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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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25 **Abstract**

26 South Asians have higher risk of type 2 diabetes after gestational diabetes mellitus (GDM) than
27 Nordic women; however the mechanisms behind this difference remain unclear. We
28 investigated insulin sensitivity, beta cell function, and hepatic insulin clearance, in 179 South
29 Asian and 108 Nordic women ~17 months after GDM (mean age 35.3 years and BMI 29.1
30 kg/m²), via an oral glucose tolerance test using deconvolution of C-peptide kinetics. 31% of
31 South Asian and 53% of Nordic participants were normoglycemic at the time of measurement.
32 South Asian women had higher areas under the curve (AUC) for glucose, pre-hepatic insulin,
33 peripheral insulin, and lower levels of insulin sensitivity, disposition index, and fasting hepatic
34 insulin clearance compared with Nordic women. In the group with prediabetes or diabetes,
35 South Asian women displayed similar AUC for glucose and pre-hepatic insulin, but higher
36 AUC for peripheral insulin, and lower levels of disposition index, and fasting hepatic insulin
37 clearance compared with Nordic women. The waist-to-height ratio mediated ~25-40% of the
38 ethnic differences in insulin sensitivity in normoglycemic women. Overall, our novel data
39 showed that normoglycemic South Asian women after GDM displayed lower insulin secretion
40 for a given insulin resistance, and lower hepatic insulin clearance compared with Nordic
41 women. South Asian women are at high risk of developing type 2 diabetes after GDM, and
42 preventive efforts should be prioritized.

43

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

46

47

48

49

50 **Introduction**

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

55

56 During normal pregnancy, insulin secretion increases to compensate for pregnancy-induced
57 insulin resistance, and GDM develops if the pancreatic beta cells cannot meet this increased
58 demand (5). South Asian women's increased susceptibility to develop diabetes after GDM may
59 also reflect a failure of the insulin secretion capacity to respond to increased insulin resistance
60 known to be present at early ages in South Asian populations, both in liver and muscle (4, 6-8).

61 Hepatic glucose production is the main determinant of the fasting glucose levels, whereas
62 glucose uptake in muscle is more important in determining postprandial plasma glucose (9).
63 The increased demand placed on the beta cells by this insulin resistance may, over time, lead to
64 failure and a decline in insulin secretion adjusted for insulin resistance, estimated as the
65 disposition index (10).

66

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

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

77

78 **Research Design and Methods**

79 The DIabetes in South Asians 1 (DIASA 1) study was approved by the South-Eastern Norway
80 Regional Committee for Medical and Health Research Ethics (reference number: 2018/689).

81 All participants provided written informed consent.

82

83 **Design, Study Population and Data Collection**

84 Between September 1, 2018, and December 31, 2021, we recruited women with a history of
85 GDM in their last pregnancy, who delivered 12-36 (± 3) months previously at one of three
86 hospitals in the Oslo area, Norway. Due to changes in the GDM definition during the last years,
87 most women were included based on the modified International Association of Diabetes and
88 Pregnancy Study Group (IADPSG) criteria (FPG 5.3-6.9 or 2-h glucose 9.0-11.0 mmol/l (n =
89 267)) (14), but a few were included according to the former WHO 1999 criteria (FPG ≥ 7.0 or
90 2-h PG ≥ 7.8 mmol/l (n = 16)) (15). Additional inclusion criteria were age ≥ 18 years, and both
91 parents born in a South Asian (Pakistan, India, Bangladesh, or Sri Lanka) or Nordic (Norway,
92 Sweden, Denmark, Finland, or Iceland) country. Exclusion criteria included new pregnancies
93 after the index pregnancy, exclusive breastfeeding at the time of examination, known diabetes
94 before the index pregnancy or at the time of examination, ongoing inflammatory or serious
95 disease, or a history of major surgical procedure < 3 months prior to inclusion. Eligible women
96 were identified by searching medical records from the three hospitals, and recruited through an
97 invitation letter. The South Asian women also received a telephone invitation in their native
98 language, to address any potential issues with communication in Norwegian (as recommended
99 by the Regional Ethics Committee). Of the 1220 (449 South Asian and 771 Nordic) eligible

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

106

107 At the study visit, we measured height, weight, waist and hip circumferences (16). Thereafter,
108 all women underwent an OGTT between 08.00-10.00 am after at least eight hours fasting.
109 Before, and 15, 30, 60 and 120 minutes after a 75 g oral glucose load, blood was collected in:
110 (i) in cooled sodium fluoride tubes for glucose analysis, and kept on ice until centrifugation at
111 4 °C within 10 minutes; and ii) serum-separating tubes for analyses of insulin and C-peptide,
112 and centrifuged after 30 minutes. Plasma glucose was analysed by enzymatic photometry
113 (Roche Diagnostics, Mannheim, Germany), whole-blood HbA_{1c} by high-performance liquid
114 chromatography (Tosoh G8 analyser, Tokyo, Japan), and serum C-peptide and insulin were
115 analysed by electrochemiluminescence immunoassay (Cobas e601, Roche Diagnostics); all
116 were performed at Oslo University Hospital, Aker. The coefficients of variation were 2.5%,
117 7.0%, 4.0-5.0%, and 1.5-2.5% for glucose, insulin, C-peptide, and HbA_{1c}, respectively. Clinical
118 and biochemical data from the women obtained during the pregnancy were retrieved from
119 medical records.

120

121 **Definitions**

122 Prediabetes was defined according to the WHO-International Expert Committee criteria as
123 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-

124 6.4% (42-47 mmol/mol) (15, 17). Diabetes was defined according to internationally agreed
125 criteria (18, 19).

126

127 **Calculations**

128 HOMA2 of beta cell function (HOMA2-B) and HOMA2 of insulin sensitivity (HOMA2-S)
129 were calculated from fasting serum C-peptide [pmol/L] or insulin (FSI) [pmol/L], respectively,
130 together with fasting plasma glucose (FPG) [mmol/L] using the HOMA calculator (20, 21).

131 HOMA2-S was considered to mainly represent the hepatic insulin sensitivity. Muscle insulin
132 sensitivity index (muscle-ISI) was calculated by the MISI-calculator (22) on the basis of the
133 reduction in plasma glucose [mmol/l] from peak to nadir, and the mean plasma insulin
134 concentration [pmol/l] during the OGTT (23). The whole-body insulin sensitivity was estimated
135 by the Matsuda insulin sensitivity index (Matsuda ISI) as

136 $10,000/\sqrt{(FSI [uIU/mL] \times FPG [mg/dL]) \times (\text{mean OGTT insulin } [uIU/mL]) \times (\text{mean OGTT}$
137 $\text{glucose } [mg/dL])}$ (24).

138

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

146

147 Indexes of insulin secretion were calculated with both peripheral insulin measurements, and
148 estimated pre-hepatic insulin levels, as the insulinogenic index = $\Delta\text{Insulin}_{0-30\text{min}}$
149 $[\text{uIU/mL}] / \Delta\text{Glucose}_{0-30\text{min}} [\text{mg/dL}]$ during the OGTT (26, 27).

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

155

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

160

161 Hepatic insulin clearance was calculated from pre-hepatic and peripheral insulin levels in the
162 fasting (hepatic insulin clearance_{fasting} = pre-hepatic insulin_{fasting}/peripheral insulin_{fasting}) and
163 postprandial state (hepatic insulin clearance_{OGTT} = pre-hepatic insulin_{AUC} / peripheral insulin
164_{AUC}) (13, 30). Hepatic insulin extraction was defined as the percent increase in hepatic insulin
165 clearance from one time interval to the next during the OGTT.

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

167

168 **Statistical Analyses**

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

172 grouped together due to low number of women with diabetes. This was considered appropriate
173 as South Asian and Nordic women showed no difference in the prevalence of diabetes (32/178
174 (18%) vs. 15/108 (14%), $p = 0.366$).

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

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

183

184 The mediation analyses were conducted using the PROCESS macro in SPSS (32). A directed
185 acyclic graph was used to visualize the relationship of the covariates, exposure and outcome in
186 the model (Supplemental Fig. 2). Several parallel mediators were visualized: age, time since
187 index pregnancy, waist-to height ratio (WHtR), parity, GDM before index pregnancy, first
188 degree relatives with diabetes, years of education (as a proxy for socioeconomic status),
189 gestational weight retention (the difference between weight at visit and prepregnancy weight),
190 glucose-lowering drugs during pregnancy, and duration of breastfeeding. Covariates with $P \leq$
191 0.25 were included in multivariate regression analyses to find the most significant mediators.
192 Statistical significance was considered at a two-tailed $p < 0.05$. We used SPSS version 27 and
193 R version 4.1.3 statistical software for the analyses.

194

195 **Data and Resource Availability**

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

198

199 **Results**

200 **Baseline Characteristics**

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

206

207 Table 1 here

208

209 **Plasma Glucose, Estimated Pre-hepatic Insulin and Peripheral Insulin Levels**

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

215

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

219

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

223

224 **Insulin Sensitivity**

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

231

232 **Beta Cell Function**

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

241

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

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

246

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

252

253 **Hepatic Insulin Clearance**

254 In the normoglycemic and prediabetes or diabetes groups, fasting hepatic insulin clearance was
255 18% and 25% lower in South Asian than in Nordic women, respectively (Table 2, Fig. 4a). In
256 South Asian women, we found that fasting hepatic insulin clearance was lower in the
257 prediabetes or diabetes than in the normoglycemic group (Table 2, Fig. 4a). Postprandial hepatic
258 insulin clearance (during the OGTT) was on average half the level of fasting hepatic insulin
259 clearance for all groups (Fig. 4b). However, the decline in hepatic insulin clearance from fasting
260 to the postprandial state was more pronounced in Nordic than in South Asian women
261 independent of glucose tolerance (Fig. 4b, and Supplemental Fig 5a). The percentage hepatic
262 insulin clearance per minute [i.e., the hepatic insulin extraction] during the OGTT did not differ
263 between the ethnic groups (Supplemental Fig. 5b). When we compared South Asian
264 normoglycemic women with Nordic women with prediabetes or diabetes, we found
265 substantially lower fasting hepatic insulin clearance ($\beta=-1.7$ [-2.7, -0.7], $p < 0.001$ {Goedecke,
266 2022 #824}).

267

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

271

272 Table 2 here

273

274 **Regression Analysis of Beta Cell Function, Hepatic Insulin Clearance, and Insulin** 275 **Sensitivity**

276 In a multiple regression analysis in normoglycemic women, ethnicity was the only significant
277 predictor of pre-hepatic disposition index ($p = 0.038$) and fasting hepatic insulin clearance ($p =$
278 0.007). With HOMA2-S as the outcomes, ethnicity and WHtR were the only significant
279 predictors ($p = 0.017$, and $p = 0.002$). With muscle-ISI as the outcome, WHtR was the most
280 significant predictor ($p = 0.013$). With Matsuda-ISI as the outcome, ethnicity and WHtR were
281 the most significant predictors ($p = 0.003$, and $p = 0.001$). We tested if the associated phenotypic
282 traits could mediate the ethnic differences shown in insulin sensitivity in normoglycemic
283 women. We found that WHtR mediated 25-29% of the ethnic differences in HOMA2-S and
284 Matsuda-ISI, and 38% of the difference in muscle-ISI (Supplemental Fig. 6a, b, c).

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

287

288 **Discussion**

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

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

294

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

306

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

313

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

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

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

343

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

351

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

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

364

365 The strengths of this study include well characterized and sufficiently large groups of the two
366 ethnicities with normoglycaemia and prediabetes or diabetes cared for in the same healthcare
367 setting. All included women had prior been referred to hospital with a GDM diagnosis, and
368 hence our findings are not valid for a non-GDM population. Many women did not reply to the
369 invitation letter, or declined due to time constraint and other reasons, hence we cannot exclude
370 a selection bias. We, therefore, compared key baseline characteristics in a sensitivity analysis
371 of women who did vs. a randomly selected subgroup of women who did not participate in the
372 study (100 South Asian and 100 Nordic women) (Supplemental Table 3). Among the South
373 Asian women no difference in age, pre-pregnancy BMI, in-pregnancy glucose values, the use
374 of glucose-lowering drugs, GDM before index pregnancy or first-degree relatives with diabetes
375 were found. The participating Nordic women were older than non-participants, but the other
376 characteristics did not differ. The older age among participating Nordic women could have led
377 to an overestimation of the proportion of women with prediabetes or diabetes in this group, and
378 thereby might have lead to an underestimation of the ethnic differences in prevalence. Further,
379 differences in the recruitment procedures may have introduced a selection bias between the
380 ethnic groups, as only one of the groups received a telephone reminder. Thus, we might have
381 recruited a higher proportion of Nordic women with “severe GDM”, as they only had the one
382 invitation by letter. Speaking against this, is the fact that a higher percentage of South Asian
383 than Nordic women were using glucose-lowering drugs in pregnancy, and by minimal
384 differences in the in-pregnancy glucose levels between the ethnic groups (as described
385 elsewhere, ‘High prevalence and significant ethnic differences in actionable HbA1c after
386 gestational diabetes mellitus’, accepted for publication). Moreover, there could also be
387 differences in lifestyle habits, not picked up by our questionnaires and examinations. We did
388 not control for menstrual cycle phase, although their effect of on glucose metabolism is debated.
389 Furthermore, pre-hepatic insulin levels are difficult to measure directly in humans, and may be

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

398

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

404

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417

418 **Author Contribution Statement**

419 AS researched the data and drafted the manuscript. AS and SLØ performed statistical analysis.
420 EQ, CS, HLG, STS, IN and KIB contributed to the design. KIB contributed to the study protocol
421 and aided in data acquisition. KIB supervised the study performance and is the guarantor of this
422 work, as such, had the full access to all the data in the study and take responsibility for the
423 integrity of the data and the accuracy of the data analysis. All authors (AS, SLØ, EQ, CS, NS,
424 JMRG, HLG, STS, IN, and KIB) contributed to analysis or interpretation of data for the work,
425 revised the manuscript critically and approved the final manuscript.

426

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436

437 **Conflict of Interest**

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

439

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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%]	<i>p</i> value	South Asian n = 123 [69%]	Nordic n = 51 [47%]	<i>p</i> 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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593 Table 2: Ethnic differences in insulin sensitivity and secretion, beta cell function, and hepatic insulin
 594 clearance by glucose tolerance categories

		NGT		Prediabetes/diabetes		All
		South Asian n=55 [31%]	Nordic n=57 [53%]	South Asian n=123 [69%]	Nordic n=51 [47%]	<i>p</i> value [†] 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 [‡]

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

596 Beta-GS: beta cell glucose sensitivity, DI: disposition index, HIC: hepatic insulin clearance, HOMA-
 597 S: HOMA2-sensitivity, IGI: insulinogenic index, ISI: insulin sensitivity index, NGT: normal glucose
 598 tolerance Peripheral' = measured peripheral insulin levels. 'Prehepatic' = estimated pre-hepatic
 599 insulin levels based on deconvolution of C-peptide kinetics.

600 **p* ≤ 0.05, ***p* ≤ 0.01, ****p* ≤ 0.001 for South Asian vs. Nordic women

601 [‡]*p* ≤ 0.05, ^{††}*p* ≤ 0.01, ^{†††}*p* ≤ 0.001 for NGT vs. prediabetes or diabetes

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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 \pm 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.

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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.

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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 \pm 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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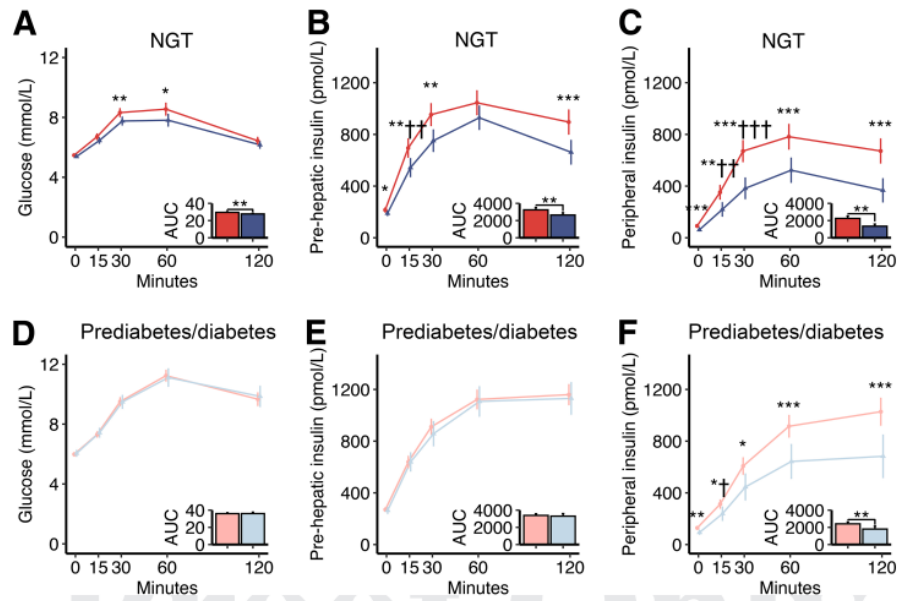


Figure 1—Glucose (A and D), estimated prehepatic insulin (B and E), and peripheral insulin (C and F) levels in South Asian (red) and Nordic (blue) participants with NGT (dark color) and prediabetes or diabetes (light color). Data are mean \pm 95% CI. * P < 0.05, ** P < 0.01, *** P < 0.001 for South Asian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

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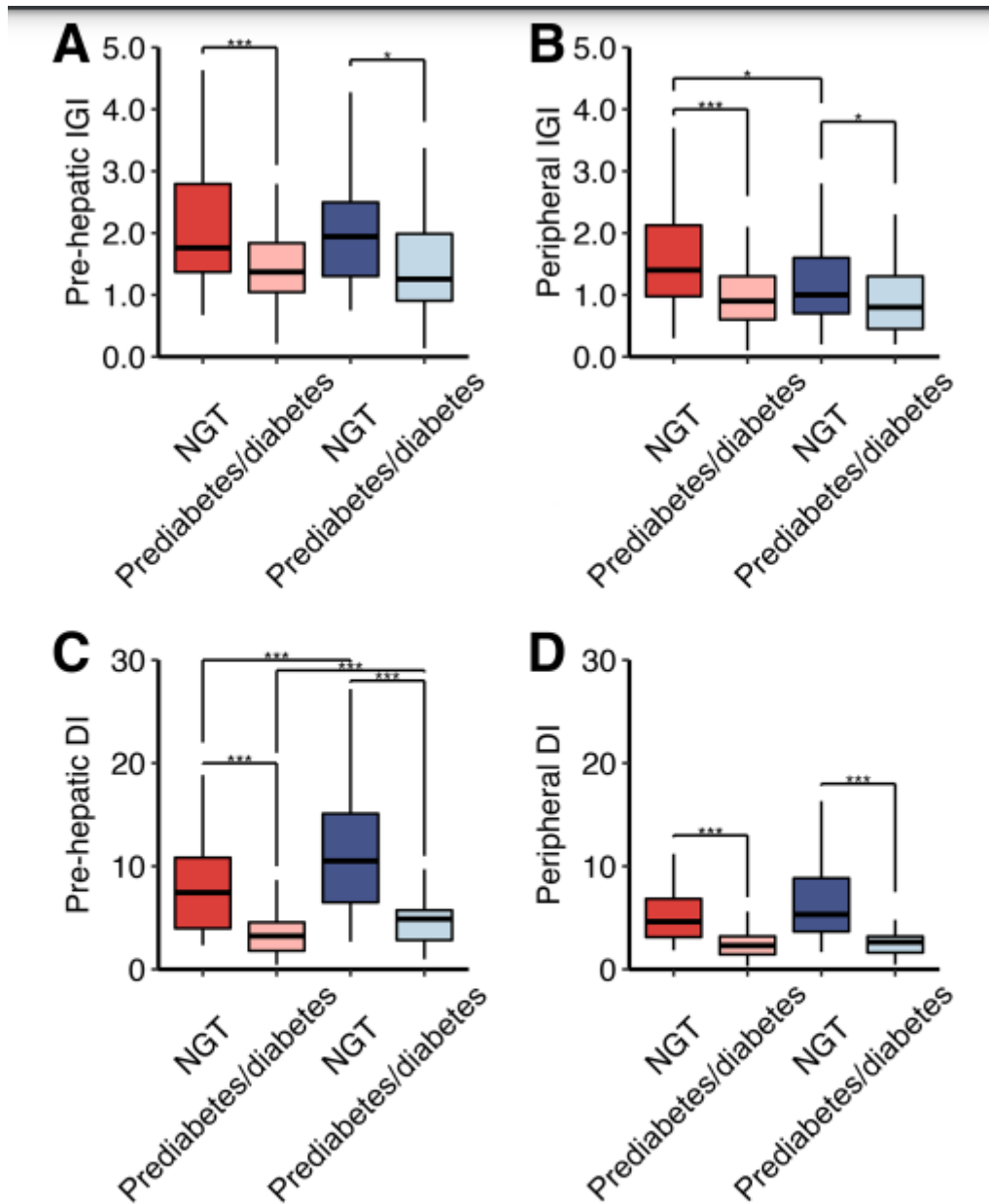


Figure 2— Box plot of early prehepatic (A) vs. early peripheral insulin secretion (prehepatic IGI vs. peripheral IGI) (B), and prehepatic (C) vs. peripheral disposition index (DI) (D) in South Asian (red) and Nordic (blue) participants with NGT (dark color) and prediabetes or diabetes (light color).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

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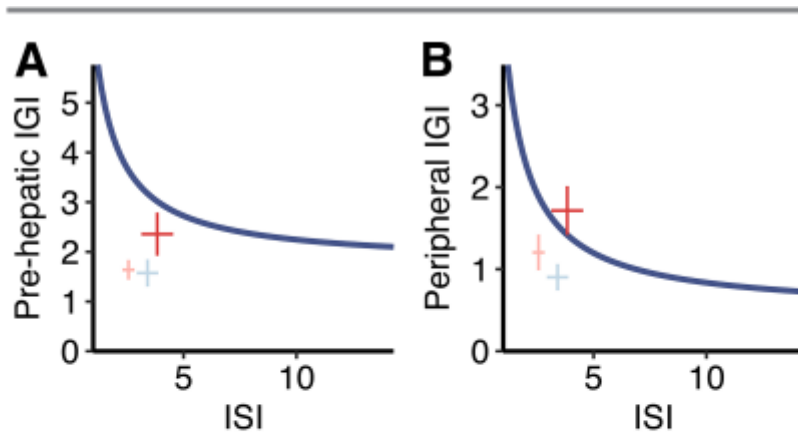


Figure 3—The disposition index curve. The relationship between early prehepatic (A) and peripheral insulin secretion (B) (prehepatic IGI vs. peripheral IGI) and insulin sensitivity (Matsuda ISI) in South Asian and Nordic participants with NGT and prediabetes or diabetes. The hyperbolic curve was regressed 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 \pm 95% CI.

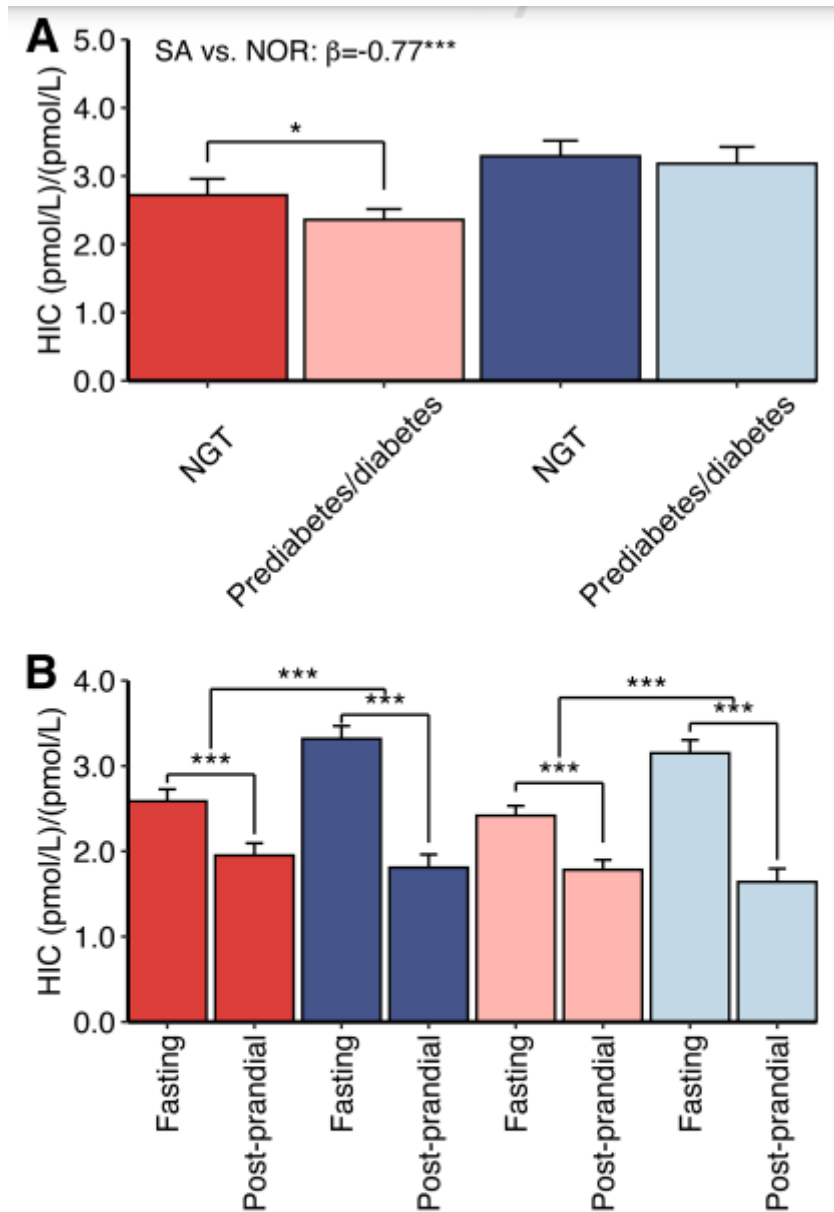


Figure 4—The ratio of prehepatic to peripheral insulin levels (HIC). *A*: Fasting HIC was lower in South Asian (red) vs. Nordic (blue) participants, in both the NGT (dark color) and prediabetes or diabetes (light color) groups. Fasting HIC declined from the NGT to prediabetes or diabetes group only in 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.