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Oral contraceptives, reproductive factors and risk of inflammatory bowel disease

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Abstract

Background—Oral contraceptive use has been associated with risk of Crohn's disease (CD) and ulcerative colitis (UC).

Objective—To determine whether this association is confounded or modified by other important lifestyle and reproductive factors.

Design—A prospective cohort study was carried out of 117 375 US women enrolled since 1976 in the Nurses Health Study I (NHS I) and 115 077 women enrolled since 1989 in the Nurses' Health Study II (NHS II) with no prior history of UC or CD. These women had provided information every 2 years, on age at menarche, oral contraceptive use, parity, menopause status and other risk factors. Diagnoses of CD and UC were confirmed by review of medical records. Cox proportional hazards models were used to calculate HRs and 95% CIs.

Results—Among 232 452 women with over 5 030 196 person-years of follow-up, 315 cases of CD and 392 cases of UC were recorded through 2007 in NHS II and 2008 in NHS I. Compared with never users of oral contraceptives, the multivariate-adjusted HRs for CD were 2.82 (95% CI 1.65 to 4.82) among current users and 1.39 (95% CI 1.05 to 1.85) among past users. The association between oral contraceptives and UC differed according to smoking history

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($p_{heterogeneity}$ = 0.04). Age at menarche, age at first birth and parity were not associated with risk of UC or CD.

Conclusion—In two large prospective cohorts of US women, oral contraceptive use was associated with risk of CD. The association between oral contraceptive use and UC was limited to women with a history of smoking.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel diseases (IBDs), are chronic inflammatory disorders of the gastrointestinal tract in which a barrier normally maintained by adaptive and innate immunity is disrupted. Despite the success of genome-wide association studies in identifying more than 100 risk loci associated with UC and CD,[1,2] the pathogenesis of the two diseases remains largely unknown. It is estimated that the risk contribution from these genetic predispositions is <25%,[3] highlighting the importance of environment in the development of incident IBD.

Several studies have previously investigated the association between oral contraceptive use and risk of CD and UC.[4-18] Many of these studies had significant limitations, including retrospective design, inability to control for important lifestyle and reproductive factors, small sample size and limited ascertainment of oral contraceptive use. We therefore sought to examine the association between reproductive factors and long-term oral contraceptive use and risk of UC and CD in two large prospective cohorts of US womendthe Nurses' Health Study (NHS) I and IIdin which detailed information about reproductive and life-style factors is collected biennially. These cohorts provided a unique opportunity to examine reproductive factors in the context of important lifestyle risk factors that may either confound or modify the association of oral contraceptive use with UC and CD.

METHODS

Study population

NHS I is a prospective cohort that began in 1976 when 121 700 US female registered nurses, aged 30–55 years, completed a mailed health questionnaire. Follow-up questionnaires have been mailed every 2 years to update health information. In 1989, a parallel cohort, the NHS II, enrolled 116 686 US female nurses aged 25–42 years. These women have been followed up with similar biennial questionnaires. Follow-up for this study exceeded 90%. The institutional review board at the Brigham and Women's Hospital approved this study.

Assessment of reproductive factors

At baseline, we collected data on age at menarche, parity, age at birth of first child and use of oral contraceptives in both cohorts. With the exception of age at menarche, this information was updated biennially. For example, a woman who reported never using oral contraceptives at study baseline contributed person-time to the never user category. If she subsequently reported use of oral contraceptives on a follow-up questionnaire, she then contributed person-time to the current user category. If she subsequently discontinued use, she then contributed person-time to the former user category. Beginning with the 1986 questionnaire, we stopped asking participants in NHS I about parity and age at birth of first child since the median age range of the cohort was 47 years. Beginning with the 1984 questionnaire, we stopped asking participants in NHS I about use of oral contraceptives since the prevalence of use was <1% in 1982. Current use of oral contraceptives was defined as use within 1 month of the date of questionnaire return; past use was defined as use that stopped at least 1 month before the date of questionnaire return. Periods of use were summed to calculate the total duration of oral contraceptive use. In a validation study,

detailed telephone interviews about oral contraceptive use were conducted in a subsample of 215 NHS II participants using a structured life events calendar.[19] Spearman's correlation coefficients for the duration of oral contraceptive use calculated between the two methods was 0.94.

Covariate information

On each questionnaire, menopausal status was determined by asking whether the participants' menstrual periods had stopped permanently and, if so, at what age and for what reason (occurring naturally or after radiation therapy or surgery). If menopause was due to surgery, the participant was asked to report the number of ovaries removed. Self-reported type of menopause and age at time of menopause in this cohort were highly accurate compared with medical records.[20] Data concerning postmenopausal use of hormones were collected at baseline and updated every 2 years in both cohorts. Past and current use of postmenopausal hormones was defined in the same manner as for oral contraceptive use.

Race was assessed in 1992 in the NHS I and 1989 in the NHS II and categorised as Caucasian, African or Hispanic origin. Since enrolment (1976 for NHS I and 1989 for NHS II) and on each biennial questionnaire, the nurses were asked whether they currently smoked or had ever smoked cigarettes regularly in the past. Thus, in our analysis, we used updated smoking information as a time-varying covariate, defining each participant's smoking status according to their response on each biennial questionnaire. Similarly, information on weight was collected at baseline and updated biennially. Body mass index (BMI) was computed using weight in kilograms divided by height in square metres as reported at baseline. Participants' self-report of body weight and height has been previously validated.[21]

Outcome ascertainment

We have previously given details of our methods for confirming cases of CD and UC.[22] In brief, since 1976 in NHS I and 1989 in NHS II, participants have reported diagnoses of UC or CD through an open-ended response on biennial surveys. In NHS I, we specifically asked participants about diagnoses of UC since 1982 and CD since 1992. In NHS II, we specifically asked participants about diagnoses of both UC and CD since 1993. When a diagnosis was reported on any biennial questionnaire, a supplementary questionnaire and related medical records were requested and reviewed by two gastroenterologists blinded to exposure information. We excluded participants who subsequently denied the diagnosis on the supplementary questionnaire or permission to review their records. Data were extracted on diagnostic tests, histopathology, anatomical location of disease and disease behaviour. Standardised criteria were used[23-26]: UC diagnosis was based on a typical clinical presentation ≥4 weeks and endoscopic or surgical pathological specimen consistent with UC (eg, evidence of chronicity); CD diagnosis was based on a typical clinical history for ≥4 weeks and endoscopy or radiological evaluation demonstrating small-bowel findings, or surgical findings consistent with CD combined with pathology suggesting transmural inflammation or granuloma contributed to a diagnosis of CD. Disagreements were resolved through consensus.

In total, 1680 (85%) of women in NHS I and 1413 (86%) of women in NHS II who had self-reported UC or CD responded to the supplementary questionnaire, with 235 women in NHS I (13%) and 218 women in NHS II (15%) refusing permission for medical record review. On the basis of a more detailed definition of CD and UC on the supplementary questionnaire, 706 in NHS I and 596 in NHS II subsequently denied the diagnosis of UC or CD. Thus, we requested medical records from 739 women in NHS I and 599 in NHS II, obtaining records with adequate information for review from 620 in NHS I (84%) and 557 (93%) in NHS II. We confirmed the diagnosis of new cases of UC, CD and chronic colitis (indeterminate

colitis, microscopic colitis) in 485 NHS I participants and 422 NHS II participants for a case confirmation rate of 78% in NHS I and 76% in NHS II. For our analysis, we excluded 139 cases of chronic colitis (83 in NHS I; 56 in NHS II), leaving a total of 420 cases of UC and 348 cases of CD before other baseline exclusions for analysis. Among those women whom we received adequate medical records, the case confirmation rate for IBD was 78% in NHS I and 74% in NHS II.[22]

The baseline characteristics of participants with or without complete medical records were similar (mean age, 38.9 vs 38.9 years; non-white, 5% vs 5%; current smoker, 22.2% vs 19.4%; mean BMI, 25.1 kg/m^2 vs 24.9 kg/m^2; current or past oral contraceptive use, 53.7% vs 55.8%; postmenopausal hormone use, 10.5% vs 11.8%; $p>0.15$ for all comparisons). Women for whom we could not confirm CD or UC were included in the analyses as non-cases.

Statistical analysis

Person-time for each participant was calculated from the date of return of their baseline questionnaires to the date of the diagnosis of UC or CD, date of last questionnaire, death from any cause, or 1 June 2008 for NHS I and 1 June 2007 for NHS II, whichever came first. We used Cox proportional hazards modelling with time-varying covariates to adjust for other known or suspected risk factors before each 2-year interval to calculate adjusted HRs and 95% CI. Because weight may be influenced by preclinical disease, we adjusted for BMI using the baseline value, consistent with prior analyses.[27] We observed no heterogeneity in the association of oral contraceptive use with CD or UC in separate analyses of NHS I and NHS II (p for heterogeneity >0.30 for both UC and CD). Thus, we pooled individual-level data from NHS I and NHS II and adjusted for cohort in all analyses. We also examined the association between oral contraceptive use and risk of UC or CD according to strata of age, smoking, BMI, and evaluated for potential interaction using cross-classified categories of these risk factors and oral contraceptive use. We tested the significance of interactions by using the log likelihood ratio test comparing the model with cross-classified categories with a model that included these factors as independent variables. We used SAS V.9.1.3 for these analyses. All p values were two-sided and $p<0.05$ was considered statistically significant.

RESULTS

Among 117 375 women in NHS I and 115 077 women in NHS II, we documented 392 incident cases of UC and 315 incident cases of CD through 2007 in NHS II and 2008 in NHS I over 5 030 196 total person-years of follow-up. The baseline characteristics of 232 452 women according to oral contraceptive use are shown in table 1. Compared with never users, past and current users of oral contraceptive were on average younger and less likely to be overweight (BMI>25) or postmenopausal. There were no significant differences between the groups according to parity, age at menarche, age at birth of first child and smoking.

We observed a significant association between oral contraceptive use and risk of CD (table 2). Compared with women who never used oral contraceptives, the age-adjusted HRs for CD were 2.88 (95% CI 1.69 to 4.89) among women who currently used oral contraceptives and 1.50 (95% CI 1.13 to 1.99) among past users. After adjusting for known or potential risk factors for CD, including BMI, smoking, hormone use, age at menarche, menopause type and parity, these risk estimates did not materially change (multivariate-adjusted HR=2.82; 95% CI 1.65 to 4.82 for current use of oral contraceptives and multivariate-adjusted HR=1.39; 95% CI 1.05 to 1.85 for past use). Parity, age at menarche and age at first birth were not associated with risk of CD (table 2).

Compared with never users, past and current users of oral contraceptives had a higher but not statistically significant multivariate-adjusted risk of developing UC (table 3). Compared with women who never used oral contraceptives, the multivariate-adjusted HRs for UC were 1.22 (95% CI 0.74 to 2.07) among women who currently used oral contraceptives and 1.18 (95% CI 0.91 to 1.52) among past users. Parity, age at menarche and age at first birth were also not associated with risk of UC (table 3).

We also explored the possibility that the link between oral contraceptive use and risk of CD might be related to endometriosis, a diagnosis for which oral contraceptives may be used. Since enrolment in 1989, we have consistently asked participants in NHS II if they have been diagnosed with endometriosis and have previously shown that self-reports are highly accurate when compared to laparoscopic findings.[28] In NHS II, compared with never users of oral contraceptives, the age-adjusted HR of CD for current users was 2.16 (95% CI 1.10 to 4.25). After additionally adjusting for endometriosis, BMI, smoking, menopause status, parity and age at menarche, this risk estimate for CD did not materially change (multivariate-adjusted HR = 2.14; 95% CI 1.08 to 4.24).

We evaluated potential differences in the influence of oral contraceptive according to strata of known or potential risk factors (tables 4 and 5). The risk of UC appeared to differ according to smoking status ($p_{interaction} = 0.04$). Among women who either previously or currently smoked, use of oral contraceptives was associated with a multivariate-adjusted HR of 1.63 (95% CI 1.13 to 2.35) for UC. In contrast, there was no statistically significant association between oral contraceptive use and risk of UC among women who never smoked (multivariate-adjusted HR=0.86, 95% CI 0.61 to 1.21). As past but not current smoking, may be associated with higher risk of UC, we further stratified the effect of oral contraceptive use on risk of UC according to never, past and current smoking status and observed similar effect modification by smoking ($p_{interaction} = 0.048$). In contrast, the risk of CD did not appear to differ according to smoking status ($p_{interaction} = 0.72$). The effect of oral contraceptive use on risk of CD or UC did not appear significantly modified within strata defined by BMI or age (all $p_{interaction}>0.08$).

DISCUSSION

In two large prospective cohorts of women, we observed a significant association between oral contraceptive use and risk of CD, which persisted even after accounting for other potential risk factors. In addition, the risk was not explained by the recently suggested association between endometriosis and risk of CD.[29] Oral contraceptives were also associated with a modest, but non-significant increase in risk of UC. Moreover, the association between oral contraceptives and risk of UC appeared to be confined to women with a history of smoking. In contrast to oral contraceptives, other reproductive factors, including parity, age at menarche and age at first birth, were not independently associated with risk of either CD or UC.

Our results relating oral contraceptives to risk of IBD are supported by several previous studies, including a meta-analysis.[30] In a caseecontrol study using the United Kingdom General Practice Research Database (UKGPRD),[18] oral contraceptive use was associated with an increased risk of CD and a non-significant risk of UC. However, in contrast with our analysis, the UKGPRD study had limited information on several key risk factors, including smoking. In addition, previous studies in total included only 75 815 people, limiting their ability to evaluate for potential interactions between oral contraceptive use and other important risk factors. Moreover, none of these studies collected detailed information on other reproductive factors potentially associated with risk. Last, the risk estimates relating smoking to risk of CD or UC in prior studies vary, probably reflecting their caseecontrol

design.[31] Our prospective design based upon incidence rates provides a more precise estimate of the true magnitude of risk associated with oral contraceptives.

Our findings have biological plausibility. Oestrogen enhances cellular proliferation and the humoural immune system,[32] modifies colonic barrier function[3334] and contributes to thrombosis, which may lead to multifocal gastrointestinal infarction.[35] Although the precise pathophysiology of UC and CD remains largely unknown, these oestrogen-mediated pathways may play a key role in aetiology and progression of the two diseases. The finding that risk of UC is confined to women with a history of smoking may provide additional support for the role of subacute thrombosis in mediating risk of UC since a synergistic effect of smoking and oral contraceptives on hypercoagulability has been well described.[36] In addition, the observation that mucosal inflammation in patients with UC is mediated by Th2-related cytokines,[37-39] together with recent animal studies linking carbon monoxide, a byproduct of smoking, to Th2-mediated colitis,[40] offers another plausible shared biological pathway by which oral contraceptives and smoking may have a synergistic effect on risk of UC.

Our study has several strengths. First, our prospective study design avoids the potential recall and selection biases of retrospective, caseecontrol studies, which collect data on drugs and lifestyle after diagnosis of CD or UC. Second, we confirmed all cases of CD and UC through medical record review, a significant advantage over studies that rely on self-report or discharge codes, which may not accurately reflect true diagnoses. Third, the availability of detailed and validated information on BMI, hormone use later in life, smoking and other important reproductive and menopausal factors allowed us to control for a number of potentially confounding factors that might have influenced our observed associations. Fourth, in our analysis, we collected information on oral contraceptive use every 2 years and used time-varying exposures in our models. Thus, we were able to account for changes in oral contraceptive use, minimising the possibility of exposure misclassification. Last, reports of oral contraceptive use by medical professionals are more likely to represent actual use than data obtained through prescription registries.

Our study has several limitations. First, our cohort may not be representative of the overall US population. However, as we have reported previously,[22] our age-specific incidence of CD and UC is largely similar to rates from other US populations. In addition, previous studies have shown that the distribution of risk factors, such as smoking and BMI, in our cohort is consistent with that of the broader population of US women.[41] Nevertheless, considering the older age of our participants we acknowledge that our data might not be generalisable to younger population. Second, it is possible that non-users of oral contraceptives were less likely to report a diagnosis of IBD. However, this is unlikely given our participants' health literacy as nurses and our response rate of >90% on each biennial questionnaire over 25 years of follow-up. Moreover, such a response bias would be unlikely to lead to an observed association of oral contraceptives with CD but not UC, as we found in our study. Third, despite our high response rate, we were unable to obtain sufficient medical records to confirm the diagnosis among a small proportion of participants. However, we confirmed that the baseline characteristics of women with and without complete records were similar. Lastly, our study is observational and we cannot exclude the possibility of residual confounding. However, adjustment for the most important risk factors previously identified for UC and CD did not significantly alter our results. In addition, our results are largely consistent with previously published meta-analysis of other studies.

In two large prospective cohorts, we found that regular use of oral contraceptives is associated with risk of CD, with a some-what weaker association with risk of UC that is confined to women with a history of smoking. Our findings shed light on new and

potentially diverging biological pathways involved in pathogenesis of CD and UC. In addition, our data suggest the importance of carefully evaluating contraceptive options among women who may be at higher risk of CD or UC.

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Significance of this study

What is already known on this subject?

- Oral contraceptive use is associated with risk of Crohn's disease (CD) and ulecerative colitis (UC).
- It is unclear whether this association is confounded or modified by other important lifestyle and reproductive factors.
- Previous studies did not have the opportunity to examine oral contraceptive use and risk of CD or UC in relation to important lifestyle and reproductive factors.

What are the new findings?

- Oral contraceptive use is associated with risk of CD.
- The association between oral contraceptive use and UC is limited to women with a history of smoking.
- Other reproductive factors, including age at menarche, age at first birth and parity, are not associated with risk of UC or CD.

How might it impact on clinical practice in the foreseeable future?

- Our findings shed light on new and potentially diverging biological pathways involved in pathogenesis of CD and UC. Understanding such pathways might lead to the development of new lines of treatment as well as interventions that may modulate the risk of incident disease.

Table 1

Baseline characteristics of participants in the Nurses' Health Study (NHS) I and II according to oral contraceptive use status*

	Oral contraceptive use		
	Never N = 81 022	**Past N = 130104**	**Current N = 21 326**
Age, years, mean (SD)	43.1 (7.8)	37.2 (5.7)	33.1 (5.5)
Body-mass index, %			
<20 kg/m^2	14	14	16
20–24.9 kg/m^2	56	57	60
25–29.9 kg/m^2	20	19	17
≥30 kg/m^2	10	10	7
Smoking %			
Never	58	53	53
Past	19	24	22
Current	23	23	25
Postmenopausal, %	16	16	0
Postmenopausal hormone use,† %			
Never	56	48	-
Past	19	34	-
Current	25	18	-
Parity, %			
0	21	16	22
1	11	14	13
2	26	32	27
≥3	42	38	38
Age at first birth, %			
<22 years	7	10	8
≥ 22 and <25 years	37	33	36
≥ 25 and <29 years	33	34	32
≥ 29 years	22	22	24
Age at menarche, %			
≤11 years	24	24	22
12 years	28	28	29
13 years	29	29	30
≥ 14 years	19	19	19

Values are means (SD) or percentages and are standardised to the age distribution of the study population.

*According to the baseline questionnaire for NHS I (1976) and NHS II (1989) except for race, which was derived from the 1992 questionnaire in NHS I and 1993 questionnaire in NHS II.

†Among postmenopausal women.

Table 2

Reproductive factors and risk of Crohn's disease in the Nurses' Health Study (NHS) I and II

	No of cases	Person-years	Age-adjusted HR (95% CI)*	Multivariate-adjusted HR (95% CI)†
Oral contraceptive use				
Never	96	2 059 995	1.00	1.00
Past	196	2 802 097	1.50 (1.13 to 1.99)	1.39 (1.05 to 1.85)
Current	23	168106	2.88 (1.69 to 4.89)	2.82 (1.65 to 4.82)
≥ 5 years	18	125 658	2.97 (1.68 to 5.25)	2.89 (1.62 to 5.14)
<5 years	5	42 446	2.59 (1.00 to 6.71)	2.58 (0.99 to 6.71)
P_{trend}‡			<0.01	<0.01
Oral contraceptive use				
Never	96	2 059 995	1.00	1.00
Ever	209	2 970 201	1.54 (1.16 to 2.03)	1.43 (1.08 to 1.90)
Parity				
0	44	561 507	1.00	1.00
1	31	512 984	0.81 (0.51 to 1.28)	0.83 (0.52 to 1.32)
2	110	1 567 093	0.97 (0.68 to 1.39)	1.00 (0.69 to 1.43)
≥3	130	2388 612	0.77 (0.53 to 1.11)	0.80 (0.55 to 1.17)
p_{trend}§			0.21	0.31
Age at menarche				
≤11 years	70	1 186 266	0.99 (0.72 to 1.37)	0.97 (0.71 to 1.34)
12 years	83	1394138	1.00	1.00
13 years	99	1 480339	1.14 (0.85 to 1.53)	1.15 (0.86 to 1.54)
≥ 14 years	63	969 453	1.11 (0.80 to 1.55)	1.14 (0.82 to 1.58)
Age at first birth¶				
<22 years	27	377 093	1.02 (0.66 to 1.57)	0.99 (0.64 to 1.53)
≥ 22 and < 25 years	111	1 689 995	1.00	1.00
≥ 25 and < 29 years	86	1 537 788	0.80 (0.60 to 1.07)	0.81 (0.61 to 1.09)
≥ 29 years	50	917 387	0.78 (0.55 to 1.11)	0.80 (0.56 to 1.15)

*Models adjusted for age (months) and cohort (NHS I, NHS II).

†Models adjusted for age (months), cohort (NHS I, NHS II), smoking (never, past, current), body mass index (<20, 20—24.9, 25—29.9, ≥30 kg/m^2), oral contraceptive use (never, past, current), parity (nulliparous, parous), age at menarche (≤10, 11, 12, 13, ≥14 years), hormonal replacement therapy (never, past, current) and menopause status (premenopause, natural menopause, surgical/radiation menopause).

‡Ptrend was estimated by entering oral contraceptive into the model as a continuous variable excluding reference and current categories.

§Ptrend was estimated by entering parity into the model as a continuous variable.

¶Analysis restricted to parous women.

Table 3

Reproductive factors and risk of ulcerative colitis in the Nurses' Health Study (NHS) I and II

	No. of cases	Person-years	Age-adjusted HR (95% CI)*	Multivariate-adjusted HR (95% CI)†
Oral contraceptive use				
Never	117	2 059 995	1.00	1.00
Past	255	2 802 097	1.28 (0.99 to 1.65)	1.18 (0.91 to 1.52)
Current	20	168106	1.35 (0.80 to 2.28)	1.22 (0.74 to 2.07)
≥ 5 years	14	125 658	1.29 (0.71 to 2.35)	1.16 (0.64 to 2.12)
<5 years	6	42 446	1.51 (0.64 to 3.58)	1.40 (0.59 to 3.30)
p_{trend}‡			0.12	0.31
Oral contraceptive use				
Never	117	2 059 995	1.00	1.00
Ever	275	2 970 201	1.29 (1.00 to 1.66)	1.18 (0.92 to 1.52)
Parity				
0	60	561 507	1.00	1.00
1	53	512 984	1.03 (0.71 to 1.49)	1.01 (0.70 to 1.47)
2	122	1 567 093	0.86 (0.62 to 1.17)	0.84 (0.61 to 1.15)
≥3	157	2388 612	0.85 (0.62 to 1.17)	0.85 (0.61 to 1.17)
p_{trend}§			0.22	0.22
Age at menarche				
≤11 years	82	1 186 266	0.84 (0.63 to 1.11)	0.84 (0.63 to 1.12)
12 years	115	1394138	1.00	1.00
13 years	116	1 480339	0.99 (0.76 to 1.28)	0.97 (0.75 to 1.26)
≥14 years	79	969 453	1.02 (0.76 to 1.35)	1.00 (0.75 to 1.34)
Age at first birth¶				
<22 years	38	377 093	1.06 (0.73 to 1.54)	1.08 (0.74 to 1.57)
≥22 and <25 years	124	1 689 995	1.00	1.00
≥25 and <29 years	102	1 537 788	0.81 (0.62 to 1.06)	0.81 (0.62 to 1.05)
≥29 years	81	917387	0.89 (0.65 to 1.21)	0.88 (0.65 to 1.20)

*Models adjusted for age (months) and cohort (NHS I, NHS II).

†Models adjusted for age (months), cohort (NHS I, NHS II), smoking (never, past, current), body mass index (<20, 20—24.9, 25—29.9, ≥30 kg/m^2), oral contraceptive use (never, past, current), parity (nulliparous, parous), age at menarche (≤10, 11, 12, 13, ≥14 years), hormonal replacement therapy (never, past, current) and menopause status (pre-menopause, natural menopause, surgical/radiation menopause) and questionnaire cycle.

‡Ptrend was estimated by entering oral contraceptive into the model as a continuous variable excluding reference and current categories.

§Ptrend was estimated by entering parity into the model as a continuous variable.

¶Analysis restricted to parous women.

Table 4

Oral contraceptive use and risk of ulcerative colitis according to strata of age, smoking and body mass index

	Never	Ever	$P_{interaction}$
Age ≤40 years			0.81
No of cases/person-years	40/610188	195/2 079 577	
Age-adjusted HR, 95% CI	1.00	1.23 (0.86 to 1.74)	
Multivariate-adjusted HR, 95% CI*	1.00	1.15 (0.81 to 1.64)	
Age >40 years			
No of cases/person-years	77/1 449 807	80/890624	
Age-adjusted HR, 95% CI	1.00	1.36 (0.95 to 1.94)	
Multivariate-adjusted HR, 95% CI*	1.00	1.28 (0.89 to 1.85)	
Never smoking			0.04
No of cases/person-years	62/1 012 745	125/1 571 377	
Age-adjusted HR, 95% CI	1.00	0.90 (0.63 to 1.27)	
Multivariate-adjusted HR, 95% CI*	1.00	0.86 (0.61 to 1.21)	
Past/current smoking			
No of cases/person-years	55/1 047 250	150/1 398 823	
Age-adjusted HR, 95% CI	1.00	1.74 (1.21 to 2.51)	
Multivariate-adjusted HR, 95% CI*	1.00	1.63 (1.13 to 2.35)	
Body mass index <25 kg/m^2			0.40
No of cases/person-years	87/1 385 147	205/2 180 254	
Age-adjusted HR, 95% CI	1.00	1.20 (0.89 to 1.60)	
Multivariate-adjusted HR, 95% CI*	1.00	1.13 (0.85 to 1.52)	
Body mass index ≥25 kg/m^2			
No of cases/person-years	30/674 848	70/789 947	
Age-adjusted HR, 95% CI	1.00	1.44 (0.87 to 2.39)	
Multivariate-adjusted HR, 95% CI*	1.00	1.27 (0.76 to 2.11)	

*Models adjusted for age (months), smoking (never, past, current), body mass index (<20, 20—24.9, 25—29.9, ≥30 kg/m^2), oral contraceptive use (never, past, current), parity (nulliparous, parous), age at menarche (≤10, 11, 12, 13, ≥14 years), hormonal replacement therapy (never, past, current) and menopause status (pre-menopause, natural menopause, surgical/radiation menopause), cohort (NHS I, NHS II) and questionnaire cycle. Models were adjusted for these covariates minus the strata variable (age, smoking and body mass index).

Table 5

Oral contraceptive use and risk of Crohn's disease according to strata of age, smoking and body mass index

	Never	Ever	$P_{interaction}$
Age ≤40 years			0.09
No of cases/person-years	34/610188	154/2 079 577	
Age-adjusted HR, 95% CI	1.00	1.18 (0.81 to 1.73)	
Multivariate-adjusted HR, 95% CI*	1.00	1.09 (0.74 to 1.61)	
Age >40 years			
No of cases/person-years	62/1 449 807	65/890624	
Age-adjusted HR, 95% CI	1.00	1.89 (1.29 to 2.75)	
Multivariate-adjusted HR, 95% CI*	1.00	1.73 (1.18 to 2.53)	
Never smoking			0.72
No of cases/person-years	42/1 012 745	100/1 571 377	
Age-adjusted HR, 95% CI	1.00	1.20 (0.79 to 1.83)	
Multivariate-adjusted HR, 95% CI*	1.00	1.17 (0.76 to 1.78)	
Past/current smoking			
No of cases/person-years	54/1 047 250	1 19/1 398 823	
Age-adjusted HR, 95% CI	1.00	1.76 (1.22 to 2.55)	
Multivariate-adjusted HR, 95% CI*	1.00	1.65 (1.14 to 2.40)	
Body mass index <25 kg/m^2			0.08
No of cases/person-years	71/1 385 147	154/2 180 254	
Age-adjusted HR, 95% CI	1.00	1.39 (1.00 to 1.92)	
Multivariate-adjusted HR, 95% CI*	1.00	1.26 (0.91 to 1.75)	
Body mass index ≥25 kg/m^2			
No of cases/person-years	25/674 848	65/789 947	
Age-adjusted HR, 95% CI	1.00	1.91 (1.11 to 3.31)	
Multivariate-adjusted HR, 95% CI*	1.00	1.89 (1.08 to 3.28)	

*Models adjusted for age (months), cohort (NHS I, NHS II), smoking (never, past, current), body mass index (<20, 20—24.9, 25—29.9, ≥30 kg/m^2), oral contraceptive use (never, past, current), parity (nulliparous, parous), age at menarche (≤10, 11, 12, 13, ≥14 years), hormonal replacement therapy (never, past, current) and menopause status (pre-menopause, natural menopause, surgical/radiation menopause), cohort (NHS I, NHS II) and questionnaire cycle. Models were adjusted for these covariates minus the strata variable (age, smoking and body mass index).