Long-term fish consumption and n-3 fatty acid intake in relation to (sudden) coronary heart disease death: the Zutphen study

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Received 7 November 2007; revised 9 June 2008; accepted 11 June 2008; online publish-ahead-of-print 18 July 2008

Aims
To assess the relationship between fish consumption or eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) intake from fish, and (sudden) coronary death.

Methods and results
The impact of recent and long-term fish consumption and EPA + DHA intake on (sudden) coronary death was investigated in the Zutphen Study, a cohort of 1373 men born between 1900 and 1920, and examined repeatedly between 1960 and 2000. Hazard ratios were obtained from time-dependent Cox regression models. The associations between long-term fish consumption, EPA + DHA intake, and (sudden) coronary death were stronger than those of recent consumption. Long-term fish consumption was inversely associated (borderline significant) with coronary heart disease (CHD) death; however, the strength of the association decreased from age 50 [HR: 0.32 (95% CI: 0.13–0.80)] until age 80 [HR: 1.34 (0.58–3.12)]. For men with a daily EPA + DHA intake from fish below 250 mg compared with no intake, CHD death risk was reduced to the same extent as for men with a daily intake above 250 mg (P-value for trend: 0.27). Moreover, long-term fatty-fish consumption lowered the risk of sudden coronary death [HR: 0.46 (0.27–0.78)].

Conclusion
The strength of the association between long-term fish consumption and CHD death decreased with increasing age. Fatty-fish consumption lowered sudden coronary death risk. There was no clear dose–response relationship between EPA + DHA intake and (sudden) coronary death.

Keywords
Fish • Eicosapentaenoic acid • Docosahexaenoic acid • Coronary heart disease • Sudden coronary death

Introduction
In most prospective cohort studies, consuming a relatively small amount of fish or fish oil was associated with a lower risk of coronary heart disease (CHD) death1 and these results were confirmed by several intervention studies.2–5 In a meta-analysis of cohort studies, He et al.1 estimated that consuming fish once a week lowers CHD death risk by 15%. In addition, Mozaffarian and Rimm6 estimated, by combining results from both randomized trials and prospective cohort studies, that consuming 250 mg eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) per day lowers CHD death risk by 36%.

EPA (C20:5n-3) and DHA (C22:6n-3), two long-chain n-3 polyunsaturated fatty acids mainly found in fatty fish, are the constituents in fish oil that may reduce the risk of CHD death. The most likely explanation by which relatively small amounts of EPA and DHA reduce the risk of CHD death are their antiarrhythmic properties.6 They are also suggestive for an inverse relation with sudden coronary death.7,8 In observational studies, consuming fish once or twice a week was associated with a 42–50% lower risk of sudden coronary death or cardiac arrest.9–11 The associations with blood12 or cell membrane10 levels of EPA + DHA were even stronger. However, little is known about the effect of long-term fish consumption or EPA + DHA intake on (sudden) coronary deaths.

For prospective studies in which fish consumption is only assessed at the baseline examination, consumption patterns are assumed to be relatively constant over the entire study period.

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However, it is unlikely that exposure measurements in the past accurately reflect long-term fish consumption since consumption patterns change during life. To get correct estimates of the long-term effects of fish consumption and EPA+DHA intake, repeated measures are needed.13,14

The objective of the present study is to assess the relationship between recent and long-term fish consumption or EPA+DHA intake from fish, and (sudden) coronary death. For this purpose, we used up to seven repeated measures of fish consumption and EPA+DHA intake from fish collected during 40 years of follow-up in a cohort of middle-aged men.

**Methods**

**Study population**

The Zutphen Study started as the Dutch contribution to the Seven Countries Study, a longitudinal study of the relationships between diet, other risk factors, and chronic diseases.15 The Zutphen Study has been carried out since 1960 among middle-aged men in Zutphen, an old industrial town in the eastern part of the Netherlands with about 30,000 inhabitants. In 1960, a random sample was drawn of 1088 men born between 1900 and 1919 and residing for at least 5 years in Zutphen. Of those men, 878 participated in the Zutphen Study (response rate: 81%) and 872 took part in both dietary and physical examinations. These examinations were repeated in 1965 and 1970. In 1985, the group of 554 survivors was extended with a new random sample of men of the same birth cohort. Of the 1266 men who were invited, 939 men participated (response rate: 74%) and 825 men took part in both dietary and physical examinations. These examinations were repeated in 1990, 1995, and 2000.

Baseline data were collected in 1960 before the Helsinki Declaration was developed and oral consent was obtained in view of follow-up data. In 1985 and 1990, the study was approved by the Medical Ethics Committee of the University of Leiden, The Netherlands, and in 1995 and 2000, by the Medical Ethics Committee of the Netherlands Organisation for Applied Scientific Research (TNO).

**Assessment of fish consumption and fish fatty acid intake**

Information on the habitual food consumption was collected by using the cross-check dietary history method,16 adapted to the Dutch situation.17,18 This method provides information about the participant’s usual food consumption pattern, 6–12 months preceding the interview. From 1985 onwards, the information about the usual food consumption pattern was limited to the month preceding the interview because consumption patterns from 1985 were much more complicated than those in the 1960s. The interviews were carried out by experienced dieticians in spring and early summer. Each participant, if possible in the presence of his wife, was interviewed about his usual food consumption during weekdays and weekends. Based on this daily pattern, average food consumption during a day or week (first check) and the quantity of foods bought per week (second check) was estimated and presented to the participants to calculate and verify the participants’ food consumption. Total fish consumption was divided into fatty (e.g. salmon, mackerel, herring, eel, and sardines) and lean (e.g. codfish, plaice, and pollack) fish. The daily intake of EPA+DHA from fish in the period 1960–1995 was calculated using the digital update of the Dutch food composition table from 1996.19,20 The daily intake of EPA+DHA from fish in 2000 was calculated using the Dutch food composition table from 2001.21

**Assessment of potential confounders**

In all dietary surveys, habitual food consumption and the use of a prescribed diet was recorded.17,18 The daily intake of energy and nutrients (including alcohol) was calculated using food composition tables close to the year of measurement. Detailed information on the type and amount of smoking was collected using standardized questionnaires.22 During physical examinations, men’s blood pressure, weight, and height were measured and body mass index (BMI) was calculated (kg/m²). Information on the prevalence of diabetes mellitus and other chronic diseases was collected and verified by contacting each participant’s general practitioner.23 The men were classified into four levels of socioeconomic status according to occupation at baseline.24

**Case ascertainment**

Participants were followed until death, or censored on 30 June 2000. Three participants were lost to follow-up during the study and were censored after their last physical examination. The final causes of death were ascertained by one clinical epidemiologist and coded according to the Eight Revision of the International Classification of Diseases.25 Because the underlying cause of death in elderly people is often difficult to establish, we included both primary and secondary causes of death in our analyses. CHD deaths were coded 410–414, including cases of sudden death. Men who died within 2 h after onset of symptoms with a high likelihood to be coronary and those with a past diagnosis of CHD were called sudden coronary deaths.

**Statistical analysis**

Cox proportional hazard analyses with age until death or censor date as the time variable26,27 were performed using the PHREG procedure of SAS/STAT software (version 9.1; SAS Institute, Inc., Cary, NC). First, we used most recent information on fish consumption and EPA+DHA intake from fish (time-dependent variables). Second, we calculated cumulative average fish consumption and EPA+DHA intake from fish to better represent long-term intake.28 With this method, (sudden) coronary death between 1960 and 1965 was related to fish consumption from the 1960 examination round; (sudden) coronary death between 1965 and 1970 was related to average fish consumption from the 1960 and 1965 examination rounds; mortality between 1970 and 1985 was related to average fish consumption from the 1960, 1965, and 1970 examination rounds, and so on. For those men who were newly included in the study in 1985, information on fish consumption and EPA+DHA intake from fish was missing in the period 1960–1970. Since average EPA+DHA intake from fish was lower in 1985 than in 1960–1970, taking cumulative averages excluding earlier intakes in those men who were newly included in the study in 1985 would underestimate their intakes compared with men included in 1960. To account for this underestimation, multiple imputation (five times)29 of fish consumption, EPA+DHA intake from fish, and other dietary covariates between 1960 and 1970 was carried out among those men who were newly included in 1985, with an adapted version of predicted mean matching.30 For each missing observation, the nearest—in terms of predicted value—non-missing observation was drawn and assigned as the imputed value to the missing observation. The variables, besides fish consumption, EPA+DHA intake, and all dietary covariates, that were used to impute the missing observations were age at start and end of follow-up, and the indicator variable for (sudden) coronary death. The SAS code that was used for the multiple imputation can be...
**Table 1** Dataset characteristics.

<table>
<thead>
<tr>
<th>Study Year</th>
<th>SELECTED</th>
<th>AGE</th>
<th>OTHERS</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>348</td>
<td>77</td>
<td>1373</td>
<td>1721</td>
</tr>
<tr>
<td>1990</td>
<td>1373</td>
<td>70</td>
<td>1721</td>
<td>2054</td>
</tr>
</tbody>
</table>

**Results**

**Population characteristics**

During 40 years of follow-up (mean survival age: 77 years), 348 of the 1373 men participating in the Zutphen Study died from CHD (Table 1). Of these deaths, 66 were sudden coronary deaths (19% of all CHD deaths).

Among the men who were included in the study in 1960, the percentage of fish consumers varied between 71 and 81% between 1960 and 2000 (Table 1) and average fish consumption ranged from 16 to 21 g per day. In all measurement rounds, lean fish was the major type of fish consumed (between 58 and 80% of the total fish consumption). Moreover, average EPA + DHA intake from fish varied between 136 and 236 mg per day in the period 1960–2000. Among those men who were newly included in the study in 1985, fish consumption and EPA + DHA intake from fish was comparable with the men who participated since 1960. The correlation between EPA + DHA intake from fish and total fish consumption ranged from 0.60 in 2000 to 0.80 in 1960.

**Fish consumption, eicosapentaenoic acid + docosahexaenoic acid intake, and coronary heart disease death**

Long-term, i.e. cumulative average, fish consumers—consuming on average 22 g per day—had a 27% lower CHD death risk (P-value: 0.16; Table 2), while recent fish consumption was not associated with CHD death (data not shown).

For the associations between long-term fish consumption or EPA + DHA intake and CHD death, we found a significant and positive interaction with age, indicating that these associations were weaker at an older age (Figure 1A and B). The HRs for long-term fish consumption compared with no fish consumption increased from 0.32 (95% CI: 0.13–0.80) at age 50 to 0.65 (0.42–1.02) at age 65 (P-value for interaction: 0.06, Figure 1A). From age 70 onwards, the confidence intervals were too wide to draw conclusions from the reported associations. For long-term fatty-fish consumption, similar associations were observed (P-value for interaction: 0.06, Figure 1A). In addition, we found an inverse association between EPA + DHA intake and CHD death among men with an intake below as well as above 250 mg per day compared with no intake (Figure 1B). However, HRs were comparable with those for total fish consumption and no dose–response relationship was found (P-value for trend: 0.27; Table 2). Adjustment for the prevalence of chronic disease, i.e. myocardial infarction, stroke, and cancer, instead of the use of a serum cholesterol lowering diet slightly strengthened the associations between fish consumption and CHD death (data not shown).

**Fish consumption, eicosapentaenoic acid + docosahexaenoic acid intake, and sudden coronary death**

Long-term, i.e. cumulative average, fatty-fish consumption—on average 7 g per day—lowered sudden coronary death risk by 54%, while no associations were found with total and lean fish consumption (Table 2). Additional analysis showed that the inverse association between fatty-fish consumption and sudden coronary death was independent of total fish consumption [HR: 0.41 (95% CI: 0.23–0.73)]. Although the association between EPA + DHA intake from fish and sudden coronary death was stronger among men with an intake above 250 mg than among those with an intake below 250 mg compared with no intake, no clear dose–response relationship was found (P-value for trend: 0.18; Table 2). Adjustment for the prevalence of chronic disease instead of the use of a serum cholesterol lowering diet slightly attenuated the associations between fatty-fish consumption and sudden coronary death, but overall conclusions remained the same (data not shown).

The effects of long-term fish consumption and EPA + DHA intake on other CHD deaths were comparable with the effects on total CHD death (data not shown).

**Discussion**

In the present study, long-term, i.e. cumulative average, fish consumption—on average 22 g per day, i.e. 1–2 servings per
Table 1 Characteristics of men participating in the Zutphen Study by year of measurement

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>1960</td>
<td>872</td>
<td>721</td>
<td>615</td>
<td>349</td>
<td>231</td>
<td>114</td>
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<tr>
<td>Cumulative number of deaths</td>
<td>——</td>
<td>13</td>
<td>40</td>
<td>176</td>
<td>231</td>
<td>297</td>
<td>348</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49 ± 6</td>
<td>54 ± 5</td>
<td>59 ± 5</td>
<td>71 ± 5</td>
<td>75 ± 5</td>
<td>80 ± 4</td>
<td>83 ± 3</td>
</tr>
<tr>
<td>Fish users (%)</td>
<td>1960</td>
<td>81</td>
<td>76</td>
<td>71</td>
<td>73</td>
<td>74</td>
<td>76</td>
</tr>
<tr>
<td>Total fish consumption (g)</td>
<td>1960</td>
<td>20 ± 24</td>
<td>21 ± 24</td>
<td>18 ± 20</td>
<td>17 ± 19</td>
<td>16 ± 20</td>
<td>19 ± 19</td>
</tr>
<tr>
<td>EPA + DHA intake from fish (mg)</td>
<td>1960</td>
<td>225 ± 419</td>
<td>236 ± 373</td>
<td>173 ± 235</td>
<td>142 ± 242</td>
<td>136 ± 220</td>
<td>188 ± 327</td>
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<td>Energy intake (kcal)</td>
<td>3107 ± 668</td>
<td>2965 ± 672</td>
<td>2599 ± 534</td>
<td>2240 ± 507</td>
<td>2102 ± 463</td>
<td>2104 ± 463</td>
<td>2073 ± 447</td>
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<tr>
<td>Alcohol intake (g)</td>
<td>4 ± 10</td>
<td>6 ± 11</td>
<td>9 ± 12</td>
<td>13 ± 17</td>
<td>10 ± 14</td>
<td>11 ± 14</td>
<td>12 ± 14</td>
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<tr>
<td>Wine users (%)</td>
<td>201 ± 74</td>
<td>176 ± 69</td>
<td>181 ± 59</td>
<td>176 ± 72</td>
<td>162 ± 71</td>
<td>161 ± 62</td>
<td>131 ± 50</td>
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<td>Fruit consumption (g)</td>
<td>112 ± 86</td>
<td>150 ± 109</td>
<td>168 ± 130</td>
<td>200 ± 141</td>
<td>234 ± 143</td>
<td>246 ± 150</td>
<td>254 ± 175</td>
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<td>Systolic blood pressure (mmHg)</td>
<td>143 ± 20</td>
<td>142 ± 18</td>
<td>147 ± 21</td>
<td>151 ± 21</td>
<td>150 ± 21</td>
<td>150 ± 21</td>
<td>146 ± 21</td>
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Type of smoking (%)

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<td>Never and long-term ex</td>
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<td>9</td>
<td>26</td>
<td>50</td>
<td>60</td>
<td>72</td>
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<tr>
<td>Recent ex</td>
<td>6</td>
<td>11</td>
<td>15</td>
<td>31</td>
<td>17</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Current cigarettes</td>
<td>74</td>
<td>61</td>
<td>53</td>
<td>30</td>
<td>23</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Current cigars or pipes</td>
<td>14</td>
<td>21</td>
<td>23</td>
<td>13</td>
<td>10</td>
<td>6</td>
<td>8</td>
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</table>

Socioeconomic status (%)

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<tbody>
<tr>
<td>Manual workers</td>
<td>38</td>
<td>37</td>
<td>38</td>
<td>30</td>
<td>29</td>
<td>30</td>
<td>29</td>
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<tr>
<td>Non-manual workers</td>
<td>34</td>
<td>36</td>
<td>37</td>
<td>41</td>
<td>42</td>
<td>41</td>
<td>45</td>
</tr>
<tr>
<td>Small-business owners</td>
<td>21</td>
<td>20</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Professionals</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>10</td>
<td>11</td>
<td>14</td>
<td>11</td>
</tr>
</tbody>
</table>

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Numbers represent means ± SD, unless indicated otherwise.

Sudden coronary deaths were defined as cases of sudden death with a high likelihood to be coronary, occurring within 2 h of onset of symptoms in diagnosed cases or in people with a past diagnosis of coronary heart disease.

Age is defined as age on 31 December, the year preceding the year of examination.

Never and long-term ex-smokers are defined as men who never smoked or stopped smoking ≥10 years ago. Recent ex-smokers are defined as men who stopped smoking <10 years ago.
In the period 1960–1995, third, since frying can affect a fish earlier, we used this table to calculate EPA with improved laboratory analyses compared with values reported for EPA. However, as composition, time-specific food composition tables are needed to calculate nutrient intake over a longer period of time. However, as missing data in the covariates, the number of events is lower than the number mentioned in Table 1, i.e. 336 coronary heart disease deaths and 63 sudden coronary deaths.

Table 2 Long-term fish consumption and EPA+DHA intake from fish in relation to 40-year coronary heart disease and sudden coronary death within the Zutphen Study

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Category</th>
<th>Coronary heart disease death</th>
<th>Sudden coronary death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR^a 95% CI</td>
<td>HR^b 95% CI</td>
</tr>
<tr>
<td>Total fish consumption</td>
<td>No</td>
<td>1.00 —</td>
<td>1.00 —</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.70 0.46–1.06</td>
<td>0.73 0.47–1.13</td>
</tr>
<tr>
<td>Fatty fish consumption</td>
<td>No</td>
<td>1.00 —</td>
<td>1.00 —</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.87 0.64–1.16</td>
<td>0.88 0.65–1.19</td>
</tr>
<tr>
<td>Lean fish consumption</td>
<td>No</td>
<td>1.00 —</td>
<td>1.00 —</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.98 0.71–1.37</td>
<td>1.03 0.73–1.45</td>
</tr>
<tr>
<td>EPA+DHA intake</td>
<td>0 mg</td>
<td>1.00 —</td>
<td>1.00 —</td>
</tr>
<tr>
<td></td>
<td>&gt;0–250 mg</td>
<td>0.72 0.47–1.10</td>
<td>0.76 0.49–1.18</td>
</tr>
<tr>
<td></td>
<td>&gt;250 mg</td>
<td>0.64 0.40–1.02</td>
<td>0.65 0.40–1.06</td>
</tr>
<tr>
<td>P-value for trend^c</td>
<td></td>
<td>0.33</td>
<td>0.27</td>
</tr>
</tbody>
</table>

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
^aCrude hazard ratios with 95% confidence limits (CI); HRs for fatty and lean fish are adjusted for each other.
^bHRs are additionally adjusted for energy intake, alcohol intake, wine use, fruit and vegetable consumption, saturated fat, trans unsaturated fatty acid, cis monounsaturated and polyunsaturated fat intake, serum cholesterol lowering diet, smoking, body mass index, prevalence of diabetes mellitus, systolic blood pressure, and socioeconomic status; because of missing data in the covariates, the number of events is lower than the number mentioned in Table 1, i.e. 336 coronary heart disease deaths and 63 sudden coronary deaths.
^cFor EPA+DHA intake from fish, a P-value for trend was calculated using the continuously distributed variable.

The present study also has some weaknesses. First, the number of sudden coronary deaths (66 events) observed in the Zutphen Study may have been too small to detect a dose–response relation for EPA+DHA intake. Second, to account for changes in product composition, time-specific food composition tables are needed to calculate nutrient intake over a longer period of time. However, as the digitally updated version of the Dutch food composition database from 1996 contains values of EPA and DHA in fish obtained with improved laboratory analyses compared with values reported earlier, we used this table to calculate EPA+DHA intake from fish in the period 1960–1995.19,20 Third, since frying can affect a fish meal’s fatty-acid composition and trans unsaturated fatty acids in frying fats may increase cardiovascular risk, Mozaffarian et al.31 suggested that these factors should be taken into account when studying the associations of fish consumption with CHD death. In the present study, it was not possible to consider different methods of fish preparation. However, detailed information on usual food consumption and nutrient intake made it possible to study the independent effects of lean, which is mostly fried, and fatty-fish consumption and to adjust for trans unsaturated fatty acid intake. Fourth, for those men who were newly included in the study in 1985, information on fish consumption was missing in the period 1960–1970. By multiple imputations of fish consumption, EPA+DHA intake from fish, and other dietary covariates in 1960–1970, we were able to counter an underestimation of cumulative average intake from 1985 onwards for those men who were newly included in the study. However, assumptions that were made in the multiple imputation method may have led to less precise effect estimates. We repeated our analysis among the participants who were included in the study from 1960 (n = 875) and found similar associations between long-term fish consumption and (sudden) coronary death. Therefore, it is unlikely that the imputation of fish consumption, EPA+DHA intake, and other dietary covariates among those men who were newly included in the study from 1985 biased our results.

Our results confirm those from other prospective cohort studies that found an inverse association between fish consumption, EPA+DHA intake from fish, and CHD death risk; however, significant inverse associations were present only until age 65. Compared with no intake, long-term EPA+DHA intake was associated with a lower CHD death risk among men with an intake below as well as above 250 mg per day and HRs were comparable. This confirms the findings from Mozaffarian et al. who showed that a dose–response relationship between EPA+DHA intake from fish and CHD death is only present up to an intake of 250 mg per day, while intakes above 250 mg did not have a significant additional risk reduction.

Moreover, the present study showed that long-term fatty-fish consumption—on average 7 g per day—lowered the risk of sudden coronary death by 54% and confirms results from other prospective cohort studies. Results from two case–control studies suggest that there is a linear dose–response relation between blood or cell membrane levels of EPA and DHA, and...
sudden coronary death or cardiac arrest. In the present study, the association between EPA+DHA from fish and sudden coronary death was indeed stronger among men with an intake above 250 mg compared with the association among men with an intake below 250 mg; however, the trend was not statistically significant (P-value: 0.18). Lean fish consumption was not associated with sudden coronary death. Besides the difference in EPA and DHA content, fatty fish also has a higher content of other bioactive compounds such as vitamin D than lean fish, which could have an additional beneficial effect. Furthermore, as already mentioned earlier, lean fish is mostly fried and although we adjusted for trans fatty acid intake, residual confounding cannot be ruled out.
Within the Zutphen population, average EPA+DHA intake from fish was ~200 mg per day. At this low level of intake, an anti-arrhythmic effect of EPA+DHA is the most likely explanation for the low risk of (sudden) coronary death. At low doses, an increase in circulating free EPA and DHA contributes to reducing arrhythmias by binding to the Na+ and L-type Ca2+ channels in cell membranes. This inhibits the Na+ and L-type Ca2+ currents in cell membranes, which prevent the generation of action potentials in injured cardiomyocytes.6,8,39

The main conclusion of this study is that long-term fish consumption, on average 22 g per day, lowers the risk of CHD, especially below age 65. Fatty-fish consumption lowers the risk of sudden coronary death. There is no clear dose–response relationship between EPA+DHA intake from fish and (sudden) coronary death.

Conflict of interest: For the Alpha Omega Trial, D.K. received grants from the Netherlands Heart Foundation and the National Institutes of Health (USA), and Unilever funded the production and distribution of the margarines, enriched with n-3 fatty acids, used in this trial.

Funding

The present study was partly supported by a grant from the former Inspectorate for Health Protection and Veterinary Public Health, The Netherlands.

References


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