Prostaglandins, Leukotrienes and Essential Fatty Acids ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Prostaglandins, Leukotrienes and Essential Fatty Acids

journal homepage: www.elsevier.com/locate/plefa

Cord blood *n*-3 LC-PUFA is associated with adiponectin concentrations at 10 years of age

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ARTICLE INFO

Article history:
Received 24 October 2014
Received in revised form
4 February 2015
Accepted 18 February 2015

Keywords:
PUFA
Fatty acids
Cord blood
Adiponectin
Children
Epidemiology

ABSTRACT

An elevated ratio of *n*-6 to *n*-3 long-chain (LC-) polyunsaturated fatty acids (PUFA) may be a potential risk factor for obesity development. *N*-3 LC-PUFA are thought to alter adiponectin concentrations, and thus may have a beneficial effect on weight development. We analysed the association between *n*-3 LC-PUFA concentrations in cord blood and adiponectin concentrations at 10 years.

Fatty acid composition was measured in cord blood and at 10 years of age by gas chromatography, and adiponectin concentrations were measured only at 10 years of age in 237 children from the Munich LISAplus birth cohort study. Linear regression models assessed associations between *n*-3 LC-PUFA, *n*-6 LC-PUFA and the *n*-6/*n*-3 ratio in cord blood with adiponectin concentrations at 10 years of age. LC-PUFA were presented as percentages and categorized into tertiles. Regression models were adjusted for LC-PUFA percentages at 10 years of age and other potential confounding factors.

Cord blood *n*-3 LC-PUFA tertiles were significantly associated with adiponectin concentrations in an inverse J-shaped relationship [2nd tertile versus 1st tertile: Beta=1.84 (SE=0.65), and 3rd tertile versus 1st tertile: 1.02 (0.68), *p*-value < 0.01 (ANOVA)]. Further, cord blood *n*-6/*n*-3 ratios were significantly associated with adiponectin concentrations [2nd tertile versus 1st tertile: 0.14 (0.67), and 3rd tertile versus 1st tertile: −1.37 (0.68), *p*-value=0.03 (ANOVA)]. The cord blood *n*-6 LC-PUFA tertiles were not associated with adiponectin concentrations.

Our results suggest that a higher *n*-3 LC-PUFA concentrations and a lower *n*-6/*n*-3 ratio in cord blood are associated with higher adiponectin concentrations at 10 years of age.

1. Introduction

It has been suggested that, among other factors, an elevated ratio of *n*-6 to *n*-3 long-chain polyunsaturated fatty acids (LC-PUFA) may be a potential risk factor for obesity [1,2].

N-6 LC-PUFA and *n*-3 LC-PUFA been proposed to have different effects on the development of adipose tissue. The main *n*-6 LC-PUFA, arachidonic acid (AA), is a precursor of eicosanoids, such as prostacyclin, which enhances the differentiation of adipose precursor cells to adipocytes. In contrast, *n*-3 LC-PUFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may be less adipogenic and may inhibit adipose tissue development by attenuating the production of eicosanoids [2,3]. Moreover, *n*-3 LC-PUFA may have a regulatory effect on adiponectin [4]. Adiponectin is an anti-inflammatory hormone secreted by adipose tissue [4]. Decreased adiponectin concentrations are associated with obesity and insulin resistance [4,5]. Several studies have shown a positive association between *n*-3 LC-PUFA and adiponectin concentrations [4,6].

Adipocyte development increases exponentially with gestational age [7]. The highest increase in number and size of adipocytes occurs during the first year of life. Following this, the differentiation of precursor cells into adipocytes continues later in life [2,8]. Thus, pre- and early postnatal life are critical periods for adipose tissue development.

However, it is not clear whether there is a long lasting priming effect of *n*-3 LC-PUFA concentrations in cord blood on adiponectin concentrations later in life [7].

In a previous analysis based on the same study population, we reported a time-varying association between the *n*-6/*n*-3 ratio in

Abbreviations: AA, arachidonic acid; ANOVA, Analysis of variance; BMI, Body mass index; DHA, Docosahexaenoic acid; DPA, Docosapentaenoic acid; EPA, Eicosapentaenoic acid; (LC-)PUFA, (long-chain) polyunsaturated fatty acids

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http://dx.doi.org/10.1016/j.plefa.2015.02.003
0952-3278/

cord blood and BMI (body mass index) up to the age of 10 years [9]. Based on these findings, we investigated the association between the *n*-3 LC-PUFA concentrations, the *n*-6 LC-PUFA concentrations and the *n*-6/*n*-3 ratio in cord blood with adiponectin concentrations at the age of 10 years. The *n*-3 LC-PUFA concentrations, the *n*-6 LC-PUFA concentrations and the *n*-6/*n*-3 ratio, measured at the 10-year follow-up examination, were included in the analysis in order to rule out confounding by life-style or dietary factors, which may be reflected in the fatty acid composition in blood. We hypothesize that higher *n*-3 LC-PUFA concentrations, lower *n*-6 LC-PUFA concentrations and a lower *n*-6/*n*-3 ratio in cord blood are associated with higher adiponectin concentrations at 10 years of age, even after accounting for later LC-PUFA concentrations in blood.

2. Materials and methods

2.1. Study population

LISAplus (Life-style Related Factors on the Immune System and the Development of Allergies in Childhood PLUS the influence of traffic emissions and genetics) is a German population based birth cohort study in which a total of 3097 neonates were recruited between 1997 and 1999 from the cities of Munich, Leipzig, Wesel and Bad Honnef. Details of the study design have been described elsewhere [10]. During the recruitment in maternity wards, cord blood samples were collected and deep frozen until the time of measurement. Questionnaires were completed by the parents at birth, 0.5, 1, 1.5, 2, 4, 6 and 10 years of age, and physical examinations took place at 2, 6 and 10 years.

This sub-study is restricted to children from the Munich study center. Of the 1467 successfully recruited children, 814 cord blood samples could be collected. Total immunoglobulin E concentrations were measured in these 814 cord blood samples [10]. Sufficient serum remained in 681 samples for further measurements of fatty acids. Of the 1467 children recruited at birth, 953 (65%) were followed-up until the age of 10 years. Of these 953 children, 581 children participated in the clinical examination of which 540 provided blood samples. Adiponectin concentrations and the fatty acid composition at age 10 years were measured successfully in 527 samples. Complete information on the fatty acid composition in cord blood as well as adiponectin concentrations and fatty acid composition at age 10 years was available for 249 children. After excluding 12 children with missing covariable information, 237 children were included in this analysis.

Approval by the local Ethics Committees (Bavarian Board of Physicians, University of Leipzig, Board of Physicians of North-Rhine-Westphalia) and written consent from each participant's family were obtained.

2.2. Physical examination and blood tests

Blood samples were collected during the physical examination at 10 years of age. The analysis of adiponectin, estradiol and testosterone has been previously described [11]. Blood samples were centrifuged after collection and stored frozen at −80 °C until assayed for adiponectin, estradiol (females) and testosterone (males). Adiponectin concentrations in serum were measured using a commercially available radioimmunoassay (Mediagnost, Reutlingen). The samples were diluted by a factor of 1:300. The sensitivity of the test was 0.6 µg/L. The intra- and interassay coefficients of variation were between 2.35% and 8.59% for adiponectin samples ranging from 3.36 mg/L to 15.19 mg/L. Testosterone and estradiol concentrations were measured in the serum samples by the fully mechanized immunoassay system Modular (Roche, Mannheim, Germany). The analytical sensitivity was 0.087 nmol/L for testosterone and 18.4 pmol/L for estradiol. Intra- and interassay coefficients of variation were below 4.06% and 2.83% for 6.2 nmol/L and 20.2 nmol/L testosterone, respectively. For estradiol, intra- and interassay coefficients of variation were below 5.29% and 3.56% for 378 pmol/L and 1941 pmol/L, respectively.

The measurement of fatty acids has been previously described in detail for the serum from cord blood and from blood samples collected at 2, 6 and 10 years of age [9,12,13].

The analysis was performed by selective transfer of glycerophospholipid fatty acids from 100 µl serum into their methyl esters and their gas chromatographic separation and quantification [14].

The total *n*-6 LC-PUFA concentration was calculated by summing the concentrations of eicosadienoic acid (C20:2*n*-6), dihomo-gamma-linolenic acid (C20:3*n*-6), AA (C20:4*n*-6), adrenic acid (C22:4*n*-6) and docosapentaenoic acid (C22:5*n*-6). Similarly, the total *n*-3 LC-PUFA concentration was calculated by summing the concentrations of eicosatrienoic acid (C20:3*n*-3), EPA (C20:5*n*-3), docosapentaenoic acid (DPA, C22:5*n*-3) and DHA (C22:6*n*-3). Total *n*-6 LC-PUFA and total *n*-3 LC-PUFA concentrations are presented as a percentage of the concentrations of all the measured fatty acids with 14–24 carbon atoms. The *n*-6/*n*-3 ratio was calculated by dividing the total *n*-6 LC-PUFA concentration by the total *n*-3 LC-PUFA concentration.

2.3. Statistical analysis

The percentages of *n*-3 and *n*-6 LC-PUFA as well as the *n*-6/*n*-3 ratio were categorized into sex-specific tertiles because of their apparent non-linear relationship with adiponectin concentrations. The cut-off values used for the construction of tertile groups are presented in Table S1 (Supplementary data). Adiponectin concentrations are presented using their mean and standard deviation (SD) and differences in adiponectin concentrations between tertile groups were tested using ANOVA (analysis of variance).

Linear regression models were applied to model the association between adiponectin concentrations with *n*-6 and *n*-3 LC-PUFA and the *n*-6/*n*-3 ratio tertiles. The first tertile was used as the reference category. Results are presented as linear regression coefficient betas with corresponding standard errors (SE). *p*-values were derived from ANOVA. The linear regression models were adjusted for sex, total serum glycerophospholipid fatty acids in cord blood and at 10 years, fasting status and exact age at the 10-year examination, BMI at 10 years, maternal age at birth, maternal pre-pregnancy BMI, maternal education level (low/medium vs. high), birth weight (<3455 g vs. ≥ 3455 g), gestational age, breastfeeding (exclusive breastfeeding >4 months vs. no exclusive breastfeeding or exclusive breastfeeding ≤ 4 months), onset of puberty (females: estradiol >18.4 vs. ≤ 18.4; males: testosterone >0.09 vs. ≤ 0.09). Furthermore, models were adjusted for *n*-6 LC-PUFA, *n*-3 LC-PUFA and the *n*-6/*n*-3 ratio tertiles, respectively, at age 10 years. To investigate if a specific LC-PUFA might be causing the effect, all LC-PUFA previously combined into either *n*-3 or *n*-6 LC-PUFA, were analyzed separately. Additionally, a sensitivity analysis stratified by sex was conducted. Statistical significance was defined by a two-sided alpha level of 5%.

Statistical analyses were performed using R, version 2.15.2 (http://www.R-project.org/) [15]. The "effects" package was used for plotting [16].

3. Results

This analysis is based on 237 children (110 girls and 127 boys) with available information on cord blood fatty acid composition, fatty acid composition and adiponectin measurements at age 10 years.

Details of the study population are presented in Table 1. The mean adiponectin concentration was 9.5 ng/mL (SD=4.2 ng/mL). The characteristics of the study population per *n*-6 and *n*-3

Please cite this article as: M Standl, et al., Cord blood *n*-3 LC-PUFA is associated with adiponectin concentrations at 10 years of age, Prostaglandins Leukotrienes Essent. Fatty Acids (2015), http://dx.doi.org/10.1016/j.plefa.2015.02.003

Table 1
Characteristics of study population.

	% or mean (SD)
Baseline (birth)	
Sex [% females]	46%
Total fatty acids[a]	647.3 (104.9)
Maternal age at birth [years]	33 (3.9)
Maternal BMI before pregnancy	22.1 (3.4)
Maternal education level [% high]	65%
Birth weight = 3455 g	50%
Gestational age [weeks]	40 (1.2)
Exclusive breastfeeding > 4 months	51%
Follow-up (10 years)	
Adiponectin [ng/mL]	9.5 (4.2)
Age in years	10.2 (0.2)
Total fatty acids[a]	1256.3 (203.8)
Fasting [% yes]	22%
BMI	16.8 (2.4)
Onset of puberty [% yes]	45%

[a] Fatty acids were measured in serum glycerophosphospholipids.

Table 2
Mean (SD) adiponectin concentrations per tertile of *n*-6 and *n*-3 LC-PUFA concentrations and the *n*-6/*n*-3 ratio.

		T1	T2	T3	*p*-value[b]
Cord blood	*n*-6 LC-PUFA[a]	9.2 (3.9)	9.5 (4.5)	9.7 (4.0)	0.73
	n-3 LC-PUFA[a]	8.3 (3.7)	11.0 (5.0)	9.4 (4.0)	< 0.01
	n-6/*n*-3 ratio[a]	9.7 (4.3)	10.0 (4.0)	8.5 (3.8)	0.03
10 years	*n*-6 LC-PUFA[a]	8.8 (3.6)	9.8 (4.3)	9.7 (4.6)	0.26
	n-3 LC-PUFA[a]	9.5 (4.0)	10.0 (4.6)	8.8 (3.6)	0.18
	n-6/*n*-3 ratio[a]	8.6 (3.6)	9.7 (4.3)	10.0 (4.0)	0.06

[a] Fatty acids were measured in serum glycerophosphospholipids and the percentages of *n*-6 and *n*-3 LC-PUFAs and the *n*-6/*n*-3 ratio are categorized into tertiles.
[b] *p*-value derived from ANOVA.

LC-PUFA and the *n*-6/*n*-3 ratio tertiles are presented in Table S2 (Supplementary data).

To investigate the effect of selective drop out, all variables were tested for differences between participants and non-participants (Supplementary data, Table S3). Non-participants were defined as children with available fatty acid measurements in cord blood but not at 10 years of age. Children included in this study had higher adiponectin concentrations at 10 years of age ($p=0.01$) and were more likely to be from older mothers ($p=0.03$).

There was no significant association between *n*-3 LC-PUFA, *n*-6 LC-PUFA or the *n*-6/*n*-3 ratio from cord blood and at age 10 years (data not shown).

Table 2 presents mean adiponectin concentrations per *n*-6 and *n*-3 LC-PUFA and the *n*-6/*n*-3 ratio tertiles, in cord blood and at 10 years of age. Mean adiponectin concentrations differed significantly across the tertiles of *n*-3 LC-PUFA in cord blood (T1: mean (SD) = 8.3 (3.7), T2: 11.0 (5.0), T3: 9.4 (4.0), $p<0.01$) and the *n*-6/*n*-3 ratio in cord blood (T1: 9.7 (4.3), T2: 10.0 (4.0), T3: 8.5 (3.8), $p=0.03$). There were no significant differences in mean adiponectin concentrations across *n*-6 LC-PUFA tertiles in cord blood or *n*-6 LC-PUFA, *n*-3 LC-PUFA and the *n*-6/*n*-3 ratio tertiles in blood measured at age 10 years.

Results of the linear regression models are presented in Table 3. Adiponectin concentrations were associated with cord blood *n*-3 LC-PUFA tertiles (T2 vs. T1: Beta (SE) = 1.84 (0.65); T3 vs. T1: 1.02 (0.68), $p<0.01$) and the cord blood *n*-6/*n*-3 ratio tertiles (T2 vs. T1: 0.14 (0.67), T3 vs. T1: −1.37 (0.68), $p=0.03$). The cord blood *n*-6 LC-PUFA tertiles were not associated with adiponectin concentrations.

Fig. 1 illustrates the associations between cord blood *n*-3 LC-PUFA tertiles and the *n*-6/*n*-3 ratio with adiponectin concentrations. The adjusted means of adiponectin concentrations per cord blood *n*-3 LC-PUFA tertile are presented in Fig. 1a. The adjusted mean of adiponectin concentrations was lowest in the first tertile and highest in the second tertile. Fig. 1b illustrates the association between the *n*-6/*n*-3 ratio in cord blood and adiponectin concentrations. The adjusted means of adiponectin concentrations are similar in the first and second tertiles, and lower in the third.

To investigate if a specific LC-PUFA might be causing the effect, all LC-PUFA previously combined into either *n*-3 or *n*-6 LC-PUFA, were analyzed separately. The results are presented in Table S4 (Supplementary data). Adiponectin concentrations were significantly associated with cord blood DPA (C22:5*n*-3) and DHA (C22:6*n*-3) tertiles, but not with tertiles of eicosatrienoic acid (C20:3*n*-3), EPA (C20:5*n*-3) or any of the *n*-6 LC-PUFA. There were no significant associations of adiponectin concentrations with any of the tertiles of *n*-6 LC-PUFA or *n*-3 LC-PUFA in blood measured at age 10 years.

In an additional sensitivity analysis, linear regression models stratified by sex were conducted (Supplementary data, Table S5). Generally, the magnitude of the effect estimates was stronger in females (Table S5a) than in males (Table S5b). The association between cord blood *n*-3 LC-PUFA tertiles and adiponectin concentrations reached significance only in females (T2 vs. T1: 2.23 (1.05), T3 vs. T1: 1.64 (1.11), $p=0.04$). At 10 years of age, a higher *n*-6/*n*-3 ratio was associated with higher adiponectin concentrations in females only (T2 vs. T1: 1.60 (1.03), T3 vs. T1: 3.04 (1.05), $p=0.02$), whereas there was no association in males.

4. Discussion

Using longitudinal data from the Munich LISAplus birth cohort, this study investigated the association between cord blood *n*-3 and *n*-6 LC-PUFA concentrations as well as the *n*-6/*n*-3 ratio in cord blood with adiponectin concentrations at 10 years of age, after accounting for LC-PUFA concentrations in blood at 10 years of age.

Our results suggest the existence of a positive association between cord blood *n*-3 LC-PUFA and adiponectin concentrations at 10 years of age, whereas this association seems to be mainly caused by DPA and DHA. Concentrations of LC-PUFA were grouped into tertiles because of their apparent non-linear relationship with adiponectin concentrations in our data, as observed in preliminary analyses. The risk estimate for the second tertile was greater than that for the third tertile (compared to the first tertile). As the range of cord blood *n*-3 LC-PUFA concentrations was much greater in the third tertile (despite the fact that the same number of observations are included in this category as in the second and first tertiles), our risk estimate for this group is likely less accurate. Thus, we are unable to comment as to whether our results indicate the existence of a non-linear association between cord blood *n*-3 LC-PUFA percentages and adiponectin concentrations. The association between the *n*-6/*n*-3 ratio in cord blood and adiponectin concentrations might be due to the fact that the third tertile is mainly comprised of children with low cord blood *n*-3 LC-PUFA concentrations. Thus, the effect estimate for the *n*-6/*n*-3 ratio in this tertile is likely primarily driven by cord blood *n*-3 LC-PUFA concentrations.

To our knowledge, this is the first study that investigates the association between cord blood *n*-3 and *n*-6 LC-PUFA concentrations as well as the *n*-6/*n*-3 ratio with adiponectin concentrations at 10 years, after accounting for LC-PUFA composition at 10 years. A randomized controlled trial comprising 533 women conducted by Rytter et al. [17] investigated the effect of maternal fish oil intake during pregnancy, as an indicator for *n*-3 LC-PUFA, on adiposity and related outcomes in 19-year old offsprings. Adiponectin concentrations measured when the 243 offspring were 19 years of age did not differ between the groups. The 19-year follow-up of this previous study is longer than the current study's 10-year follow-up. It might thus be possible that the associations we observed at 10 years are no longer apparent during early adult life. Moreover, our study is an

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Table 3
Results of linear regression models in which *n*-3 and *n*-6 LC-PUFA and the *n*-6/*n*-3 ratio, in cord blood and at 10 years of age, are regressed on adiponectin concentrations at 10 years of age.

		***n*-6 LC-PUFA**[a]			***n*-3 LC-PUFA**[a]			***n*-6/*n*-3 ratio**[a]		
		Beta[b]	**SE**	***p*-value**[c]	**Beta**[b]	**SE**	***p*-value**[c]	**Beta**[b]	**SE**	***p*-value**[c]
Cord blood	**T2 vs. T1**	0.47	0.67	0.72	1.84	0.65	< 0.01	0.14	0.67	0.03
	T3 vs. T1	0.18	0.68		1.02	0.68		−1.37	0.68	
10y	**T2 vs. T1**	1.29	0.69	0.26	0.90	0.67	0.22	0.80	0.67	0.06
	T3 vs. T1	1.49	0.74		−0.52	0.69		1.58	0.68	

[a] Fatty acids were measured in serum glycerophosopholipids and the percentages of *n*-6 and *n*-3 LC-PUFAs and the *n*-6/*n*-3 ratio are categorized into tertiles.
[b] Adjusted for sex, total serum glycerophosopholipid fatty acids in cord blood and at 10 years, fasting status and exact age at the 10-year examination, BMI at 10 years, maternal age at birth, maternal pre-pregnancy BMI, maternal education level, birth weight, gestational age, breastfeeding and onset of puberty.
[c] *p*-value derived from ANOVA.

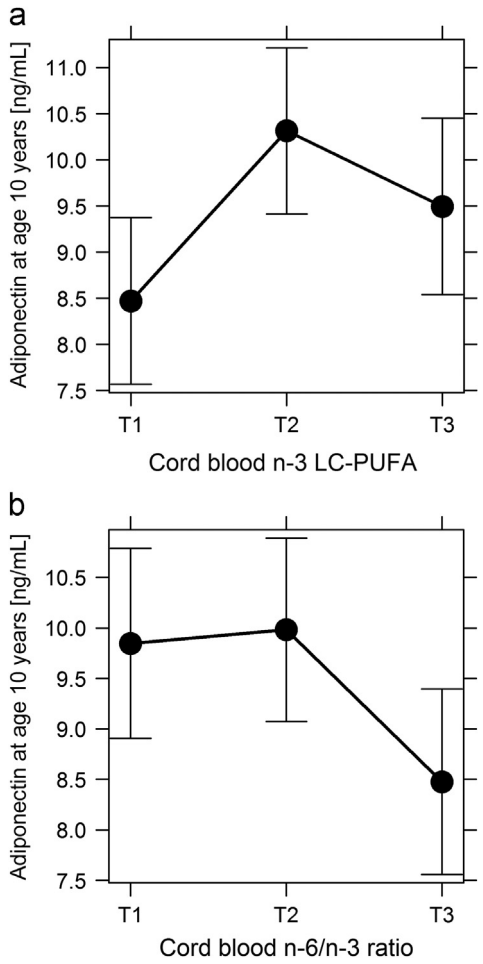

Fig. 1. Adjusted means with corresponding 95% confidence intervals of adiponectin concentrations per tertile of (a) cord blood *n*-3 LC-PUFA and (b) cord blood *n*-6/*n*-3 ratios. Fatty acids were measured in serum glycerophosopholipids and the percentages of *n*-6 and *n*-3 LC-PUFA and the *n*-6/*n*-3 ratio are categorized into tertiles.

observational study in a low fish intake population [18]. Thus, we are unable to determine whether the observed beneficial effect of cord blood *n*-3 LC-PUFA on adiponectin concentrations at age 10 years is caused by residual confounding.

Our results showed a positive significant association between adiponectin concentrations and the tertiles of the *n*-6/*n*-3 ratio at 10 years of age in females (Supplementary data, Table S5a). These findings are not well understood so far and the results in adults are conflicting [19–22]. Adiponectin concentrations in life course are complex and change over time in females [23]. Between the age of 5 and 8 years, adiponectin concentrations decrease independent of BMI. However, beyond this age, adiponectin concentrations show a negative association with percentage of body fat.

The biological mechanisms through which *n*-3 LC-PUFA may increase adiponectin concentrations are not entirely clear. The *n*-3 LC-PUFA EPA and DHA appear to activate the peroxisomal proliferator-activated receptor γ (PPARγ), which can stimulate adiponectin synthesis [24,25]. Furthermore, *n*-3 LC-PUFA may promote the synthesis of anti-inflammatory resolvins and protectins, which also enhance adiponectin production [26,27].

The major strength of this study is its prospective, longitudinal birth cohort study design, which includes a long follow-up period of up to 10 years of age and repeated fatty acid measurements. This study is a sub-study of the LISAplus birth cohort and not all blood measurements were available for all participants. Therefore, the sample size used for analysis is considerably smaller than the original cohort size. Another limitation of this study is the potential bias associated with non-random loss to follow-up (Supplementary data, Table S3). The fact that all fatty acid measurements were conducted at the same time (after the 10-year follow-up) with identical lab methods is on one hand a strength, but may also be a limitation as the storage time was substantially longer for cord blood samples than blood samples collected at the 10-year follow-up. Longer storage, even at −80 °C, might induce losses due to peroxidation, particularly of polyunsaturated fatty acids. This may potentially reduce the correlation between cord blood fatty acids and fatty acids at 10 years of age, and to adiponectin, thus underestimating the association between cord blood fatty acids and later-life adiponectin concentrations. In our study, glycerophopholipid bound fatty acids were measured. As expected, the mean percentages of DHA and AA are higher when measured in glycerophospholipids compared to total lipids [28–30]. Further, the mean percentages of glycerophopholipid DHA and AA are slightly higher compared to those measured in phospholipids [31,32]. Phospholipids combine glycerophopholipids and sphingomyelins, which are relatively low in polyunsaturated fatty acids.

Our results need to be confirmed in further studies with adequate sample size, long-term follow-up and repeated measurements to assess the persistence and possible beneficial health consequences. In summary, cord blood *n*-3 LC-PUFA concentrations and the *n*-6/*n*-3 ratio in cord blood appear to be associated with adiponectin concentrations at 10 years of age.

Acknowledgments

We thank all the families who participated in the LISAplus Study. Furthermore, we thank all members of the LISAplus Study group for their excellent work. We also acknowledge Larissa Piniek-Tzimourtas (University of Munich Medical Center, Dr von Hauner Children's Hospital, Division of Metabolic and Nutritional Medicine, Munich,

Germany) for her excellent contribution to the measurements of fatty acid composition. The LISAplus Study group consists of the following: Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology I, Munich (J Heinrich, HE Wichmann, S Sausenthaler, CM Chen, and M Schnappinger); Department of Pediatrics, Municipal Hospital "St. Georg," Leipzig (M Borte and U Diez); Marien-Hospital Wesel, Department of Pediatrics, Wesel (A von Berg, C Beckmann, and I Groß); Pediatric Practice, Bad Honnef (B Schaaf); Helmholtz Centre for Environmental Research-UFZ, Department of Environmental Immunology/Core Facility Studies, Leipzig (I Lehmann, M Bauer, C Gräbsch, S Röder, and M Schilde); University of Leipzig, Institute of Hygiene and Environmental Medicine, Leipzig (O Herbarth, C Dick, and J Magnus); IUF-Institut für Umweltmedizinische Forschung, Düsseldorf (U Krämer, E Link, and C Cramer); Technical University Munich, Department of Pediatrics, Munich (CP Bauer and U Hoffmann); and ZAUM-Center for Allergy and Environment, Technical University, Munich (H Behrendt, J Grosch, and F Martin).

This work was supported by grants 01 EG 9732, 01 EG 9705/2, and 01 EE 9401-4 from the Federal Ministry for Education, Science, Research, and Technology; FKZ 20462296 from the Federal Ministry of Environment; Ludwig-Maximilians-Universities' innovative research priority Project MC-Health; the Kompetenznetz Adipositas (Competence Network Obesity) funded by the Federal Ministry of Education and Research (FKZ: 01GI1121A). Further financial support from the Commission of the European Communities, the 7th Framework Programme, contract FP7-289346-EARLY NUTRITION and the European Research Council Advanced Grant ERC-2012-AdG – no. 322605 META-GROWTH is acknowledged. This manuscript does not necessarily reflect the views of the Commission and in no way anticipates the future policy in this area.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.plefa.2015.02.003.

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Please cite this article as: M Standl, et al., Cord blood *n*-3 LC-PUFA is associated with adiponectin concentrations at 10 years of age, Prostaglandins Leukotrienes Essent. Fatty Acids (2015), http://dx.doi.org/10.1016/j.plefa.2015.02.003