OBSTETRICS

First-trimester nuclear magnetic resonance–based metabolomic profiling increases the prediction of gestational diabetes mellitus

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BACKGROUND: Current strategies for predicting gestational diabetes mellitus demonstrate suboptimal performance.

OBJECTIVE: To investigate whether nuclear magnetic resonance-based metabolomic profiling of maternal blood can be used for first-trimester prediction of gestational diabetes mellitus.

STUDY DESIGN: This was a prospective study of 20,000 women attending routine pregnancy care visits at 11 to 13 weeks' gestation. Metabolic profiles were assessed using a high-throughput nuclear magnetic resonance metabolomics platform. To inform translational applications, we focused on a panel of 34 clinically validated biomarkers for detailed analysis and risk modeling. All biomarkers were used to generate a multivariable logistic regression model to predict gestational diabetes mellitus. Data were split using a random seed into a 70% training set and a 30% validation set. Performance of the multivariable models was measured by receiver operating characteristic curve analysis and detection rates at fixed 10% and 20% false positive rates. Calibration for the combined risk model for all gestational diabetes mellitus was assessed visually through a figure showing the observed incidence against the predicted risk for gestational diabetes mellitus. A sensitivity analysis was conducted excluding the 64 women in our cohort who were diagnosed with gestational diabetes mellitus before 20 weeks' gestation.

RESULTS: The concentrations of several metabolomic biomarkers, including cholesterol, triglycerides, fatty acids, and amino acids, differed between women who developed gestational diabetes mellitus and those who did not. Addition of biomarker profile improved the prediction of gestational diabetes mellitus provided by maternal demographic characteristics and elements of medical history alone (before addition: area under the receiver operating characteristic curve, 0.790; detection rate, 50% [95% confidence interval, 44.3%—55.7%] at 10% false positive rate; and detection rate, 63% [95% confidence interval, 57.4%—68.3%] at 20% false positive rate; after addition: 0.840; 56% [50.3%—61.6%]; and 73% [67.7%—77.8%]; respectively). The performance of combined testing was better for gestational diabetes mellitus treated by insulin (area under the receiver operating characteristic curve, 0.905; detection rate, 76% [95% confidence interval, 67.5%—83.2%] at 10% false positive rate; and detection rate, 85% [95% confidence interval, 77.4%—90.9%] at 20% false positive rate) than gestational diabetes mellitus treated by diet alone (area under the receiver operating characteristic curve, 0.762; detection rate, 47% [95% confidence interval, 37.7%—56.5%] at 10% false positive rate; and detection rate, 64% [95% confidence interval, 54.5%—72.7%] at 20% false positive rate). The calibration plot showed good agreement between the observed incidence of gestational diabetes mellitus and the incidence predicted by the combined risk model. In the sensitivity analysis excluding the women diagnosed with gestational diabetes mellitus before 20 weeks' gestation, there was a negligible difference in the area under the receiver operating characteristic curve compared with the results from the entire cohort combined.

CONCLUSION: Addition of nuclear magnetic resonance–based metabolomic profiling to risk factors can provide first-trimester prediction of gestational diabetes mellitus.

Key words: gestational diabetes, metabolomics, nuclear magnetic resonance, pregnancy, risk prediction, screening

Introduction

Gestational diabetes mellitus (GDM) affects between 5% and 18% of pregnancies globally and is associated with adverse perinatal outcomes.[1] In the long-term, it has been linked to increased risk of type 2 diabetes, obesity, and metabolic disease in both mothers and offspring.[2] Currently, GDM is not typically diagnosed until 24 to 28 weeks' gestation, when an oral glucose tolerance test (OGTT) is conducted; by this time, the fetus has already been exposed to some degree of maternal hyperglycemia and subtler metabolic alterations that precede it.[3–5] The early identification of women at high risk of developing GDM thus represents an opportunity to apply preventative and therapeutic strategies, potentially reducing the incidence and impact of disease on women and their offspring.[6,7]

The simplest and most widely applied methods of GDM prediction are based on maternal risk factors, used either individually[8,9] or integrated in predictive models.[10–14] Numerous clinically available biomarkers have also been explored in the context of early GDM identification, with variable performance.[14–23] More recently, the increasing accessibility of high-throughput metabolomic technologies has led to the exploration of maternal serum metabolites in GDM. Most studies have reported differences in metabolomic signatures between affected and unaffected pregnancies,

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AJOG at a Glance

Why was this study conducted?

Currently used strategies for the prediction of gestational diabetes mellitus (GDM) have suboptimal performance. We aimed to determine whether a selected panel of maternal serum metabolites can be used to improve first-trimester prediction of GDM beyond that provided by maternal risk factors alone.

Key findings

The combination of maternal serum metabolites with maternal risk factors improves the prediction of GDM relative to screening by maternal risk factors alone, especially when detecting women who will require insulin treatment.

What does this add to what is known?

Quantifying nuclear magnetic resonance–based metabolomic profiling can enhance the prediction of GDM in the first trimester, presenting an opportunity to apply preventative measures from early pregnancy.

offering further insight into disease pathogenesis.[24–26] A smaller number of studies have focused on the application of these findings to GDM prediction; however, they have been marked by methodological inconsistencies and small sample sizes that limit their reproducibility and clinical applicability.

We have previously created a first-trimester GDM prediction model, based on the combination of maternal clinical and demographic characteristics, which predicted 55% of cases that subsequently developed GDM, at a false positive rate (FPR) of 10%; the detection rate (DR) was 68%, at an FPR of 20%.[12] We have also explored the role of additional biomarkers, such as diacylglycerols and triacylglycerols, visfatin, resistin, adiponectin, follistatin-like 3, and sex hormone-binding globulin in the prediction of GDM with small or no improvement in predictive performance achieved by maternal risk factors alone.[16–22,27]

The objective of this first-trimester screening study is to investigate whether the maternal metabolomic profile, obtained through a high-throughput nuclear magnetic resonance (NMR) metabolomics platform, can be used for early prediction of GDM.

Materials and methods

Study population and design

The data set for this study was derived from prospective screening for adverse obstetrical outcomes in women with singleton pregnancies attending their routine first-trimester hospital visit at King's College Hospital, London between June 2015 and May 2018. This visit, at 11+0 to 13+6 weeks' gestation, included recording of maternal demographic characteristics and medical history, and ultrasound examination for determination of gestational age from the measurement of the fetal crown–rump length and diagnosis of major fetal abnormalities. We also collected and stored maternal serum samples at −70°C for future research into pregnancy complications. Women were not required to fast before sample collection to replicate the usual clinical setting, and no samples had previously been thawed and refrozen. Participants provided written informed consent to participate in the study, which was approved by the National Health Service Research Ethics Committee.

Details of maternal characteristics and the findings of the assessment at 11 to 13 weeks' gestation were recorded in our database. Patients were asked to complete a questionnaire on maternal age, self-reported ethnic origin (White, Black, South Asian, East Asian, or >1 ethnicity), method of conception (natural or assisted by in vitro fertilization or use of ovulation drugs), medical history (including pregestational diabetes mellitus type 1 or 2), family history of diabetes mellitus (first or second degree), and obstetrical history (parous or nulliparous with no previous pregnancies at or beyond 24 weeks; for parous women, we recorded whether any of the previous pregnancies were complicated by GDM). The questionnaire was then reviewed by a doctor together with the patient. The maternal weight and height were measured, and the body mass index was calculated in kg/m^2.

Data on pregnancy outcomes were obtained from the maternity computerized records or the women's general medical practitioners, and were then recorded in our database.

Inclusion and exclusion criteria

The inclusion criterion for this study was singleton pregnancy resulting in a phenotypically normal neonate at or after 28 weeks' gestation. The study cohort consisted of 20,062 first-trimester samples. We excluded pregnancies with pregestational diabetes (diabetes mellitus type 1 or 2) and those resulting in termination, miscarriage, or delivery before 28 weeks' gestation because they may not have had screening and diagnosis of GDM. The final cohort included 974 samples (4.9%) from women who subsequently developed GDM and 18,844 samples from women who did not develop GDM.

Outcome measure

The screening strategy for GDM in our unit is an adaptation of the National Institute for Health and Care Excellence (NICE) guidelines,[9] tailored to increase the number of women tested within our high-risk South London population. In the first midwife visit, women presenting with at least 1 risk factor as defined by NICE guidelines (body mass index >30 kg/m^2, previous birth of a macrosomic infant weighing >4.5 kg, previous GDM, family history with high prevalence of diabetes, first-degree relative with diabetes, polycystic ovarian syndrome, or persistent glycosuria) were offered screening for pregestational diabetes through hemoglobin A1c (HbA1c) quantification. Those with HbA1c between 39 and 41 mmol/mol were offered a 75-g OGTT at the earliest convenience; if test results were abnormal, women were classified as having early-onset

GDM (when fasting sample ≥5.6 mmol/L and <7.0 mmol/L or 2-hour sample ≥7.8 mmol/L and <11.0 mmol/L) or pregestational diabetes (if fasting sample ≥7.0 mmol/L or 2-hour sample ≥11.0 mmol/L). Those with a HbA1c ≥42 mmol/mol were also considered to have pregestational diabetes. Women diagnosed with pregestational diabetes through this method were excluded from our analysis.

At 24 to 28 weeks' gestation, all women who did not screen positive in the first trimester were offered a timed plasma glucose test 1 to 2 hours after a standardized meal containing 50 g of carbohydrate. A pragmatic approach was adopted, and in practice this screening window was extended up to 30 weeks' gestation when necessary. If the timed plasma glucose values were ≥6.7 mmol/L, women would be offered an OGTT and considered to have GDM if fasting values were ≥5.6 mmol/L or 2-hour values were ≥7.8 mmol/L as per NICE guidelines.

Beyond 30 weeks' gestation, women were screened with a 75-g OGTT if a large for gestational age fetus (defined as birthweight >90th percentile for gestational age using The Fetal Medicine Foundation fetal and neonatal growth charts[28]) or polyhydramnios was observed in routine antenatal ultrasound examination.

Once women were diagnosed with GDM, they were given dietary and exercise advice and encouraged to test capillary blood glucose before and 1 hour after each meal. Metformin was recommended as first-line treatment if fasting plasma glucose was ≥6.0 mmol/L or 2-hour glucose was ≥9.0 mmol/L at diagnosis, or if glycemic targets were suboptimal during a period of 1 to 2 weeks (premeal or 1-hour postmeal capillary glucose level ≥5.3 mmol/L and >7.0 mmol/L, respectively). Insulin was added in the event of suboptimal glycemic control despite metformin, or when metformin was not tolerated by the woman.

Metabolomic measurements

Maternal serum samples were thawed, and a high-throughput NMR metabolomics platform was used for analysis (Nightingale Health Plc, Helsinki, Finland; quantification version 2020). This platform provides simultaneous quantification of 250 metabolomic biomarker measures (hereafter denoted as metabolites) in a single assay, including routine lipids, lipoprotein subclass profiling with lipid concentrations within 14 subclasses, fatty acid composition, and various low-molecular-weight metabolites such as amino acids, ketone bodies, and glycolysis metabolites quantified in molar concentration units. Technical details and epidemiologic applications of the metabolomic biomarker data have been reviewed.[29,30] In brief, NMR spectra are acquired from native serum using the Bruker Avance III spectrometer (Bruker Corporation, Billerica, MA) operating at 500 MHz. Proprietary software algorithms are used to determine individual lipid and metabolite concentration from these spectra. The Nightingale NMR platform has received various regulatory approvals and has been validated for clinical use. We conducted a targeted analysis of 34 biomarkers in the panel, which have been clinically validated.[31]

Statistical analysis

Maternal demographic characteristics and elements from the medical history were combined with metabolite data. Samples with >15% missing metabolite values (0.07% in total) were excluded from targeted analysis, and any missing results were imputed with marker-specific median values. Given that samples were collected over several years (2015−2018), we first analyzed the effects of sample storage duration on analyte concentrations. As no relationship was found, analyte levels were not corrected for storage time. We also confirmed that samples from GDM cases and control samples from healthy term pregnancies were temporally distributed in a similar manner.

Maternal risk factor and metabolite concentration comparisons were performed between GDM and non-GDM pregnancies (analysis of variance for continuous variables and chi-square test for categorical variables). Results were expressed as percentages, means (standard deviations [SD]), or medians (interquartile range). For metabolomic profile comparison, metabolite values were normalized as multiple-of-median (MoM) values, in keeping with existing screening strategies universally applied in obstetrical care. Individual results were first transformed into log-values to obtain a normal distribution, and then all individual concentration values for each variable were divided by the median to obtain MoM values. Maternal age, weight, and ethnicity were determined to be significant confounding factors (having significant correlations with metabolites), and these effects were further corrected into MoM values.

Risk prediction was done using logistic multivariable modeling with various combinations of variables, including women diagnosed with GDM at all stages of pregnancy. For maternal factors, we used a previously published risk prediction model developed from examination of over 70,000 pregnancies, which included history of GDM, maternal age, weight, height, ethnicity, first- and second-degree family history of diabetes, conception by use of ovulation induction drugs, and previous birthweight Z score (calculated as the difference in SDs between observed and expected birthweight for gestational age).[12] Subsequently, a multivariable model using all 34 clinically validated metabolomic biomarkers under investigation was generated. Finally, the prior risk model derived from maternal risk factors was combined with the metabolite profile to yield a final posterior risk assessment. Data were split using a random seed into a 70% training set and 30% validation set. The training set contained 13,170 unaffected pregnancies and 659 GDM-affected pregnancies (207 managed with diet, 177 with metformin, and 275 with insulin). The validation set contained 5674 unaffected pregnancies and 315 GDM-affected pregnancies (116 managed with diet, 76 with metformin, and 123 with insulin). Performance of the multivariable models was measured by receiver operating characteristic (ROC) curve analysis and DRs at fixed 10% and 20% FPRs. Parameter estimates

for sensitivity and FPRs were calculated using bootstrap methodology, whereas the 95% confidence interval for DRs was calculated using the Clopper–Pearson method. The paired DeLong test for area under the curve (AUC) was used to detect significant differences when comparing ROC curves (Z statistic of ±1.96 [or 97.5th percentile] was considered significant).

Calibration of the combined risk model for all GDM cases was assessed visually using a figure comparing the observed incidence with the predicted risk for GDM. The plot was produced by grouping the data into bins according to risk. The observed incidence in each group was then plotted against the incidence predicted by the model (ie, the mean risks within each group).

A sensitivity analysis was conducted, excluding the 64 women in our cohort who were diagnosed with GDM via our early screening strategy, all before 20 weeks' gestation.

All data handling and analysis were conducted using R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided *P* value <.05 was considered statistically significant.

Results

Study population

A total of 19,818 women met the inclusion criteria, including 974 (4.9%) who developed GDM and 18,844 (95.6%) without GDM. In the GDM group, 64 women were diagnosed via the early screening strategy before 20 weeks' gestation, and 265 women were diagnosed after 30 weeks' gestation as a result of findings of a large for gestational age fetus or polyhydramnios on an ultrasound scan. A total of 323 women were treated by diet alone, 253 received metformin, and 398 received insulin with or without metformin. The maternal and pregnancy characteristics of the GDM and non-GDM groups are shown in Table 1. In the GDM group, compared with the non-GDM group, the women tended to be older, heavier, and shorter, and there was a higher proportion of Black and South Asian women, conceptions by in vitro fertilization, history of first- or second-degree relative with diabetes, and previous pregnancies complicated by GDM, and a higher incidence of large for gestational age neonates.

Metabolite profile in pregnancies with and without gestational diabetes mellitus

Nonnormalized mean and SD quantified values for 34 clinically validated metabolomic biomarkers are listed in Table 2. Both body mass index class (according to World Health Organization criteria) and ethnicity had a clear underlying effect on metabolite profiles. Therefore, MoM values were generated by normalizing serum metabolite levels by maternal age, weight, and ethnicity (Figure 1). Differences in metabolite concentrations were observed in 32 of the 34 analytes; the exceptions were APOA1 and histidine. The most pronounced metabolite changes associated with GDM pregnancies were observed in triglycerides, glucose, cholesterol, fatty acids, and branched-chain amino acids.

Predictive potential of serum metabolites for gestational diabetes mellitus

Prior risk was established using our previously published model. This model

TABLE 1
Characteristics of the study population

Characteristic	GDM (N=974)	No GDM (N=18,844)	*P* value
Maternal age, y	33.9 (30.5–37.5)	32.5 (28.9–35.7)	<.001
Maternal weight, kg	75.2 (63.0–91.0)	66.5 (59.0–76.0)	<.001
Maternal height, cm	163 (159–168)	165 (161–170)	<.001
Body mass index, kg/m^2	28.1 (23.9–33.6)	24.2 (21.8–27.7)	<.001
Ethnicity			<.001
White	538 (55.2)	13,474 (71.5)	
Black	209 (21.5)	3152 (16.7)	
South Asian	132 (13.6)	973 (5.2)	
East Asian	61 (6.3)	529 (2.8)	
More than 1 ethnicity	34 (3.5)	716 (3.8)	
Cigarette smokers	33 (3.4)	705 (3.7)	.570
Conception			<.001
Natural	894 (91.8)	17,889 (94.9)	
In vitro fertilization	71 (7.3)	795 (4.2)	
Ovulation drugs	9 (0.9)	160 (0.8)	
Family history of diabetes			<.001
First degree	227 (23.3)	2246 (11.9)	
Second degree	137 (14.1)	1802 (9.6)	
Parity			<.001
Parous	530 (54.4)	9009 (47.8)	
Nulliparous	444 (45.6)	9835 (52.2)	
Previous LGA >90th centile	88 (9.0)	846 (4.5)	<.001
Previous GDM	246 (25.3)	163 (0.9)	<.001
Gestation at delivery, wk	39.0 (38.1–39.6)	40.0 (39.1–40.9)	<.001

Results presented as median (interquartile range) or number (percentage).

GDM, gestational diabetes mellitus; *LGA*, large for gestational age.

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TABLE 2
Metabolite biomarker levels in quantified concentrations, ratios, or percentages for gestational diabetes mellitus and unaffected pregnancies

Metabolite biomarker	GDM (N=974)	No GDM (N=18,844)	*P* value[a]	Odds ratio (95% CI)	*P* value[b]
Total cholesterol (mmol/L)	5.22 (0.88)	5.04 (0.83)	<.001	1.69 (1.57–1.81)	<.001
Very-low-density lipoprotein cholesterol (mmol/L)	0.64 (0.23)	0.55 (0.19)	<.001	1.63 (1.53–1.73)	<.001
Low-density lipoprotein cholesterol (mmol/L)	2.68 (0.69)	2.51 (0.62)	<.001	1.68 (1.58–1.77)	<.001
High-density lipoprotein cholesterol (mmol/L)	1.75 (0.30)	1.81 (0.29)	<.001	0.78 (0.73–0.83)	<.001
Total triglyceride (mmol/L)	1.34 (0.62)	1.07 (0.42)	<.001	1.58 (1.47–1.70)	<.001
APO B (g/L)	0.84 (0.19)	0.79 (0.17)	<.001	1.63 (1.54–1.73)	<.001
APO A1 (g/L)	1.81 (0.24)	1.80 (0.23)	.105	1.07 (1.00–1.14)	.05
APO B/APO A1 (ratio)	0.47 (0.12)	0.44 (0.11)	<.001	1.51 (1.42–1.59)	<.001
Total fatty acids (mmol/L)	14.80 (2.73)	13.52 (2.24)	<.001	1.77 (1.65–1.89)	<.001
Omega-3 (mmol/L)	0.78 (0.21)	0.70 (0.19)	<.001	1.90 (1.78–2.02)	<.001
Omega-6 (mmol/L)	5.61 (0.75)	5.32 (0.68)	<.001	1.77 (1.66–1.89)	<.001
Polyunsaturated fatty acids (mmol/L)	6.38 (0.87)	6.01 (0.80)	<.001	1.91 (1.79–2.03)	<.001
Monounsaturated fatty acid (mmol/L)	3.56 (0.94)	3.13 (0.70)	<.001	1.62 (1.51–1.73)	<.001
Saturated fatty acids (mmol/L)	4.87 (1.11)	4.38 (0.85)	<.001	1.69 (1.58–1.82)	<.001
DHA (mmol/L)	0.36 (0.08)	0.34 (0.07)	<.001	1.75 (1.64–1.86)	<.001
Omega-3 %	5.26 (1.20)	5.14 (1.09)	<.001	1.39 (1.31–1.48)	<.001
Omega-6 %	38.27 (3.11)	39.60 (2.44)	<.001	0.63 (0.59–0.67)	<.001
Polyunsaturated fatty acids (PUFA) %	43.53 (3.36)	44.74 (2.53)	<.001	0.80 (0.75–0.86)	<.001
Monounsaturated fatty acid (MUFA) %	23.78 (2.18)	23.01 (1.81)	<.001	1.26 (1.18–1.35)	<.001
Saturated fatty acids %	32.68 (2.10)	32.25 (1.61)	<.001	1.06 (0.99–1.14)	.09
Docosahexaenoic acid %	2.46 (0.53)	2.52 (0.44)	.001	1.10 (1.04–1.18)	.002
PUFA/MUFA (ratio)	1.85 (0.28)	1.96 (0.24)	<.001	0.79 (0.74–0.85)	<.001
Omega-6/Omega-3 (ratio)	7.67 (2.07)	8.07 (1.89)	<.001	0.64 (0.61–0.68)	<.001
Alanine (mmol/L)	0.38 (0.06)	0.35 (0.06)	<.001	1.56 (1.45–1.67)	<.001
Glycine (mmol/L)	0.18 (0.04)	0.19 (0.04)	<.001	0.71 (0.67–0.74)	<.001
Histidine (mmol/L)	0.08 (0.01)	0.08 (0.01)	.400	0.70 (0.66–0.75)	<.001
Total branched-chain amino acids (mmol/L)	0.40 (0.10)	0.36 (0.09)	<.001	1.71 (1.62–1.80)	<.001
Isoleucine (mmol/L)	0.06 (0.02)	0.05 (0.02)	<.001	1.76 (1.67–1.86)	<.001
Leucine (mmol/L)	0.12 (0.03)	0.11 (0.03)	<.001	1.73 (1.63–1.83)	<.001
Valine (mmol/L)	0.22 (0.05)	0.20 (0.04)	<.001	1.64 (1.55–1.74)	<.001
Phenylalanine (mmol/L)	0.08 (0.01)	0.07 (0.01)	<.001	1.90 (1.80–2.01)	<.001
Tyrosine (mmol/L)	0.06 (0.01)	0.06 (0.01)	<.001	1.77 (1.66–1.89)	<.001
Glucose (mmol/L)	5.73 (1.15)	5.19 (0.82)	<.001	1.95 (1.84–2.07)	<.001
Lactate (mmol/L)	1.85 (0.68)	1.71 (0.64)	<.001	1.58 (1.49–1.67)	<.001

Data are presented as mean (standard deviation). The odds ratios for each metabolic biomarker were used in the final modeling of the risk prediction algorithm.

CI, confidence interval; *DHA*, docosahexaenoic acid; *GDM*, gestational diabetes mellitus.

[a] *P* value for comparison of metabolite levels between GDM and no GDM cases; [b] *P* value for odds ratio for each metabolic biomarker.

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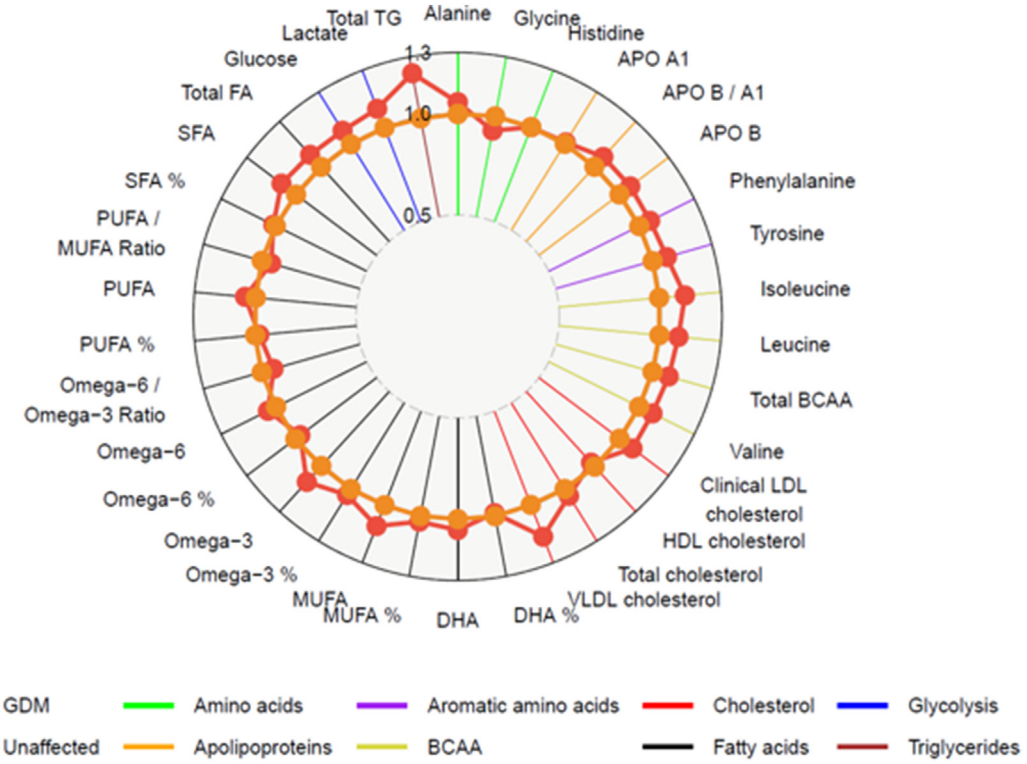
FIGURE 1
First-trimester metabolite levels presented as normalized MoM values



Normalization was done for maternal age, weight, and ethnicity. Light orange circles represent MoM values for the non-GDM group (n=18,844) and dark orange circles for the GDM group (n=974). Radial y-axis is scaled from 0.5 to 1.3 MoM. Radial lines represent each of the metabolites and are colored according to metabolite groups (amino acids, apolipoproteins, aromatic amino acids, BCAA, cholesterol FAs, glycolysis pathways, and TGs). All differences (except Apo A1 and histidine) between the GDM group and the unaffected group are statistically significant ($P<.05$).

BCAA, branched-chain amino acid; *DHA*, docosahexaenoic acid; *GDM*, gestational diabetes mellitus; *FA*, fatty acid; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *MoM*, multiple of median; *MUFA*, monounsaturated fatty acid; *PUFA*, polyunsaturated fatty acid; *SFA*, saturated fatty acid; *TG*, triglyceride; *VLDL*, very-low-density lipoprotein.

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provided a slightly lower performance in this study cohort (ROC AUC=0.790; DR, 50%; 95% CI, 44.3%−55.7% at 10% FPR; and DR, 63%; 95% CI, 57.4% −63% at 20% FPR) compared with the cohort included in the original publication (ROC AUC=0.823; DR, 55% at 10% FPR; and DR, 68% at 20% FPR).

Thirty-two of the metabolites were significantly associated with distinguishing GDM from non-GDM pregnancies. All 34 metabolites, except for APOA1, also had significantly altered odds ratios in the univariate model (Table 2) when assessing the impact of individual markers on the full metabolite profile. All 34 metabolite biomarkers were used to generate the final metabolite profile model. When used in isolation, serum metabolites did not outperform the model based on maternal risk factors alone in both the training (ROC AUC=0.716; DR, 34%; 95% CI, 30.4%−37.8% at 10% FPR; and DR, 52%; 95% CI, 48.1%−55.9% at 20% FPR) and validation (ROC AUC=0.714; DR, 31%; 95% CI, 25.9% −36.4% at 10% FPR; and DR, 49%; 95% CI, 43.3%−54.7% at 20% FPR) sets. The generation of a multivariable model through combining previous risk with the metabolite profile resulted in improved overall prediction performance in both sets (training set: ROC AUC=0.843; DR, 60%; 95% CI, 56.1% −63.8% at 10% FPR; and DR, 72%; 95% CI, 69.1%−74.8% at 20% FPR; validation set: ROC AUC=0.840; DR, 56%; 95% CI, 50.3%−61.6% at 10% FPR; and DR, 73%; 95% CI, 67.7% −77.8% at 20% FPR in the validation set) (Table 3; Supplemental Figures 1 and 2).

We also investigated whether maternal risk factors and/or metabolite profile could show improved prediction of GDM subgroups based on applied treatment/management (Table 3; Figure 2). Prediction performance improved with the severity of GDM. The performance of combined testing was better for GDM treated by insulin (training set: ROC AUC=0.880; DR, 68%; 95% CI, 62.1%−73.5% at 10% FPR; and DR, 82%; 95% CI, 76.9% −86.4% at 20%; validation set: ROC AUC=0.905; DR, 76%; 95% CI, 67.5% −83.2% at 10% FPR; and DR, 85%; 95% CI, 77.4%−90.9% at 20% FPR) than GDM treated by diet alone (training set:

TABLE 3
Performance of risk models for prediction of gestational diabetes mellitus

Group: Training	Maternal factors	Metabolite profile	Maternal factors plus metabolite profile
GDM all (n=659)			
ROC AUC (95% CI)	0.799 (0.781–0.818)	0.716 (0.695–0.737)	0.843 (0.827–0.860)
DR at 10% FPR (95% CI)	50% (46.1–53.9)	34% (30.4–37.8)	60% (56.1–63.8)
DR at 20% FPR (95% CI)	65% (61.2–68.6)	52% (48.1–55.9)	72% (69.1–74.8)
GDM treated by diet alone (n=207)			
ROC AUC (95% CI)	0.728 (0.692–0.764)	0.691 (0.654–0.727)	0.784 (0.753–0.816)
DR at 10% FPR (95% CI)	35% (28.5–41.9)	26% (20.2–32.5)	45% (38.1–52.1)
DR at 20% FPR (95% CI)	49% (42.0–56.0)	43% (36.2–50.1)	59% (52.0–65.8)
GDM treated by metformin (n=177)			
ROC AUC (95% CI)	0.818 (0.783–0.85)	0.726 (0.692–0.761)	0.861 (0.833–0.888)
DR at 10% FPR (95% CI)	54% (46.4–61.5)	35% (28.0–42.5)	59% (51.4–66.3)
DR at 20% FPR (95% CI)	66% (58.5–72.9)	51% (43.4–58.6)	77% (70.1–83.0)
GDM treated by insulin±metformin (n=275)			
ROC AUC (95% CI)	0.841 (0.815–0.86)	0.733 (0.702–0.764)	0.880 (0.857–0.903)
DR at 10% FPR (95% CI)	59% (52.9–64.9)	40% (34.2–46.1)	68% (62.1–73.5)
DR at 20% FPR (95% CI)	75% (69.4–80.0)	59% (52.9–64.9)	82% (76.9–86.4)
Group: Validation			
GDM all (n=315)			
ROC AUC (95% CI)	0.790 (0.762–0.818)	0.714 (0.684–0.745)	0.840 (0.816–0.863)
DR at 10% FPR (95% CI)	50% (44.3–55.7)	31% (25.9–36.4)	56% (50.3–61.6)
DR at 20% FPR (95% CI)	63% (57.4–68.3)	49% (43.3–54.7)	73% (67.7–77.8)
GDM treated by diet alone (n=116)			
ROC AUC (95% CI)	0.712 (0.660–0.763)	0.669 (0.615–0.723)	0.762 (0.712–0.813)
DR at 10% FPR (95% CI)	37% (28.2–46.5)	23% (15.7–31.8)	47% (37.7–56.5)
DR at 20% FPR (95% CI)	50% (40.6–59.4)	38% (29.1–47.5)	64% (54.5–72.7)
GDM treated by metformin (n=76)			
ROC AUC (95% CI)	0.790 (0.737–0.844)	0.772 (0.723–0.821)	0.859 (0.818–0.899)
DR at 10% FPR (95% CI)	43% (31.7–54.9)	30% (20.0–41.6)	62% (50.1–72.9)
DR at 20% FPR (95% CI)	63% (51.1–73.8)	51% (39.2–62.7)	75% (63.7–84.2)
GDM treated by insulin±metformin (n=123)			
ROC AUC (95% CI)	0.864 (0.829–0.899)	0.764 (0.720–0.809)	0.905 (0.877–0.934)
DR at 10% FPR (95% CI)	66% (56.9–74.3)	40% (31.1–49.2)	76% (67.5–83.2)
DR at 20% FPR (95% CI)	76% (67.5–83.2)	58% (48.8–66.9)	85% (77.4–90.9)

The maternal factors model was based on Syngelaki et al[12,20] and included history of GDM, maternal age, weight, height, ethnicity, first- and second-degree family history of diabetes, conception by use of ovulation induction drugs, and previous birthweight Z score (calculated as the difference in standard deviations between observed and expected birthweight for gestational age). The paired AUC Delong test demonstrated that the ROC for the maternal factors model was significantly better than that for the metabolite profile model ($P<.001$), and that the combined model significantly outperformed both individual models ($P<.001$).

CI, confidence interval; *DR*, detection rate; *FPR*, false positive rate; *GDM*, gestational diabetes mellitus; *ROC AUC*, area under the receiver operating characteristic curve.

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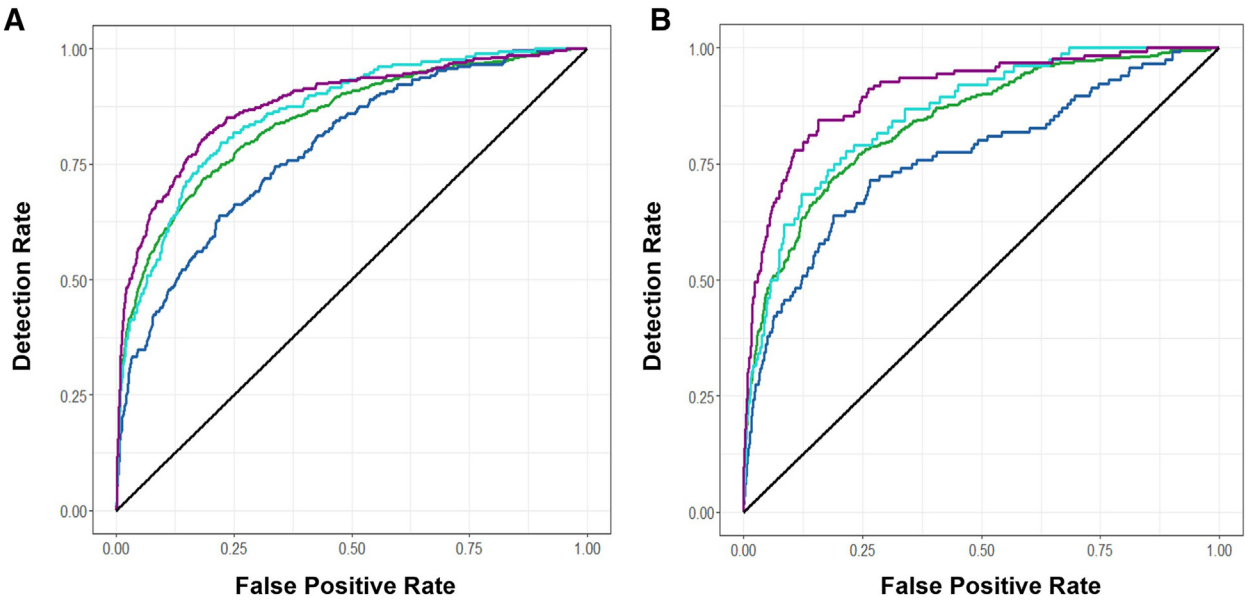
FIGURE 2
ROC curves of the model combining maternal characteristics with metabolites based on maternal treatment requirements



A, Training set. **B,** Validation set. Green line: all GDM cases; dark blue line: GDM treated with diet alone; light blue line: GDM treated with metformin; purple line: GDM treated with insulin.

GDM, gestational diabetes mellitus; *ROC*, receiver operating characteristic.

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ROC AUC=0.784; DR, 45%; 95% CI, 38.1%−52.1% at 10% FPR; and DR, 59%; 95% CI, 52.0%−65.8% at 20% FPR; validation set: ROC AUC=0.762; DR, 47%; 95% CI, 37.7%−56.5% at 10% FPR; and DR, 64%; 95% CI, 54.5% −72.7% at 20% FPR).

The calibration plot in Figure 3 demonstrates good agreement between the observed incidence of GDM and the incidence predicted by the combined risk model.

Sensitivity analysis excluding participants with early-onset gestational diabetes mellitus

We performed a sensitivity analysis by excluding 64 women diagnosed with GDM through our early screening strategy, all of whom were diagnosed before 20 weeks' gestation. Of these, 42 had been included in the original training set and 22 in the validation set. A negligible difference in ROC AUC was found in comparison with the results from the entire cohort combined (Table 4).

Comment

Principal findings

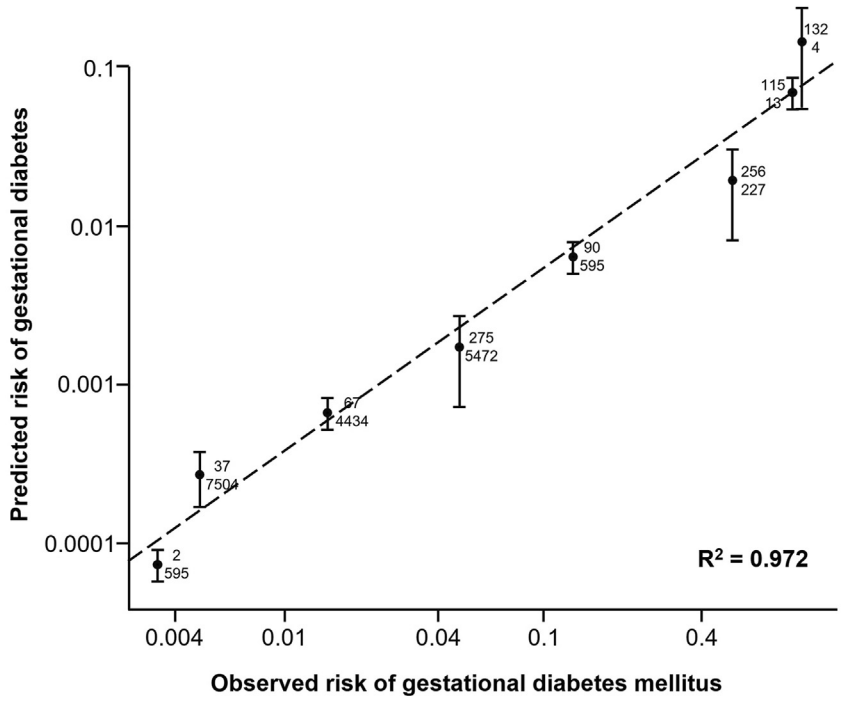
In this large first-trimester screening study involving 974 women with GDM and over 18,000 women unaffected by GDM, we demonstrated that a set of 34 metabolomic biomarkers can be used to improve early prediction of GDM achieved through screening by maternal risk factors alone. The combination of this metabolite panel with maternal risk factors showed good predictive ability, with ROC AUC of 0.84 and DRs of 56% and 73% at respective FPRs of 10% and 20%. This was a moderate improvement relative to history-based prediction, with an approximate 10% increase in DR. The combined model performed particularly well when predicting GDM requiring insulin therapy, with ROC AUC of 0.90 and DRs of 76% and 85% at respective FPRs of 10% and 20%.

In accordance with national and local guidance, we included women diagnosed with dysglycemia at any point in pregnancy as GDM cases, except for those who met the diagnostic criteria for pregestational diabetes before 20 weeks' gestation. Given the lack of universally agreed-upon criteria for diagnosis outside of usual screening windows, especially in cases of early-onset GDM, we conducted a sensitivity analysis excluding these women. This resulted in the predictive ability of our model being virtually unaffected, with changes in ROC AUC well within the CIs of the original results. This further confirms the robustness of our model.

Results in the context of what is known

Attempts at predicting GDM through metabolomics have so far failed to inform new clinical strategies and have been marked by major result inconsistencies. Barriers to clinical application are manifold, including methodological variations, lack of representation of different demographics, and challenges in controlling results for additional variables.[32,33] These issues are further exacerbated by the small sample sizes of most studies.[24,34−36] To date,

FIGURE 3
Calibration plot for the combined risk model for all GDM cases



Error bars±SD. Numbers indicate the counts of GDM (top) and unaffected control (bottom) samples in each bin.

GDM, gestational diabetes mellitus.

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only 2 published studies have been well-powered.[37,38] The first study[37] used NMR to examine samples obtained at 26 to 28 weeks' gestation, at the time of OGTT, from 8212 pregnant participants, including 666 with GDM. The authors combined 140 metabolites with maternal risk factors and reported an increase in ROC AUC from 0.69, when screening by maternal risk factors alone, to 0.78 with the addition of metabolites. However, in an external validation study of 859 obese women, including 90 who developed GDM, the prediction of combined testing was poor (ROC AUC=0.64). The second study[38] used mass spectrometry to examine samples obtained at 26 to 28 weeks' gestation at the time of OGTT from 3000 women, including 329 with GDM; the ROC AUC for maternal metabolites combined with risk factors was 0.76, and this was replicated at the validation stage in 827 women, including 172 with GDM. Despite the robust methodology, both studies were restricted to White British and Pakistani women.

Clinical implications

One of the most important aspects of our study was our decision to use a clinically validated, high-throughput and low-cost metabolomics platform. This clinically validated panel of 34 biomarkers, identified a priori, is licensed for clinical use because of its measurement accuracy and validation against standard clinical chemistry analyzers. This ensures simplification of the model and reproducibility of results with minimal analytical variation, thus offering technical advantages. The chosen biomarkers have been associated with metabolic disease,[29,39] including type 2 diabetes mellitus,[40,41] and most have been linked to GDM development, albeit with varying levels of consistency.[42–45] Our results therefore represent a promising step toward clinical implementation of metabolomic screening for GDM given that this platform may facilitate the validation of the combined model in different populations. This analytical platform has recently been clinically implemented at scale for multidisease risk detection and occupational health screening settings,[46,47] demonstrating the technical and logistic feasibility for wider implementation within maternal and fetal health care.

Strengths and limitations

Our study offers 3 main advantages over the 2 existing large studies.[37,38] First, it was conducted on a large, unselected sample of approximately 20,000 pregnant women from a heterogeneous inner-city population, nearly 1000 of whom developed GDM. Second, screening was conducted prospectively using first-trimester samples, which represents the optimal time for implementing early preventative measures. This study is notable for its large, diverse cohort and its development of a combined model for screening in the first trimester, rather than in later stages of pregnancy. In addition, our results accurately identify women who will require insulin treatment—a group prone to worse perinatal outcomes[48] and thus considered to potentially have a more severe form of the disease. These individuals are likely to benefit the most from targeted intervention. To our knowledge, no previous research has attempted to predict GDM severity or insulin use through metabolomics.

The main limitations of our study stem from the heterogeneous approach to screening, diagnosis, and management of GDM in different health care settings. In our study, the lack of universal OGTT might have resulted in the inclusion of some women with undiagnosed GDM in our unaffected group. However, our local 2-step screening approach for all women at 24 to 28 weeks' gestation is likely to have increased the number of women tested with a 75-g OGTT and reduced the number of missed cases. Although our

TABLE 4
Sensitivity analysis with the exclusion of 64 women diagnosed with gestational diabetes before 20 weeks' gestation

Group: Early diagnosis (<20 wk) removed	Training data: maternal factors plus metabolite profile			Validation data: maternal factors plus metabolite profile		
	ROC AUC <20 wk removed (95% CI)	ROC AUC Original (95% CI)	DELTA ROC AUC	ROC AUC <20 wk removed (95% CI)	ROC AUC Original (95% CI)	DELTA ROC AUC
GDM all	0.837 (0.819–0.854)	0.843 (0.827–0.860)	−0.006	0.831 (0.806–0.856)	0.840 (0.816–0.863)	−0.009
GDM treated by diet alone	0.783 (0.751–0.815)	0.784 (0.753–0.816)	−0.001	0.760 (0.709–0.811)	0.762 (0.712–0.813)	−0.002
GDM treated by metformin	0.854 (0.825–0.882)	0.861 (0.833–0.888)	−0.007	0.856 (0.815–0.898)	0.859 (0.818–0.899)	−0.003
GDM treated by insulin (±metformin)	0.872 (0.847–0.897)	0.880 (0.857–0.903)	−0.008	0.893 (0.860–0.925)	0.905 (0.877–0.934)	−0.012

The maternal factors model was based on Syngelaki et al[12,20] and included history of GDM, maternal age, weight, height, ethnicity, first- and second-degree family history of diabetes, conception by use of ovulation induction drugs, and previous birthweight Z score (calculated as the difference in standard deviations between observed and expected birthweight for gestational age). The paired AUC Delong test demonstrated that the ROC for the maternal factors model was significantly better than that for the metabolite profile model ($P < .001$), and that the combined model significantly outperformed both individual models ($P < .001$).

CI, confidence interval; *GDM*, gestational diabetes mellitus; *ROC AUC*, area under the receiver operating characteristic curve.

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results have undergone a robust internal validation, it is still necessary for our findings to be externally validated, not only in different populations, but also using diverse existing screening strategies and diagnostic thresholds.

Conclusions

We presented a GDM risk prediction model for the first trimester, based on a panel of clinically validated serum biomarkers and maternal clinical and demographic characteristics, which showed an approximately 10% improvement in DR of GDM cases. This constitutes a promising advancement toward standardization of metabolomic studies in GDM. Further studies using the same methodology are required for external validation.

CRediT authorship contribution statement

Luiza Borges Manna: Writing — original draft, Methodology, Conceptualization. **Argyro Syngelaki:** Writing — review & editing, Data curation, Conceptualization. **Peter Würtz:** Methodology, Formal analysis, Conceptualization. **Aki Koivu:** Formal analysis, Conceptualization. **Mikko Sairanen:** Writing — original draft, Methodology, Formal analysis. **Tuukka Pölönen:** Formal analysis. **Kypros H. Nicolaides:** Writing — review & editing, Supervision, Methodology, Data curation, Conceptualization.

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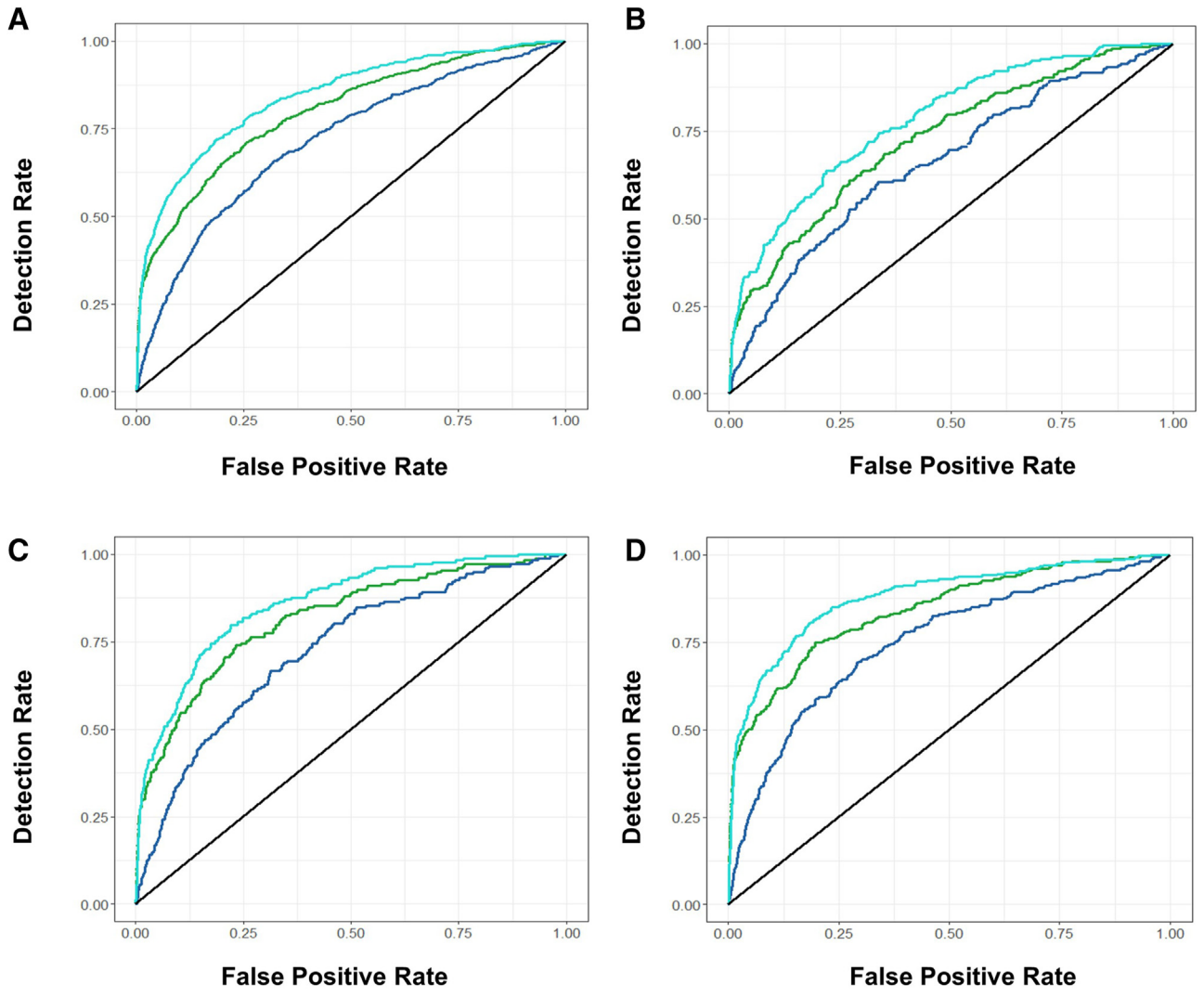
SUPPLEMENTAL FIGURE 1

ROC curves comparing the performance of each risk model in relation to maternal treatment requirements in the training data set



A, All GDM, **B,** GDM treated with diet alone, **C,** GDM treated with metformin, and **D,** GDM treated with insulin. Dark blue line=metabolite biomarkers; green line=maternal risk factors; light blue line=combined risk.

GDM, gestational diabetes mellitus; *ROC*, receiver operating characteristic.

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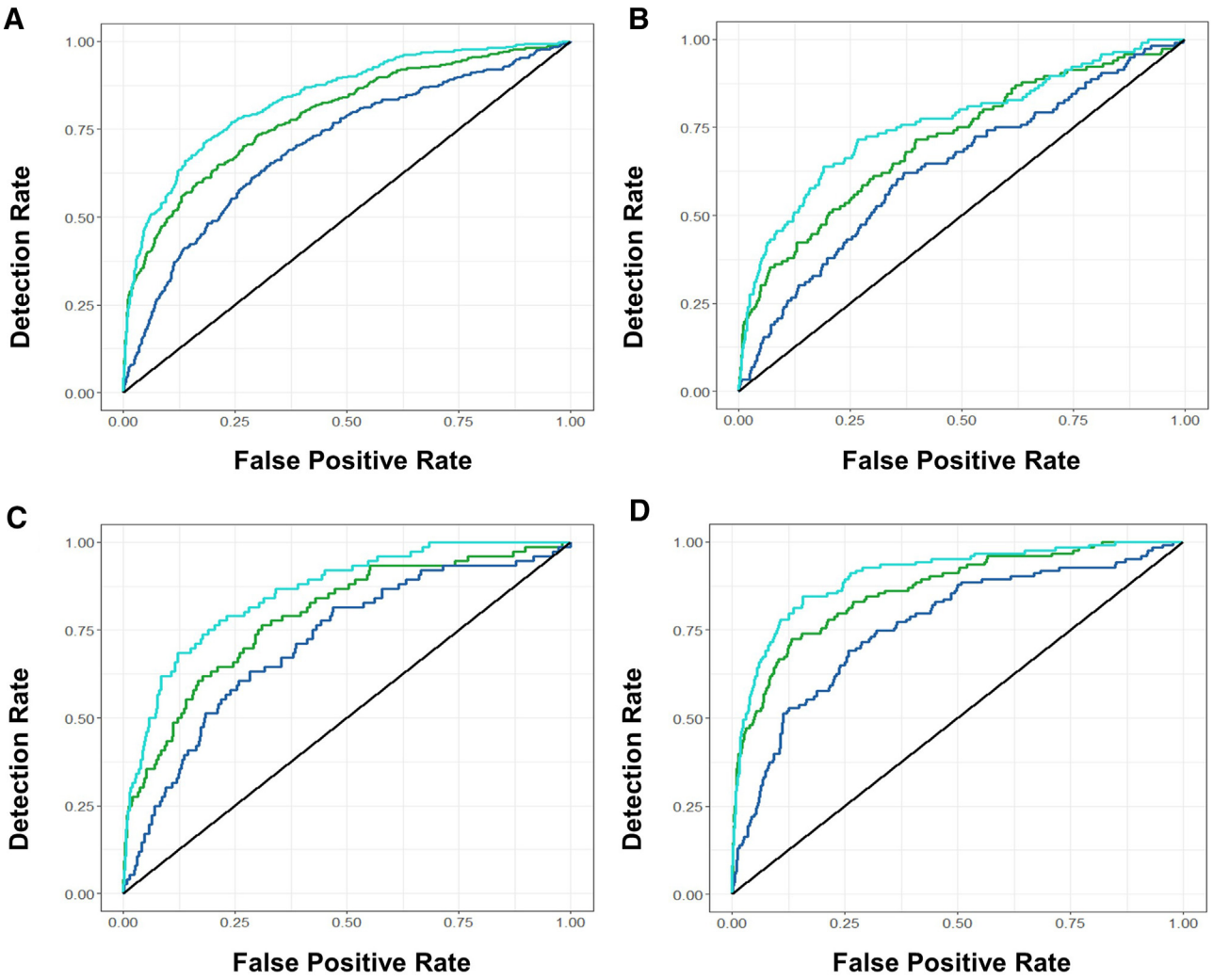
SUPPLEMENTAL FIGURE 2

ROC curves comparing the performance of each risk model in relation to maternal treatment requirements in the validation data set



A, All GDM, **B,** GDM treated with diet alone, **C,** GDM treated with metformin, and **D,** GDM treated with insulin. Dark blue line=metabolite biomarkers; green line=maternal risk factors; light blue line=combined risk.

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