Anthropometric measures and HbA1c to detect dysglycemia in young Asian women planning conception: The S-PRESTO cohort

Anne HY Chu[1], Izzuddin M Aris[1,2,3], Sharon Ng[2], See Ling Loy[4,5], Jonathan Y Bernard[1,6], Mya Thway Tint[1,2], Wen Lun Yuan[7], Keith M Godfrey[8], Jerry Kok Yen Chan[4,5], Lynette Pei-Chi Shek[1,7], Yap Seng Chong[1,2], Kok Hian Tan[5,9], Seng Bin Ang[10], Heng Hao Tan[4,5], Bernard SM Chern[5,11], Fabian Yap[12,13], Yung Seng Lee[1,7], Ngee Lek[5,13], Melvin Khee-Shing Leow[1,5], Chin Meng Khoo[14], Shiao-Yng Chan[1,2*]

[1]Singapore Institute for Clinical Sciences (SICS), Agency for Science, Technology and Research (A*STAR), Singapore
[2]Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[3]Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA
[4]Department of Reproductive Medicine, KK Women's and Children Hospital, Singapore
[5]Duke-NUS Medical School, Singapore
[6]Centre for Research in Epidemiology and Statistics, Inserm, Villejuif, France
[7]Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[8]MRC Lifecourse Epidemiology Unit and NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK
[9]Department of Maternal Fetal Medicine, KK Women's and Children's Hospital, Singapore
[10]Department of Family Medicine Service, KK Women's and Children's Hospital, Singapore
[11]Division of Obstetrics & Gynaecology, KK Women's and Children's Hospital, Singapore
[12]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[13]Department of Paediatrics, KK Women's and Children's Hospital, Singapore
[14]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Address reprints and correspondence to:
***Shiao-Yng Chan**. Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore. NUHS Tower Block Level 12, 1E Kent Ridge Road, Singapore 119228. Email: obgchan@nus.edu.sg

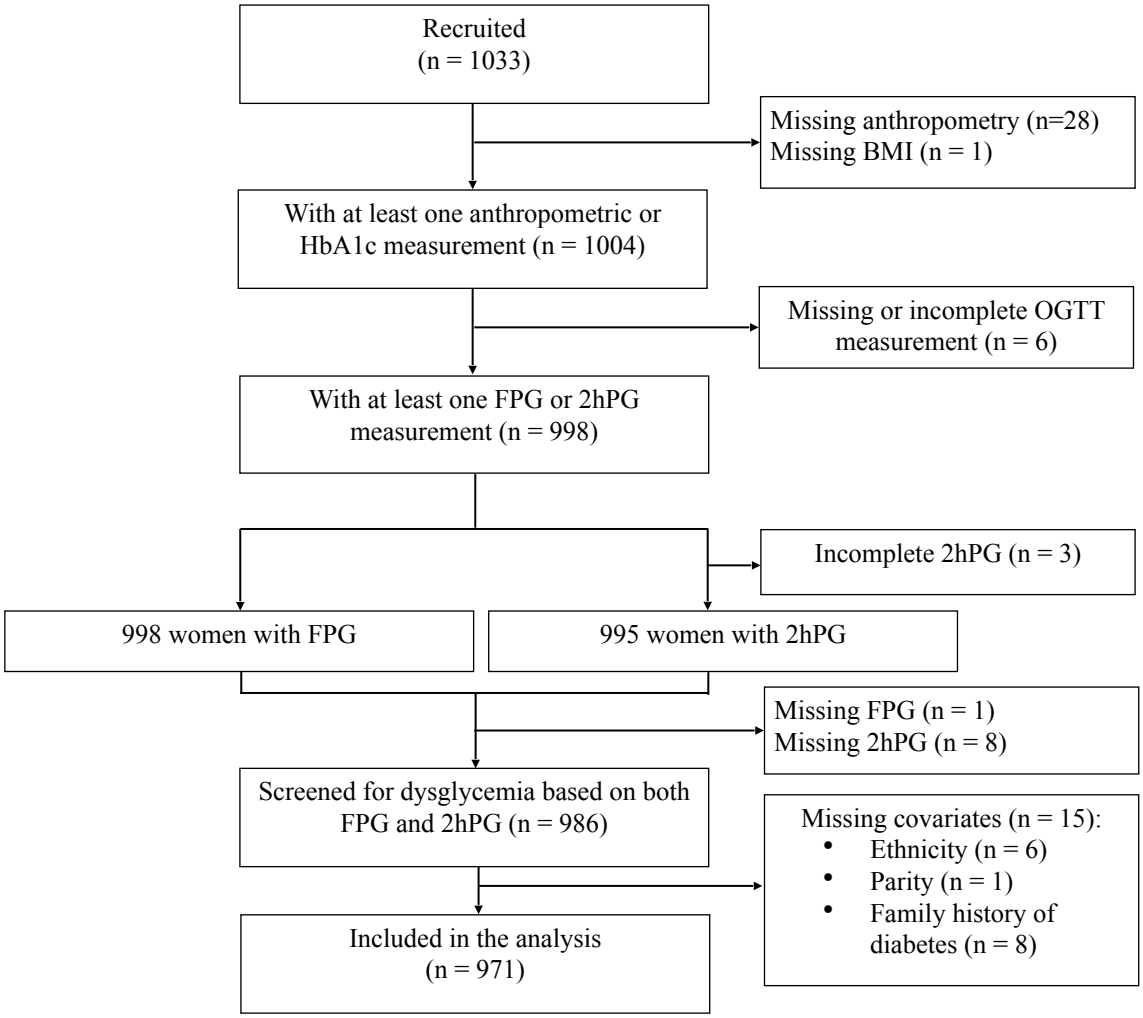

Figure S1: Study flowchart

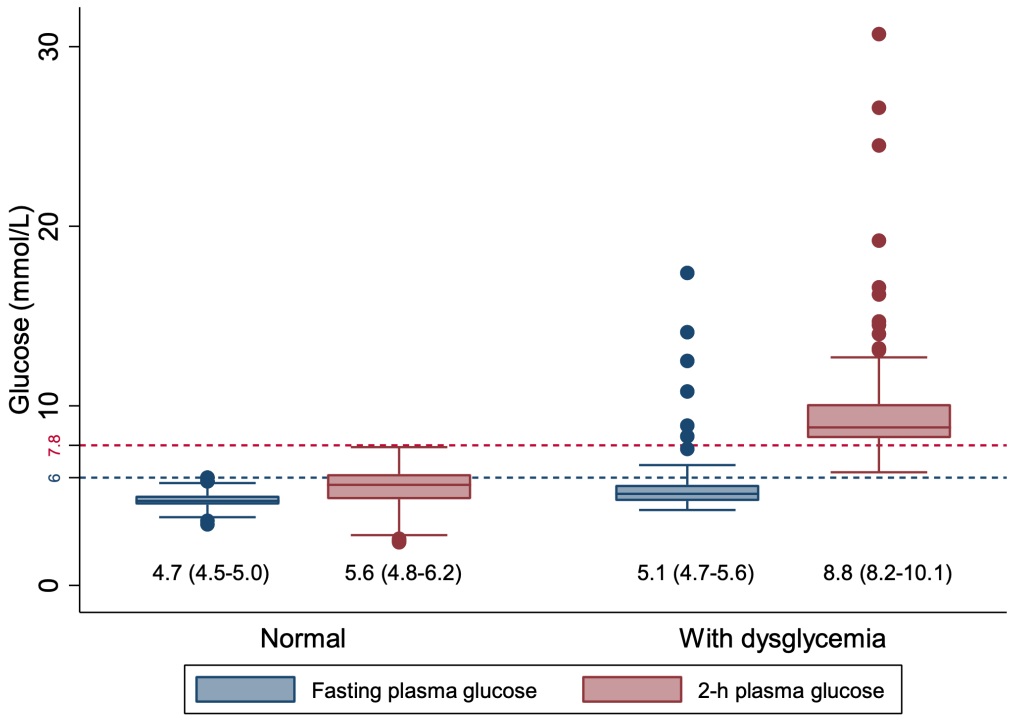

Figure S2: Boxplot distribution of fasting and 2h-glucose between women without (n=865) and with dysglycemia (n=106). Numbers below each boxplot represent median (interquartile range) values for fasting and 2-h plasma glucose (mmol/L).
Blue dashed line: fasting glucose cut-point 6.0 mmol/L; red dashed line: 2-h plasma glucose cut-point 7.8 mmol/L.

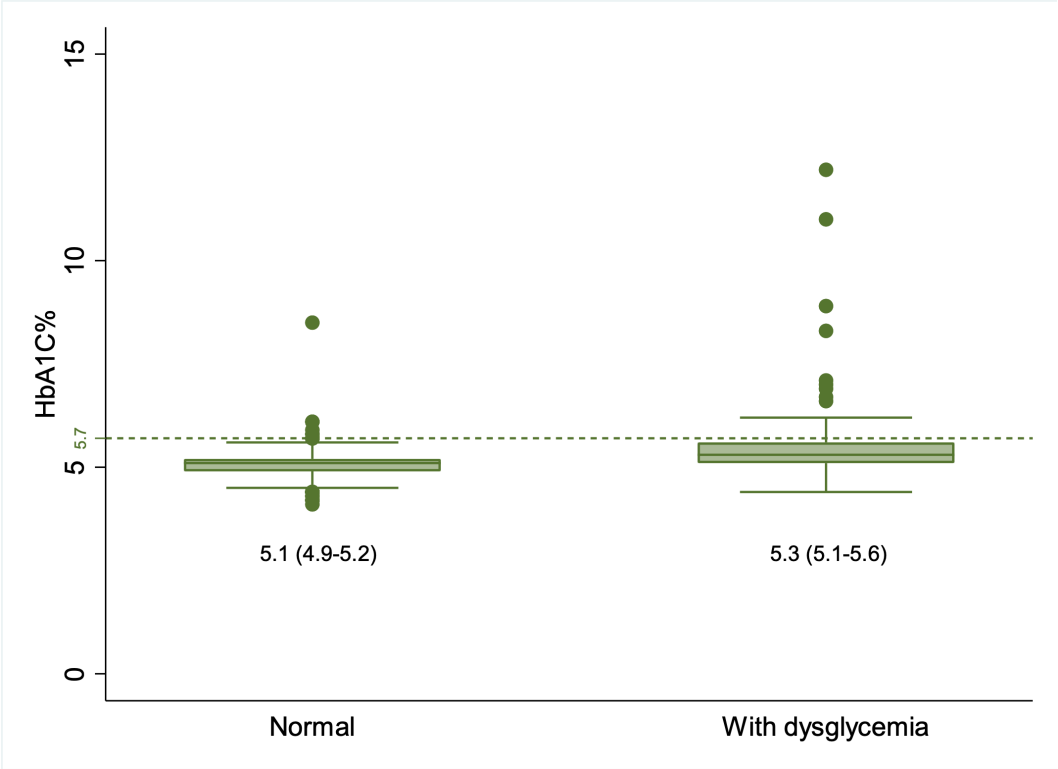

Figure S3: Boxplot distribution of HbA1c between women without (n=841) and with dysglycemia (n=105) women. Numbers below each boxplot represent median (interquartile range) values for HbA1c (%).

Table S1: Study inclusion and exclusion criteria

Inclusion criteria
Women aged 18-45 years
Intention to reside in Singapore for the next 5 years
Chinese, Malay, Indians, or a combination of these
Planning to conceive within 1 year
Able to provide written, informed consent
Exclusion criteria
Have been actively trying to conceive for more than 18 months
Currently pregnant Type 1 or Type 2 diabetes
On fertility medication (e.g. hormones injection, IVF treatments) other than *Clomid / Letrozole (Femara)* in the past 1 month
Oral or implanted contraception, or with an IUCD in situ in the past 1 month
On systemic steroids in the past 1 month
On anticonvulsants in the past 1 month
On HIV or Hepatitis B or C treatment medication in the past 1 month
Eventual multiple pregnancies

Table S2: Inter-observer technical error of measurement (TE) and coefficient of variation (CV) of anthropometry

	TE	**CV (%)**
Weight	0.06 kg	0.13
Height	0.50 cm	0.26
Waist circumference	1.36 cm	2.20
Hip circumference	1.56 cm	2.39
Triceps skinfolds	0.49 mm	4.26
Biceps skinfolds	0.52 mm	13.29
Subscapular skinfolds	1.27 mm	11.80
Suprailiac skinfolds	1.63 mm	29.91

Table S3: Comparison of characteristics between included and excluded participants†

	Included n=971	Excluded n=62	p-value
Demographics			
Age (year)	30.8 ± 3.7	31.2 ± 4.7	0.46
Ethnicity			0.14
Chinese	698 (71.9)	42 (80.8)	
Malay	153 (15.8)	2 (3.8)	
Indian	87 (8.9)	6 (11.5)	
Mixed	33 (3.4)	2 (3.9)	
Educational level			0.01
No/Primary/Secondary	114 (11.7)	11 (25.0)	
Post-secondary	243 (25.0)	14 (31.8)	
Tertiary	614 (63.2)	19 (43.2)	
Smoking history			
Never	868 (89.4)	32 (88.8)	0.94
Previous smoker	60 (6.2)	2 (5.6)	
Current smoker	43 (4.4)	2 (5.6)	
Shiftwork‡			0.72
No/Unemployed	834 (85.9)	31 (83.8)	
Yes	137 (14.1)	6 (16.2)	
Clinical characteristics			
Menstrual cycle regularity			0.17
Regular	629 (64.8)	24 (54.5)	
Irregular	342 (35.2)	20 (45.5)	
Parity			0.66
Nulliparous	627 (64.6)	28 (80.0)	
Primiparous	262 (27.0)	5 (14.3)	
Multiparous	82 (8.4)	2 (5.7)	
Previous history of GDM§			0.36
No	466 (47.8)	14 (40.0)	
Yes	24 (2.5)	0 (0)	

Family history of diabetes			0.10
No	681 (70.1)	15 (55.6)	
Yes	290 (29.9)	12 (44.4)	
Glucose test			
HbA1c	5.1 ± 0.5	5.2 ± 0.5	0.29
FPG	4.8 ± 0.7	4.9 ± 1.0	0.47
2hPG	6.0 ± 2.1	6.8 ± 3.4	0.10

† Values are means ± SD or *n* (%).
‡ Only for subjects who were employed.
§ Excluding nulliparous women
Sample sizes differ due to missing data.
P-values obtained by independent t-test (continuous) or chi-square analysis/ Fisher's exact test (categorical).

Table S4: Anthropometric measures of all women by glycemic status

	All (%)† (n=971)	Normal Glucose Tolerance (n=865)	Dysglycemia (n=106)	p-value
Anthropometric measures§				
Weight (kg)	971 (100.0)	59.9 ± 13.1	67.2 ± 16.1	<0.01
Height (m)	971 (100.0)	1.60 ± 0.55	1.59 ± 0.57	<0.01
Waist circumference (cm)	968 (99.7)	82.5 ± 11.4	89.1 ± 12.8	<0.01
Hip circumference (cm)	968 (99.7)	96.4 ± 9.8	100.6 ± 11.5	<0.01
Triceps skinfolds (mm)	969 (99.8)	22.8 ± 7.5	27.2 ± 7.3	<0.01
Biceps skinfolds (mm)	969 (99.8)	11.1 ± 5.6	15.5 ± 7.5	<0.01
Subscapular skinfolds (mm)	959 (98.8)	20.1 ± 7.8	26.9 ± 9.0	<0.01
Supra-iliac skinfolds (mm)	968 (99.7)	18.0 ± 7.4	22.5 ± 7.7	<0.01
BMI (kg/m^2)	971 (100.0)	23.4 ± 5.0	26.7 ± 6.2	<0.01
Waist-to-hip ratio	967 (99.6)	0.85 ± 0.06	0.89 ± 0.06	<0.01
Waist-to-height ratio	968 (99.7)	0.52 ± 0.07	0.56 ± 0.08	<0.01
ABSI¶	968 (99.7)	0.0802 ± 0.0053	0.0799 ± 0.0046	0.58
Peripheral (triceps + biceps) skinfolds (mm)	969 (99.8)	34.0 ± 11.7	42.7 ± 13.8	<0.01
Truncal (subscapular + suprailiac) skinfolds (mm)	958 (98.7)	38.0 ± 14.0	49.3 ± 15.5	<0.01
Total skinfolds (mm)	958 (98.7)	71.8 ± 24.3	91.7 ± 27.6	<0.01
Subscapular-to-triceps ratio	959 (98.8)	0.89 ± 0.23	0.99 ± 0.22	<0.01

† Total sample size (n) is not always 971 due to the missing values
§ Mean ± SD
¶ Rounded to four decimal places due to small values
ABSI, A Body Shape Index; BMI, body mass index

Table S5: Sensitivity analysis of categorical anthropometry and HbA1c – AUROC, sensitivity and specificity in detecting dysglycemia with adjustment for four commonly considered risk factors (age, ethnicity, previous GDM history, and family history of diabetes)

			With history		
Model	**Variables**	**n**	**AUROC[†] (95% CI)**	**Sensitivity[‡] (%)**	**Specificity[‡] (%)**
1	History[§]	971	0.59 (0.53-0.64)[y]	47.2	65.6
2	HbA1c ≥5.7%	946	0.66 (0.60-0.72)[ax]	29.5	96.3
3	BMI ≥23kg/m^2	971	0.68 (0.63-0.73)[A]	73.6	57.1
4	WHtR ≥90th percentile	968	0.61 (0.55-0.67)[y]	31.1	81.1
5	Total skinfolds ≥90th percentile	958	0.65 (0.59-0.71)[a]	33.3	86.1
6	BMI ≥23kg/m^2 + WHtR ≥90th percentile + Total skinfolds ≥90th percentile	957	0.71 (0.66-0.76)[Ay]	72.4	58.8
7	BMI ≥23kg/m^2 + HbA1c ≥5.7%	946	0.73 (0.67-0.78)[Axy]	63.8	65.2
8	BMI ≥25kg/m^2 + HbA1c ≥5.7%	946	0.74 (0.69-0.80)[Axy]	63.8	74.3
9	BMI ≥23kg/m^2 + WHtR ≥90th percentile + Total skinfolds ≥90th percentile + HbA1c ≥5.7%	932	0.75 (0.69-0.80)[Axy]	64.4	71.5

[†] AUROC values were based on cases containing only complete data on all variables (n=932).

[‡] Sensitivity and specificity estimates were based on cases with available variables used to create each model.

[§] Age (>30 years), ethnicity, GDM history, and family history of diabetes

[a] $p<0.05$; [A] $p<0.001$ vs Model 1 (history)

[x] $p<0.05$ vs Model 2 with history

[y] $p<0.05$ vs Model 3 with history

AUROC, area under receiver-operating characteristic; BMI, body mass index; HbA1c, glycated haemoglobin; WHtR, waist-to-height ratio

Table S6: Clinical utility of different strategies in detecting dysglycemia preconception among 922 women without previous history of GDM who provided both BMI and HbA1C measures (99 out of 922 women with a HbA1c measure had dysglycemia)

		Positive predictive value (%)	Negative predictive value (%)	Number to proceed to OGTT (% of all screened)	Number of dysglycemia identified (% of all dysglycemia)	Number of dysglycemia cases missed (% of all dysglycemia)
1.	HbA1c≥5.7%	65.8	91.6	38 (4.1%)	25 (25.3%)	74 (74.7%)
2.	BMI≥23kg/m² +HbA1c≥5.7%	17.2	94.6	418 (46.0%)	72 (72.7%)	27 (27.3%)
3.	BMI ≥23kg/m² + WHtR ≥90th percentile + Total skinfolds ≥90th percentile + HbA1c ≥5.7%†	17.9	94.3	380 (41.8%)	68 (69.4%)	30 (30.6%)
4.	BMI≥25kg/m² +HbA1c≥5.7%	22.9	94.2	266 (28.9%)	61 (61.6%)	38 (38.4%)
5.	BMI ≥23kg/m² + HbA1c ≥5.7% + History‡	21.1	93.7	275 (29.8%)	58 (58.6%)	41 (41.4%)

† n=909 provided all measurements (98 out of 909 women with dysglycemia).
‡ History variables included: Age (>30 years), ethnicity, educational level, smoking history, shift work, menstrual cycle regularity, parity, and family history of diabetes.

Table S7: Different thresholds of anthropometry and HbA1c for screening dysglycemia

	Without history			With history†		
	AUROC (95% CI)	**Sensitivity (%)**	**Specificity (%)**	**AUROC (95% CI)**	**Sensitivity (%)**	**Specificity (%)**
BMI (kg/m²)						
0.5 unit increment						
≥27.5	0.624 (0.58-0.67)	40.6	84.3	0.702 (0.65-0.76)	58.5	70.6
≥27	0.631 (0.58-0.68)	43.4	82.8	0.706 (0.65-0.76)	61.3	69.5
≥26.5	0.646 (0.60-0.70)	48.1	81.2	0.715 (0.66-0.77)	65.1	70.9
≥26	0.653 (0.60-0.70)	51.9	78.6	0.719 (0.67-0.77)	67.9	69.7
≥25.5	0.667 (0.62-0.72)	56.6	76.9	0.721 (0.67-0.78)	64.2	73.1
≥25	0.672 (0.62-0.72)	59.4	75.0	0.727 (0.67-0.78)	63.2	72.4
≥24.5	0.656 (0.61-0.70)	59.4	71.7	0.719 (0.67-0.77)	65.1	68.7
≥24	0.667 (0.62-0.71)	66.0	67.3	0.719 (0.67-0.77)	67.9	66.0
≥23.5	0.668 (0.62-0.71)	69.8	63.8	0.724 (0.67-0.78)	71.7	63.4
≥23	0.648 (0.60-0.69)	71.7	57.9	0.707 (0.65-0.76)	67.9	68.7
0.1 unit increment						
≥24.0	0.667 (0.62-0.71)	66.0	67.3	0.719 (0.67-0.77)	67.9	66.0
≥23.9	0.670 (0.62-0.72)	67.0	66.9	0.723 (0.67-0.78)	68.9	65.6
≥23.8	0.671 (0.62-0.72)	67.9	66.2	0.726 (0.67-0.78)	69.8	64.9
≥23.7	0.673 (0.63-0.72)	68.9	65.8	0.729 (0.68-0.78)	70.8	64.5
≥23.6	0.670 (0.62-0.72)	68.9	65.2	0.728 (0.68-0.78)	70.8	64.3
≥23.5	0.668 (0.62-0.71)	69.8	63.8	0.724 (0.67-0.78)	71.7	63.4
≥23.4	0.665 (0.62-0.71)	70.8	62.3	0.722 (0.67-0.77)	72.6	62.4
≥23.3	0.664 (0.62-0.71)	71.7	61.2	0.721 (0.67-0.77)	72.6	61.9
≥23.2	0.657 (0.61-0.7)	71.7	59.8	0.713 (0.66-0.77)	69.8	62.9
≥23.1	0.652 (0.61-0.7)	71.7	58.7	0.709 (0.65-0.76)	67.9	66.7
≥23.0	0.648 (0.6-0.69)	71.7	57.9	0.707 (0.65-0.76)	67.9	68.7
WHtR percentile						
≥99	0.525 (0.50-0.55)	1.9	99.2	0.653 (0.60-0.71)	55.7	66.8
≥95	0.566 (0.53-0.61)	9.4	95.5	0.654 (0.60-0.71)	53.8	66.9
Total Skinfolds percentile						
≥99	0.563 (0.53-0.60)	2.9	99.3	0.656 (0.60-0.71)	55.2	66.6
≥95	0.511 (0.49-0.53)	16.2	96.4	0.674 (0.62-0.73)	49.5	74.0
HbA1c (%)						
≥5.6	0.632 (0.59-0.68)	29.5	96.9	0.720 (0.66-0.78)	53.3	78.8
≥5.5	0.651 (0.60-0.70)	36.2	94.1	0.728 (0.67-0.79)	56.2	78.6
≥5.4	0.684 (0.63-0.73)	48.6	88.2	0.753 (0.70-0.81)	59.1	82.1
≥5.3	0.701 (0.65-0.75)	61.0	79.3	0.763 (0.71-0.81)	68.6	75.9
≥5.2	0.695 (0.65-0.74)	74.3	64.7	0.755 (0.71-0.80)	77.1	63.9
≥5.1	0.656 (0.62-0.69)	84.8	46.5	0.728 (0.68-0.77)	73.3	61.9

≥5.0	0.581 (0.55-0.61)	89.5	26.8	0.687 (0.64-0.74)	66.7	59.3

†Age (>30 years), ethnicity, educational level, smoking history, shift work, menstrual cycle regularity, parity, GDM history, and family history of diabetes. AUROC, area under receiver-operating characteristic; BMI, body mass index; HbA1c, glycated hemoglobin; WHtR, waist-to-height ratio

Table S8: Sensitivity analyses performed using different BMI (≥23.7 and ≥27.5 kg/m²) and HbA1c cut-offs (≥5.3 and ≥6.0%) in detecting dysglycemia

		Without history			With history		
Model		**AUROC (95% CI)**	**Sensitivity (%)**	**Specificity (%)**	**AUROC (95% CI)**	**Sensitivity (%)**	**Specificity (%)**
1	History†	-	-	-	0.65 (0.60-0.71)	55.7	67.3
BMI ≥23.7 kg/m²							
2	BMI ≥23.7 kg/m²	0.68 (0.63-0.72)[z]	68.9	65.8	0.73 (0.68-0.78)[a]	70.8	64.5
BMI ≥27.5 kg/m²							
3	BMI ≥27.5 kg/m²	0.63 (0.58-0.68)[z]	40.6	84.3	0.70 (0.65-0.76)[a]	58.5	70.6
4	BMI ≥27.5 kg/m² + WHtR ≥90th percentile + Total skinfolds ≥90th percentile	0.64 (0.59-0.69)[z]	41.9	83.9	0.71 (0.66-0.76)[a]	58.1	72.1
5	BMI ≥27.5 kg/m²+ HbA1c ≥5.7%	0.67 (0.62-0.73)[bz]	47.6	83.9	0.74 (0.68-0.79)[aw]	55.2	77.1
6	BMI ≥27.5 kg/m² + Total skinfolds ≥90th + WHtR ≥90th percentile + HbA1c ≥5.7%	0.68 (0.63-0.74)[bz]	46.2	86.1	0.73 (0.68-0.79)[aw]	53.9	79.8
HbA1c ≥5.3%							
7	HbA1c ≥5.3%	0.70 (0.65-0.75)[z]	61.0	79.3	0.76 (0.71-0.81)[a]	68.6	76.0
8	BMI ≥23 kg/m² + HbA1c ≥5.3%	0.74 (0.69-0.79)[acz]	61.0	79.3	0.77 (0.73-0.82)[a]	67.6	75.7
9	BMI ≥23.7 kg/m² + HbA1c ≥5.3%	0.75 (0.69-0.8)[acz]	61.0	79.3	0.78 (0.73-0.83)[a]	66.7	74.9
10	BMI ≥23.7 kg/m² + WHtR ≥90th percentile + Total skinfolds ≥90th percentile + HbA1c ≥5.3%	0.75 (0.70-0.81)[acz]	65.4	75.7	0.78 (0.73-0.83)[a]	69.2	75.7
HbA1c ≥6.0%							
11	HbA1c ≥6.0%	0.58 (0.54-0.62)[az]	17.1	99.6	0.69 (0.64-0.75)[a]	52.4	75.3
12	BMI ≥23 kg/m² + HbA1c ≥6.0%	0.69 (0.63-0.74)[dz]	72.4	57.9	0.74 (0.69-0.80)[ay]	61	73.4
13	BMI ≥23 kg/m² + WHtR ≥90th percentile + Total skinfolds ≥90th percentile + HbA1c ≥6.0%	0.70 (0.64-0.75)[dz]	72.1	58.5	0.74 (0.69-0.80)[ay]	60.6	73

† Age (>30 years), ethnicity, educational level, smoking history, shift work, menstrual cycle regularity, parity, GDM history, and family history of diabetes
[a] p<0.05 vs Model 1 (history)
[b] p<0.05 vs Model 3 without history (across Model 3 – 6)
[c] p<0.05 vs Model 7 without history (across Model 7 –10)
[d] p<0.05 vs Model 11 without history (across Model 11 –13)
[w] p<0.05 vs Model 3 with history (across Model 3 – 6)
[x] p<0.05 vs Model 7 with history (across Model 7 –10)
[y] p<0.05 vs Model 11 with clinical history (across Model 11 –13)
[z] p<0.05 vs with history
AUROC, area under receiver-operating characteristic; BMI, body mass index; HbA1c, glycated hemoglobin; WHtR, waist-to-height ratio