48 mmol/mol)	12.5 (8.7, 17.8)	11.8 (8.1, 16.8)	13.31 (8.9, 19.5)
FPG or HbA_{1c}	15.2 (11.4, 19.9)	15.8 (11.8, 20.7)	14.61 (10.4, 20.1)
ADA guidelines			
FPG (5.6–6.9 mmol/L)	13.3 (11.5, 15.3)	18.1 (15.3, 21.3)*	8.6 (6.6, 11.1)*
HbA_{1c} (5.7–6.4%; 39–48 mmol/mol)	33.1 (25.6, 41.7)	32.6 (24.7, 41.5)	33.7 (24.5, 43.1)
FPG or HbA_{1c}	38.3 (31.8, 45.1)	39.7 (33.0, 46.7)	36.9 (29.7, 44.6)

Data are presented as the prevalence (95% CI). Note: The denominator for prediabetes prevalence excludes individuals with self-reported diabetes and undiagnosed diabetes. *Sex-specific estimates are significantly different, $P < 0.0001$.

CONCLUSIONS

This study uses the most recent data from biospecimens that are representative of Canadians to provide the first estimates of undiagnosed type 2 diabetes and prediabetes at the population level according to newly introduced the HbA_{1c} criterion. We found that there are a substantial number of Canadians who are living with diabetes in whom the disease has not yet been diagnosed;

Table 3—Values of select risk characteristics for individuals with undiagnosed type 2 diabetes and prediabetes according to FPG-only, HbA_{1c}-only, and FPG-or-HbA_{1c} diagnostic criteria

	Diagnostic criteria		
Risk characteristic	FPG	HbA_{1c}	FPG or HbA_{1c}
Undiagnosed type 2 diabetes			
DPoRT predicted risk	0.21 (0.16, 0.25)	0.23 (0.17, 0.30)	0.23 (0.17, 0.30)
Age (years)	58.67 (59.93, 63.40)*	55.89 (53.76, 58.03)	56.69 (54.62, 58.77)
Measured BMI (kg/m^2)	32.96 (30.44, 35.49)	32.51 (29.99, 35.02)	32.21 (29.93, 34.48)
Measured WC (cm)	110.12 (104.12, 116.12)	106.80 (99.69, 113.91)	106.35 (99.90, 112.80)
Prediabetes			
DPoRT predicted risk	0.18 (0.14, 0.21)	0.14 (0.12, 0.16)	0.15 (0.13, 0.16)
Age (years)	55.24 (52.02, 58.47)	52.85 (50.38, 55.31)	53.46 (51.26, 55.66)
Measured BMI (kg/m^2)	29.42 (27.86, 30.97)	28.21 (26.97, 29.44)	28.27 (27.28, 29.26)
Measured WC (cm)	100.37 (96.08, 104.67)	94.68 (91.64, 97.72)	95.38 (92.86, 97.89)

Data are reported as the mean (95% CI). *Estimate is significantly different from other criteria, $P < 0.05$.

in addition, we found that our estimates differed according to diagnostic criteria.

According to results from the National Diabetes Surveillance System, which uses administrative data and requires at least one hospitalization or two physician claims with diabetes-specific codes over a 2-year period to diagnose diabetes, the prevalence of diabetes among Canadians ≥1 year of age was 6.2% in 2006/2007; among females and males, the prevalence was 5.9% and 6.6, respectively (2). These estimates are comparable to ours, and we also found prevalence to be slightly higher among males. Equally comparable to our results, 20–50% of individuals with diabetes in Canada are estimated to be undiagnosed under FPG criteria (29,31). To our knowledge, there is only one other study (1) that has provided national estimates of overall diabetes (diagnosed diabetes, undiagnosed diabetes, and prediabetes) prevalence; however, these estimates were not directly measured, and they did not account for changes in diagnostic criteria. According to this study based on administrative data, one in four Canadians in 2010 had prediabetes, diabetes, or undiagnosed diabetes (1); this number is larger than the one estimated here, as this study estimated prediabetes prevalence to be one in five among Canadian adults.

The proportion of undiagnosed diabetes in the U.S. compares to that in Canada, ranging from one-fifth to one-third of total diabetes cases (6,18, 32,33). For example, studies using the U.S. National Health Examination Survey have suggested that roughly one-third of the total diabetes prevalence is undiagnosed (30–32). Cowie et al. (13) estimated the prevalence of diagnosed diabetes among U.S. adults in 1999–2002 to be 6.5%, with an additional 2.8% prevalence of undiagnosed diabetes. A disproportionate number of these cases occur among ethnic minorities, males, obese and older individuals (15,19,20,30). Recent and direct estimates of prediabetes prevalence in Canada, however, are lacking. The majority of prediabetes studies are conducted outside of Canada, and often use lower diagnostic cut points (e.g., HbA_{1c} 5.7–6.4% [39–48 mmol/mol]). According to these lower cut points, our estimates of prediabetes prevalence were substantially larger than those made under the Canadian guidelines.

Following the addition of HbA_{1c} to diabetes screening guidelines, little work has been done to examine any change this may have in the prevalence of both diagnosed and undiagnosed diabetes. Internationally, research on the sensitivity and specificity of HbA_{1c} and FPG testing for undiagnosed diabetes has been inconsistent (22–25,34,35). Further, in the few studies to date that have directly compared prediabetes prevalence according to FPG and HbA_{1c} criteria, considerable differences between estimates have been noted, largely by finding HbA_{1c} (5.7–6.4% [39–48 mmol/mol]) to be a less sensitive criterion than FPG (5.6–6.9 mmol/L [or equivalently 100–125 mg/dL]). For example, Mann et al. (35) found the prevalence of prediabetes to be ~12.6% among U.S. adults according to HbA_{1c} criteria, but as high as 28.2% using FPG criteria (34). Another U.S. study (34) reported comparable prevalence estimates (14.2% for HbA_{1c} level of 5.7–6.4% [39–48 mmol/mol], 26.2% for FPG level of 100–125 mg/dL), but, similar to our study, it found prediabetes prevalence to be lower (7.0%) when using the World Health Organization guidelines for FPG levels (110–125 mg/dL). In agreement

Table 4—Odds ratio (95% CI) for the association of DPoRT risk score for undiagnosed type 2 diabetes and prediabetes and corresponding predictive accuracy of each model according to various diabetes diagnostic criteria

	Diagnostic criteria		
Model validation statistics	FPG	HbA_{1c}	FPG or HbA_{1c}
Undiagnosed diabetes			
Odds ratio (95% CI)	3.62 (2.31, 5.66)	5.22 (3.31, 8.25)	4.79 (3.00, 7.64)
C-statistic	0.77	0.79	0.78
HL-χ^2	12.05	28.78	22.59
HL-χ^2 *P* value	0.1489	0.0003	0.0039
Prediabetes			
Odds ratio (95% CI)	2.87 (2.05, 4.02)	1.95 (1.49, 2.55)	2.16 (1.70, 2.74)
C-statistic	0.76	0.68	0.70
HL-χ^2	14.20	17.69	17.30
HL-χ^2 *P* value	0.08	0.02	0.03

Validation statistics are based on the use of the natural logarithm of the DPoRT risk.

with our findings, the prevalence of prediabetes only slightly increased using a combined HbA_{1c}-or-FPG criterion (18.1% for FPG level of 110–125 mg/dL; 32.2% for FPG level of 100–125 mg/dL) (34). While the most sensitive measure resulted in a similar prevalence of prediabetes as observed in the U.S., our study showed a reverse association between HbA_{1c} and FPG sensitivity based on the currently used cut points for these measures; prediabetes prevalence was greater when HbA_{1c} criteria were used, compared with FPG. Further, in England, prediabetes (HbA_{1c} level of 5.7–6.4% [39–48 mmol/mol]) prevalence has increased from 11.6% in 2003% to 35.3% in 2011 (36). Thus, prevalence may vary considerably both internationally and temporally. These differences may be due to a number of factors, thereby emphasizing the importance of recent and country-specific estimates and further assessment of HbA_{1c}, FPG, and their respective diagnostic cut points for use in prediabetes screening in other populations.

These findings have important clinical and public health implications. Particularly, while the prevalence of diagnosed diabetes was similar across diagnostic criteria, the addition of HbA_{1c} to diagnostic guidelines resulted in the identification of a greater proportion of undiagnosed diabetes cases and thus higher prediabetes prevalence. While the measurement of HbA_{1c} levels is slightly more costly than measurement of FPG levels, although it is still less costly than performing an oral glucose tolerance test, there are considerably fewer time and inconvenience costs associated with HbA_{1c} measurement, making it attractive for opportunistic screening. This may contribute to increased diabetes screening, and potentially earlier identification of case patients and high-risk individuals. This is supported by the finding that the mean age of undiagnosed individuals in screening programs using HbA_{1c} levels was significantly younger than that identified by FPG-only diagnostic criteria. Further, all three undiagnosed groups were considered obese based on both mean BMI ($\geq$30 kg/m^2) and mean WC ($\geq$88 cm for females or $\geq$102 cm for males) and had similar DPoRT risk scores, suggesting that targeted interventions and screening programs are already recommended for these undiagnosed individuals. Our characterization of prediabetic individuals showed similar, yet nonsignificant, differences in age, BMI, and WC. In the presence of routine screening programs, the widespread acceptance of HbA_{1c} level as a diagnostic and screening criterion could potentially lead to the identification of more undiagnosed and high-risk diabetes than using FPG level only. However, it is yet to be ascertained whether these might be clinically significant changes and large enough to alter clinical outcomes, such as diabetes complications. Further research is necessary to assess how these outcomes may additionally vary across populations (e.g., U.S. vs. Canada).

Our validation of DPoRT using various diagnostic criteria suggests that DPoRT is highly discriminatory and well calibrated to predict undiagnosed diabetes and prediabetes when using FPG as a diagnostic criterion, but less so when using HbA_{1c}. Considering that DPoRT was validated using physician-diagnosed diabetes captured from administrative databases prior to the recent addition of HbA_{1c} measures to screening guidelines, most physician-confirmed cases of diabetes would have been diagnosed using FPG measurement or oral glucose tolerance test findings. As HbA_{1c} criteria become more widely used, the performance of other risk prediction tools calibrated prior to the change in guidelines may be affected (27–29). Further, this study showed HbA_{1c}, given the current suggested diagnostic cut points, to be a notably more sensitive predictor of both prediabetes and undiagnosed diabetes among females. Given what is known about the association between HbA_{1c} levels and ethnicity, it is likely that these differences would also extend across ethnic groups. Therefore, prediction tools may vary in non-negligible ways across subgroups, such as sex and ethnicity. These findings have important implications for the use of predictive tools at the population or patient level.

Limitations

This study has many strengths, such as the use of a recent, large, comprehensive, and nationally representative health survey with physical and biospecimen measures; however, there are also some limitations to consider. First, because of the small sample size, we were not able to provide sex-specific prevalence estimates for the FPG-or-HbA_{1c} diagnostic criterion, nor could we further stratify our results by age or calculate age-adjusted estimates. In addition, given the small sample size, we could not assess ethnic differences, which have been shown to affect HbA_{1c} levels (25). Another limitation of these data are that although 98% of the population is represented by the CHMS, Canadians living on a reserve or in institutions who may be at increased risk for the development of diabetes or less likely to undergo screening are excluded from this analysis (29). Consequently, our results are likely an underestimate of the true prevalence of undiagnosed diabetes. Similarly, nonresponse bias may be a concern as a result of the low response rates ($<$50%) observed within the fasting subsample of the CHMS; however, survey weights provided by Statistics Canada (26) account for nonresponse, including nonresponse within the fasting subsample. As with all surveys, there is also the possibility of reporting and measurement biases. Specifically, as CHMS is a cross-sectional survey, measurements were taken only at one point of time, and the day-to-day variability may exist. Because the diagnosis of pre-existing diabetes was based on self-report, there is also the possibility that individuals may have incorrectly reported their diabetes diagnosis; for example, those with controlled type 2 diabetes may have wrongfully reported themselves as not having diabetes. Furthermore, CHMS used fasting serum glucose levels in Cycle 1 but switched to measuring FPG in Cycle 2 to analyze blood glucose measures (23). However, a recent study by Frank et al. (37) found that the use of serum resulted in small but significant decreases in blood glucose level (1.15%), but that this difference is likely not physiologically relevant.

Conclusion

In this study of a large and nationally representative sample of Canadians with physical and biospecimen measures, we found that the prevalence of undiagnosed diabetes and prediabetes was significantly greater when using screening strategies that used HbA_{1c}

measures compared with the FPG-only diagnostic criterion, with a larger proportion of total diabetes prevalence being currently undiagnosed under the HbA_{1c} criteria. HbA_{1c}-based screening identified a younger, less overweight group of individuals. This is important for policy and intervention planning, particularly as new screening criteria become more widely used. Further, the results of this study suggest that the recalibration of prediction tools may be necessary after changes to diagnostic guidelines. Moreover, our findings confirm those among prior international studies; e.g., considerable discordance exists between various type 2 diabetes diagnostic/screening criteria and the fact that the characteristics of identified individuals also vary by such criteria. Further evaluation, surveillance, and health economic analysis research are needed to fully assess the population and health system impacts of adding HbA_{1c} measures to diabetes screening.

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