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

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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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Introduction

Concern about the adverse health effects of trans isomers of unsaturated fatty acids has increased since 1990 after the results of controlled dietary intervention studies.[1–7] Results of these studies showed a detrimental effect of trans fatty acids on LDL and HDL cholesterol. Evidence that intake of trans isomers affects the rate of coronary heart disease is derived from population-based studies done in the USA.[8–11] Until now, a fairly small number of observational studies have focused on the health effects of trans fatty acids in Europe, with weak or equivocal results.[12–14]

Trans fatty acids are mainly present in solid fats produced by part hydrogenation of oils, and are naturally found in products originating from ruminant animals. The current trans fatty acid intake contributes between 0·5% and 2·1% to energy intake in western Europe,[15] and about 2% of total energy intake in the average US diet.[16] In the Netherlands, because of publicity about adverse effects of trans fatty acids on blood lipoproteins,[17] the amount of trans fatty acids in fats for use in households has decreased substantially. In frequently used foods, such as hard margarines, the trans fatty acid content has declined from a maximum of 50% in the 1980s to an average 1–2% nowadays.[18] Consequently, the consumption of trans fatty acids in the Netherlands has decreased greatly.

Most controlled trials[1–4,6] and population-based studies[8–12] have focused on the effect of isomers with 18 carbon atoms (C18:1 trans isomers), since these isomers mainly originate from partly hydrogenated vegetable oils and ruminant fat. In addition, because of different proportions of C18:1 trans isomers, results of some observational studies have made a distinction between manufactured and ruminant trans fatty acids, and suggested more harmful health effects of manufactured trans fatty acids.[8,9,13] Although industry in the USA only uses partly hydrogenated vegetable oils, in European countries foods have also been manufactured with partly hydrogenated fish oils.[19,20] An adverse effect of high amounts of trans fatty acids from hydrogenated fish oil on blood lipids has already been shown.[5] However, the health effects of these isomers in quantities consumed in daily life are unknown.

We investigated the association between trans fatty acid intake and the risk of coronary heart disease in the Zutphen Elderly Study, a population with a fairly high dietary trans fatty acid intake at baseline, including trans fatty acids from partly hydrogenated fish oils.

Methods

Study population

The study population consisted of men who participated in the Zutphen Elderly Study, an extension of the Zutphen Study. In 1960, the Zutphen Study started with a cohort of 878 men from Zutphen (Netherlands) born between 1900 and 1919, as the Dutch contribution to the Seven Countries Study.[21] In 1985, 367 of 555

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 in 1985, 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.[22] 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.[23] National data were available for edible fats analysed by the Wageningen University, Netherlands, around 1985 and 1990, and by the TRANSFAIR Study[24] 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-dimethyloxazoline derivatives and methyl esters[25] 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.[26,27] 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,[28] 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.[29]

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 χ^2 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,[10,11] 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, monosaturated 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.[10] 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% [1·5] *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,

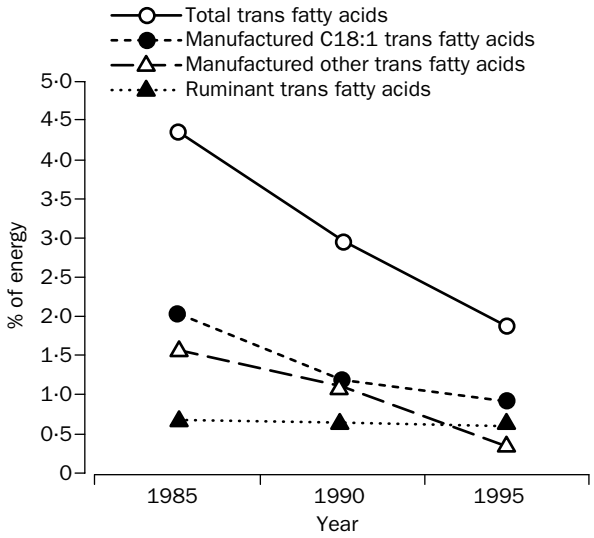

Figure 1: **Daily intake of trans fatty acids in the Zutphen Elderly Study between 1985 and 1995**

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.

	Trans fatty acid tertile (% of energy)			p value*
	<3·11 (n=222)	3·11–4·86 (n=223)	⩾4·86 (n=222)	
Median intake (% of energy)	2·36	3·87	6·38	· ·
Cases	24 (11%)	30 (14%)	44 (20%)	· ·
Relative risks (95% CI)				
Crude	1	1·26 (0·74–2·15)	2·03 (1·24–3·34)	0·003
Age+energy adjusted	1	1·36 (0·79–2·34)	2·19 (1·32–3·62)	0·002
Fully adjusted	1	1·34 (0·76–2·37)	2·00 (2·07–3·75)	0·03

*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**

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

	Total (n=667)	Trans fatty acid tertile (% of energy)			p value
		<3·11 (n=222)	3·11–4·86 (n=223)	⩾4·86 (n=222)	
Age (years)	71·1 (5·2)	71·3 (5·5)	70·8 (5·2)	71·3 (5·0)	0·47
Body mass index (kg/m²)	25·5 (3·2)	25·5 (3·1)	25·2 (3·2)	25·8 (3·2)	0·13
Physical activity (min per week)	611 (533)	577 (467)	601 (300)	656 (620)	0·91
Serum total cholesterol (mmol/L)	6·08 (1·11)	6·14 (1·15)	5·94 (1·02)	6·16 (1·13)	0·07
Serum HDL cholesterol (mmol/L)	1·14 (0·30)	1·15 (0·31)	1·14 (0·29)	1·12 (0·30)	0·64
Smoking					
Current	33%	28%	31%	38%	0·08
Past	49%	51%	48%	48%	0·73
Use of vitamin supplements	16%	21%	18%	10%	0·003
Hypertension	42%	47%	42%	38%	0·15
Diabetes mellitus	6%	5%	8%	5%	0·25
Daily intake of					
Energy (MJ)	9·2 (2·0)	8·6 (1·9)	9·4 (2·1)	9·5 (2·1)	0·0001
Total fat (% of energy)	40·3 (6·4)	37·1 (6·5)	39·8 (5·2)	44·0 (5·6)	0·0001
Saturated fat (% of energy)	18·0 (3·6)	17·0 (3·9)	18·3 (3·6)	18·7 (3·1)	0·0001
Monounsaturated fat (% of energy)	15·3 (3·2)	13·2 (2·8)	15·0 (2·2)	17·7 (2·8)	0·0001
Polyunsaturated fat (% of energy)	7·0 (2·8)	6·9 (3·5)	6·4 (2·4)	7·6 (2·1)	0·0001
Cholesterol (mg)	273 (97·0)	245 (97·4)	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%	23%	25%	0·85
⩾20 g/day (%)	27%	34%	22%	24%	0·01
Fibre (g)	24·9 (7·1)	24·4 (7·2)	25·2 (6·9)	25·1 (7·1)	0·46

Values shown as mean (SD) unless otherwise stated.

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

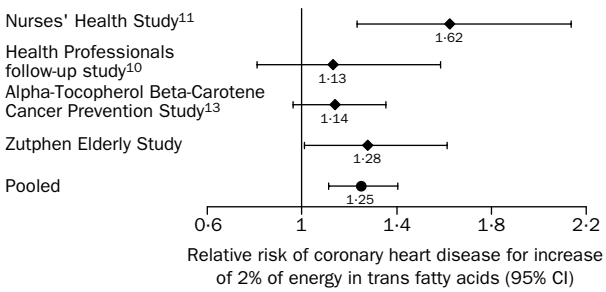

Figure 2: **The fully adjusted relative risks of coronary heart disease for an increase of 2% of energy in trans fatty acid intake at baseline according to prospective population-based studies and the pooled variance-weighted relative risk**

	Ruminant trans fatty acids	Manufactured C18:1 trans fatty acids	Other manufactured trans fatty acids
Mean (SD) intake (% of energy)	0·7 (0·2)	2·1 (1·2)	1·6 (1·4)
Relative risks (95% CI)			
Crude	1·11 (0·69–1·78)	1·07 (0·99–1·15)	1·05 (0·99–1·12)
Age+energy adjusted	1·05 (0·66–1·69)	1·08 (1·00–1·17)	1·06 (0·99–1·13)
Fully adjusted	1·17 (0·69–1·98)	1·05 (0·94–1·17)	1·07 (0·99–1·15)

*Intake of ruminant trans fatty acid, manufactured C18:1 trans, and other manufactured trans fatty acids are included simultaneously.

Table 3: **Relative risks of coronary heart disease for an increase of 0·5% in energy from trans fatty acids from different sources* at baseline**

analyses of baseline intake on coronary heart disease frequency to take into account the difference in range of intake of each type of trans fatty acid, For each 0·5% of energy, the fully adjusted relative risk of coronary heart disease for ruminant trans fatty acids, manufactured C18:1 trans fatty acids, and other manufactured trans fatty acid intake was similar (table 3).

Table 4 summarises results of previous cohort studies on the association between trans fatty acid intake and the risk of coronary heart disease. Combining the results of the four prospective cohort studies, the pooled variance-weighted relative risk of coronary heart disease associated with a difference of 2% of energy in trans fatty acid intake is 1·25 (95% CI 1·11–1·40; figure 2).

Discussion

We report that high intake of trans fatty acids at baseline was strongly associated with the risk of coronary heart disease in Dutch elderly men. Our results are similar to those from other prospective studies, such as the 16 population cohorts of the Seven Countries Study,[30] and a US case-control study.[9] However, in the EURAMIC case-control study, no significant overall association was noted between the C18:1 trans fatty acid content of adipose tissue and the risk of first myocardial infarction.[12] In this investigation, however, the trans fatty acid content of adipose tissue was very low in the Spanish centres. After excluding these outlying values, the relative risk for the highest versus the lowest quartile was 1·44 (95% CI 0·94–2·20).

We did not show any actual difference in associations between coronary heart disease and ruminant trans fatty acid intake, intake of C18:1 trans isomers, and other trans isomers from manufactured sources. Human dietary intervention studies on blood lipids that used different sources or trans isomers have similar results.[1,2,4,5] However, in the Nurses' Health Study, a non-significant inverse relative risk of coronary heart disease for ruminant trans fatty-acid intake (highest *vs* lowest quintile) of 0·59 was recorded.[8] In two other prospective studies, because of the lower intake of trans fatty acids from ruminant sources compared with manufactured sources, differences between ruminant and manufactured trans fatty acids were less clear.[9,13] We therefore conclude that the health effect of trans fatty acids from ruminant sources and from manufactured sources is similar.

Is the association between trans fatty acid intake and coronary heart disease estimated adequately with a baseline measurement in a cohort with a declining trans fatty acid intake? In the Nurses' Health Study, a stronger association between trans fatty acids and coronary heart disease was reported when cumulative average diets were used rather than baseline or only the most recent diet.[31] Taking into account changes in food composition and dietary habits among participants in our study, use of cumulative average diets or the most recent diet for the second 5 years of follow-up gave weaker results than those for the baseline diet (data not shown). When the intake of trans fatty acids is fairly stable, as in the Nurses' Health Study,[31] the cumulative average intake probably best indicates the long-term intake. However, for our population of men aged 64–84 years who changed their trans fatty acid intake only recently, the baseline measurement probably better shows the long-term intake.

Keeping misclassification to a minimum is essential to adequately detect associations with disease or to control for confounding. In our study, habitual food consumption was measured by the cross-check dietary history method, which is acknowledged as a valid method in an epidemiological setting.[22] Trans fatty acid contents of mainly Dutch foods were available to calculate trans fatty acid intake. Adjustments were made for systematic differences due to different analytical methods. Furthermore, the effect of trans fatty acid intake on coronary heart disease could be confounded by other dietary or risk factors that were not included in our analyses. To lower residual confounding, we adjusted for many dietary and lifestyle factors. All had minor effects on the relative risks. Our results for fatal coronary heart disease, including non-fatal myocardial infarction, were considered. Because of power, we focused on the association of fatal plus non-fatal coronary heart disease.

The reduction in consumption of trans fatty acids in the Netherlands and in the use of both partly

Study population	N	Sex	Number of events	Follow-up (years)	Age+energy adjusted relative risk (95% CI)	Adjusted† relativ risk (95% CI)
Nurses' Health Study[11]	80 082	Women	939	14	. .	1·62 (1·23–2·13)
Health Professionals follow-up Study[10]	43 757	Men	734	6	1·59 (1·21–2·08)	1·13 (0·81–1·58)
Alpha-Tocopherol Beta-Carotene Cancer Prevention Study[13]	21 930	Men	1399	6·1	1·19 (1·00–1·41)	1·15 (0·96–1·35)
Zuphen Elderly Study	667	Men	98	10	1·29 (1·09–1·52)	1·28 (1·01–1·61)

*Defined as non-fatal myocardial infarction and fatal coronary heart disease. †For each study, the fully adjusted model is presented here. Details can be found in the original papers.

Table 4: **Summary of the effect of an increase of 2% energy in trans fatty-acid intake on coronary heart disease* reported in prospective studies**

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.[15,18] Also, in other European countries, a fall in the trans fatty-acid content of margarines[19] contributed to a decline in trans fatty acid intake.[15] The trans fatty acid intake at baseline was much higher than the 2% of energy reported in previous studies done in the USA.[8,10,11] 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.[16]

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.[16] Several studies have shown effects of trans fatty acids on triglycerides[1,4,6,7] and lipoprotein (a) concentrations.[5,7] Trans fatty acids might have other adverse physiological effects on—eg, thrombotic mechanisms[32] or insulin resistance.[33]

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.[17] The number of coronary heart disease deaths attributable to trans fatty acids in the USA is thought to be substantial.[34] 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[21] and fast foods.[18,35] 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.[15,17–19]

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. Marga 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.

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Clinical picture: Bronchiolitis obliterans with organising pneumonia during interferon β-1a treatment

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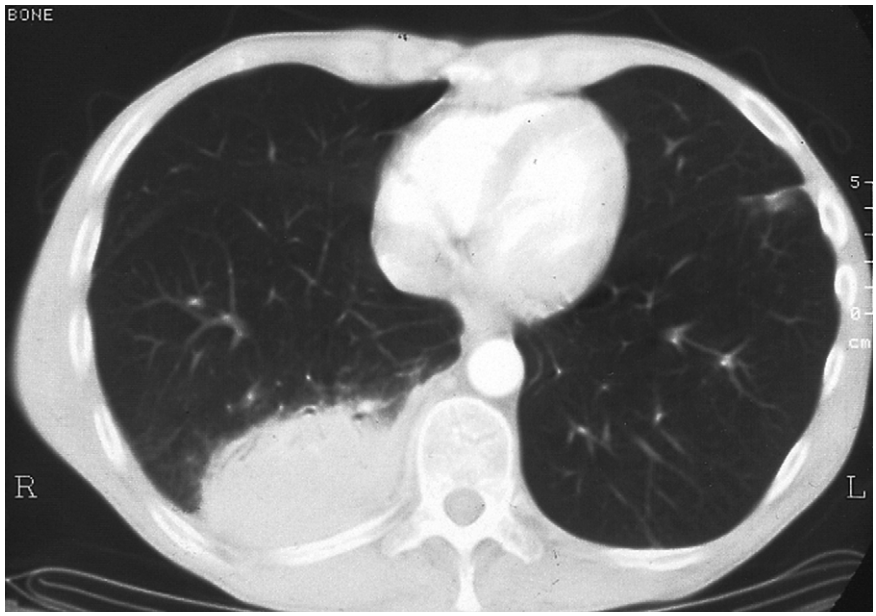

A 49-year-old man with an 8-year history of multiple sclerosis was prescribed treatment with interferon β-1a (IFNβ-1a) (Avonex, Biogen), 30 mg per week. 3 months later he presented with a progressive, unproductive cough and right hemithoracic pain without fever. Full blood count showed slight leucocytosis (13×10^9 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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