Ethnic differences in BMI, subcutaneous fat, and serum leptin levels during and after pregnancy and risk of gestational diabetes

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Abstract

Objective: To explore the differences between Europeans and South Asians in BMI, subcutaneous fat, and serum leptin (s-leptin) levels during and after pregnancy and their relationship with gestational diabetes (GDM).

Design: Multi-ethnic population-based cohort study, whereof 353 Europeans (93.1% of the included) and 190 South Asians (95.0% of the included).

Methods: S-leptin, BMI, and subcutaneous fat (sum of triceps, subscapular, and suprailiac skinfolds) were measured at 14 and 28 weeks of gestation, and 14 weeks after delivery. GDM was diagnosed with the WHO criteria 2013.

Results: South Asians had similar thickness of the triceps and suprailiac skinfolds, thicker subscapular skinfold, and higher s-leptin than Europeans in early pregnancy, despite lower BMI. South Asians retained more subcutaneous fat (mean (95% CI) 10.0 (7.4–12.7) mm vs 3.8 (1.9–5.8) mm) and BMI (1.5 (1.2–1.8) kg/m² vs 0.1 (−0.1 to 0.3) kg/m²) than Europeans 14 weeks after delivery and s-leptin decreased less in South Asians than Europeans (−0.13 (−0.27 to −0.00) μg/l vs −0.47 (−0.57 to −0.37) μg/l, P<0.001 for all). The prevalence of GDM was 23.8% (n=84) in Europeans and 42.6% (n=81) in South Asians. BMI, subcutaneous fat, and s-leptin were all positively associated with GDM, also after adjustment for covariates.

Conclusions: The relatively high amounts of subcutaneous fat and s-leptin in South Asians in early pregnancy contributed to their increased risk of GDM. South Asians retained more weight and subcutaneous fat after delivery, potentially increasing their risk of adiposity and GDM in future pregnancies.

Introduction

Obesity and diabetes constitute worldwide threats to the public health (1) and to health care systems and economies (2). South Asian migrants to Europe have a high prevalence of type 2 diabetes (3) and gestational diabetes (GDM) (4). GDM is defined as first recognition of hyperglycemia during pregnancy (5). GDM gives a sevenfold higher risk of developing type 2 diabetes in the future (6), is associated with several pregnancy complications (7, 8), and probably increases the risk of later obesity and type 2 diabetes in the offspring (9). Maternal obesity increases the risk of GDM, large for gestational age babies (10) and even of fetal death, stillbirth, and infant death (11). The adverse metabolic consequences of obesity, such as insulin resistance and diabetes, are related to the
accumulation of fat (12). Serum leptin (s-leptin) levels reflect the proportion of adipose tissue in the body (13), is highly correlated with fat mass (14), and correlates particularly with subcutaneous fat in women (14, 15). Several studies have observed higher s-leptin levels in individuals of South Asian than European descent for the same BMI (16, 17), suggesting that BMI may be a poor indicator of adiposity in South Asians. Leptin levels increase in pregnancy, due to production by the placenta, and decline rapidly after delivery (18). Thus, subcutaneous fat and leptin may be better indicators of adiposity in a multi-ethnic population of pregnant women than body weight and BMI, and may account for some of the higher GDM risk observed in South Asians. To our knowledge, ethnic differences in subcutaneous fat and leptin levels during and after pregnancy and their relationship with GDM risk have not yet been investigated.

Our objective was to explore the differences between European and South Asian women in BMI, subcutaneous fat, and s-leptin levels during and after pregnancy and their relationships with GDM.

Subjects and methods
Details of the study methods have been described previously (19). The STORK Groruddalen study is a population-based cohort study of healthy pregnant women attending child health clinics for antenatal care in three administrative city districts in Groruddalen, Oslo, Norway, from May 2008 to May 2010. General practitioners were asked to refer pregnant women to the child health clinics early in pregnancy. Women were eligible if they i) lived in the study districts, ii) planned to give birth at one of two study hospitals, iii) were > 20 weeks pregnant, and iv) could communicate in Norwegian or any of the eight translated languages. Women with pregestational diabetes or in need of intensive hospital follow-up during pregnancy were excluded. The participation rate was 81.5% among Europeans and 73.0% among South Asians.

The study was approved by The Regional Ethics Committee and The Norwegian Data Inspectorate. A written consent was obtained for all the participants after full explanation of the purpose and procedures used.

Background data
Information about maternal age, parity, and ethnic origin was collected through interviewer-administered questionnaires at 14 weeks of gestation. Parity was dichotomized into nulliparous and parous, referring to status before the current pregnancy. Ethnicity was defined as country of birth or participant’s mother’s country of birth if the participant’s mother was born outside of Europe or other western countries. Three women born in North America were categorized as Europeans. In this substudy, we included all Europeans (82% Norwegians) and South Asians (63% Pakistanis and 31% Sri Lankans). Family history of diabetes was defined as having a first-degree relative with diabetes.

Anthropometrics
Height was measured with a fixed stadiometer to the nearest 0.1 cm at 14 weeks of gestation, body weight with a calibrated digital scale with light clothing and without shoes at 14 and 28 weeks of gestation, and 14 weeks after delivery. BMI was calculated with height measured at 14 weeks of gestation and weight at the respective visits. Prepregnancy BMI was based on self-reported prepregnant body weight.

Subcutaneous fat was measured with a skinfold caliper, to the nearest 1 mm, at the triceps, subscapular, and suprailiac sites, at 14 and 28 weeks of gestation and 14 weeks after delivery (20, 21). Each skinfold was measured twice and the mean value was used. Sum of skinfolds, a proxy for overall subcutaneous fat (22), was calculated by summarizing the three skinfold sites. Inter-rater variability for maternal skinfolds, expressed as % technical error of measurement, ranged from 5 to 21% between study personnel and the reference midwife (21). Intra-rater variability was < 5% for all measurements (21).

Metabolic variables and GDM
Blood was collected at 14 and 28 weeks of gestation and 14 weeks after delivery. Fasting C-peptide and insulin were measured at the Hormone Laboratory, Oslo University Hospital, by non-competitive immunofluorometric assays (DELFIA, PerkinElmer Life Sciences, Wallac Oy, Turku, Finland). HbA1c was analyzed with HPLC (Tosoh G8, Tosoh Corporation, Tokyo, Japan). S-leptin was analyzed with the Luminex xMAP technology (Millipore Corporation, Billerica, MA, USA). A standard 75 g oral glucose tolerance test (OGTT) was performed at 28 weeks of gestation with fasting and 2-h plasma glucose analyzed on-site in venous EDTA blood samples (HemoCue, Angelholm, Sweden) (4). GDM was defined by the WHO 2013 criteria (23) (fasting glucose ≥ 5.1 mmol/l or 2-h glucose ≥ 8.5 mmol/l) and 1-h glucose was not available (4).
European Journal of Endocrinology

Comparisons of continuous variables, we used of s-leptin approached normal distribution. For simple distribution before analyses and subsequently transformed by square root to obtain normal point was transformed by square root to obtain normal distribution before analyses and subsequently trans-

Statistical analysis

Continuous variables were expressed as mean ± S.D. if normally distributed, median (interquartile range) if not normally distributed, or number (%) if categorical. Estimated means adjusted for covariates were presented as mean (95% CI), and results from the logistic regression analyses were presented as OR (95% CI). Level of significance was set at P < 0.05. S-leptin at each time point was transformed by square root to obtain normal distribution before analyses and subsequently transformed back for reporting purposes. The change variables of s-leptin approached normal distribution. For simple comparisons of continuous variables, we used t-test or Mann–Whitney U test as appropriate and χ² test to test differences in proportions. To test overall change between visits, we performed paired samples t-test. We performed multivariate general linear models (GLM) to explore ethnic difference in the changes during pregnancy and after delivery. The changes from 14 to 28 weeks of gestation were adjusted for weeks of gestation at inclusion, weeks between the two measurements, age, and parity, while changes from 14 weeks of gestation to 14 weeks after delivery were adjusted for weeks of gestation at inclusion, week after delivery, age, and parity. To explore ethnic differences in body composition at 14 weeks of gestation in nulliparous vs parous, we performed multivariate GLM across ethnic origin separately for nulliparous and parous and adjusted for weeks of gestation at inclusion and age.

We performed logistic regression analyses separately for each explanatory variable to explore the association between early pregnancy BMI, sum of skinfolds or s-leptin, and GDM. The logistic regression analyses were adjusted for weeks of gestation at inclusion, age, parity, and ethnic origin. All statistical analyses were performed using SPSS IBM Statistics 21.

Sample flow

Of the 823 women participating in the STORK Groruddalen study, we included all women with European (n = 379) and South Asian (n = 200) origin (Fig. 1). We found no differences in baseline characteristics, listed in Table 1, between those lacking OGTT or s-leptin and the included South Asians and Europeans (data not shown). When exploring ethnic differences in BMI, skinfolds and s-leptin during and after pregnancy, we excluded 76 women who did not attend the visit at 14 weeks after delivery (Fig. 1). Among the women who attended 14 weeks after delivery, there was a higher proportion of nulliparous than parous (referring to their status before the current pregnancy; 49.7% vs 38.1%, P = 0.003) and they had slightly lower prepregnant BMI (25.4 kg/m² vs 24.2 kg/m², P = 0.011) than those who did not re-attend.

Table 1 Characteristics of the sample at 15 weeks of gestation across ethnic origin. Data are expressed as mean ± S.D., n (%) or median (interquartile range).

<table>
<thead>
<tr>
<th></th>
<th>Europe (n = 353)</th>
<th>South Asia (n = 190)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.1 ± 4.5</td>
<td>28.2 ± 4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nulliparous, n (%)</td>
<td>188 (53)</td>
<td>79 (42)</td>
<td>0.013</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167 ± 6</td>
<td>160 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>70.4 ± 13.7</td>
<td>62.6 ± 11.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prepregnancy BMI, self-reported (kg/m²)</td>
<td>24.5 ± 4.8</td>
<td>23.7 ± 4.1</td>
<td>0.041</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.1 ± 0.2</td>
<td>5.2 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>32 ± 2.2</td>
<td>33 ± 3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>32.5 (23.0–48.0)</td>
<td>52.5 (36.3–78.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-peptide (pmol/l)</td>
<td>478 (384–612)</td>
<td>596 (469–804)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of diabetes, n (%)</td>
<td>48 (14.2)</td>
<td>88 (47.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*t-test if mean ± S.D. is presented, Mann–Whitney U test if median (interquartile range), and χ² if n (%) is presented.
South Asians were younger and had higher parity than Europeans (Table 1). South Asians had lower body height and weight at 14 weeks of gestation and lower prepregnancy BMI than Europeans. South Asians had higher HbA1c, C-peptide, and insulin levels than Europeans at 14 weeks of gestation (Table 1). Although the median week of inclusion was 14 for both South Asians and Europeans, the interquartile range showed that South Asians were included 1 week later (14 (12–16) vs 14 (13–17) weeks of gestation for Europeans and South Asians respectively, \( P < 0.001 \)).

At 14 weeks of gestation, we found no ethnic differences in triceps and suprailiac skinfolds, while the subscapular skinfolds were thicker and s-leptin higher in South Asians than Europeans, despite lower BMI (Table 2).

### Status at 28 weeks of gestation and 14 weeks after delivery

At 28 weeks of gestation, South Asians still had lower BMI, but larger triceps, subscapular, and sum of skinfolds (Table 2), also after adjustment for differences in weeks of gestation at inclusion, number of weeks between the two measurements, age, and parity. We found no difference between South Asians and Europeans in the increase of BMI or skinfolds (Table 2), neither after adjustments for differences in weeks of gestation at inclusion, number of weeks postpartum, age, and parity. S-leptin increased more in South Asians than Europeans from 14 to 28 weeks of gestation, also after adjustment for differences in weeks of gestation at inclusion, number of weeks between the two measurements, age, and parity.

At 14 weeks after delivery, South Asians had reached the same BMI as Europeans, but South Asians had higher levels of all skinfold measurements (Table 2 and Fig. 2), also after adjustment for weeks of gestation at inclusion, week after Table 2

| Maternal parameters during and after pregnancy. Sample of 309 Europeans and 158 South Asians participating at all the three visits; 14 and 28 weeks of gestation and 14 weeks after delivery. Values are expressed as mean ± s.d. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 14 weeks of gestation | 28 weeks of gestation | Week 14–28 P for change E vs SA | 14 weeks after delivery | Week 14–28 P for change E vs SA |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| BMI (kg/m²)     | 25.4 ± 4.9      | 24.3 ± 4.1      | 0.015           | 27.8 ± 4.8      | 26.8 ± 4.1      | 0.023           | 0.63            | 25.7 ± 5.1      | 25.6 ± 4.2      | 0.83            | < 0.001         |
| Skinfolds (mm)  |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Triceps         | 24.1 ± 6.9      | 24.2 ± 7.0      | 0.83            | 24.9 ± 6.6      | 26.3 ± 6.8      | 0.045           | 0.085           | 24.8 ± 6.7      | 27.5 ± 6.1      | < 0.001         | < 0.001         |
| Subscapular     | 19.2 ± 7.8      | 21.7 ± 7.1      | 0.002           | 20.8 ± 7.6      | 24.3 ± 7.1      | < 0.001         | 0.12            | 20.8 ± 7.9      | 25.7 ± 6.9      | < 0.001         | < 0.001         |
| Suprailiac      | 27.1 ± 7.6      | 27.1 ± 7.3      | 0.96            | 30.0 ± 6.8      | 30.8 ± 6.3      | 0.24            | 0.33            | 27.1 ± 7.8      | 30.0 ± 6.9      | < 0.001         | < 0.001         |
| Sum             | 70.4 ± 19.8     | 72.9 ± 18.5     | 0.20            | 75.4 ± 18.4     | 81.5 ± 17.5     | 0.001           | 0.053           | 72.6 ± 19.6     | 83.1 ± 16.5     | < 0.001         | < 0.001         |
| S-leptin (µg/l) d| 1.35 ± 0.17     | 1.65 ± 0.14     | 0.002           | 1.71 ± 0.18     | 2.20 ± 0.15     | < 0.001         | 0.004           | 0.90 ± 0.18     | 1.53 ± 0.16     | < 0.001         | < 0.001         |

E, Europeans; SA, South Asians.

*Transformation back from square rooted values.*
had consistently higher BMI, skinfolds, and s-leptin levels than healthy women (Fig. 2). In simple logistic regression analyses, BMI, sum of skinfolds, and s-leptin levels in early pregnancy were all positively associated with GDM (OR (95% CI); 1.09 (1.04–1.13) per kg/m² increase in BMI, 1.02 (1.01–1.03) per mm increase in sum of skinfolds, and 3.70 (2.29–5.98) per square root increase in s-leptin). In multiple logistic regression analyses (performed separately for each explanatory variable), BMI, sum of skinfolds, and s-leptin remained associated with GDM after adjustments for weeks of gestation at inclusion, age, parity, and ethnic origin (1.10 (1.06–1.15) per kg/m² increase in BMI, 1.02 (1.01–1.03) per mm increase in sum of skinfolds, and 3.31 (2.02–5.43) per square root increase in s-leptin). Parity had no effect on the associations between BMI, subcutaneous fat, or s-leptin and GDM (no significant interaction). Additional adjustment for family history of diabetes did not change the results.

Neither BMI, sum of skinfolds, nor s-leptin completely explained the higher GDM risk observed in South Asians than in Europeans. South Asians had 2.45 (1.63–3.67) higher odds of GDM than Europeans after adjustments for weeks of gestation, age, and parity. Additional adjustment for BMI increased the odds of GDM in South Asians to 2.80 (1.85–4.27) compared with Europeans, while the OR was reduced to 2.19 (1.43–3.34) after adjustment for sum of skinfolds and to 2.07 (1.37–3.14) after adjustment for s-leptin. Sum of skinfolds and s-leptin at 14 weeks of gestation, thereby explained some, but not all, of the ethnic difference in GDM risk.

## Discussion

In this population-based prospective cohort study, South Asians had larger subscapular skinfold, similar triceps and suprailiac skinfold, and higher s-leptin levels in early pregnancy than Europeans, we hypothesized that this increase in fat may influence metabolic factors in subsequent pregnancies. We therefore explored ethnic differences in body composition at 14 weeks of gestation in nulliparous vs parous women. Among nulliparous women, South Asians had lower BMI than Europeans, while there were no ethnic differences in triceps, subscapular, or suprailiac skinfolds; sum of skinfolds; or s-leptin (Table 3). Among parous women, however, South Asians and Europeans had similar BMI, but South Asians had larger triceps and subscapular skinfolds, larger sum of skinfolds, and higher s-leptin than Europeans (Table 3).
pregnancy compared with Europeans, despite having a lower BMI. At 14 weeks after delivery, South Asians had retained more weight and subcutaneous fat than Europeans, and s-leptin level was less reduced in South Asians compared with Europeans. Accordingly, parous South Asians had more subcutaneous fat and s-leptin than parous Europeans, while we did not find corresponding ethnic differences among nulliparous. BMI, subcutaneous fat, and s-leptin were all positively associated with GDM. Some of the ethnic difference in GDM risk was explained by skinfolds and s-leptin, but not by BMI. The higher retention of weight and subcutaneous fat in South Asians may increase their risk of overweight, obesity, and GDM in future pregnancies.

Our finding that South Asians had relatively high amounts of subcutaneous fat, despite having lower BMI than Europeans, is in line with other studies (24, 25). Further, the higher relative adiposity in South Asians might be present already at birth, as South Asian neonates have lower birth weight than European, but similar skinfold thickness and cord leptin levels (21, 26, 27). Supportive of these findings are also the higher leptin levels observed in adult South Asians in several studies (16, 17, 28).

The South Asians in our sample had similar suprailiac and tricep skinfolds and larger subscapular skinfolds than the Europeans in early pregnancy and the levels increased during and after pregnancy, suggesting that South Asians were capable of storing subcutaneous fat. Subcutaneous fat has been considered a healthy way of storing fat, as it may work as a ‘metabolic sink’ that buffers energy overflow (29). According to the ‘adipose tissue overflow hypothesis’ (30), South Asians have a lower capacity to store superficial subcutaneous fat, resulting in deposition of visceral fat when facing energy excess. The higher amount of metabolically active visceral fat has been proposed as one reason why South Asians have a higher diabetes risk than white Europeans (31), despite having the same BMI (32).

Since skinfold measurements are considered crude measures of subcutaneous fat (33), we cannot refute this hypothesis. Also, the suprailiac and subscapular skinfolds have been found to reflect visceral adiposity (34). However, our findings are in accordance with a study that found no differences in deep or superficial subcutaneous fat between Norwegian and Pakistani women with type 2 diabetes (35).

On the other hand, South Asians have been found to have larger adipocyte size (36), which, in turn, has been associated with insulin resistance and hyperleptinemia (37) and type 2 diabetes independently of insulin resistance (38). Therefore, the relative amount of subcutaneous fat may be the same, while the number of adipocytes may be lower and the adipocytes larger in South Asians vs Europeans. This could imply that South Asians may have adipocytes that are more metabolically active.

Parous South Asians had higher BMI, skinfolds, and s-leptin levels than parous Europeans, while we did not find the same in nulliparous. This supports our finding of higher weight and subcutaneous fat retention in South Asians than Europeans. We were not able to find any previous studies exploring the effect of parity in relation to weight and subcutaneous fat retention across ethnic origin. Parity has been associated with a decrease in lower body fat and an increase in central fat deposits (39). Possible explanations for the higher retention in South Asians may be cultural differences in physical activity and diet in general, particularly in the postpartum period (40). Weight gain during pregnancy was a strong predictor of weight retention after delivery in our cohort (40). Future studies should explore possible reasons for the higher postpartum weight retention in South Asians.

As expected, BMI, subcutaneous fat, and s-leptin levels in early pregnancy were all associated with the risk of GDM both before and after adjusting for covariates. Although s-leptin seemed to be the most important of these, it did not entirely explain the higher risk of GDM in South Asians.
Strengths of the present study include high participation rate, low risk of selection bias, and follow-up after delivery. Limitations of our study include the small difference between the ethnic groups in median weeks of gestation at inclusion, and this was adjusted for in the analyses. Also, assessment of regional fat distribution was limited to the measurement of skinfold thickness, as assessment with X-ray-based methods is considered inappropriate due to radiation hazard in pregnancy, and magnetic resonance imaging was not possible in a community-based, epidemiological study like this. Some of the raters had relatively high inter-rater variability on a few measurements, but the overall inter-rater variability was considered adequate for use at a group level. The use of sum of skinfolds instead of each skinfold separately has been found to even out potential bias (41). Although we found no indication of bias related to the inter-rater variability, the presence of random errors may increase the risk of false negative findings.

In conclusion, South Asians had more subcutaneous fat and higher s-leptin levels, despite having lower BMI, than Europeans in early pregnancy, and both subcutaneous fat and higher s-leptin in early pregnancy were associated with the risk of GDM. Despite similar gain of subcutaneous fat between 14 and 28 weeks of gestation, South Asians retained more subcutaneous fat after delivery, leaving them more adipose when entering future pregnancies. Health professionals should put more emphasis on prevention of excessive weight gain during pregnancy and maternal weight retention after delivery.

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.

Funding
The STORK Groruddalen study was funded by the Norwegian Research Council, the Norwegian Directorate of Health, and the South Eastern Norway Regional Health Authority.

Author contribution statement
C Sommer designed the substudy, performed all statistical analyses, and drafted and edited the manuscript. A K Jenum initiated and was the project leader of the STORK Groruddalen study. K Mørkrid prepared the glucose data for the analysis. L Sletner and K Mørkrid participated in the quality control of the data. K I Birkeland designed the substudy, contributed to the conception and design of the study, and is the leader of the study’s steering committee. C Petroni, A K Jenum, K Mørkrid, L Sletner, C W Waage, and K I Birkeland contributed to the interpretation of the data, discussions, critical revision of the manuscript, and have approved the final version of the manuscript.

Acknowledgements
The authors thank midwives and research staff at Grorud, Bjerke, and Stovner child health clinics and the women who participated in the STORK Groruddalen study.

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