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Associations of maternal and infant metabolite profiles with foetal growth and the odds of adverse birth outcomes

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Summary

Background: Adaptations in maternal and foetal metabolic pathways may predispose to altered foetal growth and adverse birth outcomes.

Objective: To assess the associations of maternal early-pregnancy metabolite profiles and infant metabolite profiles at birth with foetal growth from first trimester onwards and the odds of adverse birth outcomes.

Methods: In a prospective population-based cohort among 976 Dutch pregnant women and their children, serum concentrations of amino acids, non-esterified fatty acids (NEFA), phospholipids (PL) and carnitines in maternal early-pregnancy blood and in cord blood were obtained by liquid-chromatography tandem mass spectrometry. Information on foetal growth was available from first trimester onwards.

Results: After false discovery rate correction for multiple testing, higher infant total and individual NEFA concentrations were associated with a lower weight, length, and head circumference at birth. Higher infant total and individual acyl-lysophosphatidylcholine (lyso.PC.a) and alkyl-lysophosphatidylcholine concentrations were associated with higher weight and head circumference (lyso.PC.a only) at birth, higher odds of LGA and lower odds of SGA. Few individual maternal metabolites were associated with foetal growth measures in third trimester and at birth, but not with the odds of adverse birth outcomes.

Conclusions: Our results suggest that infant metabolite profiles, particularly total and individual lyso.PC.a and NEFA concentrations, were strongly related to growth measures at birth and the odds of adverse birth outcomes. Few individual maternal early-pregnancy metabolites, but not total metabolite concentrations, are associated with foetal growth measures in third trimester and at birth.

ABBREVIATIONS: AA, amino acids; AAA, aromatic amino acids; AC, abdominal circumference; BCAA, branched-chain amino acids; Carn, carnitines; Carn.a, acyl-carnitines; CRL, crown to rump length; EFW, estimated foetal weight; FDR, false discovery rate; Free Carn, free carnitine; FL, femur length; HC, head circumference; HDL, high-density lipoprotein; HPLC, high performance liquid chromatography; LDL, low-density lipoprotein; LGA, large size-for-gestational age at birth; Lyso.PC.a, acyl-lysophosphatidylcholines; Lyso.PC.e, alkyl-lysophosphatidylcholines; NEFA, non-esterified fatty acids; OR, odds ratio; PC, phosphatidycholine; PC.aa, diacyl-phosphatidylcholines; PC.ae, acyl-alkyl-phosphatidylcholines; PL, phospholipids; SD, standard deviation; SDS, standard deviation score; SGA, small size-for-gestational age at birth; SM, sphingomyelines.

Berthold Koletzko and Romy Gaillard contributed equally to this study.

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KEYWORDS
birth weight, foetal growth, metabolite profiles, metabolomics, pre-term birth, size-for-gestational age at birth

1 | INTRODUCTION

Pre-term birth, small size-for-gestational age at birth (SGA) and large size-for-gestational age at birth (LGA) are major risk factors for neonatal death and short- and long-term morbidity.[1–3] Adverse maternal lifestyle and metabolic factors such as poor diet quality, a high total energy intake, inadequate macro- and micronutrient intake, and underweight and obesity, adversely affect the intrauterine environment and foetal nutrient availability for foetal growth and development, leading to increased risks of pre-term birth, SGA and LGA.[4–7] Adaptations in maternal and foetal metabolic pathways underlie at least part of the associations between adverse maternal factors and pre-term birth, SGA and LGA. Thus far, studies mainly focused on conventional biomarkers of metabolic status, such as glucose, insulin and lipid concentrations. These studies suggest that higher maternal concentrations of glucose, cholesterol and triglycerides, already from early-pregnancy onwards, are related to altered foetal growth trajectories and increased risks of pre-term birth and LGA.[8–10]

Detailed characterization of maternal and foetal metabolite profiles by metabolomics techniques may provide more in-depth insights in these mechanisms.[11–13] Several, mostly small, metabolomics studies have been performed to identify differences in cord blood metabolite profiles related to birth weight and length of gestation. Although inconsistencies and differences between individual metabolites identified exist, these studies observed different amino acid (AA), fatty acid, phospholipid (PL) and acyl-carnitine (Carn.a) profiles in cord blood of infants born pre-term, SGA and LGA, which suggests that alterations in infant lipid- and amino acid metabolism may be involved.[14–25] For instance, studies among 163 and 700 infants from Germany showed that PL concentrations, particularly lysophosphatidylcholines, were positively associated with birth weight whereas concentrations of non-esterified fatty acids (NEFA) were negatively associated with birth weight.[20,21]

Fewer studies focused on maternal metabolite profiles, but those that did identified similar metabolite groups to be associated with length of gestation and birth weight.[26–32] Birth weight is the endpoint of foetal growth and is the result of different foetal growth trajectories. Thus far, only two studies assessed directly measured foetal growth and observed associations of maternal early-pregnancy urinary branched-chain amino acid (BCAA) concentrations, taurine, histidine and malonate and foetal weight change between 12 and 34 weeks of gestation and foetal anterior abdominal wall width at 34 weeks of gestation.[27,32] Whether these associations are also present for blood metabolite concentrations and with other foetal biometric measures from first trimester onwards remains unclear. Identifying maternal early-pregnancy and foetal metabolic profiles related to different detailed foetal growth measures throughout pregnancy and adverse birth outcomes may help to understand the mechanisms linking a suboptimal maternal environment to adverse offspring health outcomes.

Therefore, in a population-based cohort among 976 Dutch pregnant women and their children, we assessed the associations of maternal early-pregnancy and infant serum concentrations of amino acids (AA), NEFA, PL and carnitines (Carn) with foetal growth measures from first trimester onwards and the odds of adverse birth outcomes.

2 | METHODS

2.1 | Study population

This study was embedded in the Generation R Study, a prospective population-based cohort study among pregnant women and their children in Rotterdam, the Netherlands.[33,34] The study was approved by the Medical Ethical Committee of the Erasmus Medical Center, University Medical Center, Rotterdam (MEC 198.782/2001/31). Written informed consent was obtained from all women participating in the study. Metabolomics data were available in a subgroup of 1004 Dutch mother–child pairs, of which 996 had metabolomics data available in early-pregnancy and/or at birth. Of these, 976 children were singleton and live born and had information available on at least one growth measure during pregnancy or at birth (Figure S1).

2.2 | Metabolite measurements

As described in detail previously,[35] serum concentrations (μmol/L) of AA, NEFA, PL (including diacyl-phosphatidylcholines [PC.aa], acyl-alkyl-phosphatidylcholines [PC.ae], acyl-lysophosphatidylcholines [Lyso.PC.a], alkyl-lysophosphatidylcholines [Lyso.PC.e] and sphingomyelines [SM]) and Carn (including free carnitine [Free Carn] and acyl-carnitines [Carn.a]), were measured in maternal blood in early-pregnancy (median gestational age: 12.8 weeks [95% range: 9.9, 16.9]) and at birth in cord blood (median gestational age at birth: 40.3 weeks [95% range: 36.6, 42.4]). Metabolite measurements were performed at the Dr. von Hauner Children's Hospital, Munich, Germany. AA were analysed with 1100 high-performance liquid chromatography (HPLC) system (Agilent, Waldbronn, Germany) coupled to a API2000 tandem mass spectrometer (AB Sciex, Darmstadt, Germany).[36] IUPAC-IUB Nomenclature was used for notation of the AA.[37] NEFA, PL and Carn were measured with a 1200 SL HPLC system (Agilent, Waldbronn, Germany) coupled to a 4000QTRAP tandem mass spectrometer (AB Sciex, Darmstadt, Germany).[38,39] The analytical technique used is capable of determining the total number of double bonds, but not the position of the double bonds and the distribution of the

carbon atoms between fatty acid side chains. We used the following notation for NEFA, PL and Carn.a: X:Y, where X denotes the length of the carbon chain, and Y the number of double bonds. The "a" denotes an acyl chain bound to the backbone via an ester bond ("acyl-") and the "e" represents an ether bond ("alkyl-"). For analyses, we categorized metabolites into total metabolite groups based on chemical structure (AA, NEFA, PC.aa, PC.ae, Lyso.PC.a, Lyso.PC.e, SM, Free Carn and Carn.a) and in detailed metabolite subgroups based on chemical structure and physiological and biological relevance (AA: BCAA, aromatic amino acids [AAA], essential AA, non-essential AA; NEFA, PC.aa, PC.ae, Lyso.PC.a, Lyso.PC.e and SM: saturated, mono-unsaturated, poly-unsaturated; Carn.a: short-chain, medium-chain, long-chain). Detailed descriptive information on total metabolite groups, metabolite subgroups and individual metabolites have been provided elsewhere.[35] We calculated the sum of the individual metabolite concentrations per total and metabolite subgroup. To obtain normal distributions, individual metabolite concentrations were square root transformed. To facilitate interpretation of the results, SD scores (SDS) were calculated for both the metabolite groups and the individual metabolites.

2.3 | Foetal growth and adverse birth outcomes

Foetal ultrasound examinations were performed in each trimester of pregnancy. Gestational age was established using data from the first foetal ultrasound examination.[40] Second and third trimester foetal head circumference (HC), abdominal circumference (AC) and femur length (FL) were measured to the nearest millimetre using standardized ultrasound procedures. We calculated estimated foetal weight (EFW) using the formula of Hadlock et al.[41] First trimester crown to rump length (CRL) was measured between 10 weeks 0 days to 13 weeks 6 days of gestation and used as a growth measure in a subgroup of participants with reliable information on the first day of the last menstrual period and a regular menstrual cycle.[42]

Information on infant's sex, date of birth, weight, length and HC at birth was obtained from medical records. For all infants, we constructed gestational age adjusted SDS for all foetal growth characteristics using reference charts from the complete cohort[40] and gestational age and sex adjusted SDS for birth measurements using Swedish growth charts.[43] Small and LGA were defined as the lowest and the highest 10 percentiles of gestational age and sex adjusted birthweight in the study cohort. Pre-term birth was defined as a gestational age at birth <37 weeks.

2.4 | Covariates

Information on maternal age, pre-pregnancy body mass index, parity and educational level were collected by questionnaire at enrollment in the study. Information on average daily total energy intake (kcal/day) was obtained by a single food frequency questionnaire in first trimester of pregnancy. Smoking and alcohol intake during pregnancy were assessed by questionnaire in each trimester.

2.5 | Statistical analysis

First, we assessed the associations of maternal early-pregnancy total metabolite groups and individual metabolites with foetal growth measures in each trimester of pregnancy and at birth, using linear regression models. Similarly, we assessed the associations of infant total metabolite groups and individual metabolites with foetal growth characteristics at birth. For maternal and infant total metabolite groups that were significantly associated with the outcomes, we additionally assessed the associations of metabolite subgroups with these outcomes. Second, we examined the associations of maternal and foetal metabolite concentrations with the odds of SGA and LGA at birth and pre-term birth using logistic regression models. Two models were created. The crude model included the exposure only. The adjusted model additionally included maternal age, parity, education level, pre-pregnancy BMI, smoking and alcohol consumption during pregnancy and total energy intake.[4–7,44–47] These possible confounders were selected based on associations with exposure and outcomes in the existing literature. As previous analyses in the same cohort did not show any differences in metabolite concentrations between boys and girls,[35] and including infant sex in the models did not change the effect estimates, we did not include this factor in our models. Missing values of covariates were imputed using multiple imputation by chained equations (R package MICE).[48] Percentages of missing values in the population of analysis varied between 0.7% and 15.0%. Imputed values were compared to original values and no appreciable differences were observed. Pooled results from five imputed datasets were reported. All statistical tests were two-sided. False Discovery Rate (FDR)-adjusted ($p < 0.002$, FDR = 5%) and Bonferroni-adjusted ($p < 1.05e\text{-}5$, based on 4741 tests performed for the adjusted model) statistical significance thresholds are reported. _P-values lower than the FDR adjusted significance threshold were considered statistically significant. The analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing).[49]

3 | RESULTS

3.1 | Characteristics of the study population

Table 1 shows the characteristics of the study population. The children were born at a median gestational age of 40.3 weeks (95% range: 36.7, 42.4) with a median birth weight of 3550 grams (95% range: 2532, 4548).

3.2 | Infant metabolite profiles, foetal growth and adverse birth outcomes

Figure 1(A) shows that, after FDR correction for multiple testing, higher infant total NEFA concentrations were associated with a lower weight, length and HC at birth (differences: −0.13 SD [95% CI: −0.20, −0.07], −0.16 SD [95% CI: −0.24, −0.08] and − 0.14 SD [95% CI: −0.23, −0.05] respectively, per SD increase in total NEFA concentrations). Higher infant total lyso.PC.a concentrations were

TABLE 1 Characteristics of the study population

	Total study population ($n = 976$)
Maternal characteristics	
Age, mean (SD), years	31.5 (4.2)
Pre-pregnancy BMI, median (95% range), kg/m^2	22.5 (18.5, 33.4)
Education, *n* (%)	
Primary	21 (2.2)
Secondary	335 (34.6)
Higher	613 (63.3)
Parity, nulliparous (%)	590 (60.5)
Smoking during pregnancy, Yes (%)	213 (24.0)
Alcohol consumption during pregnancy, Yes (%)	603 (68.2)
Total energy intake, mean (SD), kcal/d	2127.1 (495.0)
Total AA concentrations, mean (SD), μmol/L	2897.5 (506.4)
Total NEFA concentrations, mean (SD), μmol/L	172.5 (102.4)
Total PC.aa concentrations, mean (SD), μmol/L	1877.1 (498.6)
Total PC.ae concentrations, mean (SD), μmol/L	192.0 (48.4)
Total Lyso.PC.a concentrations, mean (SD), μmol/L	187.4 (48.7)
Total Lyso.PC.e concentrations, mean (SD), μmol/L	3.1 (0.9)
Total SM concentrations, mean (SD), μmol/L	419.8 (93.07)
Total Free Carn concentrations, mean (SD), μmol/L	25.2 (6.2)
Total Carn.a concentrations, mean (SD), μmol/L	5.1 (1.35)
Offspring characteristics	
Sex, Male (%)	522 (53.5)
Gestational age at first trimester growth measurements, median (95% range), weeks	12.3 (10.6, 13.7)
First trimester CRL, mean (SD), mm	61 (11)
Gestational age second trimester growth measurements, median (95% range), weeks	20.5 (18.8, 22.8)
Second trimester AC, mean (SD), mm	157 (13)
Second trimester HC, mean (SD), mm	179 (12)
Second trimester FL, mean (SD), mm	33 (3)
Second trimester EFW, median (95% range), g	363 (254, 570)
Gestational age third trimester growth measurements, median (95% range), weeks	30.4 (28.5, 32.5)
Third trimester AC, mean (SD), mm	266 (17)
Third trimester HC, mean (SD), mm	286 (12)
Third trimester FL, mean (SD), mm	57 (3)
Third trimester EFW, median (95% range), g	1620 (1178, 2226)
Gestational age at birth, median (95% range), weeks	40.3 (36.7, 42.4)
Birth HC, mean (SD), cm	34.0 (1.6)
Birth weight, median (95% range), g	3550 (2532, 4548)
Birth length, mean (SD), cm	50.6 (2.3)
Preterm birth, n (%)	28 (2.9)
SGA, n (%)	98 (11.2)
LGA, n (%)	98 (11.2)
Total AA concentrations, mean (SD), μmol/L	3880.7 (672.6)
Total NEFA concentrations, mean (SD), μmol/L	206.3 (82.7)
Total PC.aa concentrations, mean (SD), μmol/L	786.9 (205.6)
Total PC.ae concentrations, mean (SD), μmol/L	76.7 (20.7)

TABLE 1 (Continued)

	Total study population ($n = 976$)
Total Lyso.PC.a concentrations, mean (SD), μmol/L	146.1 (36.1)
Total Lyso.PC.e concentrations, mean (SD), μmol/L	1.7 (0.5)
Total SM concentrations, mean (SD), μmol/L	230.8 (62.9)
Total Free Carn concentrations, mean (SD), μmol/L	16.8 (4.6)
Total Carn.a concentrations, mean (SD), μmol/L	6.1 (1.7)

Abbreviations: AC, abdominal circumference; AA, amino acids; EFW, estimated foetal weight; FL, femur length; HC, head circumference; NEFA, non-esterified fatty acids; PC.aa, diacyl-phosphatidylcholines; PC.ae, acyl-alkyl-phosphatidylcholines; Lyso.PC.a, acyl-lysophosphatidylcholines; Lyso.PC.e, alkyl-lysophosphatidylcholines; SM, sphingomyelines; Free Carn, free carnitine; Carn.a, acyl-carnitines; SGA, small size-for-gestational age at birth; LGA, largesize-for gestational age at birth.
Note: Values represent mean (SD), median (95% range) or number of participants (valid %).

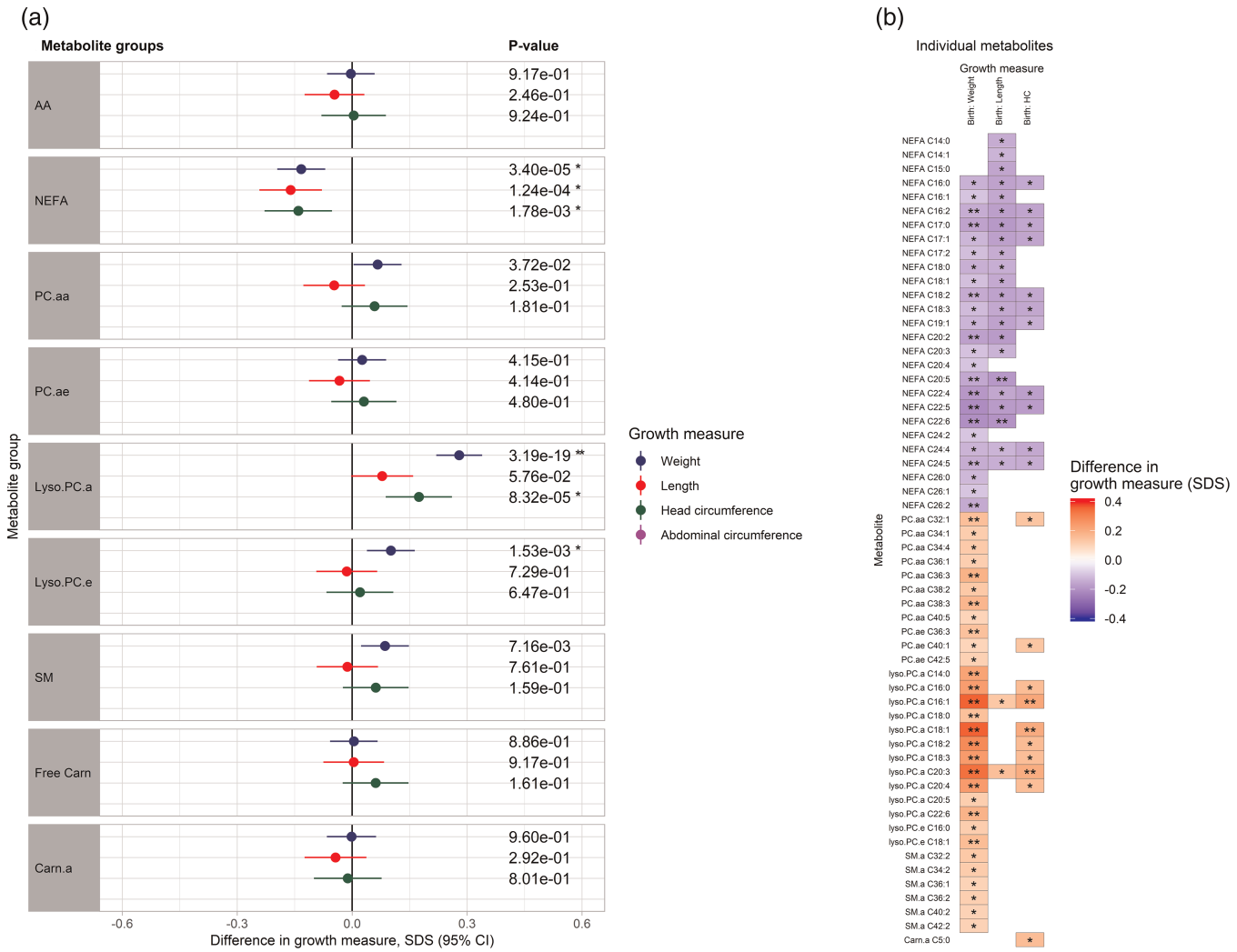

FIGURE 1 Associations of cord blood total metabolite groups and individual metabolites with growth measures at birth. Values are regression coefficients (95% CI) representing the difference in growth measures per SD increase in total metabolite group concentrations (A) or individual metabolite concentrations (B). (B) Presents only FDR significant effect estimates. All estimates are given in Table S2. Models are adjusted for maternal age, parity, education level, pre-pregnancy BMI, smoking and alcohol consumption during pregnancy and total energy intake. AA, amino acids; NEFA, non-esterified fatty acids; PC.aa, diacyl-phosphatidylcholines; PC.ae, acyl-alkyl-phosphatidylcholines; Lyso.PC.a, acyl-lysophosphatidylcholines; Lyso.PC.e, alkyl-lysophosphatidylcholines; SM, sphingomyelines; Free Carn: free carnitine; Carn.a, acyl-carnitines; HC, Head circumference. *p values < 0.002 (FDR-adjusted significance threshold). **p values < 1.05e-5 (Bonferroni-adjusted significance threshold)

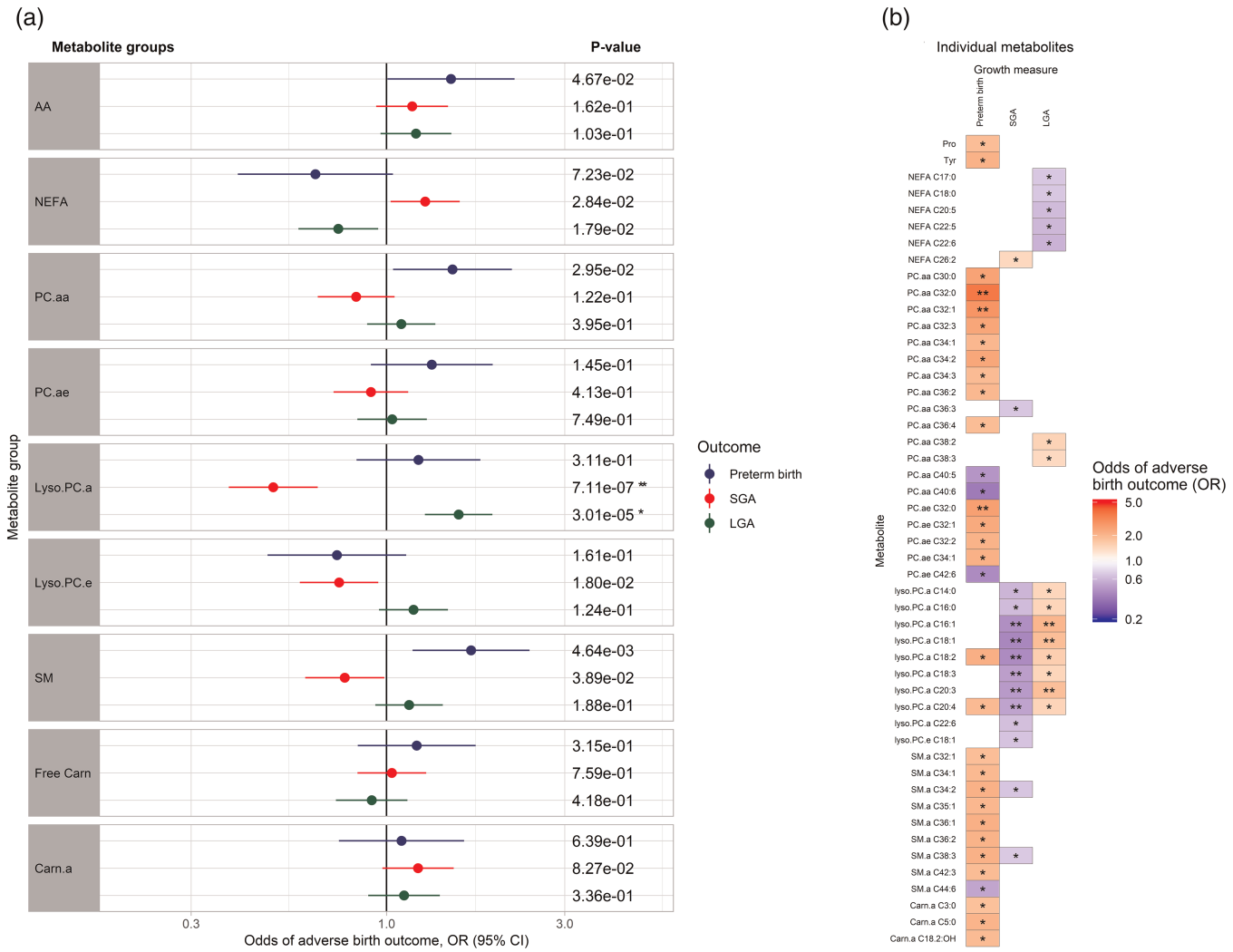

FIGURE 2 Associations of cord blood total metabolite groups and individual metabolites with the odds of adverse birth outcomes. Values are odds ratios (95% CI) representing the risk of adverse birth outcomes per SD increase in total metabolite group concentrations (A) or individual metabolite concentrations (B). (B) presents only FDR significant effect estimates are presented. All estimates are given in Table S2. Models are adjusted for maternal age, parity, education level, pre-pregnancy BMI, smoking and alcohol consumption during pregnancy and total energy intake. AA, amino acids; NEFA, non-esterified fatty acids; PC.aa, diacyl-phosphatidylcholines; PC.ae, acyl-alkyl-phosphatidylcholines; Lyso.PC.a, acyl-lysophosphatidylcholines; Lyso.PC.e, alkyl-lysophosphatidylcholines; SM, sphingomyelines; Free Carn: free carnitine, Carn.a, acyl-carnitines; SGA, small size-for-gestational age at birth; LGA, large size-for gestational age at birth. *p values <0.002 (FDR-adjusted significance threshold). **p values < 1.05e-5 (Bonferroni-adjusted significance threshold)

associated with a higher birth weight and HC at birth (differences: 0.28 SD [95% CI: 0.22, 0.34] and 0.17 SD [95% CI: 0.09, 0.26], respectively, per SD increase in total lyso.PC.a concentrations). Higher infant total lyso.PC.e concentrations were associated with a higher birth weight only (difference: 0.10 SD [95% CI: 0.04, 0.16] per SD increase in total lyso.PC.e concentrations). The association of total lyso.PC.a concentrations with birth weight persisted after Bonferroni correction. Figure S2 shows that the associations of mono-unsaturated lyso.PC.a with birth weight are stronger than those for saturated- and poly-unsaturated lyso.PC.a. No appreciable differences in the strength of the associations of lyso.PC.a subgroups with birth length and HC and of NEFA and lyso.PC.e with weight, length or HC were present. Figure 1(B) shows that higher individual infant metabolite concentrations of PL were associated with higher birth weight, whereas higher concentrations of NEFA were associated with lower birth weight. These associations were the strongest for lyso.PC.a C18:1, C16:1, C20:3, C18:2 and C20:4. The associations of individual metabolites with birth length mainly included NEFA in negative direction and were the strongest for NEFA C22:6, C20:5, C17:0, C20:2 and C22:5. Associations of individual metabolite concentrations with HC at birth were present for several individual lyso.PC.a in positive direction and NEFA in negative direction and were the strongest for lyso.PC.a C16:1, C18:1, C20:3, and NEFA C22:5 and C22:4. About half of the observed associations for individual metabolites, mainly those of lyso.PC.a and NEFA with birth weight, persisted after Bonferroni correction.

Figure 2(A) shows that higher infant total lyso.PC.a concentrations were associated with a lower odds of SGA and a higher odds of LGA (OR: 0.50 [95% CI: 0.38, 0.65] and OR: 1.56 [95% CI: 1.27, 1.92], respectively, per SD increase in total lyso.PC.a concentrations). The association of lyso.PC.a with the odds of SGA remained significant after Bonferroni correction. Figure S3 shows that the associations of mono- and poly-unsaturated lyso.PC.a subgroup concentrations with the odds of SGA and LGA were stronger than those for saturated lyso.PC.a subgroup concentrations. Figure 2(B) shows that several individual PL were associated with the odds of pre-term birth, with the strongest associations for PC.aa C32:0, C32:1, C40:6, C30:0 and PC.ae C32:0. Associations of individual metabolite concentrations with the odds of SGA were mainly present for lyso.PC.a. Higher concentrations of individual lyso.PC.a were associated with lower odds of SGA and were the strongest for lyso.PC.a C18:1, C18:2, C16:1 C20:3 and C18:3. Associations of individual metabolites with the odds of LGA were mainly present for lyso.PC.a and NEFA. Higher concentrations of individual lyso.PC.a were associated with higher odds of LGA, whereas higher concentrations of NEFA were associated with lower odds of LGA. The associations were the strongest for lyso.PC.a C16:1, C18:1, C20:3, and NEFA C22:6 and C20:5. About 20% of the observed associations for individual metabolites, mainly for lyso.PC.a with the risks of SGA and LGA, persisted after Bonferroni correction. The effect estimates and p-values for all associations assessed for infant metabolite groups and individual metabolites are given in Tables S1 (crude models) and S2 (adjusted models). Results from the crude models were similar to those of the adjusted models.

3.3 | Maternal metabolite profiles, foetal growth and adverse birth outcomes

Figure S4(A)–(D) shows that, after FDR correction for multiple testing, maternal total metabolite group concentrations in early-pregnancy were not associated with foetal growth measures from first trimester onwards. Few associations of individual maternal metabolites were present and included negative associations of mainly individual maternal PCae, and some PC.aa, lyso.PC.a, SM and Carn.a with FL and HC in third trimester and weight and HC at birth (Figure S4E). None of these associations persisted after Bonferroni correction for multiple testing.

Figure S5 and Table S3 show that no associations were present of total maternal metabolite groups or individual metabolite concentrations with the odds of adverse birth outcomes. The effect estimates and p-values for all associations assessed for maternal metabolite groups and individual metabolites are given in Tables S3 (adjusted models) and S4 (crude models). Results from the crude models were similar to those from the adjusted models.

4 | DISCUSSION

Infant metabolite concentrations, particularly total and individual NEFA and lyso.PC.a concentrations, were associated with weight, length and HC at birth and the odds of SGA and LGA. Several individual PL were associated with the odds of pre-term birth. Concentrations of a few individual maternal metabolites, mainly PC.ae, were associated with AC and FL in third trimester and weight and HC at birth.

4.1 | Interpretation of main findings

Adaptations in maternal and foetal metabolism may predispose the offspring to altered foetal growth and increased risks of adverse birth outcomes. Infant metabolite profiles related to birth weight and the risks of SGA and LGA have been studied extensively, both in small (nested-) case–control studies and in a few larger cohort studies. These studies observed that cord blood concentrations of amino acids, carnitines, PL, NEFA and several other lipids were associated with a the risk of low birth weight and foetal growth restriction, although inconsistencies in specific metabolites and direction of the effect exist.[14–25,50,51] Our observation that higher total and individual concentrations of NEFA were associated with a lower birth weight, a lower odds of LGA and a higher odds of SGA, while higher total and individual concentrations and individual concentrations of lyso.PC.a were associated with a higher birth weight, a higher odds of LGA and a lower odds of SGA is in line with those from several previous cohort studies. A study among 226 infants from Germany observed that lyso.PC C14:0, C16:1 and C18:1 were positively correlated with birth weight.[20] A study among 700 infants from Germany showed that, among other metabolites, lyso.PC.a C16:1, C18:1, C20:3, C18:2, C20:4, C14:0, C16:0, and C18:3 were positively associated with birth weight, whereas NEFA C22:6, NEFA C20:5, and PC.ae C38:0 were negatively associated with birth weight.[21] Thus far, studies assessing the associations of infant metabolite profiles with other infant anthropometrics are lacking. We observed that higher total and individual concentrations of NEFA were also associated with lower length and HC at birth. Total and individual concentrations of lyso.PC.a were associated with HC at birth, but not with birth length. Very few studies have examined the metabolite profiles of infants born pre-term. These studies generally suggest lower concentrations of AA and Carn.a in those born pre-term.[23,52,53] In contrast to the associations for SGA and LGA where we mainly observed associations for NEFA and lyso.PC.a, we observed that individual concentrations of several PC.aa, PC.ae, SM, and a few AA and Carn.a were associated with the risk of pre-term birth. This may suggest that suboptimal size-for-gestational age at birth and pre-term birth are characterized by distinct cord blood metabolite profiles. This is supported by the fact these conditions often have different etiologies.[54,55] Suboptimal size at birth mainly reflects genetic predisposition, maternal nutritional status, including maternal body mass index and gestational weight gain, and suboptimal glucose metabolism, whereas pre-term delivery might also result from infection, uteroplacental ischaemia or haemorrhage, uterine overdistension or stress.[54,55]

Cord blood metabolite profiles result from both placental transfer and endogenous synthesis in response to either maternal or foetal environment and are therefore reflective of maternal metabolism,

placental transfer and foetal metabolism.[56] The exact mechanisms linking foetal metabolite profiles to foetal growth are not clear. It has been suggested that lower lyso.PC concentrations are related to increased foetal insulin resistance and decrease insulin secretion, which might explain the positive associations between lyso.PC.a concentrations and birth weight.[20] Also, lyso.PC are involved in several inflammatory processes that may interfere with foetal growth.[21] Alternatively, given the cross-sectional nature of the associations of cord metabolite profiles with birth anthropometrics and adverse birth outcomes, infant metabolic profiles might also be the result of suboptimal foetal growth. It has been suggested that the inverse association of infant NEFA with foetal growth measures might reflect the mobilization of lipids as an alternative source of energy in those that are growth restricted[51] and decreased lipolytic activity and increased incorporation of NEFA in foetal adipose tissue in macrosomia.[21] Although the role of lyso.PC.a in foetal metabolism unknown, in adults lyso.PC are derived from phosphatidycholine (PC) mainly by transfer of fatty acids to free cholesterol by lecithin-cholesterol acyltransferase or by hydrolysis of the fatty acid at the sn-2 position by phospholipase A_2.[57] It has been suggested that larger foetuses generally experience higher levels of hypoxia, which may activate these phospholipases and subsequently the generation of lyso.PC.[20] Future studies are needed to assess the direction of the associations between cord blood metabolites and foetal growth and adverse birth outcomes, and to disentangle the exact mechanism underlying these associations.

Several previous, mostly small, studies have assessed the associations of detailed maternal serum, plasma and urinary metabolite profiles with the risks of pre-term birth, SGA, and LGA. These studies generally identified metabolites related to AA and lipid metabolism associated with length of gestation, birth weight and more detailed measures of infant adiposity.[26–32,58–61] Thus far, only two studies assessed the associations of maternal metabolite concentrations during pregnancy with more detailed measures of foetal growth and showed associations of maternal early-pregnancy urinary BCAA concentrations, taurine, histidine and malonate and foetal weight change between 12 and 34 weeks of gestation and foetal anterior abdominal wall width at 34 weeks of gestation.[27,32] In the current study, we observed very few associations of mainly individual maternal PL with FL and HC in third trimester and weight and HC at birth. No associations were observed for total metabolite concentrations. These observations are partly in line with the results of the previous studies. A study among 121 pregnant women and their children from the United States identified maternal third trimester plasma PC.ae C40:4, C40:5, C42:5, C42:6, C44:5 and C44:6 concentrations, each containing fatty acid C20:4, to be associated with infant percentage of body fat at age 1 month.[30]

In contrast to the previous studies that mainly assessed foetal or infant weight and adiposity, we observed the strongest associations between individual PC.ae concentrations and weight and HC at birth. PL in maternal blood are hydrolyzed to fatty acids preceding placental transfer.[62–64] We speculate that the observed associations of mainly maternal individual PL with offspring HC and birth weight might reflect the availability of fatty acids for placental transfer. The strongest associations were present for several individual PC.ae. Many of these contain n-3 polyunsaturated fatty acids, which have been suggested to be important for foetal growth, brain development and fat accrual.[65] We did not observe any association with first and second trimester growth measurements, which might be due to lower power resulting from a smaller number of participants included in first trimester or a smaller variability in the growth measurements. In addition, the timing of metabolite measurements might explain the limited amount of associations observed. As foetal brain growth and body fat development primarily occur in third trimester, it might be that stronger associations would be present for maternal metabolites concentrations measured later in pregnancy. Thus, only few individual maternal early-pregnancy metabolite concentrations are associated with foetal growth measures from first trimester onwards.

We identified a few maternal individual metabolites associated with foetal growth characteristics and detailed infant metabolite profiles cross-sectionally associated with infant anthropometrics at birth and adverse birth outcomes. In particular the associations of cord blood metabolites were strong, robust to correction for multiple testing, and consistent with previous research. Metabolite profiles have been shown to be strongly related to socio-demographic factors and lifestyle. However, adjusting the models for these factors did not materially change the effect estimates, suggesting that these factors do not strongly confound the associations between maternal and infant metabolite profiles and foetal growth and adverse birth outcomes. Adverse birth outcomes are major risk factors for both infant morbidity and mortality and cardio-metabolic disease in childhood and adulthood. Our results serve as a first step in understanding of the biological mechanisms underlying the associations of an adverse intrauterine environment with these outcomes. Further research is needed to assess whether differences in infant metabolite profiles are cause or result of altered foetal growth patterns.

4.2 | Strengths and limitations

This study was embedded in a large population-based cohort from early-pregnancy onwards. We had detailed measurements available on foetal biometry starting from first trimester, enabling us to prospectively study the associations of maternal metabolite profiles with foetal growth. However, it should be noted that given that the analyses with cord blood metabolites are cross-sectional, there is a possibility of reverse causation in these associations. We had metabolomics data available in a relatively large sample in both pregnant women in early-pregnancy and the offspring at birth. Metabolomics data were available in a subgroup of the cohort, consisting of Dutch, relatively high educated women and their children. This selection to a healthier, more affluent population might have affected the generalizability of our results to other populations. We applied a targeted metabolomics approach, which enabled us to study the metabolomics relevant for obesity and cardio-metabolic disease. However, relevant metabolites for the specific association under study might be missed. Due to the

analytical platform used, we not were able to determine the position of the double bonds and the distribution of the carbon atoms between fatty acid side chains, and were therefore not able to exactly identify the metabolites under study. Further untargeted and targeted metabolomics studies using different analytical platforms are desired to replicate and confirm our findings. The prevalence for pre-term birth in the study population was relatively low. This might have influenced power to detect statistically significant effect estimates for pre-term birth. We have adjusted our models for many possible confounders. However, residual confounding, for example by maternal physical activity and dietary habits cannot be excluded.

5 | CONCLUSIONS

Our results suggest that infant metabolite profiles, particularly total and individual lyso.PC.a and NEFA concentrations, were strongly related to growth measures at birth and the odds of adverse birth outcomes. Few individual maternal early-pregnancy metabolites, but not total metabolite concentrations, are associated with foetal growth measures in third trimester and at birth.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

Ellis Voerman, Vincent W. V. Jaddoe, Janine F. Felix, Berthold Koletzko, and Romy Gaillard were involved in the conception and design of the study. Engy Shokry and Berthold Koletzko were involved in data acquisition. Ellis Voerman performed the data processing and statistical analysis. Ellis Voerman and Romy Gaillard interpreted the data and drafted the article. Vincent W. V. Jaddoe, Engy Shokry, George J. G. Ruijter, Janine F. Felix and Berthold Koletzko revised the article for important intellectual content. All authors approved the final manuscript and agree to be accountable for all aspects of the work.

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REFERENCES

1. Lawn JE, Cousens S, Zupan J. Lancet neonatal survival steering T. 4 million neonatal deaths: when? Where? Why? *Lancet*. 2005;365 (9462):891-900.
2. Mendez-Figueroa H, Truong VT, Pedroza C, Chauhan SP. Morbidity and mortality in small-for-gestational-age infants: a secondary analysis of nine MFMU network studies. *Am J Perinatol*. 2017;34(4): 323-332.
3. Knop MR, Geng TT, Gorny AW, et al. Birth weight and risk of type 2 diabetes mellitus, cardiovascular disease, and hypertension in adults: a meta-analysis of 7 646 267 participants from 135 studies. *J Am Heart Assoc*. 2018;7(23):e008870.
4. Caradeux J, Serra R, Palmeiro Y, et al. Correlation between maternal characteristics during early pregnancy, fetal growth rate and newborn weight in healthy pregnancies. *Gynecol Obstet Invest*. 2016;81(3): 202-206.
5. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med*. 2008;359(1):61-73.
6. Santos S, Voerman E, Amiano P, et al. Impact of maternal body mass index and gestational weight gain on pregnancy complications: an individual participant data meta-analysis of European, North American and Australian cohorts. *BJOG*. 2019;126(8):984-995.
7. Danielewicz H, Myszczyszyn G, Dębińska A, Myszkal A, Boznański A, Hirnle L. Diet in pregnancy-more than food. *Eur J Pediatr*. 2017;176 (12):1573-1579.
8. Geurtsen ML, van Soest EEL, Voerman E, Steegers EAP, Jaddoe VWV, Gaillard R. High maternal early-pregnancy blood glucose levels are associated with altered fetal growth and increased risk of adverse birth outcomes. *Diabetologia*. 2019;62 (10):1880-1890.
9. Kulkarni SR, Kumaran K, Rao SR, et al. Maternal lipids are as important as glucose for fetal growth: findings from the Pune Maternal Nutrition Study. *Diabetes Care*. 2013;36(9):2706-2713.
10. Vrijkotte TG, Krukziener N, Hutten BA, Vollebregt KC, van Eijsden M, Twickler MB. Maternal lipid profile during early pregnancy and pregnancy complications and outcomes: the ABCD study. *J Clin Endocrinol Metab*. 2012;97(11):3917-3925.
11. Bictash M, Ebbels TM, Chan Q, et al. Opening up the "black box": metabolic phenotyping and metabolome-wide association studies in epidemiology. *J Clin Epidemiol*. 2010;63(9):970-979.

12. Tzoulaki I, Ebbels TM, Valdes A, Elliott P, Ioannidis JP. Design and analysis of metabolomics studies in epidemiologic research: a primer on -omic technologies. *Am J Epidemiol*. 2014;180(2):129-139.
13. van Roekel EH, Loftfield E, Kelly RS, Zeleznik OA, Zanetti KA. Metabolomics in epidemiologic research: challenges and opportunities for early-career epidemiologists. *Metabolomics*. 2019;15(1):9.
14. Sanchez-Pintos P, de Castro MJ, Roca I, Rite S, Lopez M, Couce ML. Similarities between acylcarnitine profiles in large for gestational age newborns and obesity. *Sci Rep*. 2017;7(1):16267.
15. Ivorra C, Garcia-Vicent C, Chaves FJ, Monleon D, Morales JM, Lurbe E. Metabolomic profiling in blood from umbilical cords of low birth weight newborns. *J Transl Med*. 2012;10:142.
16. Miranda J, Simoes RV, Paules C, et al. Metabolic profiling and targeted lipidomics reveals a disturbed lipid profile in mothers and fetuses with intrauterine growth restriction. *Sci Rep*. 2018;8(1):13614.
17. Sanz-Cortes M, Carbajo RJ, Crispi F, Figueras F, Pineda-Lucena A, Gratacos E. Metabolomic profile of umbilical cord blood plasma from early and late intrauterine growth restricted (IUGR) neonates with and without signs of brain vasodilation. *PLoS One*. 2013;8(12):e80121.
18. Favretto D, Cosmi E, Ragazzi E, et al. Cord blood metabolomic profiling in intrauterine growth restriction. *Anal Bioanal Chem*. 2012;402(3):1109-1121.
19. Perng W, Rifas-Shiman SL, McCulloch S, et al. Associations of cord blood metabolites with perinatal characteristics, newborn anthropometry, and cord blood hormones in project viva. *Metabolism*. 2017;76:11-22.
20. Lu YP, Reichetzeder C, Prehn C, et al. Cord blood Lysophosphatidylcholine 16: 1 is positively associated with birth weight. *Cell Physiol Biochem*. 2018;45(2):614-624.
21. Hellmuth C, Uhl O, Standl M, et al. Cord blood metabolome is highly associated with birth weight, but less predictive for later weight development. *Obes Facts*. 2017;10(2):85-100.
22. Sun H, Wang YC, Wang CC, et al. Metabolic profiling of umbilical cord blood in macrosomia. *Int J Obes (Lond)*. 2018;42(4):679-685.
23. Alexandre-Gouabau MC, Courant F, Moyon T, et al. Maternal and cord blood LC-HRMS metabolomics reveal alterations in energy and polyamine metabolism, and oxidative stress in very-low birth weight infants. *J Proteome Res*. 2013;12(6):2764-2778.
24. Robinson O, Keski-Rahkonen P, Chatzi L, et al. Cord blood metabolic signatures of birth weight: a population-based study. *J Proteome Res*. 2018;17(3):1235-1247.
25. Shokry E, Marchioro L, Uhl O, et al. Transgenerational cycle of obesity and diabetes: investigating possible metabolic precursors in cord blood from the PREOBE study. *Acta Diabetol*. 2019;56(9):1073-1082.
26. Kadakia R, Nodzenski M, Talbot O, et al. Maternal metabolites during pregnancy are associated with newborn outcomes and hyperinsulinaemia across ancestries. *Diabetologia*. 2019;62(3):473-484.
27. Walsh JM, Wallace M, Brennan L, McAuliffe FM. Early pregnancy maternal urinary metabolomic profile and later insulin resistance and fetal adiposity. *J Matern Fetal Neonatal Med*. 2015;28(14):1697-1700.
28. Ciborowski M, Zbucka-Kretowska M, Bomba-Opon D, et al. Potential first trimester metabolomic biomarkers of abnormal birth weight in healthy pregnancies. *Prenat Diagn*. 2014;34(9):870-877.
29. Heazell AE, Bernatavicius G, Warrander L, Brown MC, Dunn WB. A metabolomic approach identifies differences in maternal serum in third trimester pregnancies that end in poor perinatal outcome. *Reprod Sci*. 2012;19(8):863-875.
30. Hellmuth C, Lindsay KL, Uhl O, et al. Maternal Metabolomic profile and fetal programming of offspring adiposity: identification of potentially protective lipid metabolites. *Mol Nutr Food Res*. 2019;63(1):e1700889.
31. Maitre L, Fthenou E, Athersuch T, et al. Urinary metabolic profiles in early pregnancy are associated with preterm birth and fetal growth restriction in the Rhea mother-child cohort study. *BMC Med*. 2014;12:110.
32. Maitre L, Villanueva CM, Lewis MR, et al. Maternal urinary metabolic signatures of fetal growth and associated clinical and environmental factors in the INMA study. *BMC Med*. 2016;14(1):177.
33. Kooijman MN, Kruithof CJ, van Duijn CM, et al. The generation R study: design and cohort update 2017. *Eur J Epidemiol*. 2016;31(12):1243-1264.
34. Kruithof CJ, Kooijman MN, van Duijn CM, et al. The generation R study: biobank update 2015. *Eur J Epidemiol*. 2014;29(12):911-927.
35. Voerman E, Jaddoe VWV, Uhl O, et al. A population-based resource for intergenerational metabolomics analyses in pregnant women and their children: the generation R study. *Metabolomics*. 2020;16(4):43.
36. Harder U, Koletzko B, Peissner W. Quantification of 22 plasma amino acids combining derivatization and ion-pair LC-MS/MS. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2011;879(7–8):495-504.
37. IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN). Nomenclature and symbolism for amino acids and peptides. Recommendations 1983. *Eur J Biochem*. 1984;138(1):9-37.
38. Hellmuth C, Weber M, Koletzko B, Peissner W. Nonesterified fatty acid determination for functional lipidomics: comprehensive ultrahigh performance liquid chromatography-tandem mass spectrometry quantitation, qualification, and parameter prediction. *Anal Chem*. 2012;84(3):1483-1490.
39. Uhl O, Fleddermann M, Hellmuth C, Demmelmair H, Koletzko B. Phospholipid species in newborn and 4 month old infants after consumption of different formulas or breast Milk. *PLoS One*. 2016;11(8):e0162040.
40. Verburg BO, Steegers EA, De Ridder M, et al. New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. *Ultrasound Obstet Gynecol*. 2008;31(4):388-396.
41. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements-a prospective study. *Am J Obstet Gynecol*. 1985;151(3):333-337.
42. Mook-Kanamori DO, Steegers EA, Eilers PH, Raat H, Hofman A, Jaddoe VW. Risk factors and outcomes associated with first-trimester fetal growth restriction. *Jama*. 2010;303(6):527-534.
43. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). *Acta Paediatr Scand*. 1991;80(8–9):756-762.
44. Taylor K, Ferreira DLS, West J, Yang T, Caputo M, Lawlor DA. Differences in pregnancy metabolic profiles and their determinants between white European and south Asian women: findings from the born in Bradford cohort. *Metabolites*. 2019;9(9):190.
45. Hidalgo-Lopezosa P, Jiménez-Ruz A, Carmona-Torres JM, Hidalgo-Maestre M, Rodríguez-Borrego MA, López-Soto PJ. Sociodemographic factors associated with preterm birth and low birth weight: a cross-sectional study. *Women Birth*. 2019;32(6):e538-e543.
46. Tsimbos C, Verropoulou G. Demographic and socioeconomic determinants of low birth weight and preterm births among natives and immigrants in Greece: an analysis using nationwide vital registration micro-data. *J Biosoc Sci*. 2011;43(3):271-283.
47. Brooke OG, Anderson HR, Bland JM, Peacock JL, Stewart CM. Effects on birth weight of smoking, alcohol, caffeine, socioeconomic factors, and psychosocial stress. *BMJ*. 1989;298(6676):795-801.
48. Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Softw*. 2010;45(1):1-68.
49. R Foundation for Statistical Computing. *R: A Language and Environment for Statistical Computing [computer program]*. Vienna, Austria: R Foundation for Statistical Computing. 2019.
50. Alfano R, Chadeau-Hyam M, Ghantous A, et al. A multi-omic analysis of birthweight in newborn cord blood reveals new underlying

mechanisms related to cholesterol metabolism. *Metabolism*. 2020; 110:154292.
51. Patel N, Hellmuth C, Uhl O, et al. Cord metabolic profiles in obese pregnant women: insights into offspring growth and body composition. *J Clin Endocrinol Metab*. 2018;103(1):346-355.
52. Liu Q, Wu J, Shen W, et al. Analysis of amino acids and acyl carnitine profiles in low birth weight, preterm, and small for gestational age neonates. *J Matern Fetal Neonatal Med*. 2017;30(22):2697-2704.
53. Wilson K, Hawken S, Ducharme R, et al. Metabolomics of prematurity: analysis of patterns of amino acids, enzymes, and endocrine markers by categories of gestational age. *Pediatr Res*. 2014;75(2): 367-373.
54. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371(9606):75-84.
55. Alberico S, Montico M, Barresi V, et al. The role of gestational diabetes, pre-pregnancy body mass index and gestational weight gain on the risk of newborn macrosomia: results from a prospective multicentre study. *BMC Pregnancy Childbirth*. 2014;14:23.
56. Hivert MF, Perng W, Watkins SM, et al. Metabolomics in the developmental origins of obesity and its cardiometabolic consequences. *J Dev Orig Health Dis*. 2015;6(2):65-78.
57. Law SH, Chan ML, Marathe GK, Parveen F, Chen CH, Ke LY. An updated review of Lysophosphatidylcholine metabolism in human diseases. *Int J Mol Sci*. 2019;20(5):4501.
58. Chia AR, de Seymour JV, Wong G, et al. Maternal plasma metabolic markers of neonatal adiposity and associated maternal characteristics: the GUSTO study. *Sci Rep*. 2020;10(1):9422.
59. Morillon AC, Yakkundi S, Thomas G, et al. Association between phospholipid metabolism in plasma and spontaneous preterm birth: a discovery lipidomic analysis in the cork pregnancy cohort. *Metabolomics*. 2020;16(2):19.
60. Sovio U, Goulding N, McBride N, et al. A maternal serum metabolite ratio predicts fetal growth restriction at term. *Nat Med*. 2020;26(3):348-353.
61. Clinton CM, Bain JR, Muehlbauer MJ, et al. Non-targeted urinary metabolomics in pregnancy and associations with fetal growth restriction. *Sci Rep*. 2020;10(1):5307.
62. Herrera E, Ortega-Senovilla H. Maternal lipid metabolism during normal pregnancy and its implications to fetal development. *Clin Lipidol*. 2010;5(6):899-911.
63. Larque E, Demmelmair H, Gil-Sanchez A, et al. Placental transfer of fatty acids and fetal implications. *Am J Clin Nutr*. 2011;94(6 Suppl): 1908S-1913S.
64. Rice GE, Wong MH, Farrugia W, Scott KF. Contribution of type II phospholipase A2 to in vitro phospholipase A2 enzymatic activity in human term placenta. *J Endocrinol*. 1998;157(1):25-31.
65. Demmelmair H, Koletzko B. Importance of fatty acids in the perinatal period. *World Rev Nutr Diet*. 2015;112:31-47.

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