Dairy products, dietary calcium and the risk of inflammatory bowel disease: results from a European prospective cohort investigation

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ABSTRACT

Background: Dairy products may be involved in the etiology of inflammatory bowel disease by modulating gut microbiota and immune responses, but data from epidemiological studies examining this relationship are limited. We investigated the association between prediagnostic intake of these foods and dietary calcium and the subsequent development of Crohn's disease (CD) and ulcerative colitis (UC).

Methods: In total, 401,326 participants were enrolled in the European Prospective Investigation into Cancer and Nutrition cohort. At recruitment, consumption of total and specific dairy products (milk, yogurt, cheese) and dietary calcium was measured using validated food frequency questionnaires. Cases developing incident CD (n=110) or UC (n=244) during follow-up were matched with four controls. Conditional logistic regression analyses were used to calculate odds ratios (ORs) with 95% confidence intervals (CIs), adjusted for total energy intake and smoking.

Results: Compared with the lowest quartile, the ORs for the highest quartile of total dairy products and dietary calcium intake were 0.61 (95% CI 0.32-1.19, p_{trend}=0.19) and 0.63 (95% CI 0.28-1.42, p_{trend}=0.23) for CD and 0.80 (95% CI 0.50-1.30, p_{trend}=0.40) and 0.81 (95% CI 0.49-1.34, p_{trend}=0.60) for UC. Compared with nonconsumers, individuals consuming milk had significantly reduced odds of CD (OR 0.30, 95% CI 0.13-0.65) and nonsignificantly reduced odds of UC (OR 0.85, 95% CI 0.49-1.47).

Conclusions: Milk consumption may be associated with a decreased risk of developing CD, although a clear dose-response relationship was not established. Further studies are warranted to confirm this possible protective effect.

Keywords: dairy products, calcium, etiology, Crohn's disease, ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) is characterized by recurrent inflammation of the gastrointestinal tract and comprises two main conditions: Crohn's disease (CD) and ulcerative colitis (UC). Both chronic disorders are considered to result from an impaired immune response to gut microbiota in genetically predisposed individuals, but the exact etiology remains unclear.[1,2] Although over 160 susceptibility loci for IBD have been identified,[3] the limited concordance rates in identical twins highlight the importance of environmental risk factors.[4-6] The changing epidemiology of IBD, with both a rise in the incidence in industrialized countries over the last century and the recent disease emergence in developing countries,[7,8] suggests that westernization of lifestyle, including dietary changes, may contribute to the etiology of CD and UC.[9,10]

Dairy products are common components of a western diet and are being increasingly consumed in developing nations.[11] These milk-based foods constitute an important source of fats, proteins and dietary calcium,[12] and could be implicated in the development of IBD by modulating effects on intestinal microbiota and immune responses. Both molecular and clinical studies suggest that dairy nutrients are inversely associated with low-grade inflammation and affect key cytokines in the pathogenesis of IBD, such as tumor necrosis factor alpha.[13,14] However, milk-derived saturated fats may promote a rise in inflammatory markers by influencing cytokine gene expression.[13] Alternatively, consumption of (fermented) milk products may have a significant impact on the composition of gut microbes, such as lactic acid bacteria, which may result in disparate effects on intestinal inflammation.[15-18]

Despite plausible biological mechanisms linking dairy products to the etiology of IBD, there are few epidemiological studies which have examined the relationship between these foods and the development of either CD or UC.[19] An ecological study has reported a strong positive association between the intake of milk proteins and the incidence of CD in Japan.[20] However, several retrospective case-control studies have documented either no or small inverse associations between dairy products and IBD, but may have been subject to selection bias and recall bias in the assessment of presymptomatic diet.[21-24] A single prospective study in a French cohort of women has reported no association, although the sample size was relatively small and the risks for CD and UC were not separately assessed.[25] In view of the inconsistent findings of previous investigations and the lack of large prospective studies, we aimed to explore the association between the intake of total and individual dairy products and dietary calcium and incident CD and UC in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

Materials and Methods

Study population

The EPIC cohort study was designed to investigate the relationship between diet and the incidence of cancer and chronic diseases, the methods of which have been previously described.[26] In this study, participants were from a subcohort (EPIC-IBD study), namely 401,326 initially healthy men and women (aged 20-80 years) recruited from twelve centers in Denmark, France, Germany, Greece, Italy, the Netherlands, the United Kingdom (UK) and Sweden between 1991 and 1998.[27] Participants were selected from the general population in all centers, apart from France (women in a health insurance scheme for teachers), Utrecht, the Netherlands (women in a breast cancer screening program) and Oxford, UK (nationwide members of vegetarian societies and readers of health food magazines). At baseline, information on age, gender, diet, smoking and physical activity was collected in self-administered questionnaires. Anthropometric measurements were mainly taken by qualified health professionals or in few centers obtained through participants' self-reports.

Dietary assessment

The habitual diet of participants, during the year before recruitment, was assessed by self-completion of validated country-specific food frequency questionnaires (FFQs), composed of approximately 200 food items and nine frequency categories of intake (never to several times per day). The FFQs were validated against a standard 24-hour recall questionnaire in all centers and a Spearman correlation coefficient of 0.68 was documented for the intake of dairy products.[28] National databases of food composition were used to calculate the daily intakes of

specific dairy foods (in grams) and total energy (in kilocalories). Subjects with a reported total energy intake in either the lowest or highest 1% values across the distribution of the whole cohort were excluded, as these values were considered implausible.

Individual dairy products consisted of milk, yogurt and cheese. Milk included all the subtypes (whole fat, skimmed, semi-skimmed and unspecified). Yogurt comprised natural and flavored products, and fermented milk in Denmark and Sweden. Cheese was either fresh, fermented or matured cheese products. Other types of dairy products, including milk containing beverages, curd, cream desserts and milk-based puddings, dairy creams and milk for coffee and creamers, were not analyzed individually, as for these there were relatively low intakes and incomplete measurements across centers. The total dairy products intake was recorded as the sum of all types of dairy products. The standardized EPIC Nutrient Database was used to calculate the daily consumption of dietary calcium (in milligrams), which did not consider the use of calcium supplements.[29]

Follow-up & identification of cases and controls

After recruitment, participants were followed up until at least June 2004 and in some centers until December 2010. Individuals who developed a new diagnosis of CD or UC were identified using population-based disease registries (Denmark, Italy, the Netherlands and Sweden) or follow-up questionnaires (France, Germany, Greece and the Oxford cohort (UK)). Incident IBD cases within the Norfolk cohort (UK) were identified by several methods, including follow-up questionnaires, inpatient records and histology databases. The medical notes of all potential cases were reviewed by local physicians to confirm the diagnoses and to provide information on

the diagnostic examinations and disease extent. Individuals with prevalent CD or UC at enrolment were excluded, as were those diagnosed with IBD less than 18 months after recruitment to minimize the risk of reverse causation. In this case-control study nested within a prospective cohort, each case was matched with four randomly selected unique controls for gender, age at recruitment (±6 months), date of recruitment (±3 months) and center. Controls were selected by incidence density matching to ensure a similar duration of follow-up for all individuals. None of the controls had CD, UC, indeterminate or microscopic colitis.

Statistical analysis

The dietary items of interest were compared between cases and controls using the appropriate statistical test according to the nature of their distributions. The intakes of total and individual dairy products and dietary calcium were divided into quartiles based on the distribution across the matched controls. Conditional logistic regression analyses were performed to assess the associations between the intake of dairy products and dietary calcium and the development of CD and UC separately by calculating odds ratios (ORs) with 95% confidence intervals (CIs). In the multivariable analysis, total energy intake and smoking status (categorized into never smoked, past smoker and current smoker) were added to the model. Energy adjustment was included to adjust for factors affecting dietary intake, namely body size, metabolic rate and physical activity,[30] whereas adjustment for smoking status was included because previous epidemiological studies consistently demonstrated associations between this factor and IBD.[31] Trends across quartiles were computed using the median value of each as a continuous variable. The analyses were repeated, including additional adjustment for socioeconomic status using

educational level (categorized into none, primary school, technical school, secondary school and higher education), as this factor has been associated with both IBD and the consumption of dairy products.[32-35] Excluding adjustment for energy intake was performed to assess whether the effects of dairy products or dietary calcium intake might be due to substitution for consumption of other food items. When possible, the risk of CD or UC was evaluated for consumers as compared to nonconsumers of dairy products. Stratified analyses were performed to assess whether associations differed according to disease site (ileal or colonic CD, left sided or extensive UC). In further analyses, cases diagnosed within 3 years or more than 5 years after enrolment respectively were excluded to further reduce the possibility of reverse causation and to evaluate if the intake of these dietary items may be related more closely to the development of IBD and time of diagnosis. Two-sided p-values below 0.05 were considered statistically significant. All analyses were performed using SPSS version 21 (IBM Corp., Armonk, New York, United States).

Ethical considerations

Ethical approval was obtained at each center and all participants gave written informed consent.

Results

During follow-up, 110 participants (72.7% female) developed CD at a mean age of 55.4 years and 244 participants (57.4% female) developed UC at a mean age of 57.5 years (Table 1). The median time between recruitment and diagnosis was 5.1 years (range 1.5-14.3 years) and 4.8 years (range 1.5-15.7 years) for CD and UC, respectively. Colonic disease was the commonest disease site in CD (32.7%), whereas left-sided colitis (involvement limited up to the splenic flexure) was the commonest phenotype in UC (35.2%). The completeness of the dietary data was 100.0% for CD cases, 98.0% for UC cases and 99.5% for each matched control group. The median intakes of total and specific dairy products and dietary calcium were similar between CD or UC cases and their controls.

There were no statistically significant associations according to quartiles or trends between the intake of total or individual dairy products or dietary calcium and the development of either CD or UC in the univariable analysis (Tables 2 and 3). In the multivariable analysis, adjusted for total energy intake and smoking status, the effect sizes were similar and no significant associations were observed. However, compared with nonconsumers, individuals consuming milk had significantly decreased odds of developing CD (OR 0.30, 95% CI 0.13-0.65) but did not have significantly reduced odds of developing UC (OR 0.85, 95% CI 0.49-1.47) (Table 4). Additional adjustment for educational level or excluding adjustment for total energy intake did not alter the magnitude of any effect sizes (data not shown). There was a significant inverse association according to quartiles between milk intake and colonic CD ($p_{trend}=0.07$) in the multivariable analysis, whereas no associations according to disease localization were observed for UC or other dairy products for CD (Table 5). The analyses in cases diagnosed within 5 years of

recruitment (CD: n=53; UC: n=127) showed significant inverse associations according to quartiles between total dairy products and milk intake and CD (median time between recruitment and diagnosis 3.2 years), with adjusted ORs for the highest versus lowest quartile of 0.36 (95% CI 0.15-0.90, p_{trend}=0.03) and 0.33 (95% CI 0.14-0.80, p_{trend}=0.07), respectively (Table 6). No associations were detected in UC or for other dietary items in CD. When including only those who were diagnosed more than 3 years after recruitment (CD: n=85; UC: n=199), there was a significant inverse association of milk intake with UC (median time between recruitment and diagnosis 5.6 years) (adjusted OR for the highest versus lowest quartile 0.64, 95% CI 0.38-1.07, p_{trend}=0.04) and inverse but nonsignificant associations for other dietary items in UC or CD (Table 6).

Discussion

In this large European prospective cohort study, no associations according to quartiles or trends between the intake of either total or specific dairy products (milk, yogurt, cheese) or dietary calcium and the development of incident CD or UC were demonstrated. However, individuals consuming milk were found to have significantly decreased odds of developing CD as compared to nonconsumers. Milk intake was inversely associated with colonic CD. Furthermore, there was an inverse association with total dairy products and milk intake in those diagnosed with CD less than five years following recruitment and with milk consumption in those diagnosed with UC more than three years after enrolment.

Considering that ORs were less than one in most higher quartiles for both CD and UC, a protective threshold effect of dairy products and dietary calcium between the first and second quartile may exist. Accordingly, relatively low intakes of these dietary items might already have a beneficial effect, but the statistical power was insufficient to confirm this. The significant findings in CD cases diagnosed within five years of enrolment may suggest the influence of reverse causation. Information on the date of onset of symptoms attributed to IBD were not available. However, the median diagnostic delay for CD and UC is 5-9 months and 3-4 months, respectively.[36-39] As individuals who developed IBD within 18 months after inclusion were excluded in this study, it seems unlikely that this affected our results importantly, although the possibility that individuals gave up milk products due to symptoms before diagnosis cannot be fully excluded. In those diagnosed more than three years following recruitment, nonsignificant but inverse associations were seen in CD and a significant inverse association between milk intake and UC was detected.

Evidence for a causal association are the plausible biological mechanisms, large effect sizes and temporality of the data collection. Several studies have reported that milk products potentially reduce intestinal inflammation, possibly by a direct modulation of inflammatory processes or by shaping of the gut microbiota.[13-16] This may, for example, be related to vitamin D or result from an increased abundance of bacteria producing butyrate, an important colonic energy source, which is thought to interfere with the colitogenic environment.[15,40,41] A recent experimental study in mice, however, demonstrated that consumption of milk-derived saturated fats results in the development of colitis through changes of the microbial community by altering the bile acid composition.[17] This indicates that different dairy components, such as fats or proteins, may exert disparate effects, emphasizing that the exact mechanisms underlying these associations are still unclear. Overall, our findings suggest that milk consumption may have a predominantly protective effect in the etiology of CD, although an apparent dose-response relationship was not established.

Previous epidemiological studies examining foods produced from milk and the development of CD or UC are sparse and show conflicting results. Some investigations report that a higher intake of milk is associated with a moderately increased risk of IBD,[20,42] but other studies find an inverse association or none.[21-25] These inconsistent findings could be explained by different study populations or by the different dietary items measured, such as milk proteins or unpasteurized milk, but might also have resulted from methodological limitations. Most investigations were retrospective case-control studies, which are prone to measurement bias for diet as these rely on patients recalling their diet before diagnosis, which may be many years previously.[21-24] The only prospective investigation published to date could not detect a clear

association between IBD and dairy products (milk and cheese), but included only women and had a small sample size with 77 IBD cases.[25]

The strength of our study was the prospective design, which minimizes recall and selection bias as dietary intakes were measured prior to diagnoses and both cases and controls were drawn from the same baseline population. Furthermore, the habitual diet of participants was assessed using validated FFQs that reflected local dietary habits. To ensure the validity of cases, all diagnoses were confirmed by gastroenterologists and participants with indeterminate or microscopic colitis were excluded. Follow-up bias is likely to be negligible, because the number of cases identified was similar to that expected.[43] The odds of developing CD and UC were assessed separately with adjustments for covariates, such as smoking. Finally, the study population comprised both men and women from various European countries and the consumption of dairy products was in line with national surveys,[44] thereby increasing the generalizability of our results.

This study also had several limitations. FFQs may have a degree of misclassification and the assessment of the habitual diet of participants included just one measurement, which could have attenuated the effect sizes and possibly have masked small associations. Although participants may have altered their dietary habits during follow-up, previous studies demonstrated that general food patterns of adults remain relatively stable over time and we investigated categories (quartiles) of intake rather than specific amounts.[45,46] Data on the intake of calcium supplements were not available, although in another investigation within EPIC regular use of such supplements was reported in less than 10% of German participants.[47] Most patients in our study had late-onset disease, with IBD being diagnosed at an age of 50 years or older.

This may explain the relative predominance of colonic involvement in CD and limited disease extent in UC and might hamper the generalizability of these data to the whole IBD population.[48,49] Furthermore, despite the relatively large sample size, our study might lack statistical power for subgroup analyses or to detect small effect sizes. Lastly, residual confounding, namely other etiological factors related to dairy products intake and the true causal exposure, could not be excluded in this observational study.

In conclusion, although no clear dose-response relationship was observed, we found that individuals consuming milk have significantly reduced odds of developing CD as compared to nonconsumers with the effects occurring in those with colonic disease and diagnosed less than 5 years after recruitment. Further studies are needed to confirm these findings and to identify any underlying mechanisms.

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Table 1. Baseline characteristics of CD and UC cases and their controls

	CD cases (n = 110)	Controls (n = 440)	UC cases (n = 244)	Controls (n = 976)
Female (n, %)	80 (72.7)	320 (72.7)	140 (57.4)	560 (57.4)
Age (years) at recruitment (mean, SD)	50.1 (10.8)	50.1 (10.7)	51.7 (10.5)	51.7 (10.5)
Age (years) at diagnosis (mean, SD)	55.4 (11.1)	-	57.5 (10.3)	-
Distribution of CD (n, %)				
L1, ileal	31 (28.1)	-	-	-
L2, colonic	36 (32.7)	-	-	-
L3, ileocolonic	28 (25.4)	-	-	-
L4, isolated upper GI disease	1 (1.0)	-	-	-
unknown	14 (12.7)	-	-	-
Distribution of UC (n, %)				
E1, ulcerative proctitis	-	-	55 (22.5)	-
E2, left sided colitis	-	-	86 (35.2)	-
E3, extensive colitis	-	-	63 (25.8)	-
extent not determined	-	-	40 (16.4)	-
Smoking status (n, %)				
never smoked	41 (37.3)	209 (47.5)	65 (26.6)	418 (42.8)
past smoker	28 (25.5)	121 (27.5)	91 (37.3)	281 (28.8)
current smoker	38 (34.5)	107 (24.3)	82 (33.6)	255 (26.1)
unknown	3 (2.7)	3 (0.7)	6 (2.5)	22 (2.3)

Table 1 (continued)

	CD cases (n = 110)	Controls (n = 440)	UC cases (n = 244)	Controls (n = 976)
Total energy intake (kcal/day) (median, range)	2117.4 (789.6-4312.4)	2071.7 (900.1-4795.4)	2151.7 (906.8-4866.2)	2075.3 (697.4-5789.6)
Total dairy products intake (g/day) (median, range)	280.9 (0.0-1131.4)	321.3 (18.6-1672.4)	290.6 (0.6-1729.4)	306.7 (6.4-2500.9)
Milk intake (g/day) (median, range)	102.2 (0.0-914.6)	137.6 (0.0-1524.9)	129.5 (0.0-1482.5)	158.3 (0.0-2341.1)
Yogurt intake (g/day) (median, range)	35.9 (0.0-480.0)	45.6 (0.0-455.1)	23.6 (0.0-452.6)	30.2 (0.0-615.3)
Cheese intake (g/day) (median, range)	30.6 (0.0-160.5)	31.0 (0.0-248.2)	30.0 (0.0-245.4)	30.0 (0.0-678.2)
Dietary calcium intake (mg/day) (median, range)	981.5 (273.1-4031.4)	959.1 (277.3-2852.9)	1000.8 (262.1-2572.1)	988.3 (214.5-4719.3)

CD: Crohn's disease; GI: gastrointestinal; UC: ulcerative colitis

There were no significant differences in the dietary variables between CD or UC cases and controls.

Table 2. Odds of CD according to quartiles of dairy product and dietary calcium intake

Dietary item	Quartile of intake (ranges)	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Total dairy products (g/day)	1 (0.0-176.9)	36	109	1.00	1.00
	2 (177.0-321.3)	25	110	0.69 (0.38-1.21)	0.69 (0.38-1.24)
	3 (321.4-515.4)	23	110	0.61 (0.34-1.12)	0.55 (0.29-1.04)
	4 (515.5-1672.4)	26	109	0.69 (0.38-1.26)	0.61 (0.32-1.19)
				$p_{trend} = 0.30$	$p_{trend} = 0.19$
Milk (g/day)	1 (0.0-21.4)	38	109	1.00	1.00
	2 (21.5-137.6)	21	110	0.53 (0.28-0.98)	0.53 (0.28-1.00)
	3 (137.7-296.0)	23	110	0.55 (0.29-1.05)	0.53 (0.28-1.03)
	4 (296.1-1524.9)	28	109	0.69 (0.38-1.25)	0.61 (0.33-1.16)
				$p_{trend} = 0.55$	$p_{trend} = 0.36$
Yogurt (g/day)	1 (0.0-8.4)	31	109	1.00	1.00
	2 (8.5-45.6)	27	110	0.83 (0.44-1.56)	0.81 (0.42-1.56)
	3 (45.7-107.2)	30	110	0.92 (0.50-1.69)	0.97 (0.52-1.81)
	4 (107.3-480.0)	22	109	0.68 (0.36-1.30)	0.78 (0.40-1.52)
				$p_{trend} = 0.31$	$p_{trend} = 0.62$
Cheese (g/day)	1 (0.0-16.5)	28	109	1.00	1.00
	2 (16.6-31.0)	27	110	0.95 (0.52-1.73)	0.95 (0.52-1.76)
	3 (31.1-57.5)	29	110	1.03 (0.55-1.93)	0.95 (0.50-1.82)
	4 (57.6-248.2)	26	109	0.93 (0.48-1.80)	0.85 (0.42-1.72)
				$p_{trend} = 0.85$	$p_{trend} = 0.64$
Calcium (mg/day)	1 (273.1-730.4)	25	109	1.00	1.00
	2 (730.5-980.0)	30	110	1.20 (0.66-2.17)	1.12 (0.61-2.08)
	3 (980.1-1299.1)	33	110	1.31 (0.73-2.36)	0.97 (0.49-1.89)
	4 (1299.2-4031.4)	22	109	0.87 (0.46-1.65)	0.63 (0.28-1.42)
				$p_{trend} = 0.71$	$p_{trend} = 0.23$

CD: Crohn's disease; CI: confidence interval; OR: odds ratio

*adjusted for total energy intake and smoking status

Table 3. Odds of UC according to quartiles of dairy product and dietary calcium intake

Dietary item	Quartile of intake (ranges)	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Total dairy products (g/day)	1 (0.0-174.6)	64	243	1.00	1.00
	2 (174.7-306.7)	62	242	0.96 (0.64-1.44)	0.92 (0.60-1.40)
	3 (306.8-477.3)	61	243	0.94 (0.62-1.43)	0.95 (0.61-1.47)
	4 (477.4-2500.9)	52	243	0.80 (0.51-1.24)	0.80 (0.50-1.30)
				$p_{trend} = 0.31$	$p_{trend} = 0.40$
Milk (g/day)	1 (0.0-28.3)	71	243	1.00	1.00
	2 (28.4-158.3)	66	242	0.94 (0.64-1.40)	0.93 (0.62-1.40)
	3 (158.4-294.6)	46	248	0.61 (0.40-0.95)	0.59 (0.37-0.93)
	4 (294.7-2341.1)	56	238	0.78 (0.51-1.20)	0.81 (0.51-1.29)
				$p_{trend} = 0.22$	$p_{trend} = 0.32$
Yogurt (g/day)	1 (0.0-2.5)	63	243	1.00	1.00
	2 (2.6-30.2)	64	246	0.96 (0.63-1.47)	1.03 (0.67-1.59)
	3 (30.3-91.8)	55	240	0.85 (0.55-1.32)	0.88 (0.56-1.40)
	4 (91.9-615.3)	57	242	0.87 (0.57-1.35)	0.95 (0.60-1.48)
				$p_{trend} = 0.55$	$p_{trend} = 0.74$
Cheese (g/day)	1 (0.0-15.8)	66	242	1.00	1.00
	2 (15.9-30.0)	55	244	0.80 (0.54-1.19)	0.78 (0.52-1.18)
	3 (30.1-52.4)	59	242	0.86 (0.57-1.29)	0.84 (0.54-1.29)
	4 (52.5-678.2)	59	243	0.85 (0.54-1.31)	0.83 (0.52-1.32)
				$p_{trend} = 0.62$	$p_{trend} = 0.60$
Calcium (mg/day)	1 (214.5-751.5)	67	243	1.00	1.00
	2 (751.6-988.3)	51	243	0.76 (0.51-1.16)	0.77 (0.50-1.19)
	3 (988.4-1249.3)	66	243	0.99 (0.66-1.47)	1.00 (0.63-1.56)
	4 (1249.4-4719.3)	55	242	0.84 (0.56-1.26)	0.81 (0.49-1.34)
				$p_{trend} = 0.63$	$p_{trend} = 0.60$

CI: confidence interval; OR: odds ratio; UC: ulcerative colitis

*adjusted for total energy intake and smoking status

Table 4. Odds of CD and UC according to milk consumption

Dietary item	Intake	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
CD					
Milk	no consumption	20	44	1.00	1.00
	consumption	90	394	0.33 (0.15-0.72)	0.30 (0.13-0.65)
UC					
Milk	no consumption	27	86	1.00	1.00
	consumption	212	885	0.72 (0.43-1.23)	0.85 (0.49-1.47)

CD: Crohn's disease; CI: confidence interval; OR: odds ratio; UC: ulcerative colitis

*adjusted for total energy intake and smoking status

Table 5. Odds of colonic and ileal CD according to quartiles of milk intake

Dietary item	Quartile of intake (ranges)	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Colonic CD					
Milk (g/day)	1 (0.0-21.4)	13	30	1.00	1.00
	2 (21.5-137.6)	6	21	0.68 (0.22-2.13)	0.57 (0.16-2.01)
	3 (137.7-296.0)	8	54	0.26 (0.09-0.80)	0.16 (0.04-0.59)
	4 (296.1-1524.9)	9	38	0.43 (0.15-1.27)	0.23 (0.07-0.83)
				$p_{trend} = 0.22$	$p_{trend} = 0.07$
Ileal CD					
Milk (g/day)	1 (0.0-21.4)	13	40	1.00	1.00
	2 (21.5-137.6)	3	38	0.24 (0.06-0.92)	0.23 (0.06-0.94)
	3 (137.7-296.0)	7	18	1.19 (0.39-3.59)	1.09 (0.34-3.47)
	4 (296.1-1524.9)	8	28	0.93 (0.32-2.67)	0.89 (0.28-2.82)
				$p_{trend} = 0.62$	$p_{trend} = 0.66$

CD: Crohn's disease; CI: confidence interval; OR: odds ratio

*adjusted for total energy intake and smoking status

Table 6. Odds of CD in cases diagnosed more than 3 years or within 5 years after enrolment

Dietary item	Quartile of intake (ranges)	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
CD cases diagnosed >3 years after inclusion					
Total dairy products (g/day)	1 (0.0-176.9)	27	87	1.00	1.00
	2 (177.0-321.3)	16	83	0.62 (0.31-1.24)	0.63 (0.31-1.28)
	3 (321.4-515.4)	21	86	0.77 (0.40-1.50)	0.68 (0.32-1.40)
	4 (515.5-1672.4)	21	84	0.79 (0.40-1.56)	0.72 (0.34-1.53)
				$p_{trend} = 0.72$	$p_{trend} = 0.54$
Milk (g/day)	1 (0.0-21.4)	26	88	1.00	1.00
	2 (21.5-137.6)	16	84	0.63 (0.31-1.29)	0.65 (0.31-1.34)
	3 (137.7-296.0)	21	87	0.82 (0.41-1.66)	0.80 (0.38-1.67)
	4 (296.1-1524.9)	22	81	0.92 (0.45-1.86)	0.84 (0.39-1.78)
				$p_{trend} = 0.84$	$p_{trend} = 0.95$
CD cases diagnosed <5 years after inclusion					
Total dairy products (g/day)	1 (0.0-176.9)	23	53	1.00	1.00
	2 (177.0-321.3)	12	49	0.55 (0.24-1.25)	0.55 (0.24-1.29)
	3 (321.4-515.4)	6	50	0.26 (0.10-0.70)	0.27 (0.10-0.76)
	4 (515.5-1672.4)	12	58	0.44 (0.19-0.98)	0.36 (0.15-0.90)
				$p_{trend} = 0.05$	$p_{trend} = 0.03$
Milk (g/day)	1 (0.0-21.4)	24	48	1.00	1.00
	2 (21.5-137.6)	8	52	0.27 (0.10-0.71)	0.28 (0.10-0.78)
	3 (137.7-296.0)	9	53	0.26 (0.10-0.69)	0.26 (0.09-0.71)
	4 (296.1-1524.9)	12	57	0.38 (0.17-0.86)	0.33 (0.14-0.80)
				$p_{trend} = 0.10$	$p_{trend} = 0.07$

CD: Crohn's disease; CI: confidence interval; OR: odds ratio

*adjusted for total energy intake and smoking status