Higher Oily Fish Consumption in Late Pregnancy Is Associated With Reduced Aortic Stiffness in the Child at Age 9 Years

Jennifer Bryant, Mark Hanson, Charles Peebles, Lucy Davies, Hazel Inskip, Sian Robinson, Philip C. Calder, Cyrus Cooper, Keith M. Godfrey

Rationale: Higher pulse wave velocity (PWV) reflects increased arterial stiffness and is an established cardiovascular risk marker associated with lower long-chain n-3 polyunsaturated fatty acid intake in adults. Experimentally, maternal fatty acid intake in pregnancy has lasting effects on offspring arterial stiffness.

Objective: To examine the association between maternal consumption of oily fish, a source of long-chain n-3 polyunsaturated fatty acids, in pregnancy and child’s aortic stiffness age 9 years.

Methods and Results: In a mother–offspring study (Southampton Women’s Survey), the child’s descending aorta PWV was measured at the age of 9 years using velocity-encoded phase-contrast MRI and related to maternal oily fish consumption assessed prospectively during pregnancy. Higher oily fish consumption in late pregnancy was associated with lower childhood aortic PWV (sex-adjusted \( \beta = -0.084 \) m/s per portion per week; 95% confidence interval, −0.137 to −0.031; \( P = 0.002; n=226 \)). Mother’s educational attainment was independently associated with child’s PWV. PWV was not associated with the child’s current oily fish consumption.

Conclusions: Level of maternal oily fish consumption in pregnancy may influence child’s large artery development, with potential long-term consequences for later cardiovascular risk. (Circ Res. 2015;116:1202-1205. DOI: 10.1161/CIRCRESAHA.116.305158.)

Key Words: fatty acids • pregnancy • vascular stiffness

Greater aortic stiffness increases systolic blood pressure (BP) with age\(^1\) and predicts future cardiovascular risk and all-cause mortality.\(^2\) Higher pulse wave velocity (PWV) reflects increased arterial stiffness and is an established cardiovascular risk marker.\(^3,4\) There is now evidence that early developmental factors may partly set such risk.\(^3\)

Long-chain n-3 polyunsaturated fatty acids (LC-PUFAs) are associated with reduced cardiovascular risk; consumption in adulthood reduces arterial stiffness.\(^6\) Conversely, in rats, increased saturated fatty acid intake in pregnancy increases offspring arterial stiffness,\(^7\) suggesting that variations in maternal diet have long-term consequences for later arterial stiffness and cardiovascular risk. We examined maternal consumption of oily fish, a source of LC-PUFAs, in pregnancy in relation to the child’s arterial stiffness age 9 years.

Methods

In a UK mother–offspring study (Southampton Women’s Survey\(^6\)), maternal early and late pregnancy diet and child’s diet age 9 years were assessed using administered questionnaires.\(^5\) Aortic PWV was measured in 234 children aged 9 years, with approval from the local ethics committee and informed written assent/consent.

MRI phase-contrast velocity encoding sequences were acquired in the plane perpendicular to the aortic long axis, in the proximal descending aorta (level of the pulmonary trunk) and the distal descending aorta (above the aortic bifurcation; Figure 1). A phase-contrast flow mapping sequence was used with free breathing and retrospectively ECG gating. A velocity encoding gradient of 150 to 200 cm/s was applied in the through plane direction. Right brachial BP was recorded using a pediatric cuff immediately after the flow sequence acquisitions (Invivo MRI compatible patient monitor). Velocity flow curves were generated using open source software (Osirix). PWV (m/s) was calculated using Matlab (MathWorks, Natick, MA) and the transit time method\(^8\) from \( \Delta d/\Delta t \) (\( \Delta d = \) distance, \( \Delta t = \) transit time of the systolic wavefront between the 2 flow acquisition sites; Figure 1).
Univariate linear regression analyses were performed (Stata version 13.0; Statacorp LP, College Station, TX) to relate child’s PWV with maternal oily fish consumption and other maternal, infant, and childhood factors shown in Table 1; multivariate analysis included variables with significant associations. β-coefficients reflect the change in outcome when compared with the reference category.

### Results

A total of 256 participants attended for MRI; 4 declined, 7 proved claustrophobic, 10 did not complete the protocol/had substandard images from motion artifacts. One extreme outlier, attributed to measurement error, was excluded. Table 1 shows characteristics of the remaining 234 children (116 boys); mean PWV was 3.5 m/s (within previously reported childhood ranges11) and body mass index was 17.3 kg/m². 26.9% of mothers smoked prepregnancy.

Analyzed as a continuous variable, higher late pregnancy maternal oily fish consumption was associated with lower childhood aortic PWV (sex-adjusted β=−0.084 m/s per portion per week [95% confidence interval, −0.137 to −0.031]; P=0.002; Figure 2), with a similar association for early pregnancy oily fish consumption (β=−0.062 [−0.124 to −0.001]; P=0.046). Higher mother’s educational attainment (3 levels; Table 1) was associated with lower childhood PWV (β=−0.175 m/s per level [−0.278 to −0.072]; P=0.002), as was higher social class (Table 2). The coefficients above hardly changed in multivariate analysis simultaneously including both mother’s educational attainment and late pregnancy oily fish consumption; both P-values remained 0.002. Additional inclusion of maternal, neonatal, and childhood characteristics significant at P<0.1 (Table 2) had little influence on these associations (Table 3).

PWV showed the expected associations with childhood systolic and diastolic BP, mean arterial pressure, and heart rate (Table 2). After adjusting for mother’s qualification level and child’s sex, maternal oily fish consumption was not associated with childhood heart rate or BP (Online Table I). Childhood PWV showed no associations with birthweight, or child’s height, body mass index, and oily fish consumption at 9 years.

### Discussion

Greater maternal oily fish consumption in early or late pregnancy was associated with lower child’s aortic PWV and aortic stiffness at the age of 9 years. LC-PUFAs in oily fish and fish oils have anti-inflammatory properties, reduce BP, and increase endothelial relaxation, vascular compliance, and heart rate variability12; supplementation in adults reduces arterial stiffness.6 LC-PUFA levels in the fetal circulation increase in late pregnancy, when fetal docosahexaenoic acid correlates
with maternal levels. This may explain the stronger association between child’s PWV and late versus early pregnancy maternal oily fish consumption.

Table 2. Univariate Analyses of Maternal, Neonatal, and Childhood Characteristics and Child’s Cardiovascular Measures in Relation to Pulse Wave Velocity (m/s) at Age 9 Years (Adjusted for Sex)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>characteristics*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early pregnancy oily fish consumption</td>
<td>191</td>
<td>−0.062</td>
<td>−0.124, −0.001</td>
<td>0.046</td>
</tr>
<tr>
<td>Late pregnancy oily fish consumption</td>
<td>226</td>
<td>−0.084</td>
<td>−0.138, −0.031</td>
<td>0.002</td>
</tr>
<tr>
<td>Social class</td>
<td>229</td>
<td>0.109</td>
<td>0.011, 0.207</td>
<td>0.03</td>
</tr>
<tr>
<td>Educational attainment</td>
<td>234</td>
<td>−0.175</td>
<td>−0.278, −0.072</td>
<td>0.001</td>
</tr>
<tr>
<td>Parity</td>
<td>234</td>
<td>−0.026</td>
<td>−0.158, 0.107</td>
<td>0.7</td>
</tr>
<tr>
<td>Smoking</td>
<td>234</td>
<td>0.057</td>
<td>0.092, 0.206</td>
<td>0.5</td>
</tr>
<tr>
<td>Infant characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight, kg</td>
<td>231</td>
<td>0.031</td>
<td>−0.09, 0.152</td>
<td>0.6</td>
</tr>
<tr>
<td>Breastfeeding duration, mo</td>
<td>226</td>
<td>−0.015</td>
<td>−0.027, −0.003</td>
<td>0.015</td>
</tr>
<tr>
<td>Child’s characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>234</td>
<td>0.007</td>
<td>−0.004, 0.017</td>
<td>0.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>234</td>
<td>0.008</td>
<td>−0.002, 0.018</td>
<td>0.1</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>234</td>
<td>0.014</td>
<td>−0.010, 0.039</td>
<td>0.3</td>
</tr>
<tr>
<td>Oily fish consumption*</td>
<td>234</td>
<td>−0.037</td>
<td>−0.111, 0.037</td>
<td>0.3</td>
</tr>
<tr>
<td>Child’s cardiovascular measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>232</td>
<td>0.011</td>
<td>0.004, 0.019</td>
<td>0.002</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>232</td>
<td>0.018</td>
<td>0.009, 0.026</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>232</td>
<td>−0.0003</td>
<td>−0.008, 0.007</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>232</td>
<td>0.020</td>
<td>0.011, 0.029</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>234</td>
<td>0.015</td>
<td>0.009, 0.021</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; and CI, confidence interval.
*Categories shown in Table 1.

We found no association between child’s current oily fish consumption and vascular stiffness. In keeping with this, LC-PUFA supplementation during childhood offers few long-term cardiovascular benefits in terms of BP, heart rate, or arterial distensibility assessed several years after the supplementation. Cardiovascular measures taken in infants during a period of supplementation with fish oil, and docosahexaenoic acid or LC-PUFA supplemented infant formulae, did however show favorable heart rate and BP changes. These studies, together with our data showing an effect of prenatal nutrition, suggest that nutritional interventions instituted early in the lifecourse may be most effective.

PWV was linked to the child’s BP, but there was no association between maternal oily fish consumption and BP. Arterial stiffening is the principal cause of increased cardiac afterload and increasing systolic BP with advancing years; even without an independent effect on childhood BP, structural changes in the vascular wall induced by maternal diet during development may have implications for adult cardiac function and BP. Higher childhood PWV has uncertain predictive value and does not itself cause disease, but baseline PWV does predict later aortic dilatation in children with tetralogy of Fallot.

Participants in this study are part of a prospective longitudinal cohort study covering a wide socioeconomic background. Vascular stiffness was assessed at the age of 9 years, before the acquisition of significant risk burden, ensuring minimal influence of other lifestyle risk factors such as smoking. Our results are thus unlikely to be confounded by the influence of other cardiovascular risk factors.

In summary, our findings suggest that normal variations in maternal oily fish consumption in pregnancy influence vascular development of the fetus, changing childhood aortic compliance, with implications for later cardiovascular disease. The findings raise the question of the major influences on maternal diet. The quality of women’s diets is strongly dependent on their nutrition literacy and level of educational attainment, and we found an independent and additive effect of maternal educational attainment on childhood vascular stiffness, perhaps reflecting other nutritional influences. The findings raise the possibility that interventions that improve educational...
attainment and nutrition literacy could reduce cardiovascular risk in the next generation.

Acknowledgments

We are grateful to the women of Southampton and their children who gave their time and to the staff who collected and processed the data.

Sources of Funding


Disclosures

K.M. Godfrey has received reimbursement for speaking at conferences sponsored by companies selling nutritional products and is part of an academic consortium that has received research funding from Abbott. The other authors report no conflicts.

References


Novelty and Significance

Prenatal influences contribute to the risk of cardiovascular disease in adulthood, but the developmental exposures and underlying mechanisms are poorly understood. One possible mechanism is large artery structure and stiffness; this is partly determined in utero and greater stiffness is the principal cause of increased cardiac afterload and increasing blood pressure with age. Here, we show that higher maternal oily fish intake in pregnancy is associated with lower aortic stiffness in children aged 9 years. The findings highlight the importance of prenatal vascular development and suggest that interventions that improve a mother’s nutrition could reduce cardiovascular risk in the next generation.
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Circ Res. 2015;116:1202-1205; originally published online February 19, 2015; doi: 10.1161/CIRCRESAHA.116.305158

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/116/7/1202

Data Supplement (unedited) at:
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SUPPLEMENTAL MATERIAL

Detailed Methods

Magnetic resonance imaging (MRI) assessment of aortic PWV was performed on 234 children aged 9 years who were participants in the Southampton Women’s Survey (SWS), a longitudinal mother-offspring cohort study investigating developmental influences on health and disease. Maternal diet in early and late pregnancy, and child’s diet at 9 years had been previously assessed using administered food frequency questionnaires.

Ethical approval was obtained from the local research ethics committee (LREC). The participants and parent/guardian provided informed assent and consent respectively. MRI compatibility of the child and parent/guardian was determined as per local standardized operating protocols. The child’s height was measured to nearest 1 mm using a Leicester height measure, and weight measured to the nearest 0.1kg using a digital scale.

Aortic stiffness was assessed in the descending aorta. Scans were performed on a 1.5T MRI scanner (Avanto, Siemens Medical Systems, Erlangen, Germany) using a phased array spine coil in combination with a torso array coil. Flow measurements were positioned perpendicular to the long axis of the aorta from TrueFISP (true fast imaging with steady state free precession) sagittal oblique and coronal images; in the proximal descending aorta at the level of the pulmonary trunk; and in the distal descending aorta above the bifurcation (Fig. 1). A free breathing phase contrast flow mapping sequence was employed. The sequence was retrospectively ECG gated. Sequence parameters as follows: field of view 280mm, voxel size 1.1 x 1.1 x 5mm, TR/TE 27.2/3.18ms slice thickness 5mm. A velocity encoding gradient was applied in the through plane direction with a VENC of 150-200 cm/s. Images were acquired at 30 phases throughout the cardiac cycle. Right Brachial Blood Pressure was recorded using a pediatric cuff immediately following the flow sequence acquisitions with a MRI compatible patient monitor (Invivo Corp., Gainesville, FL).

Velocity flow curves were generated using open source imaging software (Osirix, http://www.osirix-viewer.com/) and PWV calculated in m/s using Matlab software (The Mathworks, Inc., Natick, MA) using the transit time method where \( \Delta d / \Delta t \) where \( \Delta d \) is the distance between the two flow acquisition sites in the central aorta, and \( \Delta t \) is the transit time difference between the arrival of the systolic wave front at the two sites (Fig. 1).

Univariate and multiple linear regression analyses were performed using Stata version 13.0 (Statacorp LP, TX, USA) to relate maternal oily fish consumption to child’s PWV, taking account of maternal (educational attainment, social class, pre-pregnancy BMI, parity, smoking status), infant (birthweight, breastfeeding duration) and childhood (body size, oily fish consumption) factors. The \( \beta \)-coefficient for sex reflects the difference in outcome for females compared with males; the educational attainment and social class variables were categorized into three groups and the \( \beta \)-coefficients represent the change in PWV associated with change from one level of the variable to the next. In keeping with the local population, the SWS includes few subjects who were not white Caucasian and racial/ethnic-based analyses were not undertaken as a consequence.
References


Supplemental Table

Table I. Regression analyses of mother’s oily fish intake (portions/week) in relation to childhood characteristics.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats per minute)*</td>
<td>227</td>
<td>-0.644</td>
<td>-1.59, 0.3</td>
<td>0.179</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)*</td>
<td>225</td>
<td>-0.466</td>
<td>-1.52, 0.59</td>
<td>0.385</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)*</td>
<td>225</td>
<td>-0.251</td>
<td>-0.95, 0.45</td>
<td>0.481</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)*</td>
<td>225</td>
<td>-0.323</td>
<td>-1.01, 0.37</td>
<td>0.357</td>
</tr>
<tr>
<td>Heart rate (beats per minute)**</td>
<td>227</td>
<td>-0.584</td>
<td>-1.53, 0.36</td>
<td>0.224</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)**</td>
<td>225</td>
<td>-0.405</td>
<td>-1.45, 0.64</td>
<td>0.446</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)**</td>
<td>225</td>
<td>-0.187</td>
<td>-0.86, 0.48</td>
<td>0.583</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)**</td>
<td>225</td>
<td>-0.259</td>
<td>-0.92, 0.40</td>
<td>0.442</td>
</tr>
</tbody>
</table>

*Adjusted for sex of child
** Adjusted for mother’s qualification level