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European Journal of Clinical Nutrition (2019) 73:566–576
https://doi.org/10.1038/s41430-018-0175-1

ARTICLE

Maternal and pediatric nutrition

Polyunsaturated fatty acid status at birth, childhood growth, and cardiometabolic risk: a pooled analysis of the MEFAB and RHEA cohorts

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Received: 26 June 2017 / Revised: 28 March 2018 / Accepted: 9 April 2018 / Published online: 16 May 2018

Abstract

Background/objectives Polyunsaturated fatty acid (PUFA) status during pregnancy has been suggested to influence offspring obesity and cardiometabolic health. We assessed whether prenatal PUFA exposure is associated with rapid infant growth, childhood BMI, and cardiometabolic profile.

Subjects/methods In the Dutch MEFAB ($n = 266$) and Greek RHEA ($n = 263$) cohorts, we measured n-3 and n-6 PUFA concentrations in cord blood phospholipids, which reflect fetal exposure in late pregnancy. We defined rapid infant growth from birth to 6 months of age as an increase in weight z-score >0.67. We analyzed body mass index (BMI) as continuous and in categories of overweight/obesity at 4 and 6 years. We computed a cardiometabolic risk score at 6–7 years as the sum of waist circumference, non-high-density lipoprotein cholesterol and blood pressure z-scores. Associations of PUFAs with child health outcomes were assessed using generalized linear models for binary outcomes and linear regression models for continuous ones after adjusting for important covariates, and for the pooled estimates, a cohort indicator.

Results In pooled analyses, we found no association of PUFA levels with rapid infant growth, childhood BMI (β per SD increase in the total n-3:n-6 PUFA ratio = −0.04 SD; 99% CI: −0.15, 0.06; $P = 0.65$ at 4 years, and −0.05 SD; 99% CI: −0.18, 0.08; $P = 0.78$ at 6 years), and overweight/obesity. We also found no associations for clustered cardiometabolic risk and its individual components. The results were similar across cohorts.

Conclusions Our findings suggest that PUFA concentrations at birth are not associated with later obesity development and cardiometabolic risk in childhood.

Introduction

Childhood obesity constitutes a major public health concern. Currently, it is estimated that around 50 million girls and 74 million boys aged over 5 years worldwide are obese [1]. Obesity and associated risk factors in childhood, such as high blood pressure (BP) and dyslipidemia, can induce metabolic changes and contribute to atherosclerosis in adulthood [2]. Therefore, it is critical to identify early determinants of obesity and cardiometabolic risk that can be targeted for preventive interventions.

Intrauterine life is an important period of developmental plasticity during which a nutritional stressor can alter body metabolism and physiology, and thus, affect child health and development [3]. Animal and in vitro studies have shown that n-6 PUFAs can increase adipose tissue deposition and promote inflammation, while n-3 PUFAs appear to exert opposite effects [4, 5].

Human studies have provided some evidence for a relation of prenatal PUFA levels with childhood BMI, waist circumference, and fat mass measures, but the lack of consistent findings precludes any conclusions [6–12]. Few studies have assessed the association of prenatal PUFA status with childhood cardiovascular traits other than

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Electronic supplementary material The online version of this article (https://doi.org/10.1038/s41430-018-0175-1) contains supplementary material, which is available to authorized users.

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adiposity, and have reported mixed results [13]. A recent systematic review underlined the importance of further studies to clarify the association of prenatal PUFA status with cardiometabolic health in childhood [13].

A limitation of prior research not allowing firm conclusions is the lack of replicated findings across populations with different characteristics and behaviors. Moreover, to the best of our knowledge, no study has previously examined the association of prenatal PUFAs with an aggregate constellation of cardiometabolic risk. Cardiometabolic risk factors including central adiposity, dyslipidemia, and BP may share common pathophysiological mechanisms, and their clustering is considered a better marker of cardiovascular health in children than single factors [14, 15]. Hence, in the present study, we pooled individual data of two birth cohorts from West and South Europe to assess whether n−3 and n−6 PUFA concentrations in cord blood phospholipids are associated with rapid infant growth, childhood BMI, and cardiometabolic risk profile.

Materials and methods

Study population

The Maastricht Essential Fatty Acid Birth (MEFAB) cohort (www.mefab.org) recruited pregnant women at the time of their first antenatal visit in the area of Limburg, The Netherlands, between 1989 and 1995. Of 1203 singleton deliveries, umbilical cord blood samples were assayed for 1008. Of these, 750 children were eligible for the follow-up evaluation at 7 years, and 306 attended the clinical examination, during which we measured anthropometry for 266 children, BP for 261, and collected blood samples for 235. A flow chart of the MEFAB participants is shown in Supplementary Fig. S1.

The RHEA Mother-Child Cohort in Crete, Greece (www.rhea.gr) recruited pregnant women at the time of their first comprehensive ultrasound examination in Heraklion city during 2007–2008. Of 1363 singleton live births, umbilical cord blood samples were essayed for fatty acid levels in a random sample of 500 children. Of these, 263 children had anthropometry measurements up to 6 years of age, 146 provided blood lipid samples, and 156 had BP measurements at 6 years. A flow chart of the RHEA participants is shown in Supplementary Fig. S2.

Written informed consent was obtained from all participants. The MEFAB study was approved by the ethics committee of Maastricht University/University Hospital of Maastricht, and the RHEA study was approved by the ethics committee of the University Hospital in Heraklion.

Comparison of the participants included in the present analysis and those excluded showed that children with follow-up data had mothers who were more likely to be older at delivery in MEFAB (mean age 29.9 vs. 29.1 years) and less likely to be smokers in RHEA (12.9% vs. 20.1%). Nevertheless, no substantial differences in maternal BMI at study entry, gestational weight gain, birth weight, gestational age, or fatty acid exposure levels were observed (Supplementary Table S1).

Polyunsaturated fatty acids

In each cohort, PUFA concentrations were assessed in cord blood phospholipids using standard procedures (Supplementary methods) and expressed as proportion of total fatty acids measured (weight percentage, wt%). To enable the comparison and pooling of cohort-specific effect estimates, we calculated *z*-scores for PUFA concentrations in each cohort. Exposures of primary interest were α-linolenic acid (ALA, C18:3n-3), the sum of eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3), the sum of total n-3 PUFAs measured in each cohort, linoleic acid (LA, C18:2n-6), arachidonic acid (AA, C20:4n-6), and the sum of total n-6 PUFAs measured. We also calculated the ratio of total n-3 to n-6 PUFAs.

Secondary exposures of interest included docosapentaenoic acid (DPA, C22:5n-3), γ-linolenic acid (GLA, C18:3n-6), dihomo-γ-linolenic acid (DGLA, C20:3n-6), and osbond acid (C22:5n-6).

Infant growth and child BMI

We had available information on weight and height from birth up to the age of 6-7 years (Supplementary Methods). Because of variation in the number of children and age at follow-ups, we estimated weight and height values at the exact age of 6 months, 4 years and 6 years using cohort-specific, age-specific, and sex-specific growth curves fitted with multilevel models with fractional polynomial of age, and random effects for the child and age terms (Supplementary methods). We chose these time points so as to reflect different developmental periods (infancy, preschool period, and school-age period). We estimated age-specific and sex-specific weight and BMI *z*-scores at the time points of interest according to the World Health Organization (WHO) growth standards [16, 17].

We defined rapid infant growth during the first 6 months of life as an increase in weight *z*-score >0.67 [18], and overweight/obesity at 4 and 6 years based on the International Obesity Task Force definition [19].

Child cardiometabolic risk

We assessed waist circumference (WC) and BP using standard procedures in both cohorts (Supplementary

methods). We also measured blood lipids following standard methods (Supplementary methods).

We derived a mid-childhood cardiometabolic risk score as the sum of the following components in each cohort: sex-specific and age-specific z scores of WC and non-high-density lipoprotein (non-HDL) cholesterol [20], and the average of sex-specific, age-specific, and height-specific z-scores for systolic BP (SBP) and diastolic BP (DBP). Child glucose and insulin levels were not available in RHEA; hence, we constructed the metabolic risk score without including glucose metabolism measurements, but we performed a sensitivity analysis including this type of measures that were available in the MEFAB cohort.

Recent research has utilized similar methods to define cardiometabolic risk in children [14]. This approach increases statistical power and is used to estimate an individual's cardiometabolic risk profile. A higher score is indicative of a less favorable profile. In our study sample, we observed a graded relationship between the continuous metabolic risk score and the number of dichotomous metabolic syndrome criteria according to the National Cholesterol Education Program definition modified for age [21] (Supplementary Table S2). We also examined the raw individual components of the cardiometabolic risk score as outcomes.

Statistical analysis

We used multivariable generalized linear models for binary outcomes (with log link, Poisson distribution and robust error variance [22]) to assess associations of each PUFA exposure with rapid infant growth and childhood overweight/obesity, and multivariable linear regression models for associations with childhood BMI z-scores and cardiometabolic risk factors. We detected no departures from linearity in the exposure-outcome associations using scatter plots and a Wald test with the STATA command nlcheck [23].

We conducted pooled analyses by including a cohort indicator variable in the models and tested for heterogeneity in the associations across cohorts by examining the interaction between PUFA exposures and cohort. We followed a Directed Acyclic Graph approach (Supplementary Fig. S3) to select variables for model adjustment. The following covariates were included in the models: maternal age at birth (years), maternal BMI at study entry (kg/m^2), maternal smoking in pregnancy (never, ever), delivery type (vaginal; caesarian), parity (primiparous; multiparous), parental education (low, medium, or high according to the highest completed education level of either parent) [24, 25], and breastfeeding (months). Gestational weight gain (kg) was also included in the multivariate models, as it has been associated with prenatal fatty acid status [26] and has been shown to predict fetal and postnatal growth (Supplementary Fig. S4) [27, 28].

Models of WC and BP were additionally adjusted for child height. We also included child sex and age in the models for raw cardiometabolic risk factors. We did not adjust for birthweight for gestational age, which is a measure of fetal growth, as it might be in the causal pathway between prenatal PUFA concentrations and child health outcomes [29–31].

To further assess our research hypothesis, we conducted additional analyses utilizing different levels of available information within each cohort. First, in MEFAB models, we repeated the analyses for the cardiometabolic risk score including z-scores for homeostasis model assessment of insulin resistance (HOMA-IR). Second, we conducted further adjustment for child plasma PUFA levels measured at the age of outcome assessment in MEFAB. Third, in RHEA, we conducted further adjustment for Mediterranean diet adherence in pregnancy (a priori defined score), child fast food intake (times/week) and television viewing (hours per day) available at 6 years [32] in models of childhood BMI and metabolic risk score at the respective time period.

In a sensitivity analysis, we examined associations of our primary PUFA exposures with rapid BMI growth from birth to 6 months of age, defined as a z-score BMI gain >0.67. We also examined overweight/obesity using the WHO definition [16, 17]. Moreover, given that our cardiometabolic score resulted in each included variable having equivalent weights, we also applied factor analysis (varimax rotation) to normalized WC, non-HDL cholesterol and BP measures to derive a new composite score with differential loadings of each measure [33]. Finally, we assessed whether the effect estimates varied by maternal weight status at study entry (BMI < 25 vs. ≥ 25 kg/m^2) and child sex (girl vs. boy) by introducing interaction terms between the potential effect modifier and the primary exposure variables. Given the large number of analyses, statistical significance was defined by $P < 0.05$ for effect measure modification and $P < 0.01$ for all other effect estimates to reduce the likelihood of chance findings. We did not apply a Bonferroni-type correction because of the strong correlations among the exposures and among the outcomes of interest [34].

Our study including 520 children for examining the association of cord blood PUFAs with childhood BMI had 80% power at the 1% significance level to detect effect sizes of as small as 0.15 for BMI z-score, and of as small as 67% for risk estimates of childhood overweight/obesity at 4 years (the outcome with the lowest prevalence in the pooled dataset; 9.4%) per SD increase in the n-3:n-6 ratio. Power analysis was conducted using GPower version 3.1 [35]. All other analyses were conducted with STATA version 13.0 (StataCorp); code is available upon request.

Table 1 Parental and child characteristics in the MEFAB and RHEA birth cohorts

	MEFAB		RHEA	
	n	Percent or Mean (SD)	*n*	Percent or Mean (SD)
Parental characteristics				
Maternal age at birth (years)	266	29.9 (4.1)	263	29.4 (4.9)
Maternal BMI at study entry (kg/m^2)	266	23.7 (4.0)	263	25.4 (5.4)
Gestational weight gain (kg)	266	11.2 (4.0)	263	13.7 (6.2)
Maternal smoking in pregnancy (%)				
Never	200	75.2	229	87.1
Ever	66	24.8	34	12.9
Mode of delivery (%)				
Vaginal	248	93.2	141	53.6
Caesarian	18	6.8	122	46.4
Parity (%)				
Primiparous	190	71.4	115	43.7
Multiparous	76	28.6	148	56.3
Parental education (%)[a]				
Low	68	25.5	30	11.4
Medium	105	39.5	132	50.2
High	93	35.0	101	38.4
Child characteristics				
Sex (%)				
Boys	147	55.3	143	54.4
Girls	119	44.7	120	45.6
Birth weight (grams)	266	3300 (496)	263	3213 (438)
Gestational age (weeks)	266	39.9 (1.6)	263	38.3 (1.5)
Breastfeeding duration (months)	266	2.2 (4.1)	263	4.4 (4.5)
Age at 6–7 year-follow-up (years)	266	7.3 (0.3)	263	6.6 (0.3)
Child outcomes				
Rapid growth from birth to 6 months (%)[b]				
No	203	79.0	172	65.4
Yes	54	21.0	91	34.6
BMI *z*-score at 4 years[c]	257	0.08 (0.83)	263	0.53 (1.00)
Weight status at 4 years (%)[d]				
Normal weight	245	95.3	226	85.9
Overweight/obese	12	4.7	37	14.1
BMI *z*-score at 6 years[c]	257	0.01 (0.93)	263	0.74 (1.30)
Weight status at 6 years (%)[d]				
Normal weight	236	91.8	190	72.2
Overweight/obese	21	8.2	73	27.8
Cardiometabolic risk score at 6–7 years[e]	230	-0.01 (1.89)	145	-0.02 (1.94)
Waist circumference at 6–7 years (cm)	266	55.9 (4.8)	161	58.8 (6.5)
Non-HDL cholesterol at 6–7 years (mg/dl)	235	109.3 (24.1)	146	101.8 (22.7)
Systolic blood pressure at 6–7 years (mm Hg)	261	100.9 (6.7)	156	94.4 (9.1)
Diastolic blood pressure at 6–7 years (mm Hg)	261	61.7 (5.6)	156	54.4 (6.1)

[a]Parental education was defined according to the highest completed education level of either parent; for RHEA: low was defined as ≤9 years of mandatory schooling, medium as >9 years of schooling up to attending postsecondary school education, and high as attending university or having a university/technical college degree); for MEFAB, low was defined as attending primary school, medium as attending secondary education, and high as attending tertiary education

[b]Rapid growth was defined as a *z*-score weight gain >0.67 SD

[c]A BMI z score represents the difference from the mean sex-specific and age-specific BMI value for the World Health Organization reference population and is expressed in standard deviations

[d]Weight status was defined based on the International Obesity Task Force definition

[e]The cardiometabolic risk score is expressed in standard deviations was derived as the sum of the following components in each cohort: sex-specific and age-specific *z*-scores of waist circumference and non-HDL cholesterol, and the average of age-specific, sex-specific, and height-specific *z*-scores for systolic and diastolic blood pressure

Results

Participant characteristics

Mothers had a mean (±SD) age at delivery of 29.7 ± 4.6 years, and were predominantly non-smokers. Participants' characteristics of the separate cohorts are presented in Table 1. Mean (±SD) concentrations of n-3 and n-6 PUFAs in MEFAB were 6.85 ± 1.60 and 32.15 ± 1.68 wt.%, respectively; the corresponding values for RHEA were 5.45 ± 1.18 and 32.26 ± 2.38 wt.% (Table 2).

Cord blood PUFAs, rapid infant growth, and child BMI

In pooled analyses on the risk of rapid weight gain in infancy, we did not find strong evidence for an association with cord blood PUFA levels (Table 3). In individual fatty acid analyses, there was some evidence for an inverse association between n-6 LA concentrations and the risk of rapid infant growth (adjusted pooled RR per SD increase in LA = 1.17 [99% CI: 1.00, 1.38]), but this was driven by the MEFAB cohort (RR = 1.56 [99% CI: 1.12, 2.17] and 1.09 [99% CI: 0.88, 1.34] for MEFAB and RHEA, respectively; *P* for LA-cohort interaction = 0.03). We did not find any evidence that ALA, EPA + DHA and AA were associated

Table 2 Distribution of cord blood phospholipid PUFA levels in the MEFAB ($n = 266$) and RHEA ($n = 263$) birth cohorts

	MEFAB Mean (SD)	RHEA Mean (SD)
Total n-3 PUFAs (wt.%)	6.85 (1.60)	5.45 (1.18)
ALA (wt.%)	0.05 (0.11)	0.07 (0.05)
DPA (wt.%)	0.46 (0.18)	–
EPA + DHA (wt.%)	6.25 (1.45)	5.35 (1.17)
Total n-6 PUFAs (wt.%)	32.15 (1.68)	32.26 (2.38)
LA (wt.%)	7.70 (1.30)	10.27 (1.70)
GLA (wt.%)	0.05 (0.04)	0.37 (0.11)
DGLA (wt.%)	5.15 (0.88)	3.93 (0.70)
AA (wt.%)	16.58 (1.58)	17.37 (2.26)
Osbond acid (wt.%)	0.83 (0.28)	–
Total n-3:n-6 PUFA ratio	0.21 (0.06)	0.17 (0.04)

AA arachidonic acid (C20:4n-6), *ALA* a-linolenic acid (C18:3n-3), *DGLA* dihomo-γ-linolenic acid (C20:3n-6), *DHA* docosahexaenoic acid (C22:6n-3), *DPA* docosapentaenoic acid (C22:5n-3), *EPA* eicosapentaenoic acid (C20:5n-3), *DHA* docosahexaenoic acid (C22:6n-3), *DPA* docosapentaenoic acid (C22:5n-3), *GLA* γ-Linolenic acid (C18:3n-6), *LA* linoleic acid (C18:2n-6), *Osbond acid* C22:5n-6, *PUFA* polyunsaturated fatty acid, *total n-3 (n-6) PUFAs* the sum of n-3 (n-6) PUFAs present in the chromatogram, *wt.%* weight percentage of total fatty acids measured

with rapid infant weight gain in both pooled (Table 3) and cohort-specific analyses (Supplementary Tables S3 and S4).

When we examined BMI at age 4 and 6 years in the pooled dataset, we also found no associations; the adjusted pooled β coefficients for BMI *z*-score at 4 years were −0.06 (99% CI: −0.16, 0.05) per SD increase in total n-3 PUFAs and −0.05 (99% CI: −0.16, 0.07) per SD increase in total n-6 PUFAs, and those for BMI *z*-score at 6 years were −0.06 (99% CI: −0.19, 0.07) for total n-3 PUFAs and −0.02 (99% CI: −0.16, 0.12) for total n-6 PUFAs (Table 3). Similarly, no associations were observed for the risk of overweight including obesity in any age group (Table 3). Effect estimates for child BMI and the risk of overweight including obesity were similar between cohorts (Supplementary Tables S3 and S4).

Cord blood PUFAs and child cardiometabolic risk

In pooled analyses, we did not find any association between cord blood PUFA levels and clustered cardiometabolic risk *z*-score at 6-7 years; the adjusted pooled β coefficients were 0.04 (99% CI: −0.22, 0.30) per SD increase in total n-3 PUFAs and 0.04 (99% CI: −0.23, 0.32) per SD increase in total n-6 PUFAs (Table 4). Similarly, no relationships were found for individual cardiometabolic risk factors including WC, non-HDL cholesterol, SBP and DBP in the pooled dataset (Table 4). Associations of PUFA levels with cardiometabolic risk were broadly similar in the cohorts (Supplementary Tables S5 and S6). There was some evidence for between-cohort heterogeneity only for the relationship between n-3 ALA and SBP (adjusted β coefficient per SD increase in ALA = 0.14 (99% CI: -0.71, 0.98) mmHg in MEFAB and 2.48 (99% CI: 0.33, 4.64) mmHg in RHEA; P for ALA-cohort interaction < 0.01).

Secondary analyses

We found no associations of cord blood DPA, GLA, DGLA, and osbond acid levels with rapid infant growth, childhood BMI and cardiometabolic risk (Supplementary Tables S7 and S8). Inclusion of child plasma PUFA levels at the age of outcome assessment in MEFAB models or further adjustment for Mediterranean diet adherence in pregnancy, child fast food intake and television viewing in RHEA models did not modify the direction and size of the effect estimates (data not shown). Additionally, no associations were observed between PUFAs and cardiometabolic risk score including HOMA-IR in MEFAB models (Supplementary Table S9).

Sensitivity analyses

Results remained similar when we examined rapid BMI growth in infancy (Supplementary Table S10) or when we used the WHO definition of childhood overweight/obesity (Supplementary Table S11). Results also did not materially change when we used the composite cardiometabolic score derived from factor analysis (data not shown). There was no evidence of effect modification by maternal weight status at study entry and child sex (all *P*-interaction > 0.10).

Discussion

In this analysis of two cohorts from West and South Europe, we found no evidence supporting an association of cord blood PUFA levels with rapid infant growth, childhood BMI, overweight including obesity, and cardiometabolic risk profile. To our knowledge, this is the first study examining the association of prenatal PUFAs with an aggregate constellation of cardiometabolic risk. The results were broadly similar when each of the two cohorts were studied separately. The EPA + DHA status in the Netherlands and Greece is characterized as very low-to-low, which is similar to most European and US populations following a Westernized diet [36].

PUFA concentrations in cord blood phospholipids are good surrogates of fetal exposure in late pregnancy, as they reflect not only maternal dietary intake of the previous 2–4 weeks [37], but also the efficiency of placental transfer [38]. The timing and biomarker used for assessing fetal

Table 3 Associations (pooled analysis) of primary cord blood phospholipid PUFAs of interest with rapid infant growth, childhood BMI and obesity ($n = 520$)

	Rapid growth[a]			BMI *z*-score[b]						Overweight/obesity[c]					
	Birth to 6 months			4 years			6 years			4 years			6 years		
	RR (99% CI)	*P*	*P*-interact[d]	β (99% CI)	*P*	*P*-interact[d]	β (99% CI)	*P*	*P*-interact[d]	RR (99% CI)	*P*	*P*-interact[d]	RR (99% CI)	*P*	*P*-interact[d]
ALA	1.00 (0.87, 1.15)	0.99	0.13	0.04 (−0.05, 0.13)	0.30	0.69	0.05 (−0.07, 0.16)	0.29	0.88	0.87 (0.54, 1.41)	0.46	0.50	1.07 (0.90, 1.28)	0.30	0.13
EPA+DHA	0.86 (0.71, 1.06)	0.07	0.60	-0.06 (-0.16, 0.05)	0.17	0.13	−0.06 (−0.19, 0.07)	0.26	0.33	0.93 (0.64, 1.38)	0.65	0.16	1.03 (0.81, 1.30)	0.75	0.09
Total n-3 PUFAs	0.86 (0.71, 1.05)	0.06	0.50	−0.06 (−0.16, 0.05)	0.17	0.12	−0.06 (−0.19, 0.07)	0.25	0.31	0.94 (0.64, 1.37)	0.65	0.14	1.04 (0.82, 1.32)	0.66	0.08
LA	1.17 (1.00, 1.38)	0.01	0.03	0.01 (-0.10, 0.13)	0.76	0.81	0.00 (−0.15, 0.15)	0.99	0.52	1.02 (0.59, 1.77)	0.91	0.88	0.97 (0.69, 1.36)	0.82	0.29
AA	1.09 (0.89, 1.34)	0.27	0.13	−0.08 (−0.19, 0.04)	0.08	0.48	−0.04 (−0.18, 0.10)	0.46	0.30	0.96 (0.63, 1.48)	0.82	0.34	0.88 (0.68, 1.14)	0.21	0.72
Total n-6 PUFAs	1.16 (0.94, 1.43)	0.06	0.04	-0.05 (-0.16, 0.07)	0.29	0.99	−0.02 (−0.16, 0.12)	0.75	0.50	0.94 (0.62, 1.43)	0.71	0.79	0.85 (0.66, 1.09)	0.10	0.63
Total n-3:n-6 ratio	0.85 (0.69, 1.04)	0.04	0.30	−0.04 (−0.15, 0.06)	0.31	0.16	−0.05 (−0.18, 0.08)	0.35	0.46	0.97 (0.65, 1.44)	0.83	0.20	1.09 (0.86, 1.38)	0.36	0.13

Relative risks (RRs) and their 99% CIs were calculated using generalized linear models for binary outcomes (modified Poisson). Beta coefficients and their 99% CIs were estimated using linear regression models. Models were adjusted for maternal age, maternal BMI at study entry, gestational weight gain, maternal smoking during pregnancy, delivery type, parental education, parity, breastfeeding duration, and cohort. Effect estimates correspond to a standard deviation score increase in PUFAs

AA arachidonic acid (C20:4n-6), *ALA* a-linolenic acid (C18:3n-3), *BMI* body mass index, *DHA* docosahexaenoic acid (C22:6n-3), *EPA* eicosapentaenoic acid (C20:5n-3), *LA* linoleic acid (C18:2n-6), *PUFA* polyunsaturated fatty acid, *total n-3 (n-6) PUFAs* the sum of n-3 (n-6) PUFAs

[a]Rapid growth was defined as a *z*-score weight gain >0.67 SD

[b]A BMI z-score represents the difference from the mean sex-specific and age-specific BMI value for the World Health Organization reference population and is expressed in standard deviations

[c]Overweight/obesity was defined based on the International Obesity Task Force definition

[d]*P* for PUFA exposure-cohort interaction estimated using the Wald test

Table 4 Associations (pooled analysis) of primary cord blood phospholipid PUFAs of interest with the cardiometabolic risk score and its components at 6–7 years of age

	Cardiometabolic risk score[a] (n = 375)			Waist circumference, cm (n = 427)			Non-HDL cholesterol, mg/dl (n = 381)			Systolic blood pressure, mm Hg (n = 417)			Diastolic blood pressure, mm Hg (n = 417)		
	β (99% CI)	*P*	*P*-interact[b]	β (99% CI)	*P*	*P*-interact[b]	β (99% CI)	*P*	*P*-interact[b]	β (99% CI)	*P*	P-interact[b]	β (99% CI)	*P*	*P*-interact[b]
ALA	0.07 (−0.14, 0.28)	0.39	0.09	0.37 (−0.14, 0.88)	0.06	0.25	0.31 (−2.43, 3.05)	0.77	0.39	0.51 (−0.31, 1.33)	0.11	<0.01	0.11 (−0.52, 0.73)	0.66	0.18
EPA+DHA	0.04 (−0.23, 0.30)	0.72	0.95	0.09 (–0.51, 0.69)	0.70	0.96	−1.05 (−4.45, 2.34)	0.42	0.76	0.49 (−0.50, 1.47)	0.20	0.71	0.28 (−0.47, 1.02)	0.34	0.22
Total n-3 PUFAs	0.04 (−0.22, 0.30)	0.72	0.89	0.11 (–0.48, 0.71)	0.62	0.92	−1.11 (-4.47, 2.26)	0.40	0.84	0.48 (−0.50, 1.46)	0.20	0.93	0.29 (−0.45, 1.03)	0.32	0.15
LA	0.22 (−0.09, 0.53)	0.07	0.50	0.23 (-0.50, 0.96)	0.41	0.51	2.60 (−1.44, 6.64)	0.10	0.22	0.74 (−0.43, 1.92)	0.10	0.63	0.32 (−0.57, 1.22)	0.35	0.18
AA	−0.09 (−0.36, 0.18)	0.38	0.75	−0.25 (−0.89, 0.39)	0.31	0.15	0.24 (−3.31, 3.79)	0.86	0.80	−0.52 (−1.56, 0.52)	0.20	0.80	−0.04 (−0.83, 0.75)	0.90	0.98
Total n-6 PUFAs	0.04 (−0.23, 0.32)	0.70	0.39	0.02 (−0.62, 0.66)	0.95	0.65	1.27 (−2.31, 4.86)	0.36	0.61	−0.37 (−1.41, 0.67)	0.36	0.63	0.28 (−0.50, 1.07)	0.35	0.37
Total n-3:n-6 ratio	0.03 (−0.24, 0.30)	0.79	0.67	0.10 (−0.50, 0.71)	0.66	0.93	−1.41 (−4.85, 2.02)	0.29	0.93	0.56 (−0.43, 1.56)	0.14	0.83	0.20 (−0.56, 0.95)	0.50	0.24

Beta coefficients and their 99% CIs were estimated using linear regression models adjusted for maternal age, maternal BMI at study entry, gestational weight gain, maternal smoking during pregnancy, delivery type, parental education, parity, breastfeeding duration, and cohort. Models of individual cardiometabolic risk factors were additionally adjusted for child sex and age at outcome assessment. Models of waist circumference and blood pressure were also adjusted for child height. Effect estimates correspond to a standard deviation score increase in PUFAs

AA arachidonic acid (C20:4n-6), *ALA* a-linolenic acid (C18:3n-3), *DHA* docosahexaenoic acid (C22:6n-3), *EPA* eicosapentaenoic acid (C20:5n-3), *LA* linoleic acid (C18:2n-6), *PUFA* polyunsaturated fatty acid, *total n-3 (n-6) PUFAs* the sum of n-3 (n-6) PUFAs

[a]The cardiometabolic risk score is expressed in standard deviations and was derived as the sum of the following components: sex- specific and age-specific *z*-scores of waist circumference and non-HDL cholesterol, and the average of age-specific, sex-specific, and height-specific *z*-scores for systolic and diastolic blood pressure

[b]*P* for PUFA exposure-cohort interaction estimated using the Wald test

exposure in our study are of high relevance as they coincide with the period during which there is an exponential increase in the rate of fetal fat accretion [39].

Rapid growth in the first few months of life is characterized mainly by a gain in fat, and has been to shown to predict obesity and cardiometabolic complications later in life [40]. A few previous studies have assessed the effect of prenatal PUFA status on infant somatic growth. The Dutch Generation R study ($n = 908$ mother-child pairs) examined PUFA levels in mid-pregnancy, and showed no consistent associations of maternal n-6 PUFA levels with infant subcutaneous fat mass measures [41]. The authors also reported transient effects of maternal n-3 PUFA levels on infant central subcutaneous fat mass development [41]. In the German INFAT study ($n = 208$), Much et al, reported no association of cord blood PUFA concentrations with adiposity measures during the first year of life [42]. Likewise, in our pooled analysis, we found no association between cord blood PUFAs and rapid weight gain from birth to 6 months.

Our findings also do not support a role of PUFA exposure in late gestation in the programming of adiposity status in mid-childhood. Our findings are in line with a 2014 systematic review and meta-analysis of randomized trials showing no effect of n-3 long-chain PUFA supplementation during pregnancy on adiposity status in preschool and school-age children [6]. Recently, an analysis from the Australian DOMINO trial also reported no effect of maternal n-3 long-chain PUFA supplementation in pregnancy on BMI and body fat percentage, as assessed by bioelectrical impedance, in children up to 7 years of age [43, 44]. Likewise, the INFAT study found that a dietary reduction in the n–6:n–3 long-chain PUFA ratio during pregnancy and lactation had no effect on several measures of child adiposity including anthropometry and sonographic assessment of abdominal fat distribution up to 5 years, and abdominal MRI at 5 years [45]. Previous results from cohort studies in Europe and the US with samples sizes varying from 234 to 4830 mother-child pairs have also provided little evidence to support that an increase in n-3 PUFA status, a decrease in n-6 PUFA status, or both in pregnancy is an effective strategy to prevent offspring obesity [7–12].

We observed no associations of PUFA levels at birth with an overall cardiometabolic risk profile in mid-childhood. Similar to our findings, two trials in Mexico ($n = 524$) and Denmark ($n = 243$) assessing n-3 long-chain PUFA supplementation in late pregnancy did not find any effect on offspring lipid profile [46, 47] and BP [48] up to 19 years. The Aarhus birth cohort study ($n = 443$) also found no association between n-3 PUFA intake in mid-pregnancy and offspring lipid profile, BP, and glucose metabolism in early adulthood [10]. By way of contrast, the Generation R study showed higher maternal plasma n-3 PUFA levels in mid-pregnancy to be associated with lower SBP and higher total cholesterol, HDL cholesterol, and insulin levels at age 6 [49, 50].

Differences in exposure definition, outcomes studied, and covariate adjustment may at least party account for the inconsistencies in previous findings. In our study, we used two cohorts from different parts of Europe for replication, and followed a centralized statistical analysis following a consensus protocol with harmonized information on exposure variables, potential confounders, and child outcomes. In our analysis, we saw differential associations of the n-6 LA with rapid infant growth, and of the n-3 ALA with mid-childhood SBP between cohorts, resulting in heterogeneity in the effect estimates. There was a positive association between LA and rapid infant growth only in MEFAB, while a positive association was observed for ALA and SBP only in RHEA. Compared to MEFAB children, those in RHEA had both higher LA concentrations (25–75% range: 9.28–12.92 vs. 6.78–8.55 wt.%) and prevalence estimates of rapid infant growth (34.6% vs. 21.0%), but largely overlapping ALA concentrations (25–75% range: 0.04–0.10 vs. 0.00–0.08 wt.%) and lower mid-childhood SBP levels (25-75% range: 88.2–99.7 vs. 96.7-105.3 mm Hg). Hence, we treat these associations with caution, as they might not reflect a biological effect, but rather they might have occurred due to chance or due to a specific confounder pattern in one cohort relative to the other (e.g., differences in diet or lifestyle).

As in any observational study, there is a possibility of unmeasured residual confounding. Although we considered television viewing in our analysis, other differences in sedentariness or physical activity patterns might have influenced the observed findings. Our study had adequate power to detect relative large effect sizes in risk estimates for binary outcomes. It is possible that some smaller but still meaningful effects were missed, especially given the small variability in the fatty acid concentrations. Nevertheless, our study was adequately powered to detect effect sizes that were similar to those previously reported [7]. Similar to most cohort studies, a limitation of the present study is loss to follow up, which raises the likelihood of attrition bias. It may be possible that the sample of children who participated in the follow-up evaluations had a lower BMI and a healthier cardiometabolic profile than those who did not, thus resulting in reduced variability in the distribution of BMI and other cardiometabolic risk factors. This might have limited our ability to detect an association. Nevertheless, our study population did not substantially differ from excluded mother-child pairs in main baseline socio-demographic characteristics. BMI, one of our main outcomes, is a measure that incorporates both lean and fat mass. However, childhood BMI has been shown to strongly correlate with dual emission X-ray absorptiometry (DXA) fat mass [51].

To conclude, this pooled analysis of two population-based cohort studies from West and South Europe suggests that fetal exposure to PUFAs in late pregnancy is not associated with rapid infant growth, childhood adiposity status, and cardiometabolic risk.

Acknowledgements We would like to thank Professor Emeritus Gerard Hornstra, who made the MEFAB study possible. We are also extremely grateful to the MEFAB and RHEA study participants for their time and commitment.

Funding The MEFAB cohort was financially supported by the University Hospital of Maastricht (Profilerings Fonds), and the Dutch Organization for Scientific Research (NWO, Grant number 904 62 186). The RHEA Mother Child Cohort in Crete project was financially supported by European projects [EU FP6-003-Food-3-NewGenerис-contract no. 16320, EU FP6 STREP Hiwate-contract no. 36224, EU FP7 ENV.2007.1.2.2.2. Project No. 211250 Escape, EU FP7-2008-ENV-1.2.1.4 Envirogenomarkers contract no. 226756, EU FP7-HEALTH-2009-single stage CHICOS contract no. 241604, EU FP7 ENV.2008.1.2.1.6. proposal no. 226285 ENRIECO, EU-FP7, proposal no. 264357 MeDALL, EU- FP7- HEALTH-2012 proposal no. 308333 HELIX], and the Greek Ministry of Health (Program of Prevention of obesity and neurodevelopmental disorders in preschool children, in Heraklion district, Crete, Greece: 2011-2014; "Rhea Plus": Prevention Program of Environmental Risk Factors for Reproductive Health, and Child Health: 2012-2015).

Author contributions The authors' responsibilities were as follows: NS, MG, LC, and MPZ designed the research; MA and EGS carried out the fatty acid analysis for the RHEA cohort; all authors contributed to the acquisition of data; NS and KM analyzed the data and performed statistical analysis; NS, MG, and LC wrote the paper; MG, LC, RHMdG, and MPZ contributed to study supervision. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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