# Beta Cell Function, Hepatic Insulin Clearance, and Insulin Sensitivity in South Asian and Nordic Women after Gestational Diabetes Mellitus

Running Title: Glucose Metabolism in South Asians after GDM

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Abstract: 220,

Word count: 3926. Tables: 2, Figures: 4.

## Abstract

South Asians have higher risk of type 2 diabetes after gestational diabetes mellitus (GDM) than Nordic women; however the mechanisms behind this difference remain unclear. We investigated insulin sensitivity, beta cell function, and hepatic insulin clearance, in 179 South Asian and 108 Nordic women ~17 months after GDM (mean age 35.3 years and BMI 29.1 $kg/m^2$), via an oral glucose tolerance test using deconvolution of C-peptide kinetics. 31% of South Asian and 53% of Nordic participants were normoglycemic at the time of measurement. South Asian women had higher areas under the curve (AUC) for glucose, pre-hepatic insulin, peripheral insulin, and lower levels of insulin sensitivity, disposition index, and fasting hepatic insulin clearance compared with Nordic women. In the group with prediabetes or diabetes, South Asian women displayed similar AUC for glucose and pre-hepatic insulin, but higher AUC for peripheral insulin, and lower levels of disposition index, and fasting hepatic insulin clearance compared with Nordic women. The waist-to-height ratio mediated ~25-40% of the ethnic differences in insulin sensitivity in normoglycemic women. Overall, our novel data showed that normoglycemic South Asian women after GDM displayed lower insulin secretion for a given insulin resistance, and lower hepatic insulin clearance compared with Nordic women. South Asian women are at high risk of developing type 2 diabetes after GDM, and preventive efforts should be prioritized.


**Keywords:** beta cell function, ethnicity, gestational diabetes mellitus, hyperinsulinemia, insulin clearance, insulin secretion rate, insulin sensitivity, normoglycemia, prediabetes, obesity

## Introduction

The risk of type 2 diabetes after gestational diabetes mellitus (GDM) (1, 2) is twice as high in South Asian compared with European women, and develops at younger ages and at a lower body mass index (BMI) (3). The mechanisms behind this higher risk for impaired glucose tolerance are still highly debated (4).

During normal pregnancy, insulin secretion increases to compensate for pregnancy-induced insulin resistance, and GDM develops if the pancreatic beta cells cannot meet this increased demand (5). South Asian women's increased susceptibility to develop diabetes after GDM may also reflect a failure of the insulin secretion capacity to response to increased insulin resistance known to be present at early ages in South Asian populations, both in liver and muscle (4, 6-8). Hepatic glucose production is the main determinant of the fasting glucose levels, whereas glucose uptake in muscle is more important in determining postprandial plasma glucose (9). The increased demand placed on the beta cells by this insulin resistance may, over time, lead to failure and a decline in insulin secretion adjusted for insulin resistance, estimated as the disposition index (10).

Peripheral insulin concentrations reflect the balance between insulin secretion and insulin clearance, with liver clearing ~50% of newly secreted insulin (11). Emerging evidence suggests that lower hepatic insulin clearance could contribute to increased peripheral insulin levels, and act as an early adaption to insulin resistance and hyperglycaemia (12). On the other side, higher insulin levels are also associated with higher insulin resistance and an increased risk of type 2 diabetes (13). Although, hepatic insulin clearance is difficult to measure directly in humans, it can be estimated indirectly by pre-hepatic insulin levels based on C-peptide deconvolution kinetics, as C-peptide clearance in liver is negligible (13). Here, we estimate measures of (i)

insulin sensitivity, (ii) beta cell function, and (iii) hepatic insulin clearance in South Asian and Nordic women undergoing an OGTT 1-3 years after GDM.

## Research Design and Methods

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

### Design, Study Population and Data Collection

Between September 1, 2018, and December 31, 2021, we recruited women with a history of GDM in their last pregnancy, who delivered 12-36 (±3) months previously at one of three hospitals in the Oslo area, Norway. Due to changes in the GDM definition during the last years, most women were included based on the modified International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria (FPG 5.3-6.9 or 2-h glucose 9.0-11.0 mmol/l (n = 267)) (14), but a few were included according to the former WHO 1999 criteria (FPG ≥ 7.0 or 2-h PG ≥ 7.8 mmol/l (n = 16)) (15). Additional inclusion criteria were age ≥ 18 years, and both parents born in a South Asian (Pakistan, India, Bangladesh, or Sri Lanka) or Nordic (Norway, Sweden, Denmark, Finland, or Iceland) country. Exclusion criteria included 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. Eligible women were identified by searching medical records from the three hospitals, and recruited through an invitation letter. The South Asian women also received a telephone invitation in their native language, to address any potential issues with communication in Norwegian (as recommended by the Regional Ethics Committee). Of the 1220 (449 South Asian and 771 Nordic) eligible

women with a GDM diagnosis, 179 South Asian (110 Pakistani, 33 Indian, 5 Bangladeshi, 31 Sri Lankan) and 108 Nordic (Norwegian, 3 Swedish, 3 Danish, and 1 Icelandic) women participated. Among the South Asians, 16 invited women were excluded due to new-onset diabetes after the index pregnancy and 29 due to a new pregnancy, while 225 declined or were not contactable. Among the Nordic women, who were only invited by letter, reasons for non-participating were not available (Supplemental Fig. 1).

At the study visit, we measured height, weight, waist and hip circumferences (16). Thereafter, all women underwent an OGTT between 08.00-10.00 am after at least eight hours fasting. Before, and 15, 30, 60 and 120 minutes after a 75 g oral glucose load, blood was collected in: (i) in cooled sodium fluoride tubes for glucose analysis, and kept on ice until centrifugation at 4 ℃ within 10 minutes; and ii) serum-separating tubes for analyses of insulin and C-peptide, and centrifuged after 30 minutes. Plasma glucose was analysed by enzymatic photometry (Roche Diagnostics, Mannheim, Germany), whole-blood $HbA_{1c}$ by high-performance liquid chromatography (Tosoh G8 analyser, Tokyo, Japan), and serum C-peptide and insulin were analysed by electrochemiluminescence immunoassay (Cobas e601, Roche Diagnostics); all were performed at Oslo University Hospital, Aker. The coefficients of variation were 2.5%, 7.0%, 4.0-5.0%, and 1.5-2.5% for glucose, insulin, C-peptide, and $HbA_{1c}$, respectively. Clinical and biochemical data from the women obtained during the pregnancy were retrieved from medical records.

**Definitions**

Prediabetes was defined according to the WHO-International Expert Committee criteria as follows: FPG 6.1-6.9 mmol/L and/or 2-h plasma glucose 7.8-11.0 mmol/L and/or $HbA_{1c}$ 6.0-

6.4% (42-47 mmol/mol) (15, 17). Diabetes was defined according to internationally agreed criteria (18, 19).

**Calculations**

HOMA2 of beta cell function (HOMA2-B) and HOMA2 of insulin sensitivity (HOMA2-S) were calculated from fasting serum C-peptide [pmol/L] or insulin (FSI) [pmol/L], respectively, together with fasting plasma glucose (FPG) [mmol/L] using the HOMA calculator (20, 21). HOMA2-S was considered to mainly represent the hepatic insulin sensitivity. Muscle insulin sensitivity index (muscle-ISI) was calculated by the MISI-calculator (22) on the basis of the reduction in plasma glucose [mmol/l] from peak to nadir, and the mean plasma insulin concentration [pmol/l] during the OGTT (23). The whole-body insulin sensitivity was estimated by the Matsuda insulin sensitivity index (Matsuda ISI) as

$10{,}000/\sqrt{}$ (FSI [uIU/mL] × FPG [mg/dL]) × (mean OGTT insulin [uIU/mL]) × (mean OGTT glucose [mg/dL]) (24).

Prehepatic insulin (pmol/L) was estimated from C-peptide deconvolution, using the ISEC software program (25) with standard settings (subjects with obesity, coefficient of variation 5%, and basal function on). The program's assumptions included that (i) the secretion of insulin and C-peptide are equimolar, (ii) C-peptide kinetics are described by a 2-compartment model, (iii) the parameters in the model were estimated from women's age, sex, height, weight classified as normal or obese and type 2 diabetes status, and (iv) the measurement errors are uncorrelated with the zero mean, and with constant SD.

Indexes of insulin secretion were calculated with both peripheral insulin measurements, and estimated pre-hepatic insulin levels, as the insulinogenic index = $\Delta Insulin0–30_{min}$ [uIU/mL]/$\Delta Glucose0–30_{min}$ [mg/dL] during the OGTT (26, 27).

Beta cell function was also estimated by calculating HOMA2-B, and insulin secretion adjusted for insulin resistance was estimated as the disposition index (insulinogenic index * Matsuda ISI) (10). The latter assumes a hyperbolic relationship between insulin secretion and insulin resistance, and that the product of these two variables is constant for women with same degree of glucose tolerance (28).

Beta cell glucose sensitivity was estimated as the relationship between glucose levels and calculated pre-hepatic insulin levels during the OGTT (29). It was derived as the slope of this linear relationship, and reflects the pmol/L increase in pre-hepatic insulin levels per mmol/L increase in plasma glucose levels.

Hepatic insulin clearance was calculated from pre-hepatic and peripheral insulin levels in the fasting (hepatic insulin clearance $_{fasting}$ = pre-hepatic insulin $_{fasting}$/peripheral insulin $_{fasting}$) and postprandial state (hepatic insulin clearance $_{OGTT}$ = pre-hepatic insulin $_{AUC}$ / peripheral insulin $_{AUC}$) (13, 30). Hepatic insulin extraction was defined as the percent increase in hepatic insulin clearance from one time interval to the next during the OGTT.

Total area under the curve (AUC) was calculated by the trapezoid rule (31).

**Statistical Analyses**

Sample size was estimated for the primary outcomes of the study as described elsewhere ('High prevalence and significant ethnic differences in actionable $HbA_{1c}$ after gestational diabetes mellitus', accepted for publication). Participants with prediabetes or diabetes were in this study

grouped together due to low number of women with diabetes. This was considered appropriate as South Asian and Nordic women showed no difference in the prevalence of diabetes (32/178 (18%) vs. 15/108 (14%), $p = 0.366$).

Characteristics were presented as mean (SD), or median (interquartile range, IQR), or number [%]. Differences between groups were assessed with unpaired t-tests for normally distributed data. Variables were log-transformed to approximate normality if necessary. Mann–Whitney tests were used for non-normally distributed data.

OGTT data were analysed with linear mixed models for repeated measures using random intercepts for participants and unstructured covariance matrix (fixed effect were ethnicity, time, and time by ethnicity interaction; and random effect was the participants). Data were estimated marginal means with corresponding 95% confidence intervals (CI).

The mediation analyses were conducted using the PROCESS macro in SPSS (32). A directed acyclic graph was used to visualize the relationship of the covariates, exposure and outcome in the model (Supplemental Fig. 2). Several parallel mediators were visualized: age, time since index pregnancy, waist-to height ratio (WHtR), parity, GDM before index pregnancy, first degree relatives with diabetes, years of education (as a proxy for socioeconomic status), gestational weight retention (the difference between weight at visit and prepregnancy weight), glucose-lowering drugs during pregnancy, and duration of breastfeeding. Covariates with $P \leq 0.25$ were included in multivariate regression analyses to find the most significant mediators. Statistical significance was considered at a two-tailed $p < 0.05$. We used SPSS version 27 and R version 4.1.3 statistical software for the analyses.

**Data and Resource Availability**

All data generated or analyzed during this study are included in the published article and its online supplemental files.

## Results

### Baseline Characteristics

At a median (IQR) of 16.5 (12.1) months after delivery 31% of the South Asian and 53% of the Nordic women had a normal OGTT ($p < 0.001$). The South Asian women had higher parity, more first-degree relatives with diabetes, and fewer years of education than comparable Nordic women. BMI did not differ between these groups, but South Asian women had higher WHtR, and were somewhat younger than the Nordic participants (Table 1).

Table 1 here

### Plasma Glucose, Estimated Pre-hepatic Insulin and Peripheral Insulin Levels

In the normoglycemic group, despite no ethnic difference in fasting or 2h OGTT glucose, South Asian women had 7% higher AUC for glucose compared to Nordic women ($p < 0.01$) (Fig. 1a). South Asian women also had 23% higher AUC for pre-hepatic insulin ($p < 0.01$), and 67% higher AUC for peripheral insulin levels ($p < 0.01$) (Fig. 1b, c). AUC for peripheral insulin levels were ~2-fold higher in South Asian than in Nordic women ($p < 0.01$) (Fig. 1c).

In women with prediabetes or diabetes, no ethnic differences in AUC for glucose and pre-hepatic insulin were found (Fig. 1d, e), but South Asians had 34% higher AUC for peripheral insulin levels than comparable Nordic women (Fig. 1f, $p < 0.01$).

Normoglycemic South Asian women showed no difference in AUC for pre-hepatic insulin levels (β=54 [365, 474], $p$ = 0.798), but higher AUC for peripheral insulin levels compared to Nordic women with prediabetes or diabetes (β=459 [32, 886], $p$ = 0.036).

**Insulin Sensitivity**

In the normoglycemic group, all estimates for insulin sensitivity were 35 (±9)% lower in South Asian than in Nordic women (Table 2). In the prediabetes or diabetes group, HOMA2-S and Matsuda-ISI were 30% and 31% lower in South Asian than in Nordic women, respectively (Table 2). HOMA2-S and Matsuda-ISI were substantially higher in the normoglycemic vs. the prediabetes or diabetes groups. No difference in muscle-ISI was found between the normoglycemic and prediabetes or diabetes groups (Table 2).

**Beta Cell Function**

In normoglycemic women, the median insulinogenic index calculated from peripheral insulin levels was 40% higher in South Asian than in Nordic women (Table 2 and Fig. 2b). However, when calculating insulinogenic index with pre-hepatic insulin, no difference was seen between the ethnic groups (Table 2, Fig. 2a). In addition, when applying the pre-hepatic insulin in estimating the disposition index, we observed a 32% lower disposition index in South Asian vs. Nordic women (Table 2, Fig. 2c). In the prediabetes or diabetes groups, we found 35% lower disposition index estimates in South Asian vs. Nordic women by applying the pre-hepatic insulin levels (Table 2, Fig. 2c).

Using the normoglycemic Nordic women as a reference, the hyperbolic relationship between pre-hepatic insulin secretion and insulin sensitivity showed that normoglycemic South Asian

women tended to "fall off the curve" and cluster to the lower left, approaching women with prediabetes or diabetes (Fig. 3 and Supplemental Fig. 3)

We observed no ethnic differences in beta cell glucose sensitivity (Table 2). Women with prediabetes or diabetes showed lower beta cell glucose sensitivity than women with normoglycemia (Supplemental Fig. 4a). In addition, responses in estimated pre-hepatic insulin at different intervals of plasma glucose levels were also largely similar between the ethnicities (Supplemental Fig. 4b).

**Hepatic Insulin Clearance**

In the normoglycemic and prediabetes or diabetes groups, fasting hepatic insulin clearance was 18% and 25% lower in South Asian than in Nordic women, respectively (Table 2, Fig. 4a). In South Asian women, we found that fasting hepatic insulin clearance was lower in the prediabetes or diabetes than in the normoglycemic group (Table 2, Fig. 4a). Postprandial hepatic insulin clearance (during the OGTT) was on average half the level of fasting hepatic insulin clearance for all groups (Fig. 4b). However, the decline in hepatic insulin clearance from fasting to the postprandial state was more pronounced in Nordic than in South Asian women independent of glucose tolerance (Fig. 4b, and Supplemental Fig 5a). The percentage hepatic insulin clearance per minute [i.e., the hepatic insulin extraction] during the OGTT did not differ between the ethnic groups (Supplemental Fig. 5b). When we compared South Asian normoglycemic women with Nordic women with prediabetes or diabetes, we found substantially lower fasting hepatic insulin clearance (β=-1.7 [-2.7, -0.7], $p < 0.001${Goedecke, 2022 #824}).

All significant differences in Table 2 remained significant in a sensitivity analysis adjusting insulin sensitivity, beta cell function and hepatic insulin clearance indexes for time since index pregnancy (Supplemental Table 1) and BMI (Supplemental Table 2).

Table 2 here

**Regression Analysis of Beta Cell Function, Hepatic Insulin Clearance, and Insulin Sensitivity**

In a multiple regression analysis in normoglycemic women, ethnicity was the only significant predictor of pre-hepatic disposition index ($p = 0.038$) and fasting hepatic insulin clearance ($p = 0.007$). With HOMA2-S as the outcomes, ethnicity and WHtR were the only significant predictors ($p = 0.017$, and $p = 0.002$). With muscle-ISI as the outcome, WHtR was the most significant predictor ($p = 0.013$). With Matsuda-ISI as the outcome, ethnicity and WHtR were the most significant predictors ($p = 0.003$, and $p = 0.001$). We tested if the associated phenotypic traits could mediate the ethnic differences shown in insulin sensitivity in normoglycemic women. We found that WHtR mediated 25-29% of the ethnic differences in HOMA2-S and Matsuda-ISI, and 38% of the difference in muscle-ISI (Supplemental Fig. 6a, b, c).

In the prediabetes or diabetes group, we did not perform the mediation analysis as no ethnic difference in WHtR was found (Table 1).

## Discussion

In the present study of women with previous GDM, assessed at median ~17 months post-pregnancy, normoglycemic South Asian women presented with lower fasting hepatic insulin clearance, and lower insulin secretion adjusted for insulin resistance than Nordic

normoglycemic women. These factors may suggest a more rapid course towards the development of type 2 diabetes.

An important observation was that calculating insulin secretion from estimated pre-hepatic insulin levels indicated a markedly lower beta cell function relative to insulin resistance in South Asian women. Hence, analysing only peripheral insulin levels may mask an early beta cell dysfunction. Although reduced beta cell function could be expected in women with previous GDM (33), our findings that document reduced beta cell function in normoglycemic South Asian women are novel. The lower beta cell function was also supported by no ethnic differences in beta cell glucose sensitivity. Current literature suggests a positive correlation between beta cell glucose sensitivity and insulin resistance to enable a limited increase in glucose levels (34). Our data, however, showed higher AUC for glucose without an increase in beta cell glucose sensitivity among South Asian compared to Nordic normoglycaemic women, reflecting a lower beta cell function.

Of note, in the prediabetes or diabetes group no ethnic differences in pre-hepatic insulin levels were found. However, after its first passage through the liver, we found significantly higher peripheral insulin levels in the South Asian compared to Nordic women. This difference in peripheral hyperinsulinemia indicates lower fasting hepatic insulin clearance among South Asian women. A similar pattern was found in the normoglycemic group, but here the South Asian women had higher pre-hepatic insulin levels than comparable Nordic women.

Insulin has a major action in, and is extracted by, the liver (13). Our findings of lower hepatic insulin clearance in South Asian women in the fasting state, may be a consequence of increased hepatic insulin resistance. However, it may also be regarded as an adaption within the hepatic

insulin clearance pathways to provide peripheral tissues with higher insulin levels. Increased insulin resistance has been demonstrated to be present several years before the diagnosis of prediabetes or type 2 diabetes among South Asian individuals (8, 35, 36). We confirmed these findings of higher insulin resistance in South Asian compared to Nordic women across categories of glucose tolerance. Despite no difference in fasting and 2h OGTT glucose, South Asian normoglycemic women displayed slightly higher glucose levels during the first hour of the OGTT. This is in accordance with previous literature (4, 8), and implies less suppression of hepatic glucose production during the OGTT. Both whole-body and muscle-ISI seemed to be lower in South Asian women, perhaps in part due to more central fat accumulation and lower muscle mass (8, 37). Notably, the muscle-ISI was similar in the normoglycemic and prediabetes or diabetes groups, supporting that a gradual reduction in insulin secretory function is the main driver for a deteriorating glucose tolerance (38). There are reports, however, suggesting a role of excess insulin in driving insulin resistance, and that suppression of high plasma insulin levels enhances insulin sensitivity (9, 12, 39, 40). We, in accordance with others (34, 41), speculate that the increased peripheral insulin levels, following reduced hepatic insulin clearance, may be an early and important adaption to developing insulin resistance. By reducing the toll of enhanced insulin secretion to compensate for insulin resistance, lower hepatic insulin clearance may offload the beta cells (41, 42). Notably, the hepatic insulin clearance was downregulated from the fasting to post-prandial state, followed by a hepatic insulin extraction that was precisely regulated throughout the OGTT, indicating a precise regulation according to the insulin demand independent of ethnicities. However, as the baseline level of hepatic insulin clearance was lower in the normoglycemic South Asians group, a metabolic inflexibility was displayed that may explain South Asian women's propensity to develop type 2 diabetes post-GDM. This interpretation is at variance with a previous study suggesting a genetic defect in a

main glycoprotein (CEACAM1) in the hepatic insulin clearance pathways as a possible reason for ethnic divergence in diabetes prevalence (40).

Another important question is how hepatic insulin clearance is associated with obesity, and with remission of diabetes by a substantial weight loss such as in the DIRECT (43) or DIADEM-1 study (44). Such weight loss is reported to improve hepatic insulin sensitivity, and may improve beta cell function, but data on hepatic insulin clearance pathways are scarce (45). A recent study showed improved beta cell function and fasting hepatic insulin clearance with time after bariatric surgery (46), but the relative importance of improved hepatic insulin sensitivity vs. hepatic insulin clearance pathways is still unclear.

Our data in normoglycemic women indicated that WHtR, potentially capturing important ethnic differences in body composition and central fat accumulation, mediated significant ethnic differences in insulin sensitivity. We, in accordance with others (8, 37, 47), therefore, suggest that central adiposity is instrumental for the lower insulin sensitivity South Asians.

This is important, as the Diabetes Prevention Program study reported a 50% decline in type 2 diabetes incidence post-GDM if weight loss was obtained (48), while no effect on glucose deterioration was observed in a similar study in South Asians without weight loss (49). Our findings thus lend support to initiatives that recommend strong preventive measures against overweight and obesity, particularly in South Asian women with high risk of diabetes. Even though hepatic insulin clearance is reported to be negatively associated with obesity (34), we did not find that our estimates of obesity mediated the ethnic differences in hepatic insulin clearances.

The strengths of this study include well characterized and sufficiently large groups of the two ethnicities with normoglycaemia and prediabetes or diabetes cared for in the same healthcare setting. All included women had prior been referred to hospital with a GDM diagnosis, and hence our findings are not valid for a non-GDM population. Many women did not reply to the invitation letter, or declined due to time constraint and other reasons, hence we cannot exclude a selection bias. We, therefore, compared key baseline characteristics in a sensitivity 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) (Supplemental Table 3). 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 could have led to an overestimation of the proportion of women with prediabetes or diabetes in this group, and thereby might have lead to an underestimation of the ethnic differerences in prevalence. Further, differences in the recruitment procedures may have introduced a selection bias between the ethnic groups, as only one of the groups received a telephone reminder. Thus, we might have recruited a higher proportion of Nordic women with "severe GDM", as they only had the one invitation by letter. 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 (as described elsewhere, 'High prevalence and significant ethnic differences in actionable HbA1c after gestational diabetes mellitus', accepted for publication). Moreover, there could also be differences in lifestyle habits, not picked up by our questionnaires and examinations. We did not control for menstrual cycle phase, although their effect of on glucose metabolism is debated. Furthermore, pre-hepatic insulin levels are difficult to measure directly in humans, and may be

best estimated from modelling of C-peptide kinetics. We also acknowledge that our estimates of insulin sensitivity are indirect, and direct measurements of insulin sensitivity with euglycemic clamp were not available. Importantly, our study did not directly measure hepatic insulin resistance, which may, in addition to hepatic insulin clearance, contribute to ethnic difference in peripheral insulin levels. This, in addition to analyses on ethnic differences in hepatic insulin clearance pathways, such as a glycoprotein (CEACAM1) that promotes hepatic insulin clearance (50), deserves further studies. Finally, the cross-sectional nature of our data can only describe associations and cannot imply causality.

In conclusion, normoglycemic South Asian women investigated a few years after GDM displayed lower beta cell function, lower hepatic insulin clearance and higher insulin resistance compared to Nordic women. Our novel observations accordingly add to our understanding of diabetes pathophysiology in South Asians and whites in general, and in the context of prior GDM.

**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 at Akershus University Hospital, Oslo University Hospital, and Vestre Viken Health Trust (Drammen) for invaluable help in the recruitment and examination of the participants. We would also like to thank the librarian, Åse Marit Hammersbøen at Akershus University

Hospital, and the statistician Ragnhild S. Falk at Oslo University Hospital for assistance with various aspect of this study.

## Author Contribution Statement

AS researched the data and drafted the manuscript. AS and SLØ performed statistical analysis. EQ, CS, HLG, STS, IN 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, 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, SLØ, EQ, CS, NS, JMRG, HLG, STS, IN, and KIB) contributed to 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; writing the manuscript; and did not impose any restrictions regarding the publication of the manuscript.

## Prior Presentation

This work is accepted for an oral presentation at the 58$^{th}$ Annual Meeting of the European Association for the Study of Diabetes, 19-23 September 2022.

## Conflict of Interest

The authors declare that there are no potential conflicts of interest relevant to this article.

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577 Table 1: The participants' characteristics by ethnicity and glucose tolerance

| | **NGT** | | | **Prediabetes or diabetes** | | |
|---|---|---|---|---|---|---|
| | **South Asian** n = 55 [31%] | **Nordic** n = 57 [53%] | ***p* value** | **South Asian** n = 123 [69%] | **Nordic** n = 51 [47%] | ***p* value** |
| Age (years) | 34.2 (4.0) | 36.3 (4.9) | 0.007 | 34.3 (4.2) | 35.7 (4.7) | 0.031 |
| Time since index pregnancy (months)‡ | 14.9 (12.4) | 16.4 (9.6) | 0.088 | 15.1 (11.0) | 19.0 (13.0) | 0.144 |
| Weight (kg)‡ | 69.5 (16.7) | 71.8 (28.1) | 0.117 | 71.6 (19.7) | 86.6 (21.6) | <0.001 |
| Height (cm) | 158.4 (5.4) | 167.7 (6.0) | <0.001 | 160.1 (6.7) | 165.5 (6.1) | <0.001 |
| BMI ($kg/m^2$)‡ | 27.3 (5.5) | 25.4 (9.1) | 0.147 | 28.7 (6.1) | 32.2 (6.1) | 0.005 |
| Waist circumference (cm) | 94.2 (12.4) | 91.8 (14.5) | 0.586 | 97.6 (11.6) | 101.2 (12.7) | 0.185 |
| Waist-hip ratio | 0.89 (0.00) | 0.87 (0.10) | 0.213 | 0.91 (0.07) | 0.90 (0.09) | 0.351 |
| Waist-height ratio | 0.60 (0.08) | 0.55 (0.09) | 0.007 | 0.61 (0.07) | 0.61 (0.08) | 0.657 |
| Parity | 2.1 (1.0) | 1.7 (0.7) | 0.028 | 2.2 (1.0) | 1.7 (0.8) | <0.001 |
| GDM prior to the index pregnancy | 13/54 [24] | 9 [16] | 0.274 | 42/121 [35] | 15 [29] | 0.500 |
| First degree relatives with diabetes | 38/51 [75] | 10/46 [22] | <0.001 | 87/117 [74] | 12/45 [27] | <0.001 |
| Years of education | 14.3 (3.3) | 17.0 (3.0) | <0.001 | 15.0 (3.5) | 16.2 (3.0) | 0.022 |
| Gestational weight retention (kg)‡ | 2.5 (8.7) | 1.0 (6.3) | 0.654 | 2.9 (5.6) | 2.4 (6.3) | 0.312 |
| Insulin ± Metformin use in pregnancy | 26 [47] | 14 [25] | 0.012 | 71 [58] | 26 [51] | 0.415 |
| Insulin use in pregnancy | 19 [35] | 11 [19] | 0.069 | 53 [43] | 23 [45] | 0.808 |
| Breastfeeding (months) | 10.0 (6.7) | 10.2 (5.6) | 0.821 | 9.3 (7.4) | 8.6 (5.9) | 0.453 |
| Breastfeeding (≥ 3 months) | 48 [87] | 50 [88] | 0.943 | 95 [77] | 39 [76] | 0.913 |

578 Characteristics presented as mean and (standard deviation, SD) or ‡median and (IQR) or number (n)

579 and [%]. NGT: normal glucose tolerance

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Table 2: Ethnic differences in insulin sensitivity and secretion, beta cell function, and hepatic insulin clearance by glucose tolerance categories

| | | **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‡ | 75 (41) | 110 (54)*** | 44 (37) | 63 (42)** | <0.001 |
| | Muscle-ISI | 0.17 (0.10) | 0.23 (0.12)** | 0.13 (0.12)‡ | 0.16 (0.20)‡ | 0.341 |
| | Matsuda-ISI‡ | 3.1 (1.8) | 5.5 (3.7)*** | 2.2 (1.6) | 3.2 (2.1)*** | <0.001 |
| Insulin secretion | HOMA2-B | 126 (28) | 114 (28)* | 124 (29) | 115 (40) | 0.967 |
| | Pre-hepatic IGI‡ | 1.8 (1.6) | 2.0 (1.4) | 1.4 (0.9) | 1.3 (1.1) | <0.001 |
| | Peripheral-IGI‡ | 1.4 (1.4) | 1.0 (0.9)* | 0.9 (0.7) | 0.8 (1.0) | <0.001 |
| Beta cell function | Beta-GS | 185 (57) | 171 (63) | 152 (55) | 149 (62) | <0.001 |
| | Pre-hepatic-DI‡ | 7.4 (7.2) | 10.9 (9.8)*** | 3.2 (2.8) | 4.9 (3.0)** | <0.001 |
| | Peripheral-DI‡ | 4.4 (4.1) | 5.2 (5.3) | 2.3 (1.8) | 2.7 (1.6) | <0.001 |
| HIC | HIC-fasting | 2.7 (0.9) | 3.3 (0.8)*** | 2.4 (0.8) | 3.2 (1.1)*** | <0.001 |
| | HIC-OGTT | 1.9 (0.6) | 1.7 (0.4) | 1.7 (0.8)‡ | 1.6 (0.6)‡ | 0.205‡ |

Data presented as mean (SD) or ‡median (IQR) or number [n].

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

615 **Fig. 1.** (a) Glucose (b) estimated pre-hepatic insulin and (c) peripheral insulin levels in South
616 Asian (red) and Nordic women (blue) with normal glucose tolerance (NGT, dark color) (a-c),
617 and prediabetes or diabetes (preDM or DM, light color) (d-f). Data are means ± 95% CI. *$p <$
618 0.05, **$p < 0.01$, ***$p < 0.001$ for South Asian vs. Nordic women; †$p < 0.05$, ††$p < 0.01$,
619 †††$p < 0.001$ for the group by time response.
620
621 **Fig. 2.** Boxplot of (a) early pre-hepatic vs. (b) early peripheral insulin secretion (pre-hepatic
622 IGI vs peripheral IGI), and (c) prehepatic vs. (d) peripheral disposition index (DI) in South
623 Asian (red) and Nordic women (blue) with normal glucose tolerance (NGT, dark colour), and
624 prediabetes or diabetes (preDM or DM, light colour). *p<0.05, **p<0.01 and ***p<0.001.
625
626 **Fig. 3.** The disposition index curve. The relationship between (a) early pre-hepatic vs. (b)
627 peripheral insulin secretion (pre-hepatic IGI vs peripheral IGI), and insulin sensitivity
628 (Matsuda-ISI) in South Asian and Nordic women with normal glucose tolerance (NGT) and
629 prediabetes or diabetes (preDM or DM). The hyperbolic curve was regressed in Nordic
630 women with NGT (blue line). NGT South Asian women (red cross) tended to 'fall off the
631 curve' and cluster to the lower left, approaching South Asian (red light cross) and Nordic
632 women with preDM or DM (blue light cross). Data are means ± 95% CI.
633
634 **Fig 4.** The ratio of pre-hepatic to peripheral insulin levels [hepatic insulin clearance (HIC)].
635 (a) Fasting HIC was lower in South Asian (red) vs. Nordic women (blue), both in the normal
636 glucose tolerance (NGT, dark colour) and prediabetes or diabetes (preDM or DM, light
637 colour) groups. Fasting HIC declined from the NGT to preDM or DM only in South Asian
638 women. (b) The decline in HIC from fasting to postprandial levels were steeper in Nordic

639 than in South Asian women, both for the NGT and preDM or DM groups. HIC was on
640 average half in the postprandial vs. fasting state. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
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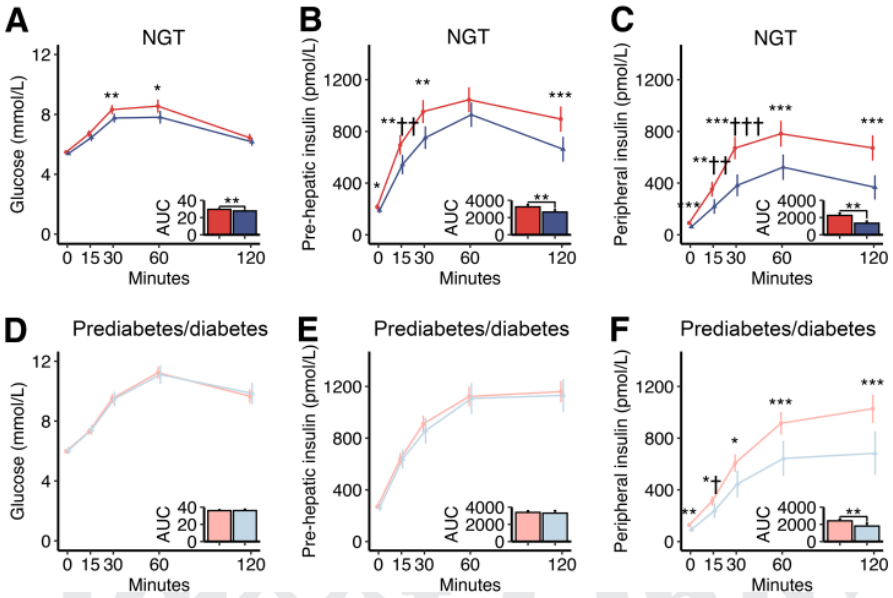


**Figure 1**—Glucose (*A* and *D*), estimated prehepatic insulin (*B* and *E*), and peripheral insulin (*C* and *F*) levels in South Asian (red) and Nordic (blue) participants with NGT (dark color) and prediabetes or diabetes (light color). Data are mean ± 95% CI. **P* < 0.05, ***P* < 0.01, ****P* < 0.001 for South Asian vs. Nordic participants; †*P* < 0.05, ††*P* < 0.01, †††*P* < 0.001 for the group-by-time response.

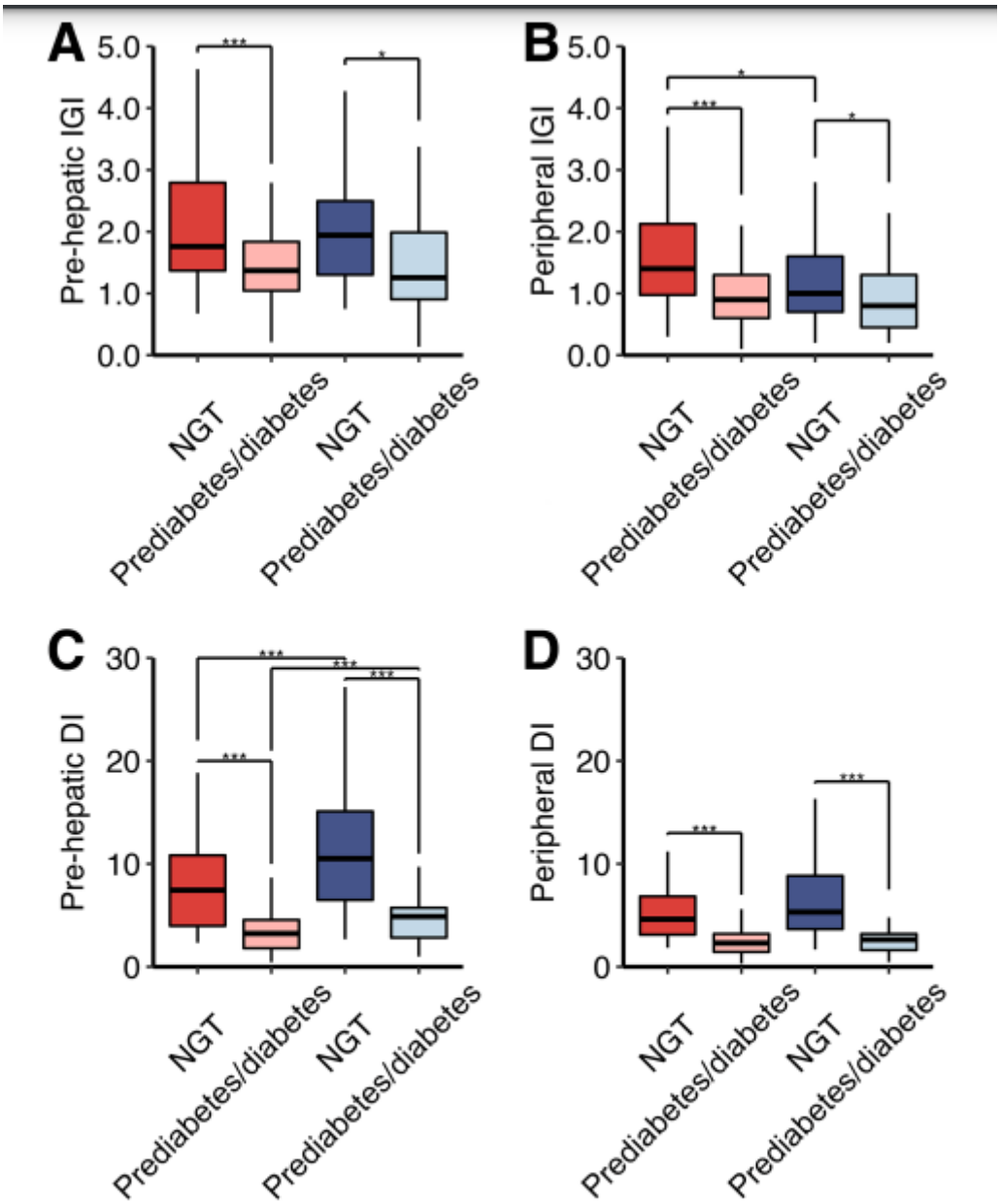


**Figure 2**—Box plot of early prehepatic (*A*) vs. early peripheral insulin secretion (prehepatic IGI vs. peripheral IGI) (*B*), and prehepatic (*C*) vs. peripheral disposition index (DI) (*D*) in South Asian (red) and Nordic (blue) participants with NGT (dark color) and prediabetes or diabetes (light color). *$P < 0.05$, ***$P < 0.001$.

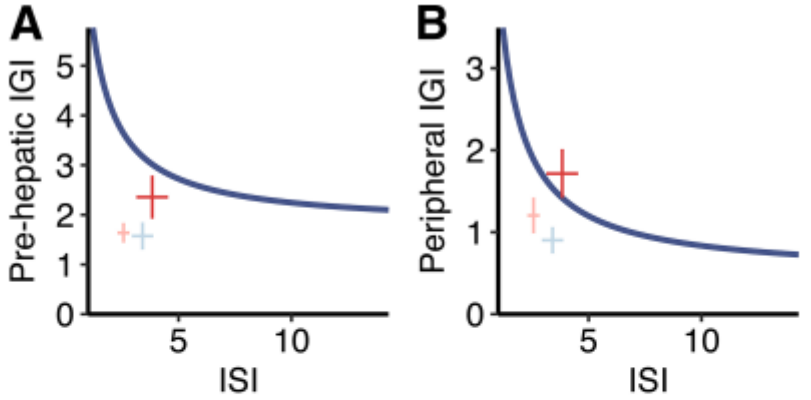


**Figure 3**—The disposition index curve. The relationship between early prehepatic (*A*) and peripheral insulin secretion (*B*) (prehepatic IGI vs. peripheral IGI) and insulin sensitivity (Matsuda ISI) in South Asian and Nordic participants with NGT and prediabetes or diabetes. The hyperbolic curve was regressed in Nordic participants with NGT (blue line). South Asian participants with NGT (red cross) tended to fall off the curve and cluster to the lower left, approaching South Asian (light red cross) and Nordic participants with prediabetes or diabetes (light blue cross). Data are mean ± 95% CI.

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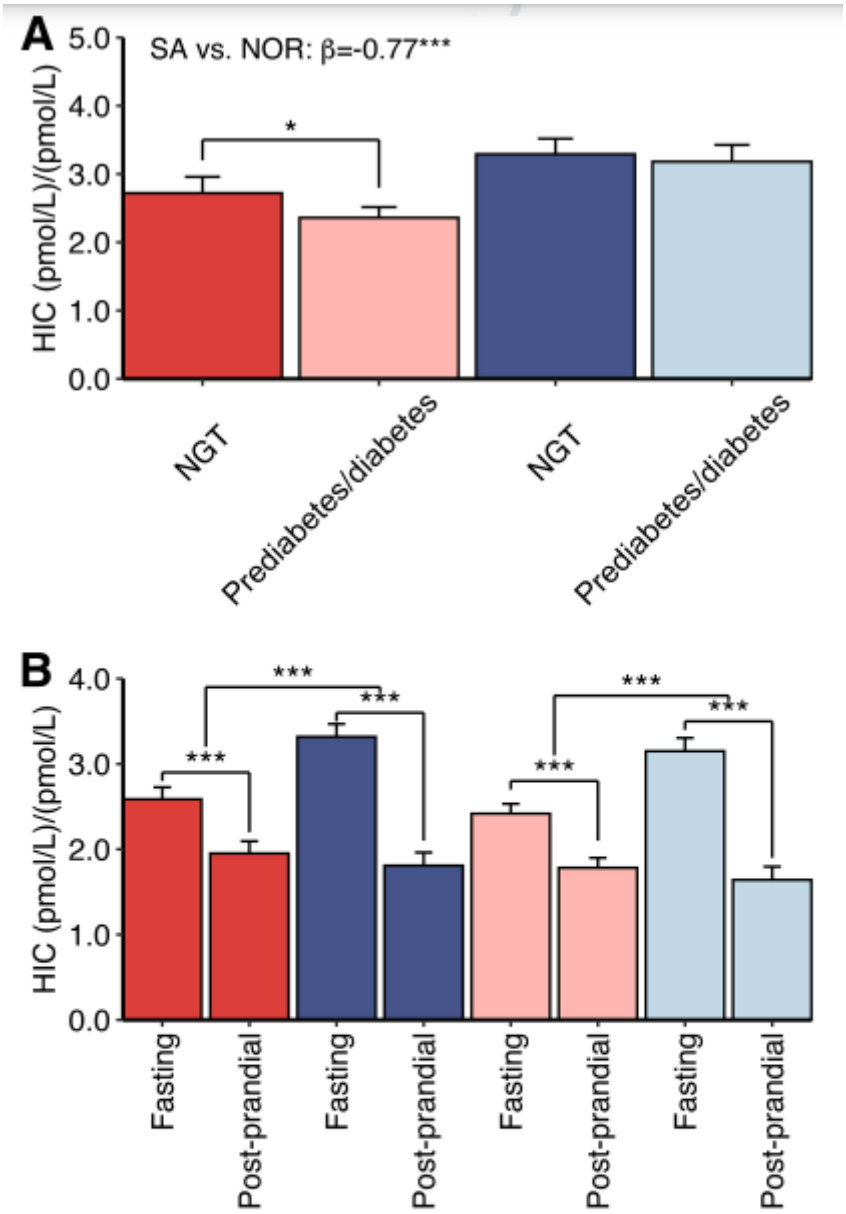


**Figure 4**—The ratio of prehepatic to peripheral insulin levels (HIC). *A*: Fasting HIC was lower in South Asian (red) vs. Nordic (blue) participants, in both the NGT (dark color) and prediabetes or diabetes (light color) groups. Fasting HIC declined from the NGT to prediabetes or diabetes group only in South Asian participants. *B*: The decline in HIC from fasting to postprandial levels were steeper in Nordic than in South Asian participants for both the NGT and prediabetes or diabetes groups. HIC was, on average, one-half in the postprandial vs. fasting state. $*P < 0.05$, $***P < 0.001$. NOR, Nordic; SA, South Asian.

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