


RESEARCH ARTICLE

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High prevalence and significant ethnic differences in actionable HbA_{1c} after gestational diabetes mellitus in women living in Norway

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Abstract

Background: The type 2 diabetes risk after gestational diabetes mellitus (GDM) is twice as high in South Asian compared to European women. Current guidelines differ regarding which test to use as a screening-tool post-GDM. We aimed to identify ethnic differences in the prevalence rates and early predictors for actionable HbA_{1c} (defined as prediabetes and diabetes) short time after GDM.

Methods: This cross-sectional study, enrolling South Asian and Nordic women 1–3 years after a diagnosis of GDM, was undertaken at three hospitals in Norway. We performed a clinical and laboratory evaluation including an oral glucose tolerance test (OGTT). Medical records were used to retrieve data during pregnancy. Prediabetes was classified with HbA_{1c} alone or combined with OGTT glucose measurements according to the WHO, WHO-IEC, and ADA criteria (fasting plasma glucose (FPG) 6.1–6.9 mmol/L, FPG 6.1–6.9 mmol/L and/or HbA_{1c} 42–47 mmol/mol (6.0–6.4%), and FPG 5.6–6.9 mmol/L and/or HbA_{1c} 39–47 mmol/mol (5.7–6.4%)). Ethnic differences in prevalence and predictors of glucose deterioration were assessed by χ^2 (Pearson) tests and logistic regression models.

Results: We included 163 South Asian and 108 Nordic women. Actionable HbA_{1c} levels were highly prevalent and more so among South Asian than Nordic women (WHO-IEC-HbA_{1c}: 25.8% vs. 6.5% ($p \leq 0.001$), ADA-HbA_{1c}: 58.3% vs. 22.2% ($p \leq 0.001$)). Although adding OGTT-data gave higher combined prevalence rates of prediabetes and diabetes (WHO: 65.6% vs. 47.2% ($p \leq 0.05$), WHO-IEC: 70.6% vs. 47.2% ($p \leq 0.001$), ADA: 87.8% vs. 65.7% ($p \leq 0.001$)), the excess risk in the South Asian women was best captured by the HbA_{1c}. Important predictors for glucose deterioration after GDM were: South Asian ethnicity, GDM before the index pregnancy, use of glucose-lowering drugs in pregnancy, higher age, and higher in-pregnancy fasting glucose levels.

Conclusions: In women with GDM 1–3 year previously, we found high prevalence and significant ethnic differences in actionable ADA-HbA_{1c} levels, with South Asian ethnicity, GDM before the index pregnancy, and the use of glucose-lowering drugs in pregnancy as the most important risk factors. This study reinforces the importance of annual screening—preferably with HbA_{1c} measurements—to facilitate early intervention after GDM.

Keywords: Gestational diabetes mellitus, Glucose metabolism disorders, Ethnic groups, Prevention, Overweight, Glycated haemoglobin

Background

Gestational diabetes mellitus (GDM) is associated with an increased risk of diabetes later in life [1, 2], particularly among South Asian women living in high-income

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countries [3]. The prevalence of both GDM [4, 5] and subsequent type 2 diabetes [2, 3] are twice as high in South Asian compared to European women; additionally type 2 diabetes seems to develop earlier and at a lower body mass index (BMI) in South Asian women post-GDM [6].

Accordingly, accurate diagnostic tools are important not only when considering preventive measures to counteract the development of diabetes but also to detect women at high risk of GDM in subsequent pregnancies. Several national guidelines recommend lifelong screening by glycated haemoglobin (HbA_{1c}), fasting plasma glucose (FPG), or oral glucose tolerance test (OGTT) post-GDM to identify women at high-risk [7–9]. In clinical practice, however, HbA_{1c} rather than FPG or performing an OGTT are preferred, due to advantages as (i) less pre-analytical and day-to-day variation, and, of greater importance, (ii) the stronger association including in seminal meta-analyses between glycated haemoglobin and diabetes complications, both for retinopathy [10] and cardiovascular disease [11, 12] as compared to 2-h glucose. Further, more convenient blood sampling without the need for fasting and the (unpleasant) time-consuming OGTT is a major benefit. Notwithstanding this, available literature refers to OGTT as gold-standard test when comparing different modes for diagnosis of prediabetes and diabetes [13, 14] and suffers from variation in the use of diagnostic criteria to define GDM and prediabetes post-GDM [15]. Similarly, risk factors for prediabetes and diabetes among different ethnicities cared for in the same healthcare setting post-GDM have not been clearly characterized.

With this background, in women with previous GDM living in Norway, we investigated the impact of South-Asian and Nordic ethnicity on (1) the prevalence of prediabetes and diabetes using HbA_{1c} without and with OGTT measurements by the WHO, WHO-IEC, or ADA criteria [16–18] and (2) pre- and in-pregnancy predictors for actionable HbA_{1c} (defined as prediabetes or diabetes) 1–3 years after delivery.

Methods

The ongoing DIAbetes in South Asians 1 (DIASA 1) study was approved by the Regional Committee for Medical and Health Research Ethics of South-Eastern Norway (reference number: 2018/689). All participants signed study-specific consent forms.

Design, study population, and data collection

Between September 1, 2018, and November 1, 2021, the DIASA 1 cross-sectional study recruited women with a diagnosis of GDM in their last pregnancy, who delivered 12–36 (\pm 3) months previously at one of three hospitals

in the Oslo area, Norway. The inclusion criteria were age \geq 18 years, ethnic origin from a South Asian (Pakistan, India, Bangladesh, or Sri Lanka) or Nordic (Norway, Sweden, Denmark, Finland, or Iceland) country. Exclusion criteria were new pregnancies after the index pregnancy, exclusive breastfeeding at the time of examination, known diabetes before the index pregnancy or at the time of examination, ongoing inflammatory or serious disease, or a history of major surgical procedure $<$ 3 months prior to inclusion. The eligible women, identified by searching medical records from the three hospitals, were recruited through an invitation letter. Additionally (as recommended by Regional Ethics Committee), the South Asian women received a telephone invitation in their native language.

At the study visit, we measured height, weight, waist, and hip circumferences [19]. Thereafter, all women underwent a two-hour 75 g OGTT between 08.00 and 10.00 am after at least 8 h fasting at their local hospitals.

Blood for glucose analysis were collected in cooled sodium fluoride tubes and kept on ice until centrifugation, and plasma was analysed at Oslo University Hospital (Aker) using enzymatic photometry (Roche Diagnostics, Mannheim, Germany). Whole-blood HbA_{1c} was analysed by high-performance liquid chromatography (Tosoh G8 analyser, Tokyo Japan). The coefficients of variation were 2.5% for glucose and 1.5–2.5% for HbA_{1c}.

Clinical and biochemical data from the women obtained during the pregnancy, including the results of the 75 g OGTT performed at gestational weeks 24–28, were retrieved from medical records.

Definitions of GDM, prediabetes, and diabetes

Until April 2017, the Norwegian healthcare system used targeted screening for GDM in high-risk groups and applied the WHO 1999 criteria (FPG \geq 7.0 or 2-h PG \geq 7.8 mmol/l) [16]. From April 2017, this routine changed to universal screening and modified International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria with FPG 5.3–6.9 or 2-h glucose 9.0–11.0 mmol/l [7] (no 1-h glucose). For the few cases registered as GDM in pregnancy, where OGTT data were not available, we recorded FPG \geq 5.3 mmol/L or initiating glucose-lowering drugs in pregnancy as diagnostic of GDM (n = 6).

The prevalence of prediabetes was assessed according to the following criteria:

- 1) The WHO criteria: FPG 6.1–6.9 mmol/L and/or 2-h plasma glucose 7.8–11.0 mmol/L [16]
- 2) The WHO-IEC criteria: FPG 6.1–6.9 mmol/L and/or 2-h plasma glucose 7.8–11.0 mmol/L and/or HbA_{1c} 42–47 mmol/mol (6.0–6.4%) [16, 17]

- 3) The ADA criteria: FPG 5.6–6.9 mmol/L and/or 2-h plasma glucose 7.8–11.0 mmol/L and/or HbA_{1c} 39–47 mmol/mol (5.7–6.4%) [18]

The prevalence of diabetes was assessed according to the internationally-agreed criteria: FPG ≥ 7.0 mmol/L and/or 2-h plasma glucose ≥ 11.1 mmol/L and/or HbA_{1c} ≥ 48 mmol/mol ($\geq 6.5\%$) [18, 20]. For a clinical diagnosis of diabetes in asymptomatic individuals, two separate tests are required. In the present study, however, we accepted only one test.

Statistical analyses

Based on a published study [21], we expected the proportion of women with prediabetes or diabetes to be 35% in South Asian and 20% in Nordic women. Accordingly, with $\alpha = 0.05$, the study needed a total number of 324 subjects to have a statistical power of 80% to detect differences in the prevalence between the ethnic groups. However, due to higher prevalence rates, greater difference between the groups, and delayed recruitment during the COVID-19 pandemic, we performed an interim data analysis that ensured sufficient power (97%) to detect differences between the groups with the included 271 women in 2021.

Differences between groups were assessed with unpaired t-tests for normally distributed data, and with Mann–Whitney test for non-normally distributed data. χ^2 (Pearson) and Fisher's exact tests were applied to compare group proportion differences for prediabetes and diabetes. Characteristics were presented as mean (SD), or median (interquartile range, IQR), or number [%]. We calculated confidence intervals (CI) for proportions, and used plots to show the distribution of HbA_{1c} by ethnicity, and FPG by HbA_{1c}.

Evaluated against the different diagnostics criteria, we compared the diagnostic performance of the FPG, HbA_{1c}, and the combination of both for sensitivity, specificity, and positive and negative predictive value in the South Asian and Nordic group.

Logistic regression analyses were performed to identify determinants for actionable ADA-HbA_{1c}. Age, ethnicity, glucose-lowering drugs, in-pregnancy FPG and 2-h OGTT values, pre-pregnancy BMI, gestational weight gain (GWG, calculated as the difference between weight within 4 weeks before delivery and pre-pregnancy weight), parity, education (as a proxy for socio-economic status), first-degree relatives with diabetes, and GDM before index pregnancy were entered as adjustment covariates. Covariates with p -values ≤ 0.25 in the univariate logistic regression analyses were included in a multivariate logistic regression analysis to find the most significant predictors for actionable HbA_{1c}. The results

were expressed as odds ratio (OR) with 95% CI. For all analysis, p -values < 0.05 were considered statistically significant, except for interactions, where a p -value < 0.001 was applied to reduce the number of sporadic findings as we looked for interactions among all the covariates. We used SPSS 27 and STATA 17.

Results

Of the 1169 (398 South Asian and 771 Nordic) eligible women with a GDM diagnosis, 271 (98 Pakistani, 30 Indian, 5 Bangladeshi, 30 Sri Lankan, 101 Norwegian, 3 Swedish, 3 Danish, and 1 Icelandic) women participated. Among the South Asians, 14 were excluded due to new-onset diabetes after index pregnancy and 22 due to a new pregnancy, whilst 199 declined or were not contactable. Among the Nordic women, who were only invited by letter, reasons for non-participating were not defined (Additional file 1: Fig. S1).

Baseline characteristics

At a median (IQR) of 16.8 (12.2) months after delivery, the South Asian group had higher parity, more first-degree relatives with diabetes, and fewer years of education than the Nordic group. BMI did not differ between the groups, but South Asian women had higher waist-to-hip ratio (WHR) at the study visit, and were younger than the Nordic women (Table 1). In total, 58.3% ($n = 158$) had prediabetes or diabetes according to the WHO criteria, and 74.2% ($n = 201$) according to the ADA criteria, whilst the ADA-HbA_{1c} criteria captured 43.9% ($n = 119$) of these women.

Prevalence of prediabetes and diabetes by HbA_{1c}

Independent of criteria used, prediabetes or diabetes was found in a sizeable proportion of South Asian women post-GDM, and prediabetes was significantly more prevalent among South Asian than Nordic women (Additional file 1: Fig. S2).

When applying the WHO-IEC criteria for prediabetes based on HbA_{1c}, 22.7% ($n = 37$) of the South Asian and 3.7% ($n = 4$) of the Nordic women qualified for this diagnosis ($p < 0.001$). With the ADA criteria, the proportions were 55.2% ($n = 90$) in the South Asian and 19.4% ($n = 21$) in the Nordic group ($p < 0.001$), respectively (Fig. 1). The distribution of individual HbA_{1c} levels, and the mean glycated haemoglobin showed higher values among South Asian women (Fig. 2a).

Further, as determined by a single HbA_{1c} measurement, the prevalence of diabetes was 3.1% ($n = 5$) in South Asian and 2.8% ($n = 3$) in the Nordic group, with no difference between the groups ($p = 0.598$) (Fig. 1).

Table 1 The participants' characteristics and demographics by ethnicity

	South Asian <i>n</i> = 163 [60%]	Nordic <i>n</i> = 108 [40%]	<i>P</i> -value
Characteristics at study visit:			
Age (years)	34.5 (4.1)	36.5 (4.9)	< 0.001
Time since index pregnancy (months) ^a	16.1 (12.5)	18.3 (11.2)	0.104
Weight (kg)	73.9 (14.5)	81.7 (19.6)	0.001
Height (cm)	159.5 (6.3)	166.9 (6.1)	< 0.001
BMI (kg/m ²)	29.0 (5.3)	29.3 (6.8)	0.688
Waist circumference (cm)	97.0 (11.6)	96.1 (14.0)	0.605
Waist/hip ratio	0.91 (0.07)	0.88 (0.09)	0.033
FPG at OGTT	5.8 (0.7)	5.7 (0.8)	0.136
2-h OGTT glucose	8.7 (2.7)	7.9 (2.6)	0.013
HbA _{1c} (mmol/mol)	(39 (5))	37 (4)	< 0.001
HbA _{1c} [%]	[5.7 (2.6)]	[5.5 (2.5)]	< 0.001
Parity	2.1 (1.0)	1.7 (0.7)	< 0.001
GDM prior to the index pregnancy	51 [32]	24 [22]	0.096
1.degree relatives w/diabetes	115/155 [74]	22/91 [24]	< 0.001
Tertiary educated (college/university)	87 [53]	81 [75]	< 0.001
Years of education	14.8 (3.3)	16.8 (3.0)	< 0.001
Employed	89 [55]	99 [92]	< 0.001
Characteristics related to index pregnancy:			
Pre-pregnancy age (years)	33.4 (4.1)	35.2 (4.7)	< 0.001
Self-reported pre-pregnancy weight (kg)	70.6 (13.8)	79.3 (18.0)	< 0.001
Pre-pregnancy BMI (based on self-reported weight)	27.6 (5.0)	28.4 (6.2)	0.242
Ethnicity-specific pre-pregnancy overweight ± obesity (based on self-reported weight)	137 [84.0]	73 [67.6]	< 0.001
Last weight reported before delivery (kg)	80.8 (14.0)	90.0 (16.8)	< 0.001
Gestational weight gain (kg)	10.2 (5.8)	10.7 (7.1)	0.594
Pregnancy FPG at OGTT	5.5 (0.7)	5.3 (0.7)	0.017
Pregnancy 2-h OGTT glucose	9.3 (1.8)	9.0 (1.7)	0.108
Breastfeeding (months) ^a	9.4 (10)	11.0 (7.8)	0.738
Insulin ± metformin use in pregnancy	89 [55]	40 [37]	0.005
Insulin use in pregnancy	65 [40]	34 [31]	0.160

Data presented as mean (SD) or ^amedian (IQR) or number (*n*) [%]

Ethnicity-specific pre-pregnancy BMI by the WHO definition: "overweight" in the general populations as > 25 kg/m² and in the Asian population as > 23 kg/m² [22]

FPG fasting plasma glucose, GDM gestational diabetes mellitus, OGTT oral glucose tolerance test

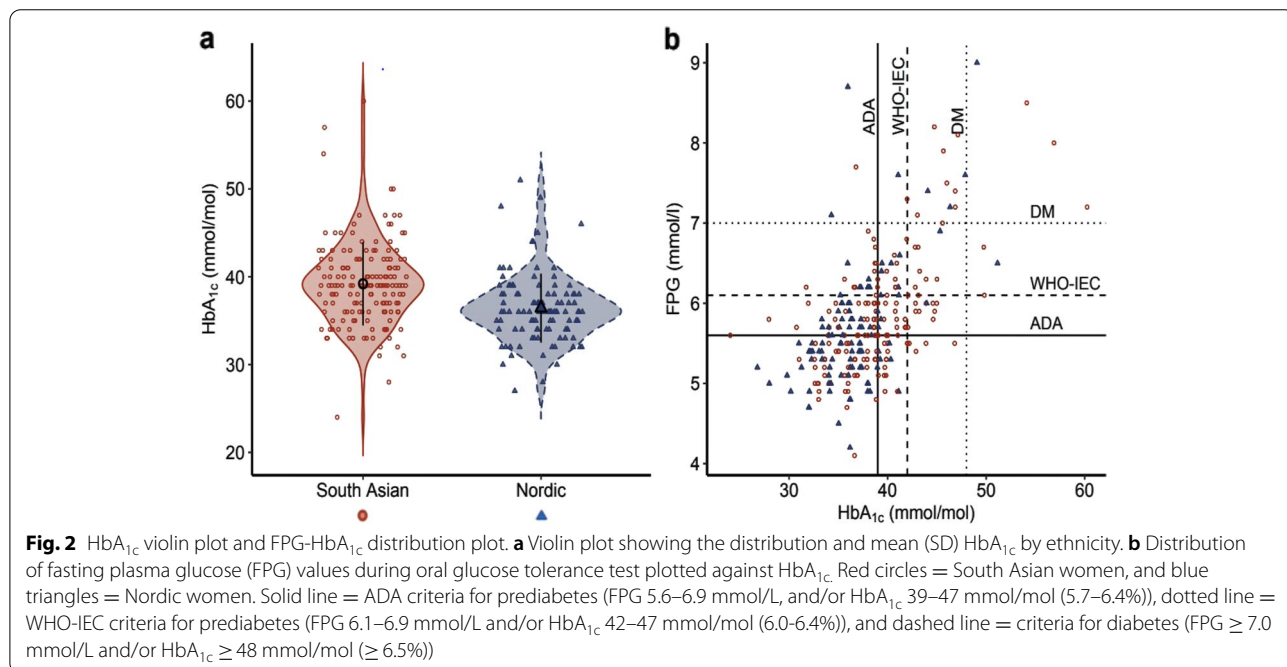
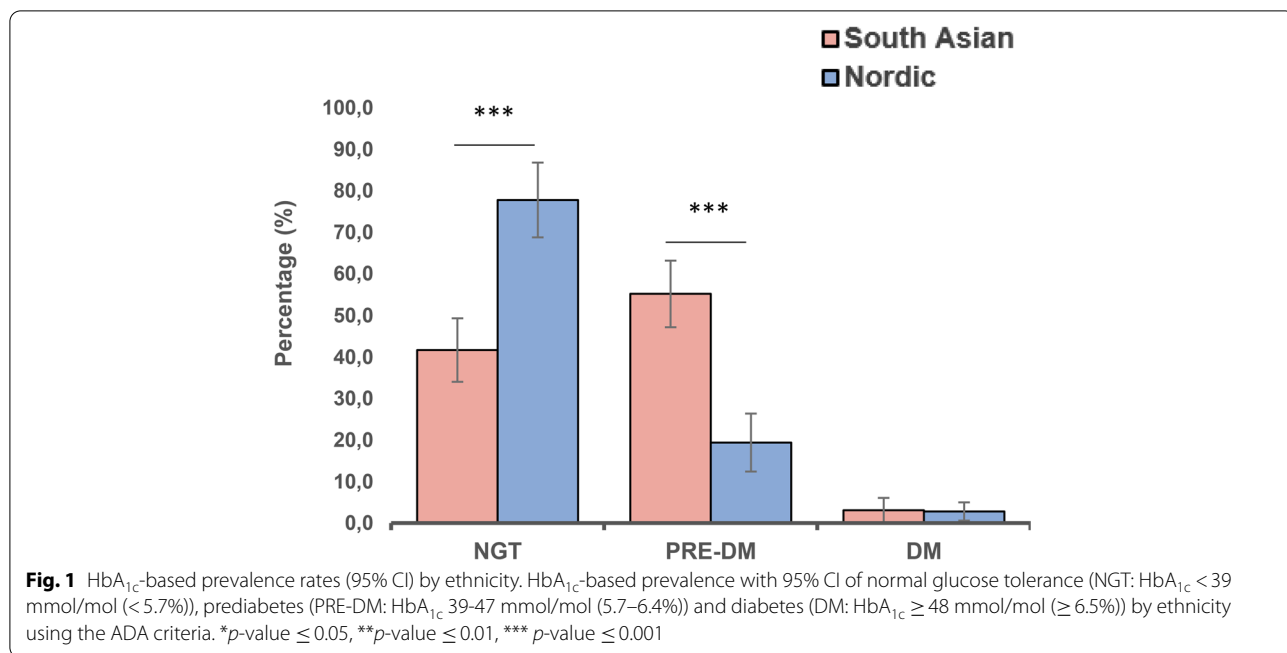
Prevalence of prediabetes and diabetes by different diagnostic criteria

By including the OGTT data and applying the WHO criteria, 65.6% (*n* = 107) of the South Asian women could be defined as having prediabetes or diabetes. If we used the WHO-IEC criteria, the proportion increased to 70.6% (*n* = 115), whilst by the current ADA criteria, 87.8% (*n* = 143) of South Asian women had prediabetes or diabetes. The percentage of women with diabetes was 19.0% (*n* = 31). The comparable proportion of prediabetes or diabetes among the Nordic women by applying the WHO, WHO-IEC and the ADA criteria were 47.2% (*n* = 51), 47.2% (*n* = 51), and 65.7%

(*n* = 71). The percentage of women with diabetes was 13.9% (*n* = 15) (Additional file 1: Fig. S2).

Comparing different modes for diagnosis prediabetes and diabetes with the debated assumption that OGTT is gold standard

HbA_{1c} detected fewer cases of prediabetes or diabetes than when we also included OGTT glucose measurements. We, therefore, calculated the sensitivity, specificity, and positive and negative predictive value of using HbA_{1c} alone for prediabetes and diabetes diagnosis by ethnicity and different diagnostic criteria (Additional file 2: Table S1), also including different combinations of



FPG and HbA_{1c} by ethnicity and different diagnostic criteria (Additional file 2: Table S2).

Compared to the compound diagnostic criteria, the sensitivity (with 95% CI) of using only HbA_{1c} for detecting prediabetes or diabetes was low, but better in South Asian than in Nordic women (WHO-IEC: 37 (28–46)% and ADA: 66 (58–74)% in the South Asian group vs.

WHO-IEC: 14 (6–26)% and ADA: 34 (23–46)% in the Nordic group).

HbA_{1c} also diagnosed fewer women with diabetes as compared with the compound diagnostic criteria, but there were no differences in its sensitivity between the ethnic groups (16 (5–34)% vs. 20 (4–48%)) (Additional file 2: Table S1). By adding FPG to HbA_{1c}, more women

were identified with prediabetes or diabetes independent of ethnicity and criteria used. The benefits of adding HbA_{1c} to FPG in detecting prediabetes or diabetes, however, was only significant in the South Asian group (FPG: WHO-IEC: 38 (29–48)%, ADA: 71 (63–79)% vs. FPG and HbA_{1c}: WHO-IEC: 55 (45–64)%, ADA: 86 (79–91)%) (Additional file 2: Table S1). A cut-off for FPG of 5.6 mmol/l and HbA_{1c} of 38 mmol/mol (5.6%) performed best in the South Asians, and similarly, FPG of 5.6 mmol/l and HbA_{1c} of 37 mmol/mol (5.5%) performed best in the Nordic group (Additional file 2: Table S2).

Percentage of South Asian and Nordic women with actionable HbA_{1c} levels

Adding FPG to HbA_{1c} increased its sensitivity, however, the FPG-HbA_{1c} distribution plot indicated that a single ADA-HbA_{1c} captured most of the glucose values that deserved action (i.e., ADA-HbA_{1c} detected few with FPG <5.6 mmol/L, and most of the elevated FPG levels), yet better in South Asian than Nordic women (Fig. 2b). Similarly, the number of women that needed to be tested to identify an actionable ADA-HbA_{1c} value was only one in two (95/163) for the South Asian and one in five (24/108) for the Nordic women. The corresponding number by the WHO-HbA_{1c} cut-points, however, was one in four (42/163) and one in fifteen (7/108) for the South Asian and Nordic women.

Predictors for prediabetes or diabetes by ethnicity

We sought to identify variables before or during the index pregnancy that predicted actionable HbA_{1c} 16.8 months after delivery. As shown in Table 2, the single strongest

predictor was South Asian ethnicity. In women without GDM prior to the index pregnancy, the strongest predictor was the use of glucose-lowering drugs during pregnancy, whilst this did not impact the risk in women with multiple GDM pregnancies (*p* for interaction = 0.009).

South Asian ethnicity [OR 7.05 (95% CI (2.94–16.92))], GDM before the index pregnancy [OR 3.24 (1.11, 9.45)], using glucose lowering drugs in pregnancy [2.87 (1.31–6.30)], higher age [OR 1.11 (1.02, 1.21)], and higher in-pregnancy fasting OGTT glucose [1.96 (1.16, 3.29)] had a higher likelihood of actionable HbA_{1c} (Table 2). The association was not statistically significant for in-pregnancy 2-h OGTT glucose, pre-pregnancy BMI, and first-degree relatives with diabetes. GWG, education, and parity were not associated with actionable HbA_{1c}.

A sensitivity analysis replacing pre-pregnancy BMI with WHR was performed to link at-visit adiposity status to at-visit HbA_{1c} levels. Adiposity was here significantly associated with actionable HbA_{1c} (Additional file 2: Table S3).

Discussion

Identifying women with prediabetes or early type 2 diabetes in a high-risk group of relatively young women post-GDM is important for the planning of a potential next pregnancy and for implementing appropriate measures to prevent the development of type 2 diabetes and its complications. Our study showed that prediabetes was highly prevalent and more so among South Asian than Nordic women. Both the HbA_{1c} and the compound diagnostic criteria detected a pattern of excess risk in the South Asian compared to the Nordic women.

Table 2 Logistic regression analysis for actionable ADA-HbA_{1c} (defined as prediabetes or diabetes) after adjusting for covariates

Risk factors	Estimated coefficients	P-value	OR	OR (95% CI)	
				Lower	Upper
Age (years)	0.11	0.015	1.11	1.02	1.21
Ethnicity	1.95	<0.001	7.05	2.94	16.92
Glucose-lowering drugs (yes)	1.06	0.008	2.87	1.31	6.30
FPG at OGTT in pregnancy (mmol/l)	0.67	0.011	1.96	1.16	3.29
2-h OGTT glucose in pregnancy (mmol/l)	0.12	0.246	1.13	0.92	1.37
Pre-pregnancy BMI (kg)	0.04	0.255	1.04	0.97	1.12
GWG (kg)	−0.03	0.366	0.98	0.92	1.03
> 3 children (yes)	0.07	0.879	1.07	0.45	2.54
Low education (yes)	0.25	0.476	1.28	0.65	2.55
1.degree relatives w/diabetes (yes)	0.66	0.070	1.93	0.95	3.91
GDM before index pregn (yes)	1.18	0.031	3.24	1.11	9.45
Glucose-lowering drugs * GDM before index pregn	−1.96	0.009	0.14	0.03	0.61

The model includes the covariates (odds ratio (OR) with 95% CI): age, ethnicity, glucose-lowering drugs, fasting plasma glucose (FPG) and 2-h oral glucose tolerance test (OGTT) values in pregnancy, pre-pregnancy BMI, gestational weight gain (GWG), parity, education, first-degree relatives with diabetes, gestational diabetes mellitus (GDM) before index pregnancy, and the interaction term: Glucose-lowering drugs * GDM before index pregnancy

However, HbA_{1c} seemed to capture this ethnic difference just as well as other tests and speculatively better. Adding the measurement of FPG to HbA_{1c} identified more women at risk and might be an option to consider in women planning further pregnancies. Important predictors for actionable HbA_{1c} were South Asian ethnicity, GDM before index pregnancy, use of glucose-lowering drugs in pregnancy, higher age, and higher in-pregnancy FPG. Whilst pre-pregnancy BMI did not feature as a significant predictor, when it was replaced by actual WHR, obesity appeared as a key modifiable risk factor.

Prevalence of prediabetes and diabetes

In our population, applying the ADA-HbA_{1c} cut-offs of 39 mmol/mol (5.7%) identified 58.3% and 22.2% of South Asian and Nordic women with prediabetes or diabetes, of whom most had pre-diabetes. Hence, only two South Asian or five Nordic women would need to be tested to identify one woman with an actionable ADA-HbA_{1c} result. The comparable percentages by the WHO-HbA_{1c} cut-offs of 42 mmol/mol (6.0%) were 25.8 and 6.5%.

Similar to our findings in the Nordic population, a few studies [23–25] have reported a prevalence of 16–19% (applying the ADA-HbA_{1c} cut-points) for the diagnosis of prediabetes or diabetes in mostly white women 1–2.5 years post-GDM. Comparable data in the South Asian population is, so far, scarce.

As current guidelines differ regarding which test to use as post-GDM screening [7, 9, 26], we also assessed the prevalence of prediabetes and diabetes including the OGTT data. We then found that 87.8% and 65.7% of the South Asian and Nordic qualified for this diagnosis. These high prevalence rates, however, seems rather unrealistic in terms of future workload for prevention. One reason for this increase may be that some women have isolated peaks of postprandial glucose that do not translate into higher HbA_{1c} or into long-term diabetes complications [10, 11]. Although some studies defend the use of OGTT as a predictor of diabetes outcomes, they do not apply to our younger prediabetic population [27, 28]. Another possibility is that, despite our best efforts, perhaps some did not fast for as long as requested before their OGTT, once again reiterating the importance of using tests which have better analytical performance and are less prone to pre-analytical factors, which may vary by ethnicity. Even so, both the use of stand-alone HbA_{1c} and different compound diagnostic criteria confirmed a higher prevalence among the South Asian than the Nordic women (Fig. 1).

Two previous studies performed in India and Ireland with similar design to ours [6, 13] also reported high (albeit somewhat lower than the present study) prevalence rates of prediabetes or diabetes post-GDM (by the

compound diagnostic ADA-criteria), 57.7% and 18.4%, respectively. In these studies, the IADPSG criteria were used for diagnosing GDM, in contrast to our WHO 99 (4.8%) or modified IADPSG (93%) criteria with higher cut-off values for the diagnosis. This might explain our higher prevalence rates, as a higher cut-off values are associated with higher conversion rates to diabetes [14, 29]. Nevertheless, the comparable proportion of Nordic women that developed prediabetes or diabetes in our study was unexpectedly high (65.7% vs. 18.4% in the Irish study), since the Irish women had similar age and higher mean BMI (32.4 vs 29.3 kg/m²) and waist circumference (100.1 vs 96.1 cm). A Finnish study [30] reported the prevalence of prediabetes or diabetes to be >50% 6 years post-GDM, which is in broad accordance with our results, acknowledging the differences in the GDM criteria applied.

A high prevalence of diabetes short time after pregnancy in South Asian women is consistent with current literature, reporting a cumulative conversion rate to diabetes of 10.5% and 22.0% within ~4 and 5 years post-GDM on the basis of OGTT data [6, 14]. In Western women, however, studies have indicated a lower cumulative conversion rate of 2.3% and 5.8% within 5 and ~10 years [13, 30]. Notwithstanding this, the early post-GDM development of diabetes in both populations, yet meaningfully lower by the HbA_{1c}, underscores the importance of annually screening for prediabetes and diabetes post-GDM.

Comparing different modes for diagnosing prediabetes and diabetes with diagnosis based on OGTT

Our study resonates strongly with previous work [13, 14, 31], acknowledging that adding a measurement of FPG to HbA_{1c} increases the diagnostic sensitivity for prediabetes and diabetes significantly. We also found that more women were identified by applying the ADA rather than the WHO-IEC criteria. Interestingly, the benefits of adding HbA_{1c} to FPG was only significant in the South Asian group. This finding emphasise that HbA_{1c} may efficiently capture the pattern of excess risk in South Asians, and is consistent with studies showing higher HbA_{1c} levels in South Asian than white women despite lower FPG [32]. Accordingly, this could partially explain the difference in HbA_{1c} between the ethnic groups for the best performance of the combined FPG and HbA_{1c} in our study (South Asian group 5.6 mmol/l and 38 mmol/mol (5.6%) vs 5.6 mmol/l and 37 mmol/mol (5.5%) in the Nordic group) (Additional file 2: Table S2), again with the assumption that OGTT is gold standard, which can now be strongly debated.

Whether adding FPG to HbA_{1c} identifies more women at risk for high glucose levels in subsequent pregnancies, and thereby adverse pregnancy outcomes [33–35], are not answered by our study and deserve further studies. In clinical practice, we support the use of HbA_{1c} testing for women post-GDM.

Predictors for prediabetes or diabetes by ethnicity

In our multivariate analysis, South Asian ethnicity was the strongest risk factor for an actionable HbA_{1c} post-GDM. Although this finding was not unexpected and is supported by recent literature, these studies all held the assumption that OGTT is gold standard for the diagnosis of prediabetes or diabetes [14, 36, 37]. To the best of our knowledge, this is the first study that sought to identify determinants for actionable ADA-HbA_{1c}. And by doing so, it was reassuring to see that the predictors for glucose deterioration were consistent regardless of criteria used [30, 36, 38] (Table 2).

Of note, intake of glucose-lowering drugs did not impact the risk of actionable HbA_{1c} in women with GDM before index pregnancy, contrary to findings in women without GDM before index pregnancy, emphasizing the strong impact of previous GDM itself as a risk factor. This finding indicates that a GDM-pregnancy may result in a severe deterioration of the glucose metabolism, as stated by others [39], fitting with the high GDM recurrence rate in following pregnancies [40].

Overweight and obesity are well known risk factors for prediabetes and diabetes, and in our study 86% (82/95) of the South Asians, and 81% (17/21) of the Nordic women identified with actionable HbA_{1c} were either overweight or obese before the pregnancy. Type 2 diabetes is strongly associated with excess total and ectopic fat in all ethnicities, and the greater risk in South Asians may be linked to larger visceral fat and lower skeletal muscle mass for a given BMI [41]. Accordingly, we found larger WHR in South Asian than in Nordic women at similar BMI, and an increased risk for actionable HbA_{1c} by WHR, but not by BMI. There is also an emerging suggestion that South Asians have more rapid genetically-determined beta cell deterioration [42]; consistent with our findings that the increased risk of actionable HbA_{1c} among South Asians was not greatly attenuated after adjustment for WHR. Whatever the mechanism, we strongly encourage weight reduction in overweight women post-GDM, as modest weight loss can prevent diabetes [43] and greater weight loss can reverse diabetes [44]. Such weight loss reduces liver fat, and may improve beta cell function in whites, at least [45], though weight loss led to similar or even greater diabetes remission in a Qatari population [46].

Strengths and limitations

The major strengths of this multicentre study is the inclusion of a relatively large sample size from two different ethnic groups living in the same area and cared for in the same healthcare setting. Furthermore, the application of different definitions for prediabetes that might make comparison between studies easier is also a major strength. Finally, reporting on ethnic difference in HbA_{1c}-based prevalence of prediabetes and diabetes post-GDM is novel and important, especially as rates of diabetes and obesity are rising worldwide, especially in “metabolically higher risk” South Asians communities.

Our study has limitations. First, we only recruited women referred to hospital for treatment of GDM. Our findings are, therefore, not applicable to women with diet-treated GDM cared for in primary healthcare.

Second, we cannot exclude a selection bias due to the low participation rate (45% and 14% in the South Asian and the Nordic groups). We, therefore, compared significant baseline characteristics in the regression analysis of women who did vs. a randomly selected subgroup of women who did not participate in the study (100 South Asian and 100 Nordic women) (Additional file 2: Table S4). Among the South Asian women no difference in age, pre-pregnancy BMI, in-pregnancy glucose values, the use of glucose-lowering drugs, GDM before index pregnancy, or first-degree relatives with diabetes were found. The participating Nordic women were older than non-participants, but the other characteristics did not differ. The older age among participating Nordic women might have led to an overestimation of the proportion of women with actionable HbA_{1c} in this group. Third, differences in the recruitment procedures may have introduced a selection bias between the ethnic groups. After sending invitation letters to eligible women, only South Asian women received a telephone invitation to enhance recruitment. It is therefore possible that Nordic women with higher in-pregnancy glucose levels may have been more likely to respond to the invitation. Speaking against this is the fact that a higher percentage of South Asian than Nordic women were using glucose-lowering drugs in pregnancy and by minimal differences in the in-pregnancy glucose levels between the ethnic groups (Table 1). Fourth, our analyses did not include assessments of dietary habits and physical activity that may have important impact on the prevalence rates in the two groups. Our study had limited power to detect ethnic difference in the prevalence of diabetes. Finally, causality cannot be inferred from a cross-sectional study, and a single measurement of HbA_{1c} or OGTT is not sufficient for a diagnosis of diabetes in asymptomatic women.

Conclusions

We found high prevalence rates of actionable HbA_{1c} in women with GDM 1–3 years previously. Both the HbA_{1c} and the established compound diagnostic criteria for pre-diabetes including OGTT measurements detected a pattern of excess risk in the South Asian compared to the Nordic women. The HbA_{1c}-based criteria captured the ethnic difference best. Significant risk factors for actionable HbA_{1c} were South Asian ethnicity, GDM before index pregnancy, use of glucose-lowering drugs in pregnancy, higher age, and in-pregnancy fasting glucose levels; all factors linked downstream to excess adiposity in both ethnicities. In terms of public health recommendations, our results confirm the need for regular screening of pre-diabetes and diabetes post-GDM, and support the use of HbA_{1c} to improve women's adherence to follow-ups and better predict long-term risks after GDM, particularly in South Asian communities.

Abbreviations

FPG: Fasting plasma glucose; GDM: Gestational diabetes mellitus; GWS: Gestational weight gain; IADPSG: International Association of Diabetes and Pregnancy Study Group; OGTT: Oral glucose tolerance test; WHO-IEC: World Health Organization-International Expert Committee.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12916-022-02515-w>.

Additional file 1: Fig. S1. Participant flow-chart. **Fig. S2.** HbA_{1c} and OGTT-based prevalence (95% CI) of prediabetes and diabetes by ethnicity and different diagnostic criteria.

Additional file 2: Table S1. Performance of FPG, HbA_{1c}, and FPG & HbA_{1c} by ethnicity for diagnosing prediabetes and diabetes compared to different diagnostic criteria. **Table S2.** Performance of different combinations of FPG and HbA_{1c} cut-offs for diagnosing prediabetes or diabetes compared to ADA criteria. **Table S3.** Logistic regression analysis showing odds ratio (OR) with 95 % CI for actionable ADA-HbA_{1c} (defined as prediabetes or diabetes) after adjusting for covariates. **Table S4.** The participating and non-participating women's characteristics by ethnicity.

Acknowledgements

We would like to dedicate this paper to the memory of Dr Cecilie Wium, who passed away shortly before completion of this study. She conceptualized and designed the study, wrote the protocol and obtained the funding—the study would never have been performed without her. She will be sorely missed by her colleagues, the patients she treated, and her family and friends. The authors would also like to thank the women who participated in the study, the study nurses Åshild Stavik, Åse Halsne, Jesini Anurathan, and Karin Pleym, and study coordinator Ellen Hillestad for invaluable help in the recruitment and examination of the participants. We would also like to thank Dr. Sindre Lee-Ødegård, the librarian, Åse Marit Hammersbøen, and the statistician Ragnhild S. Falk, for assistance with various aspect of this study.

Authors' contributions

AS researched the data and drafted the manuscript. IN, EQ, ATT, CS, HLG, STS, and KIB contributed to the design. KIB contributed to the study protocol and aided in data acquisition. KIB supervised the study performance and is the guarantor of this work and, as such, had the full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors (AS, IN, EQ, ATT, CS, NS, JMRG, HLG, STS, and KIB)

contributed to the analysis or interpretation of data for the work, revised the manuscript critically, and approved the final manuscript.

Funding

This study was funded by the Research Council of Norway, grant number 273252. The study funder was not involved in the design of the study; the collection, analysis, and interpretation of data or writing the manuscript.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate

The DIASA 1 study was approved by the Regional Committee for Medical and Health Research Ethics of South-Eastern Norway (reference number: 2018/689). All participants signed study-specific consent forms.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 17 March 2022 Accepted: 3 August 2022

Published online: 23 September 2022

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