Association between trans fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study

Claudia M Oomen, Marga C Ocké, Edith J M Feskens, Marie-Agnes J van Erp-Baart, Frans J Kok, Daan Kromhout

Summary

Background Evidence on the relation between trans fatty acid intake and coronary heart disease is limited. We investigated this relation in a Dutch population with a fairly high trans fatty acid intake, including trans fatty acids from partly hydrogenated fish oils.

Methods We prospectively studied 667 men of the Zutphen Elderly Study aged 64–84 years and free of coronary heart disease at baseline. We used dietary surveys to establish the participants’ food consumption patterns. Information on risk factors and diet was obtained in 1985, 1990, and 1995. After 10 years of follow-up from 1985–95, there were 98 cases of fatal or non-fatal coronary heart disease.

Findings Between 1985 and 1995, average trans fatty acid intake decreased from 4.3% to 1.9% of energy. After adjustment for age, body mass index, smoking, and dietary covariates, trans fatty acid intake at baseline was positively associated with the 10-year risk of coronary heart disease. The relative risk for a difference of 2% of energy in trans fatty acid intake at baseline was 1.28 (95% CI 1.01–1.61).

Interpretation A high intake of trans fatty acids (all types of isomers) contributes to the risk of coronary heart disease. The substantial decrease in trans fatty acid intake, mainly due to industrial lowering of trans contents in Dutch edible fats, could therefore have had a large public-health impact.

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participants who were still alive were re-examined. In addition, 711 other men from the town of Zutphen in the same age category were asked to participate. A total of 939 men (response rate 74%) was examined in 1985, 560 in 1990 (response rate 78%), and 343 in 1995 (response rate 74%). Of the 343 men who participated in 1995, a random sample of 280 men took part in the dietary survey. Complete information on diet and risk factors was available for 824 men in 1985. We excluded 157 men with previously diagnosed myocardial infarction or angina pectoris, which left 667 men at baseline, of whom 435 and 225 participated in the dietary survey in 1990 and 1995, respectively.

Data collection
Dietary surveys and medical examinations were completed between March and June in 1985, 1990, and 1995. We obtained information about the habitual food consumption with the cross-check dietary history method, adapted to the Dutch situation. Each participant, and if possible his partner, was interviewed about his average food consumption pattern in the month before interview. A checklist of foods and quantities of food bought per week was used to calculate and verify the participant’s food consumption pattern.

We calculated nutrient intake with corresponding Dutch food tables. Time-specific tables with trans fatty acid content of consumed foods were compiled. National data were available for edible fats analysed by the Wageningen University, Netherlands, around 1985 and 1990, and by the TRANSFAIR Study in 1995. In 1995, products such as biscuits and pastries (Wageningen University) and dairy products and meats (TRANSFAIR Study) were analysed. The trans fatty acid contents of the remaining foods were based on analyses from abroad, derived from recipes, or deduced from other foods. Because the gas chromatographic method underestimates measurement of trans fatty acids, contents were adjusted by taking the combination of gas-liquid chromatography of 4,4-dimethylxazoline derivatives and methyl esters or the infra-red spectrometry as a reference.

During medical examinations, we took non-fasting venous blood samples. Serum total cholesterol and HDL cholesterol were determined enzymatically. We measured blood pressure in duplicate with a random zero sphygmomanometer while participants were supine. Hypertension was defined as use of antihypertensive medication, a systolic blood pressure of 160 mm Hg or greater, or a diastolic blood pressure of 95 mm Hg or greater. We calculated total minutes of physical activity per week, information on cigarette smoking, and diabetes mellitus, with a questionnaire. We ascertained history of coronary-heart disease with the Dutch translation of the Rose questionnaire.

Follow-up
Incident cases included fatal coronary heart disease plus non-fatal myocardial infarction (whichever arose first) occurring between baseline assessment in 1985 and January, 1995. Three participants were lost to follow-up. We obtained information on vital status of the participants from the municipal registries, and on cause of death between 1985 and June 1990 from Statistics Netherlands. For deaths thereafter, or if data were not available from Statistics Netherlands, information was obtained from hospital discharge data or general practitioners. We coded causes of death in accordance with the ninth revision of the International Classification of Diseases. Coronary heart disease refers to codes 410–414. Because the underlying cause of death in elderly people is often difficult to establish, we classified coronary heart disease as a primary (n=46) as well as a secondary (n=3) cause of death in the analyses.

We obtained information on non-fatal myocardial infarction by a standardised medical questionnaire, or, in case of non-response, by a short questionnaire completed by the participants or their closest relative. All reported myocardial infarctions were verified with hospital-discharge data. Also, in men who died, information on disease history was obtained from the general practitioner. Diagnosis of myocardial infarction required at least two of the following criteria: a specific medical history, characteristic electrocardiographic changes, and specific increases in concentration of enzymes.

Statistical methods
All statistical analyses were carried out using the SAS (version 6.12) package. Men were divided into tertiles on the basis of the contribution of trans fatty acids to energy intake at baseline. To compare the baseline major risk factors and dietary factors across categories of trans fatty acid intake, we used analysis of variance for normally distributed variables, the Kruskal-Wallis test for skewed variables, and the χ² test for categorical variables.

We used Cox’s proportional-hazard analysis to calculate relative risks, with the lowest trans fatty acids tertile as the reference group, or including trans fatty acid intake as the continuous variable. In the continuous analyses, we estimated the relative risk associated with a difference of 2% of energy in total trans fatty acid intake. This difference was based on the reports of two prospective studies, which is in agreement with the range in trans fatty acid intake at baseline, and the 10-year decrease in trans fatty acid intake in the present study. Adjustments were made for age, intake of energy, body mass index, smoking, alcohol intake, use of vitamin supplements, intake of saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, and cholesterol. We also adjusted for fibre because the association between trans fatty acid intake and coronary heart disease was strongly attenuated after adjustment for fibre in another prospective study. Alcohol intake was used as a categorical variable (included as two dummies into the model, with non-drinkers as a reference).

Results
The mean daily trans fatty acid intake fell from 1985 to 1990 and 1995 (10·9 g [SD 6·3] vs 6·9 [4·0] vs 4·4 g [1·7]). The mean contribution of trans fatty acid intake to total energy intake decreased from 1985 to 1990 and 1995 (4·3% [SD 2·2] vs 2·9% [1·9] vs 1·9% [0·6]). There was a similar reduction in trans fatty acid intake (−2·1% of energy) in the men who were examined in all three examination years. The intake of manufactured C18:1 trans (a proxy for partly hydrogenated vegetable oils) as well as the manufactured other trans fatty acids (including partly hydrogenated fish oils) decreased substantially between 1985 and 1995, but the intake of ruminant trans fatty acids did not do so (figure 1). The Spearman correlation coefficient between the total trans fatty acid intake expressed in % of energy in 1985 and 1990 was 0·43, and between 1985 and 1995 was 0·24.

The total daily intake of trans fatty acids at baseline was positively associated with the daily intake of energy, total fat, saturated and unsaturated fat, and cholesterol,
and inversely associated with the daily intake of carbohydrates, protein, alcohol, and the use of vitamin supplements (table 1). No significant associations between total trans fatty acid intake and major risk factors were recorded. However, although not statistically significant, men with a high intake of trans fatty acids were more often smokers and had a higher serum total cholesterol concentration. For manufactured trans fatty acids, similar associations were noted. By contrast, trans fatty acid intake from ruminant sources was inversely associated with the daily intake of energy, polyunsaturated fat, and fibre, and positively associated with the daily intake of protein.

During 10 years of follow-up, we documented 98 (15% of the baseline population) coronary heart disease cases (including 49 cardiac deaths). Table 2 shows the crude relative risks of 10-year coronary heart disease frequency for the different tertiles of trans fatty acid intake at baseline. The relative risks were similar after adjustment for age, body mass index, smoking, use of vitamin supplements, intake of energy, alcohol, specific types of fat, dietary cholesterol, and fibre.

In the continuous analyses we calculated the relative risk associated with a difference of 2% of energy in total trans fatty acid intake at baseline. Adjusted for age and energy intake, this relative risk of 10-year incidence of coronary heart disease was 1.29 (95% CI 1.09–1.52). After additional adjustment for body mass index, smoking, use of vitamin supplements, intake of alcohol, specific types of fat, dietary cholesterol and fibre, the relative risk amounted to 1.28 (1.01–1.61). For fatal coronary heart disease the fully adjusted relative risk for a difference of 2% of energy in trans fatty acid intake was 1.33 (0.96–1.86).

Because of different proportions of C18:1 trans isomers in each source, and because of different trans isomers from manufactured sources, we assessed the difference in effect of ruminant trans fatty acids, manufactured C18:1 trans fatty acids, and other manufactured trans fatty acids. We did continuous

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**Table 1:** Characteristics at baseline by tertiles of total trans fatty acid

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total (n=667)</th>
<th>Trans fatty acid tertile (% of energy)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;3·11 (n=222)</td>
<td>3·11–4·86 (n=223)</td>
<td>&gt;4·86 (n=222)</td>
</tr>
<tr>
<td><strong>&lt;3·11</strong></td>
<td>71·1 (5·2)</td>
<td>71·3 (5·5)</td>
<td>70·8 (5·2)</td>
</tr>
<tr>
<td><strong>3·11–4·86</strong></td>
<td>25·5 (3·2)</td>
<td>25·2 (3·3)</td>
<td>25·8 (3·2)</td>
</tr>
<tr>
<td><strong>&gt;4·86</strong></td>
<td>22·3 (3·1)</td>
<td>21·9 (3·2)</td>
<td>25·8 (3·2)</td>
</tr>
</tbody>
</table>

| Physical activity | 611 (533) | 577 (467) | 601 (300) | 656 (620) | 0·91 |
| min per week | 6·08 (1·11) | 6·14 (1·15) | 5·94 (1·02) | 6·16 (1·13) | 0·07 |

| Serum total cholesterol (mmol/L) | 1·14 (0·30) | 1·15 (0·31) | 1·14 (0·29) | 1·12 (0·30) | 0·64 |

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Current</th>
<th>Past</th>
<th>Use of vitamin supplements</th>
<th>Hypertension</th>
<th>Diabetes mellitus</th>
<th>Alcohol (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>33%</td>
<td>49%</td>
<td>16%</td>
<td>42%</td>
<td>6%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>28%</td>
<td>51%</td>
<td>21%</td>
<td>47%</td>
<td>5%</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>31%</td>
<td>48%</td>
<td>18%</td>
<td>42%</td>
<td>8%</td>
<td>34%</td>
</tr>
<tr>
<td></td>
<td>38%</td>
<td>48%</td>
<td>10%</td>
<td>38%</td>
<td>5%</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>0·08</td>
<td>0·73</td>
<td>0·003</td>
<td>0·15</td>
<td>0·25</td>
<td>0·01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Daily intake of Energy (MJ)</th>
<th>9·2 (2·0)</th>
<th>8·6 (1·9)</th>
<th>9·4 (2·1)</th>
<th>9·5 (2·1)</th>
<th>0·0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fat (% of energy)</td>
<td>40·3 (6·4)</td>
<td>37·1 (6·5)</td>
<td>39·8 (5·2)</td>
<td>44·0 (6·5)</td>
<td>0·0001</td>
</tr>
<tr>
<td>Saturated fat (% of energy)</td>
<td>18·0 (3·6)</td>
<td>17·0 (3·9)</td>
<td>18·3 (3·6)</td>
<td>18·7 (3·1)</td>
<td>0·0001</td>
</tr>
<tr>
<td>Monounsaturated fat (% of energy)</td>
<td>15·3 (3·2)</td>
<td>13·2 (2·8)</td>
<td>15·0 (2·2)</td>
<td>17·7 (2·8)</td>
<td>0·0001</td>
</tr>
<tr>
<td>Polyunsaturated fat (% of energy)</td>
<td>7·0 (2·8)</td>
<td>6·9 (3·5)</td>
<td>6·4 (2·4)</td>
<td>7·6 (2·1)</td>
<td>0·0001</td>
</tr>
</tbody>
</table>

| Cholesterol (mg) | 273 (70·0) | 245 (74·4) | 280 (89·0) | 292 (98·5) | 0·0001 |
| Carbohydrates (% of energy) | 41·0 (7·3) | 42·2 (8·0) | 42·0 (6·6) | 38·7 (6·8) | 0·0001 |
| Protein (% of energy) | 14·3 (2·6) | 14·8 (2·8) | 14·3 (2·4) | 13·7 (2·5) | 0·0001 |
| Alcohol (g per day) | 13·8 (17·3) | 17·0 (20·0) | 12·7 (16·7) | 11·7 (14·2) | 0·05 |
| Non-drinkers | 24% | 23% | 22% | 24% | 0·01 |
| >20 g/day (%) | 27% | 34% | 34% | 24% | 0·01 |
| Fibre (g) | 24·9 (7·1) | 24·4 (7·2) | 25·2 (6·9) | 25·1 (7·1) | 0·46 |

*Values were obtained by modelling the median value of each category as a continuous variable.

**Table 2:** Relative risks of coronary heart disease according to tertiles of trans fatty acid intake at baseline

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hydrogenated vegetable and fish oils explains the decline in the contribution of trans fatty acids to total energy intake. In 1996, a further decrease in trans fatty acid content of edible fats was recorded in the Netherlands. Also, in other European countries, a fall in the trans fatty-acid content of margarines contributed to a decline in trans fatty acid intake. The trans fatty acid intake at baseline was much higher than the 2% of energy reported in previous studies done in the USA. However, in the USA, the trans fatty acid intake remained stable, because a decrease in trans fatty acids from margarines was counterbalanced by an increase in trans fatty acids from commercially baked products and fast foods.

We did not record a clear cross-sectional association between trans fatty acid intake and total or HDL cholesterol at baseline. However, by use of longitudinal analyses of both trans fatty acids and cholesterol concentrations, there was an association in accordance with the results of controlled dietary intervention studies (unpublished data). Also other mechanisms might be implicated in increasing the risk for coronary heart disease, since relative risk is higher than can be predicted from the effects of trans fatty acids on cholesterol concentrations alone. Several studies have shown effects of trans fatty acids on triglycerides and lipoprotein (a) concentrations. Trans fatty acids might have other adverse physiological effects on—eg, thrombotic mechanisms or insulin resistance.

Evidence from observational and dietary intervention studies suggests that a decrease in trans fatty acid intake has a role in lowering coronary heart disease mortality. The number of coronary heart disease deaths attributable to trans fatty acids in the USA is thought to be substantial. The decrease in trans fatty acid intake of 2-4% of energy we report could have contributed to about 23% less coronary deaths (ie, about 4600 of 20 000 coronary deaths in the Netherlands per year).

Possibilities for further industrial reductions in trans fatty acid contents are restricted nowadays to bakery products and fast foods. Also, the substitution of trans fatty acids requires further attention, because in the current manufacturing process trans fatty acids are partly replaced by saturated fatty acids.

Contributors
Claudia M Oomen collected information on the trans fatty acids contents in foods, analysed the data, and prepared the first draft of the manuscript. Margie C Ocké contributed to analysis and interpretation of the results. Edith J M Feskens contributed to the design of the study, analysis, and interpretation of the results. Marie-Agnes J van Erp-Baart provided data from the TRANSFAIR Study and contributed to the interpretation of the results. Frans J Kok contributed to the analysis and interpretation of the results. Daan Kromhout was responsible for design and data collection, and contributed to analysis and interpretation of the results.

Acknowledgments
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References
A 49-year-old man with an 8-year history of multiple sclerosis was prescribed treatment with interferon β-1a (IFNβ-1a) (Avonex, Biogen), 30 mg per week. 3 months later he presented with a progressive, unproductive cough and right hemithoracic pain without fever. Full blood count showed slight leucocytosis (13\times10^9 cells/L) with 75% neutrophils. The erythrocyte sedimentation rate was raised (50 mm/h). Chest radiography revealed an alveolar opacity in the right inferior lobe, which expanded progressively over 10 days. Computed tomography confirmed the presence of a right basal pulmonary infiltrate (figure). Serological tests for atypical pneumonia were negative. Transbronchial biopsies showed oedematous granulation tissue occluding the bronchioles and alveolar ducts, with associated areas of fibrous thickening of the intra-alveolar walls consistent with bronchiolitis obliterans with organising pneumonia (BOOP). IFNβ-1a was discontinued. Prednisone was initiated (50 mg daily) and a dramatic improvement was observed. 2 months later, chest radiography and CT scan were normal. To our knowledge, this is the first case of BOOP probably induced by IFNβ.

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