Higher Maternal Plasma n–3 PUFA and Lower n–6 PUFA Concentrations in Pregnancy Are Associated with Lower Childhood Systolic Blood Pressure 1–3

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Abstract

Background: Suboptimal maternal diet during pregnancy might lead to fetal cardiovascular adaptations with persistent consequences in the offspring.

Objective: We assessed the associations of maternal polyunsaturated fatty acid (PUFA) concentrations during pregnancy with childhood blood pressure.

Methods: In a population-based prospective cohort study among 4455 mothers and their children, we measured maternal second-trimester n–3 (ω-3) and n–6 (ω-6) PUFA concentrations in plasma glycerophospholipids and expressed n–3 and n–6 PUFAs as proportions of total PUFAs (wt%). Childhood blood pressure was measured at the median age of 6.0 y (95% range: 5.7–7.9 y).

We used linear regression models to assess the associations of maternal PUFA wt% with childhood blood pressure at 6 y.

Results: Higher total maternal n–3 PUFA wt% and, specifically, docosahexaenoic acid (DHA; 22:6n–3) wt% were associated with lower childhood systolic blood pressure (differences: −0.29 (95% CI: −0.54, −0.03) and −0.29 mm Hg (95% CI: −0.54, −0.03) per SD increase of total n–3 PUFAs and DHA wt%, respectively), but not with childhood diastolic blood pressure. Total maternal n–6 PUFA wt% was positively associated with childhood systolic blood pressure (differences: 0.36 mm Hg (95% CI: 0.09, 0.62) per SD increase of total n–6 PUFA wt%), but not with childhood diastolic blood pressure. A higher n–6:n–3 PUFA ratio was associated with higher childhood systolic blood pressure (P < 0.05). Pregnancy and childhood characteristics only partly explained the observed associations.

Conclusions: Higher maternal plasma n–3 PUFA and lower n–6 PUFA concentrations during pregnancy are associated with a lower systolic blood pressure in childhood. Further studies are needed to replicate these findings, explore the underlying mechanisms, and examine the long-term cardiovascular consequences.

Keywords: PUFAs, pregnancy, blood pressure, childhood, cohort

Introduction

Suboptimal maternal and fetal nutrition might lead to fetal cardiovascular developmental maladaptations and a subsequent increased risk of cardiovascular disease in later life (1). In humans, support for this hypothesis is largely based on historical cohort studies showing associations of maternal exposure to extreme famine during pregnancy with the development of hypertension in later life (2). To our knowledge, little is known about specific maternal nutritional factors during pregnancy, which may affect cardiovascular development in the offspring in less extreme environments. It has been hypothesized that maternal intake of long-chain PUFAs during pregnancy is important for fetal and

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3 Supplemental Figure 1 and Supplemental Table 1 are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
infant development (3, 4). During pregnancy there is an increase in the demand for PUFAs because of the increased need for maternal tissue and fetal development (5). Lower maternal n–3 PUFA concentrations and higher n–6 PUFA concentrations have been associated with increased risks of gestational hypertensive disorders and low birth weight (6–8). A previous study among 293 mother-child pairs showed that higher maternal plasma n–6 PUFA concentrations during pregnancy, but not n–3 PUFA concentrations, were associated with higher offspring fat mass (9). In addition, a study in rats suggested that moderate n–3 PUFA deficiency in the perinatal period was associated with hypertension in later life, despite reversal of the deficiency months before the assessment of blood pressure (6). A study among Dutch children showed that children who received human milk with a relatively high concentration of n–3 PUFAs in the first year of life had a lower systolic blood pressure at the age of 12 y (10). Thus far, to our knowledge, no studies among humans have examined the associations of maternal PUFA status during pregnancy with offspring blood pressure.

Therefore, we examined in a population-based prospective cohort study from early pregnancy onward, among 4455 mothers and their children, the associations of maternal n–3 and n–6 PUFA plasma concentrations during pregnancy with childhood blood pressure.

Methods

Study design. This study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life to adulthood in Rotterdam, Netherlands (11). The study has been approved by the Medical Ethical Committee of the Erasmus Medical Center in Rotterdam (MEC 198.782/2001/31). All mothers gave written consent. Pregnant women with an expected delivery date from April 2002 to January 2006 were enrolled in the study. In total, 8879 mothers were enrolled during pregnancy, of whom 6925 had PUFA concentrations available and gave birth to singleton live-born children. Childhood blood pressure was available in 4455 of these children (Supplemental Figure 1).

Maternal PUFA status. Maternal nonfasting venous samples were drawn at a median gestational age of 20.6 wk (95% range: 18.5–23.2 wk). To analyze PUFA concentrations, EDTA plasma samples were picked and transported to the Division of Metabolic Diseases and Nutritional Medicine, Dr. v. Hauner Children’s Hospital, University of Munich Medical Center. After being thawed, an analysis of plasma glycerophospholipid PUFA composition was performed by a sensitive and precise high-throughput method, suitable in large epidemiologic studies, as previously described (12). Based on findings from previous studies, we selected maternal PUFA concentrations for our analyses, which have been associated with a risk of cardiovascular disease in adults and with maternal and fetal mortality outcomes (8, 9, 13–16). Selected maternal PUFA concentrations were total n–3 PUFA, which included α-linolenic acid (ALA9; 18:3n–6), EPA (20:5n–3), docosapentaenoic acid (DPA; 22:5n–3), and DHA (22:6n–3), and total n–6 PUFA, which included linoleic acid (18:2n–6), γ-linolenic acid (18:3n–6), eicosadienoic acid (20:2n–6), dihomoy-γ-linolenic acid (20:3n–6), arachidonic acid (AA; 20:4n–6), and docosatetraenoic acid (DTA; 22:4n–6). The ratio of total n–6:n–3 PUFA was calculated. PUFA concentrations were expressed as proportion of total PUFA present in the chromatogram (wt%) (17). We observed similar results when we used FA concentrations expressed as mg/L instead of percentages (results not shown).

Childhood blood pressure. We measured blood pressure at the median age of 6.0 y (95% range: 5.7–7.9 y) 4 times with 1-min intervals at the right brachial artery with the child in the supine position, using the validated automatic sphygmomanometer Datascopc Accutor Plus TM (Paramus) (18). A cuff was selected with a cuff width ~40% of the arm circumference and long enough to cover 90% of the arm circumference. We used mean systolic and diastolic blood pressure values calculated from the last 3 blood pressure measurements.

Covariates. Information on maternal age, educational level, ethnicity, and maternal folic acid supplement use was obtained at enrollment (11). We measured maternal height and blood pressure at enrollment and obtained information about maternal prepregnancy weight by questionnaire. We calculated BMI. Maternal weight gain during pregnancy was calculated as the difference between maternal weight at the third trimester and maternal prepregnancy weight. Information on maternal smoking and alcohol consumption was assessed by questionnaires during pregnancy. Homocysteine and folate concentrations were analyzed using an immunenlotrochemiluminescence assay on the Architect System (Abbott Diagnostics B.V.). We used FFQs to assess maternal nutritional information during early pregnancy at the median gestational age of 13.8 wk (95% range: 9.9–22.6 wk). We also assessed infant PUFA intake at 13 mo by an FFQ questionnaire in a subgroup of the study cohort (n = 2153) (19). Information about pregnancy complications, childhood sex, gestational age, and weight at birth was obtained from medical records (20, 21). Information about breastfeeding and timing of the introduction of solid foods was obtained by questionnaires in infancy (19). At the age of 6 y, childhood height and weight were measured and BMI was calculated.

Statistical analysis. We examined the associations of maternal PUFA wt%, expressed as SD difference, with childhood systolic and diastolic blood pressure using linear regression models. We used 4 regression models: 1) a basic model including gestational age at maternal blood sampling and the child’s age and sex; 2) a pregnancy factor–adjusted model, which was additionally adjusted for maternal age, educational level, ethnicity, parity, prepregnancy BMI, gestational weight gain, blood pressure at enrollment, smoking, alcohol consumption, folic acid and homocysteine concentrations in plasma, total caloric intake during pregnancy, and pregnancy complications; 3) a childhood factor–adjusted model, which was the basic model additionally adjusted for gestational age and weight at birth, breastfeeding duration, timing of the introduction of solid foods, and childhood current BMI; and 4) a fully adjusted model, which includes all of the aforementioned factors. Included covariates were selected based on their associations with the outcomes of interest based on previous studies or a change in effect estimate of >10%. We performed a sensitivity analysis among a subgroup of children, using information that was available on PUFA intake at 13 mo, by adjusting further the performed analyses for PUFA intake in infancy. We tested for interaction terms between the child’s sex and maternal PUFA wt% in relation to blood pressure in childhood. Because no significant interaction terms were present, no further stratified analyses were performed. To reduce potential bias associated with missing data and to maintain statistical power, we performed multiple imputations of missing covariates by generating 5 independent data sets using the Markov chain Monte Carlo method, after which the pooled effect estimates were calculated. All analyses were performed using the Statistical Package for the Social Sciences version 21.0 for Windows (SPSS, Inc.). Values represent means ± SDs, medians (95% range), numbers (valid percentage), or estimates (95% CI) obtained from linear regression models. We used the 5% level of significance.

Results

Maternal and childhood characteristics are given in Table 1. Second-trimester total maternal n–3 and n–6 PUFA concentrations were 104 ± 27.5 mg/L and 597 ± 87.5 mg/L, respectively (Table 2). Results from the nonresponse analysis are given in Supplemental Table 1 and indicated that mothers who were not included in the analyses smoked more often during pregnancy and developed preeclampsia more often than those who were included in the analyses (P < 0.05). Also, birth weight, gestational age at birth, and breastfeeding duration were lower among children who were not included in the analyses than those who were included in the analyses (P < 0.05).
Maternal n–3 PUFA wt% and childhood blood pressure. Table 3 shows that in the models adjusted for gestational age at blood sampling, the child’s age and sex, a higher total n–3 PUFA wt%, and, specifically, higher ALA, EPA, DPA, and DHA wt% were associated with lower childhood systolic blood pressure ($P < 0.05$). Additional adjustment for pregnancy and childhood factors fully explained the associations of ALA, EPA, and DPA wt% with childhood systolic blood pressure. In the fully adjusted models higher total maternal n–3 PUFAs and DHA wt% were associated with lower childhood diastolic blood pressure ($P < 0.05$), whereas in the childhood model only higher total maternal n–6 PUFAs and DTA wt% were associated with a higher childhood diastolic blood pressure ($P < 0.05$). No associations were present in the pregnancy and fully adjusted models.

Maternal n–6:n–3 PUFA ratio and childhood blood pressure. Figure 1 shows that a higher maternal n–6:n–3 PUFA ratio was associated with a higher childhood systolic and diastolic blood pressure in the basic models ($P < 0.05$). Adjustment for pregnancy and childhood factors separately slightly attenuated these associations. In the fully adjusted model higher maternal n–6:n–3 PUFA ratios were associated with an increased childhood systolic blood pressure [differences: 0.36 mm Hg (95% CI: 0.09, 0.62) per SD increase of total n–6:n–3 PUFA ratio], whereas in the childhood model only higher total maternal n–6:n–3 PUFAs and DTA wt% were associated with childhood diastolic blood pressure ($P < 0.05$). No associations were present in the pregnancy and fully adjusted models.

Discussion
In this population-based, prospective cohort study we observed that higher maternal plasma n–3 PUFA (total and DHA) and lower n–6 PUFA concentrations during pregnancy were associated with a lower systolic blood pressure in school-age children. These associations were only partly explained by maternal and childhood characteristics.

Interpretation of main findings. Suboptimal nutrition in early life is associated with an increased risk of cardiovascular diseases in later life (22, 23). Multiple studies have shown that maternal intake of long-chain PUFAs during pregnancy is important for fetal development (4, 5). Little is known about the associations of...
TABLE 3  Associations of maternal n–3 PUFA wt% with blood pressure in children 6 y of age participating in the Generation R Study (n = 4455)1

<table>
<thead>
<tr>
<th>Differences in childhood systolic and diastolic blood pressure per SD difference in n–3 PUFAs</th>
<th>Total n–3 PUFAs (SD)</th>
<th>18:3n–3 (SD)</th>
<th>20:5n–3 (SD)</th>
<th>22:5n–3 (SD)</th>
<th>22:6n–3 (SD)</th>
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<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
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<tr>
<td>Basic model1</td>
<td>–0.60 (–0.84, –0.36)</td>
<td>–0.32 (–0.56, –0.08)</td>
<td>–0.30 (–0.54, –0.06)</td>
<td>–0.42 (–0.66, –0.17)</td>
<td>–0.58 (–0.82, –0.34)</td>
</tr>
<tr>
<td>Pregnancy model2</td>
<td>–0.33 (–0.59, –0.07)</td>
<td>–0.12 (–0.37, 0.13)</td>
<td>–0.07 (–0.32, 0.18)</td>
<td>–0.24 (–0.48, 0.01)</td>
<td>–0.33 (–0.59, –0.07)</td>
</tr>
<tr>
<td>Childhood model4</td>
<td>–0.35 (–0.58, –0.11)</td>
<td>–0.15 (–0.38, 0.09)</td>
<td>–0.08 (–0.31, 0.15)</td>
<td>–0.26 (–0.50, –0.03)</td>
<td>–0.37 (–0.59, –0.12)</td>
</tr>
<tr>
<td>Full model5</td>
<td>–0.28 (–0.54, –0.03)</td>
<td>0.12 (–0.36, 0.12)</td>
<td>–0.03 (–0.28, 0.22)</td>
<td>–0.22 (–0.46, 0.02)</td>
<td>–0.29 (–0.54, –0.03)</td>
</tr>
</tbody>
</table>

| Diastolic blood pressure, mm Hg |                  |              |              |              |              |
| Basic model                    | –0.38 (–0.58, –0.17) | –0.19 (–0.40, 0.00) | –0.12 (–0.32, 0.08) | –0.35 (–0.55, –0.15) | –0.36 (–0.57, –0.16) |
| Pregnancy model                 | –0.11 (–0.33, 0.11) | –0.04 (–0.25, 0.17) | 0.12 (–0.08, 0.34) | –0.19 (–0.40, 0.02) | –0.13 (–0.35, 0.09) |
| Childhood model                 | –0.26 (–0.47, –0.06) | –0.13 (–0.33, 0.07) | 0.02 (–0.22, 0.18) | –0.28 (–0.48, –0.07) | –0.27 (–0.47, –0.06) |
| Full model                      | –0.10 (–0.32, 0.12) | –0.04 (–0.25, 0.17) | 0.13 (–0.08, 0.34) | –0.18 (–0.38, 0.03) | –0.12 (–0.34, 0.10) |

1 Values are regression coefficients (95% CIs) obtained from linear regression models and reflect the difference in childhood blood pressure levels expressed as mm Hg per SD difference in each maternal n–3 PUFA, respectively. *P < 0.05.
2 Basic models are adjusted for gestational age at blood sampling, child age, and sex.
3 Pregnancy models are basic models additionally adjusted for maternal age, educational level, ethnicity, parity, prepregnancy BMI, gestational weight gain, blood pressure at enrollment, smoking, alcohol consumption, folic acid and homocysteine concentrations in plasma, total caloric intake during pregnancy, and pregnancy complications.
4 Childhood models include maternal plasma n–3 PUFAs, linoleic acid, and AA during pregnancy were associated with an increased risk of obesity and higher fat mass levels in children aged 4 and 6 y (9). However, a small, randomized controlled trial among 208 healthy pregnant women did not find a beneficial effect of the reduction of the n–6:n–3 PUFA ratio in the maternal diet on the adipose tissue level in infants (24). In our current study, we observed that higher maternal plasma n–3 PUFA and lower n–6 PUFA concentrations during pregnancy were associated with lower systolic blood pressure in childhood. Of all the specific PUFAs, the strongest associations were present for DHA and DTA. These associations were only partly explained by maternal and childhood characteristics.
5 Full models are adjusted for all covariates.

TABLE 4  Associations of maternal n–6 PUFA wt% with blood pressure in children 6 y of age participating in the Generation R Study (n = 4455)1

<table>
<thead>
<tr>
<th>Differences in childhood systolic and diastolic blood pressure per SD difference in n–6 PUFAs</th>
<th>Total n–6 PUFAs (SD)</th>
<th>18:2n–6 (SD)</th>
<th>18:3n–6 (SD)</th>
<th>20:2n–6 (SD)</th>
<th>20:3n–6 (SD)</th>
<th>20:4n–6 (SD)</th>
<th>22:4n–6 (SD)</th>
</tr>
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<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
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</tr>
<tr>
<td>Basic model1</td>
<td>0.62 (0.38, 0.86)</td>
<td>0.22 (–0.02, 0.46)</td>
<td>0.22 (–0.02, 0.46)</td>
<td>0.01 (–0.22, 0.25)</td>
<td>0.23 (–0.01, 0.47)</td>
<td>0.42 (0.18, 0.66)</td>
<td>0.45 (0.21, 0.69)</td>
</tr>
<tr>
<td>Pregnancy model2</td>
<td>0.41 (0.14, 0.88)</td>
<td>0.23 (–0.03, 0.48)</td>
<td>0.09 (–0.15, 0.33)</td>
<td>0.03 (–0.21, 0.28)</td>
<td>0.04 (–0.22, 0.29)</td>
<td>0.11 (–0.14, 0.36)</td>
<td>0.19 (–0.06, 0.44)</td>
</tr>
<tr>
<td>Childhood model4</td>
<td>0.33 (0.09, 0.56)</td>
<td>0.12 (–0.12, 0.35)</td>
<td>0.17 (–0.06, 0.40)</td>
<td>–0.03 (–0.23, 0.23)</td>
<td>0.12 (–0.12, 0.35)</td>
<td>0.22 (–0.02, 0.45)</td>
<td>0.24 (0.00, 0.47)</td>
</tr>
<tr>
<td>Full model5</td>
<td>0.38 (0.09, 0.62)</td>
<td>0.20 (–0.05, 0.45)</td>
<td>0.10 (–0.13, 0.34)</td>
<td>0.05 (–0.19, 0.29)</td>
<td>0.01 (–0.24, 0.26)</td>
<td>0.11 (–0.14, 0.36)</td>
<td>0.15 (–0.10, 0.40)</td>
</tr>
</tbody>
</table>

| Diastolic blood pressure, mm Hg |                  |              |              |              |              |              |              |
| Basic model                    | 0.37 (0.17, 0.58) | 0.14 (–0.06, 0.34) | 0.17 (–0.02, 0.38) | 0.06 (–0.14, 0.27) | 0.17 (–0.03, 0.37) | 0.21 (0.01, 0.42) | 0.40 (0.20, 0.61) |
| Pregnancy model                 | 0.10 (–0.13, 0.33) | 0.04 (–0.18, 0.25) | 0.08 (–0.13, 0.28) | 0.01 (–0.19, 0.22) | 0.10 (–0.11, 0.31) | 0.01 (–0.21, 0.22) | 0.17 (–0.04, 0.38) |
| Childhood model                 | 0.24 (0.04, 0.45) | 0.09 (–0.11, 0.29) | 0.16 (–0.04, 0.36) | 0.06 (–0.14, 0.26) | 0.16 (–0.04, 0.37) | 0.11 (–0.09, 0.31) | 0.31 (0.11, 0.51) |
| Full model                      | 0.09 (–0.14, 0.32) | 0.04 (–0.17, 0.26) | 0.09 (–0.17, 0.29) | 0.03 (–0.18, 0.23) | 0.10 (–0.11, 0.31) | –0.02 (–0.23, 0.19) | 0.16 (–0.05, 0.37) |

1 Values are regression coefficients (95% CIs) obtained from linear regression models and reflect the difference in childhood blood pressure levels expressed as mm Hg per SD difference in each maternal n–6 PUFA, respectively. *P < 0.05.
2 Basic models are adjusted for gestational age at blood sampling, child age, and sex.
3 Pregnancy models are basic models additionally adjusted for maternal age, educational level, ethnicity, parity, prepregnancy BMI, gestational weight gain, blood pressure at enrollment, smoking, alcohol consumption, folic acid and homocysteine concentrations in plasma, total caloric intake during pregnancy, and pregnancy complications.
4 Childhood models are basic models additionally adjusted for birth characteristics, breastfeeding duration, timing of the introduction of solid foods, and BMI at the age of 6 y, respectively.
5 Full models are adjusted for all covariates.
that n–3 PUFA deficiency in the perinatal period leads to higher blood pressure later in life (25). A review of animal experiments, human observational studies, and randomized clinical trials has shown that the intake of n–3 PUFAs was associated with a lower systolic and diastolic blood pressure in adults and with a reduced risk of coronary heart disease (26). Also, a meta-analysis of clinical trials suggested that fish oil reduced blood pressure levels in humans (27). In children, the effects of n–3 and n–6 PUFA intakes on blood pressure have been examined in early postnatal life. A European study among 147 children from the United Kingdom, Belgium, and Italy showed that children who as infants had been fed with a formula supplemented with AA and DHA had lower mean systolic blood pressure and diastolic blood pressure at the age of 6 y than those who were not supplemented (28). A randomized trial among 83 Danish children at the age of 9 mo showed that systolic blood pressure was lower among children who received fish oil supplementation for 3 mo (29). A study among 973 Dutch children showed that children who received human milk with a relatively high content of DHA and EPA had lower systolic blood pressure at the age of 12 y. This association was not influenced from total n–3 PUFAs measured in the erythrocyte membrane at the age of 12 y (10). In line with these studies, our current study suggests that maternal n–3 and n–6 PUFA concentrations may already influence cardiovascular development from early fetal life onward.

Several potential mechanisms may explain the observed associations of maternal n–3 and n–6 PUFA concentrations during pregnancy with childhood blood pressure (13, 23, 30–33). n–3 PUFAs in fish oil are shown to have hypotensive properties through stimulation of PGs that control sodium and water excretion, inhibition of the vasoconstrictor thromboxane, and decrease of the response to vasopressor hormones (34–36). On the other hand, a higher n–6 PUFA intake can inhibit the conversion of ALA to EPA, which can downregulate the production of PGE2, which induces vascular relaxation (36, 37). n–6 PUFAs are precursors of the potent 2-series PGs and the vasoconstrictor thromboxane A2, which can stimulate vasoconstriction (38). n–3 PUFAs are also shown to affect the expression of inflammatory genes and may reduce the production of proinflammatory leukotrienes and cytokines (39). It has been suggested that, specifically, the balance of n–3 and n–6 PUFAs is important for optimal cardiovascular development (40, 41). Our findings support the hypothesis that lowering of the n–6:n–3 PUFA ratio during pregnancy might have beneficial health effects in the offspring (40, 41). However, additional studies are needed to examine whether the observed associations are indeed causal or reflect confounding by family based sociodemographic and lifestyle-related characteristics and to further explore the underlying mechanisms and examine whether they persist into adulthood.
Methodologic considerations. We used a population-based, prospective cohort study design with a large number of subjects. Of all children whose maternal PUFA concentrations were available, 64% participated in the cardiovascular follow-up studies. The nonresponse could lead to biased effect estimates if the associations of maternal PUFA concentrations with childhood blood pressure are different between children who were included and children who were not included in the analyses. Nonresponse analysis showed various differences between subjects included and not included in the analyses. It is hard to speculate whether these differences would affect the observed associations materially. Although we measured a large number of maternal PUFA concentrations in blood samples, they were measured only once during pregnancy. To our knowledge, no information was available about PUFA concentrations in early or late pregnancy. Additional studies are needed to examine critical periods of maternal PUFA status for offspring outcomes. Also, concentrations of maternal PUFAs may not fully reflect the concentrations of PUFAs that the fetus was exposed to, because this also depends on placental transfer (42). Finally, although we performed an extensive adjustment for a large number of potential confounders, residual confounding still might be an issue, as in any observational study. Most importantly, we did not have detailed information about maternal diet during pregnancy, on childhood diet, or on PUFA concentrations available in the full cohort. We assessed maternal dietary intake during the first trimester by an FFQ, but we did not have information about maternal diet during the second trimester. We were able to adjust for childhood intake of PUFAs in a subgroup of the study population and observed that the associations were not materially affected. Additional studies are needed to explore the role of the potential confounding by maternal and childhood dietary factors in these observed associations.

Conclusions. Suboptimal maternal diet during pregnancy might lead to fetal cardiovascular adaptations with persistent cardiovascular consequences in later life. Maternal intake of PUFAs during pregnancy is important for fetal and infant development. We observed that higher maternal plasma n–3 PUFA and lower n–6 PUFA concentrations during pregnancy are associated with a lower systolic blood pressure in childhood. These results should be considered as hypothesis generating for future studies. Additional observational and experimental studies are needed to explore the underlying mechanisms and to examine the long-term cardiovascular consequences.

Acknowledgments
AJV, VVVJ, and RG designed the research project; AH, HT, and VVVJ were involved in the design and planning of the study and data collection; AJV, OG, and RG conducted the analyses; AJV, OG, VVVJ, and RG wrote the paper; AJV, VVVJ, and RG had primary responsibility for the final content; JS-­DG, MAW, LD, and JFF critically reviewed and approved the final manuscript. All authors read and approved the final manuscript.

References


