Online Supplemental Materials

Supplemental Table

Supplemental Table 1. Ethnic Differences in Insulin Sensitivity and Secretion, Beta Cell Function, and Hepatic Insulin Clearance by Glucose Tolerance Categories after Adjusting for Time Since Index Pregnancy

		NGT		**Prediabetes/diabetes**		**All**
		South Asian	Nordic	South Asian	Nordic	*p* value†
		n=55 [31%]	n=57 [53%]	n=123 [69%]	n=51 [47%]	n=286
Insulin sensitivity	HOMA2-S	102 (9)	137 (20)***	63 (6)	81 (13)**	<0.001
	Muscle-ISI	0.24 (0.02)	0.31 (0.05)**	0.27 (0.03)	0.31 (0.06)	0.460
	Matsuda-ISI	5.7 (0.5)	7.7 (1.1)***	2.9 (0.3)	3.7 (0.6)**	<0.001
Insulin secretion	HOMA2-B	113 (5)	100 (11)*	108 (5)	99 (12)	0.646
	Pre-hepatic IGI	2.1 (0.4)	2.1 (0.8)	1.5 (0.2)	1.5 (0.4)	<0.001
	Peripheral-IGI	0.9 (0.2)	0.4 (0.4)*	1.0 (0.2)	0.7 (0.4)	<0.001
Beta cell function	Beta-GS	167 (11)	153 (24)	154 (10)	151 (21)	<0.001
	Pre-hepatic-DI	11.8 (1.6)	16.3 (3.3)**	4.4 (0.5)	5.3 (1.0)*	<0.001
	Peripheral-DI	4.8 (0.6)	5.5 (1.4)	2.4 (0.3)	2.3 (0.7)	<0.001
HIC	HIC-fasting	3.2 (0.2)	3.8 (0.3)***	3.1 (0.2)	3.9 (0.3)***	<0.001
	HIC-OGTT	2.1 (0.1)	2.0 (0.2)	2.0 (0.1)	1.9 (0.2)	0.385

Data presented as mean (SEM). Beta-GS: beta cell glucose sensitivity, DI: disposition index, HIC: hepatic insulin clearance, HOMA-S: HOMA2-sensitivity, IGI: insulinogenic index, ISI: insulin sensitivity index, NGT: normal glucose tolerance Peripheral' = measured peripheral insulin levels. 'Prehepatic' = estimated pre-hepatic insulin levels based on deconvolution of C-peptide kinetics.

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$ for South Asian vs. Nordic women

†$p \leq 0.05$, ††$p \leq 0.01$, †††$p \leq 0.001$ for NGT vs. prediabetes or diabetes

Supplemental Table 2. Ethnic Differences in Insulin Sensitivity and Secretion, Beta Cell Function, and Hepatic Insulin Clearance by Glucose Tolerance Categories after Adjusting for BMI

		NGT		**Prediabetes/diabetes**		**All**
		South Asian	Nordic	South Asian	Nordic	*p* value†
		n=55 [31%]	n=57 [53%]	n=123 [69%]	n=51 [47%]	n=286
Insulin sensitivity	HOMA2-S	203 (8)	236 (22)***	145 (5)	167 (17)***	<0.001
	Muscle-ISI	0.40 (0.02)	0.46 (0.07)*	0.40 (0.02)	0.46 (0.08)	0.896
	Matsuda-ISI	12.3 (0.5)	14.1 (1.4)***	7.3 (0.3)	8.5 (0.8)***	<0.001
Insulin secretion	HOMA2-B	61 (5)	51 (12)*	63 (5)	50 (18)*	0.475
	Pre-hepatic IGI‡	1.8 (1.1)	0.8 (1.3)	1.7 (1.1)	0.6 (1.4)	<0.001
	Peripheral-IGI‡	1.6 (1.1)	0.2 (1.3)*	1.6 (1.1)	0.2 (1.5)	<0.001
Beta cell function	Beta-GS	36 (10)	27 (25)	58 (9)	48 (31)	<0.001
	Pre-hepatic-DI	10.8 (1.5)	14.9 (4.6)**	7.7 (0.5)	8.9 (1.7)*	<0.001
	Peripheral-DI	5.9 (0.6)	6.9 (1.9)	2.8 (0.3)	2.9 (1.1)	<0.001
HIC	HIC-fasting	3.2 (0.2)	3.8 (0.4)***	3.0 (0.2)	3.8 (0.5)***	<0.001
	HIC-OGTT	1.9 (0.1)	1.8 (0.3)	1.6 (0.1)	1.5 (0.3)	0.515

Data presented as mean (SEM). Beta-GS: beta cell glucose sensitivity, DI: disposition index, HIC: hepatic insulin clearance, HOMA-S: HOMA2-sensitivity, IGI: insulinogenic index, ISI: insulin sensitivity index, NGT: normal glucose tolerance Peripheral' = measured peripheral insulin levels. 'Prehepatic' = estimated pre-hepatic insulin levels based on deconvolution of C-peptide kinetics.

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$ for South Asian vs. Nordic women

†$p \leq 0.05$, ††$p \leq 0.01$, †††$p \leq 0.001$ for NGT vs. prediabetes or diabetes

‡Log-transformed data

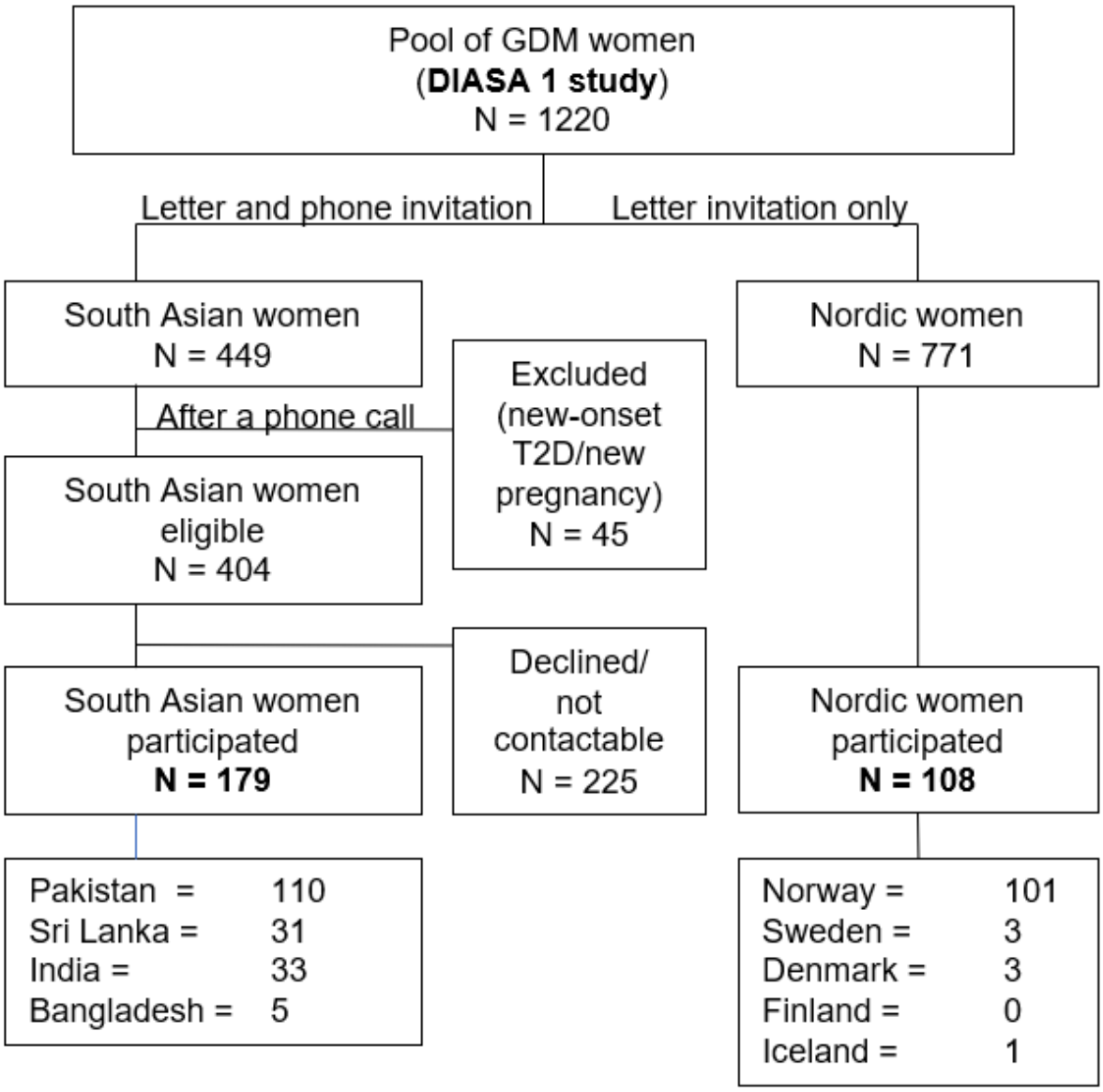
Supplemental Table 3. The Participating and Non-Participating Women's Characteristics by Ethnicity

	South Asian			Nordic		
	Participants n = 179	Non-participants n = 100	p-value	Participants n = 108	Non-participants n = 100	p-value
Pre-pregnancy age (years)	33.3 (4.0)	33.0 (4.2)	0.556	35.2 (4.7)	33.3 (6.2)	0.013
Self-reported pre-pregnancy weight (kg)	70.3 (13.4)	69.7 (15.9)	0.738	79.3 (18.0)	81.5 (18.7)	0.388
Pre-pregnancy BMI (based on self-reported weight)	27.5 (4.7)	27.1 (5.7)	0.529	28.4 (6.2)	29.4 (5.9)	0.236
Pregnancy FPG at OGTT	5.5 (0.7)	5.4 (0.7)	0.254	5.3 (0.7)	5.5 (1.0)	0.094
Pregnancy 2-h OGTT glucose	9.2 (1.8)	9.4 (1.9)	0.384	9.0 (1.7)	9.2 (1.3)	0.345
Insulin ± Metformin use in pregnancy	97 [54]	55 [55]	0.873	40 [37]	41/99 [41]	0.556
Insulin use in pregnancy	72 [40]	40 [40]	0.971	34 [31]	36/99 [36]	0.447
GDM prior to the index pregnancy	55/175 [31]	27 [27]	0.485	24 [22]	14 [14]	0.136
1.degree relatives w/diabetes	125/168 [74]	69/92 [75]	0.860	22/91 [24]	20/80 [25]	0.531

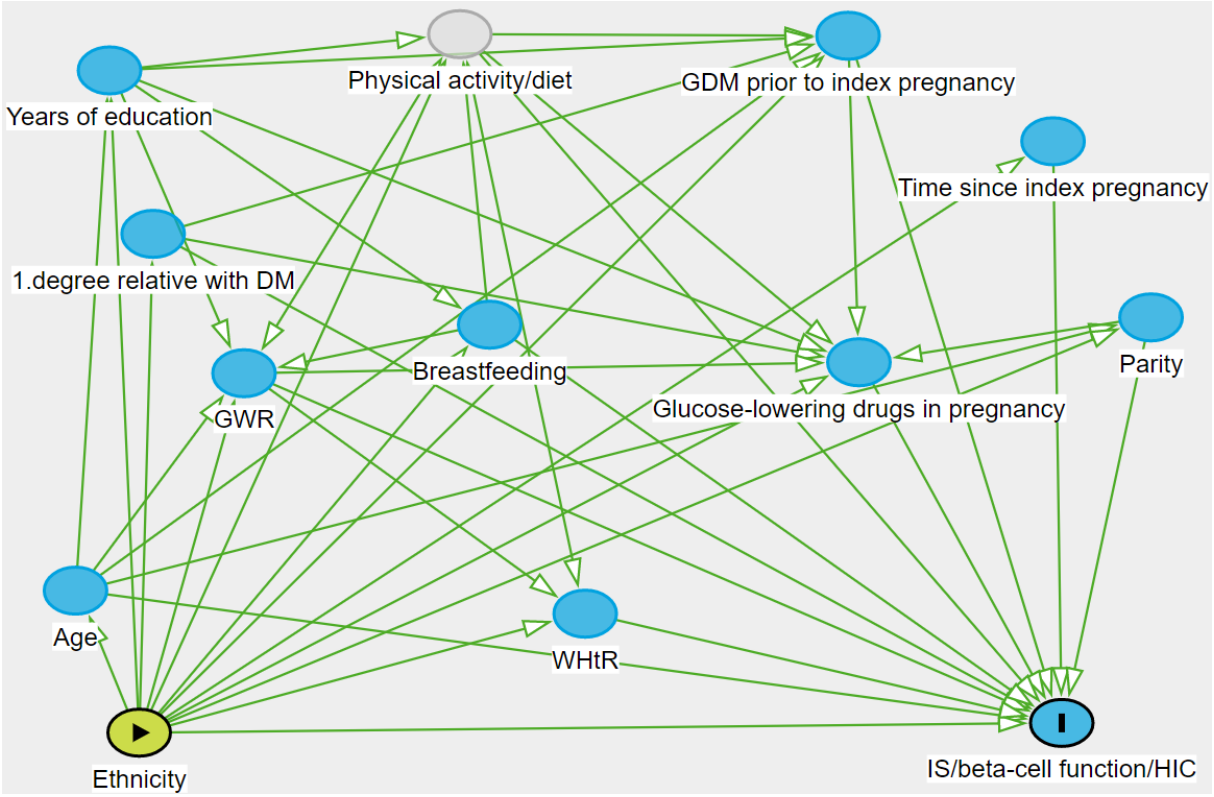
Data presented as mean (SD) or number (n) [%] for women who participated vs. a subgroup of women who did not participate in the study.

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

Supplemental Figures

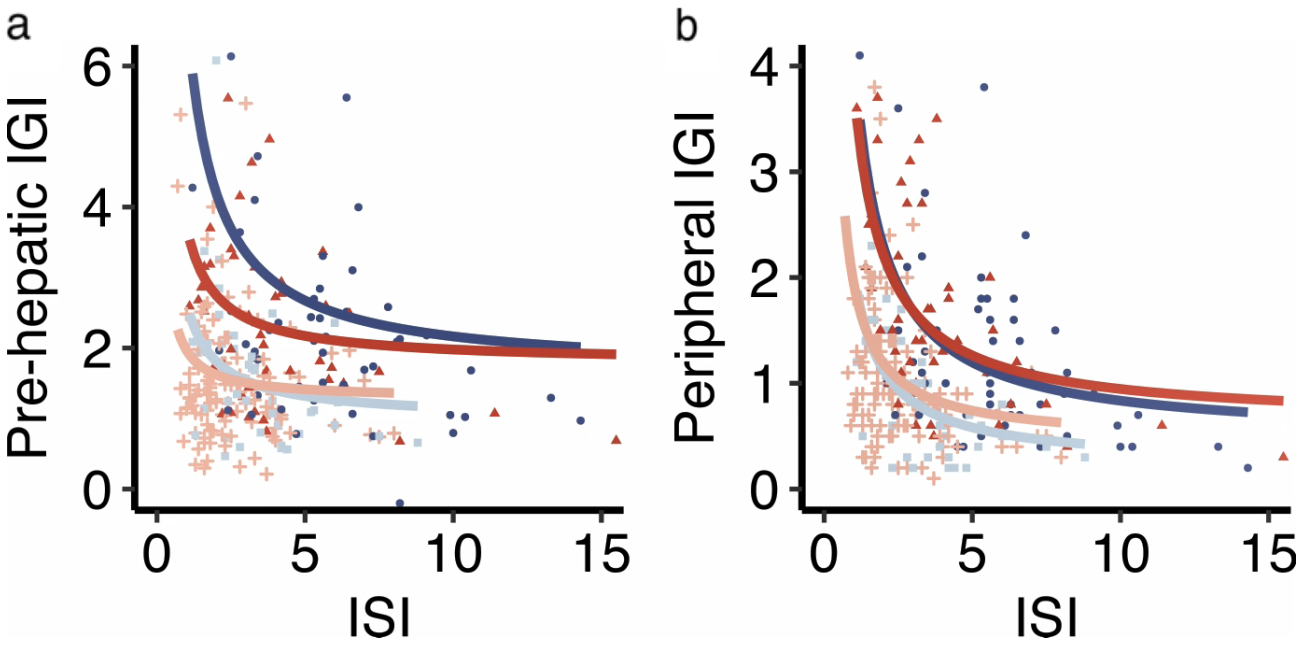


Supplemental Fig. 1. Participant flow-chart

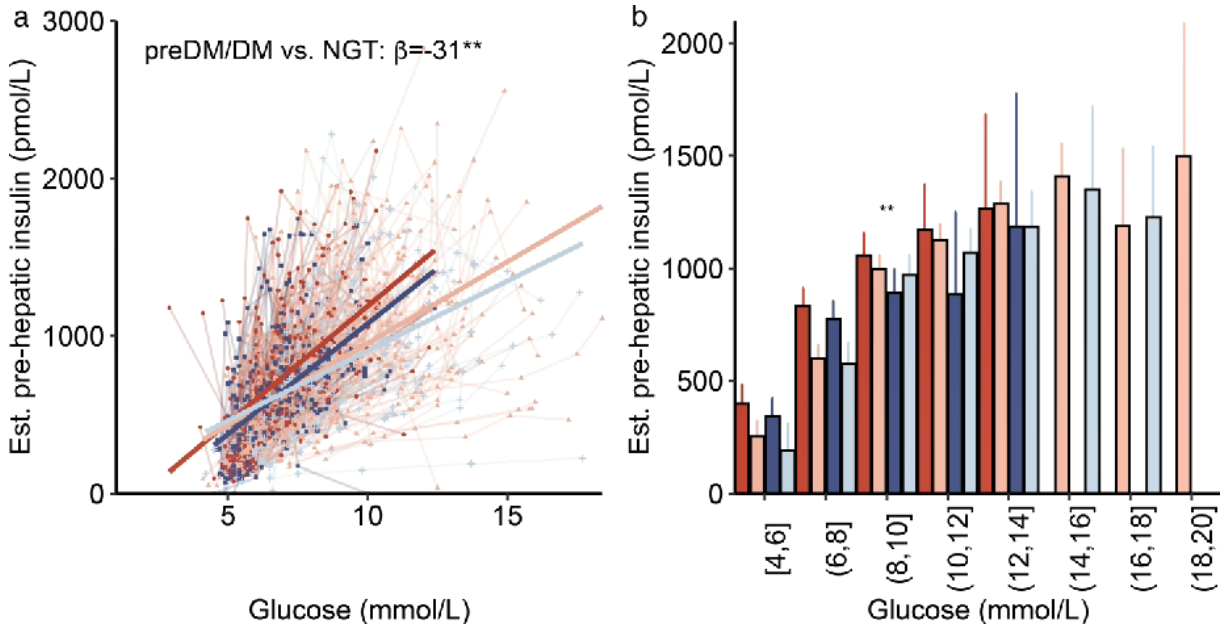


Supplemental Fig. 2. A directed acyclic graph representing the relationships between covariates (blue circle) (including unobserved covariates (grey circle)) and exposure (green circle) and outcome (blue circle with I). Green lines represent causal paths. We did not interpret interaction between mediators.

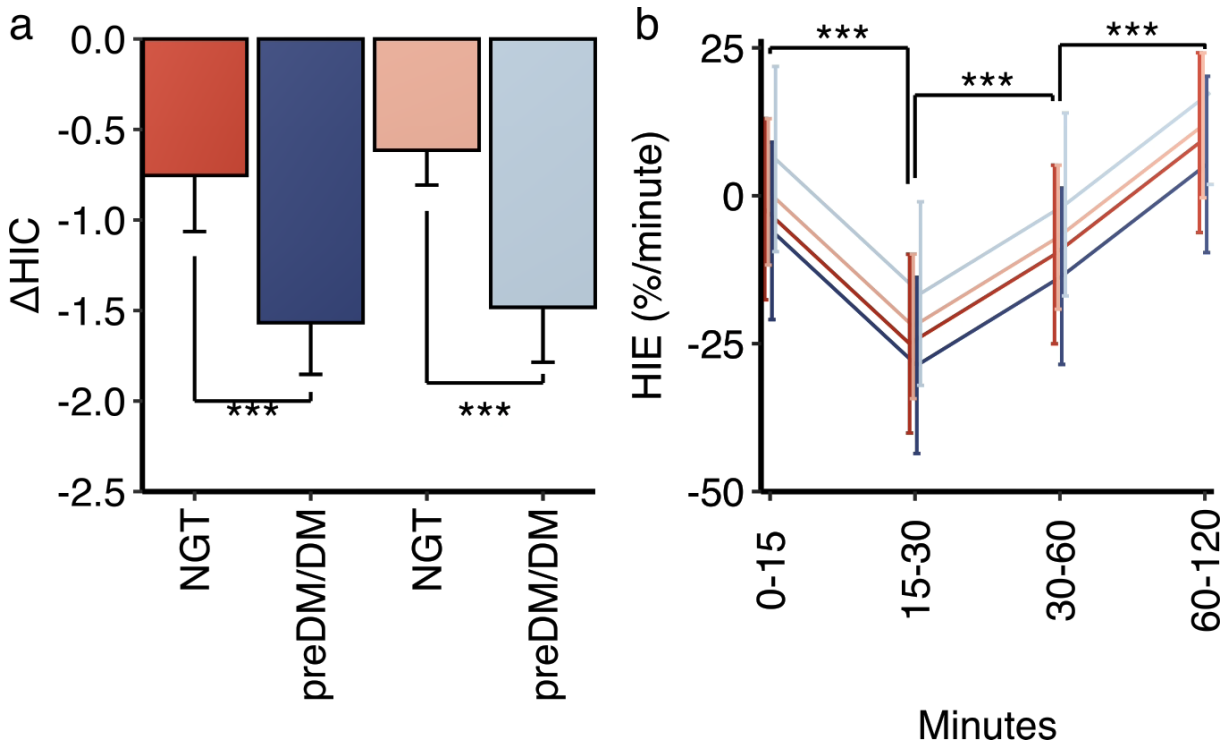
DM: diabetes mellitus, GDM: gestational diabetes mellitus, GWR: gestational weight retention, HIC: hepatic insulin clearance, IS: insulin sensitivity index, WHtR: weight-to-height ratio.



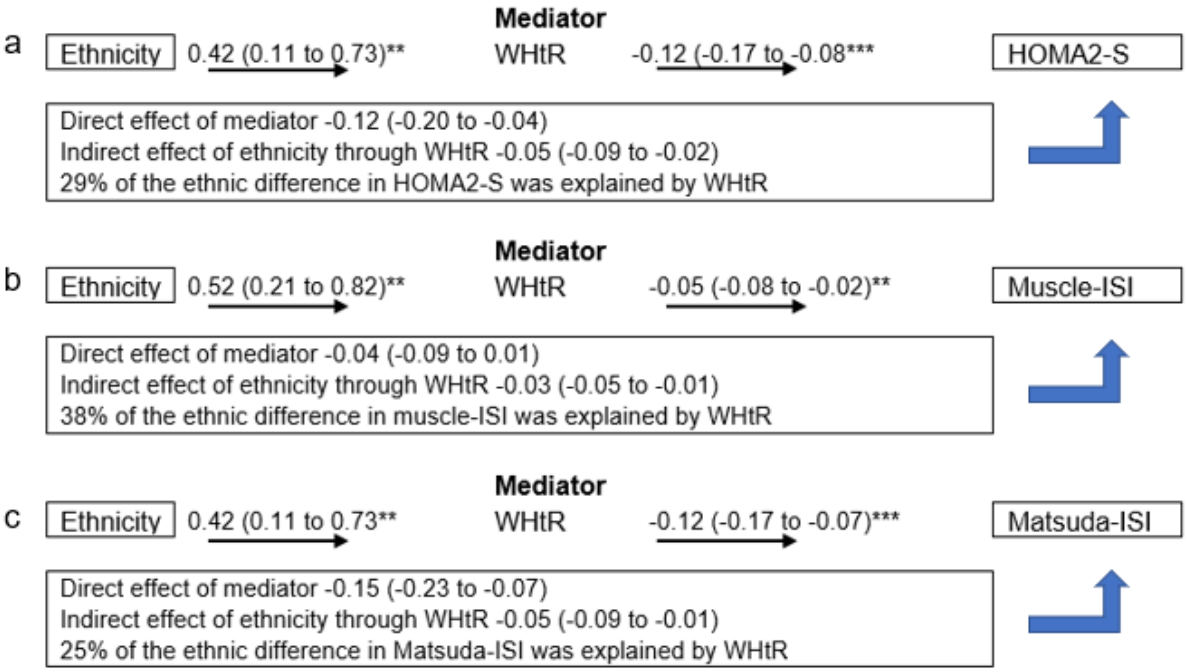
Supplemental Fig. 3. The disposition index curve with full curves for each group. The relationship between (a) early pre-hepatic vs. (b) peripheral insulin secretion (pre-hepatic IGI vs peripheral IGI), and insulin sensitivity (Matsuda-ISI) in South Asian and Nordic women with normal glucose tolerance (NGT) and prediabetes or diabetes (preDM or DM). The hyperbolar curve was regressed for each group: Nordic women with NGT (dark blue line), South Asian women with NGT (dark red line), Nordic women with preDM or DM (light blue line), and South Asian women with preDM or DM (light red line). NGT South Asian women (dark red triangles) tended to 'fall off the curve' and cluster to the lower left compared to NGT Nordic women (dark blue circles), approaching South Asian (red light cross) and Nordic women with preDM or DM (blue light square). Data are means ± 95% CI.



Supplemental Fig. 4. (a) Pre-hepatic insulin secretion correlated with plasma glucose levels. The connected dots are data from one person. The large lines are group-wise correlations. The regression lines represent beta cell glucose sensitivity (beta-GS). No difference between South Asian (red) and Nordic (blue) women was found. Beta-GS was shifted up and to the left in the pre-DM or DM group (light colour) compared the NGT (dark colour) groups. (b) Mean increase in pre-hepatic insulin secretion per 2 mmol/L plasma glucose intervals for each group. Data are means ± SEM. *$p < 0.05$, **$p < 0.01$.



Supplemental Fig. 5. (a) The difference between fasting and postprandial hepatic insulin clearance (HIC) in South Asian (red) and Nordic (blue) women with normal glucose tolerance (NGT, dark color) and prediabetes or diabetes (preDM or DM, light color). (b) Hepatic insulin extraction (HIE) defined as the percent increase in HIC from one time interval to the next during the OGTT. * p <0.05, ** p < 0.01, *** p < 0.001.



Supplemental Fig. 6: WHtR mediated ~25-40% of the ethnic difference in (a) HOMA2-sensitivity, (b) muscle-ISI and (c) Matsuda-ISI. Data are β-coefficients with 95% CI. HOMA2-S and Matsuda-ISI are log-transformed due to the skewed distribution. HOMA2-S: HOMA2- sensitivity, ISI: insulin sensitivity index, WHtR: weight-to-height ratio. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$