Blood Pressure in 12-Year–Old Children Is Associated With Fatty Acid Composition of Human Milk

The Prevention and Incidence of Asthma and Mite Allergy Birth Cohort

Lenie van Rossem, Alet H. Wijga, Johan C. de Jongste, Gerard H. Koppelman, Marieke Oldenwening, Dirkje S. Postma, Marieke Abrahamse-Berkeveld, Bert van de Heijning, Bert Brunekreef, Henriëtte A. Smit

Abstract—Breastfed individuals have a lower blood pressure than formula-fed individuals. Supplementation with n-3 long-chain polyunsaturated fatty acids in adults is also associated with a lower blood pressure. We studied whether children receiving human milk with a relatively high content of n-3 long-chain polyunsaturated fatty acids have a lower blood pressure at age 12 years, and, if so, whether this association is explained by the n-3 long-chain polyunsaturated fatty acids content in erythrocyte membranes at age 12 years. Within a 12-year follow-up of a population-based birth cohort, we compared blood pressure of 205 never-breastfed children and 109 children who had fatty acid composition of their mothers’ breast milk measured during lactation. In addition, 973 children had information on erythrocyte fatty acid composition and blood pressure at age 12 years. Children who received human milk with an n-3 long-chain polyunsaturated fatty acids content above the median (ie, 0.51 weight percentage) had a 4.79-mm Hg lower systolic (95% CI, −7.64 to −1.94) and a 2.47-mm Hg lower diastolic (95% CI, −4.45 to −0.49) blood pressure at age 12 years than never-breastfed children. N-3 long-chain polyunsaturated fatty acids levels in human milk below the median value and current n-3 long-chain polyunsaturated fatty acid status were not associated with blood pressure at age 12 years. Thus, a relatively high content of n-3 long-chain polyunsaturated fatty acids in human milk is associated with a lower blood pressure in children at age 12 years, a finding not explained by current n-3 long-chain polyunsaturated fatty acids status. (Hypertension. 2012;60:1055-1060.) • Online Data Supplement

Key Words: fatty acids □ EPA □ DHA □ n-3 LC PUFA □ human milk □ blood pressure □ childhood

Breast feeding is associated with a modestly lower blood pressure in childhood and adulthood, as reported in 2 meta-analyses.1,2 In contrast to formula feeding up to the 1990s, human milk contains n-3 long-chain (LC) polyunsaturated fatty acids (PUFAs),3,5 which are important structural components of the vascular endothelium. Hence, it is hypothesized that the lowering effect of human milk on blood pressure may be the result of a long-term effect of n-3 LC PUFAs, in particular, docosahexaenoic acid (DHA; 22:6n-3) and eicosapentaenoic acid (EPA; 20:5n-3), as present in many fish oils.3,6 Other than that n-3 LC PUFAs may lead to lower blood pressure in early childhood, supplementation with n-3 LC PUFAs in adulthood also results in a lower blood pressure after a mean study duration of 11 weeks.7

In an observational birth cohort study, we tested the association between the n-3 LC PUFA composition of human milk and the current fatty acid status, as a biomarker of DHA and EPA intake, with blood pressure in children. Therefore, we studied the prospective association between fatty acid composition of human milk and blood pressure at age 12 years and the cross-sectional association between fatty acid composition of erythrocyte membranes at age 12 and blood pressure at age 12. In addition, we studied whether erythrocyte fatty acid status at age 12 years explained the association between human milk fatty acids composition and blood pressure.
Subjects and Methods

Study Design and Setting

We used the data from a population-based Dutch birth cohort study, the Prevention and Incidence of Asthma and Mite Allergy Study. Details of the study are described elsewhere. In short, pregnant women were recruited from the general population during their first antenatal visit in 1996–1997. Yearly, around the child’s birthday, data were collected by questionnaires. In addition, in a subgroup of children, a home visit was performed around the age of 3 months, and extensive medical examinations were performed at the ages of 4, 8, and 12 years. The study protocol was approved by the medical ethics committees of the participating institutes, and all of the parents gave written informed consent.

Study Population

A total number of 1432 children had blood pressure measurements at age 12 years. The fatty acid analyses were performed in a subsample. In this population, 2 subgroups were identified, all children who were never breastfed (n=205) and children from a subsample of mothers who collected a human milk sample for fatty acid analysis (n=109). Thus, we could assess the association between fatty acid composition of infant milk feeding and blood pressure in 314 participants. Data on erythrocyte membrane fatty acid composition were available for 973 participants. Because 64 children did not have information on fatty acids at both measurements, we had complete data for fatty acid composition of infant milk feeding, erythrocyte membrane fatty acid composition at age 12 years, and blood pressure in 250 children.

Fatty Acid Composition of Human Milk

We collected information on fatty acid composition of human milk but not on the fatty acid content of other food sources in infancy. Data on breastfeeding initiation was assessed by questionnaire at age 3 months. In the current study, children who were never breastfed served as reference, because at the time of the study (1996–1997), infant formula did not contain n-3 LC PUFAs in the Netherlands, and, therefore, this reference group had never received DHA and EPA in their first months of life. Details of human milk collection and analysis have been reported elsewhere. Fatty acids were measured as weight percentage (wt%) of the total fat content. Fatty acids of main interest in relation to blood pressure in 250 children.

Venous blood was sampled in a serum-separating tube with clot activator and gel for serum separation (BD Vacutainer). After clotting (30 minutes, room temperature), tubes were stored in the refrigerator until centrifuged at 1300 relative centrifugal force for 10 minutes. Serum was removed, and clotted cells were stored at −20°C. Fatty acid composition of clotted cell material was analyzed similarly as described above for the human milk samples.

Blood Pressure

Systolic and diastolic blood pressures were measured according to the recommendations of the American Heart Association Council on High Blood Pressure Research. Blood pressure was measured with the automatic Omron M6 upper arm device, which is based on the oscillometric method. An equivalent device using the same algorithm was validated in children. The child was calm and in a seated position for ≥10 minutes before the first measurement, and after 5 minutes a second measurement was performed. A child cuff size was used, but for children with an arm circumference >22 cm, a larger cuff was used. When the measurements differed >5 mm Hg, a third measurement was done. The averages of the (2 or 3) systolic and diastolic blood pressure measurements were used.

Potential Confounders and Mediators

The following variables were considered potential confounders: sex, gestational age, maternal smoking during pregnancy (any smoking by the mother during pregnancy ≥4 weeks after onset of pregnancy), birth weight, maternal and paternal educational level, and maternal and paternal body mass index (BMI). These variables were retrieved from questionnaires administered during pregnancy and in the first year of life. Mother’s BMI was calculated as weight (in kilograms)/height² (in meters). Father’s BMI was similarly calculated and obtained from the questionnaire at child’s age 8 years. An effect of parental smoking on blood pressure in preschool children, as mentioned in the study of Simonetti et al, may cause confounding if parental smoking is also associated with fatty acid composition of breast milk. However, in this data set there was no association, and, thus, we did not adjust our associations for parental smoking.

Child’s weight and height were measured during the medical examination, from which BMI was calculated. Child’s BMI can be a confounder or mediator, because it may be in the causal pathway in the association between infant milk feeding fatty acids and blood pressure.

Statistical Analysis

Because the fatty acid composition of human milk and erythrocyte membranes was not normally distributed and the association between fatty acids and blood pressure may not be linear, we created categories. N-3 LC PUFA content of human milk was categorized above or under the median of 0.51 wt%, respectively, “high” or “low.” Hence, infant milk feeding fatty acid composition had 3 categories, no n-3 LC PUFAs (infant formula), “low” in n-3 LC PUFAs, and “high” in n-3 LC PUFAs. Each fatty acid in erythrocyte membrane fatty acid composition was categorized separately in tertiles, with the highest tertile serving as the reference group. The association between fatty acid composition of human milk and blood pressure and erythrocytes with blood pressure was analyzed with multiple linear regression analyses for which we report regression coefficients and 95% CIs. The regression coefficient for human milk can be interpreted as the mean difference between high or low fatty acid content and the reference group of no fatty acids (infant formula). All of the blood pressure analyses were adjusted for cuff size. The fully adjusted model included all of the potential confounders described earlier. Missing values in the confounders did not exceed 2%, with the exception of parental BMI (<10%). We applied multiple imputation for the missing values in the confounding variables to prevent loss of information and bias. Ten imputed data sets were generated using a fully conditional specified model. Imputations were based on the relations between all of the covariates in the study. The multiple imputation was performed with SPSS (version 18.0). The 10 imputations were summarized in a pooled estimate.

We performed analyses stratified for breastfeeding, sex, and child’s overweight status to identify different associations within strata, but none of these factors appeared to be an effect modifier. Therefore, we did not perform stratified analysis. Data analysis was conducted with SAS software version 9.2 (SAS Institute, Inc, Cary, NC).

Results

Subject Characteristics

Table 1 shows the characteristics of the total study population and of the 2 study subsamples. Children who were never breastfed had more often a smoking, lower educated, and heavier mother and had a lower birth weight and shorter gestational age compared with children in the human milk fatty acids analyses sample. The characteristics of the subsample with erythrocyte membrane fatty acids available were similar to the total study population. Characteristics were not associated with blood pressure, except for father’s BMI (Table S1, available in the online-only Data.
Supplement). Table 2 shows the fatty acid composition of human milk and of the erythrocyte membranes of children at age 12 years. Mean n-3 LC PUFA content was 0.58 wt% (SD 0.34) in human milk and 2.68 wt% (SD 1.38) in erythrocyte membranes.

### Associations Between Infant Milk Feeding and Blood Pressure

Children who were fed human milk with a relatively high content (above the median, ie, ≥0.51 wt%) of n-3 LC PUFAs had a 4.79-mm Hg lower systolic (95% CI, −7.64 to −1.94; Table 3) and a 2.47-mm Hg lower diastolic blood pressure (95% CI, −4.45 to −0.49; Table 3) than children who were never breastfed. The blood pressure of children never breastfed did not differ from the blood pressure of children receiving human milk with a relatively low amount of n-3 LC PUFAs (below the median, ie, <0.51 wt%) for both systolic (β=−0.08 mm Hg [95% CI, −2.92 to 2.77]) and diastolic (β=−0.07 mm Hg [95% CI, −2.05 to 1.90]) blood pressures (Table 3). Child’s BMI was a strong predictor of blood pressure at age 12 years, with a standardized β of 0.12 mm Hg per BMI z score unit increase (95% CI, 0.02 to 0.22).

### Table 2. Fatty Acid Composition (Percentages of Total Fatty Acids) of Human Milk and Erythrocyte Membranes at Age 12 y

<table>
<thead>
<tr>
<th>Fatty Acids</th>
<th>Mean wt% (SD)</th>
<th>Median wt% (Interquartile Range)</th>
<th>Mean wt% (SD)</th>
<th>Median wt% (Interquartile Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA (C22:6n3)</td>
<td>0.23 (0.22)</td>
<td>0.18 (0.13-0.24)</td>
<td>1.41 (0.75)</td>
<td>1.26 (0.88-1.84)</td>
</tr>
<tr>
<td>EPA (C20:5n3)</td>
<td>0.06 (0.06)</td>
<td>0.05 (0.03-0.07)</td>
<td>0.36 (0.40)</td>
<td>0.31 (0.18-0.43)</td>
</tr>
<tr>
<td>Total n-3 LC PUFA</td>
<td>0.58 (0.34)</td>
<td>0.51 (0.43-0.63)</td>
<td>2.68 (1.38)</td>
<td>2.41 (1.77-3.37)</td>
</tr>
</tbody>
</table>

DHA indicates docosahexaenoic acid; EPA, eicosapentaenoic acid; LC PUFA, long-chain polyunsaturated fatty acids; wt, weight.
Table 3. Differences in Blood Pressure at Age 12 y for Fatty Acid Composition in Infant Milk Feeding

<table>
<thead>
<tr>
<th>Fatty Acids*</th>
<th>Systolic Blood Pressure, mm Hg</th>
<th>Diastolic Blood Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted (n=314)</td>
<td>Adjusted† (n=314)</td>
</tr>
<tr>
<td>DHA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No breastfeeding</td>
<td>ref (0)</td>
<td>ref (0)</td>
</tr>
<tr>
<td>Breastfeeding DHA levels less than median‡</td>
<td>−1.15 (−3.97 to 1.67)</td>
<td>−1.06 (−3.96 to 1.84)</td>
</tr>
<tr>
<td>Breastfeeding DHA levels at or more than median</td>
<td>−3.94 (−6.75 to −1.12)‖</td>
<td>−3.73 (−6.58 to −0.88)§</td>
</tr>
<tr>
<td>EPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No breastfeeding</td>
<td>ref (0)</td>
<td>ref (0)</td>
</tr>
<tr>
<td>Breastfeeding EPA levels less than median‡</td>
<td>0.42 (−2.38 to 3.21)</td>
<td>0.06 (−2.77 to 2.90)</td>
</tr>
<tr>
<td>Breastfeeding EPA levels at or more than median</td>
<td>−5.43 (−8.20 to −2.67)¶ ‖</td>
<td>−4.96 (−7.81 to −2.10)¶ ‖</td>
</tr>
<tr>
<td>n-3 LC PUFA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No breastfeeding</td>
<td>ref (0)</td>
<td>ref (0)</td>
</tr>
<tr>
<td>Breastfeeding n-3 LC PUFA levels less than median‡</td>
<td>0.04 (−2.76 to 2.84)</td>
<td>−0.08 (−2.92 to 2.77)</td>
</tr>
<tr>
<td>Breastfeeding n-3 LC PUFA levels at or more than median</td>
<td>−5.10 (−7.88 to −2.32)¶ ‖</td>
<td>−4.79 (−7.64 to −1.94)¶ ‖</td>
</tr>
</tbody>
</table>

DHA indicates docosahexaenoic acid; EPA, eicosapentaenoic acid; LC PUFA, long-chain poly-unsaturated fatty acids; BMI, body mass index; wt, weight; ref, reference.
*Associations represent regression coefficients and 95% CIs.
†Adjustments were made for size of cuff (also in unadjusted analyses), birth weight, gestational age, child’s sex, mother’s smoking during pregnancy, educational level of father and mother, BMI of father and mother, and child’s BMI at age 12 y.
‡Median was 0.18 wt% for DHA, 0.05 wt% for EPA, and 0.51 wt% for n-3 LC PUFA.
¶P<0.05.
‖P<0.01.
§P<0.001.

pressure in itself, but it had little influence on the association between a relatively high n-3 LC PUFA fatty acid composition and lower blood pressure. Similar results were obtained for the single n-3 LC PUFAs EPA and DHA.

Association Between Erythrocyte Membrane Fatty Acid Composition and Blood Pressure

Differences in blood pressure between tertiles of n-3 LC PUFAs in erythrocyte membranes were <1 mm Hg and not statistically different from 0. This was the case for systolic and diastolic blood pressures and for all fatty acids studied (Table 4).

Discussion

Main Findings

This study shows that children receiving human milk with a relatively high content of DHA, EPA, or total n-3 LC PUFAs had a significantly lower systolic blood pressure at age 12 years. A similar tendency was observed for diastolic blood pressure, but the associations were not all statistically significant after adjustment for potential confounders.

Erythrocyte membrane fatty acid composition at age 12 years was not associated with blood pressure at that age, and, therefore, the association between human milk fatty acid composition and blood pressure at age 12 years was not explained by erythrocyte membrane fatty acid composition at age 12 years.

Strengths and Limitations

Strengths of this study are the prospective design of the study and the availability of fatty acid composition in human milk, as well as in erythrocyte membranes, at age 12 years. However, some methodological considerations should be taken into account when interpreting the results. Because we obtained only 1 sample of human milk, we do not know whether the fatty acid composition in the human milk sample reflects the fatty acid composition of the human milk of the entire lactation period. However, breast milk fatty acid composition reflects long-term food intake by the mother and predicts infant DHA status.13 If misclassification occurred, this misclassification is, however, unlikely to be differentially associated with later blood pressure, that is, it is unlikely that all of the mothers with a lower than normal content of n-3 LC PUFAs in their milk on the day they collected the sample will have children with a higher blood pressure at age 12 years. We used erythrocyte membrane fatty acid content as an indicator of the child’s diet. Erythrocyte fatty acid content has been shown to be a valid indicator of EPA and DHA intake,10 but it reflects a rather short period of previous diet. These limitations may have led to nondifferential misclassification and may, therefore, have diluted the associations.

We collected data on fatty acid composition of human milk and erythrocytes in a subsample of the children. The mothers who were willing to donate a milk sample had higher education and a healthier lifestyle than those who did not breastfeed. However, we consider it to be unlikely that the association between human milk fatty acid composition and blood pressure at age 12 years is different in the group that we studied from that in the total study population. Although we were able to adjust for a wide range of lifestyle confounders, residual confounding by lifestyle factors can never be excluded.
Comparison With Other Studies

So far, no observational studies are available on effects of fatty acid composition of human milk on long-term blood pressure. Therefore, we compare our results with studies on effects of fatty acid supplementation in infant formula feeding and supplementation of mothers during breastfeeding. Our finding that n-3 LC PUFAs in infant milk feeding are associated with a lower blood pressure in childhood is consistent with a trial that supplemented infant formula with n-3 LC PUFAs (mainly DHA and EPA). Blood pressure at age 6 years was lower in children who received the supplemented formula and in children who were breastfed compared with children who received standard formula. In contrast, a study in which lactating mothers rather than the children themselves were administered fish oil reported no decrease in blood pressure in the children at age 2.5 years, and a follow-up of this study even reported a higher blood pressure in the children at age 7.0 years in children whose mothers received fish oil supplementation during lactation. Fish intakes vary concerning exposure assessment and study population characteristics, but from these studies and ours, there is currently no convincing evidence for an association between n-3 LC PUFAs and blood pressure in a healthy, young population.

Perspectives

Although an observational study cannot prove causation, the mechanism by which early n-3 LC PUFA intake may influence later blood pressure may be via programming. This means that at key stages of response to nutritional, metabolic, or endocrine cues, such as those occurring during infant development, certain exposures may predispose later health by metabolic adaptation, altered cell differentiation, or epigenetic changes. Later exposure to the same variable may hardly have any effect on health.

The results are relevant for population health. N-3 LC PUFA content of human milk can be increased with mother’s diet. In addition, DHA in human milk is a stronger determinant for infant n-3 LC PUFA status than direct supplementation of fatty acids to infants, highlighting the importance of optimizing fatty acid composition of human milk. However, before any specific recommendations can be given concerning fatty acid intake of lactating women, our findings should be replicated in other populations. For now, clinicians should advise pregnant women to start breastfeeding and to follow dietary guidelines for intake of foods containing fatty acids. Blood pressure in childhood tracks into adulthood. In middle-aged people, it has been described that a 2-mm Hg reduction in population blood pressure results in a 10% lower stroke mortality and a 7% lower mortality from ischemic heart disease.

Conclusions

A relatively high content of n-3 LC PUFAs in human milk is associated with a lower blood pressure in children.
PUFA status at age 12 years is not associated with blood pressure in this healthy population.

Acknowledgments

We thank Martin Balvers for analyzing the erythrocyte membrane fatty acids and Ada Wolse for data management.

Sources of Funding

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Disclosures

M.A.-B. and B.v.d.H. are employed by Danone Research BV.

References


Summary

A relatively high content of fatty acids like fish oils in human milk is associated with a lower blood pressure at age 12 years, independent of current fatty acid status.
Blood Pressure in 12-Year-Old Children Is Associated With Fatty Acid Composition of Human Milk: The Prevention and Incidence of Asthma and Mite Allergy Birth Cohort

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ONLINE SUPPLEMENT

BLOOD PRESSURE IN 12-YEAR OLD CHILDREN IS ASSOCIATED WITH FATTY ACID COMPOSITION OF HUMAN MILK. THE PIAMA BIRTH COHORT.

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Table S1: Bivariate association between potential confounders and blood pressure*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Blood pressure</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td></td>
</tr>
<tr>
<td>Maternal smoking in pregnancy (n=313)</td>
<td>yes</td>
<td>-0.74 (-3.65, 2.17)</td>
<td>-0.66 (-2.63, 1.30)</td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Mother’s educational level (n=314)</td>
<td>low</td>
<td>0.10 (-2.69, 2.88)</td>
<td>-0.06 (-1.94, 1.81)</td>
</tr>
<tr>
<td></td>
<td>middle</td>
<td>1.65 (-0.81, 4.10)</td>
<td>1.26 (-0.39, 2.91)</td>
</tr>
<tr>
<td></td>
<td>high</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Child’s gender (n=314)</td>
<td>boy</td>
<td>0.00 (-2.12, 2.11)</td>
<td>-0.44 (-1.86, 0.99)</td>
</tr>
<tr>
<td></td>
<td>girl</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Birth weight (n=314)</td>
<td>per 100 g</td>
<td>-0.06 (-0.25, 0.13)</td>
<td>-0.05 (-0.18, 0.08)</td>
</tr>
<tr>
<td>Gestational age (n=314)</td>
<td>per week</td>
<td>0.23 (-0.11, 0.57)</td>
<td>0.14 (-0.09, 0.37)</td>
</tr>
<tr>
<td>Mother’s prepregnancy BMI (n=284)</td>
<td></td>
<td>0.23 (-0.11, 0.57)</td>
<td>0.14 (-0.09, 0.37)</td>
</tr>
<tr>
<td>Father’s BMI (n=289)</td>
<td></td>
<td>0.41 (0.07, 0.75)</td>
<td>0.04 (-0.20, 0.28)</td>
</tr>
</tbody>
</table>

* adjusted for cuff size