Prevalence and risk factors of gestational diabetes in Punjab, North India: results from a population screening program

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Abstract

Objective: The World Health Organization (WHO) has in 2013 changed the diagnostic criteria for gestational diabetes mellitus (GDM) to acknowledge the putative effect of mildly elevated fasting plasma glucose (FPG) levels on pregnancy outcomes. We aimed to determine the prevalence and risk factors of GDM comparing the previous WHO 1999 criteria to the WHO 2013 criteria in North India.

Methods: In a population-based screening programme, 5100 randomly selected North Indian women were studied using a cross-sectional design with a questionnaire, venous FPG and 2-h capillary plasma glucose (PG) after a 75 g oral glucose tolerance test performed between 24 and 28 weeks of pregnancy.

Results: The prevalence of GDM was 35% using WHO 2013 criteria vs 9% using WHO 1999 criteria. FPG measurements identified 94% of WHO 2013 GDM cases as opposed to 11% of WHO 1999 GDM cases. In contrast, 2-h PG measurements identified only 13% of WHO 2013 GDM cases compared with 96% of the WHO 1999 GDM cases. Using logistic regression with backward elimination, urban habitat, illiteracy, non-vegetarianism, increased BMI, Hindu religion and low adult height were all independent risk factors of GDM using the 1999 criteria, whereas only urban habitat, low adult height and increased age were independent risk factors of GDM using the 2013 criteria.

Conclusions: Intervention studies are needed to justify the WHO 2013 GDM criteria increasing the prevalence four fold to include more than one third of North Indian pregnant women.

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Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy (1) and was first recognised in 1823 (2). However, there is still no uniform definition of the diagnostic criteria of GDM. GDM is associated with an increased risk of developing type 2 diabetes (T2D) in both mother and child (3), and therefore represents a window of opportunity to prevent diabetes in two generations. However, the antepartum plasma glucose levels that predict macrosomia differ from those that predict later development of prediabetes or diabetes in mothers and

their offspring (4), and the extent to which pregnancy complications associated with GDM are determined by increased plasma glucose levels *per se* (fasting or postprandial), or whether they are due to confounding from other common GDM risk factors, is unknown (5).

The World Health Organization (WHO) 1999 criteria defined GDM by fasting plasma glucose (FPG) level ≥ 7.0 mmol/l (126 mg/dl) or 2-h plasma glucose (PG) levels after a 75 g oral glucose tolerance test (OGTT) ≥ 7.8 mmol/l (140 mg/dl). The Indian criteria for GDM use only the 2-h criteria (DIPSI) (6, 7). The prevalence of GDM,

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when using the WHO 1999 criteria range between 1 and 14% in different populations (8, 9, 10).

In order to define the thresholds for FPG and 2-h PG levels after a 75 g OGTT for GDM diagnosis, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study followed 23 000 pregnant women until delivery. This study documented a linear relationship between the level of maternal hyperglycaemia during pregnancy and the risk of complications in both mother and child (11). Importantly, no safe thresholds for FPG or 2-h PG levels were identified below which no association between plasma glucose and pregnancy complications existed. Based on this finding, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) has proposed to lower FPG for diagnosis of GDM, namely to ≥ 5.1 mmol/l (92 mg/dl) while using a 2-h PG threshold of ≥ 8.5 mmol/l (153 mg/dl) (12). The World Health Organization (WHO) recently decided to adopt the IADPSG criteria, hereafter named the WHO 2013 criteria (13).

The prevalence of GDM in the HAPO study using the WHO 2013 criteria was $\sim 18\%$ (14). However, the HAPO study was not population-based, and blinding of investigators and participants for plasma glucose measurements below a predefined level that needed treatment may have precluded some high-risk women from participating in the study (11).

While studies using WHO 1999 criteria have shown that glucose-lowering treatment reduces the risk of pregnancy complications (15, 16), studies to document the cost-effectiveness of screening and introducing glucose-lowering treatment in women with GDM using the proposed WHO 2013 diagnostic criteria are lacking. Consequently, the National Institute of Health, USA, recommended that more knowledge are required to determine the public health consequences of the WHO 2013 criteria before these are universally applied (10). In a recent Norwegian study, the GDM prevalence was 2.4 times higher using the WHO 2013 compared with the WHO 1999 criteria, and the highest risk of GDM of around 40% was found among pregnant women of South Asian ethnic origin (17).

The present study was undertaken to determine the prevalence and risk factors of GDM using the WHO 1999 vs the WHO 2013 criteria in a population-based screening study in the state of Punjab in North India. Furthermore, we aimed to study the extent to which a range of putative GDM risks factors influence risk of GDM by the two different criteria as well as the absolute level of fasting vs 2-h PG levels in the total population of pregnant women.

Subjects and methods

Recruitment

To screen a representative group of at least 5000 pregnant women in Punjab, North India, for GDM, all pregnant women in gestational week (GW) 24–28 visiting selected study sites, including departments of obstetrics/gynaecology and diabetes clinics, for antenatal care were approached consecutively during the study period. Nearly all pregnant women in the region attend antenatal care, and only a few women from the upper middle class or with a high socio-economic status attend private hospitals.

A multistage random screening technique was applied to ensure representative participation of women. Multistage refers to the process of first choosing three representative regions in Punjab, then sub-staging into three different hospitals that provided most of the population with health care, and finally recruiting pregnant women visiting antenatal clinics. Thus, this cross-sectional study not only screened women who were considered at high risk of developing GDM, but called for universal screening of all pregnant women irrespective of age, BMI, family history of diabetes, religion, diet, socio-economic status or residence. Women with pre-gestational diabetes were excluded from the study.

The data were collected from August 2009 until December 2012. During this period there were ~ 12 000 births at the selected study sites. In total, 6255 women were invited to participate, of which 1014 declined participation (Fig. 1). Consequently, 5241 women were screened for GDM. Due to missing data related to glucose measurements, age and/or BMI, data from 141 women were not included in the statistical analyses, resulting in 5100 participants, i.e., a participation rate of 81.5%. The main reason for declining participation was fear of GDM diagnosis as it is considered a social stigma. Lack of time due to household routines (mainly urban) and demands put on daily wagers and labourers (mainly rural) were additional reasons for not participating.

All information material and consent forms were in three languages, including Hindi (National), Punjabi (Regional), and English. Informed written consent was obtained according to the Indian Medical Research Council (ICMR, New Delhi) guidelines in the form of a signature or a thumb impression (a proxy for illiterate subjects). The study was approved by the Regional Ethics Committee and by the Directorate of Medical Research Education of India.

Figure 1
Participant inclusion.

Setting

To represent the main health care systems in Punjab, nine prominent hospitals were chosen as study sites; namely three public hospitals from different districts run by the government, three primary health centres – governmental subunits located in rural areas – and three private hospitals. At each hospital, a team of paramedical staff, nurses/mid-wives or diabetic educators were assigned to inform and recruit eligible pregnant women as well as to perform the GDM screening.

Variables collected

All women were subjected to personal interviews using a structured questionnaire, which was subsequently filled out by the personnel. The questions asked included age, place of residence (rural/urban), education status (educated if able to provide a signature, and illiterate if only able to give a thumb impression), religion, diet (vegetarianism), family history of diabetes (irrespective of type, in first- and second-degree relatives), parity, present and past obstetric history with any complication, history of any specific medications as well as age at marriage. The GW was calculated from the first day of the woman's last menstrual period as recorded on the antenatal card. Furthermore, weight and height was measured and recorded by standard methods for each subject and the BMI (kg/m^2) calculated.

The majority ($\sim 70\%$) of the pregnant women came in the fasting state defined as an overnight fast of 8–12 h.

Women who were not fasting were asked to come back the next day, and only fasting women were thus included in the study. The women who were not fasting the first day and who despite the invitation did not show up the following day were counted as having declined participation (Fig. 1). To ensure uniformity of all procedures, guidelines and protocols were distributed to all medical and paramedical personnel involved in the study and training sessions were held on a regular basis.

A fasting venous blood sample was drawn from an antecubital vein in 10 ml EDTA vacutainers (no fluoride). Venous samples were drawn only in the fasting state to avoid discomfort from sitting with the syringe during the 2-h OGTT. For the 2-h plasma glucose measurements during the OGTTs as described below, we used capillary blood samples. The approach of using 2-h capillary glucose measurements is in accordance with routine practice in many low-income settings including Punjab. Before centrifugation of venous samples, FPG concentration was measured using Accu-Chek glucometers (Roche Diagnostics). Glucometers were calibrated as recommended and measurements were further validated in a subset of women as described below. The glucometer was used for both fasting and post-glucose load measures at a main assembly site of laboratory and bed-side sampling.

OGTT procedures were standardized and performed the same way at all sites. Briefly, the women were requested to drink the 250 ml glucose solution within 5 min, and 2 h after finalizing the glucose ingestion, a single-prick capillary plasma glucose (CPG) concentration was measured using the Accu-Chek glucometer.

Comparative analyses of capillary vs venous plasma glucose

In a randomly chosen subset of 183 women, two samples were drawn simultaneously 2 h after the OGTT for comparative analyses of CPG measured at bed-side by glucometers with venous plasma glucose levels (VPG) measured in the laboratory by the glucose oxidase peroxidase (GOD-POD) method (Microlab 300, Merck Diagnostics) (18). The mean difference in plasma glucose measurements between the two methods was 15%, with the CPG values being higher, which is in accordance with previous reports (19). Accordingly, the post-OGTT CPG measurements were corrected (reduced) by 15%, and with the WHO criteria of GDM, the 2-h cut-off level of 7.8 mmol/l being equal to a measured CPG level of 8.9 mmol/l. There was a significant positive correlation between the CPG and VPG levels ($r=0.82$, $P<0.0001$).

Statistics

Due to the proposal by WHO to lower the fasting diagnostic criteria for GDM, as well as the *a priori* assumption that this might significantly change the prevalence and the characteristics of GDM women in a native Asian setting, separate analyses of prevalence and risk factors was performed based on relevant selected fasting cut-off levels only. ANOVA was used to compare group means of FPG and 2-h PG levels as well as group means of non-GDM and GDM women. The χ^2 test (Pearson) was used for comparison of group frequencies. Multivariate logistic regression analysis with backward elimination of independent variables was used to test the relationship between GDM and variables possibly related to GDM. A linear regression analysis with backward elimination of independent variables was used to test the relationship between FPG and 2-h PG and variables possibly influencing FPG and 2-h PG. All statistical analyses were performed using Stata 13 (StataCorp, College Station, TX, USA). Two-sided *P* values of <0.05 were considered statistically significant.

Results

Subject characteristics

A total of 5100 pregnant women were included in the study. When applying both diagnostic criteria, GDM women had significantly higher FPG and 2-h PG levels ($P<0.001$) compared to non-GDM women. GDM women had increased BMI ($P=0.01$), were older ($P<0.001$) and shorter ($P=0.01$) applying WHO 2013, and were shorter ($P<0.001$) using WHO 1999 criteria compared to non-GDM women (Table 1). Furthermore, non-GDM women had significantly higher FPG ($P<0.0001$) and 2-h PG ($P=0.004$) when applying WHO 1999 criteria, whereas the

GDM women had significantly higher 2-h PG ($P<0.0001$) and significantly lower age ($P=0.02$) and height ($P=0.01$) when diagnosed using WHO 1999 as compared to WHO 2013 criteria.

The risk factor distribution is shown in Table 2. The women had a mean age of 21.5 ± 3.3 years, BMI of 24.2 ± 4.4 kg/m² and a mean GW of 25.4 ± 2.5 weeks (mean $\pm$ s.d.). Information regarding parity was only obtained for 42% of the women, and of these 78% were primipara. As shown in Table 2, the mean FPG ($P<0.001$) and 2-h PG ($P<0.001$) levels were significantly higher in urban compared to rural women. Furthermore, in the unadjusted analyses, Sikh women displayed higher mean FPG ($P=0.04$) and 2-h PG ($P<0.001$) levels compared to Hindu women. Interestingly, vegetarian women displayed significantly increased mean FPG levels compared to non-vegetarian women ($P=0.004$) with no differences between groups for the 2-h PG levels ($P=0.45$). Both FPG and 2-h PG increase with age ($P<0.001$ for both) as well as with BMI ($P<0.001$ for both). Women with a family history of diabetes had increased FPG levels and 2-h PG ($P<0.001$ for both). Finally, there was no statistically significant difference in FPG between illiterate vs illiterate women ($P=0.06$), whereas the 2-h PG level was significantly increased ($P=0.05$) among illiterate compared to literate women (Table 2).

Prevalence of GDM

The overall prevalence of GDM was 9.0% using the WHO 1999 diagnostic criteria (Table 3). However, it increased to 34.9% when applying WHO 2013 criteria. The FPG measurements identified 94% of WHO 2013 GDM cases as opposed to 11% of WHO 1999 GDM cases (Supplementary Table 2, see section on supplementary data given at the end of this article). In contrast, 2-h PG

Table 1 Baseline characteristics for non-GDM and GDM women for FPG, 2-h PG, BMI, age and height when applying the WHO 2013 and WHO 1999 criteria respectively. Data are mean $\pm$ s.d. Comparisons of mean values are performed by ANOVA.

Variables	WHO 2013			WHO 1999			WHO 2013 vs 1999	
	Non-GDM (n=3321)	GDM (n=1779)	P value	Non-GDM (n=4642)	GDM (n=458)	P value	Non-GDM	GDM
							P value	P value
FPG (mmol/l)	4.44 ± 0.49	5.51 ± 0.68	<0.001	4.75 ± 0.65	5.47 ± 1.28	<0.001	<0.0001	0.44
2-h PG (mmol/l)	5.88 ± 1.02	6.87 ± 1.66	<0.001	5.95 ± 0.93	9.07 ± 1.74	<0.001	0.004	<0.0001
BMI (kg/m ²)	24.1 ± 4.28	24.4 ± 4.48	0.01	24.2 ± 4.3	24.5 ± 4.8	0.15	0.33	0.83
Age (years)	21.4 ± 3.3	21.7 ± 3.4	<0.001	21.5 ± 3.3	21.3 ± 3.5	0.16	0.07	0.02
Height (cm)	148 ± 15	147 ± 14	0.01	148 ± 15	145 ± 14	<0.001	0.70	0.01

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Table 2 Mean FPG and 2-h PG levels in relation to subject characteristics (unadjusted data). Data are mean $\pm$ s.d. Applying a *post-hoc* test with Sidak correction, significant differences were found between the following categories: $P \leq 0.05$, FPG: (Hindu and Sikh), (age ≤ 20 and age > 30), (BMI < 20 and $25 \leq \text{BMI} < 30$), ($20 \leq \text{BMI} < 25$ and $25 \leq \text{BMI} < 30$). 2-h PG: (age ≤ 20 and age > 30); $P \leq 0.001$, FPG: (age ≤ 20 and $20 < \text{age} \leq 25$), (age ≤ 20 and $25 < \text{age} \leq 30$), ($25 < \text{age} \leq 30$ and age > 30), (BMI < 20 and BMI ≥ 30), ($20 \leq \text{BMI} < 25$ and BMI ≥ 30). 2-h PG: (Hindu and Sikh), (age ≤ 20 and $20 < \text{age} \leq 25$), (age ≤ 20 and $25 < \text{age} \leq 30$), between all BMI categories.

	n (%)	FPG (mmol/l), Mean $\pm$ s.d.	P ANOVA	2-h PG (mmol/l), Mean $\pm$ s.d.	P ANOVA
Total	5100 (100)	4.81 $\pm$ 0.76		6.23 $\pm$ 1.36	
Habitat					
Rural	2921 (57.27)	4.77 $\pm$ 0.71	<0.001	6.16 $\pm$ 1.30	<0.001
Urban	2179 (42.73)	4.86 $\pm$ 0.82		6.31 $\pm$ 1.44	
Religion					
Hindu	2788 (54.67)	4.79 $\pm$ 0.76	0.04	6.16 $\pm$ 1.44	<0.001
Sikh	2210 (43.33)	4.84 $\pm$ 0.77		6.31 $\pm$ 1.24	
Others	102 (2.00)	4.75 $\pm$ 0.77		6.33 $\pm$ 1.53	
Diet					
Vegetarian	3048 (59.76)	4.84 $\pm$ 0.79	0.004	6.24 $\pm$ 1.29	0.45
Non-vegetarian	2052 (40.24)	4.77 $\pm$ 0.71		6.21 $\pm$ 1.47	
Age (years)					
Age ≤ 20	2068 (40.55)	4.74 $\pm$ 0.79	<0.001	6.02 $\pm$ 1.42	<0.001
$20 < \text{age} \leq 25$	2448 (48.00)	4.85 $\pm$ 0.72		6.34 $\pm$ 1.33	
$25 < \text{age} \leq 30$	540 (10.59)	4.94 $\pm$ 0.78		6.47 $\pm$ 1.19	
Age > 30	44 (0.86)	4.89 $\pm$ 0.96		6.56 $\pm$ 1.15	
BMI (kg/m ²)					
BMI < 20	885 (17.35)	4.75 $\pm$ 0.71	<0.001	5.86 $\pm$ 1.38	<0.001
$20 \leq \text{BMI} < 25$	2221 (43.55)	4.78 $\pm$ 0.74		6.11 $\pm$ 1.43	
$25 \leq \text{BMI} < 30$	1523 (29.86)	4.86 $\pm$ 0.81		6.48 $\pm$ 1.20	
BMI ≥ 30	471 (9.24)	4.93 $\pm$ 0.77		6.65 $\pm$ 1.26	
Family history					
Yes	1938 (38.00)	4.89 $\pm$ 0.69	<0.001	6.60 $\pm$ 1.15	<0.001
No	3162 (62.00)	4.76 $\pm$ 0.79		6.00 $\pm$ 1.43	
Literacy					
Illiterate	1679 (32.92)	4.84 $\pm$ 0.79	0.06	6.28 $\pm$ 1.49	0.05
Literate	3421 (67.08)	4.80 $\pm$ 0.74		6.20 $\pm$ 1.30	

measurements identified only 13% of WHO 2013 GDM cases compared to 96% of the WHO 1999 GDM cases.

Figure 2 shows the relationship between FPG and 2-h PG levels in the women. Although the FPG and 2-h PG values were clearly correlated, the diversity of measurements was increasing with increased values of both measurements, resulting in not only markedly different prevalence of GDM with the WHO 1999 (blue) vs the WHO 2013 (red) criteria. Furthermore, the figure reveals that different women are classified as GDM when using the WHO 1999 vs WHO 2013 criteria.

When looking at the prevalence according to risk factor, urban women had a significantly increased GDM prevalence compared to rural women using both GDM criteria ($P < 0.001$ for WHO 2013 and $P = 0.001$ for WHO 1999) (Table 3). The GDM prevalence was increased in Hindu as compared to Sikh women using WHO 1999 criteria only (overall $P = 0.02$). Interestingly, vegetarianism unadjusted for confounders resulted in a significantly higher GDM prevalence than non-vegetarianism when

WHO 2013 criteria was applied ($P = 0.04$), while non-vegetarian women had significantly higher prevalence when WHO1999 criteria were applied ($P = 0.001$) (Table 3). Age was associated with an increasing GDM prevalence using the WHO 2013 criteria ($P = 0.004$), and there was no effect of increasing BMI on GDM prevalence using either criteria. Family history of diabetes was not associated with increased prevalence of GDM. Illiteracy among pregnant women was associated with increased GDM prevalence compared to literate women using the WHO 1999 criteria only ($P < 0.001$).

Regression analyses

A multivariate logistic regression with backward elimination of independent variables was used to test the relationship between GDM and variables possibly related to GDM (Table 4). A linear regression analysis with backward elimination of independent variables was used to test the relationship between FPG and 2-h PG and

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Table 3 Prevalence (%) of GDM according to GDM diagnostic criteria (unadjusted data). Overall *P* value is determined by a Pearson's χ^2 test. Applying a *post-hoc* test with Sidak correction, significant differences were found between the following categories: WHO 2013, age ≤ 20 and $20 < \text{age} \leq 25$ ($P=0.003$), age ≤ 20 and $25 < \text{age} \leq 30$ ($P=0.005$); WHO 1999, Hindu and Sikh ($P=0.01$).

	WHO 2013	<i>P</i> value	WHO 1999	<i>P</i> value
	FPG ≥ 5.1 or 2-h PG ≥ 8.5 (mmol/l) (<i>n</i> = 1779)		FPG ≥ 7.0 or 2-h PG ≥ 7.8 (mmol/l) (<i>n</i> = 458)	
Overall prevalence (%)	34.9		9.0	
According to risk factor (%)				
Habitat				
Rural	31.9	<0.001	7.9	0.001
Urban	38.8		10.5	
Religion				
Hindu	34.5	0.78	9.8	0.02
Sikh	35.2		7.8	
Others	37.3		12.8	
Diet				
Vegetarian	36.0	0.04	7.9	0.001
Non-vegetarian	33.2		10.6	
Age (years)				
Age ≤ 20	32.1	0.004	8.7	0.87
$20 < \text{age} \leq 25$	36.3		9.2	
$25 < \text{age} \leq 30$	38.5		9.1	
Age > 30	43.2		11.4	
BMI (kg/m ²)				
BMI < 20	33.0	0.24	8.7	0.26
$20 \leq \text{BMI} < 25$	34.3		9.1	
$25 \leq \text{BMI} < 30$	35.9		8.3	
BMI ≥ 30	37.8		11.3	
Family history				
Yes	35.2	0.67	9.0	0.99
No	34.7		9.0	
Literacy				
Illiterate	36.3	0.13	11.3	$P < 0.001$
Literate	34.2		7.8	

possibly related variables (Table 5). The full model included the following variables: habitat_rural, religion_Sikh, religion_Hindu, diet_non-vegetarian, age, height, BMI, family history and literate. Age, height and BMI were continuous variables. The backward elimination was applied to reduce the variable set to include only significant variables as presented in Tables 4 and 5.

In the reduced model including all 5100 women, analysis using the presence or absence of GDM as dependent variable and subject characteristics as independent variables showed that when applying the WHO 2013 criteria, urban habitat ($P < 0.001$), increasing age ($P = 0.001$) and decreasing height ($P = 0.001$) were significant independent GDM risk factors (Table 4). When using the WHO 1999 diagnostic criteria, independent GDM risk factors were urban habitat ($P = 0.001$), Hindu religion ($P < 0.001$), illiteracy ($P < 0.000$), non-vegetarian diet ($P < 0.001$), decreasing height ($P < 0.001$) and increasing BMI ($P = 0.02$) (Table 4).

Independent variables associated with FPG were urban habitat ($P < 0.001$), family history ($P = 0.003$), illiteracy ($P = 0.007$), age ($P < 0.001$) and BMI ($P < 0.001$), whereas independent variables associated with 2-h PG were urban habitat ($P < 0.001$), height ($P < 0.001$), illiteracy ($P < 0.001$), BMI ($P < 0.001$) and family history ($P < 0.001$) (Table 5).

Discussion

In this study of 5100 North Indian pregnant women, we showed an almost four-fold difference (9.0% vs 34.9%) in the prevalence of GDM in North India when comparing the WHO 1999 to the new WHO 2013 criteria. Several distinct factors, including BMI, education (illiteracy), habitat and family history of diabetes all independently influenced both FPG and 2-h PG concentrations. However, increased FPG was also significantly influenced by increasing age and, somewhat paradoxically, by a

Figure 2

Relationship between fasting plasma glucose (FPG) vs 2-h plasma glucose (2-h PG) values during oral glucose tolerance tests for 5100 women. WHO 2013 cut-off is shown in red and WHO 1999 in blue. The figure illustrates that the relationship is not straightforward nor linear, that in particular the different FPG cut-off levels create the large differences in GDM prevalence, and that different women are classified as having GDM using the two criteria. The percentage of women classified as having GDM was 7.2% by both criteria, 1.8% by the 1999 criteria only, and 27.7% by the 2013 criteria only. The remaining 63.3% of all women were classified as non-GDM using both criteria.

vegetarian diet, whereas increased 2-h PG was influenced independently by low adult height. Thus, the relationship between FPG and 2-h PG measurements was not straightforward (Fig. 2), and defining GDM by the somewhat arbitrary WHO 1999/DIPSI vs WHO 2013 criteria identified different distinct risk factors.

Our finding of a higher GDM prevalence of 34.9% using the WHO 2013 criteria, compared to the HAPO study reporting a prevalence of ~18 and ~24% among Asian women (20), may reflect differences in inclusion criteria. Importantly, we included women from the lowest socio-economical classes, many of whom are living in rural areas. Asian women included in the HAPO study were from the most developed Asian cities, Shanghai and Singapore, and may not be entirely representative for the quantitatively largest proportion of women in Asia. From a pilot survey, we were informed by the health authorities maintaining records at the study sites that the average age of women giving birth at the chosen sites was between 20 and 23 years, and that 65–70% were primipara. However, due to a lack of exact records of all of the estimated 12 000

women giving births at the different study sites during the entire period, the extent to which the 5100 women included in the study are fully representative of the population cannot be guaranteed. Overall, the women included in the study were relatively young and predominantly primipara, meaning that we theoretically could have underestimated the true prevalence of GDM.

Our finding of a GDM prevalence of 34.9% using WHO 2013 criteria in North Indian women appears inconsistent with the recently reported prevalence of 14.6% in South Indian women (9). This may be due to a different genetic and cultural admixture of North vs South Indian women. However, this is unlikely to be the full explanation for the more than two-fold difference in GDM prevalence between the studies, and it is noteworthy that the former study, in contrast to our data, reported no significant difference in GDM prevalence using WHO 2013 vs WHO 1999/DIPSI criteria (9). Interestingly, our GDM prevalence using WHO 2013 criteria of 34.9% was close to that of 37% reported among a group of ethnic minority women in Norway (17).

BMI was not an independent risk factor of GDM using the WHO 2013 criteria, and was only weakly associated with increased risk of GDM using the WHO 1999 criteria

Table 4 Logistic regression analysis with backward elimination of independent variables possibly influencing GDM diagnosis applying the WHO 2013 and WHO 1999 criteria. Data are odds ratios (OR) with 95% CI. The full model included the following: habitat_rural, religion_Sikh, religion_Hindu, diet_non-vegetarian, age, height, BMI, family history and literate. Age, height and BMI were continuous variables.

Independent variables applying Criteria (WHO 2013/WHO1999)	OR (95% CI)	P value
WHO 2013		
Habitat (rural vs urban)	0.74 (0.66–0.83)	<0.001
Age ^a	1.10 (1.04–1.17)	0.001
Height ^a	0.92 (0.87–0.98)	0.005
Diet (non-vegetarian vs vegetarian)	0.91 (0.80–1.02)	0.09
Constant	0.82 (0.42–1.60)	0.55
WHO 1999		
Habitat (rural vs urban)	0.72 (0.60–0.88)	0.001
Religion Sikh	0.69 (0.56–0.85)	<0.001
Literacy (literate vs illiterate)	0.69 (0.57–0.85)	<0.001
Diet (non-vegetarian vs vegetarian)	1.44 (1.18–1.75)	<0.001
Height ^a	0.99 (0.98–0.99)	<0.001
BMI ^a	1.12 (1.02–1.24)	0.02
Constant	0.47 (0.14–1.55)	0.21

^aOR resulting from an increase of one s.d.

Table 5 Linear regression analysis with backward elimination of independent variables possibly influencing FPG and 2-h PG. Data are β coefficient with 95% CI. The full model included the following: habitat_rural, religion_sikh, religion_hindu, diet_non-vegetarian, age, height, BMI, family history and literate. Age, height and BMI were continuous variables.

Independent variables for FPG/2-h PG	β coefficient (95% CI)	P value
FPG		
Habitat (rural vs urban)	-0.09 (-0.13 to -0.05)	<0.001
Family history	0.07 (0.02 to 0.12)	0.003
Literacy	-0.06 (-0.11 to -0.02)	0.007
Diet (non-vegetarian vs vegetarian)	-0.04 (-0.08 to 0.0003)	0.05
Age	0.01 (0.006-0.02)	<0.001
BMI	0.01 (0.004-0.02)	<0.001
Constant	4.39 (4.21-4.56)	<0.001
2-h PG		
Habitat (rural vs urban)	-0.16 (-0.23 to -0.08)	<0.001
Religion Sikh	-0.07 (-0.14 to 0.01)	0.10
Height	-0.007 (-0.010 to -0.004)	<0.001
Literacy	-0.17 (-0.25 to -0.09)	<0.001
Age	0.01 (-0.001 to 0.02)	0.08
BMI	0.04 (0.02-0.05)	<0.001
Family history	0.48 (0.40-0.57)	<0.001
Constant	6.13 (5.65-6.61)	<0.001

(Table 4). Reasons for the weak or missing impact of BMI on GDM risk may be that BMI determinations were based on weight in GW 24–28, as well as the possibility that the effect of BMI to some extent may be mediated via other factors such as non-vegetarian diet. Other recent studies have reported a weak impact of BMI on risk of T2D in a low income country (21).

Increasing age is major risk factor for T2D (22, 23). Increasing age was independently associated with increasing FPG but not significantly with increased 2-h PG levels in the linear regression analysis including all 5100 pregnant North Indian women. Thus, the overall effect of age on plasma glucose levels was weak and, in accordance with the regression analyses, increased age was only identified as an independent risk factor of GDM using the WHO 2013 and not the WHO 1999 criteria (Table 5). The age effect may be explained by the decline in pancreatic insulin secretion capacity with age (24, 25), and indeed decreased insulin secretion may influence FPG levels relatively more than the 2-h PG levels, which in contrast may be relatively more influenced by insulin resistance (26).

Illiteracy is a proxy of social class and was also independently associated with increased FPG and 2-h PG measurements in the entire group of women. However, the relative impact (β coefficients, Table 5) of illiteracy was more pronounced on the 2-h PG compared with the FPG measurements, which in turn may explain why illiteracy was only identified as an independent risk factor of GDM using the WHO 1999 compared with WHO 2013 criteria

(Table 4). Other studies have previously found indications of a low social class and poverty being associated with increased risk of developing GDM (8, 27). The explanation for this is unknown, but may include a lower degree of physical activity, differences in diet compositions and body composition factors beyond BMI (such as lower muscle mass), a more adverse intrauterine environment, increased exposure to toxic endocrine disruptors and/or other factors such as low vitamin B12 levels (28) associated with poverty in India.

Adult height is another factor associated with social class and may to some extent express growth 'stunting'. Indeed, low adult height was identified as an independent risk factor of GDM, even above and beyond the effect of illiteracy, using both the WHO 1999 as well as the WHO 2013 criteria (Table 4). Besides social class, adult height may be a marker of early pre- and post-natal nutrition and growth, and may to some extent support the role of the early environment and developmental programming on risk of developing GDM in India (29).

Vegetarianism is a lifestyle chosen by around 50% of all Indians. In the linear regression analyses we found that vegetarianism was not statistically significantly associated with FPG or 2-h PG levels (Table 5). However, in the logistic regression analysis, non-vegetarianism was associated with increased risk of developing GDM by the WHO 1999 but not WHO 2013 criteria (Table 4). Other studies have previously reported vegetarianism to be associated with reduced risk of GDM (30), and may be explained by

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the beneficial effect of vegetables on glucose regulation (31, 32). The reason for the differential effect of vegetarianism on FPG vs 2-h PG levels, explaining the differential impact of vegetarianism on risk of GDM using WHO 1999 or WHO 2013 criteria, may be a somewhat different and skewed distribution of FPG levels among vegetarian compared with non-vegetarian women. This in turn could be due to their lower BMI (Supplementary Table 1, see section on supplementary data given at the end of this article) or perhaps to an insufficient protein, zinc or vitamin D intake.

In accordance with other studies in low- and middle-income countries, we identified a strong positive impact of urban vs rural habitat on FPG and on 2-h PG levels (Table 5), as well as on the risk of GDM using both the WHO 1999 and 2013 criteria (Table 4). This may be due to a general lower level of physical activity, unhealthier diet, low B12 or B12/folate imbalance, as well as other factors such as increased pollution in urban compared to rural habitats (27, 28, 33, 34).

Family history of diabetes is another conventional risk factor of GDM and is supposed to represent the genetic risk dimension of the disease (33). Indeed, family history of diabetes was independently associated with increased FPG as well as increased 2-h PG levels among all women in the analyses. However, family history of diabetes was not identified as an independent risk factor of GDM using either the WHO 1999 or the WHO 2013 criteria (Table 4). This suggests that the chosen cut-off levels defining GDM by either the WHO 1999 or the WHO 2013 criteria may not appropriately reflect the otherwise documented impact of family history of diabetes on FPG and 2-h PG levels, and consequently that analyses of genetic risk factors of glucose intolerance in pregnancy among Indian women should apply analytical approaches to determine the impact of genetic determinants (SNPs) on plasma glucose levels irrespective of any of the currently proposed or applied diagnostic GDM criteria. Another reason for the absent impact of family history of diabetes on risk of GDM could be that 38% of all pregnant women showed a relatively strong family history of diabetes, thereby decreasing its specificity as a risk factor. Finally, the genetic dimension could be inherent in the religion category and explain the increased risk of GDM among Hindu vs Sikh women using the WHO 1999 criteria (Table 4). Whether this difference may be due to variations in body composition, including muscle mass, and/or genetic differences in insulin secretion and/or insulin action remains to be determined. The somewhat paradoxical finding of increased GDM prevalence among Hindu vs Sikh women using the WHO 1999 criteria, despite

slightly higher mean FPG and 2-h PG values among Sikh women, may be explained by differences in distribution and range of plasma glucose levels in the two groups.

We used standard Accu-Chek bedside glucometers to determine the FPG and 2-h PG levels. The 2-h PG measurements were validated in a subset of women using a standardized GOD-POD method, and in accordance with previous results (19) we found an acceptable concordance between the two measurements. This supports the conclusion that bedside glucometers can be used as a cost-effective GDM screening solution in a low-income setting (18, 19, 20). Accordingly, the current study proved to be the most cost-effective among all of the included screening programs in a recent report (22, 21). Furthermore, the overall attendance rate of 82% compared with 54% in the HAPO study (7) and 74% in a recent Norwegian GDM screening study (35) is high, and the results are therefore likely to be representative for the general population of Punjab. For reasons of convenience, we used capillary blood samples for the 2-h PG measurements, which due to the fluctuating plasma glucose levels after glucose ingestion exhibit a higher variability compared with fasting measurements obtained during steady state glucose levels. This may to some unknown extent contribute to the relatively large variation between fasting and 2-h PG measurements across the full range of glucose tolerance status as illustrated in Fig. 2, and may have caused some degree of misclassification of cases with 2-h PG measurements near the respective GDM cut-off levels. However, given that the variability of measurements influence glucose measurements in both directions, this is unlikely to have influenced the GDM prevalence determinations.

The new WHO 2013 criteria in addition recommend 1-h post-OGTT PG measurements, which was not performed in this study, initiated before these criteria were ultimately defined. However, inclusion of 1-h PG measurements could only increase the already extremely high GDM prevalence using the WHO 2013 criteria fasting and 2-h cut-off levels.

The data available for the current study does not include pregnancy outcomes. While follow-up studies of mothers and offspring are planned for the future, it needs to be emphasized that such studies will not answer the most crucial questions of the causality of adverse outcomes associated with GDM. A meta-analysis from 2008 concluded that there is insufficient evidence to show beneficial effects of intensive glucose-lowering treatment for long-term adverse GDM complications, including risk of dysmetabolic traits in the offspring (23). Importantly,

it was mentioned that potential residual confounding risk factors such as educational status, body fat content and distribution, urbanisation, etc., and not necessarily elevated plasma glucose level *per se*, might be responsible for some adverse pregnancy outcomes associated with GDM. This may in particular be the case for the mildest elevations of plasma glucose levels in pregnancy, which was a major argument for the US committee not to endorse the proposed GDM criteria by the IASDPG (10).

The group defined as literate in this study may have included an unknown proportion of women with limited writing skills who are likely also to have been defined as illiterate women if more elaborate tests had been used. Nevertheless, using the very simple criteria of being able to write own name, we identified the one third of all of the screened women with the lowest degree of education, justifying our approach in this unique low-income North Indian setting.

Taken together, we have shown that GDM would affect more than one third of all pregnant women in North India if the WHO 2013 GDM criteria were implemented. However, there is insufficient knowledge of the short- and long-term clinical outcomes of lifestyle as well as pharmacological interventions against GDM using WHO 2013 criteria, and therefore it can be questioned whether these criteria really should be endorsed uncritically in India. Besides being associated with enormously increased health care expenditures, defining every third Indian woman with a GDM diagnosis carries with it an important personal adverse stigmatizing dimension, since being diagnosed with diabetes in India may have strong social consequences for a young woman. Altogether, we therefore recommend awaiting further significant outcome data before introducing the proposed WHO 2013 criteria in India.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-14-14-0428>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

G P Arora designed the study, acquired data, analysed and interpreted data and drafted the manuscript. R G Thaman, R B Prasad and C Brøns interpreted data and drafted the manuscript. P Almgren performed statistical analyses. L C Groop and A A Vaag designed the study, interpreted data and drafted the manuscript. All authors have approved the final version of the manuscript to be published.

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