Relationship between circulating n-3 fatty acid concentrations and endothelial function in early adulthood

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Aims Fish consumption is inversely associated with cardiovascular mortality, presumably because of n-3 fatty acids in fish. Whether the protection of n-3 fatty acids extends beyond clinical coronary disease to influence the early vascular biology of atherosclerosis remains unclear. This study determined whether circulating levels of n-3 fatty acids are associated with vascular endothelial function in early adulthood.

Methods and Results Three hundred and twenty-six adults (157 males, 169 females, aged 20 to 28 years) had high-resolution ultrasound measurements of flow-mediated brachial artery dilatation (FMD) (endothelium-dependent) and arterial response to glyceryl trinitrate (endothelium-independent). Levels of the n-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid in plasma and erythrocyte membranes of subjects were measured. n-3 Fatty acid levels were not related to vascular function in the whole group. In smokers, however, n-3 fatty acids were positively related to flow-mediated dilatation (plasma DHA vs FMD: 0.045 mm . %1 , 95% CI 0.011 to 0.079, P=0.01). Flow-mediated dilatation was also associated with n-3 fatty acid levels in subjects in the top third of the insulin, glucose and triglyceride distributions.

Conclusion In young smokers and those with higher fasting insulin, glucose or triglyceride concentrations (factors associated with endothelial dysfunction), n-3 fatty acid levels were positively associated with flow-mediated dilatation. This raises the possibility that physiological levels of circulating n-3 fatty acids may protect the endothelium from early adulthood.

Introduction

Increased fish consumption has been associated with a decreased risk of both fatal and non-fatal myocardial infarction in epidemiological studies[1–4], as well as having beneficial influences on blood pressure and lipid profile[5–7]. These relationships are probably due to the high levels of the n-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) found in fish oil[8–10]. n-3 Fatty acids have been shown to affect pathological processes important during the clinical stages of coronary disease, including platelet activity, thrombotic tendency and arrhythmogenesis[11–15].

Experimental studies also indicate that n-3 fatty acid levels modify endothelial function[13], which is important early in the pathogenesis of cardiovascular disease[15]. Endothelium-derived nitric oxide has antiatherogenic properties, which include inhibition of platelet aggregation, smooth muscle cell migration and growth and adhesion molecule expression[16–18]. In humans with evidence of cardiovascular disease or its risk factors, dietary supplementation with n-3 fatty acids is associated with enhanced endothelium-dependent arterial
vascular disease. Whether the protective effect of n-3 fatty acids on endothelial function, extends to young people without overt evidence of cardiovascular disease, and whether the range of n-3 fatty acids seen in the population is sufficient to influence endothelial function remains unknown. However, if so, then dietary intake of n-3 fatty acids may have potential cardiovascular benefits from early in life.

In a group of young adults, we related flow-mediated brachial artery dilatation — an endothelium-dependent response that can be measured non-invasively with high resolution ultrasound — to plasma and red blood cell membrane n-3 fatty acid content. This allowed us to determine whether n-3 fatty acid levels, within the range found in normal populations, have a beneficial impact on vascular endothelial function early in life and might thereby influence the longer term development of cardiovascular disease.

Methods

Study design

We studied 326 adults (157 males, 169 females, aged 20 to 28 years). Invitations to attend a clinic for cardiovascular risk profile evaluation by venepuncture, questionnaire, physical measurements and vascular studies, were sent to random samples of those born between 1969 and 1975 in the Cambridge Maternity Hospital. Ethical approval was received from local research ethics committees and informed consent was obtained at the time of the visit.

Measurement of cardiovascular risk factors

Personal and family medical histories were gathered by questionnaire at interview. Current or past smoking was recorded and for current smokers the dose effect of smoking was measured by allocating a ‘pack years’ score; one pack year being equivalent to smoking 20 cigarettes a day for a year. Subjects were coded into standard socio-economic groups based on recent occupation and education level. Blood pressure was measured as the average of the last two of three seated readings using an automated oscillometric device (Critikon Inc, U.S.A.). Weight was recorded (to ± 0.1 kg) using scales (Soehnle Ltd) and height (to ± 0.1 mm) with a portable stadiometer.

Food frequency questionnaire

Each subject completed a food frequency questionnaire with an interviewer to quantify dietary intake, including fish consumption during an average week. For each class of food a score of zero was given if never eaten, 1 if eaten less than once a week, 2 if eaten 1 or 2 days a week, 3 if eaten most days, 4 if eaten once a day and 5 if eaten more than once a day.

Vascular study measurements

Endothelium-dependent and independent responses were measured for each adult with the subject lying supine on a couch, as described previously. After 10 min, the right brachial artery was imaged in longitudinal section between 10 and 15 cm above the antecubital fossa using a 7 MHz linear array transducer and a standard Acuson 128XP/10 system. Baseline brachial artery diameter was measured using an automated Wall Tracking System (Medical Systems, Arnhem, The Netherlands), which utilizes the movement over the cardiac cycle in the radiofrequency amplitude peaks, to identify the arterial walls. A pneumatic cuff was then inflated to suprasystolic pressure on the forearm for 4.5 min to induce a reactive hyperaemia. Cuff deflation resulted in increased flow through the brachial artery, stimulating endothelial-dependent flow-mediated dilatation. The change in brachial artery diameter 1 min after cuff release was measured. Ten minutes rest was allowed for vessel recovery and then a further measurement of arterial diameter made between 3 and 4 min after a single sublingual spray (100–300 μg) of glyceryl trinitrate, which produces endothelium-independent dilatation. Endothelium-dependent and independent responses were represented as absolute change in vessel diameter after increased blood flow (flow-mediated dilatation or FMD) and after glyceryl trinitrate (GTND) respectively.

Biochemical measurements and analysis of n-3 fatty acid status

In each subject, fasting venous blood samples were analysed by routine methods for insulin, glucose, total cholesterol, HDL, LDL and triglyceride concentrations. A further sample was collected for analysis of n-3 fatty acid status in plasma and red blood cell membranes. Plasma was separated and erythrocyte membrane ‘ghosts’ were immediately prepared from the red blood cells. Samples were stored at −70 °C prior to analysis.

Total fatty acid methyl esters (FAMES) from the erythrocyte membranes were prepared using the direct one-step trans-esterification method. FAMES were analysed using a Hewlett Packard 6890 gas chromatograph with flame ionisation detection with separation by a BPX70 cyanopropyl polysilphenylene siloxane ‘fast’ column (10 m, 100 μm internal diameter, 0.2 μm film thickness) (SGE Ltd). The helium carrier gas flow rate was 0.4 ml.min⁻¹ at 48.7 psi and injections were made in split mode (25:1). Temperatures at the injector port and detector were 220 °C and 300 °C, respectively, and FAMES were separated with a temperature programme (150 °C at start, ramped to
The continuous relationship between fish consumption, n-3 fatty acid status, cardiovascular risk factors and vascular function were assessed using multiple regression models. The variables representing n-3 fatty acid status were added to a model of FMD, which included resting vessel size, age and sex as independent variables. Analysis was performed on the whole cohort and then the relationship between n-3 fatty acids and vascular function was compared between subgroups; specifically males and females, smokers and non-smokers and thirds of the distributions of cardiovascular risk factors. The significance of any apparent difference in the relationship between groups was determined using standard interaction models. Unless stated otherwise, results are presented as means ± 1 standard deviation. Where presented, correlation coefficients are Pearson correlations and the significance of differences in variables between discrete groups of subjects (such as male and female) was calculated by the Student’s unpaired t-test.

### Results

#### Population characteristics

Invitations were sent to 1526 young adults of whom 344 (23%) subjects were able to attend for full vascular investigations. Stored plasma for measurement of n-3 fatty acid status was available for 326 subjects (95% of subjects). The characteristics of the study population are summarized in Tables 1 and 2 and are similar to those of the general young adult population in the U.K.
Vascular measures and cardiovascular risk factors

Females had smaller resting brachial arteries compared to males (2.9 ± 0.3 mm and 3.7 ± 0.5 mm; P < 0.001). There were, however, no relationships between resting vessel size or brachial artery blood flow and n-3 fatty acid levels or other cardiovascular risk factors. There were no differences in FMD or GTND by age or sex. Smokers had lower FMD than non-smokers (FMD in smokers = 0.690 ± 0.080 mm vs. non-smokers = 0.109 ± 0.081 mm, P = 0.04) but similar GTND. There were no associations between other risk factors (cholesterol, LDL-cholesterol, HDL-cholesterol, fasting triglycerides, fasting insulin, glucose, blood pressure) and vascular function across the narrow ranges in this young study group.

n-3 Fatty acids, diet and cardiovascular risk factors

There was a positive association between fish consumption and both plasma and red blood cell DHA levels in both sexes (plasma DHA vs fish consumption; reg. coeff. = 0.562 frequency mmol$^{-1}$·L$^{-1}$, 95% CI 0.388 to 0.736, P < 0.001) with non-significant positive trends with plasma and red blood cell EPA levels. Females had significantly higher levels of DHA but lower levels of plasma EPA than males (Table 2), and smokers had significantly lower mean levels of DHA in plasma and red blood cell membranes than non-smokers (plasma 1.71 ± 0.47 and 1.94 ± 0.52% and red blood cell membrane 2.79 ± 0.99 and 3.21 ± 1.10%, respectively).

Increased HDL-cholesterol concentrations were significantly related to both increased plasma DHA and EPA in the total group (HDL-cholesterol vs plasma DHA; reg. coeff. = 0.096 · mmol$^{-1}$·L$^{-1}$, 95% CI 0.052 to 0.140, P = 0.001, HDL-cholesterol vs plasma EPA; reg. coeff. = 0.129 · mmol$^{-1}$·L$^{-1}$, 95% CI 0.026 to 0.232, P = 0.01) with trends towards higher red blood cell membrane n-3 fatty acid status. These associations were significant in women but only reached significance with plasma EPA in men.

There were no significant associations between endothe-lial function and n-3 fatty acid status in the whole group or within sexes. In smokers, however, there was a significant positive relationship between FMD and plasma and red blood cell DHA levels (Table 3 and Fig. 1). There was no relationship in non-smokers and there was a significant difference in the association between smoking groups in interaction models (significance of interaction term: P = 0.01). There was no difference in the association between sexes (reg. coeff. for the relationship between plasma DHA and FMD in male smokers = 0.026 mm. %$^{-1}$ and in female smokers = 0.053 mm. %$^{-1}$).

n-3 Fatty acids, smoking and endothelial function

There were no significant associations between endothelial function and n-3 fatty acid status in the whole group or within sexes. In smokers, however, there was a significant positive relationship between FMD and plasma and red blood cell DHA levels (Table 3 and Fig. 1). There was no relationship in non-smokers and there was a significant difference in the association between smoking groups in interaction models (significance of interaction term: P = 0.01). There was no difference in the association between sexes (reg. coeff. for the relationship between plasma DHA and FMD in male smokers = 0.026 mm. %$^{-1}$ and in female smokers = 0.053 mm. %$^{-1}$).

There was no relationship between smoking dose, as assessed by either smoking pack years or cigarettes per day, and n-3 fatty acid levels, and inclusion of these factors in the main model did not alter the relationship between DHA and FMD (reg. coeff. plasma DHA vs FMD after including smoking pack years = 0.047 mm. %$^{-1}$, 95% CI 0.011 to 0.083, P = 0.01). Inclusion of other factors including lipid profile, fasting triglyceride and HDL concentrations did not alter the relationship (reg. coeff. plasma DHA vs FMD after including triglycerides = 0.038 mm. %$^{-1}$, 95% CI 0.006 to 0.070, P = 0.02). There was no consistent association

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**Table 3** Regression coefficients (plus 95% CI and P values) for the association between flow-mediated dilatation and n-3 fatty acids in smokers and non-smokers. Units of the regression coefficient are mm.%$^{-1}$

<table>
<thead>
<tr>
<th></th>
<th>Smokers</th>
<th></th>
<th>Non-smokers</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Reg. coeff.</td>
<td>95% CI</td>
<td>P</td>
<td>Reg. coeff.</td>
</tr>
<tr>
<td>Plasma DHA (%)</td>
<td>0.045</td>
<td>0.011 to 0.079</td>
<td>0.01</td>
<td>−0.011</td>
</tr>
<tr>
<td>Plasma EPA (%)</td>
<td>0.036</td>
<td>−0.030 to 0.011</td>
<td>0.28</td>
<td>−0.007</td>
</tr>
<tr>
<td>Plasma EPA+DHA (%)</td>
<td>0.035</td>
<td>0.008 to 0.063</td>
<td>0.01</td>
<td>−0.007</td>
</tr>
<tr>
<td>Red blood cell DHA (%)</td>
<td>0.021</td>
<td>0.004 to 0.038</td>
<td>0.02</td>
<td>0.010</td>
</tr>
<tr>
<td>Red blood cell EPA (%)</td>
<td>0.008</td>
<td>−0.057 to 0.072</td>
<td>0.82</td>
<td>0.037</td>
</tr>
<tr>
<td>Red blood cell EPA+DHA (%)</td>
<td>0.017</td>
<td>0.002 to 0.033</td>
<td>0.03</td>
<td>−0.009</td>
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</table>
between endothelial function and EPA levels (Table 3). Vascular function was not related to fish intake nor were n-3 fatty acids associated with GTND.

**n-3 Fatty acids, endothelial function and other variables**

Increased DHA levels were associated with greater FMD in subjects in the top third for each of the insulin, glucose and triglyceride distributions (Table 4). The interaction models to determine whether the association differed depending on the level of the risk factor, however, did not reach significance. Similar patterns were seen in both sexes and in smokers and non-smokers. There were no significant associations in the top third of the distributions of total cholesterol, LDL-cholesterol, HDL-cholesterol or blood pressure.

**Discussion**

This study shows that during early adult life there is a positive relationship between n-3 fatty acid status and flow-mediated dilatation, but only in those who smoke or have higher levels of fasting insulin, glucose or triglycerides. All these factors have been related to endothelial dysfunction[21,32–34] and our findings raise the possibility that higher n-3 fatty acid levels may protect or optimize endothelial function in their presence.

N-3 fatty acid supplementation to levels above the population range has previously been shown to influence...

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**Figure 1** The positive association between n-3 fatty acids and endothelial function in smokers and the lack of a relationship in non-smokers. Smokers in the highest fifth for n-3 fatty acids reach the level of flow-mediated dilatation seen in non-smokers. The mean level of flow-mediated dilatation with standard errors is presented at the mean percentage of plasma docosahexaenoic acid (DHA) for each fifth of the n-3 fatty acid distribution.

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**Table 4 Relationship between plasma DHA and flow-mediated dilatation in thirds of the study group divided according to the level of the different risk factors (1=lowest third to 3=highest third)**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Plasma DHA vs FMD (mm.%⁻¹)</th>
<th>Register coeff.</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting insulin (mU.l⁻¹)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>0·013</td>
<td>−0·029 to 0·054</td>
<td>0·54</td>
<td></td>
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<tr>
<td>2</td>
<td>−0·014</td>
<td>−0·044 to 0·017</td>
<td>0·37</td>
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<tr>
<td>3</td>
<td>0·031</td>
<td>0·002 to 0·059</td>
<td>0·03</td>
<td></td>
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<td>Fasting glucose (mmol.l⁻¹)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>0·002</td>
<td>−0·034 to 0·039</td>
<td>0·88</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>−0·006</td>
<td>−0·043 to 0·029</td>
<td>0·72</td>
<td></td>
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<tr>
<td>3</td>
<td>0·004</td>
<td>0·009 to 0·067</td>
<td>0·01</td>
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<tr>
<td>Fasting triglycerides (mmol.l⁻¹)</td>
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<tr>
<td>1</td>
<td>0·009</td>
<td>−0·034 to 0·051</td>
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<td>−0·046 to 0·008</td>
<td>0·18</td>
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<td>3</td>
<td>0·038</td>
<td>0·006 to 0·070</td>
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endothelial function in those with cardiovascular disease or significant levels of risk factors. Our study now shows that n-3 fatty acid levels are related to endothelial function in relatively young subjects, without overt evidence of cardiovascular disease, across the range of n-3 fatty acids resulting from normal dietary variation. Epidemiological studies have demonstrated that normal dietary intake of fish, the major source of n-3 fatty acids, also relates to risk of coronary heart disease. Although this may be due to the antiarrhythmic and antithrombotic properties of n-3 fatty acids, relevant in the later stages of cardiovascular disease, this may also be explained, in part, by a protective effect of n-3 fatty acids on endothelial function from early in life.

The impact of n-3 fatty acids was only seen in smokers and those at the higher end of the distribution for insulin, glucose and triglyceride concentrations. The difference in association by smoking bears striking similarities to the findings from the Honolulu Heart Program in which the cardiovascular protection from fish intake was much more apparent in smokers. The relationships in the top third for insulin, glucose and triglycerides are of interest as, in contrast to smokers, there was no evidence of significant endothelial dysfunction in these groups. Nevertheless, those with clinically significant insulin resistance or hypertriglyceridaemia have disrupted endothelial responses and our study may not have had sufficient power to demonstrate differences in endothelial function across narrower ranges of these factors. Blood pressure and lipid profile had no interaction with n-3 fatty acid levels. Potentially, their biological association with endothelial function may be less open to modification by n-3 fatty acids than that between endothelial function and smoking or hyperinsulinaemia. Alternatively, an impact may only be seen in those with hypertension or hypercholesterolaemia.

n-3 Fatty acids were not related to blood pressure, body size, glucose, insulin levels or LDL-cholesterol but were associated with higher HDL-cholesterol and lower triglyceride levels. The associations with lipid profile are consistent with previous studies of normal subjects and we considered whether improved lipid profile could explain the favourable relationships between n-3 fatty acid and endothelial function in smokers. The improved lipid profile, however, was seen in both smokers and non-smokers and in a multivariate model inclusion of triglyceride and HDL concentrations had no effect on the relationship between n-3 fatty acids and flow-mediated dilatation.

The mean n-3 fatty acid level in smokers was lower than in non-smokers. This could be related to dietary differences between smokers and non-smokers although these were not apparent from our food frequency questionnaire. Alternatively, absorption of n-3 fatty acids from the diet may differ in the two groups or there may be increased lipid peroxidation of the n-3 fatty acids in the smokers as a result of increased oxidative stress. Lower levels of n-3 fatty acids in smokers were not entirely responsible for the association between n-3 fatty acids and endothelial function, however, as the association was graded across the whole range of n-3 fatty acid levels. Smokers in the bottom fifth for n-3 fatty acids had lower levels of flow-mediated dilatation than non-smokers with equivalent circulating n-3 fatty acid levels, whereas there was no difference between smoking groups in the top fifth.

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How n-3 fatty acids might interact with endothelial function is not fully established. Raised concentrations of n-3 fatty acids are associated with greater membrane fluidity, which results in increased activity of membrane bound enzymes and receptors. n-3 Fatty acids may, therefore, optimize an endothelial response limited by the presence of other factors such as smoking. This hypothesis would be consistent with our finding that the relationship between flow mediated dilatation and n-3 fatty acids was primarily accounted for by DHA rather than EPA. Whereas EPA is important in prostaglandin synthesis, DHA is more closely involved with membrane architecture. Previous clinical studies have also suggested that DHA and EPA may have different effects, with DHA being particularly beneficial for reduction of elevated blood pressure. There were trends between EPA and endothelial function and an effect of EPA cannot be excluded from this work, particularly as there is combined intake of these n-3 fatty acids in the diet. Further work would be of interest to relate prospectively our findings to the development of cardiovascular disease over time and also to investigate the effect of n-3 fatty acids on the basal release of nitric oxide in addition to stimulated nitric oxide production.

This study showed that in young adults there was a positive association between levels of circulating n-3 fatty acids — derived from normal dietary variation — and endothelial function in those who smoked or had higher levels of fasting insulin, glucose or triglycerides. Given the central position of the endothelium in early atherogenesis, a protective influence of n-3 fatty acids may, in part, explain the epidemiological association between increased fish intake and reduced cardiovascular mortality and morbidity. These findings also now raise the possibility that moderate increases in n-3 fatty acid intake may have cardiovascular benefit from early in adult life.

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