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Neonatal fatty acid status and cardiometabolic health at 9 years

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ABSTRACT

Background: Long chain polyunsaturated fatty acid (LCPUFA) status is associated with risk of cardiovascular diseases in adulthood. We previously demonstrated no effect of LCPUFA supplementation after birth on BP and anthropometrics. Little is known about the association between fatty acid status at birth and cardiometabolic health at older ages.
Aim: To evaluate associations between docosahexaenoic acid (DHA) and arachidonic acid (AA) levels in the umbilical cord and blood pressure (BP) and anthropometrics at 9 years.
Study design: Observational follow-up study. Multivariable analyses were carried out to adjust for potential confounders.
Subjects: 229 children who took part in a randomized controlled trial (RCT) on the effects of LCPUFA formula supplementation.
Outcome measures: BP was chosen as primary outcome; heart rate and anthropometrics as secondary outcomes.
Results: AA levels in the wall of the umbilical vein and artery were negatively associated with diastolic BP (B: vein −0.831, 95% CI: −1.578; −0.083, p = 0.030; artery: −0.605, 95% CI: −1.200; −0.010, p = 0.046). AA was not associated with systolic BP; DHA not with diastolic nor systolic BP. The AA:DHA ratio in the umbilical vein was negatively associated with diastolic BP (B: −1.738, 95% CI: −3.141; −0.335, p = 0.015). Heart rate and anthropometrics were not associated with neonatal LCPUFA status.
Conclusions: Higher AA levels and a higher AA:DHA ratio at birth are associated with lower diastolic BP at age 9. This suggests that the effect of LCPUFAs at early age is different from that in adults, where DHA is regarded anti-adipogenic and AA as adipogenic.

1. Introduction

The prenatal nutritional environment is known to be related to an individual's health in later life [1]. According to the ‘Developmental Origins of Health and Disease (DOHaD)-hypothesis’, environmental factors acting during the phase of developmental plasticity may lead to adaptive changes, and may potentially affect the capacity of an individual to cope with its environment in later life [2]. Adequate supply of necessary nutrients such as long chain polyunsaturated fatty acids (LCPUFAs) to the fetus presumably are required for optimal fetal-programming, and insufficient levels may affect blood pressure (BP) and anthropometrics [3].

The effect of LCPUFAs on adipose tissue development is not uniform. Docosahexaenoic acid (DHA) is regarded anti-adipogenic and arachidonic acid (AA) as adipogenic [4,5]. It has also been suggested that it is the AA:DHA ratio that matters [6].

Studies on the effects of LCPUFA supplementation during pregnancy or lactation on body composition provided inconsistent results [3]. Even less is known on the correlation between neonatal LCPUFA levels measured in the umbilical cord and anthropometrics. Much et al. reported a negative association between neonatal DHA and eicosapentaenoic acid (EPA) and parameters of neonatal body fat mass, yet, the association was no longer detectable in later infancy [7]. In contrast, Donahue et al. did report an association between umbilical DHA and EPA concentrations and cardiometabolic parameters after infancy; higher levels corresponded with leaner skinfolds and less obesity in 3-year-olds [8]. Helland et al., however, did not demonstrate a correlation between fatty acid status at birth and body mass index (BMI) at 7 years [9]. To

Abbreviations: LCPUFA, long-chain polyunsaturated fatty acid; DHA, docosahexaenoic acid; AA, arachidonic acid; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; OOS, obstetric optimality score; BMI, body mass index; EPA, eicosapentaenoic acid; DOHaD, Developmental Origins of Health and Disease; UMCG, University Medical Center Groningen.

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our knowledge, no studies addressed the association between neonatal fatty acid status and cardiometabolic health beyond the age of 7, or with BP at any age.

The current study is part of the Groningen LCPUFA study, a RCT on the effects of postnatal LCPUFA supplementation on the health and development of term infants. We previously reported that postnatal LCPUFA supplementation was not associated with BP and anthropometrics at 9 years [10]. In a subgroup of children, the fatty acid status in the umbilical cord was analysed. The aim of the present paper is to evaluate the associations between concentrations of AA, DHA and the AA:DHA ratio in the wall of the umbilical vessels and BP and anthropometrics in 9-year-olds. BP was chosen as our primary outcome measure, heart rate and anthropometrics (weight, body length, BMI and head circumference) as secondary outcome measures. Based on the current literature we hypothesize that a low AA:DHA ratio is associated with a more favourable cardiometabolic condition. Special attention was paid to an effect modification of sex [11].

2. Methods

2.1. Participants

Participants were part of the Groningen LCPUFA project, a RCT designed to assess effects of LCPUFA supplementation during the first two months after term birth on neurodevelopment and cardiometabolic health. Details on the inclusion period, study design and exact diet compositions are described elsewhere [12].

Directly after parturition, umbilical cord tissue was obtained from 317 of the 474 infants (67%), which was used to determine neonatal fatty acid status. Information on social background, obstetric conditions and pre- and perinatal circumstances was collected and allowed us to form an obstetric optimality score (OOS) [13]. Of the 317 children of whom umbilical cords were available, 235 (74%) children (121 boys, 108 girls) participated in the follow-up at 9 years. At this time systolic BP (SBP) and diastolic BP (DBP), heart rate, body length and weight were assessed. Parents and examiners were unaware of the type of formula-feeding and neonatal fatty acid status.

The study was approved by the Ethics Committee of the University Medical Center Groningen (UMCG, ISRCTN52788665). Prior to the follow-up assessment at 9 years parents provided renewed informed consent. Depending on the wish of the participants, the assessment was carried out at the department of Paediatrics of the UMCG or at home.

2.2. Analysis of the fatty acids of the umbilical vessels

Samples of 7–10 cm of the walls of the umbilical vein and artery were taken proximally to the placenta to determine neonatal fatty acid status. The samples were stored in saline at 4 °C (<24 h) until further processing with gas chromatography [14,15]. The present analysis focuses on AA, DHA and the AA:DHA ratio. Fatty acids were expressed as percentages of weight of total fatty acids with a chain length of 14–24 carbon atoms [16].

2.3. Cardiovascular parameters and anthropometrics

BP and heart rate were measured twice with an interval of an hour. BP was measured in millimeters mercury using an automated BP-monitor (Datascope Accutorr plus; Datascope corporation, Mahwah) with an appropriate cuff size (10.6–23.9 cm) around the left arm while the child was sitting. The mean of two recordings was used.

Weight was measured with a precision of 500 mg using a calibrated scale (Radwag, Radom, Poland) and body length was measured with the precision of millimeters using a stadiometer (Seca Deutschland, Hamburg, Germany). Subsequently, BMI was calculated. Head circumference was measured with a 'lasso' tape and recorded in millimeters. The assessments were performed between January 2006 and May 2008.

2.4. Statistical analyses

Baseline characteristics of participants and non-participants were compared using Fisher's exact tests, Student's *t*-test and Mann-Whitney *U* tests where applicable. For participating children we first tested whether sex was associated with neonatal fatty acid status and with the outcome measures (SBP, DBP, heart rate, weight, body length, BMI and head circumference). When these analyses indicated that sex could have acted as an effect modifier, the association between neonatal fatty acid status and our outcome measures was determined for boys and girls separately. If no effect modification of sex occurred, the effects were determined for the total group of children to maximize power. Pearson's or Spearman's rho was used to determine unadjusted correlations.

Multivariable linear regression analyses were performed to adjust for confounders. Based on the literature, the following seven covariates were selected: postnatal type of feeding (LCPUFA supplemented formula, control formula or breastfeeding), maternal level of education (middle/high versus low), maternal smoking during pregnancy (in line with other developmental studies smoking was dichotomized into <5 cigarettes/day or ≥5 cigarettes/day), intrauterine growth restriction (yes/no), sex, obstetric optimality score (OOS) and maternal BMI. We checked whether home versus hospital examination influenced the outcome measures and if necessary 'location of measurement' was entered as confounder. The level of significance was set at 0.05. Statistical analyses were carried out with SPSS 20 (SPSS, Inc., Chicago IL).

3. Results

3.1. Participation

Background information on participating and non-participating children is presented in Table 1. Importantly, neonatal fatty acid status did not differ between participants and non-participants. Yet, parents with a low level of education less often continued to participate than higher educated parents. Furthermore, children who were breastfed more often continued to participate than children who were not breastfed.

3.2. Parameters of cardiometabolic outcome at 9 years

An overview of cardiometabolic health at age 9 is given in Table 2. The values indicate that all cardiometabolic parameters are within the normal range [17,18]. We checked whether home versus hospital examination influenced the outcomes. Only BP depended on the measurement situation (SBP at home: mean 103, sd 9; hospital: mean 106, sd 8; $p = 0.007$; DBP at home: mean 60, sd 8; hospital: mean 64, sd 7; $p < 0.001$). The location of the measurements was therefore considered as an additional confounder in the BP analyses.

3.3. Effect modification of sex

We tested whether an interaction between sex and neonatal fatty acid status on our outcome measures existed. The analyses indicated the absence of a significant association between sex and all of our outcome measures, except for the outcome measure head circumference. Boys had a larger head circumference (mean 53.93 cm, sd 1.62) than girls (mean 52.92 cm, sd 1.57) ($p < 0.001$). We therefore separately assessed the association between neonatal fatty acid status and head circumference for boys and girls in the univariable analyses. In the multivariable analyses, sex was considered as an additional confounder in the head circumference analyses.