The relation between dietary intake of individual fatty acids, FEV_1 and respiratory disease in Dutch adults

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ABSTRACT

Background: A reduced dietary intake of n-3 fatty acids, in association with increased n-6 fatty acid intake, has been proposed as a potential aetiological factor for chronic obstructive pulmonary disease (COPD) and asthma. However, the relative importance of individual fatty acids within the n-3 and n-6 categories on this effect has not been widely investigated. We have studied the relation between individual fatty acid intakes, lung function and self-reported respiratory symptoms and diagnoses in a representative sample of more than 13 000 Dutch adults.

Methods: Intake of individual fatty acids was estimated by a food frequency questionnaire and analysed in relation to measures of forced expiratory volume in 1 s (FEV_1) and to questionnaire reported wheeze, asthma and COPD symptoms.

Results: After adjusting for confounding, we found no protective association between individual n-3 fatty acid intakes and FEV_1. Higher intakes of some n-6 fatty acids were associated with lower FEV_1, this effect being most marked for c22:4 n-6 docosatetraenoic acid (reduction in FEV_1 between the highest and lowest quintile of intake 54.5 ml (95% CI −81.6 to −27.4)). Most of the n-6 fatty acid effects interacted significantly with smoking, their effects being strongest in current smokers. Individual n-3 fatty acid intakes were generally associated with a higher risk of wheeze in the past year, but otherwise there was little or no association between fatty acid intake and wheeze, doctor diagnosed asthma or other respiratory symptoms.

Conclusions: A high intake of n-3 fatty acids does not appear to protect against COPD or asthma, but a high intake of several n-6 fatty acids is associated with a significant reduction in FEV_1, particularly in smokers. These findings indicate that high dietary intake of n-6 fatty acids, rather than reduced n-3 intake, may have an adverse effect on lung health.

Recent evidence has implicated dietary intake of unsaturated fatty acids in the aetiology of both asthma and chronic obstructive pulmonary disease (COPD). Specifically it has been proposed that a secular trend towards reduced intake of n-3 and increased intake of n-6 fatty acids[1] may have contributed to the recent rise in asthma prevalence in many developed countries,[2] but also that high n-3 intake may protect against COPD.[3] Experimental evidence supports this hypothesis, since n-6 fatty acids have been shown to stimulate production of proinflammatory eicosanoids, including prostaglandin E_2 and leukotriene B4, which in turn also increases production of IgE, whereas the n-3 fatty acids are anti-inflammatory and inhibit this process through metabolism into less biologically active eicosanoids, such as leukotriene B5.[4] In addition, recent evidence also suggests that reduced lung function is associated with increased systemic inflammation,[5] and therefore the specific anti-inflammatory effects of n-3 fatty acids might also be expected to protect from this effect. It is therefore plausible that high n-3 and low n-6 fatty acid intake might reduce the risk of both asthma and COPD, and this hypothesis is supported by evidence that a high intake of fish oils, a rich source of n-3 fatty acids, protects against asthma and COPD.[3 6–8]

To date, the majority of research in this area has investigated the relation between individual fatty acid intake and allergic disease,[4 6 7 9] with a few studies examining the effect on asthma. There is very limited evidence of the effect of individual fatty acid intake on lung function or COPD. In this study, we have therefore used data from an established cross sectional survey to investigate the relation between estimated intakes of individual fatty acids measured by food frequency questionnaire and lung function measure, as forced expiratory volume in 1 s (FEV_1). We have also investigated the relation between individual fatty acids and the occurrence of self-reported wheeze, doctor diagnosed asthma and of chronic cough and breathlessness as markers of COPD.

METHODS

Study population

The MORGEN-EPIC study is a cross sectional investigation into the prevalence of, and risk factors for, chronic disease in a random sample of adults aged 20–59 years from three towns in The Netherlands (Amsterdam, Doetinchem and Maastricht) studied between 1994 and 1997.[10 11] Just over 17 000 subjects were available for inclusion in the current analyses but data were missing or incomplete in 3713 individuals for lung function (lung function was not measured for practical reasons in 1635, and technically unacceptable or non-reproducible FEV_1 measurements were found in 1493 subjects), pregnancy excluded an additional 84 and there were missing data on exposure or confounders in 310 individuals. The final study population included in the present analyses therefore comprised 13 820 subjects.

Data collection

Participants completed two self-administered questionnaires. One of these was a 178 item food frequency questionnaire developed and validated for this research project as part of the European Prospective Investigation into Cancer and Nutrition[12 13] and which provided estimates of

individual fatty acid intakes. These included the n-3 fatty acids c18:3 n-3 α-linolenic acid, c20:5 n-3 eicosapentaenoic acid (EPA), c22:5 n-3 docosapentaenoic acid (DPA3) and c22:6 n-3 docosahexaenoic acid (DHA), and the n-6 fatty acids c18:2 n-6 linoleic acid, c20:2 n-6 eicosadienoic acid, c20:3 n-6 dihomo-gamma linolenic acid, c20:4 n-6 arachidonic acid, c22:4 n-6 docosatetraenoic acid (DTA) and c22:5 n-6 docosapentaenoic acid (DPA6). The total intake of trans fatty acids was also estimated. The other questionnaire collected information on demographic variables, smoking history, physical activity, socioeconomic status, environmental factors, and self-reported respiratory symptoms and diagnosed disease. The respiratory symptom questions were derived from those used in the Dutch components of the European Community Respiratory Health Survey.[14 15]

Lung function was measured by trained paramedics using a heated pneumotachometer (E Jaeger, Wurzburg, Germany) in a seated upright position. The best of at least three technically acceptable measurements, of which two were reproducible according to the criteria of the European Respiratory Society,[16] was accepted for inclusion in the analysis. Both FEV_1 and forced vital capacity (FVC) were recorded. Height (to within 0.5 cm) and weight (to within 1 kg) were measured and used to calculated body mass index (BMI kg/m^2), which was then recoded into four categories: <20, 20–25, 25–30 and ⩾30.

Statistical analyses

The relation between individual fatty acids and lung function (FEV_1) was modelled using linear regression. Each individual fatty acid effect was examined for linearity and since the majority were non-linear, intakes were analysed in quintiles. FEV_1 was modelled initially with adjustment for age, age squared, sex, height and smoking (both current status and pack-years). Other models for FEV_1 were examined and produced similar results and therefore the above model was retained.

Table 1 Characteristics of the population used in the analyses (n = 13 820)

	n (%)	Mean (SD)
Sex		
Male	6354 (46)	
Female	7466 (54)	
Age (y)		42.2 (11.2)
Smoking		
Never	4679 (34)	
Ex	4056 (29)	
Current	5085 (37)	
Pack-years*		12.2 (4.5, 22.5)
BMI (kg/m^2)		24.9 (3.9)
Energy intake (MJ/day)		9.5 (2.9)
FEV_1 (l)		3.6 (0.9)
Wheeze†	1872 (14)	
Asthma†	432 (3)	
Other respiratory symptoms†	2170 (16)	
COPD (n = 13189)†	533 (4.0)	

*Median and interquartile range (data presented only for ex-smokers and current smokers).
†Wheeze was defined as wheeze in the past 12 months. Asthma was defined as a self-reported doctor diagnosis. Other respiratory symptoms was defined by having one or more of the following symptoms: chronic cough (cough during the winter time on most days for at least 3 months), chronic phlegm (productive cough during the winter time for at least 3 months a year) or breathlessness (shortness of breath when walking on level ground with people of same age) and COPD defined as GOLD stage 2 or higher.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s.

Adjustment for a number of potential confounding variables including BMI, education level, supplement use, antioxidant intake (vitamin C, vitamin E and beta-carotene), energy intake, place of residence and physical activity was explored and those variables which influenced effect estimates by more that 10% were retained in the analysis. Individual fatty acids that were significantly associated with FEV_1 were then included together in a mutually adjusted model to determine the strongest independent effects using backward regression. The new mutually adjusted model was then checked using forward regression for each of the other fatty acids that were not individually significantly associated with FEV_1 and retaining any that were now significantly associated, and these models were investigated for multicollinearity within the models. In addition, a correlation matrix was also examined to determine which individual fatty acids were strongly correlated, and then the mutually adjusted model was re-investigated using this information.

As previous studies have suggested that the effects of fatty acids might differ with smoking status, we tested each of the fatty acid effects for interactions with smoking status. For this analysis, fatty acid intakes were recategorised as binary exposures by dividing the data above and below the median levels of intake. FVC was examined using a similar approach. Using logistic regression, a similar modelling strategy was used to examine the relation between individual fatty acids and wheeze, doctor diagnosed asthma, presence of other respiratory symptoms (defined as having one or more of the following symptoms: chronic cough (cough during the winter time on most days for at least 3 months a year), chronic phlegm (productive cough during the winter time for at least 3 months a year) or breathlessness (shortness of breath when walking on level ground with people of same age)) and COPD global initiative for chronic obstructive lung disease (GOLD) stage 2 or higher[17] (determined using lung function data and creating per cent predicted by modelling lung function in the non-smokers, and non-asthmatics but not post-bronchodilator). Each fatty acid was investigated for a linear association with the respiratory outcome and then these associations were examined for potential confounding factors, including age, sex, smoking, BMI, energy intake and other potential confounders, as mentioned previously. To explore the extent of any impact of multiple hypothesis testing, we also assessed our results in relation to a p value of 0.005, the value obtained by applying the Bonferroni correction for testing 11 different individual fatty acids in our analyses. All analyses were conducted using Stata (V.8, College Station, Texas, USA).

RESULTS

The 13 820 subjects included in the analysis had a mean age of 42 (SD 11) years, 54% were females, 34% were current smokers and 29% ex-smokers (table 1). There were no appreciable differences in these characteristics from subjects excluded because of incomplete data (data not shown). Fourteen per cent of participants had wheeze in the past 12 months; 16% reported other respiratory symptoms in the past year, 3% a doctor diagnosis of asthma, 4% GOLD stage 2 or higher COPD (not post-bronchodilator) and 8% of the population more than one respiratory diagnosis. A summary of the levels of individual fatty acid intake is shown in table 2.

No statistically significant associations were observed between intakes of most of the n-3 fatty acids and FEV_1 (table 3). Contrary to expectations, increased intake of DHA was significantly associated with a lower FEV_1; the highest

Table 2 Summary of the intake of individual fatty acids (g/day) (n = 13 820)

	Mean (g/day)	SD	Median	20th, 80th centile
n-3 fatty acids				
c18:3 (n-3) α-Linolenic acid	1.27	0.55	1.16	0.84, 1.62
c20:5 (n-3) Eicosapentaenoic acid (EPA)	0.05	0.05	0.03	0.01, 0.07
c22:5 (n-3) Docosapentainoic acid (DPA3)	0.011	0.013	0.007	0.002, 0.017
c22:6(n-3) Docosahexaenoic acid (DHA)	0.10	0.08	0.08	0.04, 0.14
n-6 fatty acids				
c18:2 (n-6) Linoleic acid	13.8	5.9	12.7	9.0, 17.9
c20:2 (n-6) Eicosadienoic acid	0.05	0.03	0.04	0.02, 0.07
c20:3 (n-6) Eicosatrienoic acid or dihomo-gamma linolenic acid	0.01	0.007	0.012	0.008, 0.019
c20:4 (n-6) Arachidonic acid	0.09	0.04	0.08	0.05, 0.12
c22:4 (n-6) Docosatetraenoic acid (DTA)	0.01	0.007	0.011	0.006, 0.017
c22:5 (n-6) docosapentaenoic acid (DPA6)	0.003	0.007	0.0007	0.0001, 0.004
Trans fatty acid	3.8	1.9	3.4	2.3, 4.9

quintile of intake was associated with 39.3 ml (95% CI −64.8 to −13.8) lower FEV_1 compared with the lowest quintile of intake. There were no interactions between n-3 fatty acid effects and smoking status.

In general, higher levels of intake of n-6 polyunsaturated fatty acids were associated with lower FEV_1 (table 4). The only exception to this was increased c22:5 (n-6) DPA6 intake, which was associated with higher FEV_1, particularly in the fourth and fifth quintiles of intake (27.1 (95% CI 1.4 to 52.7) ml and 40.5 (95% CI 14.4 to 66.6) ml, respectively). Six of the n-6 fatty acids demonstrated significant interactions with smoking status (table 5), each having the strongest effects in smokers and ex-smokers and no effect in never smokers.

The final model for FEV_1 included adjustment for age, age squared, sex, smoking (status and pack-years), BMI, energy intake, vitamin C intake and education status. Other nutrients, including beta-carotene and vitamin E, were also investigated as potential confounders but only vitamin C was included in the model as it was most strongly associated with lung function and had the biggest impact on the effect estimates for the individual fatty acids. The exclusion of 9537 participants who reported using supplements did not alter the findings. In a mutually adjusted model, only linoleic acid, DTA and DPA6 remained as important independent predictors of lung function and their adjusted estimates for differences in FEV_1 between the 5th and 1st quintiles of intake were reduced slightly, to −32.2 ml (95% CI −64.9 to −0.42), −50.9 ml (95% CI −78.2 to −23.5) and 33.4 ml (95% CI 7.0 to 59.7), respectively. However, there were strong correlations between three of the significantly associated n-6 fatty acids (c20:2 (n-6) eicosadienoic acid, c20:4 (n-6) arachidonic acid and c22:4 (n-6) DTA, r>0.7) so that their effects in the mutually adjusted model were highly

Table 3 Association between individual n-3 fatty acids and forced expiratory volume in 1 s (ml)

n-3 fatty acid		β* (ml)	β† (ml)	95% CI	p Value
c18:3 n-3 α-Linolenic acid	1	0	0		0.14
	2	36.4	28.3	2.8 to 53.8	
	3	29.4	17.3	−9.2 to 43.8	
	4	11.7	2.1	−25.9 to 30.0	
	5	29.7	18.0	−14.3 to 50.2	
c20:5 n-3 Eicosapentaenoic acid (EPA)	1	0	0		0.28
	2	−3.4	−14.6	−40.0 to 10.4	
	3	−6.2	−22.8	−48.0 to 2.3	
	4	−7.7	−25.1	−50.3 to 0.2	
	5	2.1	−22.9	−48.5 to 2.7	
c22:5 n-3 Docosapentainoic acid (DPA3)	1	0	0		0.29
	2	−13.6	−22.6	−47.6 to 2.4	
	3	−8.8	−20.7	−45.8 to 4.4	
	4	−7.3	−22.9	−48.1 to 2.3	
	5	−4.3	−24.0	−49.4 to 1.3	
c22:6 n-3 Docosahexaenoic acid (DHA)	1	0	0		0.04
	2	−13.9	−17.8	−42.8 to 7.2	
	3	−16.2	−26.6	−51.8 to −1.5	
	4	1.3	−13.5	−38.7 to 11.7	
	5	−24.0	−39.3	−64.8 to −13.8	
Trans fatty acid	1	0	0		0.54
	2	−6.2	−7.4	−33.0 to 18.2	
	3	−1.6	−4.8	−31.8 to 22.2	
	4	−21.9	−23.5	−52.6 to 5.7	
	5	−20.2	−19.0	−54.0 to 16.0	

*Adjusted age, age squared, sex, smoking, pack-year, height.
†Adjusted age, age squared, sex, smoking, pack-years, height, energy intake, vitamin C, body mass index and education status.

Table 4 Association between individual n-6 fatty acids and forced expiratory volume in 1 s (ml)

n-6 fatty acid		β* (ml)	β† (ml)	95% CI	p Value
c18:2 (n-6) Linoleic acid	1	0	0		0.02
	2	5.1	−7.7	−33.2 to 17.9	
	3	14.6	−0.2	−26.6 to 26.3	
	4	26.9	5.1	−22.9 to 33.1	
	5	−9.2	−38.1	−70.7 to −5.5	
c20:2 (n-6) Eicosadienoic acid	1	0	0		0.04
	2	−17.1	−15.3	−40.5 to 9.9	
	3	−28.3	−24.5	−50.2 to 1.3	
	4	−23.8	−16.2	−42.7 to 10.3	
	5	−55.7	−45.4	−74.3 to −16.5	
c20:3 (n-6) Eicosatrienoic acid or dihomo-gamma linolenic acid	1	0	0		0.67
	2	3.5	4.2	−21.1 to 29.6	
	3	−7.4	−4.4	−30.4 to 21.6	
	4	−0.5	2.8	−24.1 to 29.8	
	5	−22.6	−14.2	−43.4 to 14.9	
c20:4 (n-6) Arachidonic acid	1	0	0		0.0005
	2	15.6	16.4	−8.8 to 41.6	
	3	4.2	4.9	−20.7 to 30.5	
	4	−9.8	−8.8	−35.2 to 17.6	
	5	−44.3	−41.8	−70.0 to −13.6	
c22:4 n-6 Docosatetraenoic acid (DTA)	1	0	0		<0.0001
	2	−13.6	−11.2	−36.3 to 13.9	
	3	1.2	2.9	−22.6 to 28.3	
	4	−7.0	−2.0	−28.0 to 24.0	
	5	−62.9	−54.5	−81.6 to −27.4	
c22:5 (n-6) Docosapentaenoic acid (DPA6)	1	0	0		0.0003
	2	7.7	2.7	−22.3 to 27.7	
	3	−2.8	−11.3	−36.6 to 13.9	
	4	40.4	27.1	1.4 to 52.7	
	5	59.6	40.5	14.4 to 66.6	

*Adjusted age, age squared, sex, smoking, pack-year, height.
†Adjusted age, age squared, sex, smoking, pack-years, height, energy intake, vitamin C, body mass index and education status.

Table 5 Association between individual n-6 fatty acids and forced expiratory volume in 1 s (ml) according to smoking status

		Never smokers		Ex-smokers		Current smokers	
	p Value interaction	β* (ml)	(95% CI)	β* (ml)	(95% CI)	β* (ml)	(95% CI)
c20:2 (n-6) Eicosadienoic acid	0.02	0		0		0	
		8.9	(−31.6 to 49.4)	−27.3	(−74.1 to 19.5)	−20.3	(−64.4 to 23.9)
		12.9	(−29.3 to 55.1)	−36.5	(−83.9 to 11.0)	−37.8	(−82.7 to 7.1)
		34.0	(−9.9 to 77.9)	−70.3	(−119.4 to −21.2)	−7.2	(−52.8 to 38.4)
		21.0	(−28.4 to 70.4)	−66.6	(−120.1 to −13.2)	−72.9	(−121.4 to −24.4)
c20:3 (n-6) Eicosatrienoic acid or dihomo-gamma linolenic acid	0.005	0		0		0	
		−6.4	(−46.9 to 34.1)	36.1	(−11.5 to 83.7)	−7.8	(−52.0 to 36.4)
		13.9	(−28.0 to 55.7)	5.0	(−43.4 to 53.5)	−24.4	(−69.7 to 21.0)
		48.9	(4.8 to 93.0)	−24.5	(−75.0 to 26.0)	−8.7	(−54.9 to 37.5)
		35.1	(−14.8 to 84.9)	−15.8	(−70.1 to 38.5)	−44.6	(−93.2 to 4.1)
c20:4 (n-6) Arachidonic acid	0.01	0		0		0	
		37.7	(−3.0 to 78.3)	−4.1	(−51.0 to 42.8)	19.4	(−24.8 to 63.6)
		31.3	(−10.2 to 72.8)	−24.7	(−72.7 to 23.4)	14.2	(−30.2 to 58.7)
		51.9	(8.6 to 95.2)	−34.2	(−83.8 to 15.4)	−30.2	(−75.4 to 15.1)
		9.6	(−38.5 to 57.6)	−68.1	(−120.8 to −15.4)	−60.1	(−107.4 to −12.8)
c22:4 n-6 Docosatetraenoic acid (DTA)	0.05	0		0		0	
		24.0	(−17.4 to 65.4)	−39.3	(−86.5 to 7.9)	−24.6	(−67.2 to 18.1)
		58.8	(17.2 to 100.4)	−41.8	(−88.9 to 5.3)	−10.4	(−54.4 to 33.7)
		66.0	(22.8 to 109.2)	−59.5	(−107.8 to −11.2)	−8.2	(−52.3 to 35.9)
		6.0	(−39.7 to 51.7)	−73.7	(−124.4 to −22.9)	−87.8	(−133.2 to −42.5)
c22:5 (n-6) Docosapentaenoic acid (DPA6)	0.0008	0		0		0	
		15.9	(−29.2 to 61.1)	3.6	(−41.7 to 49.0)	−7.7	(−48.2 to 32.7)
		−12.9	(−57.6 to 31.9)	12.4	(−33.8 to 58.6)	−21.0	(−62.1 to 20.1)
		13.2	(−31.0 to 57.4)	44.7	(−2.9 to 92.2)	28.8	(−13.9 to 71.5)
		28.2	(−16.0 to 72.3)	48.4	(1.3 to 95.6)	42.9	(−2.7 to 88.5)

*Adjusted age, age squared, sex, smoking, pack-years, height, energy intake, vitamin C and education status.

collinear. When each was examined separately in the mutually adjusted model, both DTA and arachidonic acid had significant effects and when the other was removed from the model, however, eicosadienoic acid was no longer significant in the mutually adjusted model without the other correlated fatty acids in the model. Broadly similar findings emerged from analyses of FVC as the outcome (data not shown). After applying the Bonferroni correction, three of the n-6 fatty acids (arachidonic acid, DTA and DPA6) would have been considered significantly related to FEV_1; none of the n-3 fatty acid effects remained significant.

Overall there was no consistent pattern of association between intake of individual fatty acids and respiratory symptoms or diagnosed asthma (table 6). Contrary to expectations and irrespective of allowance for multiple hypothesis testing, increased intakes of the n-3 fatty acids α- linolenic, EPA, DPA3 and DHA were associated with a small (approximately 20%) but significant increase in the risk of wheeze in the past year in the 5th versus the 1st quintiles of intake. However, intakes of n-3 or n-6 fatty acids were predominately not otherwise associated with doctor diagnosed asthma or other respiratory symptoms, with the exceptions of increased intake of α- linolenic acid, which was also associated with an increased risk of disease, and intake of DPA6 which was associated with a risk of disease. Increased intake of four of the n-6 fatty acids was associated with an increased risk of COPD, and similar results to FEV_1 increased intake of DPA3 was protective against COPD. Again, if we apply the Bonferroni correction, only the n-3 fatty acids increased association with wheeze would be considered statistically significant associations.

DISCUSSION

The findings of this study indicate that in general, higher intakes of individual n-6 fatty acids (particularly linoleic acid, eicosadienoic acid, arachidonic acid and DTA) were associated with impairment of FEV_1, and that these effects tended to be stronger in smokers than in never smokers. The exception to this was that increased intake of the n-6 fatty acid DPA6 was associated with higher FEV_1. Contrary to expectations on the grounds of previous evidence,[18–29] intake of the n-3 fatty acid DHA was associated with a lower FEV_1, while the other n-3 fatty acids investigated were unrelated to lung function. Only the effects of three n-6 fatty acids (arachidonic, DTA and DPA6) remained significant after applying the Bonferroni correction. Increased intakes of n-3 fatty acids did not appear to reduce the occurrence of doctor diagnosed asthma, current wheeze or other respiratory symptoms; in fact, increased intakes of α-linolenic acid, EPA, DPA3 and DHA were associated with a small but significant increase in risk of wheeze, while increased intakes of four of the n-6 fatty acids were associated with an increased risk of COPD.

As intake of fatty acids has changed dramatically over the past 30 years in many developed countries it is important to understand how these changes in diet may have impacted on lung health. In this study we were able to investigate the relation between intakes of a number of different individual fatty acids and lung function in a large cross sectional population. Even after adjusting for potential confounding factors, the size of the observed effects on FEV_1 we observed remained consistent, suggesting that these are true effects. If we allow for the multiple comparisons inevitably involved in exploring the effects of this range of individual fatty acid intakes the overall message from the paper is similar, that n-3 fatty acids were unrelated to FEV_1, but that several n-6 fatty acids were associated with a decrease in lung function. The exception was DPA6, which was associated with higher lung function. Intake of four of the n-3 fatty acids was associated with an increased risk of wheeze in the past year, however, we also must recognise the limitations of using adjusted p values which could potentially lead to type II error.[30] We recognise that a large number of participants were using some form of supplements (not all would include fatty acids) but adjustment for this or stratification by this factor did not alter the results. We also acknowledge that estimates of dietary intake from food frequency questionnaires are qualitatively imprecise, but that they are good for determining the relative ranking of intakes between individuals. The questionnaire we used has been thoroughly validated[12] and we have previously demonstrated

Table 6 Association between individual fatty acids and respiratory symptoms, presented as effect from 5th to 1st quintile and p value for trend

	Wheeze*		Asthma*		Other respiratory symptoms*		COPD (GOLD stage 2 or higher)*	
	OR† (95% CI)	p Value	OR† (95% CI)	p Value	OR† (95% CI)	p Value	OR† (95% CI)	p Value
n-3 fatty acids								
c18:3 (n-3) α-Linolenic acid	1.2 (1.0 to 1.4)	0.009	1.1 (0.9 to 1.4)	0.02	1.2 (0.8 to 1.7)	0.42	1.07 (0.74 to 1.55)	0.49
c20:5 (n-3) Eicosapentaenoic acid (EPA)	1.2 (1.1 to 1.5)	0.005	1.2 (1.0 to 1.3)	0.13	1.3 (1.0 to 1.7)	0.26	0.84 (0.63 to 1.11)	0.19
c22:5 (n-3) docosapentainoic acid (DPA3)	1.3 (1.1 to 1.5)	0.008	1.1 (0.9 to 1.2)	0.71	1.3 (0.9 to 1.7)	0.55	0.75 (0.56 to 0.99)	0.11
c22:6 (n-3) Docosahexaenoic acid (DHA)	1.2 (1.0 to 1.4)	0.007	1.1 (1.0 to 1.3)	0.23	1.0 (0.8 to 1.4)	0.96	0.95 (0.71 to 1.25)	0.50
n-6 fatty acids								
c18:2 (n-6) Linoleic acid	1.1 (0.9 to 1.4)	0.27	1.1 (0.9 to 1.3)	0.28	0.8 (0.6 to 1.2)	0.44	0.95 (0.68 to 1.34)	0.27
c20:2 (n-6) Eicosadienoic acid	1.1 (0.9 to 1.3)	0.32	0.9 (0.8 to 1.1)	0.22	1.4 (1.0 to 1.9)	0.13	1.85 (1.32 to 2.58)	0.001
c20:3 (n-6) Eicosatrienoic acid or dihomo-gamma linolenic acid	1.0 (0.8 to 1.2)	0.61	0.9 (0.7 to 1.0)	0.10	1.3 (1.0 to 1.9)	0.07	1.56 (1.12 to 2.17)	0.01
c20:4 (n-6) Arachidonic acid	1.1 (0.9 to 1.3)	0.16	1.2 (1.0 to 1.4)	0.14	1.1 (0.8 to 1.5)	0.49	1.63 (1.20 to 2.22)	0.002
c22:n-6 Docosatetraenoic acid (DTA)	1.0 (0.9 to 1.2)	0.82	1.0 (0.9 to 1.2)	0.78	1.3 (0.9 to 1.8)	0.15	1.65 (1.22 to 2.22)	0.001
c22:5 (n-6) docosapentaenoic acid (DPA6)	1.0 (0.8 to 1.1)	0.81	0.8 (0.7 to 1.0)	0.01	1.2 (0.9 to 1.7)	0.42	0.71 (0.53 to 0.96)	0.036
Trans fatty acid	1.1 (0.9 to 1.3)	0.40	1.1 (0.9 to 1.4)	0.25	1.3 (0.8 to 1.8)	0.58	1.38 (0.95 to 2.02)	0.15

*Wheeze was defined as wheeze in the past 12 months. Asthma was defined as a self-reported doctor diagnosis. Other respiratory symptoms was defined by having one or more of the following symptoms: chronic cough (cough during the winter time on most days for at least 3 months), chronic phlegm (productive cough during the winter time for at least 3 months a year) or breathlessness (shortness of breath when walking on level ground with people of same age), and COPD defined as GOLD stage 2 or higher.
†Adjusted age, age squared, sex, smoking, pack-year, height, body mass index and energy intake.
COPD, chronic obstructive pulmonary disease.

that a food frequency questionnaire can estimate dietary intake of many individual fatty acids reliably.[31] One other potential explanation for our findings is that the variability in the Dutch diet is not sufficient to allow us to detect an effect, particularly for the n-3 fatty acids as the intakes of these fatty acids was relatively low and it may be a certain level needs to be reached for a protective effect to be achieved or that the range of intake (and thus possibly the size of the relative risk) is too small to detect an association in this study population.

There is only limited evidence on the relation between individual fatty acids and lung function. A recent study examined the relation between four individual fatty acids and FEV_1 in children, and found results similar to ours such that increased levels of two n-6 fatty acids, linoleic acid and arachidonic acid in serum cholesteryl esters, were associated with a significant decrease in lung function whereas the two n-3 fatty acids, α-linolenic acid and EPA, were not associated with FEV_1.[32] Most other previous studies have used less specific measures of fatty acid exposure; for example, one study demonstrated that increased fish intake was associated with increased FEV_1 in a general population, suggesting (but not proving) a protective effect through n-3 fatty acids in fish.[33] Another study in a general population sample found that increased intake of n-3 fatty acid was associated with higher lung function in smokers, but not never smokers, and that increased intake of the n-3 fatty acids decreased the risk of chronic bronchitis, physician diagnosed emphysema and spirometry detected COPD in ever smokers.[3]

Epidemiological evidence on the relation between individual fatty acids and respiratory symptoms or disease is also inconsistent. One cross sectional study in young adults found evidence that higher plasma n-6 fatty acid increased the risk of asthma, with 20:3 n-6 (DHGLA) in particular being associated with a higher risk of current asthma, self-reported asthma and doctor diagnosed asthma.[22] Other n-6 fatty acids, including 20:2 and 22:5, were associated with an increased risk of at least one of the definitions of asthma or atopy.[22] This study also found that of the four n-3 fatty acids that were measured, only DPA (22:5 n-3) demonstrated a significant association with disease and, rather than a protective effect as hypothesised, higher intakes were associated with an increased risk of self-reported asthma. Evidence from case control or cohort studies is also mixed. In four studies, higher levels of individual n-3 fatty acid were found to be associated with a decreased risk of disease,[23–25] in three studies increased levels of n-6 fatty acids were observed in patients with asthma,[23 25 26] in two studies the ratio of n-6/n-3 fatty acids increased the risk of wheeze or asthma[34 35] and 10 studies found other results generally contrary to or inconclusive of the hypothesis that n-3 fatty acids protect or n-6 fatty acids increased the risk of asthma.[21 23–26 34 36–39]

Evidence from randomised controlled trials of n-3 supplementation in patients with asthma has also produced differing results. The most dramatic beneficial effect is demonstrated in subjects with exercise induced bronchoconstriction, in whom supplementation with n-3 fatty acid significantly reduced the fall in FEV_1 following exercise.[27 40] Other studies found a positive effect in patients with asthma on respiratory health following supplementation.[19 20 28 29] In contrast, a number of studies have found no change in respiratory health following supplementation[41–47] but two of these did find a reduction in leukotrienes,[41 42] another study found a reduction in thromboxane b2 with supplementation of n-3 fatty acids[47] and finally one study found a reduction in tumour necrosis factor α in the group supplemented with n-3 fatty acids.[46]

The current evidence for the effect of dietary trans fatty acids on respiratory health is very limited. The first study to address this issue was an ecological analysis which demonstrated a positive correlation between intake of trans fatty acids and the prevalence of asthma, eczema and hay fever.[48] These findings were partially supported by data from a cross sectional survey which found that increased margarine consumption was association with an increased risk of allergic sensitisation and allergic rhinitis in boys, although there was no association with asthma.[49] However, the PIAMA birth cohort study found no association between margarine intake at age 2 years and asthma or recent wheeze at age 3 years.[50]

A clear understanding of the association between individual fatty acids and respiratory health has thus yet to emerge. Some potential reasons for the inconsistency in evidence to date is that a variety of different methods have been used to measure fatty acids, different populations have been studied and a range of different individual fatty acids intakes have been measured. The relation between individual fatty acids and respiratory disease might also be different through the life course of an individual, and may include different effects on the incidence versus the severity of disease. However, our main study findings suggest that n-3 fatty acid intake does not have a major protective effect on lung function or disease symptoms, but that n-6 acids have a predominantly adverse effect on lung function. The effects of fatty acids on lung disease may therefore be more complex than has previously been thought.

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