Inflammatory bowel disease

Linoleic acid, a dietary n-6 polyunsaturated fatty acid, and the aetiology of ulcerative colitis: a nested case–control study within a European prospective cohort study

The IBD in EPIC Study Investigators

ABSTRACT

Objective: Dietary linoleic acid, an n-6 polyunsaturated fatty acid, is metabolised to arachidonic acid, a component of colonocyte membranes. Metabolites of arachidonic acid have pro-inflammatory properties and are increased in the mucosa of patients with ulcerative colitis. The aim of this investigation was to conduct the first prospective cohort study investigating if a high dietary intake of linoleic acid increases the risk of developing incident ulcerative colitis.

Design and setting: Dietary data from food frequency questionnaires were available for 203 193 men and women aged 30–74 years, resident in the UK, Sweden, Denmark, Germany or Italy and participating in a prospective cohort study, the European Prospective Investigation into Cancer and Nutrition (EPIC). These participants were followed up for the diagnosis of ulcerative colitis. Each case was matched with four controls and the risk of disease calculated by quartile of intake of linoleic acid adjusted for gender, age, smoking, total energy intake and centre.

Results: A total of 126 participants developed ulcerative colitis (47% women) after a median follow-up of 4.0 years (range, 1.7–11.3 years). The highest quartile of intake of linoleic acid was associated with an increased risk of ulcerative colitis (odds ratio (OR) = 2.49, 95% confidence interval (CI) = 1.23 to 5.07, p = 0.01) with a significant trend across quartiles (OR = 1.32 per quartile increase, 95% CI = 1.04 to 1.66, p = 0.02 for trend).

Conclusions: The data support a role for dietary linoleic acid in the aetiology of ulcerative colitis. An estimated 30% of cases could be attributed to having dietary intakes higher than the lowest quartile of linoleic acid intake.

Ulcereative colitis is a chronic condition that produces distressing symptoms, impairs patients’ quality of life and is associated with an increased risk of complications such as colorectal cancer.¹ The causes of ulcerative colitis are unknown although it is plausible that dietary n-6 polyunsaturated fatty acids (n-6 PUFAs) could be involved. The essential n-6 PUFA, linoleic acid, is present in many sources including red meat, various cooking oils and certain margarines. Linoleic acid undergoes metabolic conversion to a further n-6 PUFA, arachidonic acid, which is a component of colonic cell membranes. Arachidonic acid can be released from this phospholipid membrane and metabolised to pro-inflammatory eicosanoids including prostaglandin E₂, leukotriene B₄ and thromboxane A₂. These eicosanoids are present in excess in the mucosa of patients with ulcerative colitis and in animal models of the disease.² ³ The concentrations correlate with the degree of histological inflammation⁴ and medications containing 5-aminosalicylic acid inhibit their formation.⁵ Data from epidemiological studies are needed to examine the linoleic acid hypothesis generated from the experimental and clinical observations. Several such investigations have reported a positive association with an increased total polyunsaturated fatty acid intake.⁶ ⁷ However, only one used a prospective cohort design,⁷ and just one, a retrospective case–control investigation, specifically investigated linoleic acid consumption.⁶

The aim of this study was to conduct the first prospective cohort investigation of dietary linoleic acid intake and the risk of developing incident ulcerative colitis. Participants were enrolled in the European Prospective Investigation into Cancer and Nutrition (EPIC) study⁸ which recruited a total of 519 978 volunteers in 23 centres in 10 countries. Participants provided information on diet and lifestyle and were followed up for health endpoints including ulcerative colitis. The methodological advantages of this prospective cohort design over retrospective case–control work, are that the dietary information is more accurate, as current intake is recalled which is less affected by recall bias. Additionally, the cohort design avoids potential selection biases, as those who develop ulcerative colitis and those who remain disease-free are drawn from the same population.

METHODS

Participants were resident in seven regions in five European countries. These EPIC sub-cohorts constituted 203 193 men and women in the age range 30–74 years (table 1). At recruitment, between 1991 and 1998, participants provided information on diet, physical activity, and other lifestyle factors such as smoking and alcohol intake. Diet was measured by country-specific food frequency questionnaires (FFQs) that were designed to capture local dietary habits and to give high compliance. Nutrient intake was calculated by multiplying the frequency of consumption of relevant foods by their fatty acid content as determined from national databases of food content. The dietary fatty acids which were calculated were: linoleic acid (n-6 PUFA), α-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid (n-3 PUFAs) and oleic acid (an n-9 monounsaturated fatty acid). In all

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centres, the FFQs were validated against 24 h recall questionnaires and most centres also compared their questionnaire data against plasma and urinary biomarkers for specific nutrients including vitamin C, vitamin E and protein. The research protocols were approved by ethics committees in each centre and all participants gave written informed consent.

Incident cases of ulcerative colitis which developed in participants who were initially free of the disease were identified by several methods. These were disease registries of inflammatory bowel disease in Italy, Sweden and Denmark, from follow-up questionnaires in Germany and in the Norfolk, UK, cohort by a combination of follow-up questionnaires and hospital inpatient and pathology databases. For each case, physicians were asked to confirm the diagnosis of ulcerative colitis according to whether there was information available from radiological, endoscopic and histological reports. Information on both the extent of colonic inflammation and the investigations used to confirm disease were collected. Prevalent cases of ulcerative colitis at recruitment were excluded as well as participants who were diagnosed less than 18 months after recruitment into the EPIC study. This helped to ensure that the dietary data reflected participants’ dietary intake prior to the development of symptoms. Incident cases were identified up to the end of June 2004 for most centres.

In the analysis, using a nested case–control method within a prospective cohort study, each case was matched with four randomly selected controls (from the same centre), of the same gender, date of birth (±6 months) and date of recruitment into EPIC (±3 months). Controls were alive on the date when the matched case was diagnosed. The last two criteria ensured that the periods of follow-up for both cases and controls were similar. The dietary intakes of linoleic acid and the other fatty acids were divided into gender-specific quartiles from the distribution across both cases and controls. A multivariate analysis was performed, using unconditional logistic regression, adjusting for age at recruitment, gender, total energy intake, cigarette smoking and centre. Energy adjustment helps to account for variables which affect dietary intake, namely body mass index, metabolic rate and physical activity. Smoking was included in the analysis due to the observed inverse association with the risk of ulcerative colitis. Only one measure of smoking was used, namely that at recruitment. Adjustment for centre helps correct for possible differences in the methodology of the food frequency questionnaires between countries. Finally, the odds ratios for the individual fatty acids were adjusted for each of the four other fatty acids, for the centres for which complete data was available. The rationale for this was that oleic acid and α-linolenic acid competitively inhibit the metabolism of linoleic acid and reduce the formation of arachidonic acid. Additionally, the n-3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid have anti-inflammatory properties. The quoted p values for levels of statistical significance were two-sided. The attributable fraction, namely the percentage of all cases of ulcerative colitis attributed to the higher three intakes of dietary linoleic acid, was calculated using the formula, attributable fraction = (OR − 1/OR) * % cases in that quartile. The data were analysed by A Hart and R Luben using the STATA statistical package. A full cohort analysis was not used in this study as for some countries there were no regional or national databases of patients with inflammatory bowel disease; hence, here, case ascertainment may be incomplete. The hypothesis regarding linoleic acid, was an a priori one, developed approximately 2 years before the data on linoleic acid were analysed.

RESULTS
A total of 126 incident cases of ulcerative colitis were identified of which 47% were women. The age at diagnosis was known for 111 (88%) cases with the median age being 60.0 years (range, 39.6–80.8 years) with a median time between recruitment and

<table>
<thead>
<tr>
<th>Centre and country</th>
<th>Size of cohort</th>
<th>Nature of cohort</th>
<th>No of participants identified with incident ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florence, Italy</td>
<td>13583</td>
<td>Population-based cohort, men and women aged 34–64 years. Recruitment between 1993 and 1996. Cases identified from regional databases of inflammatory bowel disease</td>
<td>8</td>
</tr>
<tr>
<td>Aarhus and Copenhagen, Denmark</td>
<td>57053</td>
<td>Population-based cohort of men and women aged 50–64 years. Recruited between 1993 and 1997. Cases identified from national databases of inflammatory bowel disease</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td>203193</td>
<td></td>
<td>126</td>
</tr>
</tbody>
</table>
acid, including prostaglandin E2, leukotriene B4 and thromboxane
taxis and release of lysosomal enzymes from neutrophils. 14–16

The highest quartile of intake of linoleic acid was associated
with an increased risk of ulcerative colitis (OR = 2.49, 95% CI = 1.25 to 5.07, p = 0.01) when adjusted for age at recruit-
ment, gender, centre, energy intake and cigarette smoking (table 2). Similarly, there was a statistically significant trend
across quartiles of linoleic acid intake (OR = 1.32 per quartile
increase, 95% CI = 1.04 to 1.66, p = 0.02). Furthermore, the
effect of linoleic acid intake adjusted for aspirin use, for which
data were available for 78.1% of subjects, still maintained the
statistically significant effect. Similarly, adjusting for educa-
tional level did not affect the results for linoleic acid. The
highest quartile of linoleic acid increased the risk of ulcerative
colitis in both genders, which was statistically significant in
women (OR = 3.47, 95% CI = 1.15 to 10.62, p = 0.05), but not
men (OR = 2.05, 95% CI = 0.80 to 5.26, p = 0.18). The results
were similar if only cases were analysed, for whom details of the
case recruitment did not affect the risk of incident ulcerative colitis
(0.6%) controls were. In this cohort, cigarette smoking at
before interview, reported that a high intake of total poly-
saturated fatty acids increased the risk of ulcerative colitis by
30%; ie, nearly a third of cases of ulcerative colitis could be attributed to the intake of that in the highest
three quartiles. The effect of linoleic acid intake, adjusted for
other fatty acids, for which complete data was available from
six of the seven centres, showed a similar effect size to the
previous analyses, although it was of borderline statistical significance (trend OR = 1.28, 95% CI = 0.97 to 1.68, p = 0.08).

The only other fatty acid for which an association was found
with the development of ulcerative colitis was a negative one
with an increasing dietary intake of the n-3 polynsaturated fatty acid, docosahexaenoic acid, when adjusted for the other
nutrients. For the highest quartile, the odds ratio was 0.23 (95%
CI = 0.06 to 0.97) with a significant negative trend across
quartiles (OR for trend = 0.59, 95% CI = 0.37 to 0.94, p = 0.03).

**DISCUSSION**

The main finding of this study was more than a doubling of the
risk of ulcerative colitis with the highest intake of the dietary n-6
PUFA, linoleic acid. If the association is causative then 30% of all
cases could be attributed to such higher intakes. This finding is
supported by plausible biological mechanisms. n-6 PUFAs are
present in colonocyte membranes as arachidonic acid (n-6-derived)
which can be released from cell membranes and metabolised to
prostaglandins, leukotrienes and thromboxanes. These have
immuno-stimulatory effects24–26 and may predispose to the
development of ulcerative colitis. The metabolites of arachidonic
acid, including prostaglandin E2, leukotriene B4 and thromboxane
A2, have pro-inflammatory effects including aggregation, chem-
okinesis and release of lysosomal enzymes from neutrophils.14–16

Thromboxanes have many actions including activation of
neutrophils,27 production of leukotriene B428 and modulation of
T cell function.29 A high dietary intake of n-6 PUFAs and their
metabolites, prostaglandin E2, leukotriene B4 and thromboxane
B2, are found in the colonic mucosa of patients with ulcerative
colitis.2 4 5 20 The degree of inflammatory cell infiltrate also
 correlates with the mucosal arachidonic acid concentration
(9 = 0.89, p < 0.08) in humans.2 Finally, the first-line drugs used
to treat ulcerative colitis, namely 5-aminosalicylic compounds,
suppress prostaglandin E2 levels in a dose-dependent manner.4

The positive association with linoleic acid was unlikely to be a
confounding effect of the other PUFAs, as adjustment for these,
did not alter the magnitude of the odds ratio. However, the p
value changed from a significant (p = 0.02) to a borderline
significant effect (p = 0.08) which may be due to a reduced
sample size for this particular analysis, as data on certain n-3
PUFAs were not available from one centre. Furthermore, the
intake of linoleic acid is likely to be lower in this southern
European centre than northern regions, making any true
differences more difficult to detect.

This investigation also found a statistically significant
negative association with an increasing dietary intake of
docosahexaenoic acid, when adjusted for the other fatty acids
which can affect its metabolism. The highest dietary intake of
this n-3 PUFA was associated with a 77% (95% CI = 53 to 94%)
reduction in the chances of developing ulcerative colitis. There
are several plausible biological mechanisms to support how,
through its anti-inflammatory properties, docosahexaenoic may
prevent colonic inflammation. These include promoting the
release of phospholipases D from membranes, which leads to
the activation of its anti-proliferative effects in lymphoid cells.31

The nutrients also inhibit protein kinase C,22 23 which decreases
the levels of secondary messengers involved in inflammation.
Finally, they may have a direct action on gene expression for
inflammatory mediators, as fish oil has such effects on several
tissues, including spleen lymphocytes.24 The independent effects
of linoleic and docosahexaenoic acid make confounding by
social class less likely, as both may be associated with higher
social classes.

The effect of total dietary polynsaturated fatty acids on the
risk of developing incident ulcerative colitis has been investig-
ated in only a few epidemiological studies.6–8 21 In the only
prospective investigation, again in this EPIC cohort, a marginal-
ly significant positive association was reported with an
increasing percentage intake of energy from the total of all
polysaturated fatty acids (trend across quartiles OR = 1.19
(95% CI = 0.99 to 1.43) p = 0.067).27 Three case–control studies
from Israel, Holland and Japan have investigated total
PUFAs,4 28 29 although by the nature of this study design, recall
bias may exist. The investigation from Israel of 54 patients with
ulcerative colitis, most of whom were diagnosed 3–4 months
before interview, reported that a high intake of total poly-
utsaturated fatty acids increased the risk of ulcerative colitis by
6.54 times (95% CI = 1.45 to 29.68).27 Similar results were
**Table 2** Odds ratios for developing ulcerative colitis by quartile of intake of specific polyunsaturated fatty acids (PUFAs)

<table>
<thead>
<tr>
<th>Macro-nutrient</th>
<th>Quartile of increasing intake</th>
<th>Quartile range</th>
<th>Unadjusted ORs (plus 95% CIs) for quartiles of intake*</th>
<th>Adjusted ORs (plus 95% CIs) for quartiles of intake†</th>
<th>Adjusted ORs (plus 95% CIs) for quartiles of intake‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linoleic acid (n-6 PUFA) (g/day)</td>
<td>1 (27, 131)</td>
<td>1.9–6.1</td>
<td>3.1–7.8</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>2 (31, 126)</td>
<td>6.2–8.8</td>
<td>7.9–11.3</td>
<td>1.21 (0.68 to 2.17)</td>
<td>1.38 (0.74 to 2.56)</td>
</tr>
<tr>
<td></td>
<td>3 (26, 132)</td>
<td>8.9–12.5</td>
<td>11.4–14.8</td>
<td>1.00 (0.54 to 1.85)</td>
<td>1.20 (0.61 to 2.38)</td>
</tr>
<tr>
<td></td>
<td>4 (41, 115)</td>
<td>12.6–37.5</td>
<td>14.9–35.4</td>
<td>1.85 (1.03 to 3.32)</td>
<td>2.49 (1.23 to 5.07)</td>
</tr>
<tr>
<td>α-Linolenic acid (n-3 PUFA) (g/day)</td>
<td>1 (33, 125)</td>
<td>0.4–0.9</td>
<td>0.5–1.0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>2 (24, 133)</td>
<td>1.0–1.2</td>
<td>1.1–1.5</td>
<td>0.68 (0.38 to 1.23)</td>
<td>0.78 (0.41 to 1.47)</td>
</tr>
<tr>
<td></td>
<td>3 (33, 125)</td>
<td>1.3–1.6</td>
<td>1.6–2.0</td>
<td>1.00 (0.57 to 1.75)</td>
<td>1.22 (0.63 to 2.39)</td>
</tr>
<tr>
<td></td>
<td>4 (35, 121)</td>
<td>1.7–3.7</td>
<td>2.1–5.0</td>
<td>1.11 (0.62 to 1.99)</td>
<td>1.46 (0.67 to 3.14)</td>
</tr>
<tr>
<td>Oleic acid (n-9 MUFA) (g/day)</td>
<td>1 (31, 127)</td>
<td>5.0–15.5</td>
<td>7.4–19.6</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>2 (28, 128)</td>
<td>15.6–20.7</td>
<td>19.7–26.2</td>
<td>0.88 (0.50 to 1.57)</td>
<td>0.97 (0.52 to 1.81)</td>
</tr>
<tr>
<td></td>
<td>3 (35, 123)</td>
<td>20.8–28.2</td>
<td>26.3–33.4</td>
<td>1.16 (0.6 to 2.03)</td>
<td>1.30 (0.63 to 2.66)</td>
</tr>
<tr>
<td></td>
<td>4 (31, 125)</td>
<td>28.3–69.8</td>
<td>33.5–78.4</td>
<td>1.02 (0.55 to 1.89)</td>
<td>1.21 (0.48 to 3.01)</td>
</tr>
<tr>
<td>Docosahexaenoic acid (n-3 PUFA) (g/day)</td>
<td>1 (34, 114)</td>
<td>0.0–0.10</td>
<td>0.00–0.11</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>2 (30, 117)</td>
<td>0.11–0.18</td>
<td>0.12–0.21</td>
<td>0.79 (0.43 to 1.44)</td>
<td>0.76 (0.41 to 1.41)</td>
</tr>
<tr>
<td></td>
<td>3 (24, 123)</td>
<td>0.19–0.32</td>
<td>0.22–0.40</td>
<td>0.57 (0.29 to 1.10)</td>
<td>0.53 (0.27 to 1.05)</td>
</tr>
<tr>
<td></td>
<td>4 (29, 118)</td>
<td>0.33–1.35</td>
<td>0.41–2.00</td>
<td>0.70 (0.3 to 1.37)</td>
<td>0.64 (0.32 to 1.30)</td>
</tr>
<tr>
<td>Eicosapentaenoic acid (n-3 PUFA) (g/day)</td>
<td>1 (30, 118)</td>
<td>0.0 1–0.04</td>
<td>0.00–0.05</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>2 (30, 117)</td>
<td>0.05–0.09</td>
<td>0.06–0.11</td>
<td>1.00 (0.54 to 1.86)</td>
<td>1.02 (0.54 to 1.90)</td>
</tr>
<tr>
<td></td>
<td>3 (27, 120)</td>
<td>0.10–0.16</td>
<td>0.12–0.18</td>
<td>0.87 (0.46 to 1.67)</td>
<td>0.86 (0.44 to 1.66)</td>
</tr>
<tr>
<td></td>
<td>4 (30, 117)</td>
<td>0.17–0.73</td>
<td>0.19–1.05</td>
<td>1.00 (0.52 to 1.91)</td>
<td>0.96 (0.49 to 1.88)</td>
</tr>
</tbody>
</table>

*Odds ratios (ORs) adjusted for age at recruitment into the European Prospective Investigation into Cancer and Nutrition (EPIC), gender and centre.
†Odds ratios adjusted for age at recruitment into EPIC, gender, centre, cigarette smoking and total energy intake.
‡Odds ratios adjusted for age at recruitment into EPIC, gender, centre, cigarette smoking, total energy intake and the other listed fatty acids.

Results in parentheses are number of cases and number of controls.

CI, confidence interval; MUFA, mono-unsaturated fatty acid.

This table shows the odds ratios for developing ulcerative colitis by quartile of intake of specific polyunsaturated fatty acids (PUFAs). The table includes data for linoleic acid, α-linolenic acid, oleic acid, docosahexaenoic acid, and eicosapentaenoic acid. Each quartile is represented with its respective range and odds ratios adjusted for various factors such as age, gender, centre, and other listed fatty acids. The odds ratios are provided with 95% confidence intervals (CIs).

The study found significant associations between higher intakes of n-3 PUFAs and a reduced risk of ulcerative colitis, with the highest quartile having an odds ratio of 0.75 (0.58 to 1.0) compared to the lowest quartile. In contrast, higher intakes of n-6 PUFAs were associated with an increased risk of the disease, with the highest quartile having an odds ratio of 1.68 (1.27 to 2.21) compared to the lowest quartile.

This study supports the hypothesis from clinical studies in patients with established ulcerative colitis that the arachidonic acid composition of phospholipids in the colonic mucosa was found to be higher in patients than in healthy controls (12.5 mol% vs 6.8 mol%, p<0.001). Furthermore, the amount of inflammatory exudate correlated with the arachidonic acid composition of phospholipids in the colonic mucosa (r = 0.89, p<0.005). Other clinical studies have reported significantly higher concentrations of arachidonic acid and linoleic acid in the plasma and neutrophil phospholipids in patients with ulcerative colitis than controls.

The principal advantage of this prospective cohort investigation over previous case–control studies was the minimisation of recall biases, as the dietary information was recorded prior to the diagnosis of the disease. Also, this design reduced the selection biases inherent in retrospective case–control studies, as cases and controls were prospectively ascertainment from the same, and a large, baseline population. Random measurement error in the food frequency questionnaire will result in an under-

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estimation of the odds ratios for dietary constituents rather than produce spurious positive associations. A more accurate method of assessing diet is weighed records of food intake, but these are impractical to use in large-scale epidemiological studies. A validation study, conducted in EPIC-Norfolk, UK, comparing dietary intakes between 16-day weighed records and food frequency questionnaires reported correlation coefficients between 0.59 and 0.90 for dietary variables. Of particular relevance to the findings of this study was a Spearman correlation coefficient of 0.64 for fat intake. A limitation of our methodology was that we only had smoking data at recruitment and not during subsequent follow-up. Ulcerative colitis may be more common in those who cease smoking. The generalisability of any cohort study, namely its external validity, needs to be considered. The population in this investigation was predominantly middle-aged to elderly, whereas ulcerative colitis is traditionally regarded as a disease presenting in earlier life. However, a large incidence study of patients with ulcerative colitis, treated in centres across Europe, showed that the age at diagnosis was similar across all ages in men, but in women the incidence declined with increasing age. Therefore, our study had an under-representation of younger women with ulcerative colitis. The disease distribution was similar in this cohort compared with the European incidence study (52% vs 21% for disease proximal to the splenic flexure). Finally, data from a UK population showed the dietary intake of n-6 PUFAs is similar across adult age ranges. Although we did not detect a negative association with cigarette smoking at recruitment, this may be because healthier volunteers are more likely to participate in a cohort study who are less likely to smoke.

The findings from aetiological studies may help identify potential new treatments for patients with inflammatory bowel disease. There are no dietary modifications of benefit in patients with ulcerative colitis, although, based on this study’s findings, a diet low in linoleic acid may merit investigation. In patients with Crohn’s disease, enteral diets can induce remission and, in these, the fat content may be important. In one trial, 62 patients with active Crohn’s disease were randomised to receive either a diet high in oleate and low in linoleate, a diet high in linoleate and low in oleate, or oral prednisolone. At 4 weeks, the diet high in linoleate resulted in a higher remission rate than that with the lower content (63% vs 27%, p = 0.008). These findings are surprising as it was expected that linoleate, through its conversion to pro-inflammatory eicosanoids, would stimulate inflammation. The reasons for this finding are unknown, although possibilities are the relative proportions of other fatty acids and the quantitative amounts. Clinical studies which have compared the percentage of linoleic in plasma between patients with Crohn’s disease and controls have either reported no difference or lower amounts.

In summary, this prospective cohort study found that a high dietary intake of the n-6 PUFAs linoleic acid more than doubled the risk of developing incident ulcerative colitis. Measurement error in the food frequency questionnaire means the size of this reported effect is probably an under-estimate of the true effect. The positive association may reflect a causal association because of both a plausible biological mechanism and supportive evidence from other epidemiological studies. The association needs to be further investigated in other aetiological work in different populations to assess consistency. If the positive association is causal, then there is substantial potential for reducing the incidence of ulcerative colitis through dietary modification.

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Competing interests: None.

Ethics approval: The names and locations of the ethics committees that approved the collection of data were: Norwich District Ethics Committee, UK; Ethical Committee of the Medical Faculty at the University of Heidelberg, Germany; Regionala etikprövningsnämnden i Umeå, Sweden; De Videnskabsetiske Komitéer for Region Hovedstaden, Regionsgården, Denmark; Comitato Etico Locale dell’Azienda Sanitaria di Firenze, Italy; Ethics Committee at The Medical Association of the State of Brandenburg in Cottbus, Germany; and Lund University Ethics Committee, Sweden.

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