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Failure to increase insulin secretory capacity during pregnancy-induced insulin resistance is associated with ethnicity and gestational diabetes.

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Abstract

Objective: To assess changes in insulin resistance and β-cell function in a multiethnic cohort of women in Oslo, Norway, from early to 28 weeks' gestation and three months postpartum, and relate the findings to gestational diabetes (GDM).

Method: Population-based cohort study of 695 healthy pregnant women from Western Europe (41%), South Asia (25%), Middle East (15%), East Asia (6%) and elsewhere (13%). Blood samples and demographics at mean 15 (V1) and 28 (V2) weeks' gestation, and 3 months postpartum (V3). Universal screening by 75-g oral glucose tolerance test at V2, GDM with modified IADPSG criteria (no 1-hour measurement): Fasting Plasma Glucose (FPG) ≥5.1 or 2-hour PG ≥8.5 mmol/l. HOMA-β (β-cell function) and HOMA-IR (insulin resistance) calculated from fasting glucose and C-peptide.

Result: Characteristics were comparable across ethnic groups, except age (South Asians: younger, P<0.001) and prepregnant BMI (East Asians: lower, P=0.040). East and South Asians were more insulin resistant than Western Europeans at V1. From V1-V2 the increase in insulin resistance was similar across the ethnic groups, but the increase in β-cell function was significantly lower for the East and South Asians compared with Western Europeans. GDM compared with non-GDM women were more insulin resistant at V1, from V1-V2 their β-cell function increased significantly less and the percentage increase in β-cell function did not match the change in insulin resistance.

Conclusion: Pregnant women from East Asia and South Asia were more insulin resistant and showed poorer HOMA-β-cell function than Western Europeans.

Introduction

During pregnancy, insulin resistance is reported to increase by 50-60% to secure shunting of nutrients to the foetus (1). This increase is mediated partly through secretion of hormones from the placenta and increase in body fat depots (2). B-cells increase their insulin production through hyperplasia, hypertrophy and hyperfunction to compensate for the pregnancy induced insulin resistance in healthy women. The Homeostatic Model Assessment (HOMA) provides estimates of insulin resistance and gives an indication of the insulin secretion from fasting blood sample values (3). If the insulin secretion is inadequate to meet the insulin demands, maternal hyperglycaemia may ensue (2).

Glucose intolerance with onset or first recognition during pregnancy is known as gestational diabetes mellitus (GDM) (2). The initial GDM criteria were established in 1964, and primarily set to predict future diabetes in the mother (4, 5). The most frequently used GDM criteria today, are with only minor modifications similar to the initial GDM criteria or adopted from standards used outside pregnancy (6). Hence, GDM screening is thought to identify women with a failing β-cell function at high risk for the development of diabetes later in life (2).

The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study was conducted to clarify unanswered questions of the associations between maternal glycaemia and the risk of adverse outcomes (7). The HAPO-study's main findings were a continuous linear relationship between maternal glycaemia and adverse foetal outcomes defined as >90th percentiles of birth weight, percent body fat and cord C-peptide (7, 8).

Based on the findings from the HAPO-study, the International Association of Diabetes in Pregnancy Study Groups (IADPSG) have proposed new criteria for GDM (8). The IADPSG criteria were defined to identify women with an odds ratio of 1.75 for adverse foetal outcomes. Compared with the WHO criteria, the cut-off values in the IADPSG criteria are lowered for fasting plasma glucose (FPG) and raised for 2-hour plasma glucose (PG) (5, 8). One abnormal glucose value is adequate for the IADPSG GDM diagnosis, and the majority of cases are reported to be identified by the FPG cut-off value (8-10). The IADPSG criteria thus identify some women who have not previously been identified with

GDM (11). An important question is to which degree the IADPSG criteria identify women with a failing β-cell function and therefore at risk for future diabetes.

We recently reported that the prevalence of GDM with both the WHO and the modified IADPSG criteria were high for Western European and immigrant women living in Oslo (9). GDM is increasing in line with the diabetes type 2 prevalence worldwide (12, 13). Ethnic minority groups in Western countries are more insulin resistant and have higher diabetes prevalence rates compared with the host population (14). It is unclear if the relationship between the pregnancy induced insulin resistance and the β-cell function differ across ethnic groups.

The aim of the present study was to assess the changes in insulin resistance and β-cell function by HOMA in a multiethnic cohort of women from early gestation to 28 weeks of gestation and three months postpartum, and further to assess how this appears in GDM women identified with the IADPSG criteria, modified due to lack of 1 hour glucose values.

Subjects and methods

Study population and data collection

The Stork Groruddalen Study is a population-based cohort study that collected data at three public Child Health Clinics (CHC) in Eastern Oslo, Norway, from May 6th 2008 to May 15th 2010 (15). The Regional Ethics committee and The Norwegian Data Inspectorate approved the study protocol. The methods are described in details elsewhere (9, 15). Women were eligible if they 1) lived in the districts, 2) planned to give birth at one of two study hospitals, 3) were in <20 weeks of gestation at visit 1 (V1), 4) could communicate in Norwegian, Arabic, English, Sorani, Somali, Tamil, Turkish, Urdu or Vietnamese and 5) were able to give a written consent to participate. Women with pregestational diabetes or other diseases necessitating intensive hospital follow-up during pregnancy, were excluded. Women were followed up at 28±2 weeks of gestation (V2) and three months postpartum (V3). Staff members were certified after training, and assisted by professional translators when needed. Questionnaire data through interviews (demographics), anthropometric measurements (body height (fixed stadiometer), body weight (Tanita BC 418MA, Tokyo, Japan)) and venous fasting

blood samples were collected at V1-V3. A 75 g oral glucose tolerance test (OGTT) was performed at V2. Ethnic origin was defined by country of birth of the participant, or that of the participant's mother if the participant's mother was born outside Europe or North America (9).

From the total cohort of 823 (74% of the invited) women originally included in the STORK-Groruddalen study, 772 attended V2 (9). Totally 695 singleton pregnant women with available fasting glucose and C-peptide values from both V1 and V2 were included in the present study and constitute the study population. Five hundred and ninety-six of these women attended V3 where 523 delivered fasting blood samples to estimate HOMA-values. The reduced number at V3 was mainly due to resource limitations at the CHC, however, ethnic minority women and those with GDM with the WHO criteria were prioritized.

Laboratory methods

All glucose values were measured from venous blood on gel tubes, allowed to clot for 30 minutes before cells were separated from serum, stored at +4^{o}C and daily shipped and handled at the Department of Multidisciplinary Laboratory Medicine and Medical Biochemistry, Akershus University Hospital (Vitros 5.1 FS, Ortho Clinical Diagnostics, slide adapted colorimetric method)). Glycated hemoglobin (HbA1c) was measured with HPLC (Tosoh G8, Tosoh Corporation, normal reference range 4-6%). Fasting C-peptide and Insulin was measured at the Hormone Laboratory, Oslo University Hospital by non-competitive immunofluorometric assays (DELFIA, PerkinElmer Life Sciences, Wallac Oy, Turku, Finland). FPG and 2-hour PG for the diagnosis of GDM at V2 was measured on site in venous EDTA blood (HemoCue 201+, Angelholm, Sweden) (9).

GDM was diagnosed at V2 when FPG ≥5.1 mmol/l or 2-h PG ≥8.5 mmol/l according to a modified version of the IADPSG criteria, as one hour glucose values were not available (8). Insulin resistance (HOMA-IR) and β-cell function (HOMA-β) were estimated by the Oxford University HOMA Calculator 2.2 with fasting glucose and C-peptide concentrations (16).

Statistical analyses

Differences in characteristics between groups were tested with t-tests and one-way ANOVA for normally distributed, and Mann-Whitney U and Kruscal-Wallis test for non-normally distributed continuous variables, presented as mean with standard deviation (S.D.) or median with inter quartile range [IQR] as appropriate. The Sign test was used for related samples and the exact p-values were reported. Statistical significance was set at a 2-tailed probability level of $p<0.05$ and Bonferroni-corrections for multiple testing were used. SPSS version 19 was used for all analyses.

The percentage change in the HOMA values from V1 to V2 were calculated by the formula $(^{(\text{HOMA at V2} - \text{HOMA at V1})}/_{\text{HOMA at V1}})*100$. Univariate and multiple linear regression analyses were performed with HOMA-IR at V1 and percentage change in HOMA-β from V1 to V2 as dependent variables. The dependent variables were adjusted for gestational week at inclusion and ethnic origin in Model 1 and in addition prepregnant BMI in Model 2. The residuals were checked for normality and independence. Sensitivity analyses in non-GDM women only were done to test the robustness of the findings. Univariate and multiple logistic regression analyses were performed to identify the effect of HOMA-IR at V1 and percentage change in HOMA-β from V1 to V2 on GDM separately, after adjustments for gestational week at inclusion, prepregnant BMI and ethnic origin.

The reference group was Western Europe, mainly women from Norway (93%) and Sweden/Denmark (4%). The ethnic minority groups were; South Asia mainly from Pakistan (62%) and Sri Lanka (31%); Middle East mainly from Iraq (28%), Turkey (23%) and Morocco (21%); East Asia mainly from Vietnam (44%) and Philippines (28%); and Others from Sub-Saharan Africa (mainly Somalia (62%) and Nigeria (7%)) and other ethnic minorities (Eastern Europe and South- and Central America).

Results

The mean (S.D.) maternal age was 29.8 years (4.9), and the prepregnant BMI 24.5 kg/m^2 (4.8) (Table 1). East Asian women had lower prepregnant BMI compared with the Western European women (P=0.040). Women from South Asia were younger (P<0.001), and like the East Asian and African women they were recruited into the study slightly later in pregnancy compared with Western Europeans (P≤0.001). The East Asians had higher 2-hour glucose values at V2 than the Western

Europeans (P=0.06). The proportion identified with GDM with the modified IADPSG criteria was for Western Europeans 25%, South Asians 40%, Middle Easterners 37%, Sub-Saharan Africans 41% and East Asians 28%. There were no statistically significant difference between the 695 women included and the 128 women excluded from the present study with respect to ethnic origin (Western Europe vs. Ethnic minority), age, parity, prepregnant BMI, body height or level of education.

The overall insulin resistance measured by HOMA-IR increased from median [IQR] 1.1 [0.6] at V1 to 1.7 [0.9] at V2 (P<0.001). South Asians had higher HOMA-IR compared with Western Europeans, at V1 (1.2 vs. 1.0, P<0.001) and V2 (1.8 vs.1.5, P<0.001) (Fig 1a). There were no statistically significant differences between the ethnic groups in the absolute or percentage change in HOMA-IR from V1 to V2 (Table 2).

The overall β-cell function measured by HOMA-β increased from 133.2 [42.6] at V1 to 173.5 [49.3] at V2 (P<0.001). South Asians had higher HOMA-β compared with Western Europeans at V1 (143.6 vs. 125.9, P<0.001), but not at V2 (178.6 vs. 172.6, P=0.25) (Fig 1b). The absolute and percentage change in HOMA-β from V1 to V2 was less for the South Asian (P<0.005) and East Asian (P<0.002) compared with the Western European women (Table 2).

Linear regression analyses with HOMA-IR at V1 as the dependent variable revealed that South Asian and Middle Eastern women were more insulin resistant compared with Western Europeans in early gestation also after adjustments for gestational week at inclusion (Model 1; Table 3a). After further adjustments for prepregnant BMI, this difference in HOMA-IR was no longer found for the Middle Easterners, it was still present for the South Asians, while the East Asians became significantly more insulin resistant (Model 2). The findings still persisted after additional adjustments for parity and family history of diabetes (data not shown).

With the percentage change in HOMA-β from V1 to V2 as the dependent variable, the lesser increase in β-cell function among the East Asian and South Asian compared with the Western European women persisted after adjustments for gestational week at inclusion (Model 1; Table 3b), and with

further adjustments for prepregnant BMI (Model 2). The findings still persisted after additional adjustments for parity and family history of diabetes (data not shown).

The mean prepregnant BMI was significantly higher in women with GDM compared with women with normal glucose levels (Table 4). Their mean increase in BMI units from prepregnancy to V2 was similar (p=0.760). Women with GDM compared with women without GDM, were more insulin resistant, measured by HOMA-IR, at V1 (1.3 vs. 1.0, P<0.001) and V2 (2.0 vs. 1.5, P<0.001) (Fig 2a), but their β-cell function, measured by HOMA-β, was similar at V1 (136.3 vs. 132.0) and lower at V2 (166.7 vs. 176.5, P=0.003) (Fig 2b). The absolute change in HOMA-IR from V1 to V2 was significantly higher for the GDM compared with non-GDM women, but the percentage change was similar (Table 4). The absolute and percentage change in HOMA-β from V1 to V2 was significantly less in the GDM compared with the non-GDM women. Logistic regression analysis revealed that there was a highly significant increased odds ratio (OR) for GDM per unit increase in HOMA-IR at V1, also after adjustments for gestational week, prepregnant BMI and ethnic origin, OR 4.62 (95% CI 3.00–7.12). Per percentage increase in HOMA-β from V1 to V2 gave a highly significant protective OR for GDM, also after adjustments as previous, 0.99 (0.98-0.99).

At V3, the South Asian women had higher HOMA-IR and HOMA-β compared with the Western Europeans (P<0.001) (Table 5). For the GDM compared with non-GDM women at V3, the BMI was 27.5 kg/m^2 (5.3) vs. 25.3 kg/m^2 (4.5) (P<0.001), the HOMA-IR 1.7 [0.95] vs. 1.2 [0.66] (P<0.001) and the HOMA-β 129.4 [52.5] vs. 123.0 [38.8] (P=0.029). At V3 the GDM women had higher mean HbA1c and fasting glucose values compared with the non-GDM women 5.5% (0.3) vs. 5.4% (0.3) and 5.0 mmol/l (0.5) vs. 4.7 mmol/l (0.4) (both P<0.001), but no women had fasting glucose ≥7mmol/l or HbA1c ≥6.5%. There were no significant differences between the 523 women with and the 180 women without HOMA values at all three visits with respect to age, parity, prepregnant BMI, level of education or GDM with the modified IADPSG criteria.

Discussion

The prevalence of GDM and type 2 diabetes varies between ethnic groups, and is reported to be high in immigrants from Asia (12-14, 17). However, few studies have compared insulin resistance and β-cell function during pregnancy in a multiethnic cohort. In the present study we found that the East Asian and South Asian women were more insulin resistant in early pregnancy compared with Western Europeans, and the differences were larger after adjustments for BMI. From early to 28 weeks of gestation, all women irrespective of ethnic origin and baseline level became equally more insulin resistant. During the same period, the β-cell function to the East Asian and South Asian women did not compensate to the same extent as the Western Europeans. Women identified with GDM with the modified IADPSG criteria were more insulin resistant and their β-cell function was not able to meet the insulin demands induced by the pregnancy.

Insulin resistance is impinged by adiposity, and overweight and obese women start their pregnancy more insulin resistant compared with normal weight women (1). In the present study, a higher mean BMI explained the increased insulin resistance found in the Middle Eastern women. Middle Eastern women were also in previous studies identified with higher BMI levels than women from other ethnic groups (14, 18). On the other hand, the East Asian and South Asian women were more insulin resistant after adjustments for BMI compared with the Western Europeans. Asians are known to have more fat per BMI unit compared with Western subjects (14, 19-21). This may contribute to increased insulin resistance which is especially shown in South Asians (19, 20, 22). An increase in insulin resistance is a normal physiological phenomenon during pregnancy (1). Regardless of ethnic origin and baseline level, the insulin resistance increased approximately 40-45% from early to 28 weeks of gestation, a finding that is in concert with previous reports (1).

To maintain normoglycaemica during pregnancy, an increase in insulin secretion is needed to compensate for the increased insulin resistance (2). The precise mechanisms of β-cells mass expansion during human pregnancy have only partially been elucidated, but reports indicate that there is an adaptive increase in β-cell numbers (23-25). From early to 28 weeks of gestation the women from South Asia were not able to increase their β-cell function mutual to the insulin resistance. The β-cell response relative to the pregnancy induced insulin resistance was therefore unbalanced compared with

the Western Europeans. Reduced levels of adiponectin, a hormone secreted from adipose tissue and the placenta are in pregnancy associated with β-cell dysfunction (26). Pregnant women from South Asia are reported to have hypoadiponectinaemia to a greater extent compared with Caucasians (27), but this needs to be explored further.

The women from East Asia, like the South Asians, showed less increase in β-cell function from early to 28 weeks of gestation compared with the Western Europeans. Even though there were no statistical significant ethnic differences in the increase in the insulin resistance during the same period of time, the East Asians showed numerically less increase. Their increase in β-cell response relative to the increase in insulin resistance was therefore more in balance compared with the South Asians. East Asian subjects have in previous studies shown marked postprandial hyperglycaemia compared with matched Caucasian subjects (17, 18, 28), and might therefore be more predisposed to peripheral insulin resistance (29). Our results are in line with these findings, as the East Asian women showed a lesser degree of fasting hyperglycaemia, and higher 2-hour glucose values (9). The HAPO-study has also reported that GDM women in East Asia (Bangkok and Hong Kong) were less likely to be diagnosed based on the FPG value compared with women at other HAPO-study sites (10).

GDM screening with the most frequently used GDM criteria today (6, 12), is thought to identify women with an underlying β-cell defect not able to handle the metabolic stress that occurs during pregnancy (2). In the present study, using the modified IADPSG criteria, the GDM women were much more insulin resistant in early and at 28 weeks of gestation compared with the non-GDM women. However, in line with other studies, the percentage increase in insulin resistance was similar (1). The GDM women had poorer β-cell function at 28 weeks of gestation, and showed inequality between the increase in insulin resistance and β-cell response from early to 28 weeks of gestation, compared with the non-GDM women. Impaired fasting glucose, at least outside pregnancy, is suggested to be an effect of hepatic insulin resistance (29). Further, it has been reported that elevated endogenous glucose production, pointing to hepatic insulin resistance during pregnancy may lead to the development of type 2 diabetes. This together with our results could indicate that the IADPSG criteria, primarily set to

prevent adverse foetal outcomes (7), also identify women with a β-cell dysfunction at risk for developing diabetes later in life (30).

The South Asians were more insulin resistant and had elevated β-cell function compared with the Western Europeans three months postpartum, similar to the differences found at V1. No women qualified for a diagnosis of diabetes by using either FPG or HbA1c-criteria. The GDM women were more insulin resistant compared to the non-GDM women three months postpartum, but the β-cell function did not seem to differ to the same extent. The GDM women's higher fasting glucose and HbA1c values might indicate that their β-cell function in relation to the higher insulin resistance was inappropriate, and could therefore be a sign of relative β-cell failure. It has been reported that GDM women seem able to compensate for the increased insulin resistance in the first months postpartum, but that they may manifest progressive loss of β-cell function in the long run (2). Severe hepatic insulin resistance, which is linked to elevated FPG (29) is reported to deteriorate β-cell function in the first year postpartum after gestational dysglycaemia (31). Recent reports indicate that subjects with elevated FPG have impaired first-phase insulin secretion and therefore β-cell failure (32).

Although no significant differences between those who did and did not attended V3 were found, we can not rule out that selection bias might have affected the results three months postpartum. The Stork Groruddalen study was not purely observational as 13% of the women identified with GDM with the WHO criteria received lifestyle advice at 28 weeks of gestation (9). The Stork Groruddalen study was planned prior to the announcement of the IADPSG criteria and used the WHO criteria with fasting and 2-hour glucose values to diagnose GDM according to Norwegian standards. The lack of the 1-hour glucose value is therefore an additional limitation of the present study. However, the majority of women identified with GDM with the IADPSG criteria in previouse studies are identified with the FPG value. Due to limited resources and the wish to include a high percentage of women from all ethnic groups, the recourse intensive "gold standard" methods, clamp studies or intravenous glucose tolerance tests, to quantify insulin resistance and β-cell function in vivo, were not feasible. The HOMA is a surrogate measure of these parameters, estimated from fasting glucose and insulin or C-peptide concentrations (3). HOMA-β has therefore limited ability to detect chronic β-cell dysfunction,

and might explain the absence of a difference in β-cell function between the GDM and non-GDM women in early gestation. However, HOMA is feasible in large studies and has also been validated in studies of pregnant women (16, 33, 34).

The strength of this study is the follow-up design and high response rate both during and after pregnancy across the ethnic groups (9, 15). It is important to characterise the diabetes pathogenesis and ethnic differences in order to curb the diabetes pandemic, where Asians are especially affected (12, 13). Asians are the fastest growing minority group in the US, and South Asians the largest minority group in several European countries (20). The results from the present study should therefore be relevant outside the Norwegian context as the sample is fairly representative for the largest ethnic groups included (9).

Conclusion

We found ethnic differences in insulin resistance and β-cell function measured by HOMA, through pregnancy and three months postpartum. East Asian and South Asian women were more insulin resistant compared with Western Europeans after adjustments for BMI, and showed poorer β-cell function. GDM diagnosed with modified IADPSG criteria was associated with less ability to compensate to the pregnancy-induced insulin resistance. We therefore conclude that the IADPSG criteria, primarily set to prevent adverse foetal outcomes, may also identify women with a latent β-cell failure presumably at risk of future diabetes.

Declaration of interest

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

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Reference list

1. Catalano PM. Obesity, insulin resistance, and pregnancy outcome. *Reproduction* 2010 **140** 365-371.
2. Buchanan TA, Xiang A, Kjos SL & Watanabe R. What is gestational diabetes? *Diabetes Care* 2007 **30 Suppl 2** S105-111.
3. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF & Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985 **28** 412-419.
4. O'Sullivan JB, Gellis SS, Dandrow RV & Tenney BO. The potential diabetic and her treatment in pregnancy. *Obstet.Gynecol.* 1966 **27** 683-689.
5. Alberti KG & Zimmet PZ. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva: World Health Organisation, 1999.
6. Paglia MJ & Coustan DR. Gestational diabetes: evolving diagnostic criteria. *Curr Opin Obstet Gynecol* 2011 **23** 72-75.
7. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS & Sacks DA. Hyperglycemia and adverse pregnancy outcomes. *N.Engl.J Med.* 2008 **358** 1991-2002.
8. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva A, Hod M, Kitzmiler JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y & Schmidt MI. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010 **33** 676-682.
9. Jenum AK, Morkrid K, Sletner L, Vangen S, Torper JL, Nakstad B, Voldner N, Rognerud-Jensen OH, Berntsen S, Mosdol A, Skrivarhaug T, Vardal MH, Holme I, Yajnik CS & Birkeland KI. Impact of ethnicity on gestational diabetes identified with the WHO and the modified International Association of Diabetes and Pregnancy Study Groups criteria: a population-based cohort study. *Eur J Endocrinol* 2012 **166** 317-324.
10. Sacks DA, Hadden DR, Maresh M, Deerochanawong C, Dyer AR, Metzger BE, Lowe LP, Coustan DR, Hod M, Oats JJ, Persson B & Trimble ER. Frequency of Gestational Diabetes Mellitus at Collaborating Centers Based on IADPSG Consensus Panel-Recommended Criteria: The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Diabetes Care* 2012 **35** 526-528.
11. Leary J, Pettitt DJ & Jovanovic L. Gestational diabetes guidelines in a HAPO world. *Best.Pract.Res.Clin.Endocrinol.Metab* 2010 **24** 673-685.
12. Jiwani A, Marseille E, Lohse N, Damm P, Hod M & Kahn JG. Gestational diabetes mellitus: results from a survey of country prevalence and practices. *J Matern Fetal Neonatal Med* 2011.
13. Nolan CJ, Damm P & Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management. *Lancet* 2011 **378** 169-181.

14. Jenum AK, Diep LM, Holmboe-Ottesen G, Holme IM, Kumar BN & Birkeland KI. Diabetes susceptibility in ethnic minority groups from Turkey, Vietnam, Sri Lanka and Pakistan compared with Norwegians - the association with adiposity is strongest for ethnic minority women. *BMC Public Health* 2012 **12** 150.
15. Jenum AK, Sletner L, Voldner N, Vangen S, Morkrid K, Andersen LF, Nakstad B, Skrivarhaug T, Rognerud-Jensen OH, Roald B & Birkeland KI. The STORK Groruddalen research programme: A population-based cohort study of gestational diabetes, physical activity, and obesity in pregnancy in a multiethnic population. Rationale, methods, study population, and participation rates. *Scand J Public Health* 2010 **38** 60-70.
16. Wallace TM, Levy JC & Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004 **27** 1487-1495.
17. Gunton JE, Hitchman R & McElduff A. Effects of ethnicity on glucose tolerance, insulin resistance and beta cell function in 223 women with an abnormal glucose challenge test during pregnancy. *Aust N Z J Obstet Gynaecol* 2001 **41** 182-186.
18. Wong VW. Gestational diabetes mellitus in five ethnic groups: a comparison of their clinical characteristics. *Diabet Med* 2012 **29** 366-371.
19. Misra A & Khurana L. Obesity-related non-communicable diseases: South Asians vs White Caucasians. *Int J Obes (Lond)* 2011 **35** 167-187.
20. Eapen D, Kalra GL, Merchant N, Arora A & Khan BV. Metabolic syndrome and cardiovascular disease in South Asians. *Vasc Health Risk Manag* 2009 **5** 731-743.
21. Wulan SN, Westerterp KR & Plasqui G. Ethnic differences in body composition and the associated metabolic profile: a comparative study between Asians and Caucasians. *Maturitas* 2010 **65** 315-319.
22. Retnakaran R, Hanley AJ, Connelly PW, Sermer M & Zinman B. Ethnicity modifies the effect of obesity on insulin resistance in pregnancy: a comparison of Asian, South Asian, and Caucasian women. *J Clin Endocrinol Metab* 2006 **91** 93-97.
23. Butler AE, Cao-Minh L, Galasso R, Rizza RA, Corradin A, Cobelli C & Butler PC. Adaptive changes in pancreatic beta cell fractional area and beta cell turnover in human pregnancy. *Diabetologia* 2010 **53** 2167-2176.
24. Ernst S, Demirci C, Valle S, Velazquez-Garcia S & Garcia-Ocana A. Mechanisms in the adaptation of maternal beta-cells during pregnancy. *Diabetes Manag (Lond)* 2011 **1** 239-248.
25. Van Assche FA, Aerts L & De Prins F. A morphological study of the endocrine pancreas in human pregnancy. *Br J Obstet Gynaecol* 1978 **85** 818-820.
26. Retnakaran R, Qi Y, Connelly PW, Sermer M, Hanley AJ & Zinman B. Low adiponectin concentration during pregnancy predicts postpartum insulin resistance, beta cell dysfunction and fasting glycaemia. *Diabetologia* 2010 **53** 268-276.
27. Retnakaran R, Hanley AJ, Connelly PW, Maguire G, Sermer M & Zinman B. Low serum levels of high-molecular weight adiponectin in Indo-Asian women during pregnancy: evidence of ethnic variation in adiponectin isoform distribution. *Diabetes Care* 2006 **29** 1377-1379.
28. Dickinson S, Colagiuri S, Faramus E, Petocz P & Brand-Miller JC. Postprandial hyperglycemia and insulin sensitivity differ among lean young adults of different ethnicities. *J Nutr* 2002 **132** 2574-2579.
29. Faerch K, Borch-Johnsen K, Holst JJ & Vaag A. Pathophysiology and aetiology of impaired fasting glycaemia and impaired glucose tolerance: does it matter for prevention and treatment of type 2 diabetes? *Diabetologia* 2009 **52** 1714-1723.
30. Miyakoshi K, Saisho Y, Tanaka M, Shimada A, Itoh H & Yoshimura Y. Pancreatic beta-cell function in women with gestational diabetes mellitus defined by new consensus criteria. *Diabetes Care* 2011 **34** e8.
31. Retnakaran R, Qi Y, Ye C, Hanley AJ, Connelly PW, Sermer M & Zinman B. Hepatic Insulin Resistance Is an Early Determinant of Declining {beta}-Cell Function in the First Year Postpartum After Glucose Intolerance in Pregnancy. *Diabetes Care* 2011.
32. Kanat M, Mari A, Norton L, Winnier D, DeFronzo RA, Jenkinson C & Abdul-Ghani MA. Distinct beta-cell defects in impaired fasting glucose and impaired glucose tolerance. *Diabetes* 2012 **61** 447-453.

33. Radaelli T, Farrell KA, Huston-Presley L, Amini SB, Kirwan JP, McIntyre HD & Catalano PM. Estimates of insulin sensitivity using glucose and C-Peptide from the hyperglycemia and adverse pregnancy outcome glucose tolerance test. *Diabetes Care* 2010 **33** 490-494.
34. Wallace TM & Matthews DR. The assessment of insulin resistance in man. *Diabet Med* 2002 **19** 527-534.

Table 1 Characteristics of the total cohort, and stratified into ethnic groups. Values are mean and standard deviation (S.D.) or otherwise stated.

	Total n=695 (100 %)		Western Europe n=286 (41 %)		South Asia n=174 (25 %)		Middle East n=105 (15 %)		Sub-Saharan Africa n=42 (6 %)		East Asia n=39 (6 %)		Others n=49 (7 %)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Age, years	29.8	4.9	30.9	4.5	28.6	4.4	29.3	5.4	27.9	5.3	31.0	4.6	29.3	5.2
Body height, cm	163.6	6.7	167.3	5.6	160.1	5.7	161.2	5.5	162.6	6.1	157.0	6.4	165.5	6.3
BMI prepregnancy, kg/m^2	24.5	4.8	24.7	4.9	23.6	4.1	25.7	5.1	26.1	5.4	22.3	3.4	24.7	5.2
Visit 1														
Weeks of gestation	15	3	14	2	15	4	15	3	17	4	17	4	15	3
Weight, kg	67.6	14.1	70.9	14.0	62.0	11.4	69.6	15.2	71.1	14.6	57.0	10.6	69.5	14.0
BMI, kg/m^2	25.2	4.8	25.3	4.8	24.2	4.0	26.7	5.4	26.8	5.0	23.1	3.6	25.4	4.9
HbA1c , %	5.2	0.3	5.2	0.2	5.2	0.3	5.1	0.3	5.2	0.3	5.2	0.4	5.1	0.3
Fasting glucose, mmol/l	4.4	0.4	4.4	0.4	4.5	0.4	4.5	0.5	4.4	0.5	4.3	0.3	4.4	0.4
Insulin, pmol/l[a]	40.0	33.0	32.0	26.0	52.5	40.0	40.0	35.0	43.0	49.0	39.0	26.0	37.0	32.0
C-peptide, nmol/l[a]	0.52	0.26	0.48	0.23	0.59	0.30	0.52	0.27	0.48	0.29	0.53	0.22	0.51	0.23
Visit 2														
Weeks of gestation	28	1	28	1	28	1	28	1	28	1	28	1	28	1
Weight, kg	74.3	14.0	77.5	13.9	68.7	11.6	76.7	14.7	76.0	14.97	63.2	10.3	77.6	12.6
BMI, kg/m^2	27.7	4.6	27.7	4.7	26.8	4.0	29.5	5.1	28.7	5.1	25.6	3.4	28.3	4.4
HbA1c , %	5.2	0.3	5.1	0.3	5.3	0.3	5.2	0.4	5.3	0.3	5.2	0.3	5.2	0.3
Fasting glucose, mmol/l	4.4	0.5	4.4	0.5	4.5	0.5	4.5	0.6	4.4	0.6	4.4	0.4	4.4	0.6
2-h glucose, mmol/l	5.7	1.5	5.6	1.4	5.9	1.6	5.9	1.7	5.5	1.3	6.3	1.5	5.7	1.5
Insulin, pmol/l[a]	57.0	44.0	48.0	36.0	75.0	42.0	60.0	46.0	62.0	52.0	52.0	35.0	56.0	38.0
C-peptide, nmol/l[a]	0.76	0.39	0.71	0.34	0.86	0.39	0.76	0.46	0.74	0.35	0.71	0.35	0.73	0.27

[a] median, IQR

Table 2 Absolute (Δ) and percentage change (%Δ) in biochemical parameters and HOMA values from visit 1 to visit 2 in study participants according to ethnic group. Values in median and Inter Quartile Range (IQR) or otherwise stated.

	Western Europe		South Asia		Middle East		Sub-Saharan Africa		East Asia		Others	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Δ Fasting glucose[a], mmol/l	-0.1	0.4	0.0	0.4	0.1	0.5	0.0	0.6	0.0	0.4	0.0	0.5
Δ Insulin, pmol/l	13.0	25.0	18.0	34.0	15.0	30.0	10.5	35.0	12.0	29.0	19.0	32.0
Δ C-peptide, nmol/l	0.22	0.25	0.24	0.28	0.22	0.30	0.16	0.31	0.19	0.20	0.22	0.25
Δ HOMA-IR	0.45	0.54	0.50	0.58	0.47	0.70	0.32	0.69	0.42	0.52	0.45	0.45
Δ HOMA-β	43.5	39.5	32.5**	45.1	35.9	43.8	37.2	46.0	23.8**	45.3	46.0	43.9
% Δ HOMA-IR	46.0	57.6	43.0	56.1	43.6	66.8	31.5	76.5	33.2	40.3	47.7	75.0
% Δ HOMA-β	33.6	35.7	22.9**	33.7	31.3	32.0	29.4	43.7	17.8*	36.5	34.4	31.6

[a] mean. S.D. * p<0.05 difference from Western European, Bonferroni corrected ** p< 0.005 difference from Western European, Bonferroni corrected.

Table 3 Linear regression analyses with a) HOMA-IR at visit 1 (V1) and b) percentage change (*%Δ)* in HOMA-β from V1 to visit 2 as the dependent variable.

	Univariate		Multiple Model 1[a]		Multiple Model 2[b]	
	β-Coefficient	p-value	β-Coefficient	p-value	β-Coefficient	p-value
a) V1 HOMA-IR						
Weeks of gestation V1	0.02	<0.001	0.02	0.001	0.02	0.002
South Asia	0.29	<0.001	0.27	<0.001	0.33	<0.001
Middle East	0.11	0.046	0.10	0.086	0.05	0.271
East Asia	0.11	0.171	0.07	0.422	0.19	0.009
Others	0.04	0.468	0.01	0.810	-0.02	0.735
BMI prepregnancy	0.05	<0.001			0.05	<0.001
b) %Δ HOMA-β						
Weeks of gestation V1	-2.20	<0.001	-2.00	<0.001	-1.73	<0.001
South Asia	-12.28	0.003	-10.00	0.015	-11.05	0.005
Middle East	-5.74	0.237	-4.15	0.390	-3.36	0.432
East Asia	-20.68	0.005	-16.08	0.028	-19.27	0.006
Others	-0.63	0.902	2.16	0.673	-0.69	0.889
BMI prepregnancy	-0.98	0.003			-1.14	0.001

[a] adjusted for weeks of gestation at V1 and ethnic origin with Western Europe as reference
[b] additional adjustments for prepregnant BMI

Table 4 Characteristics and biochemical parameters at visit 1 (V1), and absolute (Δ) and percentage change (%Δ) from V1 to visit 2 for the GDM and non-GDM women. Values in mean and standard deviation (S.D.), median and Inter Quartile Range (IQR) or otherwise stated. P-values for the difference between the groups.

	GDM n=220 (32%)		Non-GDM n=475 (68%)		
	Mean	S.D.	Mean	S.D.	p-value
Weeks of gestation at V1	15	3	15	3	0.905
Age, years	30.2	5.1	29.6	4.7	0.176
BMI prepregnancy, kg/m^2	25.9	5.5	23.9	4.2	<0.001
Body height, cm	162.9	6.6	163.9	6.7	0.071
Weight, kg	70.7	16.2	66.2	12.9	<0.001
HbA1c, %	5.3	0.3	5.1	0.3	<0.001
Fasting glucose, mmol/l	4.7	0.4	4.3	0.3	<0.001
Insulin[b], pmol/l	55.0	47.0	36.0	26.0	<0.001
C-peptide[b], nmol/l	0.63	0.35	0.48	0.21	<0.001
	Median	IQR	Median	IQR	p-value
Δ Weight[a], kg	6.8	3.3	6.6	3.0	0.557
Δ Fasting glucose [a], mmol/l	0.2	0.5	-0.1	0.4	<0.001
Δ Insulin, pmol/l	19.0	34.0	12.0	26.0	0.008
Δ C-peptide, nmol/l	0.26	0.28	0.20	0.24	<0.001
Δ HOMA-IR	0.6	0.7	0.4	0.5	<0.001
Δ HOMA-β	30.0	40.8	43.5	40.1	<0.001
% Δ HOMA-IR	47.5	63.3	41.4	57.6	0.161
% Δ HOMA-β	21.9	32.5	32.9	35.3	<0.001

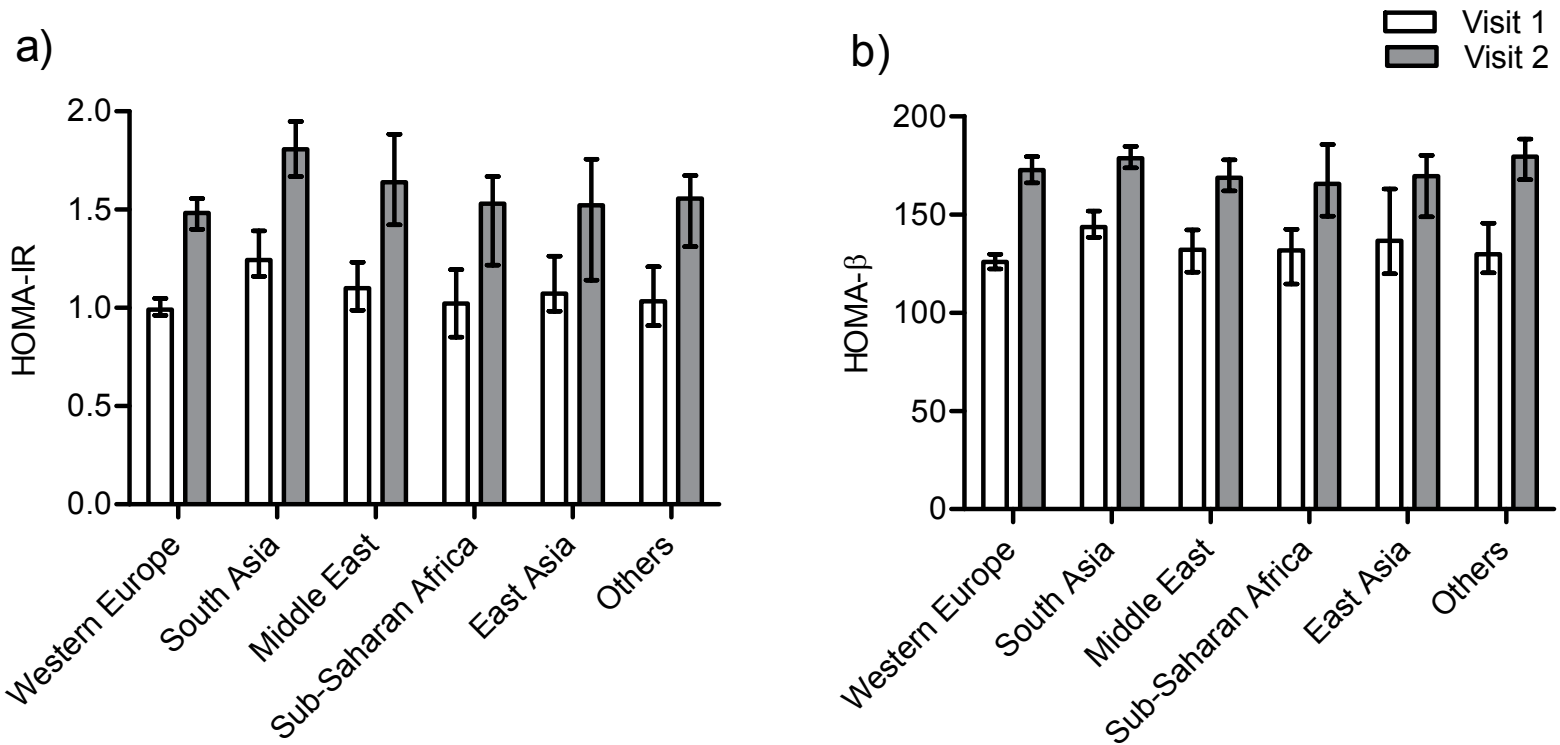
[a] mean, S.D. [b] median, IQR

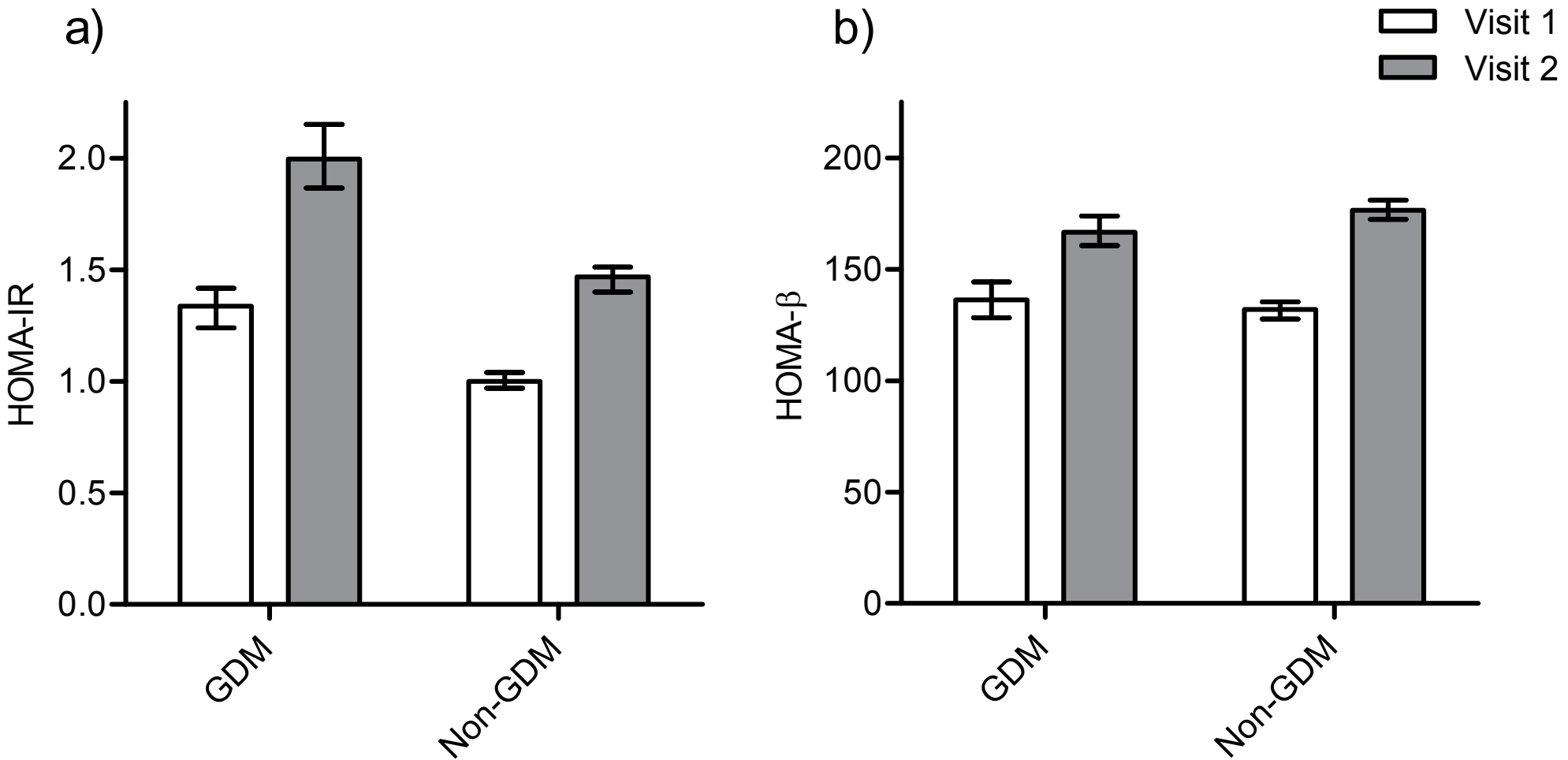
Table 5 Post-partum characteristics, biochemical parameters and HOMA values of the total cohort, and stratified into ethnic groups. Values are mean and standard deviation (S.D.) or otherwise stated.

	Total n=523 (100 %)		Western Europe n=203 (39 %)		South Asia n=141 (27 %)		Middle East n=85 (16 %)		Sub-Saharan Africa n=26 (5 %)		East Asia n=31 (6 %)		Others n=37 (7 %)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Weeks postpartum	14	3	14	2	14	3	14	3	15	3	15	3	14	2
Weight, kg	69.7	14.3	72.1	14.7	65.4	11.5	72.3	15.8	73.1	13.8	59.5	10.0	71.3	13.6
BMI, kg/m^2	26.0	4.9	25.7	5.0	25.5	4.2	27.8	5.3	28.1	5.0	24.0	3.3	26.1	4.9
HbA1c , %	5.4	0.3	5.4	0.2	5.5	0.3	5.3	0.3	5.5	0.3	5.5	0.4	5.4	0.3
Fasting glucose, mmol/l	4.8	0.4	4.7	0.4	4.8	0.4	4.9	0.5	4.8	0.4	4.8	0.4	4.8	0.6
Insulin, pmol/l[a]	39.0	31.5	31.0	25.0	52.0	40.0	43.5	28.0	42.0	44.0	33.0	30.0	36.0	18.0
C-peptide, nmol/l[a]	0.61	0.36	0.57	0.31	0.73	0.35	0.64	0.36	0.53	0.32	0.53	0.35	0.55	0.26
HOMA-IR[a]	1.3	0.8	1.2	0.7	1.6	0.8	1.4	0.8	1.2	0.8	1.2	0.8	1.2	0.6
HOMA-β[a]	125.7	41.3	121.3	40.4	138.1	45.9	124.7	40.0	118.9	27.4	116.8	34.0	119.2	25.9

[a] median, IQR

Figure 1.


a)
HOMA-IR
2.0
1.5
1.0
0.5
0.0
Western Europe
South Asia
Middle East
Sub-Saharan Africa
East Asia
Others
b)
Visit 1
Visit 2
HOMA-β
200
150
100
50
0
Western Europe
South Asia
Middle East
Sub-Saharan Africa
East Asia
Others


a)
HOMA-IR
2.0
1.5
1.0
0.5
0.0
GDM
Non-GDM
b)
Visit 1
Visit 2
HOMA-β
200
150
100
50
0
GDM
Non-GDM