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Maternal mid-pregnancy long-chain polyunsaturated fatty acid profile is associated with pregestational body mass index and neonatal anthropometric measures at birth among non-obese pregnancies: results from two Italian multicenter cohorts

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Abstract

Background Long-chain polyunsaturated fatty acids (LC-PUFAs) are essential nutrients for feto-placental development. We aimed to evaluate the associations between maternal pregestational BMI, mid-pregnancy LC-PUFA status, and delivery outcomes in non-obese pregnancies.

Methods This was a secondary analysis of two Italian cohorts including healthy non-obese women with singleton spontaneous pregnancies previously studied for maternal nutritional habits, multivitamin supplementation, blood biomarkers and infant biometry/measures. In the present analysis, included women were stratified according to pregestational BMI (normal weight (NW) versus overweight (OW) groups). Fasting venous blood samples were collected between 24 and 34 gestational weeks for fatty acid (FA) analysis. Pregnancy outcomes were recorded at delivery. Multi-adjusted generalized linear models were applied to first assess the associations between BMI-based groups and mid-pregnancy LC-PUFA concentrations, and second to evaluate the associations between the LC-PUFA profile and pregnancy outcomes.

Results 283 pregnancies were included. The OW group showed lower eicosapentaenoic acid (EPA) levels (β= -0.09; 95%CI= -0.16; -0.03) and a higher arachidonic acid/EPA ratio (β = 8.06; 95%CI = 0.00; 16.3) compared with the NW group in multi-adjusted models. After excluding women with gestational diabetes mellitus (*n* = 13), a significant association between LC-PUFA status and birth weight was also proved with increased birth weights in case of lower LC-PUFA n-6/n-3 ratio (β= -78.9; 95%CI= -148.5; -9.2) and higher docosahexaenoic acid (DHA) (β = 26.5; 95%CI = 0.4; 52.6), total LC-PUFA n-3 (β = 22.9; 95%CI = 0.7; 45.1) and n-3 index (β = 24.9; 95%CI = 0.03; 49.8). A positive association

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was further detected between LC-PUFA n-6 and neonatal ponderal index (β = 0.01; 95%CI = 0.00; 0.02). No associations were detected between LC-PUFAs and gestational age at delivery.

Conclusions These findings underscore significant associations between maternal pregestational BMI and mid-pregnancy LC-PUFA n-3 and n-6 status, with further associations with birth weight and neonatal ponderal index. Our results suggest that LC-PUFA n-3 and n-6 series may serve as valuable clinical biomarkers, particularly among OW women, and may act as predictors of intrauterine growth.

Trial registration NCT04438928.

Keywords Maternal nutrition, Body mass index, DHA, EPA, Omega-3, Omega-6, Long-chain polyunsaturated fatty acids, Pregnancy, Birth weight, Neonatal ponderal index

Background

Maternal nutritional intake and status have been consistently associated with fetal development, placental function, and long-term health in the offspring [1–3]. In particular, maternal fatty acids (FAs), and primarily long-chain polyunsaturated fatty acids (LC-PUFAs), represent essential regulators of feto-placental development, likely through the modulation of intrauterine oxidative stress, angiogenesis, and inflammation [4]. Based on the first double bond location, LC-PUFAs are grouped into the omega-3 (n-3) and omega-6 (n-6) series. The n-3 series derives from the essential PUFA alpha-linolenic acid (ALA) and includes eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The n-6 series derives from the essential PUFA linoleic acid and includes arachidonic acid (ARA). LC-PUFAs are detectable in various blood fractions and tissues. In particular, red blood cell n-3 PUFA concentrations were more strongly associated with dietary intake than serum concentrations, as the half-life of erythrocytes is much longer than that of plasma lipoproteins [5].

Lipid metabolism is known to significantly change along gestation, mostly as a result of modifications in lipoprotein profiles, hormonal milieu, and placental metabolism [6]. Of note, the human body does not produce significant amounts of LC-PUFAs, whose blood concentrations, placental transfer, and fetal availability are therefore strictly dependent on maternal dietary intake and metabolism [7]. Maternal LC-PUFA intake and status during pregnancy have been strongly associated with fetal brain development, particularly between 24 and 34 weeks of gestation, a time interval that plays a critical role in neurodevelopment [8, 9]. During this window, the fetus accumulates DHA and ARA, which are essential for neuronal membrane formation, synaptogenesis, myelination, overall brain maturation, long-term cognitive outcomes, susceptibility to atopic diseases, and inflammation-mediated pregnancy complications, including preterm birth [10–14].

Deranged maternal, placental, and feto-neonatal lipid profiles have been reported in pregnancies with excessive maternal pregestational body mass index (BMI), as well as in those adhering to a high-fat dietary pattern [15–17]. Moreover, significant changes in the placental expression of metabolites related to lipid synthesis and energy production were described in obese pregnancies, suggesting a shift towards increased placental lipid metabolism and disrupted LC-PUFA biomagnification processes (i.e. the physiological enrichment of LC-PUFAs in the fetal circulation, mainly occurring through the preferential placental transfer of DHA and ARA) [17].

While extreme BMI values are considered high-risk conditions and managed accordingly, a better understanding of metabolic risk profiles in overweight pregnancies could potentially help identify high-risk individuals. The present study aims to evaluate the maternal mid-pregnancy erythrocyte FA profile in healthy, non-obese, Caucasian women with singleton spontaneous pregnancies stratified according to pre-pregnancy BMI. The secondary aim is to investigate the associations between the mid-pregnancy erythrocyte FA profile and delivery outcomes, including adjustment for BMI-based groups. The results could lay the foundation to identify clinical FA biomarkers that may serve both as indicators of status and predictors of outcomes among normal- and overweight women.

Methods

The present study represents a secondary analysis of two Italian cohorts aimed to investigate the effects of maternal dietary pattern adherence and supplementation with multiple micronutrients and DHA(200 mg) on maternal biomarker status, pregnancy outcome, and infant growth. The studies were conducted between September 2016 and June 2020, with the primary results described elsewhere [18–20]. The studies were conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures were approved by the Institutional Ethical Committee "Comitato Etico Milano Area 1" (reference numbers 8292/2016, 33043/2018, and 11187/2016 with trial registration identifier: NCT04438928 [21]). Written informed consent was obtained from all subjects/patients. All participants were pregnant individuals

who self-identified as women; sex and gender identity were not assessed separately.

Briefly, healthy Caucasian non-smoker women (never smoked or having stopped at least before conception), aged between 18 and 42 years, with a pre-gestational body mass index between 18.5 and 29.9 kg/m^2 and a singleton spontaneous pregnancy, were eligible for recruitment. No information on passive smoking was available. Exclusion criteria were: any known maternal pregestational disease or chronic therapy, substance or alcohol abuse, specific diet (i.e. vegan or vegetarian diet), and known fetal anomalies. Included women were grouped based on pregestational BMI in normal weight (NW, pregestational BMI between 18.5 and 24.9 kg/m^2) and overweight groups (OW, pregestational BMI between 25 and 29.9 kg/m^2).

For the present analysis, women who provided venous blood sampling for extensive FA profile determination between 24 and 34 gestational weeks were included. General questionnaires detailing demographic and medical data were collected (age, pregestational BMI, obstetric and medical history). Nutritional supplement use was recorded and women further categorized according to the DHA 200 mg-containing supplement use.

Maternal fasting blood samples were collected from the radial vein at the antenatal clinics of ASST Fatebenefratelli Sacco, Milan and University Hospital Federico II, Naples, Italy. All samples were analyzed at the Department of Biomedical and Clinical Sciences (Università degli Studi di Milano), Milan, Italy. Blood samples were centrifuged for 10 min at 1000 g at 4 °C. Erythrocytes for FA analyses were washed once with a 0.2 M EDTA + 150 nM NaCl solution through gentle inversion, and then 15 min centrifugation at 2000 g at 4 °C. The erythrocytes' membrane FA composition, reflecting maternal FA status over the previous 120 days, was determined by gas chromatography of FA methyl esters by using Hewlett-Packard 6890 gas chromatograph with flame ionization detector as previously described [22]. Briefly, erythrocyte lipids were extracted with chloroform/methanol (2:1, v/v) containing 0.2% butylated hydroxytoluene as antioxidant. FA methyl esters (FAMEs) were prepared by incubation with 140 g/l boron trifluoride in methanol at 90° C for 90 min, extracted with hexane, and analyzed by capillary gas chromatography by using SUPELCOWAX™ 10 (Merck, Milan, Italy) fused silica capillary column (50 m X 0.32 mm id., 0.25 µm film thickness). Pure FAMEs standards (Supelco 37 Component FAME Mix certified reference material, Merck) were used for building the calibration curves. Their retention times were used as a reference to identify the FAMEs obtained from the erythrocyte samples, heptadecanoic acid (Supelco, Merck) was used as the internal standard. The amount of each FA was calculated as µg/mL of red blood cells and expressed as a percentage of the total FA concentration. The detection limit was 1 µg/mL of red blood cells. The FA profile included the following: myristic acid, palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, arachic acid, ALA, behenic acid, cis 8–11–14 eicosanoic acid, cis 11–14–17 eicosanoic acid, ARA, lignoceric acid, EPA, nervonic acid, docosapentahenoic acid (DPA) and DHA. In addition, the amounts of saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), and PUFAs were calculated, further divided into the n-3 and n-6 series, as well as the omega-3 index by summing the percentage of EPA and DHA [23].

Furthermore, maternal dietary FA intake over the previous three months was assessed at 24–34 weeks using validated semi-quantitative food frequency questionnaires (FFQ) developed for the Italian population and administered by trained personnel [19, 20]. The FFQ consists of food items structured according to meal patterns and includes questions on consumption frequency and portion size. Energy and nutritional intakes were determined by using a Food Composition Database for Epidemiological Studies in Italy (Banca Dati di Composizione degli Alimenti per Studi Epidemiologici in Italia—BDA) [24]. The FFQs were checked in a standardized manner for completeness and consistency.

Pregnancy, maternal, and neonatal outcomes were collected at delivery, including data on gestational age, diagnosis of gestational diabetes mellitus (GDM) or hypertensive disorders during pregnancy (HDP), APGAR score at five minutes, neonatal sex and anthropometric measures (birth weight, length, head circumference (HC), and ponderal index (PI) as calculated by the formula: neonatal weight in grams × 100/(neonatal length in centimeters) [3]).

Statistical analysis

The sample size was calculated using G*Power based on the study by Hai-Tao Yu et al., 2022 [25]. This study reported a significant difference in maternal DHA levels between the overweight and control groups (7.22 ± 0.21 µg/mL vs. 6.07 ± 0.31 µg/mL). Based on these values, a total of 28 participants (14 per group) was determined to be required to achieve a statistical power of 80% ($\beta = 0.80$) at a significance level of $\alpha = 0.05$. All participants in the main cohort studies who met the inclusion criteria and underwent blood sampling were subsequently included.

Maternal characteristics, biomarker concentrations, and delivery outcomes were compared between the BMI-based groups by using the Chi-square or exact tests for ordinal variables, and Mann–Whitney U test or Student's t-test for continuous variables, as appropriate. For the primary aim, generalized linear models were performed to assess the associations between the BMI-based group

and mid-pregnancy FA concentrations, with adjustment for gestational age at blood sampling and potential confounders (maternal age, DHA-containing supplementation, n-3 dietary intake, and GDM diagnosis). To account for multiple testing, a Bonferroni correction was applied. When correcting for multiple testing, the statistical significance level was set at 0.006 (0.05/8). Second, the same models were used with pregestational BMI as scale variable to assess continuous associations. To explore the associations between mid-pregnancy FA concentrations and pregnancy and neonatal outcomes (secondary aim), generalized linear models were fitted after excluding women diagnosed with GDM, given the significant metabolic disturbances affecting the FA profile and delivery outcomes in this subgroup [26]. Gestational age at delivery, birth weight, and neonatal PI were used as dependent variables and proxies of intrauterine growth and pregnancy duration. Confounders for adjustment included the BMI-based group, maternal age, gestational weight gain at delivery, gestational age at blood sampling, use of n-3-containing supplements, and neonatal sex. Gestational age at delivery was additionally included for adjustment in models with neonatal PI and birth weight as dependent variables. Given that the timing of blood sample collection varied by up to 10 weeks among participants and to support the robustness of the results, an additional sensitivity analysis was performed by restricting the sample to non-GDM women whose blood sampling occurred between 25.4 and 29.6 weeks of gestation, corresponding to the 25th and 75th percentiles of the gestational age distribution.

Table 1 Maternal baseline characteristics, pregnancy, and neonatal outcomes in the total study population and BMI-based groups

	Total study population (*n* = 283)	NW group (*n* = 236)	OW group (*n* = 47)	*p*
Maternal characteristics				
Pregestational BMI, kg/m^2, median (IQR)	21.4 (19.8–23.8)	20.8 (19.6–22.5)	26.3 (25.6–28.4)	**0.001**
Age, years, median (IQR)	32 (29–35)	32 (29–35)	32.5 (28.8–35.3)	0.88
DHA supplement use, n (%)	167 (59.9)	140 (59.8)	27 (60.0)	0.98
Parity, multiparous, n (%)	110 (39.6)	90 (39.0)	20 (42.6)	0.65
GWG at delivery, kg, median (IQR)	13.0 (10.0–15.0)	12.5 (10.0–15.0)	13.0 (10.0–16.0)	0.55
Pregnancy outcome				
GDM, n (%)	13 (4.6)	10 (4.2)	3 (6.4)	0.52
HDP, n (%)	4 (1.4)	3 (1.3)	1 (2.1)	0.65
Preterm birth, n (%)	8 (2.8)	7 (3.0)	1 (2.1)	0.75
Neonatal outcome				
GA at delivery, weeks, median (IQR)	39.9 (39.0–40.4.0.4)	39.9 (39.0–40.4.0.4)	39.6 (38.7–40.6)	0.47
Sex, male, n (%)	140 (49.5)	116 (49.2)	24 (51.1)	0.81
Birth weight, g, median (IQR)	3300 (3025–3600)	3290 (3021–3598)	3340 (3030–3700)	0.29
Birth weight, centile, median (IQR)	49.5 (23.0–72.0)	45.0 (23.8–70.3)	59.0 (22.0–80.0)	0.21
Neonatal PI, g/cm^3, median (IQR)	2.68 (2.54–2.84)	2.67 (2.52–2.85)	2.76 (2.60–2.83)	**< 0.01**
Neonatal length, cm, median (IQR)	50 (48–51)	50 (48–51)	49 (48–51)	0.77
Neonatal HC, cm, median (IQR)	34 (34–35)	34 (34–35)	35 (33.4–36.0)	0.52
APGAR 5′ min, median (IQR)	10 (9–10)	10 (9–10)	10 (9–10)	0.22

Fisher test or Chi-square test for categorical variables and Mann Whitney-U test or Student's t-test for continuous variables were used for comparisons as appropriate. Bold type highlights significant results

NW: normal weight; OW: overweight; BMI: body mass index; IQR: interquartile range; DHA: docosahexaenoic acid; GWG: gestational weight gain; GDM: gestational diabetes mellitus; HDP: hypertensive disorders of pregnancy; Preterm birth (<37 gestational weeks); GA: gestational age; PI: ponderal index; HC: head circumference

Results

283 pregnant women were included in the present analysis, including 47 in the OW group. Table 1 shows the baseline characteristics, pregnancy and neonatal outcomes of the total study population and of BMI-based subgroups. The two groups were homogeneous for all characteristics, with the only exception of neonatal PI which resulted significantly higher in the OW compared to the NW group.

Table 2 shows maternal fasting mid-pregnancy FA erythrocyte concentrations and daily dietary intake in the total study population with comparisons between the BMI-based groups. The two study groups showed significant differences in the maternal concentrations of palmitoleic and lignoceric acids, as well as in the LC-PUFA n-3 and n-6 series. Notably, the OW group exhibited significantly higher erythrocyte ARA/EPA and LC-PUFA n-6/n-3 ratios, along with lower levels of DHA, EPA, and n-3 index compared to the NW group, despite comparable daily FA dietary intakes and gestational age at blood sampling.

Table 3 presents the results from generalized linear models examining the associations between BMI-based groups and the LC-PUFA n-3 and n-6 profile, including adjustment for gestational age at blood sampling, maternal age, n-3 containing supplementation and dietary intake, and GDM status. These models confirmed significant associations between the BMI-based groups and maternal mid-pregnancy LC-PUFA profile. Specifically, for the n-3 and n-6 series, the OW group showed a lower EPA level and a higher ARA/EPA ratio compared to the NW group. After Bonferroni correction, only EPA

Table 2 Maternal FA erythrocyte profile and daily dietary intake in the total study population and BMI-based groups

	Total study population ($n=283$)	NW group ($n=236$)	OW group ($n=47$)	p
Blood biomarker assessment				
GA at blood sampling, weeks	28.6 (25.4–29.6)	28.5 (25.3–29.6)	28.7 (25.7–30.0)	0.57
Myristic acid, %	0.45 (0.39–0.54)	0.45 (0.38–0.53)	0.46 (0.41–0.56)	0.14
Palmitic acid, %	24.9 (23.5–26.5)	24.8 (23.4–26.4)	25.3 (23.9–26.8)	0.75
Palmitoleic acid, %	0.29 (0.23–0.38)	0.28 (0.22–0.34)	0.38 (0.27–0.49)	**< 0.001**
Stearic acid, %	15.4 (14.2–16.3)	15.4 (14.2–16.5)	15.0 (14.0–16.0)	0.19
Oleic acid, %	15.7 (14.6–16.5)	15.7 (14.7–16.5)	15.8 (14.5–16.5)	0.85
Linoleic acid, %	10.2 (9.23–11.2)	10.2 (9.20–11.2)	10.3 (9.41–11.1)	0.47
Arachidic acid, %	0.17 (n.d.–0.21)	0.17 (n.d.–0.21)	0.17 (n.d.–0.21)	0.54
ALA, %	0.38 (0.31–0.44)	0.38 (0.31–0.45)	0.37 (0.26–0.44)	0.31
Behenic acid, %	1.88 (0.63–2.37)	1.89 (0.64–2.32)	1.82 (0.58–2.57)	0.99
cis 8–11–14 Eicosanoic acid, %	0.09 (n.d.–1.58)	0.07 (n.d.–1.60)	0.11 (n.d.–1.11)	0.24
cis 11–14–17 Eicosanoic acid, %	0.00 (n.d.-n.d.)	0.00 (n.d.-n.d.)	0.00 (n.d.-n.d.)	0.68
ARA, %	15.5 (14.3–16.7)	15.4 (14.3–16.6)	15.9 (14.3–16.9)	0.72
Lignoceric acid, %	1.60 (1.36–1.89)	1.62 (1.38–1.93)	1.49 (1.30–1.68)	**0.03**
EPA, %	0.42 (0.29–0.57)	0.43 (0.31–0.57)	0.33 (0.23–0.46)	**< 0.01**
ARA/EPA ratio	35.1 (26.1–52.2)	34.3 (25.7–49.1)	45.8 (30.7–64.3)	**< 0.01**
Nervonic acid, %	2.63 (1.90–3.83)	2.61 (1.93–3.75)	2.90 (1.82–4.21)	0.87
DPA, %	2.25 (1.90–2.74)	2.28 (1.90–2.77)	2.21 (1.79–2.54)	0.24
DHA, %	7.06 (5.92–8.27)	7.19 (6.07–8.35)	6.53 (5.54–7.95)	**0.05**
SFA, %	44.4 (41.7–46.7)	44.5 (41.6–46.4)	44.2 (41.9–46.9)	0.59
MUFA, %	18.8 (17.6–20.4)	18.8 (17.6–20.4)	19.2 (17.2–20.8)	0.69
LC-PUFA, %	36.9 (34.6–38.8)	36.9 (34.6–38.9)	36.7 (34.7–38.4)	0.78
LC-PUFA n-3, %	10.2 (8.64–11.8)	10.2 (8.75–11.9)	9.75 (8.22–11.0.22.0)	0.13
LC-PUFA n-6, %	26.5 (24.8–28.0)	26.5 (24.7–28.0)	26.8 (25.4–27.9)	0.29
LC-PUFA n-6/n-3 ratio	2.58 (2.22–3.07)	2.52 (2.21–3.02)	2.69 (2.49–3.20)	**0.03**
LC-PUFA n-3 index	7.48 (6.27–8.83)	7.55 (6.34–8.86)	6.68 (5.94–8.40)	**0.04**
FA daily dietary intake assessment				
SFA, g	20.7 (16.3–26.4)	20.5 (16.2–26.6)	21.4 (16.5–25.0)	0.74
MUFA, g	29.8 (24.1–36.3)	29.6 (24.1–36.7)	30.3 (24.0–35.1.0.1)	0.71
LC-PUFA, g	10.1 (7.38–13.7)	10.1 (7.46–13.9)	9.57 (6.47–11.5)	0.14
LC-PUFA n-3, g	0.61 (0.36–0.84)	0.62 (0.38–0.85)	0.57 (0.30–0.82)	0.33
ARA, g	0.18 (0.12–0.23)	0.17 (0.12–0.22)	0.18 (0.13–0.24)	0.38
EPA, g	0.23 (0.13–0.31)	0.23 (0.13–0.31)	0.22 (0.12–0.29)	0.34
ARA/EPA ratio	0.81 (0.62–1.18)	0.80 (0.63–1.15)	0.91 (0.58–1.66)	0.37
DHA, g	0.37 (0.22–0.52)	0.38 (0.24–0.53)	0.34 (0.18–0.52)	0.29

Fatty acids are expressed as a percentage of the total red blood cell fatty acids according to the detection limit (1 mg/ml of red blood cells). Data are presented as medians and IQR (interquartile ranges). Mann Whitney-U test or Student's t-test were used for comparisons, as appropriate. Bold type highlights significant results

NW: normal weight; OW: overweight; n.d.: not detectable because under the detection limit; GA: gestational age; ALA: α-Linolenic acid; ARA: arachidonic acid; EPA: eicosapentahenoic acid; DPA: docosapentaenoic acid; DHA: docosahexanoic acid; SFA: saturated fatty acid; MUFA: monounsaturated fatty acid; LC-PUFA: long-chain polyunsaturated fatty acid

concentrations were significantly lower in the OW compared to the NW group. The observed associations were confirmed in multi-adjusted models with BMI included as a continuous variable (EPA: β = −0.01, 95% CI: −0.02 to − 0.00, $p < 0.05$), together with an additional significant result for the LC-PUFA n-6/n-3 ratio (β = 0.03, 95% CI: 0.00 to 0.06, $p < 0.05$). The sensitivity analysis performed by including only non-GDM women with blood sampling collection between the 25th and 75th percentile of GA distribution (25.4–29.6 gestational weeks) further confirmed the main results (OW versus NW group: EPA: β = −0.13 (95% CI: −0.23; −0.04), $p < 0.05$; ARA/EPA ratio: β = 13.5 (95% CI: 2.8; 24.2), $p = 0.01$).

Multi-adjusted generalized linear models were secondly performed to evaluate the associations between maternal mid-pregnancy FA profile and delivery outcomes, after excluding women with a GDM diagnosis ($n = 13$). No associations were detected between any selected FA and gestational age at delivery (data not shown). Table 4 shows the effect estimates on the associations between maternal mid-pregnancy PUFA profile and neonatal birth weight or PI. In detail, erythrocyte DHA, LC-PUFA n-3 and LC-PUFA n-3 index were positively

Table 3 Generalized linear models assessing associations between BMI-groups and maternal erythrocyte PUFA n-3 and n-6 profiles in the total study population ($n = 283$)

	β (95%IC)	*p*
Linoleic acid, %	0.20 (−0.30; 0.69)	0.43
ALA, %	−0.03 (−0.08; 0.02)	0.24
ARA, %	0.19 (−0.35; 0.73)	0.48
EPA, %	−0.09 (−0.16; −0.03)	**< 0.01**
ARA/EPA ratio	8.06 (0.00; 16.3)	**0.05**
DHA, %	−0.32 (−0.89; 0.24)	0.26
LC-PUFA n-6/n-3 ratio	0.17 (−0.04; 0.38)	0.12
LC-PUFA n-3 index	−0.43 (−1.02; 0.15)	0.15

Generalized linear models were performed including adjustment for confounding factors (gestational age at blood sampling, maternal age, n-3 supplementation and dietary intake, GDM status). Fatty acids (dependent variables) are expressed as a percentage of the total red blood cell fatty acids. Beta values (confidence interval) represent the amount of change in the specific fatty acid in the OW versus NW group (independent variable). Bold type highlights significant results

ALA: α-linolenic acid; ARA: arachidonic acid; EPA: eicosapentahenoic acid; DHA: docosahexaenoic acid; LC-PUFA: long-chain polyunsaturated fatty acid

Table 4 Generalized linear models for the associations between maternal erythrocyte PUFA profile, neonatal and pregnancy outcome

Fatty acid	Birth weight, g		Neonatal PI, g/cm^3	
	β (95%IC)	*p*	β (95%IC)	*p*
Linoleic acid, %	−21.1 (−50.8; 8.7)	0.16	0.06 (−0.02; 0.02)	0.75
ALA, %	−81.3 (−368; 205.7)	0.58	0.03 (−0.17; 0.22)	0.79
ARA, %	−11.5 (−38.5; 5.2)	0.40	0.01 (−0.00; 0.03)	0.27
EPA, %	108.4 (−107.1; 323.8)	0.32	−0.07 (−0.21; 0.07)	0.33
ARA/EPA ratio	−0.47 (−2.2; 1.3)	0.59	0.001 (0.000; 0.002)	0.18
DHA, %	26.5 (0.4; 52.6)	**< 0.05**	0.01 (−0.00; 0.03)	0.19
LC-PUFA n-3, %	22.9 (0.7; 45.1)	**< 0.05**	0.01 (−0.01; 0.02)	0.27
LC-PUFA n-6, %	−12.6 (−32.2; 7.1)	0.21	0.01 (0.00; 0.02)	**< 0.05**
LC-PUFA n-6/n-3 ratio	−78.9 (−148.5; −9.2)	**< 0.05**	−0.00 (−0.05; 0.04)	0.93
LC-PUFA n-3 index	24.9 (0.03; 49.8)	**< 0.05**	0.01 (−0.01; 0.03)	0.25

Generalized linear models were performed after excluding women with a GDM diagnosis (n=13) (included women in the present analysis: n=270). Fatty acids are expressed as percentage of the total red blood cell fatty acids. Adjustment for confounding factors is included (maternal age, parity, BMI-based group, gestational age at blood sampling and delivery, n-3 supplement use, gestational weight gain at delivery, neonatal sex). Beta values (and confidence intervals) represent the amount of change in the dependent variable (birth weight, neonatal PI) for every unit increase of the FA concentration. Bold type highlights significant results

ALA: α-linolenic acid; ARA: arachidonic acid; EPA: eicosapentahenoic acid; DHA: docosahexaenoic acid; LC-PUFA: long-chain polyunsaturated fatty acid

associated with birth weight, while LC-PUFA n-6/n-3 ratio showed a negative association. Conversely, neonatal PI was positively associated with LC-PUFA n-6. The sensitivity analyses on the subgroup of non-GDM women tested between 25.4 and 29.6 gestational weeks for blood sampling confirmed the main results (birth weight: DHA: β = 42.5 (95% CI: 2.5 to 82.5), $p < 0.05$; LC-PUFA n-3: 30.8 (95% CI: 0.7 to 62.8), $p < 0.05$; LC-PUFA n-6/n-3 ratio: β= −107.8 (95% CI: −214.1 to −1.5), $p < 0.05$; LC-PUFA n-3 index: β = 42.1 (95% CI: 3.6 to 80.6), $p < 0.05$).

Discussion

The present study shows significant associations between pregestational BMI-based groups and the maternal mid-pregnancy erythrocyte FA profile among non-obese pregnancies. In particular, the OW group showed lower EPA levels and higher ARA/EPA ratios compared to the NW group in multi-adjusted models. Furthermore, our results proved a significant association between LC-PUFA n-3 and n-6 status and neonatal outcomes in multi-adjusted models, showing increased birth weights in case of lower LC-PUFA n-6/n-3 ratio and higher DHA, total LC-PUFA n-3 and n-3 index among non-GDM women. Neonatal PI is often calculated as a proxy of thinness and a better reflection of adiposity and nutritional status in the newborn compared to the crude birth weight, despite its associations with long-term health outcomes are still debated [27, 28]. Neonatal PI was found to be positively associated with LC-PUFA n-6 concentrations. These results overall indicate that the LC-PUFA profile is significantly associated with non-obese pregestational BMI and further associated with intrauterine growth trajectories and body composition. Conversely, no associations were detected between any investigated FA level and gestational age at delivery. The main results were further confirmed by secondary sensitivity analyses, including non-GDM women with a restricted gestational age interval at blood sampling and considering pregestational BMI as a continuous variable, thus supporting the robustness of our findings.

Therefore, the present study confirms the association between OW pregestational BMI and LC-PUFA n-3 and n-6 status. In particular, despite comparable gestational age at blood sampling and dietary intake, the OW group exhibited 10% lower red blood cell DHA levels, 30% lower EPA levels, and 16% lower n-3 indexes, along with 25% higher ARA/EPA ratios and 7% higher n-6/n-3 ratios compared to the NW group. Nevertheless, the LC-PUFA n-3 index (the sum of EPA and DHA) in both groups and across the entire study population did not reach the recommended range of 8–11% for cardiovascular disease protection, which is also considered optimal during pregnancy [29]. After including multiple adjustment and Bonferroni correction, only differences in EPA concentrations remained significant, meaning differences mainly mediated by confounders for other FAs.

Our results are in line with a recent Norwegian study on 107 pregnancies showing a reduction in the ratio of LC-PUFAs to total FAs, especially DHA, in overweight/obese compared to underweight/normal weight women,

which was most pronounced toward term and almost unaffected by gestational weight gain (GWG) [30]. The present study shows the advantage of a larger sample size, a more homogeneous population including only normal- and overweight women, and an extensive FA profile determination. These results align with evidence that maternal obesity is associated with altered PUFA metabolism at both hepatic and systemic levels, including increased oxidative stress, reduced desaturase activity, and changes in serum and erythrocyte FA composition, even when dietary intake is comparable [31].

We secondly investigated the associations between the extended panel of maternal mid-pregnancy PUFAs and neonatal outcomes, by focusing on gestational age at delivery, birth weight, and neonatal PI as dependent variables. Despite the well-known effect of DHA and/or EPA + DHA intake and status on reducing the risk of preterm and early preterm birth, we found no associations between the extended FA profile and gestational age at delivery [12]. Additionally, the low rate of preterm birth in our population precluded logistic regression modelling. The first explanation for this result may lie on the maternal DHA baseline status. A baseline red blood cell DHA threshold of 5% to 6% has been recently proposed to define women at low risk for early preterm birth, with no or scarce effects of high-dose DHA supplementation (1000 mg) in this subset of DHA-repleted women [32]. Only 10.6% of our population showed mid-pregnancy DHA values below this threshold, in line with the detected very low rates of preterm birth and possibly explaining the lack of associations with gestational age at delivery. Our results contrast with a recent study in a smaller Belgian cohort, reporting a 2.19 days longer gestational duration for each point increase in maternal first trimester DHA level [33]. It can be hypothesized that differences in baseline DHA levels (5% versus 7% in our cohort), timing of blood sampling, and maternal baseline characteristics (i.e. inclusion of obesity, smoking habit, and low educational levels) may justify these different results. Confirming this hypothesis, a recent study in a Latvian cohort with baseline characteristics similar to the present study population (age, educational level, BMI) showed significant differences in maternal EPA levels and n-3 index according to infant birth weights, with no associations with gestational age at birth [34].

Our results additionally indicate significant associations between maternal mid-pregnancy LC-PUFA status and intrauterine growth, as highlighted by higher birth weights associated with higher DHA, LC-PUFA n-3 levels, and n-3 index, and with a lower LC-PUFA n-6/n-3 ratio. Nevertheless, as larger does not necessarily mean healthier, the neonatal PI was calculated as a better reflection of body adiposity, showing increased neonatal PI associated with LC-PUFA n-6. These results are consistent with previous data showing a reduced risk of low birthweight infants (15.6% versus 14%; RR 0.90, 95% CI 0.82 to 0.99) and a non-significant trend toward higher rates of large-for-gestational age infants (RR 1.15, 95% CI 0.97 to 1.36) among women exposed to LC-PUFA n-3 interventions (supplements and food) compared with no n-3 exposure [35]. Prospective cohort studies further report associations between higher LC-PUFA n-6 and lower birth weight, higher fat mass and higher body fat, as well as long-term associations of LC-PUFA n-3 with higher lean mass and lower adiposity in childhood [36–39]. Therefore, the growth trajectory may reflect divergent lipid pathways (n-3 versus n-6), suggesting a need for integrated analyses of FA profiles, adiposity, and intrauterine growth trajectories. The modulation of maternal inflammation, insulin sensitivity and lipid metabolism, as well as the effects on feto-placental development and function were suggested as possible mechanisms linking maternal LC-PUFA intake/status and intrauterine growth, with consequent postnatal metabolic reprogramming [40–42]. Evidence indicates that n-3 LC-PUFAs reduce pro-inflammatory cytokines and NF-κB signaling, possibly improving placental perfusion and nutrient transfer, which can lastly support appropriate fetal growth and long-term insulin sensitivity [43]. In contrast, n-6 LC-PUFA pathways may elevate ARA-derived eicosanoids, potentially promote inflammatory states and altered placental lipid transport [44]. Both FA classes influence placental FA transporters (FATP, FATP4, CD36) and may drive epigenetic changes in growth-related genes, shaping fetal size and future obesity risk [45].

The present study has some limitations. First, pregestational BMI -the main independent variable- represents only a crude proxy for body composition, without differentiating between lean mass, fat mass, or adiposity distribution. Nevertheless, when combined with GWG, it remains the principal measure of nutritional status and metabolic derangements in clinical settings. Second, the low rate of pregnancy complications could not support regression modelling of adverse pregnancy outcomes, such as preterm birth or HDP. The wide confidence intervals for birth weight estimates require prudent interpretation, suggesting the need for a larger sample size to draw stronger conclusions. Additionally, while the strict inclusion criteria ensured a homogeneous study population and minimized potential confounding factors, the highly selected population may reduce the external validity and generalizability of the observed results. Lastly, the red blood cell fatty acid profile reflects dietary and physiological status over the past 120 days; thus, samples collected at 24–34 weeks of gestation better reflect the maternal state during the second trimester, when maternal adaptations to pregnancy (e.g., increased blood

volume, hemodilution) become evident. Nevertheless, to better understand the impact of gestation on the FA panel, longitudinal sampling taken at multiple time points during pregnancy would be more informative.

Several strengths should be addressed as well. The comprehensive FA determination at mid-pregnancy provides a reliable picture of red blood cell FA levels that were measured by 'gold-standard' method, even though standardized protocol and appropriate cutoff values are not available yet. Moreover, the included population represents a well-defined and homogeneous sample of healthy women, with the exclusion of smoking habit, extreme BMI values, and pregestational comorbidities. Indeed, on one side this may explain the detected low incidence of pregnancy complications, but on the other side it may also reduce any maternal confounding possibly impacting the LC-PUFA status. Additional adjustment for confounding factors associated with lipid metabolism and birth outcomes, along with maternal n-3 dietary intake and supplementation, were considered, further increasing the data reliability. The robustness of the detected associations was further confirmed by the sensitivity analyses excluding women with extreme gestational age at blood sampling and using pregestational BMI as a continuous variable.

Conclusions

Based on the present results, several noteworthy conclusions can be drawn. First, OW women during pregnancy exhibit a more imbalanced FA profile compared to NW women, despite comparable FA dietary intake across the groups. These differences in lipid profiles suggest that the OW BMI may influence maternal FA metabolism and circulating FA composition. Furthermore, PUFA n-3 and n-6 levels were associated with birth weight and neonatal PI, potentially indicating variations in intrauterine growth and neonatal body composition. Considering this, examining FA panels in pregnancies at high risk for fetal growth restriction may provide informative insights.

In summary, OW women tended to have a less favorable FA profile, which is further associated with prenatal growth, although no direct links with pregnancy duration were observed. Further research is warranted to evaluate the use of both maternal n-3 and n-6 series as potential predictor and marker of pregnancy outcome.

Abbreviations

ALA	Alpha-linolenic acid
ARA	Arachidonic acid
BMI	Body mass index
DHA	Docosahexaenoic acid
DPA	Docosapentahenoic acid
EPA	Eicosapentaenoic acid
FA	Fatty acids
FAMEs	FA methyl esters
FFQ	Food frequency questionnaires
GA	Gestational age
GDM	Gestational diabetes mellitus
GWG	Gestational weight gain
HC	Head circumference
HDP	Hypertensive disorders during pregnancy
IQR	Interquartile range
LC-PUFA	Long-chain polyunsaturated fatty acids
MUFA	Monounsaturated fatty acids
NW	Normal weight
OW	Overweight
PI	Ponderal index
PUFA	Polyunsaturated fatty acids
SFA	Saturated fatty acids

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Author contributions

Conceptualization, I.C., F.P., C.M. and R.C.; Formal analysis, F.P., P.A.; Investigation, C.N., G.M.A., R.C., C.L. and F.L.; Resources, L.S. and E.M.; Funding acquisition, I.C.; Writing—original draft preparation, F.P.; Writing—review and editing, C.M., C.N., G.M.A., R.C., C.L., P.A., I.C. All authors have read and agreed to the submitted version of the manuscript.

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Data availability

All data that support the findings of this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethical Committee "Comitato Etico Milano Area 1" (reference numbers 8292/2016, 33043/2018 and 11187/2016 with trial registration identifier: NCT04438928 [19]). Informed consent was obtained from all subjects involved in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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