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RESEARCH ARTICLE

Basic science

Serum bile acid measurements in women of European and South Asian ethnicity with or without gestational diabetes mellitus: A cohort study

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Abstract

Objective: Investigation of serum bile acid profiles in pregnancies complicated by gestational diabetes mellitus (GDM) in a multi-ethnic cohort of women who are lean or obese.

Design: Prospective cohort study.

Setting: UK multicentre study.

Population: Fasting serum from participants of European or South Asian self-reported ethnicity from the PRiDE study, between 23 and 31 weeks of gestation.

Methods: Bile acids were measured using ultra-performance liquid chromatography-tandem mass spectrometry. Log-transformed data were analysed using linear regression in STATA/IC 15.0.

Main outcome measures: Total bile acids (TBAs), C4, fasting glucose and insulin.

Results: The TBAs were 1.327-fold (1.105–1.594) increased with GDM in European women ($P = 0.003$). Women with GDM had 1.162-fold (1.002–1.347) increased levels of the BA synthesis marker C4 ($P = 0.047$). In South Asian women, obesity (but not GDM) increased TBAs 1.522-fold (1.193–1.942, $P = 0.001$). Obesity was associated with 1.420-fold (1.185–1.702) increased primary/secondary BA ratio ($P < 0.001$) related to 1.355-fold (1.140–1.611) increased primary BA concentrations ($P = 0.001$). TBAs were positively correlated with fasting glucose ($P = 0.039$) in all women, and with insulin ($P = 0.001$) and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) ($P = 0.001$) in women with GDM.

Conclusions: Serum BA homeostasis in late gestation depends on body mass index and GDM in ethnicity-specific ways. This suggests ethnicity-specific aetiologies may contribute to metabolic risk in European and South Asian women, with the relationship between BAs and insulin resistance of greater importance in European women. Further studies into ethnicity-specific precision medicine for GDM are required.

KEYWORDS
bile acids, ethnic differences, gestational diabetes mellitus, obesity

*Hanns-Ulrich Marschall, who contributed to this research, died in August 2023, before publication.

1 | INTRODUCTION

In pregnancy, circulating concentrations of glucose, lipids and insulin increase to accommodate the demands of the fetus. In some pregnant women, these changes are exacerbated, increasing their susceptibility to diseases such as gestational diabetes mellitus (GDM).[1] Bile acids (BAs), which are synthesised from cholesterol in the liver and enter the intestine via the bile, emulsify dietary lipids for absorption. BAs also have glucoregulatory roles through the activation of farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5).[1] In uncomplicated pregnancy, serum BA concentrations are elevated and changes in the BA pool occur, especially with advancing gestation.[2,3] These changes become pathological if BAs are elevated beyond the normal range for pregnancy, resulting in a diagnosis of intrahepatic cholestasis of pregnancy (ICP).[1,4] Women with ICP are at higher risk of developing GDM.[5] Moreover, female mice deficient in *Fxr* or *Tgr5* have abnormal glucose tolerance tests specifically in pregnancy (but not prior to pregnancy),[6] implying a relationship between altered BA signalling and gestational glucose intolerance.

Some authors report associations between elevated serum BAs in early pregnancy and the risk of developing GDM.[7,8] However, studies performed during the second half of gestation found both increases and reductions in individual BA species in women with GDM.[9,10,11,12] These inconsistent results may relate to different BA quantification techniques, different gestational ages and a failure to stratify participants according to body mass index (BMI) or ethnicity.

Bile acid (BA) concentrations may be affected by BMI, with higher circulating concentrations, increased BA synthesis and compositional alterations reported in individuals who are obese.[13–15] Ethnicity has been used to identify and screen individuals susceptible to GDM, and differences in metabolites including lipids, HbA1c and amino acids have been observed in people with type 2 diabetes mellitus (T2DM) of different ethnic origins.[16,17] Moreover, there were ethnicity differences in total serum BA concentrations in women with uncomplicated pregnancy.[18] Thus, it is plausible that BA profiles are affected by BMI and ethnicity in pregnancies complicated by GDM. Very few studies examine ethnicity differences in metabolites in GDM pregnancies,[19] and to date none have investigated BAs. Identifying how BAs differ between women with GDM of different ethnicities and different BMIs may help further the understanding of the ethnicity/weight disparities in GDM risk and pathophysiology. Therefore, this study aimed to establish BA profiles in pregnancies complicated by GDM using a multi-ethnic cohort of pregnant women who are lean or obese and at risk of developing GDM.

2 | METHODS

2.1 | Human serum samples

Serum samples were obtained from the Micronutrients in Pregnancy as a Risk Factor for Diabetes and Effects on Mother and Baby (PRiDE; trial registration NCT03008824; ethics reference 12/WM/0010) multicentre cohort study conducted in the UK. Full methods and exclusion criteria were previously published,[20] but women met the inclusion criteria if they had one or more of the following risk factors: previous GDM pregnancy; family history of diabetes mellitus; previous stillbirth; previous macrosomic infant; South Asian ethnicity; aged >35 years; BMI of >30 mg/kg^2; or diagnosis of polycystic ovary syndrome. Fasting serum was collected between 2013 and 2018 at the oral glucose tolerance test diagnostic examination for GDM. For this study, only women at 23–31 weeks of gestation of European and South Asian self-reported ethnicity were included. GDM was diagnosed using the International Association of the Diabetes and Pregnancy Study Groups criteria (fasting plasma glucose of ≥5.1 mmol/L and/or 2-h plasma glucose of ≥8.5 mmol/L).[21] Five women were diagnosed based on their capillary blood glucose levels (with three or more readings above the threshold: fasting glucose of ≥5.6 mmol/L and 1-hour post-meal glucose of ≥7.8 mmol/L). Samples were stratified by BMI, with participants classified as lean (European, <25 kg/m^2; South Asian, <23 kg/m^2) or obese (European, ≥30 kg/m^2; South Asian, ≥27 kg/m^2) (Figure S1). Participant characteristics can be found in Table 1. Serum glucose data were obtained from the oral glucose tolerance test.[20] One participant was excluded because of a previous cholecystectomy, which is known to affect serum bile acid concentrations.

2.2 | Ultra-high performance liquid chromatography tandem mass spectrometry

Bile acids (BAs) were analysed in serum samples by ultra-high performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS), as previously described,[22] by investigators blinded to experimental groups. The detected BA species included in this study were the free, glycine- and taurine-conjugated forms of cholic acid (CA), chenodeoxycholic acid (CDCA), deoxycholic acid (DCA), ursodeoxycholic acid (UDCA) and litocholic acid (LCA). The concentration of total bile acids (TBAs) refers to the sum of these species. Samples were sent for UPLC-MS/MS in two batches. In the second batch of samples, insulin ($n = 206$) and fibroblast growth factor 19 (FGF19, $n = 194$) were measured using the same methodology.

2.3 | Statistical analysis

Data were analysed using STATA/IC 15.0 (StataCorp LLC, College Station, TX, USA) and expressed as median [interquartile range] for concentrations or fold change [95% confidence interval] for effect sizes. Biochemical parameters were transformed using the natural log or $\log_2$ and analysed using multiple linear regression corrected for maternal age, gestational age, parity and batch effects during UPLC-MS/MS. Further details about data exploration and statistical analysis are provided in Appendix S1. $P < 0.05$ was considered significant; the P-values presented in Table 2 and Tables S2 and S3 were corrected for multiple testing using the false discovery rate (FDR) method. Figures were created using Prism 9.5.1 (GraphPad, La Jolla, CA, USA).

TABLE 1 Participant characteristics of the subset of the PRiDE cohort used for this study.

PRiDE cohort	European lean control	European lean GDM	European obese control	European obese GDM	South Asian lean control	South Asian lean GDM	South Asian obese control	South Asian obese GDM
	n = 63	*n* = 27	*n* = 74	*n* = 73	*n* = 61	*n* = 10	*n* = 75	*n* = 39
Maternal age (years)	29.1 [24.5–35.2]	33.6 [30.8–35.8]	28.9 [26.6–32.5]	30.9 [28.5–24.8]	29.8 [26.4–32.7]	30.8 [28.7–32.9]	31.7 [28.7–35.5]	33.2 [28.9–37.6]
Gestational age (weeks)	27.4 [26.9–28.0]	27.3 [26.3–28.6]	27.5 [26.7–28.3]	26.9 [26.3–27.7]	26.7 [26.1–27.9]	26.8 [26.3–27.9]	26.7 [26.1–27.4]	27.0 [28.9–37.6]
BMI	19.7 [18.7–22.2]	23.5 [21.5–24.3]	46.4 [36.3–50.3]	41.8 [40.6–44.0]	20.7 [20.2–21.0]	21.8 [20.2–22.3]	31.9 [30.1–34.3]	31.4 [29.2–34.2]
Singleton, numbers (%)	62/62 (100%)	26/26 (100%)	71/72 (99%)	71/71 (100%)	56/57 (98%)	9/10 (90%)	70/73 (96%)	38/39 (97%)
Primiparous, numbers (%)	31/63 (49%)	13/27 (48%)	34/74 (46%)	38/73 (52%)	43/61 (70%)	5/10 (50%)	46/75 (61%)	17/39 (44%)
Multiparous with previous GDM, numbers (%)	2/32 (6%)	4/14 (29%)	0/40 (0%)	1/35 (3%)	0/18 (0%)	0/5 (0%)	3/29 (10%)	2/22 (9%)
Glucose (mmol/L)								
0 h	4.3 [4.0–4.5] *n* = 63	4.9 [4.4–5.3] *n* = 27	4.5 [4.3–4.8] *n* = 74	5.3 [5.1–5.7] *n* = 73	4.2 [4.0–4.4] *n* = 61	5.1 [5.1–5.2] *n* = 10	4.5 [4.3–4.7] *n* = 75	5.3 [4.9–5.5] *n* = 39
2 h	5.2 [4.3–6.2] *n* = 63	8.0 [6.5–9.2] *n* = 24	5.7 [5.1–6.7] *n* = 74	6.8 [5.8–8.7] *n* = 71	5.1 [4.5–5.7] *n* = 61	6.1 [5.5–8.7] *n* = 10	5.9 [5.2–6.8] *n* = 75	8.1 [6.1–9.4] *n* = 39
Insulin (mIU/mL)	6.3 [5.4–7.6] *n* = 28	6.1 [4.7–15.4] *n* = 8	18.4 [12.2–22.4] *n* = 35	20.2 [13.8–28.9] *n* = 47	6.6 [5.1–9.2] *n* = 34	–*n* = 2	10.0 [8.0–12.5] *n* = 32	10.8 [8.1–16.3] *n* = 18
HOMA-IR	1.18 [1.02–1.49] *n* = 28	1.35 [0.91–3.88] *n* = 8	3.60 [2.40–4.54] *n* = 35	4.78 [3.30–6.92] *n* = 47	1.24 [0.91–1.85] *n* = 34	–*n* = 2	1.98 [1.63–2.42] *n* = 32	2.49 [1.69–4.06] *n* = 18

Note: Characteristics in participants of European ethnicity with body mass indexes (BMIs) of <25 kg/m^2 (lean) or ≥30 kg/m^2 (obese) and South Asian ethnicity with BMIs of <23 kg/m^2 (lean) or ≥27 kg/m^2 (obese), with or without gestational diabetes mellitus (GDM).

Abbreviation: HOMA-IR, Homeostatic Model Assessment for Insulin Resistance.

TABLE 2 Serum bile acid composition in pregnant women of European and South Asian ethnicity.

European	**European-lean-con**	**European-lean-GDM**	**European-Ob-con**	**European-Ob-GDM**	**GDM effect**	**Obesity effect**
	***n*=63**	***n*=27**	***n*=74**	***n*=73**		
CA/CDCA	0.67 [0.45–1.14]	0.86 [0.57–1.13]	0.84 [0.50–1.10]	0.77 [0.60–1.11]	1.09 [0.93–1.28], $p=0.350$	1.02 [0.88–1.19], $p=0.864$
[Total CDCA]	0.44 [0.25–0.82]	0.42 [0.20–0.90]	0.46 [0.28–0.74]	0.72 [0.43–1.24]	1.27 [1.02–1.80], $p=0.068$	1.24 [1.00–1.54], $p=0.234$
[Total CA]	**0.30 [0.17–0.74]**	**0.35 [0.20–0.89]**	**0.38 [0.21–0.82]**	**0.60 [0.31–1.19]**	**1.39 [1.07–1.79], $p=0.047$**	1.27 [0.99–1.63], $p=0.234$
[Total DCA][a]	0.45 [0.26–0.75]	0.63 [0.45–0.97]	0.37 [0.22–0.64]	0.54 [0.31–1.08]	1.49 [1.07–2.07], $p=0.054$[a]	0.89 [0.64–1.23], $p=0.705$[a]
[Total UDCA]	0.04 [0.02–0.09]	0.05 [0.01–0.09]	0.04 [0.02–0.07]	0.06 [0.03–0.11]	1.20 [0.91–1.58], $p=0.285$	1.12 [0.85–1.47], $p=0.705$
[Total LCA][a]	0.15 [0.01–0.03]	0.01 [0.01–0.02]	0.01 [0.01–0.02]	0.01 [0.01–0.02]	1.25 [0.90–1.74], $p=0.267$[a]	0.90 [0.65–1.24], $p=0.696$[a]
12α-OH ratio[a]	1.76 [1.20–2.66]	2.20 [1.77–2.79]	1.49 [1.09–2.13]	1.50 [1.17–2.01]	1.15 [0.98–1.35], $p=0.158$[a]	0.82 [0.70–0.97], $p=0.153$[a]
[12α-OH]	**0.83 [0.58–1.57]**	**1.17 [0.69–1.61]**	**0.80 [0.52–1.17]**	**1.23 [0.81–2.30]**	**1.44 [1.18–1.76], $p<0.001$**	0.99 [0.81–1.20], $p=0.931$
[non-12α-OH]	0.51 [0.30–0.87]	0.47 [0.29–1.04]	0.54 [0.29–0.81]	0.84 [0.50–1.35]	1.26 [1.02–1.55], $p=0.068$	1.19 [0.97–1.47], $p=0.273$
Prim/Sec	1.31 [0.75–3.41]	1.19 [0.64–2.38]	2.02 [1.32–3.76]	1.70 [1.14–4.03]	0.94 [0.73–1.22] $p=0.647$	1.42 [1.10–1.83], $p=0.126$
[Primary]	0.88 [0.48–1.36]	0.73 [0.52–1.79]	0.87 [0.53–1.55]	1.40 [0.75–2.43]	1.30 [1.04–1.63], $p=0.057$	1.24 [1.00–1.55], $p=0.234$
[Secondary]	**0.55 [0.30–0.82]**	**0.73 [0.50–1.06]**	**0.43 [0.28–0.72]**	**0.63 [0.39–1.12]**	**1.38 [1.10–1.73], $p=0.023$**	0.88 [0.70–1.09], $p=0.604$
Conj. Ratio	2.30 [1.16–4.63]	2.54 [1.39–4.96]	2.57 [1.45–4.52]	2.56 [1.20–3.71]	1.10 [0.85–1.43], $p=0.494$	0.96 [0.74–1.24], $p=0.864$
[Unconj.]	0.38 [0.23–0.72]	0.49 [0.21–0.85]	0.37 [0.20–0.72]	0.55 [0.39–1.38]	1.24 [0.97–1.60], $p=0.144$	1.11 [0.86–1.42], $p=0.696$
[G-conj.]	**0.67 [0.40–1.04]**	**0.69 [0.55–1.30]**	**0.64 [0.41–0.94]**	**1.02 [0.63–1.54]**	**1.40 [1.13–1.73], $p=0.018$**	1.09 [0.88–1.34], $p=0.710$
[T-conj.]	**0.27 [0.12–0.57]**	**0.30 [0.14–0.47]**	**0.20 [0.13–0.34]**	**0.29 [0.20–0.54]**	**1.43 [1.13–1.80], $p=0.018$**	1.00 [0.80–1.25], $p=0.992$
G-conj. Ratio	0.43 [0.34–0.55]	0.47 [0.42–0.58]	0.49 [0.39–0.56]	0.49 [0.37–0.57]	1.05 [0.96–1.16], $p=0.364$	1.04 [0.95–1.15], $p=0.705$
T-conj. Ratio	0.17 [0.11–0.30]	0.17 [0.14–0.24]	0.15 [0.10–0.22]	0.15 [0.09–0.22]	1.08 [0.90–1.16], $p=0.468$	0.96 [0.81–1.14], $p=0.797$
South Asian	**South Asian-Lean-Con**	**South Asian-Lean-GDM**	**South Asian-Ob-Con**	**South Asian-Ob-GDM**	**GDM effect**	**Obesity effect**
	***n*=61**	***n*=10**	***n*=75**	***n*=39**		
CA/CDCA[a]	0.81 [0.57–1.13]	1.03 [0.61–1.48]	0.87 [0.61–1.29]	1.03 [0.72–1.41]	1.19 [0.98–1.45], $p=0.270$[a]	1.20 [1.00–1.44], $p=0.099$[a]
[Total CDCA]	**0.51 [0.28–0.82]**	**0.42 [0.25–1.08]**	**0.68 [0.39–1.35]**	**0.69 [0.39–1.14]**	0.97 [0.72–1.30], $p=0.890$	**1.55 [1.18–2.05], $p=0.007$**
[Total CA]	**0.34 [0.20–0.67]**	**0.40 [0.31–1.02]**	**0.68 [0.27–1.36]**	**0.69 [0.28–1.55]**	1.15 [0.82–1.61], $p=0.677$	**1.86 [1.35–2.55], $p<0.001$**
[Total DCA]	0.50 [0.31–0.80]	0.50 [0.22–1.40]	0.61 [0.32–1.32]	0.50 [0.32–0.79]	0.79 [0.55–1.13], $p=0.347$	1.19 [0.85–1.67], $p=0.397$
[Total UDCA]	0.04 [0.03–0.11]	0.03 [0.02–0.07]	0.05 [0.03–0.13]	0.04 [0.03–0.09]	0.68 [0.48–0.96], $p=0.174$	1.32 [0.96–1.82], $p=0.144$
[Total LCA]	**0.01 [0.01–0.02]**	**0.01 [0.00–0.02]**	**0.02 [0.01–0.03]**	**0.01 [0.00–0.01]**	**0.39 [0.24–0.64], $p<0.001$**	1.00 [0.64–1.57], $p=0.998$
12α-OH ratio[a]	1.67 [1.25–2.36]	2.16 [1.68–2.52]	1.86 [1.18–2.58]	1.75 [1.33–2.30]	1.05 [0.86–1.29], $p=0.853$[a]	1.01 [0.84–1.23], $p=0.943$[a]
[12α-OH]	**0.93 [0.54–1.58]**	**0.81 [0.58–1.90]**	**1.51 [0.64–2.99]**	**1.33 [0.69–2.06]**	0.98 [0.74–1.30], $p=0.890$	**1.54 [1.19–2.00], $p=0.006$**
[non-12α-OH]	**0.62 [0.34–0.95]**	**0.49 [0.26–1.13]**	**0.81 [0.40–1.64]**	**0.73 [0.43–1.28]**	0.93 [0.70–1.24], $p=0.795$	**1.52 [1.17–1.98], $p=0.007$**
Prim/Sec	**1.48 [0.97–2.46]**	**2.02 [1.00–2.28]**	**1.83 [1.00–4.04]**	**2.54 [1.20–4.30]**	1.28 [0.96–1.71], $p=0.270$	**1.44 [1.10–1.89], $p=0.023$**
[Primary]	**0.95 [0.54–1.49]**	**0.77 [0.57–2.10]**	**1.34 [0.69–2.90]**	**1.31 [0.75–2.56]**	1.04 [0.77–1.41], $p=0.795$	**1.69 [1.27–2.25], $p<0.001$**

(Continues)

TABLE 2 (Continued)

South Asian	South Asian-Lean-Con	South Asian-Lean-GDM	South Asian-Ob-Con	South Asian-Ob-GDM	GDM effect	Obesity effect
	n **= 61**	***n*** **= 10**	***n*** **= 75**	***n*** **= 39**		
[Secondary]	0.60 [0.37–0.83]	0.55 [0.25–1.46]	0.78 [0.38–1.45]	0.60 [0.37–0.86]	0.81 [0.61–1.08], $p = 0.270$	1.17 [0.90–1.53], $p = 0.339$
Conj. Ratio[a]	2.29 [1.24–4.14]	2.30 [2.32–3.88]	2.12 [1.20–4.25]	2.44 [1.60–4.42]	1.31 [0.96–1.79], $p = 0.270$[a]	0.96 [0.72–1.28], $p = 0.871$[a]
[Unconj.]	**0.41 [0.25–0.62]**	**0.34 [0.19–0.60]**	**0.58 [0.28–1.56]**	**0.46 [0.24–0.87]**	0.78 [0.57–1.08], $p = 0.329$	**1.50 [1.11–2.03], p = 0.023**
[G-conj.]	**0.83 [0.51–1.30]**	**0.82 [0.79–2.02]**	**1.09 [0.46–2.17]**	**1.04 [0.58–1.75]**	0.98 [0.73–1.31], $p = 0.890$	**1.43 [1.08–1.88], p = 0.027**
[T-conj.]	**0.23 [0.12–0.43]**	**0.29 [0.23–0.42]**	**0.30 [0.16–0.64]**	**0.33 [0.16–0.67]**	1.24 [0.91–1.69], $p = 0.362$	**1.42 [1.06–1.90], p = 0.038**
G-conj. Ratio[a]	0.51 [0.40–0.57]	0.52 [0.42–0.56]	0.49 [0.38–0.61]	0.48 [0.43–0.55]	1.04 [0.93–1.16], $p = 0.696$[a]	0.94 [0.85–1.04], $p = 0.335$[a]
T-conj. Ratio	0.16 [0.11–0.21]	0.17 [0.13–0.21]	0.13 [0.09–0.21]	0.19 [0.11–0.27]	1.32 [1.08–1.13], $p = 0.072$	0.93 [0.77–1.13], $p = 0.569$

Note: Women of self-reported European ethnicity (top) with body mass indexes (BMIs) of <25 kg/m^2 (lean) or ≥30 kg/m^2 (obese), or South Asian ethnicity (bottom) with BMIs of <23 kg/m^2 (lean) or ≥27 kg/m^2 (obese), without (control) or with gestational diabetes mellitus (GDM). Bile acids are shown in order of their concentration in the serum (from highest to lowest). Main effect estimates for GDM and obesity reflect fold changes (ratio of the geometric mean) calculated by multiple linear regression, adjusted for gestational age (non-interaction model), maternal age, parity and batch effects during UPLC-MS/MS. 'G-' refers to glycine-conjugated bile acids; 'T-' refers to taurine-conjugated bile acids. *P*-values reflect false discovery rate-adjusted *P*-values for the main effects of GDM and obesity, respectively. Significant results ($P_{adj} < 0.05$) are highlighted in bold.

Abbreviations: 12α-OH, 12α-hydroxylated; CA, cholic acid; CDCA, chenodeoxycholic acid; Conj., conjugated or conjugation; DCA, deoxycholic acid; LCA, lithocholic acid; Prim/Sec, the ratio between primary and secondary bile acids; UDCA, ursodeoxycholic acid.

[a]Signifies that the overall model for this parameter is not statistically significant: $P < 0.05$.

3 | RESULTS

3.1 | Participant characteristics

We studied women of European and South Asian self-reported ethnicity who either had an obese (European, ≥30 kg/m^2; South Asian, ≥27 kg/m^2) or lean (European, <25 kg/m^2; South Asian, <23 kg/m^2) BMI, with or without a GDM diagnosis. Women with GDM had increased serum glycaemia, insulin concentrations and insulin resistance, compared with controls (Table 1). Insulin (resistance) was increased in women with an obese BMI compared with a lean BMI, and in European women who were obese compared with South Asian women who were obese (Table 1).

In this cohort of pregnant women, 67.5% [53.3%–79.2%] of serum BAs were conjugated, the majority of which were conjugated with glycine, 47.9% [38.6%–56.3%], rather than taurine, 15.7% [10.1%–22.4%] (Table 2). Primary BAs were more predominant, 60.2% [47.3%–75.6%], than secondary BAs. CDCA was the most common BA type, followed by DCA and CA (Table 2). The 12α-hydroxylated (12α-OH) BAs (CA, DCA and their conjugates) were slightly more prevalent, 61.4% [53.2%–67.3%], than the non-12α-OH BAs. The median CA/CDCA ratio was 0.83 [0.57–1.17].

3.2 | GDM is associated with a global increase in serum BAs in European women

When serum TBA concentration data were explored in the whole cohort (including women of both ethnicities) both visually and statistically, it became apparent that obesity and GDM affected TBAs in women of European and South Asian ethnicity differently (Figure 1A; for statistical exploration, see Table S1). Therefore, follow-up analysis of BA data was performed in these two groups separately (Tables 2 and S1–S3).

In European women, GDM was associated with a 1.33-fold increase in TBA concentrations independent of obesity (effect of GDM 1.327 [1.105–1.594], $P = 0.003$; Figure 1A; Table S1). No effect of obesity was detected (1.043 [0.87–1.25], $P = 0.646$). Specifically, concentrations of G-CDCA, G-CA, G-DCA, T-CDCA and T-CA were increased by 34%–57% with GDM, and a similar pattern was observed in many other species (Table S2). Similarly, concentrations of primary, secondary, unconjugated, total conjugated, glycine-conjugated, taurine-conjugated, 12α-OH and non-12α-OH BAs were all found to be increased in European women with GDM compared with control women (around 40% increase on average), without notable differences in their relative contributions to the serum BA pool (Figure 1B; Table 2). In contrast to European women, there was no association between GDM and TBA concentrations in South Asian women (Figure 1A, Table S1, 0.938 [0.72–1.22], $P = 0.627$), although in South Asian women GDM was associated with decreased concentrations of the secondary trace BA LCA concentrations (0.28 [0.17–0.45]; Table S3), total LCA concentrations

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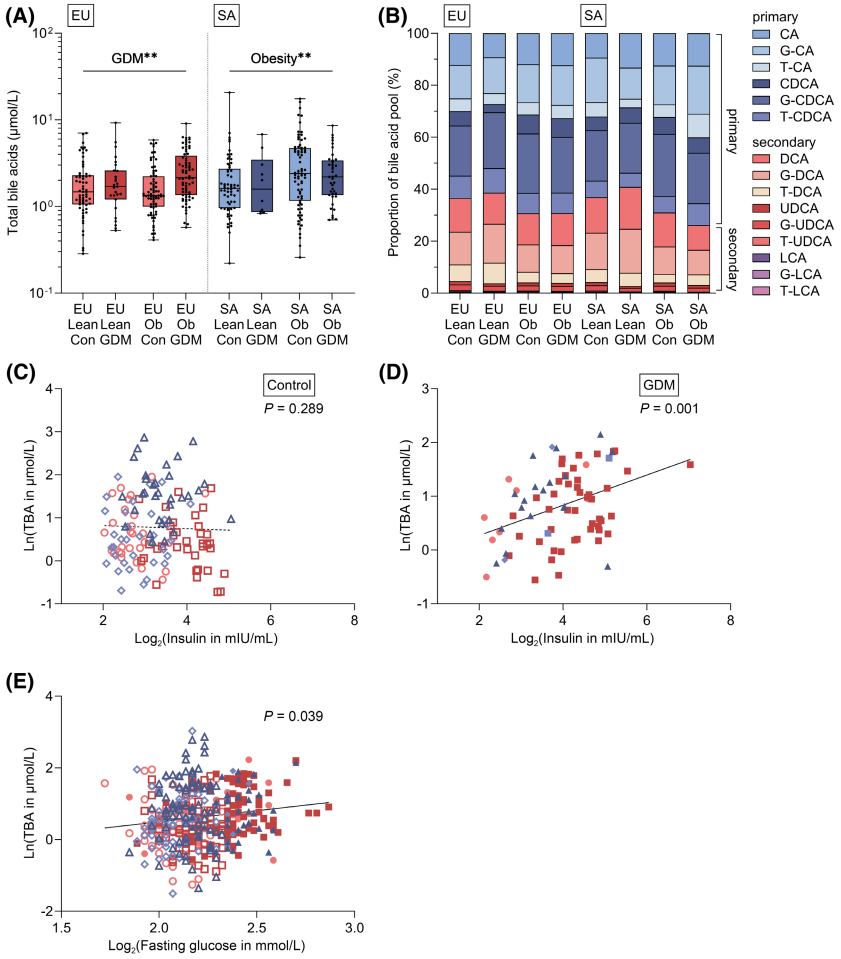

FIGURE 1 Total bile acid concentrations and serum bile acid pool composition. (A) Serum total bile acid (TBA) levels in all eight groups. Data were analysed separately for European and South Asian women. Numbers in the groups: $n = 63$ European-Lean-Con; $n = 27$ European-Lean-GDM; $n = 74$ European-Ob-Con; $n = 73$ European-Ob-GDM; $n = 61$ South Asian-Lean-Con; $n = 10$ South Asian-Lean-GDM; $n = 75$ South Asian-Ob-Con; and $n = 39$ South Asian-Ob-GDM. Whiskers represent minimum and maximum values. (B) Contribution of each individual BA species to the total serum BA pool, expressed as a percentage of the total pool. (C, D) Relationships between fasting serum TBA and insulin in women without (C, $n = 129$) and with (D, $n = 75$) gestational diabetes mellitus (GDM). (E) Relationship between fasting serum TBA and glucose ($n = 422$). Open symbols, control; closed symbols, GDM; pink, European; blue, South Asian; lighter symbols, lean; darker symbols, obese; open light-pink circles, European-Lean-Con; closed light-pink circles, European-Lean-GDM; open dark-pink squares, European-Ob-Con; closed dark-pink squares, European-Ob-GDM; open light-blue diamonds, South Asian-Lean-Con; closed light-blue diamonds, South Asian-Lean-GDM; open dark blue triangles = South Asian-Ob-Con; closed dark blue triangles = South Asian-Ob-GDM. 'G-' refers to glycine-conjugated bile acids; 'T-' refers to taurine-conjugated bile acids. BA, bile acid; CA, cholic acid; CDCA, chenodeoxycholic acid; Con, controls, without gestational diabetes; DCA, deoxycholic acid; GDM, gestational diabetes mellitus; LCA, lithocholic acid; Lean, women with BMIs of <25 kg/m^2 (European) or <23 kg/m^2 (South Asian); Ob, women with obesity, i.e. BMIs of ≥30 kg/m^2 (European) or ≥27 kg/m^2 (South Asian); TBA, total bile acids; UDCA, ursodeoxycholic acid. $^{**}P < 0.01$. *P*-values reflect outcomes of multiple linear regression adjusted for GDM, obesity, ethnicity and confounding factors.

(0.39 [0.24–0.64]; Table 2) and trend for increased prevalence of tauro-conjugated BAs (1.32 [1.08–1.13]; Table 2).

3.3 | Obesity is associated with increased total serum BA concentrations in South Asian women and increased primary BAs in both ethnic groups

The TBAs were increased 1.52-fold in South Asian women who were obese, compared with South Asian women who were lean (effect of obesity 1.522 [1.193–1.942], $P = 0.001$; Figure 1A). Obesity in South Asian women was not associated with changes in conjugation rates or the relative abundance of 12α-OH BAs: despite increases in the absolute concentrations of these BA subtypes their relative contributions to the TBA pool did not seem to be affected by obesity (Table 2).

The ratio of primary to secondary BAs was increased with obesity in both European and South Asian women (main effect of obesity 1.420 [1.185–1.702], $P < 0.001$ [with no interaction with ethnicity $P = 0.960$]; for ethnicity-separated data see Table 2). This was related to increased concentrations of primary BAs (main effect of obesity 1.355 [1.140–1.611], $P = 0.001$), whereas secondary BA concentrations were not affected (0.955 [0.806–1.131], $P = 0.591$).

3.4 | BA levels correlate with serum insulin in women with GDM, but not in control women

Serum insulin correlated with serum TBA in women with GDM, but not in control women (interaction between GDM and insulin $P = 0.001$; Figure 1C,D): a doubling in serum insulin was associated with a 1.348-fold [1.129–1.610] ($P = 0.001$) increase in serum TBA in women with GDM (Figure 1D). A similar relationship was observed between TBA and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) (interaction between GDM and HOMA-IR, $P = 0.002$; GDM 1.322 [1.124–1.554], $P = 0.001$). There was a positive relationship between fasting glucose and TBA in the whole cohort (1.777-fold [1.030–3.066] increased TBA for each doubling of glucose, $P = 0.039$; Figure 1E), but interactions with GDM could not be determined as the GDM diagnosis was (partly) based on fasting glucose.

3.5 | The BA biosynthesis intermediate C4 is increased in women with GDM

Gestational diabetes mellitus (GDM) was associated with increased concentrations of 7α-hydroxy-4-cholesten-3-one (C4; effect of GDM 1.162 [1.002–1.347], $P = 0.047$) independent of ethnicity or obesity (Figure 2A). Concentrations of C4 correlated inversely with FGF19 concentrations (0.775-fold [0.706–0.850] change in C4 with each doubling of FGF19, $P < 0.001$; Figure 2B); this relationship was not affected by GDM or ethnicity. There was no difference in FGF19 between groups (not shown). Notably, fasting C4 concentrations correlated with fasting TBA in South Asian women but not in European women (Figure 2C,D).

4 | DISCUSSION

4.1 | Main findings

This study reports ethnicity-specific differences in serum BA concentrations in women with GDM/obesity during the second half of pregnancy. GDM was associated with increased serum BA concentrations in European women, whereas the BA pool composition was largely unaffected. This was not seen in South Asian women with GDM, who instead showed decreased concentrations of the secondary BA LCA. In South Asian women, obesity was associated with elevated TBAs compared with lean women. BMI also affected the serum BA pool composition, with increased primary BAs in both European and South Asian women. Lastly, there were GDM- and ethnicity-specific correlations between TBA and metabolic parameters/C4, respectively.

Data regarding BA concentrations in pregnancies complicated by GDM are sparse. Most studies involve lean Chinese

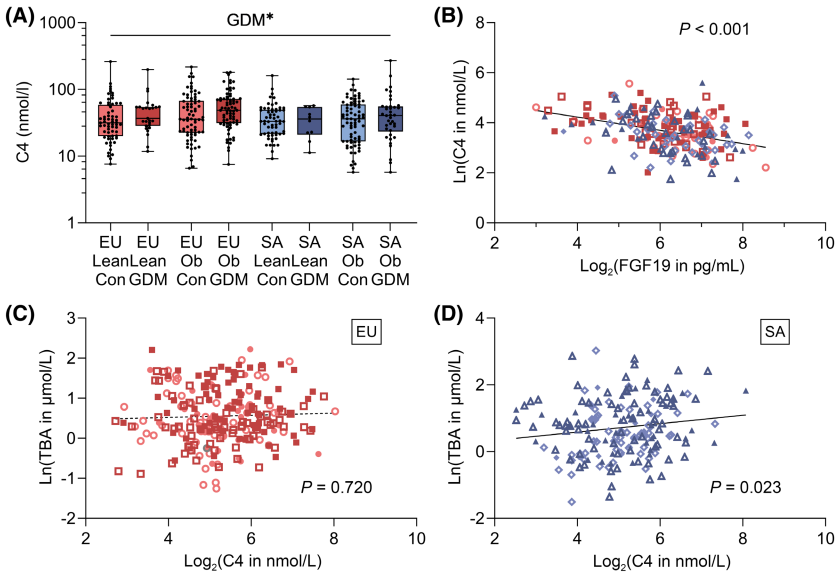

FIGURE 2 7α-Hydroxy-4-cholesten-3-one (C4) concentrations and relationships with other serum parameters. (A) Fasting serum C4 concentrations in all eight groups. Numbers in the groups: $n = 63$ European-Lean-Con; $n = 27$ European-Lean-GDM; $n = 74$ European-Ob-Con; $n = 73$ European-Ob-GDM; $n = 61$ South Asian-Lean-Con; $n = 10$ South Asian-Lean-GDM; $n = 75$ South Asian-Ob-Con; $n = 38$ South Asian-Ob-GDM. Whiskers represent minimum and maximum values. (B) Relationship between C4 and circulating FGF19 ($n = 192$). (C, D) Relationship between C4 and TBA in European women (C, $n = 237$), and in South Asian women (D, $n = 184$). Open symbols, control; closed symbols, GDM; pink symbols, European; blue symbols, South Asian; lighter symbols, lean; darker symbols, obese; open light-pink circles, European-Lean-Con; closed light-pink circles, European-Lean-GDM; open dark-pink squares, European-Ob-Con; closed dark-pink squares, European-Ob-GDM; open light-blue diamonds, South Asian-Lean-Con; closed light-blue diamonds, South Asian-Lean-GDM; open dark-blue triangles, South Asian-Ob-Con; closed dark-blue triangles, South Asian-Ob-GDM. Controls, women without gestational diabetes; European, women of European ethnicity; GDM, gestational diabetes mellitus; Lean, women with BMIs of <25 kg/m^2 (European) or <23 kg/m^2 (South Asian); Ob, women with obesity, i.e. BMIs of ≥30 kg/m^2 (European) or ≥27 kg/m^2 (South Asian); SA, women of South Asian ethnicity; TBA, total serum bile acids. *$P < 0.05$. P-values reflect outcomes of multiple linear regression adjusted for GDM, obesity, ethnicity and confounding factors.

women,[9,12,23] although one small European study ($n=20$ per group) described decreased concentrations of four trace BA species not assessed in the current study.[11] South Asian women with GDM have not yet been studied, nor did previous work include a comparison of different ethnicities. Our novel data indicate clear ethnicity-specific differences in BA levels in pregnancy, a finding relevant to the interpretation of pre-existing literature with implications for future study design.

4.2 | Interpretation

This study is the first to describe late-gestation changes in TBAs in European women with GDM (33% increase). Our findings in European women with GDM are similar to an Italian cohort of T2DM patients who were obese,[24] which also reported increased BA concentrations without compositional changes. These findings were not replicated in healthy volunteers with insulin resistance,[24] suggesting that elevated BA concentrations might be associated with pathogenic progression to T2DM or GDM in individuals who are obese. This is supported by the correlation between BA parameters and HOMA-IR in women with GDM in the current study and that reported by Gagnon et al.[3]

Basal BA production may be increased in European women with GDM, supported by the 16% increase in serum C4 with GDM. Normal pregnancy is mildly cholestatic,[2] and the perturbed regulation of BA homeostasis (likely through FXR) is reported in pregnant humans (e.g. increased C4 without changes in FGF19, as seen in the GDM group) and mice.[25] Therefore, the phenotype in European women with GDM could reflect an exaggerated response to normal gestational signals. Additionally, experimental manipulation of BA receptors FXR and TGR5 results in an improvement or a deterioration of glycaemic control.[1] Therefore, altered FXR sensitivity or signalling in GDM pregnancies could contribute to both enhanced BA synthesis and the development of insulin resistance.

Alternatively, aberrant glucose homeostasis could influence BA production. Both T2DM patients and insulin-resistant non-pregnant women show abnormal regulation of BA synthesis,[26,27] and in both our study and other published work glucose concentrations in pregnancy have been shown to correlate with BA.[28] Culturing human hepatocytes in high-glucose conditions decreased chromatin methylation and increased mRNA expression of the BA synthesis enzyme *CYP7A1*, and increased BA release in the medium.[28] Later confirmed in vivo in mice,[29] this suggests hyperglycaemia might increase BA production through epigenetic mechanisms. Rodent and human data also support links between hepatic insulin resistance and enhanced BA synthesis,[29] with several studies finding that insulin treatment represses *Cyp7a1* activity/transcription.[30,31] Furthermore, insulin-stimulated BA clearance from the circulation might be impaired in insulin-resistant conditions, as the effect of insulin infusion in decreasing the BA levels during euglycaemic–hyperinsulinaemic clamping was blunted in insulin-resistant human subjects.[13] This suggests that insulin resistance and hyperglycaemia might contribute to the altered set point of BA synthesis in European women with GDM in this study, although further research is required to substantiate this.

In South Asian women, obesity was associated with >52% elevated TBAs compared with lean women, perhaps explaining why GDM was not associated with further increased TBAs. This agrees with our previous work showing the normal range of TBAs is higher in South Asian compared with European women in a largely obese cohort of uncomplicated pregnancy.[18] Instead, South Asian women with GDM had decreased levels of some secondary BAs, which was also found in Chinese women with GDM in several studies,[12,23] suggesting that this phenotype might be common in women of South Asian and Chinese origin. Our study also showed a 42% increased prevalence of tauro-conjugated BAs in South Asian women with GDM, which was previously described in a multi-ethnic T2DM cohort.[32] Interestingly, elevated tauro-BAs are also seen in ICP,[4] a disease associated with higher GDM risk,[5] suggesting potential aetiological similarities between these disorders in South Asian women.

This study showed ethnicity-specific differences in BA homeostasis and its interaction with GDM/obesity during pregnancy, emphasising the need for multi-ethnic studies including non-European populations. This might relate to distinct pathologies underlying the incidence of diabetes in European and South Asian women. Cluster analysis highlighted differences in the prevalence of T2DM subtypes between European (Scandinavian) and South Asian (Indian) individuals, with Indian individuals showing a predominance of β-cell dysfunction over insulin resistance.[33] Furthermore, Chinese work found increased TBAs in early gestation in the 'GDM-Resistance' subgroup but not in the 'GDM-Dysfunction' subgroup,[34] suggesting a relationship between TBAs and insulin resistance rather than secretion. Notably, GDM rates are higher in European compared with South Asian women with ICP, implying the relationship between BAs and insulin resistance/GDM may be more important for the development of GDM in European populations.[35] An ethnicity-specific aetiology where insulin resistance (correlating with TBA in our cohort) is more important in European individuals might explain why GDM was not associated with changes in TBA in our South Asian population. Others suggested that South Asian individuals may have lower subcutaneous fat storage capacity, leading to ectopic lipid deposition at lower BMIs.[36] Increased susceptibility to liver dysfunction secondary to lipid accumulation could contribute to altered BA homeostasis and increased TBAs, as observed with healthy obesity in our South Asian women.

Obesity was associated with a 42% increased primary/secondary BA ratio in an ethnicity-independent manner. Increased concentrations of primary (without changes in secondary) BAs were previously observed in non-pregnant individuals who were obese, versus lean, although the ratio was not directly assessed.[13,14] One putative mechanism relates to microbiome changes, including decreased intestinal microbiotal diversity with obesity,[37] resulting in less conversion from primary to secondary BAs. Indeed, restoring

microbiotal diversity leads to a decrease in primary BAs.[28] Alternatively, an overabundance of primary BAs might reflect decreased gallbladder contractility, enhanced BA synthesis to eliminate dietary cholesterol,[38] or the decreased intestinal reabsorption of secondary BAs.[27]

4.3 | Strengths and limitations

We are the first to investigate ethnicity differences in serum BA profile during pregnancies complicated by GDM in a single cohort, to report on serum BAs in women with GDM of South Asian ethnicity and to have performed an obesity-segregated analysis of serum BAs in pregnant women. Our findings are therefore particularly novel. A limitation is the small numbers for some groups, especially the South Asian-Lean-GDM group, which hindered the interpretation of GDM effects in lean South Asian women. Women did not undergo mixed meal testing, hence no post-meal samples were available for BA measurement. Lastly, further work should include a wider variety of ethnicities, especially women of African ancestry for whom non-fasting TBA concentrations in pregnancy also differ from European women.[18]

5 | CONCLUSION

This study has shown that total serum BA concentrations in the second half of gestation depend on ethnicity, obesity and GDM. These different phenotypes might underly the ethnicity-specific regulation of BA homeostasis and different aetiologies contributing to GDM risk in European and South Asian women. This work provides a stepping stone into further understanding the complexity of GDM pathology and future work investigating ethnicity-specific precision medicine for this prevalent metabolic disorder of pregnancy.

AUTHOR CONTRIBUTIONS

Conceptualisation: CW. Data curation: HMF, JMS, NP, NS, PS and YW. Formal analysis: JMS, with help from PTS. Funding acquisition: CW and PS. Investigation: ALS, HUM, NP and NS. Methodology: CW and PS. Project administration: CW and HMF. Resources: CW, HUM and PS. Supervision: CW. Visualisation: JMS. Writing – original draft: JMS. Writing – review & editing: ALM, AM, CW, HMF, JMS and PS. All authors reviewed the data and approved the final version of the article, with the exception of HUM (deceased), who had approved the final data and data interpretation prior to the preparation of the final article.

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GUARANTOR & TRANSPARENCY DECLARATION

JMS and CW are joint guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JMS and CW affirm that this article is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

CONFLICT OF INTEREST STATEMENT

CW is a paid consultant for Mirum Pharmaceuticals. Mirum Pharmaceuticals were not involved with this work. The other authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

ETHICS APPROVAL

This study was approved by the National Research Ethics Committee (12/WM/0010) on 14 March 2012. Informed written consent was obtained from all participants. For further information, see Saravanan et al.[20]

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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