Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

Serum metabolomic signatures of Gestational Diabetes in South Asian and white European women

ONLINE-ONLY SUPPLEMENTAL MATERIAL

Table of Contents

Supplemental Tables

Supplemental Figures

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

Supplemental Figure S3. Schematic of the metabolic pathways, and their inter-relationships, associated with GDM in START and FAMILY

Supplemental Figure S4. Partial least-squares discriminant analysis (PLS-DA) results, scores plot and variable importance plot, among women with GDM (n = 133), IADPSG diagnostic criteria, comparing metabolites concentrations between South Asian (START study; n = 81) and white European women (FAMILY study; n = 52)

Supplemental Figure S5. Standardized mean difference (95% CI) in serum metabolites among women with GDM (n = 133), comparing South Asian (n = 81) to white European (n = 52) women, p < 0.05

Supplemental Figure S6. Standardized mean difference (95% CI) in serum metabolites among all women (n = 590), comparing South Asian (n = 299) to white European (n = 291) women, p < 0.05

Supplemental Figure S7. Partial least-squares discriminant analysis (PLS-DA) results, scores plot and variable importance plot, IADPSG diagnostic criteria, START and FAMILY

References

Supplemental Table S1.

Search details: We updated the systematic reviews of Huynh et al. and Chen et al., (1-2), by searching MEDLINE (via Ovid 2017 to November 30, 2020), using search terms *"metabolomic*", "metabonomic*", "magnetic spectroscopy", "mass spectrometry", "metabolic profil*", "amino acid*", "metabolite*", or "metabolome*"* were combined with *"gestational diabete*".* An update was deemed appropriate based on guidance from the panel for updating guidance for systematic reviews (PUGs), which suggest that a review can be updated if the previous reviews are well conducted, address the same question, and uses valid methods (3). We included any studies that included pregnant women classified as having GDM, that used metabolomic techniques such as LC-MS or NMR spectroscopy, and metabolites were examined in maternal plasma, serum, urine, hair, placenta, or amniotic fluid. Studies were excluded if they were randomized control trials, did not have an appropriate control group, or were not in English. There were 234 eligible articles based on our 2017–November 30, 2020 search, of which 34 final articles were retained (excluded n = 1 duplicate; n = 170 not about metabolites or GDM; n = 16 animal studies; n = 2 not in English; n = 5 collected >3 years post-partum; n = 6 no appropriate control).

Summary of metabolomic studies (excluding glucose) investigating metabolite profile significantly associated with GDM, stratified by biospecimen collection time

Author, Year Country	Study design & (Analytical platform)	Sample collection time	Bio-specimens (fasting?)	n GDM/ non-GDM	GDM diagnostic criteria	Metabolites in GDM vs. non-GDM		
						Upregulated (higher [ ] = increased GDM)	Downregulated (higher [ ] decreased GDM)	No change
A. COLLECTED PRIOR TO GDM DIAGNOSIS (N = 25)								
Chen, 2010 US (45% Hispanic, 38% Black, 17% other) [4]	Nested case-control (targeted on FA, GC-MS)	15 weeks GA	Serum (fasting)	49/98	Carpenter–Coustan criteria (dx at 28 weeks GA)	Myristic acid, palmitic acid, palmitoleic acid, EPA, NEFAs, total SFAs	None	Stearic acid, oleic acid, linoleic acid, linolenic acid, arachidonic acid, DHA
Graça, 2010 Portugal* [5]	Nested case-control (untargeted, ¹H NMR spectroscopy)	14-25 weeks GA	Amniotic fluid (non-fasting)	27/82	Unknown (dx at 24-28 weeks GA)	None	Glycine, proline, serine, taurine, acetate, formate, creatinine, glutamate, glycerophosphocholine	Alanine, allantoin, ascorbate, α-ocoisolvalerate, citrate, glutamine, isoleucine, lactate, leucine, methionine, phenylalanine, myo-inositol, N-acetyl, pyruvate, succinate, threonine, tyrosine, valine
Diaz, 2011 Portugal* [6]	Nested case-control (untargeted, ¹H NMR spectroscopy)	14-25 weeks GA	Plasma and urine (non-fasting)	27/82	Unknown	Plasma: None Urine: 3-hydroxyisovalerate, 2-hydroxyisobutyrate, N-methyl-nicotinamide, choline, N-methyl-2-pyridone-5-carboxamide	Plasma: trimethylamine N-oxide, betaine Urine: None	Plasma: 3-hydroxyisovalerate, 2-hydroxyisobutyrate, N-methyl-nicotinamide, choline, N-methyl-2-pyridone-5-carboxamide Urine: Trimethylamine N-oxide, betaine
Graça, 2012 Portugal [7]	Nested case-control (untargeted, UPLC-MS)	15-25 weeks GA	Amniotic fluid and urine (non-fasting)	23/26	Unknown (dx at 24-28 weeks GA)	Choline	Glutamate	Leucine, isoleucine, histidine, methionine, phenylalanine, valine, N-methyl-nicotinamide, hippurate, threonine, cis-aconitate, hypoxanthine, pyroglutamate

3

Sachse, 2012 Norway [8]	Nested case-control (untargeted, ^{1}H NMR spectroscopy)	8-20 weeks GA	Urine (fasting)	79/530	WHO criteria (dx at 26-30 weeks GA)	Citrate, lysine	None	Valine, leucine, 3-aminoisobutyrate, 3-hydroxyisovalerate, 2-hydroxyisobutyrate, alanine, N-acetylglutamine, dimethylamine, trimethylamine N-oxide, glycine, creatine, creatinine, 1-methyl-nicotinamide,1,6-anhydroglucose, 4-hydroxy-phenylacetate, tyrosine, histidine, formate, N-phenylacetylglycine
Diaz, 2013 Portugal [9]	Nested case-control (untargeted, ^{1}H NMR spectroscopy)	14-26 weeks GA	Urine (non-fasting)	42/84	Unknown (dx at 19-38 weeks GA)	Choline, N-methylnicotinamide, xylose	4-hydroxyphenylacetate, hippurate	N-methyl-2-pyridone-5-carboxamide, desethylamiodarone, acetate, acetone, carnitine, citrate, creatine, creatinine, DMA, glycine, lactose, phenylacetyl-glutamine, tartrate, trimethylamine
De Seymour, 2014 New Zealand [10]	Nested case-control (untargeted, GC-MS)	20 weeks GA	Serum (not known if fasting)	22/26	Unknown	Itaconic acid, cis-aconitate	None	2-hydroxybutyric acid, creatinine, nicotinamide, 4-methyl-2-oxopentanoic acid, cysteine, oleic acid, 9-heptadecenoic acid, ornithine, 11,14-eicosadienoic acid, EPA, DHA, palmitic acid, adrenic acid, γ-linolenic acid, palmitoleic acid, alanine, glutamic acid, phenylalanine, arachidonic acid, glycine, proline, asparagine, isoleucine, pyruvic acid, aspartic acid, quinic acid, azelaic acid, lactic acid, serine, benzoic acid, leucine, stearic acid, linoleic acid, succinic acid, lysine, threonine, cis-vaccenic acid, margaric acid, tryptophan, citraconic acid, methionine, tyrosine, citric acid, myristic acid, valine
Bentley-Lewis, 2015 US [11]	Nested case-control (untargeted, LC-MS)	1^{rst} trimester GA	Serum (fasting)	96/96	Carpenter–Coustan criteria (dx in 3rd trimester)	Anthranilic acid, allantoin, alanine, glutamate, and serine	Creatinine	Other metabolites measured (specific metabolites not outlined)
Law, 2017 China part 1 and 2 [12-13]	Nested case-control (untargeted, LC-MS)	11-14 weeks GA	Plasma (fasting)	27/34	IADPSG (dx at 24-28 weeks GA)	Sesaminol 2-O-triglucoside, tricin 7-neohesperidoside. Pathways: trytophan metabolism, purine nucleosides (e.g. uridine, hypoxanthine, xanthine, xanthosine), amino acid derivatives (e.g. homocitrulline), steroid and sterol conjugates (e.g. 5-androstenediol), fatty acid derivates (e.g. 3-hydroxybutyric acid), carnitines, amino acids (e.g D-galactose)	(2E)-14-hydroxytetradec-2-enoic acid, (2E,13R)-13-hydroxytetradec-2-enoic acid, 2,15-dihydroxypentadecanoi acid, (7R,8S,9Z,12Z,15Z)-7,8-dihydroxy-9,12, 15-octadecatrienoic acid	183 other metabolites measured (others NS)

4

Leitner, 2017 Italy [14]	Case-control (GC-MS)	12-26 weeks GA	Urine (not clear if fasting)	14/18	IADPSG (dx at 24-28 weeks)	2-hydroxybutanoic acid, 3-hydroxybutanoic acid, valine, alanine, beta-alanine, tryptophan, b-sitosterol, octadecadienoic acid, tyrosine, leucine, phenylalanine, 2,4-dihydroxybutyrate, citrate, malate, succinate, uracil, lactate, pentahydroxyhexanoic acid	None	Other metabolites measured (specific metabolites not outlined)
Zhang, 2017 China [15]	Cohort study (HILIC-MS)	9-12 weeks GA	Serum (fasting)	533/ 5175	IADPSG (dx at 24-28 weeks)		Thyroxin	No other metaboites measured
Barzilay 2018, Canada (45% European, 25% Asian, 9% Latin, 7% Black) [16]	Nested case-control (LC-MS)	12-16 weeks GA	Plasma (non-fasting)	18/296	Canadian Diabetes Association 2008 practice guideline (dx 24-28 weeks GA)	None	None	Pyridoxal 5' phosphate, choline, dimethylglycine, betaine, trimethylamine N-oxide, homocysteine, folic acid
Li, 2018 China & Liu, 2020 China [17-18]	Nested case-control (LC-MS)	<24 weeks GA	Serum (fasting)	243/243	WHO-2013 criteria (dx at 24-28 weeks GA)	None	Deoxycholic acid, Glycoursodeoxycholic acid, glycochenodeoxycholic acid, glycodeoxycholic acid, taurochenodeoxycholic acid, glycocholic acid, L-α-lysophosphatidylcholine, LPC (15:0, 17:0, 18:0, 18:1)	Cholic acid, deoxycholic acid, taurocholic acid, LPC 14:0
O'Neill, 2018 US (90% white Europeans) [19]	Nested case-control (targeted, GC-MS/LC-MS)	16-18 weeks GA	Amniotic fluid	20/20	Self-report at postnatal visit	2-hydroxybutyrate, 3-(4-hydroxyphenyl)-propionate, 3-methyl-2-oxovalerate, 2-hydroxy-3-methylvalerate, LCFAs (palmitoleate, stearate, eicosenoate); PUFAs (EPA, DHA, linoleate, linolenate, dihomo-linolenate, arachidonate, DPA), stearoyl sphingomyelin	1,5-anhydroglucitol, glycine, betaine, histidine, pyroglutamine, phenylacetyl-glutamine, p-cresol sulfate, p-cresol-glucuronide, urea, hydrocinnamate, isovaleryl-glycine, isobutrylglycine, N2, N5-diacetylornithine, N-acetylcitrulline, 5-methylthioadensine, γ-glutamylglycine, γ-glutamylleucine, γ-glutamylphenylalanine, γ-glutamylthreonine, γ-glutamyltyrosine, γ-glutamylvaline	459 metabolites measured (others NS)

5

Roy, 2018 Quebec, Canada [20]	Nested case-control (targeted, UHRQ-TOF-MS)	7-15 weeks GA	Plasma (non-fasting)	50/50	2008 Canadian Diabetes Association criteria (dx at 24-28 weeks)	leucine, iso-butyrylcarnitine, isoleucine, tyrosine, valine	None	Acylcarnitines (C0, C2, C4, C5DC, C6, C8), arginine, glutamine, methionine,
Hou, 2018 China [21]	Nested case-control (UPLC-TQ-MS, GC/TOF-MS)	12 weeks GA	Serum (fasting)	131/138	IADPSG (dx at 24-28 weeks)	Acetylaspartic acid, alanine, glutamic acid, leucine, valine, 2- and 4-aminobutanoic acid, 2-hydroxybutyric acid, 2-oxo-4-methylvaleric acid, aminomalonic acid, malic acid, pyruvic acid, 1-monooleoylglycol, 2-ethylhexanoic acid, mannose, threitol, lithocholic acid, hyodeoxycholic acid, 6,7 diketocholic acid, fatty acids (C14:1, C16:1, C17:1, C18:1, C19:1, C20:1, C12:0, C16:0, C17:0, C20:0, C16:2, C18:2, C18:3, C22:3, C18:3, C20:4, C20:3, C20:2, C22:5), triglycerides, cholinesterase, retinol binding protein, 2-oxo-4-methylvaleric acid, 4-aminobutanoic acid	Cysteine, isoleucine, 2,3,4-trihydroxybutryic acid, maltose, threonic acid, cholic acid, dehydro-LCA, isodeoxycholic acid	Alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, blood urea nitrogen, creatinine, uric acid, cholesterol (total, HDL, LDL), 131 metabolites measured (others NS)
Li, 2018 China [22]	Nested case-control (UPLC-MS)	20 weeks GA	Plasma (fasting)	276/552	IADPSG (dx at 24-32 week GA)	TMAO, triglycerides	None	Cholesterol (total, HDL, LDL); no other metabolites measured
Huo, 2019 China [23]	Nested case-control (LC-MS)	first antenatal care visit	Plasma (fasting)	243/243	WHO-2013 criteria (dx at 24-28 weeks GA)	Alanine aminotransferase, trimethylamine	Betaine, L-carnitine, choline chloride, trimethylamine N-oxide, deoxycholic acid, glycoursodeoxycholic acid	None
Sakurai, 2019 Japan [24]	Nested case-control (HICT-MS)	<24 weeks GA	Serum, Urine (unclear if fasting)	121/121	Medical records at time of delivery (but GDM dx at 24-28 weeks)	Serum: glutamine, pyrophosphate, octulose-1,8-bisphosphate Urine: shikimate-3-phosphate, ethanolamine, 1,3-diphopshateglycerate, leucine-isoleucine, p-hydroxybenzoate,	None	42 serum and 263 urine other metabolites measured (not NS)

6

						hydroxyphenylpyruvate, N-acetyl-alanine, hydroxyproline, octulose-monophosphate, N-acetyl-glucosamine, shikimate, cellobiose, threonine, methylcysteine, methionine sulfoxide, urea, deoxyribose-phosphate, methionine, acadesine, D-sedoheptulose-7-phosphate. Pathways: valine, leucine and isoleucine biosynthesis, ABC transporters, betaine-homocysteine S-methyltransferase, methionine synthases, aminoacyl-tRNA biosynthesis, phenylalanine, tyrosine and tryptophan biosynthesis, pentose phosphate		
Liu, 2019 China [25]	Case-control (LC-MS)	6-8 weeks	Urine (not clear if fasting)	15/50	IADPSG (dx at 24-28 weeks)	L-phenylalanyl-L-proline, hydroxylauroylcarnitine, levoglucosan, 1'-acetoxyeugenol acetate, 3,4-dimethyl-5-pentyl-2-furanundecanoic acid, polyethylene glycol, 6-hydroxy-5-methoxyindole glucuronide. Pathway: steroid hormone biosynthesis	Pathway: tyrosine metabolism	Other metabolites measured (specific metabolites not outlined)
Zhao, 201 9 China [26]	Case-control (UHPLC-MS)	Median 13 weeks GA	Serum (fasting)	107/107	American Diabetes Association 2011 (dx at 24-28 weeks)	Hypoxanthine, xanthosine, glutamic acid, lysine, ornithine, proline, pantothenic acid, succinic acid semialdehyde, acetohydroxamic acid, glycerophosphocoline, taurine, creatine, acetylcarnitine, uracil, propionylcarnitine, aspartyl-isoleucine, pantothenic acid, 2 methylbutyroylcarnitine, LysoPC (14:0, 20:5, 16:1, 15:0, 22:6, 20:4, 20:3, 16:0,	Inosine, prolyhydroxyproline, threoninyl-phenylalanine, asparaginyl-tryptopham, phenylalanyl-gamma-glutamate, valyl-isoleucine, aspartyl-phenylalanine, phenylalanyl-valine, DL-2 -aminooctanoic acid, phenylalanyl-isoleucine, acetylglycine	Other metabolites measured (NS)

7

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

						20:3, 18:1, 17:1, 18:0, 22:4), palmitoylcarnitine, linoleoyl carnitine, histidine, succinic acid, malic acid, ascorbic acid-2-sulfate, glycocholic acid, chenodeoxycholic aicd, lysophosphatidic acid		
Furse, 2020 UK (10% Black, 6% Asian, 68% White) [27]	Cohort study (DI-MS/LC-MS)	15-18 weeks GA	Plasma (not clear if fasting)	249/582	IADPSG (dx 24-30 weeks GA)	Triglycerides (48:0, 50:1, 50:2, 51:5, 53:4), phosphatidylcholine (38:5)	Sphingomyelins (32:1, 41:2, 42:3), lyso-phosphatidylcholine (16:0, 18:1), phosphatidylcholines (35:2, 40:7, 40:10), polyunsaturated triglycerides (46:5, 48:6), oxidized triglycerides (48:6, 54:4, 56:4, 58:6)	565 other triglyceride and phospholipid metabolites measured (specific metabolites not outlined)
Jiang, 2020 China [28]	Cohort study (UHPLC-MS)	12-16 weeks GA	Serum (fasting)	65/366	WHO-2013 criteria (dx at 24-28 weeks GA)	Alanine, glutamate, isoleucine, phenylalanine, tyrosine, triglycerides	None	Arginine, asparaginase, aspartic acid, citrulline, glycine, hydroxyproline, leucine, valine, tryptophan, threonine, serine, proline, lysine, total cholesterol
Koos, 2020 US [29]	Nested case-control (UPLC-MS, GC-MS)	6-19 weeks GA	Urine (not clear if fasting)	46/46	American Diabetes Association 2017 (post urine)	Argininate, saccharopine, dihydroorotate, dopamine, isocitrate lactone, octanoylcarnitine, 3-methylglutarate or 2-methylglutarate, nicotinate ribonucleoside, 7,8-dihydroneopterin, phenol glucuronide	Lanthionine	626 total metabolites measured (others NS)
Li, 2020 China [30]	Nested case-control (GC-MS)	10-16 weeks GA	Plasma (fasting)	305/305	IADPSG (dx at 24-28 weeks)	Fatty acids (C20:5, C18:3 ,C18:1, C20:3, C16:1, C14:0, C16:0, C22:0)	Fatty acids (C20:2, C22:4, C20:0, C24:0, C18:2)	Fatty acids (C17:0, C18:3, C18:0, C22:5, C15:0, C20:4, C20:1, C22:3, C18:1, C22:6)
B. COLLECTED AFTER OR SAME TIME AS GDM DIAGNOSIS (N = 38)								
Butte, 1999 US (Mexican or Central American descent) [31]	Case-control (amino acid analyser with 12cm high-performance sodium column with sodium buffers)	32-36 weeks GA	Plasma (fasting)	8/8	O'Sullivan and Mahan criteria	Taurine, hydroxyproline, glutamic acid, glutamine, cysteine, tyrosine, phenylalanine, tryptophan, histidine	N/A	Threonine, serine, proline, glycine, alanine, valine, cystine, methionine, isoleucine, leucine, ornithine, lysine, arginine
Seghieri, 2003 Italy [32]	Case-control (targeted, fluorescence	24-28 weeks GA	Serum (unclear if fasting)	15/78	Carpenter–Coustan criteria	Homocysteine	Vitamin B12	Folate, uric acid, HDL, cholesterol, triacylglycerols, albumin

8

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

	polarisation immunoassay)							
Tarim, 2004 Turkey [33]	(fluorescence polarisation immunoassay)	24-28 weeks GA	Plasma (fasting)	28/210	Carpenter–Coustan criteria	None	None	Homocysteine, triglycerides, cholesterol (total, HDL, LDL), vitamin B12, folic acid, creatinine
Guven, 2006 Turkey [34]	Case-control (Immunolite 2000 assay)	24-28 weeks GA	Serum (unclear)	30/147	Carpenter–Coustan criteria	Homocysteine	None	Folate, vitamin B12
Pappa, 2007 Greece [35]	Case-control (HPLC; enzymatic colorimetric assay)	30-33 weeks GA	Plasma (fasting)	25/46	Fourth International Gestational Diabetes Workshop criteria	β-hydroxybutyrate, free fatty acids	Acylcarnitine, methionine, glycine, alanine, citrulline, ornithine	Carnitine, histidine, isoleucine, leucine, lysine, phenylalanine, threonine, valine, arginine, aspartate, glutamate, serine, taurine, tyrosine, α-aminobutyric acid
Idzior-Waluś, 2008 Poland [36]	Case-control (ELISA-based assay)	26-32 weeks GA	Serum (fasting)	44/17	WHO criteria	Triglycerides, NEFAs, fasting glycose	None	Homocysteine, HDL, LDL, cholesterol, insulin, folate, cystatin C, vitamin B12
Telekjo, 2009 Poland [37]	Case-control (ELISA-based assay)	24-32 weeks GA	Plasma (unclear if fasting)	56/68	WHO criteria	Cholesterol (total and HDL), triglycerides, endothelin-1	None	HDL cholesterol, ADMA, E-selection, soluble vascular cell adhesion molecule-1
Akturk, 2010 Turkey [38]	Case-control (targeted, HPLC/fluorescence spectroscopy)	32-39 weeks GA	Plasma (fasting)	54/69	Carpenter–Coustan criteria	ADMA, triglycerides, HOMA-IR	None	Homocysteine, folic acid, vitamin B12
Sertkaya 2011 Turkey [39]	HPLC/fluorescence spectroscopy	24-28 weeks GA	Plasma (not clear if fasting)	58/50	Carpenter–Coustan criteria	ADMA	None	None
Chen, 2010 US (45% Hispanic, 38% Black) [4]	Nested case-control (targeted on FA, GC-MS)	28 weeks GA	Serum (fasting)	49/98	Carpenter–Coustan criteria	Palmitic acid, palmitoleic acid, oleic acid, linoleic acid, linolenic acid, arachidonic acid, EPA, DHA	None	Myristic acid, stearic acid
Sachse, 2012 Norway [8]	Nested case-control (untargeted, ^{1}H NMR spectroscopy)	26-30 weeks GA	Urine (fasting)	79/530	WHO criteria	Citrate	None	See section a. above (Sachse, 2012)
Dudzik, 2014 & Lorenzo, 2015 Poland [40-41]	Case-control (untargeted, GC-MS/LC-MS/CE-MS)	22-28 weeks GA	Plasma and urine (fasting)	20/20	WHO-1998	Plasma: phosphatidylethanolamines (38:6, 36:5), Phosphatidylcholines (38:1, 40:3), acetylcarnitine, linoleic acid, glycerol, 3-hydroxybutyrate, 2-hydroxybutyrate, fumaric	Plasma: LPE (16:0, 18:0, 18:2, 20:0, 20:1, 20:2, 22:4, 22:6), LPC (16:0; 18:0, 18:1, 18:2, 18:3, 20:3, 20:4, 20:5 acyl chains), LPI (20:4), LPS (20:0), LPA (18:2), lipoxin C4, trihydroxy-cholestanoyl	Alanine, valine, threonine, norleucine, proline, isoleucine, serine, leucine, cysteine, aspartic acid, methionine tyrosine, ornithine, lysine, arginine, histidine, methionine sulfone

9

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance
placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

						acid Urine: histidine, glutamine, phenylalanine, tryptophan, cystine	taurine, taurolithocholic acid glucuronide, araquidonate, DHA methyl esters, glycerol-phosphocholine, creatinine, pyruvic acid, glycine, glutamate, tryptophan, lauric acid; Urine: carnitine	
Prentice, 2014 US [42]	Case-control (untargeted GC-MS/LC-MS)	24–28 weeks GA	Plasma (fasting)	24/24	NIH	3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid	Did not measure other metabolites	
Scholtens, 2014 Northern Europe [43]	Case-control (targeted on amino acids and untargeted, MS/GC-MS)	24–32 weeks GA	Serum (fasting)	67/50	IADPSG	Alanine, proline, leucine, isoleucine, valine, arginine, phenylalanine, lactate, palmitic acid, lauric acid, heptadecanoic acid, β-tocopherol, β-hydroxybutyric acid, acetoacetic acid, pyruvic acid, α-ketoglutaric acid, 2-hydroxybutyric acid, isocitric acid, creatinine, triglycerides	1,5-Anhydroglucitol, mannitol and other hexitols, β-sitosterol	Glycerol, citrulline, valine, tyrosine, ornithine, histidine, serine, methionine, glycine
Hajduk, 2015 Poland [44]	Case-control (targeted on amino acids, LC-MS)	24-28 weeks GA	Plasma (unclear if fasting)	18/13	Polish Gynecological Society Standards	L-Citrulline	L-Asparagine, L-valine, and L-ornithine	Other amino acids measured (specific metabolites not outlined)
He, 2016 China [45]	Case-control (untargeted, GC-MS)	24-28 weeks GA	Hair	47/47	IADPSG	Adipic acid		2-oxobutyric acid, glycine, proline, 2-oxoglutaric acid, lactic acid, pyroglutamic acid, leucine, pyruvic acid, alanine, malonic acid, quinic acid, aspartic acid, methionine, serine, citramalic acid, n-acetylglutamic acid, stearic acid, citric acid, octanoic acid, succinic acid, cysteine, oxalic acid, threonine, fumaric acid, palmitic acid, tyrosine, valine, glutamic acid, phenylalanine
Lehmann, 2015 Germany [46]	Case-control (targeted, GC-MS/LC-MS)	24-27 weeks GA	Plasma (fasting)	9/15	IADPSG	Acetylcarnitine, leucine, oleate, triglycerides	glycerophospholipids [diacyl-phosphatidylcholine (PC aa) C38:6, PC aa C40:0, PC aa C42:0, PC aa C42:1, glycine, LPC (26:1, 28:1), fatty acids (C22:4, C22:5)	Creatinine, cholesterol (total, HDL, LDL), C-reactive protein 231 metabolites measured (specific metabolites not outlined)
Gao, 2016 China [47]	Case-control (targeted on	~28 weeks GA	Serum (fasting)	38/27	IADPSG	β-muricholic acid, glycohyo-deoxycholic acid,	None	

10

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

	bile acid, LC-MS)					taurohyo-deoxycholic acid, 5 sulfated (dehydro-1S, mono-2S+ mono-3S, mono-4S, and mono-5S)		
Liu, 2016 China [48]	Nested case-control (untargeted, LC-MS)	28-36 weeks GA	Serum (fasting)	12/10	IADPSG	1-Methyladenosine, homovanillic acid, trans-3-octenedioic acid, glucosamine, LPC (16:1, 20:2), 3-methylthiopropionic acid, L-lactic acid, tyrosine, L-2-hydroxyglutaric acid, phosphorylcholine	Gluconolactone, serinyl-glycine, LPC (20:4), 3-methylhistidine, 2-oxo-4-methylthiobutanoic acid, sphingomyelin (d18:0/18:0), arabinonic acid indoleacetaldehyde, LPE (14:1/ 20:0), 3-oxooctadecanoic acid, glycine, pyridoxal, capric acid, stearic acid, 3-methylhistidine	Other metabolites measured (specific metabolites not outlined)
Law, 2017 China part 1 and part 2 [12-13]	Nested case-control (untargeted, LC-MS)	23-27 & 29-33 weeks GA	Plasma (fasting)	27/34	IADPSG	Prostanoic acid, sesaminol 2-O-triglucoside, tricin 7-neohesperidoside, and dihydro-12-oxo-15-phytoenoic acid. Pathways: trytophan metabolism (e.g. oxitriptan (5-hydroxytryptamine), serotonin), purine nucleosides (e.g. uridine, hypoxanthine, xanthine, xanthosine), amino acid derivatives (e.g. homocitrulline), steroid and sterol conjugates (e.g. 5-androstenediol), fatty acid derivates (e.g. 3-hydroxybutyric acid), carnitines, amino acids (e.g D-galactose)	(2E)-14- hydroxytetradec-2-enoic acid, (2E,13R)-13-hydroxytetradec-2-enoic acid, 2,15-dihydroxypentadecanoic acid, (7R,8S,9Z,12Z,15Z)-7,8-dihydroxy-9,12,15-octadecatrienoic acid, 11α,20,26-trihydroxyecdysone	183 other metabolites measured (others NS)
Leitner, 2017 Italy [14]	Case-control (GC-MS)	12-26 weeks GA	Urine (not clear if fasting)	14/18	IADPSG (dx at 24-28 weeks)	2-hydroxybutanoic acid, 3-hydroxybutanoic acid, valine, alanine, beta-alanine, tryptophan, b-sitosterol, octadecadienoic acid, tyrosine, leucine, phenylalanine, 2,4-dihydroxybutyrate, citrate, malate, succinate, uracil, lactate, pentahydroxyhexanoic acid	None	Other metabolites measured (specific metabolites not outlined)

11

Zhang, 2017 China [15]	Cohort study (HILIC-MS)	9-12 weeks GA	Serum (fasting)	533/5175	IADPSG (dx at 24-28 weeks)		Thyroxin	No other metabolites measured
Barzilay 2018, Canada (45% European, 25% Asian, 9% Latin, 7% Black) [16]	Nested case-control (LC-MS)	12-16 weeks GA	Plasma (non-fasting)	18/296	Canadian Diabetes Association 2008 practice guideline (dx 24-28 weeks GA)	None	None	Pyridoxal 5' phosphate, choline, dimethylglycine, betaine, trimethylamine N-oxide, homocysteine, folic acid
Chorell, 2017 Sweden [49]	Case-control (GC-TOF/MS)	27-38 weeks GA	Serum (fasting)	11/24	European Association for the Study of Diabetes 1991 criteria	None	Cholesterol, LDL	120 metabolites (e.g. leucine, isoleucine, valine, HDL cholesterol) NS
Dudzik, 2017 Poland [40]	Nested case-control (GC-MS)	22-28 weeks GA	Plasma (fasting)	24/24	WHO-1998 criteria	2- and 3-hydroxybutyrate, linoleic acid, oleic acid, palmitoleic acid, palmitic acid, glycerol, triglycerides,	None	Other metabolites measured (specific metabolites not outlined), cholesterol (total, HDL, LDL)
Rahimi, 2017 Iran [50]	Case-control (HPLC)	>25 weeks GA	Plasma (fasting)	27/25	American Diabetes Association 2015 criteria (dx at 24-28 weeks GA)	Asparagine, aspartate, threonine, phenylalanine, glutamine, arginine	None	Histidine, serine, glutamate, citrulline, glycine, leucine, lysine, isoleucine, leucine, ornithine, tyrosine, tryptophan, valine, alanine
Delplancke, 2018 New Zealand (18% Indian/Asian, 63% European, 18% Pacific Islander) [51]	Case-control (GC-MS/LC-MS)	34-37 weeks GA	Hair	11/73	IADPSG	1-hydroxy-3-nonanone, 22-oxavitamin D3	Tryptophan, leucine, citric acid, 3,4-oxazolidinecarboxylic acid, 2-oxovaleric acid, 3-pyridinecarboxamide, 2-methylpentan-2-y trifluoroacetate, 2-oxobutyric acid	980 total metabolites measured (others NS)
Batchuluun, 2018 Canada (28% White, 8% Black, 26% Asian, 35%	Nested case-control (SRM-MS)	24-28 weeks GA	Plasma (fasting)	13/11	Carpenter–Coustan criteria	Short chain acylcarnitines, medium chain acylcarnitines (hexanoyl-carnitine, octanoyl-carnitine, decanoyl-carnitine, lauroyl-carnitine)	None	Long chain acylcarnitines (C14, C16, C18)

12

Hispanic) [52]								
Bukowiecka-Matusiak, 2018 Poland [53]	Case-control (GC-MS)	24-28 weeks GA	Plasma (fasting)	32/11	WHO-2013 criteria	Vaccenic acid	Stearic acid	Fatty acids (myristic, palmitic, sapienic, palmitoleic, oleic, linoleic, alpha-linolenic, gamma-linolenic, arachidonic, EPA, DPA, DHA)
Chen, 2018 China [54]	Case-control (GC-MS/LC-MS)	26-28 weeks GA	Urine and serum (fasting), hair	49/44	IADPSG	Serum: 2-aminobutyric acid	None	Other metabolites measured (232 metabolites in urine, 96 metabolites in serum, 160 metabolites in hair; specific metabolites not outlined), adjusted for multiple testing
Li, 2019 China [55]	Case-control (LC-MS)	24-28 weeks GA	Serum (not clear if fasting)	30/30	IADPSG	Tetrahydrocortisol, rumenic, linoleic acid, lysoPC, psychosine, traumatic acid, prostaglandin c2, prostaglandin j2, prostaglandin b2, prostaglandin a2, urocortisone, corticosterone, 11-deoxycortisol, thromboxane b2, prostaglandin d2-d4, prostaglandin e2-d4, oleic acid, 2-hydroxyestrone, dehydroepiandrosterone, 2s-hydroxybutanoic, d(-)-beta-hydroxy, 4-hydroxy-butyric, crotonoyl-coa, methacrylyl-coa, lysophosphatidic acid, pravastatin, THB, DPA	Lutein, zeaxanthin, lathosterol, prostaglandin-endoperoxide synthase 2, 6-keto prostaglandin E1, coenzyme Q10, HDL cholesterol	Triglyceride, other metabolites measured (specific metabolites not outlined)
López-Hernández, 2019 Mexico [56]	Case-control (UPLC-MS)	>24 weeks	Urine (not clear if fasting)	24/11	American College of Obstetricians and Gynecologists (dx at 24-28 weeks)	5-carboxy-alpha-chromanol, aspartame, DG (24:0/14:1), tryptophan L-urobilinogen, cer (d18:0/23:0), SM (d18:0/22:0), steroids/derivatives (11-oxo-androsterone-glucuronide, cortolone-3-glucuronide, tetrahydroaldosterone-3-glucuronide, 5-androstene-3b,16b,17a-triol, 21-deoxycortisol, 11b, 17a,21-triydroxypreg-nonolone, cucurbitacin c), creatinine,	None	Other metabolites measured (4598 features detected, specific metabolites not outlined)

13

						urea. Pathways: tryptophan metabolism, steroid hormone biosynthesis		
Taylor et al., 2019 United Kingdom (54% South Asian; 46% White) [57]	Case-control (targeted NMR)	92% between 26-28 weeks	Serum (fasting)	734/ 8774	WHO criteria (dx at 24-28 weeks)	vLDL, small HDL, triglycerides (HDL and LDL), total fatty acids, SFAs, glucose, lactic acid, pyruvic acid, citric acid, glycerol, alanine, phenylalanine, tyrosine, 3-hydroxybutyric acid, BCAAs, acetate, glycoprotein acetyls	Glutamine	LDL, medium and large HDL, total cholesterol, choline, phosphatidylcholine, ApoA, ApoB, histidine, glycine, creatinine, albumin
He, 2020 China [58]	Cohort study (GC-MS)	3rd trimester GA	Plasma (fasting)	177/387	IADPSG (dx at 24-28 weeks)	Triglycerides	None	Serum fatty acids (All PUFAs, MUFAs, SFA), cholesterol (total, HDL, LDL)
Zhao, 2019 China [26]	Case-control (UHPLC-MS)	Median 26 weeks GA	Serum (fasting)	107/107	American Diabetes Association 2011 (dx at 24-28 weeks)	Guanosine, glutamic acid, acetylcarnitine, propionylcarnitine, 2-Octenoylcarnitine, LysoPC (14:0, 16:1, 20:3, 16:0 17:0), palmitoylcarnitine, lysophosphatidic Acid	Threoninyl-Phenylalanine, Phenylalanyl-Gamma-glutamate, Phenylalanyl-Isoleucine	Other metabolites measured (NS)
Burzynska-Pedziwiat, 2020 Poland [59]	Case-control (HPLC–MS/MS)	24-28 weeks GA	Plasma (fasting)	29/35	WHO-2013 criteria	None	Arginine, glutamine, histidine, methionine, phenylalanine, serine	Alanine, asparagine, glutamic acid, glycine, isoleucine, leucine, lysine, proline, threonine, tryptophan, tyrosine, valine, cholesterol (total, HDL, LDL), C-reactive protein, triglycerides
Walejko, 2020 Florida (59% White, 29% Black, 7% Asian, 6% Hispanic) [60]	Case-control (1H NMR spectroscopy)	1rst, 2nd, 3rd trimester	Plasma (both fasting and non-fasting)	12/57	Not clear	(CH2n) fatty acids, ch2ch=c fatty acids, alpha-ch2 fatty acids, glyceryl c1, 3h, glyceryl c2h, ch=ch fatty acids, n-acetyl-glycoproteins. Pathways: butanoate metabolism, synthesis and degradation of ketone bodies	Glutamine, glycine, serine, threonine, succinate, acetate, creatinine, formate. Pathways: glyoxylate and dicarboxylate, glycine, serine, and threonine, alanine, aspartate and glutamine metabolism	Alanine, arginine, asparagine, leucine, isoleucine, valine, dimethylglycine, glutamate, histidine, methionine, lysine, ornithine, dimethylsulfone, phenylalanine, proline, citrate, lactate, pyruvate, acetoacetate, acetone, 3-hydroxybutyrate, betaine, choline, glycolipids, creatine, 2-oxoisovalerate, tyrosine, valine
Wang, 2020 China [61]	Case-control (GC-MS)	Unclear	Urine (not clear if fasting)	59/48	IADPSG (dx at 24-28 weeks)	D-galactose, 2-methoxytyrosine	2-o-methyl-l-ascorbic acid, citraconic acid, N-methylglutamc aicd, cysteine-glycine, glutamine, glycine, galactitol, trehalose, isocitric acid, 2-hydroxyhexaoic acid, nicotinic acid, 2-dehydroshikimic acid	Other metabolites measured (specific metabolites not outlined)
Tan, 2020	Case-control	post GDM	Serum	29/29	WHO-2013	LPC (18:0, 16:0), palmitic	LPC (22:6), behenic acid,	14-Methyl hexadecenoic acid, other

14

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

China [62]	(UHPLC-MS)	dx (week not recorded)	(fasting)		criteria	acid, phytosphingosine	sphingosine, 1,25-dihydroxyvitamin D3-26,23-lactone	metabolites measured (specific metabolites not mentioned)
C. COLLECTED DURING DELIVERY OR POSTPARTUM (< 2 YEARS POSTPARTUM) (N = 11)								
Butte, 1999 US (Mexican or Central American descent) [31]	Case-control (amino acid analyser with 12cm high-performance sodium column with sodium buffers)	6 weeks PP	Plasma (fasting)	8/8	O'Sullivan and Mahan criteria	Taurine, hydroxyproline, glutamic acid, glutamine, cysteine, tyrosine, phenylalanine, tryptophan, histidine, proline, valine, isoleucine, leucine, lysine, arginine	None	Threonine, serine, glycine, alanine, cystine, methionine, ornithine
Cetin, 2005 Italy [63]	Case-control (HPLC/ dual wavelength spectrophotometry)	During delivery; GDM gx at 37-41 weeks GA	Plasma (likely non-fasting)	17/16	Carpenter–Coustan criteria	Ornithine	None	Lysine, histidine, threonine, valine, methionine, isoleucine, leucine, phenylalanine, proline, arginine, taurine, serine, glutamic acid, glutamine, glycine, alanine, tyrosine
Sachse, 2012 Norway [8]	Nested case-control (untargeted, ^{1}H NMR spectroscopy)	10-16 weeks PP	Urine (fasting)	79/530	WHO	None	None	See section a. above (Sachse, 2012)
Anderson, 2014 UK (70% European, 25% South Asian) [64]	Case-control (untargeted, LCMS)	22 months PP	Serum (fasting)	18/43	WHO	Phospholipids (20:1, 18:1, 37:0), oxodecenoic acid, decanol, nonadienoic acid, elaidoylamide, octenedioic acid, hydroxydodecanoic acid, hydroxyadipic acid, 8-amino-7-oxononanoate, oxobutanoic acid, octanoic acid, oxopentanoic acid, oxo-hydroxy-aminovaleric acid, itaconic acid, hydroxymethyl-pentanoic acid, 5beta-cholane-3alpha-24-diol, pgf2alpha-11-acetate, 11alpha-hydroxy-9,15-dioxoprost-13-enoate, 3alpha,11beta,17alpha-trihydroxy-5beta-pregnan-20-one, uric acid, proline, leucine, isoleucine, dimethyluric acid	Phospholipids (10:1, 36:3, 34:0, 38:9, 16:2, 18:1), tetradecenoic acid, decadiynoic acid, hydroxydodecanoic acid, hydroxyoctadecanoic acid, docosanol, hydroxypyruvic acid, acetic acid, methylmalonic acid semialdehyde, propanoic acid, 2-amino-3-phosphonopropanoic acid, methylvaleric acid, diglycerides (40:1), chenodeoxycholic acid 3-sulphate, 4alpha,24beta-dimethyl-5alpha-cholest-22-en-3beta-4beta-diol, 4alpha-hydroxymethyl-4beta-methyl-5alpha-cholesta-8-en-3beta-ol, n-(aminomethyl)urea, phosphoshikimate,	None

15

							tryptophan, 2-polyprenylphenol, benzosemiquinone, 2-hexaprenylphenol, 5,6,7,8-tetrahydrofolate	
Liu, 2016 China [48]	Nested Case-control (untargeted, LCMS)	Within 3 days PP	Serum (fasting)	12/10	IADPSG	L-Carnitine, creatine	L-lysine, vitamin A, LPE (22:6), ribothymidine, corticosterone, , 17-hydroxyprogesterone, 1, 4-beta-D-glucan	Other metabolites measured (specific metabolites not outlined)
Chertok, 2017 Israel [65]	Case-control (chromatograph equipped with a fused-silica capillary column)	first 5 days PP	Colostrum (not mentioned if fasting)	29/34	Hospital records	Arachidonic acid, docosatetraenoic acid, linoleic acid, eiosatrienoic acid, heptadecanoic acid	Pentadecanoic acid	Fatty acids (palmitic, lignoceric, oleic, myristic, vaccenic, myristoleic, cis-10-pentadecanoic, margaric, docosanoic, dh, lauric, gondoic, nervonic, epa, erucic, eicosadienoic, tridecylic, linoleic, stearic, arachidic, heneicosylic, clupanodonic, y-linolenic, a-linolenic, trans-oleic, tricosylic, palmitoleic)
Dudzik, 2017 Poland [40]	Nested case-control (GC-MS)	4 weeks and 12 weeks PP	Plasma (fasting)	24/24	WHO-1998 criteria	1 month PP: lactic acid, proline 3 months PP: 2- and 3-hydroxybutyrate, gluconic acid, palmitic acid, linoleic acid, oleic acid, glycerol, C-peptide	2-ketoisocaproic acid	Other metabolites measured (specific metabolites not outlined), cholesterol (total, HDL, LDL)
Chorell, 2017 Sweden [49]	Case-control (GC-TOF/MS)	6-12 months PP	Serum (fasting)	11/24	European Association for the Study of Diabetes 1991 criteria	leucine, isoleucine, valine	DHA, palmitic acid, linoleic acid, elaidic acid, oleic acid	Cholesterol (total, HDL, LDL), 112 metabolites analyzed NS
Barzilay 2018, Canada (45% European, 25% Asian, 9% Latin, 7% Black) [16]	Nested case-control (LC-MS)	At delivery (37-42 weeks GA)	Plasma (non-fasting)	18/296	Canadian Diabetes Association 2008 practice guideline (24-28 weeks GA)	None	None	Pyridoxal 5' phosphate, choline, dimethylglycine, betaine, trimethylamine N-oxide, homocysteine, folic acid
Lu, 2018 Germany [66]	(FIA–ESI–MS/MS)	Time of birth	Serum	31/381	German Diabetes Association and German Association for	acylcarnitine (C4:1), diacyl-phosphatidyl-cholines (PC cc 36:5, PC aa C36:6), acyl-alkyl-phosphatidyl-cholines (Pc ae C38:0, 38:3, 40:1, 40:5), sum of hexoses	None	163 total metabolites measured: 40 acylcarnitines, 14 amino acids, hexoses, 92 glycerophospholipids (15 LPCs and 77 phosphatidylcholines), and 15 sphingolipids) [NS]

16

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

					Gynecology and Obstetrics			
Chu, 2020 Singapore [67]	Nested case-control (LC-MS)	PP	Placenta	154/845	WHO-1999 criteria (dx at 26 weeks GA)	Inositol	No other metabolites measured	

* Same study population, but different bio-specimens (counted as 1 study).

Abbreviations: GA = gestational age; PP = post partum; NS = not significant; US = United States of America; IADPSG = International Association of Diabetes and Pregnancy Study Groups; WHO = World Health Organization; GC-MS = gas chromatography/mass spectrometry; LC-MS = liquid chromatography/mass spectrometry; CE-MS = capillary electrophoresis/mass spectrometry; UPLC-MS = ultra-performance liquid chromatography–mass spectrometry; UHPLC-MS = ultra-high-performance liquid chromatography–mass spectrometry; HPLC = High-performance liquid chromatography; ^{1}H NMR = high resolution proton nuclear magnetic resonance; SRM-MS = semiquantitative selected reaction monitoring mass spectroscopy; HPLC–MS/MS = high pressure liquid chromatography coupled with triple quadrupole tandem mass spectrometry; FIA–ESI–MS/MS = flow injection analysis–electrospray ionization– tandem mass spectrometry; LCQ-TOF-MS = liquid chromatography coupled with quadrupole time-of-flight mass spectrometry; GC-TOF/MS = gas chromatography–time-of-flight mass spectrometry; DI-MS = direct infusion mass spectrometry; UPLC-TQ-MS = ultra-performance liquid chromatography coupled with tandem quadrupole mass spectrometry; UHRQ-TOF-MS = ultra-high resolution quadrupole time-of-flight mass spectrometry; HICT-MS = hydrophilic interaction chromatography tandem mass spectrometry; HILIC-MS = hydrophilic interaction liquid chromatography coupled with tandem mass-spectrometry; SFAs = saturated fatty acids; NEFAs = non-esterified fatty acids.

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

Supplemental Table S2.

Key characteristics of studies up to November 2020 investigating metabolites associated with GDM (n = 61 studies)

Characteristic	N studies (%)	Range in # of GDM cases
GDM cases		
Conducted using < 80 GDM cases	48 (78.7)	8-80
Country		
China	18 (30.0)	12-533
Japan	1 (1.6)	121
Singapore	1 (1.6)	154
New Zealand	2 (3.3)	11-22
United States	7 (11.5)	8-96
Mexico	1 (1.6)	24
Canada	3 (5.0)	13-50
United Kingdom	3 (5.0)	18-8774
Poland	7 (11.5)	18-56
Germany	2 (3.3)	9-31
Italy	3 (5.0)	14-17
Portugal	3 (5.0)	23-42
Sweden	1 (1.6)	11
Norway	1 (1.6)	79
Greece	1 (1.6)	25
Northern Europe	1 (1.6)	67
Turkey	4 (6.6)	28-58
Israel	1 (1.6)	29
Iran	1 (1.6)	27
Fasting status when metabolites measured		
Fasting	34 (55.7)	8-8774
Non-fasting	7 (11.5)	18-50
Fasting not typical (placenta, amniotic fluid, hair bio-specimens)	4 (6.5)	11-154
Unclear	15 (24.6)	14-249
Both fasting and non-fasting	1 (1.6)	12
Metabolite collection time*		
Prior to GDM diagnosis	25 (41.0)	14-533
After or at same time as GDM diagnosis	39 (63.9)	8-8774
During delivery or postpartum (< 2 years postpartum)	11 (18.0)	8-154
GDM diagnostic method		
IADPSG	18 (29.5)	9-533
WHO criteria (years 1998, 1999, 2013)	14 (23.0)	18-8774
Carpenter–Coustan criteria	9 (14.8)	13-96
Associations (e.g., Canadian Diabetes Association, Polish Gynecological Society)	11 (18.0)	11-107
Other (O'Sullivan and Mahan criteria, self-report, hospital records)	4 (6.6)	8-121
Not reported	5 (8.2)	12-27

*One study can measure same metabolites at different gestational ages.

18

Supplemental Table S3.

Fasting serum metabolites measured in START (n = 63) and FAMILY (n = 62) using MSI-CE-MS

Metabolite	*m/z*:RMT:mode	HMBD ID or Molecular Formula/mass error	Identification Level
2-Aminooctanoic acid	160.133:0.714:p	HMDB0000991	2
2-Hydroxybutyric acid	103.040:1.295:n	HMDB0000008	1
3-Hydroxybutyric acid	103.040:0.950:n	HMDB0000357	1
3-Methyl-2-oxovaleric acid	129.056:1.268:n	HMDB0000491	1
3-Methylhistidine	170.092:0.643:p	HMDB0000479	1
Acetylcarnitine	204.123:0.765:p	HMDB0000201	1
Alpha-ketoisovaleric acid	115.040:1.340:n	HMDB0000019	1
Alanine	90.056:0.762:p	HMDB0000161	1
Aminoadipic acid	162.076:0.918:p	HMDB0000510	1
Arginine	175.119:0.609:p	HMDB0000517	1
Asparagine	133.057:0.887:p	HMDB0000168	1
Aspartic acid	134.044:0.974:p	HMDB0000191	1
Asymmetric-dimethylarginine	203.150:0.645:p	HMDB0001539	1
Carnitine	162.112:0.723:p	HMDB0000062	1
Choline	104.108:0.578:p	HMDB0000097	1
Citric acid	191.020:2.519:n	HMDB0000094	1
Citrulline	176.102:0.936:p	HMDB0000904	1
Creatine	132.077:0.748:p	HMDB0000064	1
Creatinine	114.066:0.621:p	HMDB0000562	1
Cysteinylglycine disulfide	298.053:0.808:p	HMDB0000709	2
Cystine	241.030:0.934:p	HMDB0000192	1
Dimethylglycine	104.071:0.808:p	HMDB0000092	1
γ-Butyrobetaine	146.118:0.690:p	HMDB0001161	1
Gluconic acid	195.052:1.160:n	HMDB0000625	1
Glucose	179.056:0.999:n	HMDB0000122	1
Glutamic acid	148.060:0.925:p	HMDB0000148	1
Glutamine	147.076:0.911:p	HMDB0000641	1
Glycine	76.039:0.710:p	HMDB0000123	1
Guanidinoacetic acid	118.053:0.701:p	HMDB0000128	2
Hippuric acid	178.051:1.134:n	HMDB0000714	1
Histidine	156.077:0.628:p	HMDB0000177	1
Hypoxanthine	137.046:1.077:p	HMDB0000157	1
Isoleucine	132.102:0.846:p	HMDB0000172	1
Lactic acid	89.025:1.412:n	HMDB0000190	1
Leucine	132.102:0.856:p	HMDB0000687	1
Lysine	147.113:0.588:p	HMDB0000182	1
Malic acid	133.014:2.293:n	HMDB0000744	1
Methionine	150.058:0.897:p	HMDB0000696	1
Monomethylarginine	189.134:0.613:p	HMDB0029416	1
Ornithine	133.097:0.586:p	HMDB0000214	1
Oxo-proline	128.035:1.262:n	HMDB0000267	1
Phenylacetylglutamine	263.104:1.087:n	HMDB0006344	1
Phenylalanine	166.086:0.925:p	HMDB0000159	1

19

Pipecolic acid	130.086:0.588:p	HMDB0000070	2
Proline	116.070:0.907:p	HMDB0000162	1
Proline betaine	144.099:0.962:p	HMDB0004827	1
Propionylcarnitine	218.114:0.790:p	HMDB0000824	1
Pyruvic acid	87.009:1.629:n	HMDB0000243	1
Serine	106.050:0.846:p	HMDB0000187	1
Symmetric-dimethylarginine	203.1450:0.657:p	HMDB0003334	1
Taurine	124.007:0.990:n	HMDB0000251	2
Threonine	120.065:0.887:p	HMDB0000167	1
Trimethylamine N-oxide	76.077:0.555:p	HMDB0000925	1
Tryptophan	205.097:0.925:p	HMDB0030396	1
Tryptophan betaine	247.144:1.153:p	HMDB0061115	1
Tyrosine	182.081:0.956:p	HMDB0000158	1
Unknown singly charged ion[*]	129.066:0.739:p	$C_5H_8N_2O_2$/7.7 ppm	3
Unknown[†]	334.688:0.805:p	$C_{20}H_{47}N_{18}O_6S$/3.6 ppm	3
Unknown[‡]	471.738:0.888:p	$C_{30}H_{55}N_{25}O_{11}$/9.6 ppm	4
Unknown singly charged ion, identified as 2-hydroxyvaleric acid	117.056:1.244:n	$C_5H_{10}O_3$/0 ppm	3
Uric acid	167.021:1.198:n	HMDB0000289	1
Valine	118.086:0.835:p	HMDB0000883	1
Xanthine	151.026:1.192:n	HMDB0000292	2

* Identified as a cation amino acid analog (see reference 68).

† Not measured in FAMILY. Unknown identified as a doubly charged peptide, containing histidine, proline, and leucine.

‡ Unknown identified as a doubly charged peptide, containing alanine, glutamic acid, and histidine.

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

Supplemental Table S4.

Metabolites that were significantly associated with GDM status (univariate p < 0.10)

1. Glucose
2. Glutamic acid
3. Glutamine
4. 2-Aminooctanoic acid
5. Creatinine
6. Ornithine
7. Proline betaine
8. Arginine
9. Acetylcarnitine
10. Tryptophan
11. Oxo-proline
12. Propionylcarnitine
13. Cystine
14. Pyruvic acid
15. Citric acid
16. 2-Hydroxybutyric acid
17. 3-Hydroxybutyric acid
18. 3-methyl-2-oxovaleric acid
19. Unknown m/z: 129.066 ($C_5H_8N_2O_2$), identified as a cation amino acid analog (see reference 68)
20. Unknown m/z: 417.738 (most likely molecular formula: $C_{30}H_{55}N_{25}O_{11}$), identified as a doubly charged peptide, containing alanine, glutamic acid, and histidine
21. Glucose-to-creatinine ratio
22. Glucose-to-glutamine ratio
23. Glutamic acid-to-glutamine ratio
24. Alanine-to-glycine ratio
25. Leucine-to-glutamine ratio
26. Valine-to-glutamine ratio
27. Arginine-to-ornithine ratio
28. Citrulline-to-ornithine ratio

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

Supplemental Table S5

Median (IQR) metabolite concentrations (micromoles, µmol), metabolites with univariate p <0.10, IADPSG diagnostic criteria, START and FAMILY

Metabolite*	Overall (n = 590)		START (n = 299)		FAMILY (n = 291)	
	GDM (n = 133)	No GDM (n = 457)	GDM (n = 81)	No GDM (n = 218)	GDM (n = 52)	No GDM (n = 239)
Glucose	5114.87 (738.09)	4745.30 (521.87)	5222.57 (781.83)	4819.01 (459.05)	5072.33 (606.09)	4667.12 (603.38)
Glutamic acid	86.57 (36.71)	79.59 (32.85)	84.17 (35.06)	76.03 (33.18)	90.59 (37.62)	81.19 (34.76)
Glutamine	490.37 (153.31)	494.14 (129.33)	487.59 (166.65)	493.15 (138.37)	495.14 (154.82)	495.57 (125.26)
Creatinine	27.23 (10.19)	29.70 (10.34)	26.41 (8.55)	26.62 (9.79)	29.40 (10.41)	31.47 (8.48)
Ornithine	32.64 (16.18)	38.25 (15.01)	31.01 (11.02)	32.92 (15.84)	36.19 (17.27)	41.03 (13.09)
Proline betaine	1.38 (3.47)	1.96 (3.82)	1.27 (2.48)	1.61 (2.42)	1.69 (6.07)	2.45 (5.30)
Arginine	111.02 (50.38)	100.52 (46.41)	124.27 (64.75)	120.73 (68.9)	95.41 (36.06)	88.71 (27.52)
Acetylcarnitine	2.15 (0.75)	2.05 (0.80)	2.15 (0.78)	2.17 (0.87)	2.17 (0.59)	1.95 (0.70)
Tryptophan	27.32 (2.83)	26.59 (2.58)	26.59 (3.16)	26.10 (2.71)	28.09 (2.01)	26.85 (2.24)
Oxo-proline	22.51 (7.69)	24.57 (8.22)	21.54 (6.41)	22.26 (8.93)	24.52 (8.00)	25.41 (6.75)
Propionylcarnitine	3.03 (0.70)	2.87 (0.56)	3.10 (0.73)	2.97 (0.75)	2.89 (0.52)	2.82 (0.39)
Cystine	14.18 (5.62)	16.57 (5.52)	13.01 (0.93)	13.11 (1.19)	18.71 (1.83)	18.5 (1.88)
Pyruvic acid	133.05 (60.64)	115.34 (64.42)	112.00 (57.38)	102.45 (65.13)	149.86 (63.30)	124.95 (61.20)
Citric acid	187.92 (73.75)	169.89 (66.65)	187.91 (90.14)	159.58 (86.56)	197.12 (63.66)	176.79 (57.34)
2-Hydroxybutyric acid	58.48 (25.67)	49.77 (23.27)	52.30 (24.30)	48.36 (22.86)	65.59 (29.60)	51.49 (26.68)
3-Hydroxybutyric acid	140.97 (45.34)	123.10 (43.95)	140.81 (41.79)	120.93 (34.15)	143.15 (50.20)	126.73 (49.03)
3-methyl-2-oxovaleric acid	38.53 (16.86)	35.19 (13.15)	38.14 (17.04)	36.77 (13.69)	40.29 (14.31)	33.54 (11.76)
Glucose-to-creatinine ratio	183.63 (61.23)	159.70 (59.06)	192.57 (71.78)	181.55 (59.42)	170.03 (62.95)	145.69 (42.39)
Glucose-to-glutamine ratio	10.61 (3.12)	9.46 (2.20)	10.95 (3.27)	9.7 (2.31)	10.41 (2.88)	9.35 (1.99)
Arginine-to-ornithine ratio	3.43 (2.64)	2.75 (1.87)	4.10 (2.41)	3.93 (2.20)	2.45 (1.24)	2.15 (0.97)
Citrulline-to-ornithine ratio	0.62 (0.30)	0.57 (0.23)	0.65 (0.27)	0.63 (0.31)	0.57 (0.29)	0.53 (0.17)
Alanine-to-glycine ratio	1.82 (0.46)	1.75 (0.49)	1.80 (0.57)	1.79 (0.46)	1.86 (0.40)	1.67 (0.51)
Glutamic acid-to-glutamine ratio	0.19 (0.08)	0.16 (0.08)	0.18 (0.08)	0.15 (0.07)	0.19 (0.08)	0.16 (0.08)
Valine-to-glutamine ratio	0.46 (0.13)	0.42 (0.12)	0.47 (0.13)	0.42 (0.11)	0.45 (0.18)	0.43 (0.11)
Leucine-to-glutamine ratio	0.14 (0.05)	0.13 (0.03)	0.14 (0.04)	0.14 (0.03)	0.14 (0.04)	0.13 (0.03)

*Concentrations not available for 2-aminooctanoic acid, or unknowns (129.066 and 417:738)

22

Supplemental Table S6.

Results of k-fold cross validation for relationship between metabolites and GDM, adjusted for ethnicity, maternal age, maternal height, pre-pregnancy BMI, gestational age at recruitment family history of diabetes, smoking history, and diet quality (k = 10), START and FAMILY (n = 590)

Metabolite	AUC (SD)	Sensitivity (SD)	Specificity (SD)	Accuracy (SD)	Kappa (SD)
Glucose	0.75 (0.06)	0.94 (0.04)	0.22 (0.12)	0.79 (0.03)	0.22 (0.12)
Glutamic acid	0.71 (0.07)	0.96 (0.05)	0.16 (0.10)	0.79 (0.03)	0.18 (0.14)
Glutamine	0.70 (0.05)	0.97 (0.02)	0.17 (0.10)	0.78 (0.04)	0.16 (0.14)
2-Aminooctanoic acid	0.70 (0.11)	0.97 (0.03)	0.16 (0.13)	0.79 (0.03)	0.17 (0.13)
Creatinine	0.71 (0.06)	0.97 (0.02)	0.17 (0.11)	0.79 (0.03)	0.17 (0.14)
Ornithine	0.70 (0.07)	0.96 (0.02)	0.17 (0.08)	0.78 (0.04)	0.17 (0.13)
Proline betaine	0.70 (0.08)	0.97 (0.03)	0.16 (0.13)	0.79 (0.02)	0.17 (0.11)
Arginine	0.71 (0.09)	0.97 (0.03)	0.13 (0.07)	0.78 (0.03)	0.14 (0.14)
Acetylcarnitine	0.70 (0.12)	0.97 (0.03)	0.16 (0.11)	0.78 (0.03)	0.16 (0.11)
Tryptophan	0.70 (0.08)	0.96 (0.02)	0.17 (0.11)	0.78 (0.04)	0.18 (0.17)
Oxo-proline	0.71 (0.09)	0.96 (0.04)	0.17 (0.09)	0.78 (0.04)	0.17 (0.15)
Propionylcarnitine	0.71 (0.08)	0.96 (0.03)	0.17 (0.12)	0.79 (0.03)	0.19 (0.11)
Cystine	0.71 (0.09)	0.97 (0.03)	0.17 (0.06)	0.78 (0.03)	0.17 (0.10)
Pyruvic acid	0.71 (0.11)	0.96 (0.04)	0.19 (0.12)	0.78 (0.03)	0.15 (0.13)
Citric acid	0.70 (0.07)	0.97 (0.03)	0.16 (0.06)	0.79 (0.03)	0.18 (0.15)
2-Hydroxybutyric acid	0.72 (0.09)	0.97 (0.03)	0.17 (0.10)	0.78 (0.03)	0.15 (0.12)
3-Hydroxybutyric acid	0.71 (0.09)	0.97 (0.04)	0.18 (0.07)	0.78 (0.03)	0.16 (0.16)
3-methyl-2-oxovaleric acid	0.72 (0.09)	0.97 (0.03)	0.14 (0.07)	0.78 (0.02)	0.14 (0.12)
$C_5H_8N_2O_2$ (129.066)[*]	0.71 (0.09)	0.97 (0.03)	0.18 (0.05)	0.79 (0.03)	0.19 (0.10)
$C_{30}H_{55}N_{25}O_{11}$ (417.738)[†]	0.70 (0.06)	0.97 (0.02)	0.16 (0.07)	0.79 (0.03)	0.17 (0.15)
Glucose-to-glutamine ratio	0.76 (0.07)	0.95 (0.04)	0.25 (0.10)	0.79 (0.03)	0.23 (0.14)
Glutamic acid-to-glutamine ratio	0.72 (0.08)	0.96 (0.04)	0.20 (0.11)	0.79 (0.04)	0.18 (0.22)
Alanine-to-glycine ratio	0.69 (0.12)	0.97 (0.02)	0.17 (0.08)	0.79 (0.03)	0.17 (0.16)
Leucine-to-glutamine ratio	0.70 (0.07)	0.97 (0.03)	0.18 (0.16)	0.78 (0.04)	0.17 (0.13)
Valine-to-glutamine ratio	0.71 (0.10)	0.97 (0.03)	0.16 (0.11)	0.78 (0.03)	0.16 (0.16)
Glucose-to-creatinine ratio	0.73 (0.09)	0.95 (0.04)	0.19 (0.05)	0.78 (0.03)	0.18 (0.10)
Arginine-to-ornithine ratio	0.71 (0.07)	0.96 (0.03)	0.14 (0.09)	0.78 (0.03)	0.15 (0.10)
Citrulline-to-ornithine ratio	0.71 (0.10)	0.97 (0.03)	0.15 (0.12)	0.78 (0.03)	0.170.07)

* Unknown identified as a cation amino acid analog (see reference 68), reported as most likely molecular formula (*m/z*)
† Unknown identified as a doubly charged peptide, containing alanine, glutamic acid, and histidine, reported as most likely molecular formula (m/z)

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance
placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

Supplemental Table S7.

Ethnic-specific associations between metabolites and odds of GDM (95% CI), per 1-SD log-transformed metabolite RPA, IADPSG diagnostic criteria

Metabolite	Overall, START and FAMILY, adjusted[*] (n = 590)	START, South Asian women, adjusted[†] (n = 299)	FAMILY, white European women, adjusted[†] (n = 291)	p-value for ethnicity interaction unadjusted	p-value for ethnicity interaction adjusted[†]
Glucose	2.07 (1.58-2.71)	2.22 (1.54-3.20)	1.95 (1.30-2.92)	0.64	0.71
Glutamic acid	1.35 (1.08-1.69)	1.48 (1.11-1.98)	1.18 (0.82-1.69)	0.50	0.46
Glutamine	0.86 (0.70-1.06)	0.79 (0.61-1.02)	1.02 (0.70-1.50)	0.46	0.29
2-Aminooctanoic acid	1.09 (0.87-1.37)	1.13 (0.86-1.49)	0.98 (0.64-1.50)	0.55	0.62
Creatinine	0.92 (0.74-1.14)	1.02 (0.79-1.33)	0.70 (0.46-1.07)	0.12	0.12
Ornithine	0.83 (0.67-1.03)	0.89 (0.69-1.15)	0.66 (0.42-1.01)	0.08	0.25
Proline betaine	0.97 (0.78-1.21)	0.99 (0.74-1.32)	0.94 (0.66-1.34)	0.42	0.78
Arginine	1.10 (0.87-1.40)	1.01 (0.77-1.34)	1.43 (0.87-2.35)	0.17	0.23
Acetylcarnitine	1.05 (0.83-1.31)	0.95 (0.72-1.25)	1.28 (0.83-1.96)	0.07	0.24
Tryptophan	1.17 (0.95-1.45)	1.14 (0.88-1.48)	1.21 (0.81-1.79)	0.07	0.67
Oxo-proline	0.86 (0.69-1.06)	0.90 (0.71-1.15)	0.69 (0.44-1.09)	0.66	0.37
Propionylcarnitine	1.35 (1.08-1.69)	1.25 (0.99-1.58)	1.63 (1.11-2.41)	0.06	0.11
Cystine	0.77 (0.57-1.04)	0.75 (0.56-1.02)	1.20 (0.85-1.69)	**0.02**	0.17
Pyruvic acid	1.31 (1.04-1.63)	1.23 (0.95-1.59)	1.61 (1.01-2.57)	**0.04**	0.30
Citric acid	1.03 (0.85-1.26)	1.04 (0.85-1.27)	1.00 (0.44-2.25)	0.63	0.97
2-Hydroxybutyric acid	1.44 (1.15-1.81)	1.39 (1.04-1.86)	1.51 (1.03-2.20)	0.43	0.76
3-Hydroxybutyric acid	1.31 (1.04-1.67)	1.29 (0.94-1.76)	1.33 (0.92-1.93)	0.93	0.73
3-methyl-2-oxovaleric acid	1.28 (1.03-1.57)	1.14 (0.88-1.48)	1.54 (1.07-2.21)	**0.02**	0.16
$C_5H_8N_2O_2$ (129.066)[‡]	0.76 (0.60-0.95)	0.68 (0.51-0.91)	0.88 (0.61-1.26)	**0.04**	0.32
$C_{30}H_{55}N_{25}O_{11}$ (417.738)[§]	0.98 (0.74-1.30)	0.86 (0.60-1.24)	1.18 (0.76-1.82)	0.10	0.27
Glucose-to-glutamine ratio	2.15 (1.65-2.80)	2.41 (1.70-3.41)	1.88 (1.22-2.89)	0.79	0.52
Glutamic acid-to-glutamine ratio	1.46 (1.16-1.83)	1.73 (1.28-2.33)	1.15 (0.80-1.65)	0.18	0.18
Alanine-to-glycine ratio	1.14 (0.92-1.42)	0.91 (0.69-1.21)	1.66 (1.13-2.43)	**0.01**	**0.02**
Leucine-to-glutamine ratio	1.03 (0.84-1.26)	0.99 (0.81-1.22)	1.59 (0.74-3.42)	0.20	0.26
Valine-to-glutamine ratio	1.16 (0.94-1.44)	1.24 (0.95-1.63)	1.04 (0.72-1.50)	0.41	0.47
Glucose-to-creatinine ratio	1.79 (1.39-2.32)	1.53 (1.13-2.09)	2.51 (1.56-4.02)	0.07	0.08
Arginine-to-ornithine ratio	1.34 (1.03-1.75)	1.14 (0.84-1.56)	2.17 (1.25-3.74)	**0.02**	0.06
Citrulline-to-ornithine ratio	1.22 (0.99-1.51)	1.11 (0.87-1.42)	1.60 (1.03-2.48)	**0.03**	0.19

* Adjusted for adjusted for ethnicity, maternal age, maternal height, pre-pregnancy BMI, gestational age at recruitment, family history of diabetes, smoking history, and diet quality
† Adjusted for maternal age, maternal height, pre-pregnancy BMI, gestational age at recruitment, family history of diabetes, smoking history, and diet quality
‡ Unknown identified as a cation amino acid analog (see reference 68), reported as most likely molecular formula (m/z)
§ Unknown identified as a doubly charged peptide, containing alanine, glutamic acid, and histidine, reported as most likely molecular formula (m/z)

24

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

Supplemental Table S8.

Metabolic pathways significantly impacted by GDM, with p < 0.05 and impact > 0.10, sorted by impact, KEGG database, by cohort

Pathway name	Cohort	Significant metabolites	Measured metabolites	Total metabolites	Metabolites Involved	p-value	FDR	Impact
a. Pathways significant in both START and FAMILY studies (tested independently in each cohort) (n = 6)								
Alanine, aspartic acid, and glutamic acid metabolism*	START	4	7	28	Glutamic acid, glutamine, citric acid, alanine, pyruvic acid, aspartic acid, asparagine	0.022	0.077	0.56
	FAMILY					0.029	0.068	0.56
Glyoxylic acid and dicarboxylic acid metabolism*	START	4	6	32	Glutamic acid, glutamine, glycine, citric acid, serine, pyruvic acid	0.021	0.077	0.23
	FAMILY					0.011	0.039	0.23
Production of ketone bodies*	START	1	1	5	3-hydroxybutyric acid	0.022	0.077	0.14
	FAMILY					0.013	0.040	0.14
Butyric acid metabolism*	START	2	2	15	Glutamic acid, 3-hydroxybutyric acid	0.001	0.009	0.13
	FAMILY					0.014	0.041	0.13
Glutathione metabolism*	START	1	4	28	Glutamic acid, ornithine, 5-oxoproline, glycine	0.038	0.113	0.12
	FAMILY					0.019	0.047	0.12
Glycolysis/Gluconeogenesis*	START	3	3	26	Glucose, pyruvic acid, lactic acid	<0.001	<0.001	0.10
	FAMILY					<0.001	<0.001	0.10
b. Pathways significant in South Asian women (START Study) only (n = 4)								
Arginine biosynthesis*		2	6	14	Glutamic acid, glutamine, aspartic acid, arginine, ornithine, citrulline	0.022	0.077	0.56
Glutamine and glutamic acid metabolism*		2	2	6	Glutamic acid, glutamine	0.001	0.009	0.50
Histidine metabolism*		1	4	16	Glutamic acid, histidine, aspartic acid, 3-methylhistitide	0.032	0.103	0.33
Nitrogen metabolism*		2	2	6	Glutamic acid, glutamine	0.001	0.009	0.25
c. Pathways significant in white European women (FAMILY Study) only (n = 8)								
Valine, leucine, and isoleucine biosynthesis*		1	6	8	Threonine, isoleucine, 3-methyl-2-oxovaleric acid, leucine, valine, α-ketoisovaleric acid	0.010	0.037	1.00
Glycine, serine, and threonine metabolism		2	8	33	Choline, pyruvic acid, dimethylglycine, glycine, threonine, serine, creatinine, guanidinoacetic acid	0.015	0.041	0.56
Arginine and proline metabolism*		3	7	38	Arginine, guanidinoacetic acid, creatine, proline, glutamic acid, ornithine, pyruvic acid	0.001	0.012	0.37
Pyruvic acid metabolism*		1	2	22	Pyruvic acid, lactic acid	0.005	0.024	0.21
Tryptophan metabolism*		1	1	41	Tryptophan	0.001	0.012	0.14
Tyrosine metabolism*		1	2	42	Pyruvic acid, tyrosine	0.003	0.014	0.14
Citric acid cycle (TCA cycle)*		2	2	20	Pyruvic acid, citric acid	0.002	0.014	0.14
Cysteine and methionine metabolism*		1	4	33	Serine, methionine, cysteine, pyruvic acid	0.003	0.014	0.13

* When both cohorts are analyzed together, this pathway is significant, p < 0.10 and impact > 0.10

25

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

Supplemental Table S9.

Associations between metabolites and odds of GDM (95% CI), per 1-SD log-transformed metabolite RPA, sensitivity analyses: a) unadjusted vs adjusted b) IADPSG vs. Born in Bradford criteria c) complete case vs. multiple imputation, among metabolites univariate p < 0.10 (n = 600)

Metabolite	IADPSG				BiB in START, IADPSG in FAMILY	
	Unadjusted, complete case	Adjusted*, complete case	Adjusted†, complete case	Adjusted*, multiple imputation (m = 10)	Unadjusted, complete case	Adjusted*, complete case
Glucose	2.25 (1.78-2.84)	2.07 (1.58-2.70)	2.07 (1.58-2.71)	1.99 (1.56-2.55)	1.99 (1.61-2.47)	1.73 (1.35-2.22)
Glutamic acid	1.37 (1.12-1.67)	1.34 (1.07-1.67)	1.35 (1.08-1.69)	1.27 (1.02-1.58)	1.29 (1.08-1.55)	1.31 (1.06-1.61)
Glutamine	0.78 (0.64-0.95)	0.86 (0.70-1.06)	0.86 (0.70-1.06)	0.85 (0.69-1.04)	0.77 (0.64-0.92)	0.84 (0.69-1.02)
2-Aminooctanoic acid	1.29 (1.06-1.57)	1.09 (0.87-1.37)	1.09 (0.87-1.37)	1.13 (0.90-1.40)	1.37 (1.14-1.65)	1.07 (0.86-1.32)
Creatinine	0.82 (0.68-1.00)	0.91 (0.74-1.14)	0.92 (0.74-1.14)	0.91 (0.74-1.13)	0.80 (0.67-0.96)	0.98 (0.80-1.20)
Ornithine	0.75 (0.63-0.91)	0.83 (0.67-1.03)	0.83 (0.67-1.03)	0.78 (0.63-0.97)	0.68 (0.57-0.81)	0.81 (0.66-0.99)
Proline betaine	0.85 (0.70-1.03)	0.97 (0.78-1.21)	0.97 (0.78-1.21)	0.95 (0.77-1.18)	0.84 (0.71-1.01)	1.02 (0.82-1.25)
Arginine	1.25 (1.03-1.51)	1.10 (0.87-1.40)	1.10 (0.87-1.40)	1.07 (0.85-1.36)	1.48 (1.24-1.77)	1.15 (0.92-1.43)
Acetylcarnitine	1.23 (1.01-1.49)	1.05 (0.83-1.31)	1.04 (0.83-1.31)	1.07 (0.86-1.32)	1.26 (1.05-1.51)	1.05 (0.85-1.30)
Tryptophan	1.24 (1.02-1.49)	1.17 (0.94-1.44)	1.17 (0.95-1.45)	1.20 (0.98-1.47)	1.25 (1.04-1.49)	1.30 (1.06-1.59)
Oxo-proline	0.81 (0.67-0.99)	0.86 (0.69-1.06)	0.86 (0.69-1.06)	0.85 (0.69-1.05)	0.77 (0.64-0.92)	0.85 (0.69-1.03)
Propionylcarnitine	1.38 (1.11-1.71)	1.35 (1.08-1.69)	1.35 (1.08-1.69)	1.36 (1.09-1.70)	1.33 (1.09-1.61)	1.30 (1.07-1.59)
Cystine	0.78 (0.65-0.93)	0.77 (0.57-1.03)	0.77 (0.57-1.04)	0.80 (0.60-1.08)	0.69 (0.58-0.82)	0.95 (0.72-1.25)
Pyruvic acid	1.32 (1.08-1.61)	1.31 (1.05-1.63)	1.31 (1.05-1.64)	1.30 (1.04-1.61)	1.18 (0.98-1.42)	1.25 (1.02-1.54)
Citric acid	1.02 (0.84-1.24)	1.03 (0.84-1.25)	1.03 (0.85-1.26)	1.04 (0.85-1.26)	1.09 (0.91-1.31)	1.16 (0.96-1.40)
2-Hydroxybutyric acid	1.40 (1.14-1.70)	1.44 (1.15-1.81)	1.44 (1.15-1.81)	1.41 (1.13-1.77)	1.19 (0.99-1.42)	1.26 (1.02-1.56)
3-Hydroxybutyric acid	1.35 (1.11-1.63)	1.28 (1.02-1.60)	1.32 (1.04-1.67)	1.21 (0.97-1.51)	1.33 (1.11-1.59)	1.34 (1.07-1.66)
3-methyl-2-oxovaleric acid	1.42 (1.17-1.72)	1.27 (1.03-1.57)	1.28 (1.03-1.57)	1.26 (1.03-1.55)	1.51 (1.26-1.81)	1.33 (1.09-1.62)
$C_5H_8N_2O_2$ (129.066)‡	0.71 (0.58-0.87)	0.75 (0.60-0.94)	0.75 (0.60-0.94)	0.77 (0.62-0.95)	0.75 (0.63-0.90)	0.81 (0.66-1.00)
$C_{30}H_{55}N_{25}O_{11}$ (417.738)§	1.19 (0.98-1.45)	0.99 (0.75-1.30)	0.98 (0.74-1.30)	1.01 (0.77-1.32)	1.48 (1.23-1.79)	1.07 (0.82-1.38)
Glucose-to-glutamine ratio	2.44 (1.94-3.09)	2.14 (1.65-2.78)	2.15 (1.65-2.80)	2.13 (1.65-2.75)	2.27 (1.83-2.81)	1.90 (1.48-2.43)
Glutamic acid-to-glutamine ratio	1.53 (1.25-1.87)	1.45 (1.16-1.82)	1.46 (1.16-1.83)	1.39 (1.12-1.74)	1.47 (1.22-1.76)	1.44 (1.16-1.79)
Alanine-to-glycine ratio	1.23 (1.01-1.50)	1.15 (0.92-1.43)	1.14 (0.92-1.42)	1.14 (0.92-1.41)	1.34 (1.12-1.61)	1.26 (1.02-1.55)
Leucine-to-glutamine ratio	1.04 (0.85-1.27)	1.03 (0.84-1.26)	1.03 (0.84-1.26)	1.03 (0.85-1.26)	1.06 (0.88-1.28)	1.08 (0.89-1.30)
Valine-to-glutamine ratio	1.22 (1.01-1.48)	1.17 (0.94-1.44)	1.16 (0.94-1.44)	1.16 (0.94-1.43)	1.23 (1.03-1.47)	1.17 (0.96-1.43)
Glucose-to-creatinine ratio	2.03 (1.63-2.53)	1.79 (1.39-2.32)	1.79 (1.39-2.32)	1.77 (1.38-2.27)	1.94 (1.58-2.38)	1.47 (1.16-1.86)
Arginine-to-ornithine ratio	1.46 (1.20-1.77)	1.34 (1.03-1.75)	1.34 (1.03-1.76)	1.39 (1.07-1.80)	1.80 (1.49-2.17)	1.43 (1.11-1.84)
Citrulline-to-ornithine ratio	1.28 (1.06-1.54)	1.21 (0.98-1.50)	1.22 (0.99-1.51)	1.30 (1.06-1.59)	1.36 (1.14-1.62)	1.22 (1.00-1.50)

* Adjustments: ethnicity, maternal age, maternal height, pre-pregnancy BMI, gestational age at recruitment, family history of diabetes, smoking history, and diet quality.
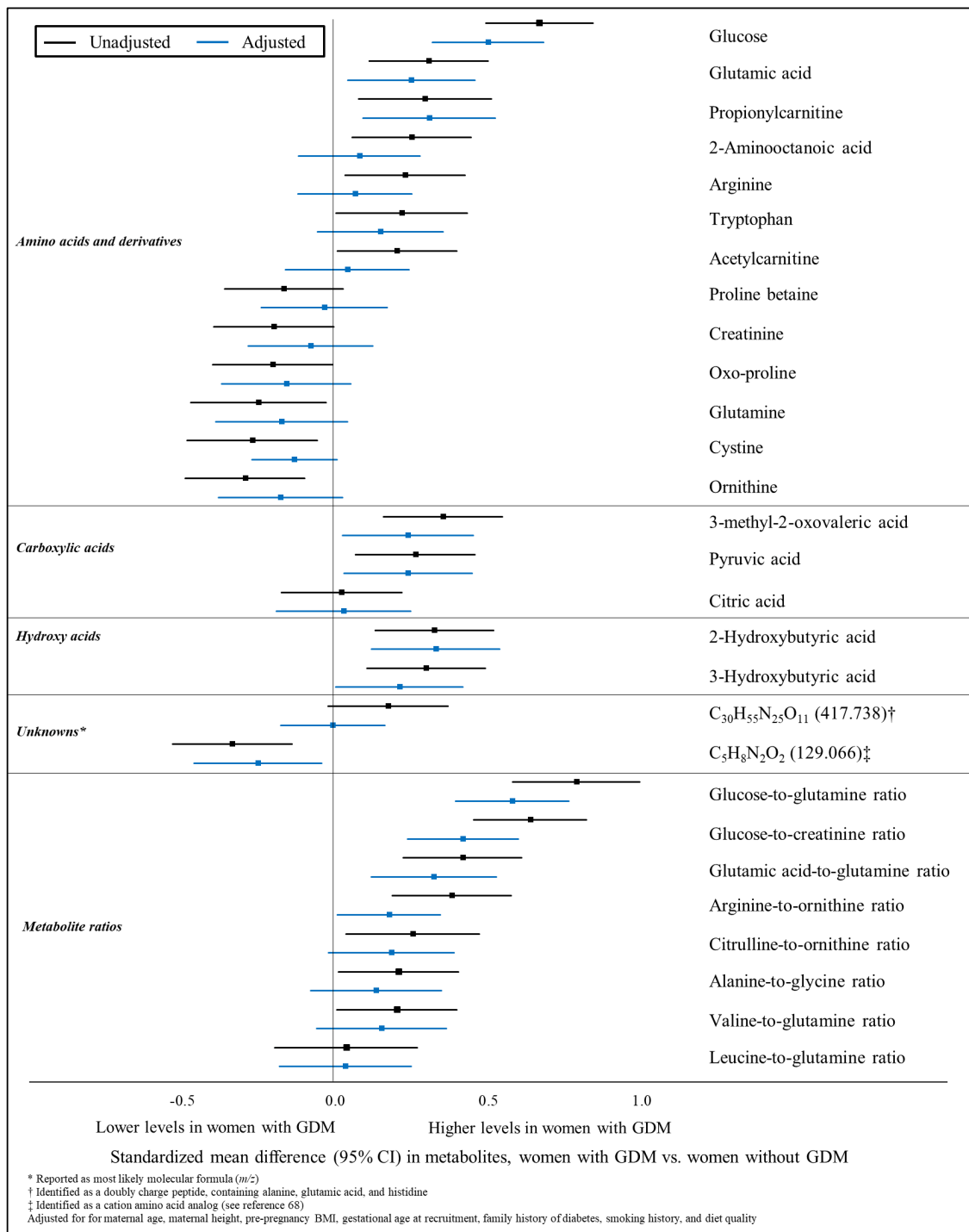
† Adjustments: ethnicity, maternal age, maternal height, pre-pregnancy BMI, gestational age at recruitment, family history of diabetes, smoking history, diet quality, and plant protein intake.
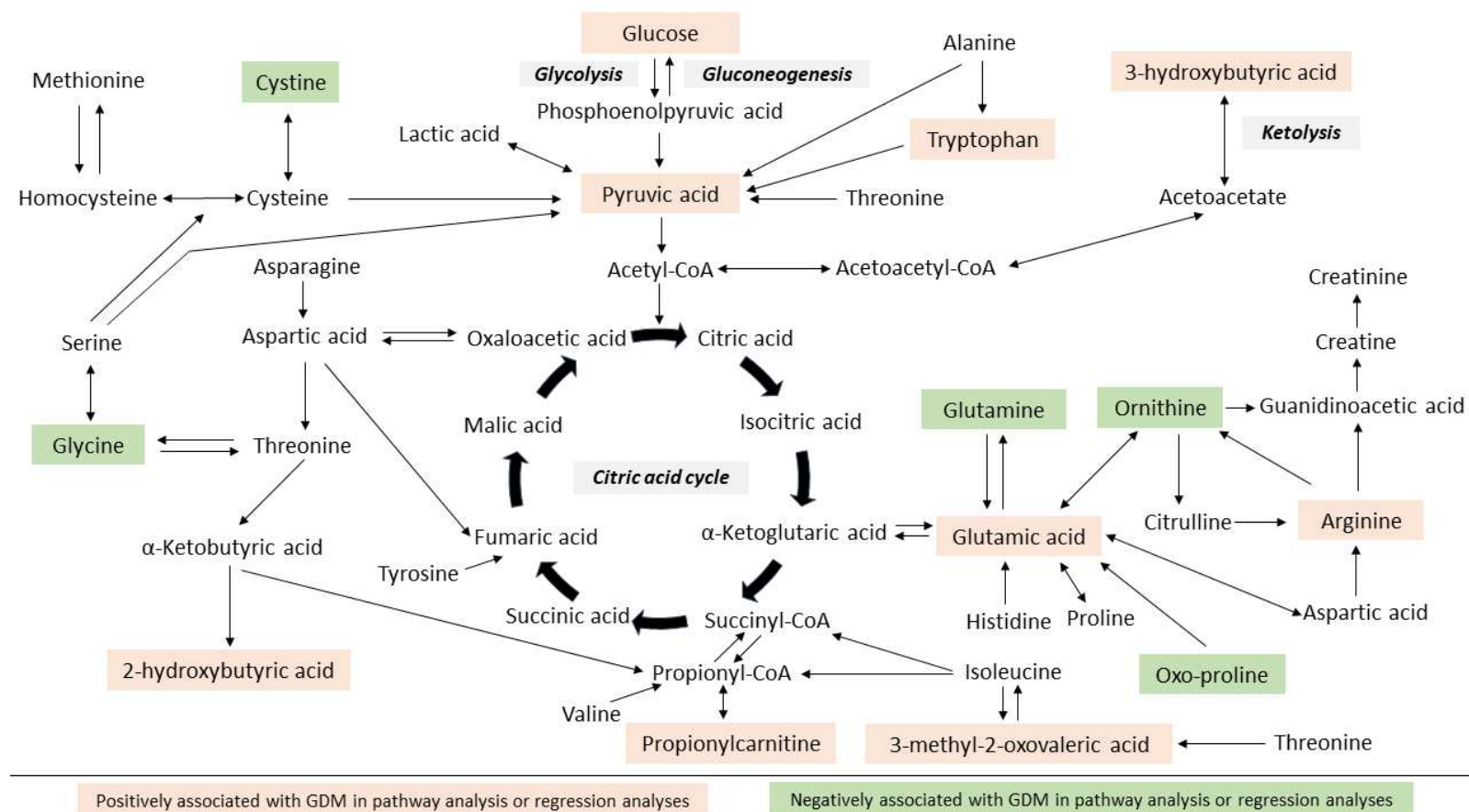
‡ Unknown identified as a cation amino acid analog (see reference 68), reported as most likely molecular formula (m/z).

§ Unknown identified as a doubly charged peptide, containing alanine, glutamic acid, and histidine, reported as most likely molecular formula (m/z).
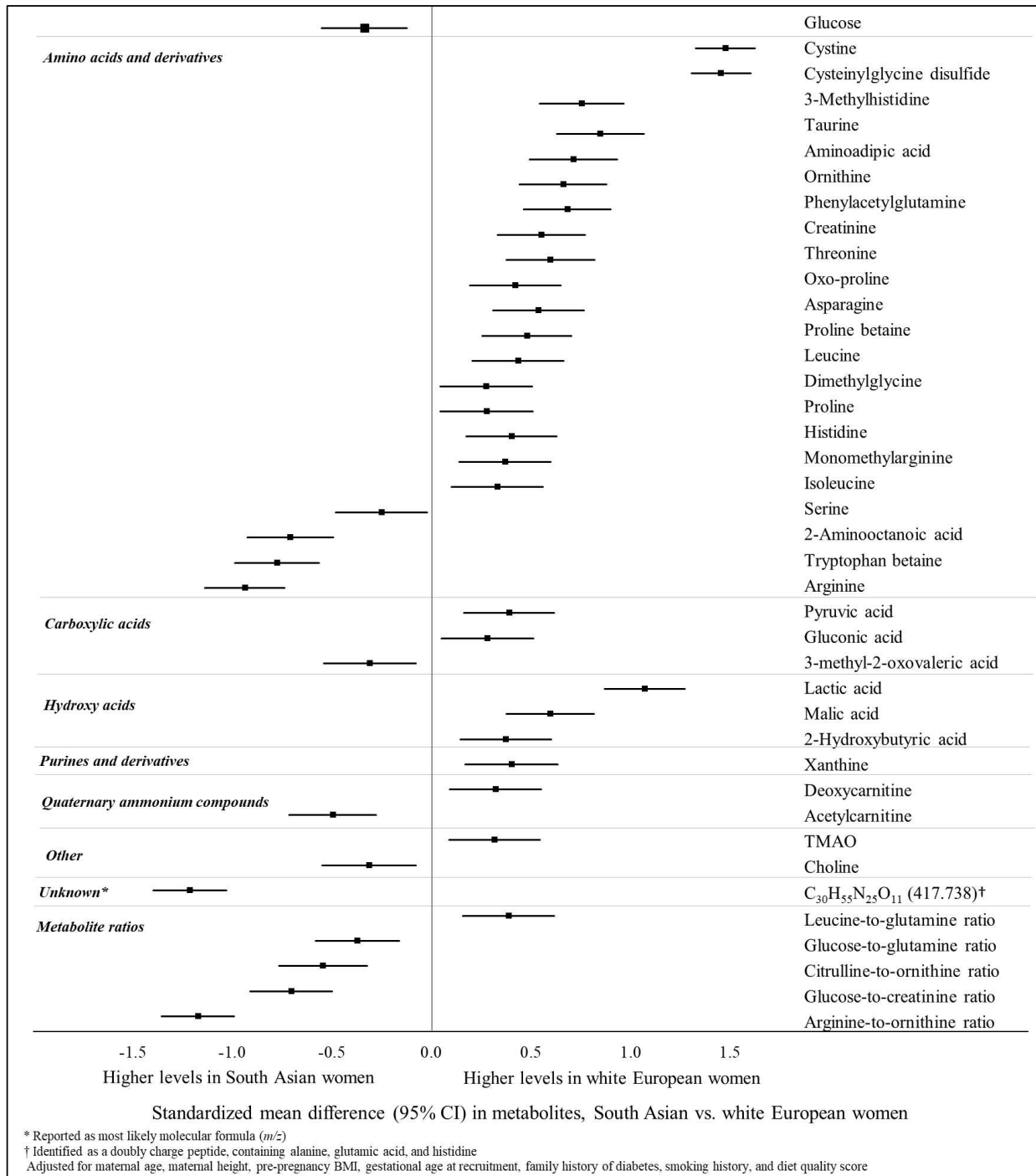
26

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

Supplemental Figure S1.

Standardized mean difference (95% CI) in serum metabolites, comparing women with GDM (n = 133) to women without GDM (n = 457), p < 0.05

* Reported as most likely molecular formula (m/z)
† Identified as a doubly charge peptide, containing alanine, glutamic acid, and histidine
‡ Identified as a cation amino acid analog (see reference 68)
Adjusted for for maternal age, maternal height, pre-pregnancy BMI, gestational age at recruitment, family history of diabetes, smoking history, and diet quality

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

Supplemental Figure S2.

Correlation plot of metabolites significantly associated with GDM (p < 0.10), IADPSG diagnostic criteria, START and FAMILY

*Unknowns, reported as most likely molecular formulas (*m/z*),: $C_5H_8N_2O_2$ (129.066) identified as a cation amino acid analog (see reference 68); $C_{30}H_{55}N_{25}O_{11}$ (417.738) was identified as a doubly charged peptide, containing alanine, glutamic acid, and histidine.

Supplemental Figure S3.

Schematic of the metabolic pathways, and their inter-relationships, associated with GDM in START and FAMILY

29

Supplemental Figure S4.

Standardized mean difference (95% CI) in serum metabolites among all women (n = 590), comparing South Asian (n = 299) to white European (n = 291) women, p < 0.05
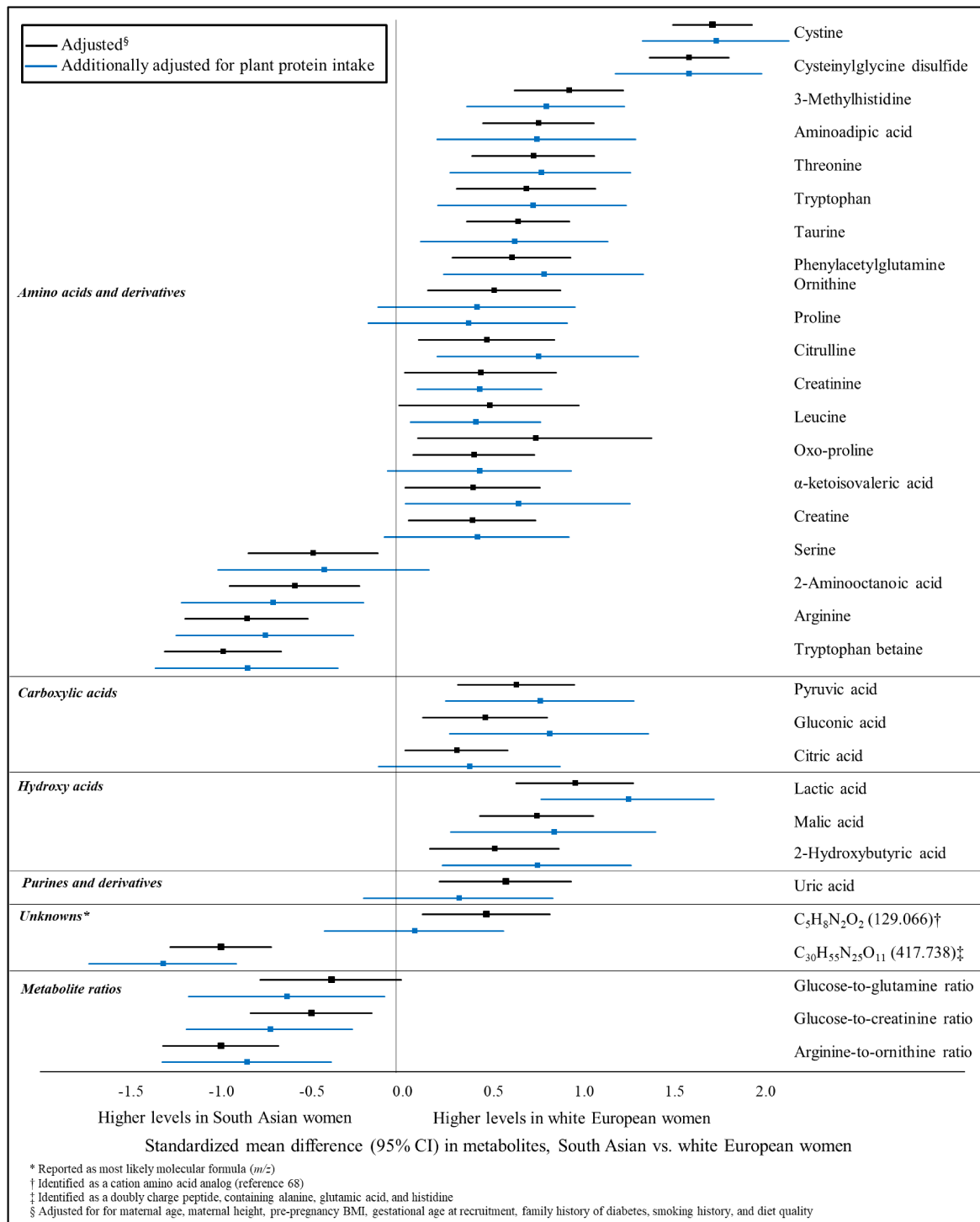

Standardized mean difference (95% CI) in metabolites, South Asian vs. white European women

* Reported as most likely molecular formula (*m/z*)

† Identified as a doubly charge peptide, containing alanine, glutamic acid, and histidine

Adjusted for maternal age, maternal height, pre-pregnancy BMI, gestational age at recruitment, family history of diabetes, smoking history, and diet quality score

30

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

Supplemental Figure S5.

Partial least-squares discriminant analysis (PLS-DA) results, scores plot and variable importance plot, among women with GDM (n = 133), IADPSG diagnostic criteria, comparing metabolites concentrations between South Asian (START study; n = 81) and white European women (FAMILY study; n = 52)

31

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

Supplemental Figure S6.

Standardized mean difference (95% CI) in serum metabolites among women with GDM (n = 133), comparing South Asian (n = 81) to white European (n = 52) women, p < 0.05

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance
placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

Supplemental Figure S7.

Partial least-squares discriminant analysis (PLS-DA) results, scores plot and variable importance plot, IADPSG diagnostic criteria, START and FAMILY
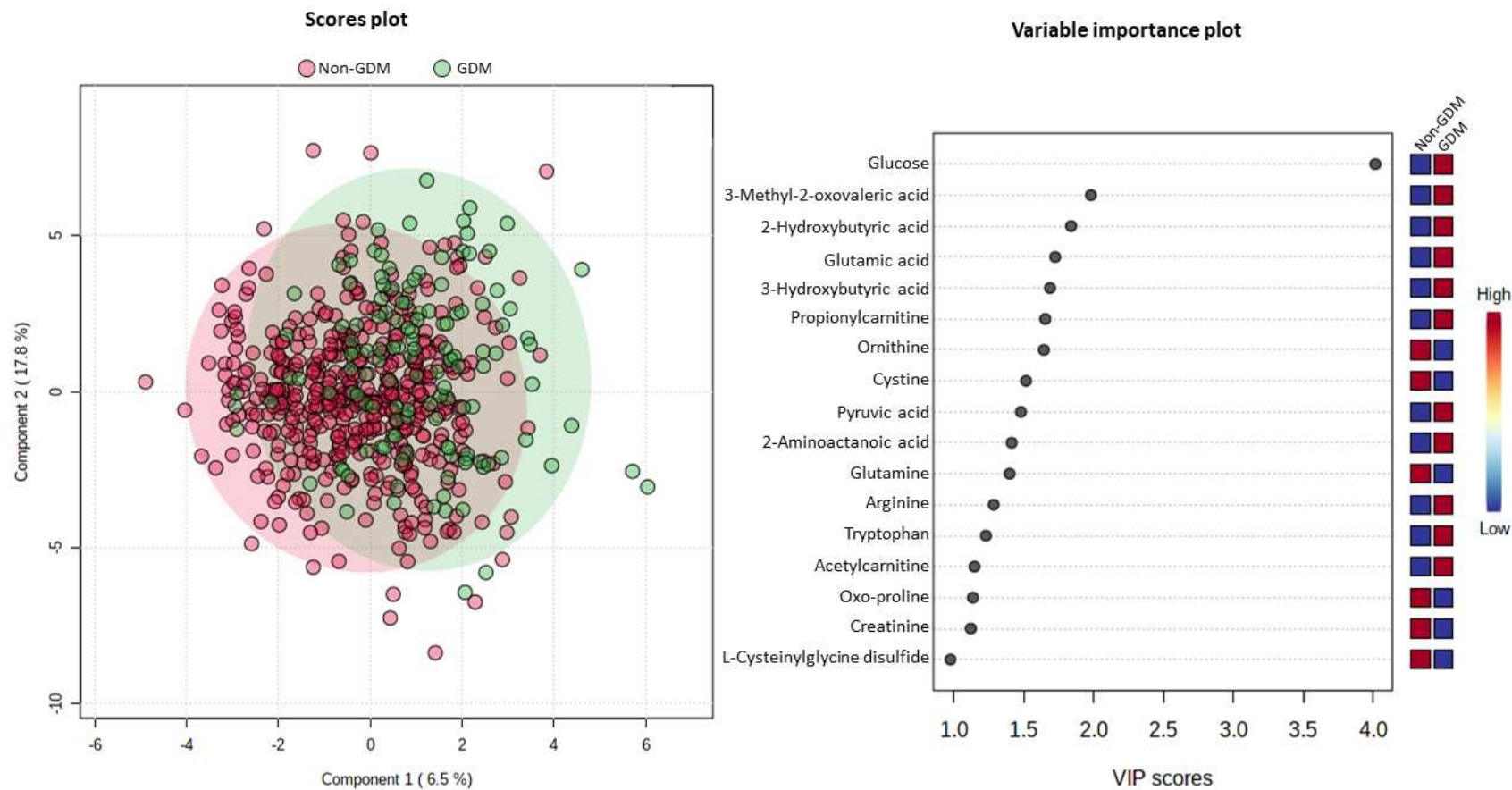
References

1. Huynh J, Xiong G, Bentley-Lewis R. A systematic review of metabolite profiling in gestational diabetes mellitus. Diabetologia. 2014 Dec 1;57(12):2453-64

2. Chen Q, Francis E, Hu G, Chen L. Metabolomic profiling of women with gestational diabetes mellitus and their offspring: review of metabolomics studies. Journal of Diabetes and its Complications. 2018 May 1;32(5):512-23.

3. Garner P, Hopewell S, Chandler J, MacLehose H, Akl EA, Beyene J, Chang S, Churchill R, Dearness K, Guyatt G, Lefebvre C. When and how to update systematic reviews: consensus and checklist. bmj. 2016 Jul 20;354.

4. Chen X, Scholl TO, Leskiw M, Savaille J, Stein TP. Differences in maternal circulating fatty acid composition and dietary fat intake in women with gestational diabetes mellitus or mild gestational hyperglycemia. Diabetes care. 2010 Sep 1;33(9):2049-54.

5. Graça G, Duarte IF, Barros AS, Goodfellow BJ, Diaz SO, Pinto J, Carreira IM, Galhano E, Pita C, Gil AM. Impact of prenatal disorders on the metabolic profile of second trimester amniotic fluid: a nuclear magnetic resonance metabonomic study. Journal of proteome research. 2010 Nov 5;9(11):6016-24.

6. Diaz SO, Pinto J, Graça G, Duarte IF, Barros AS, Galhano E, Pita C, Almeida MD, Goodfellow BJ, Carreira IM, Gil AM. Metabolic biomarkers of prenatal disorders: an exploratory NMR metabonomics study of second trimester maternal urine and blood plasma. Journal of proteome research. 2011 Aug 5;10(8):3732-42.

7. Graça G, Goodfellow BJ, Barros AS, Diaz S, Duarte IF, Spagou K, Veselkov K, Want EJ, Lindon JC, Carreira IM, Galhano E. UPLC-MS metabolic profiling of second trimester amniotic fluid and maternal urine and comparison with NMR spectral profiling for the identification of pregnancy disorder biomarkers. Molecular BioSystems. 2012;8(4):1243-54.

8. Sachse D, Sletner L, Mørkrid K, Jenum AK, Birkeland KI, Rise F, Piehler AP, Berg JP. Metabolic changes in urine during and after pregnancy in a large, multiethnic population-based cohort study of gestational diabetes. PloS one. 2012 Dec 21;7(12):e52399.

9. Diaz SO, Barros AS, Goodfellow BJ, Duarte IF, Galhano E, Pita C, Almeida MD, Carreira IM, Gil AM. Second trimester maternal urine for the diagnosis of trisomy 21 and prediction of poor pregnancy outcomes. Journal of proteome research. 2013 Jun 7;12(6):2946-57.

10. de Seymour JV, Conlon CA, Sulek K, Bôas SG, McCowan LM, Kenny LC, Baker PN. Early pregnancy metabolite profiling discovers a potential biomarker for the subsequent development of gestational diabetes mellitus. Acta diabetologica. 2014 Oct 1;51(5):887-90.

11. Bentley-Lewis R, Huynh J, Xiong G, Lee H, Wenger J, Clish C, Nathan D, Thadhani R, Gerszten R. Metabolomic profiling in the prediction of gestational diabetes mellitus. Diabetologia. 2015 Jun 1;58(6):1329-32.

12. Law KP, Mao X, Han TL, Zhang H. Unsaturated plasma phospholipids are consistently lower in the patients diagnosed with gestational diabetes mellitus throughout pregnancy: a longitudinal metabolomics study of Chinese pregnant women part 1. Clin Chim Acta. 2017;465:53-71, https://doi.org/10.1016/j.cca.2016.12.010.

13. Law KP, Han TL, Mao X, Zhang H. Tryptophan and purine metabolites are consistently upregulated in the urinary metabolome of patients diagnosed with gestational diabetes mellitus throughout pregnancy: A longitudinal metabolomics study of Chinese pregnant women part 2. Clinica chimica acta. 2017 May 1;468:126-39.

14. Leitner M, Fragner L, Danner S, Holeschofsky N, Leitner K, Tischler S, Doerfler H, Bachmann G, Sun X, Jaeger W, Kautzky-Willer A. Combined metabolomic analysis of plasma and urine reveals AHBA, Tryptophan and Serotonin metabolism as potential risk factors in Gestational Diabetes Mellitus (GDM). Frontiers in Molecular Biosciences. 2017 Dec 21;4:84.

15. Zhang Y, Dai X, Yang S, Zhang C, Han M, Huang HF, Fan J. Maternal low thyroxin levels are associated with adverse pregnancy outcomes in a Chinese population. PloS one. 2017 May 23;12(5):e0178100.

16. Barzilay E, Moon A, Plumptre L, Masih SP, Sohn KJ, Visentin CE, Ly A, Malysheva O, Croxford R, Caudill MA, O'Connor DL. Fetal one-carbon nutrient concentrations may be affected by gestational diabetes. Nutrition Research. 2018 Jul 1;55:57-64.

17. Li J, Huo X, Cao YF, Li SN, Du Z, Shao P, Leng J, Zhang C, Sun XY, Ma RC, Fang ZZ. Bile acid metabolites in early pregnancy and risk of gestational diabetes in Chinese women: A nested case-control study. EBioMedicine. 2018 Sep 1;35:317-24.

18. Liu J, Li J, Li S, Leng J, Li W, Yang W, Huo X, Chen L, Ma RC, Hu G, Fang Z. Circulating lysophosphatidylcholines in early pregnancy and risk of gestational diabetes in Chinese women. The Journal of Clinical Endocrinology & Metabolism. 2020 Apr;105(4):e982-93.

19. O'Neill K, Alexander J, Azuma R, Xiao R, Snyder NW, Mesaros CA, Blair IA, Pinney SE. Gestational diabetes alters the metabolomic profile in 2nd trimester amniotic fluid in a sex-specific manner. International journal of molecular sciences. 2018 Sep;19(9):2696.

20. Roy C, Tremblay PY, Anassour-Laouan-Sidi E, Lucas M, Forest JC, Giguère Y, Ayotte P. Risk of gestational diabetes mellitus in relation to plasma concentrations of amino acids and acylcarnitines: A nested case-control study. Diabetes research and clinical practice. 2018 Jun 1;140:183-90.

21. Hou W, Meng X, Zhao A, Zhao W, Pan J, Tang J, Huang Y, Li H, Jia W, Liu F, Jia W. Development of multimarker diagnostic models from metabolomics analysis for gestational diabetes mellitus (GDM). Molecular & Cellular Proteomics. 2018 Mar 1;17(3):431-41.

22. Li P, Zhong C, Li S, Sun T, Huang H, Chen X, Zhu Y, Hu X, Peng X, Zhang X, Bao W. Plasma concentration of trimethylamine-N-oxide and risk of gestational diabetes mellitus. The American journal of clinical nutrition. 2018 Sep 1;108(3):603-10.

23. Huo X, Li J, Cao YF, Li SN, Shao P, Leng J, Li W, Liu J, Yang K, Ma RC, Hu G. Trimethylamine N-Oxide Metabolites in Early Pregnancy and Risk of Gestational Diabetes: A Nested Case-Control Study. The Journal of Clinical Endocrinology & Metabolism. 2019 Nov;104(11):5529-39.

24. Sakurai K, Eguchi A, Watanabe M, Yamamoto M, Ishikawa K, Mori C. Exploration of predictive metabolic factors for gestational diabetes mellitus in Japanese women using metabolomic analysis. Journal of diabetes investigation. 2019 Mar;10(2):513-20.

25. Liu X, Wang X, Sun H, Guo Z, Liu X, Yuan T, Fu Y, Tang X, Li J, Sun W, Zhao W. Urinary metabolic variation analysis during pregnancy and application in Gestational Diabetes Mellitus and spontaneous abortion biomarker discovery. Scientific reports. 2019 Feb 22;9(1):1-9.

26. Zhao H, Li H, Chung AC, Xiang L, Li X, Zheng Y, Luan H, Zhu L, Liu W, Peng Y, Zhao Y. Large-scale longitudinal metabolomics study reveals different trimester-specific alterations of metabolites in relation to gestational diabetes mellitus. Journal of proteome research. 2019 Nov 29;18(1):292-300.

27. Furse S, White SL, Meek CL, Jenkins B, Petry CJ, Vieira MC, Ozanne SE, Dunger DB, Poston L, Koulman A. Altered triglyceride and phospholipid metabolism predates the diagnosis of gestational diabetes in obese pregnancy. Molecular omics. 2019;15(6):420-30.

28. Jiang R, Wu S, Fang C, Wang C, Yang Y, Liu C, Hu J, Huang Y. Amino acids levels in early pregnancy predict subsequent gestational diabetes. Journal of diabetes. 2020 Jul;12(7):503-11.

29. Koos BJ, Gornbein JA. Early pregnancy metabolites predict gestational diabetes mellitus: implications for fetal programming. American Journal of Obstetrics and Gynecology. 2020 Jul 31.

30. Li X, Huang Y, Xing Y, Hu C, Zhang W, Tang Y, Su W, Huo X, Zhou A, Xia W, Xu S. Association of urinary cadmium, circulating fatty acids, and risk of gestational diabetes mellitus: A nested case-control study in China. Environment International. 2020 Apr 1;137:105527.

31. Butte NF, Hsu HW, Thotathuchery M, Wong WW, Khoury J, Reeds P. Protein metabolism in insulin-treated gestational diabetes. Diabetes Care. 1999 May 1;22(5):806-11.

32. Seghieri G, Breschi MC, Anichini R, De Bellis A, Alviggi L, Maida I, Franconi F. Serum homocysteine levels are increased in women with gestational diabetes mellitus. Metabolism. 2003 Jun 1;52(6):720-3.

33. Tarim E, Bagis T, Kilicdag E, Erkanli S, Aslan E, Sezgin N, Kuscu E. Elevated plasma homocysteine levels in gestational diabetes mellitus. Acta obstetricia et gynecologica Scandinavica. 2004 Jan 1;83(6):543-7.

34. Guven MA, Kilinc M, Batukan C, Ekerbicer HC, Aksu T. Elevated second trimester serum homocysteine levels in women with gestational diabetes mellitus. Archives of gynecology and obstetrics. 2006 Oct 1;274(6):333-7.

35. Pappa KI, Vlachos G, Theodora M, Roubelaki M, Angelidou K, Antsaklis A. Intermediate metabolism in association with the amino acid profile during the third trimester of normal pregnancy and diet-controlled gestational diabetes. American journal of obstetrics and gynecology. 2007 Jan 1;196(1):65-e1.

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

36. Idzior-Waluś B, Cyganek K, Sztefko K, Seghieri G, Breschi MC, Waluś-Miarka M, Kawalec E, Seretny M, Sieradzki J. Total plasma homocysteine correlates in women with gestational diabetes. Archives of gynecology and obstetrics. 2008 Oct 1;278(4):309-13.

37. Telejko B, Zonenberg A, Kuzmicki M, Modzelewska A, Niedziolko-Bagniuk K, Ponurkiewicz A, Nikolajuk A, Gorska M. Circulating asymmetric dimethylarginine, endothelin-1 and cell adhesion molecules in women with gestational diabetes. Acta diabetologica. 2009 Dec 1;46(4):303.

38. Akturk M, Altinova A, Mert I, Dincel A, Sargin A, Buyukkagnici U, Arslan M, Danisman N. Asymmetric dimethylarginine concentrations are elevated in women with gestational diabetes. Endocrine. 2010 Aug 1;38(1):134-41.

39. Sertkaya AC, Kafkasli A, Turkcuoglu I, Karabulut AB. Asymmetric dimethylarginine level in hyperglycemic gestation. Endocrine. 2011 Oct 1;40(2):237-42.

40. Dudzik D, Zorawski M, Skotnicki M, Zarzycki W, Kozlowska G, Bibik-Malinowska K, Vallejo M, García A, Barbas C, Ramos MP. Metabolic fingerprint of gestational diabetes mellitus. Journal of proteomics. 2014 May 30;103:57-71.

41. Lorenzo MP, Dudzik D, Varas E, Gibellini M, Skotnicki M, Zorawski M, Zarzycki W, Pellati F, García A. Optimization and validation of a chiral GC–MS method for the determination of free d-amino acids ratio in human urine: application to a gestational diabetes mellitus study. Journal of pharmaceutical and biomedical analysis. 2015 Mar 25;107:480-7.

42. Prentice KJ, Luu L, Allister EM, Liu Y, Jun LS, Sloop KW, Hardy AB, Wei L, Jia W, Fantus IG, Sweet DH. The furan fatty acid metabolite CMPF is elevated in diabetes and induces β cell dysfunction. Cell metabolism. 2014 Apr 1;19(4):653-66.

43. Scholtens DM, Muehlbauer MJ, Daya NR, Stevens RD, Dyer AR, Lowe LP, Metzger BE, Newgard CB, Bain JR, Lowe WL, HAPO Study Cooperative Research Group. Metabolomics reveals broad-scale metabolic perturbations in hyperglycemic mothers during pregnancy. Diabetes Care. 2014 Jan 1;37(1):158-66.

44. Hajduk J, Klupczynska A, Dereziński P, Matysiak J, Kokot P, Nowak DM, Gajęcka M, Nowak-Markwitz E, Kokot ZJ. A combined metabolomic and proteomic analysis of gestational diabetes mellitus. International journal of molecular sciences. 2015 Dec;16(12):30034-45.

45. He X, de Seymour JV, Sulek K, Qi H, Zhang H, Han TL, Villas-Bôas SG, Baker PN. Maternal hair metabolome analysis identifies a potential marker of lipid peroxidation in gestational diabetes mellitus. Acta diabetologica. 2016 Feb 1;53(1):119-22.

46. Lehmann R, Friedrich T, Krebiehl G, Sonntag D, Häring HU, Fritsche A, Hennige AM. Metabolic profiles during an oral glucose tolerance test in pregnant women with and without gestational diabetes. Exp Clin Endocrinol Diabetes. 2015 Jul 1;123(7):483-38.

47. Gao J, Xu B, Zhang X, Cui Y, Deng L, Shi Z, Shao Y, Ding M. Association between serum bile acid profiles and gestational diabetes mellitus: a targeted metabolomics study. Clinica Chimica Acta. 2016 Aug 1;459:63-72.

48. Liu T, Li J, Xu F, Wang M, Ding S, Xu H, Dong F. Comprehensive analysis of serum metabolites in gestational diabetes mellitus by UPLC/Q-TOF-MS. Analytical and bioanalytical chemistry. 2016 Feb 1;408(4):1125-35.

49. Chorell E, Hall UA, Gustavsson C, Berntorp K, Puhkala J, Luoto R, Olsson T, Holmäng A. Pregnancy to postpartum transition of serum metabolites in women with gestational diabetes. Metabolism. 2017 Jul 1;72:27-36.

50. Rahimi N, Razi F, Nasli-Esfahani E, Qorbani M, Shirzad N, Larijani B. Amino acid profiling in the gestational diabetes mellitus. Journal of Diabetes & Metabolic Disorders. 2017 Dec 1;16(1):13.

51. Delplancke TD, de Seymour JV, Tong C, Sulek K, Xia Y, Zhang H, Han TL, Baker PN. Analysis of sequential hair segments reflects changes in the metabolome across the trimesters of pregnancy. Scientific reports. 2018 Jan 8;8(1):1-2.

52. Batchuluun B, Al Rijjal D, Prentice KJ, Eversley JA, Burdett E, Mohan H, Bhattacharjee A, Gunderson EP, Liu Y, Wheeler MB. Elevated medium-chain acylcarnitines are associated with gestational diabetes mellitus and early progression to type 2 diabetes and induce pancreatic β-cell dysfunction. Diabetes. 2018 May 1;67(5):885-97.

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open Diab Res Care

53. Bukowiecka-Matusiak M, Burzynska-Pedziwiatr I, Sansone A, Malachowska B, Zurawska-Klis M, Ferreri C, Chatgilialoglu C, Ochedalski T, Cypryk K, Wozniak LA. Lipid profile changes in erythrocyte membranes of women with diagnosed GDM. PLoS One. 2018 Sep 14;13(9):e0203799.

54. Chen X, de Seymour JV, Han TL, Xia Y, Chen C, Zhang T, Zhang H, Baker PN. Metabolomic biomarkers and novel dietary factors associated with gestational diabetes in China. Metabolomics. 2018 Nov 1;14(11):149.

55. Li G, Gao W, Xu Y, Xie M, Tang S, Yin P, Guo S, Chu S, Sultana S, Cui S. Serum metabonomics study of pregnant women with gestational diabetes mellitus based on LC-MS. Saudi Journal of Biological Sciences. 2019 Dec 1;26(8):2057-63.

56. López-Hernández Y, Oostdam HV, Sofía A, Toro-Ortiz JC, López JA, Salgado-Bustamante M, Murgu M, Torres-Torres LM. Urinary metabolites altered during the third trimester in pregnancies complicated by gestational diabetes mellitus: relationship with potential upcoming metabolic disorders. International journal of molecular sciences. 2019 Jan;20(5):1186.

57. Taylor K, L Santos Ferreira D, West J, Yang T, Caputo M, A Lawlor D. Differences in pregnancy metabolic profiles and their determinants between white European and South Asian women: findings from the born in Bradford Cohort. Metabolites. 2019 Sep;9(9):190.

58. He XJ, Dai RX, Tian CQ, Hu CL. Neurodevelopmental outcome at 1 year in offspring of women with gestational diabetes mellitus. Gynecological Endocrinology. 2020 Apr 20:1-5.

59. Burzynska-Pedziwiatr I, Jankowski A, Kowalski K, Sendys P, Zieleniak A, Cypryk K, Zurawska-Klis M, Wozniak LA, Bukowiecka-Matusiak M. Associations of Arginine with Gestational Diabetes Mellitus in a Follow-Up Study. International journal of molecular sciences. 2020 Jan;21(21):7811.

60. Walejko JM, Chelliah A, Keller-Wood M, Wasserfall C, Atkinson M, Gregg A, Edison AS. Diabetes Leads to Alterations in Normal Metabolic Transitions of Pregnancy as Revealed by Time-Course Metabolomics. Metabolites. 2020 Sep;10(9):350.

61. Wang X, Liu H, Li Y, Huang S, Zhang L, Cao C, Baker PN, Tong C, Zheng P, Qi H. Altered gut bacterial and metabolic signatures and their interaction in gestational diabetes mellitus. Gut Microbes. 2020 Nov 9;12(1):1-3.

62. Tan B, Ma Y, Zhang L, Li N, Zhang J. The application of metabolomics analysis in the research of gestational diabetes mellitus and preeclampsia. Journal of Obstetrics and Gynaecology Research. 2020 Jun 4.

63. Cetin I, De Santis MS, Taricco E, Radaelli T, Teng C, Ronzoni S, Spada E, Milani S, Pardi G. Maternal and fetal amino acid concentrations in normal pregnancies and in pregnancies with gestational diabetes mellitus. American journal of obstetrics and gynecology. 2005 Feb 1;192(2):610-7.

64. Anderson SG, Dunn WB, Banerjee M, Brown M, Broadhurst DI, Goodacre R, Cooper GJ, Kell DB, Cruickshank JK. Evidence that multiple defects in lipid regulation occur before hyperglycemia during the prodrome of type-2 diabetes. PLoS One. 2014 Sep 3;9(9):e103217.

65. Chertok IR, Haile ZT, Eventov-Friedman S, Silanikove N, Argov-Argaman N. Influence of gestational diabetes mellitus on fatty acid concentrations in human colostrum. Nutrition. 2017 Apr 1;36:17-21.

66. Lu YP, Reichetzeder C, Prehn C, von Websky K, Slowinski T, Chen YP, Yin LH, Kleuser B, Yang XS, Adamski J, Hocher B. Fetal serum metabolites are independently associated with gestational diabetes mellitus. Cellular Physiology and Biochemistry. 2018;45(2):625-38.

67. Chu AH, Tint MT, Chang HF, Wong G, Yuan WL, Tull D, Nijagal B, Narayana VK, Meikle PJ, Chang KT, Lewis RM. High placental inositol content associated with suppressed pro-adipogenic effects of maternal glycaemia in offspring: the GUSTO cohort. International Journal of Obesity. 2020 May 20:1-1.

68. Shanmuganathan M, Kroezen Z, Gill B, Azab S, de Souza RJ, Teo KK, Atkinson S, Subbarao P, Desai D, Anand SS, Britz-McKibbin P. The maternal serum metabolome by multisegment injection-capillary electrophoresis-mass spectrometry: a high-throughput platform and standardized data workflow for large-scale epidemiological studies. Nature Protocols. 2021 Mar 5:1-29. https://doi.org/10.1038/s41596-020-00475-0