Supplementary data: Rosacea, Use of Tetracycline, and Risk of Incident Inflammatory Bowel Disease in Women

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Assessment of covariates

The cohort collected detailed information on life-style characteristics of the participants. Data on body mass index (BMI), physical examination, smoking status, oral contraceptive use, use of non-steroidal anti-inflammatory drugs (NSAIDs) and menopausal status and use of menopausal hormone therapy were collected at baseline and updated in the follow-up questionnaires. A validated assessment of physical activity was collected in 1991, 1997, 2001, 2005 and 2009. Data on alcohol consumption were collected every four years beginning in 1991. Data on self-reported ancestry and history of severe teenage acne were collected in the 1989 questionnaire. State of residence at different ages was reported in 1993, based on which the UV index was

divided into three categories: 5 (low), 6 (medium), or 7 (high). Depressive symptoms were assessed using the Mental Health Index-5 in 1993, 1997, and 2001. Data on personal history of major auto-immune diseases, including rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and multiple sclerosis, were also collected.

In the multivariate models, BMI, alcohol consumption, physical activity, smoking status, oral contraceptive use, menopausal status and postmenopausal hormone therapy, use of NSAIDs were adjusted for in the following categories: BMI (<25, 25-29.9, 30-34.9, or ≥35 kg/m^2), alcohol consumption (none, 1-4, 5-9, 10-14, or ≥15 g/d), physical activity (in quintiles, metabolic equivalent hours/wk), smoking status (never, past, current smokers with 1-14, 15-32, or ≥25 cigarettes/d), oral contraceptive use (never, past, or current), menopausal status and menopausal hormone therapy (pre-menopause, post-menopause without hormone use, post-menopause with hormone replacement therapy), and use of NSAIDs (<2 or ≥2 tablets/day). Other covariates were adjusted for as two categories: yes or no.

Sensitivity and secondary analyses

We conducted several sets of sensitivity and secondary analyses for the association between rosacea and inflammatory bowel disease (IBD) risk. First, acne vulgaris (acne) is another common skin condition and has been shown as a key component of some systemic diseases and syndromes.[1] We therefore conducted analyses that further adjusted for personal history of severe teenage acne or excluded participants with history of severe teenage acne. Second, to address the concern of the observed association due to medications rather than rosacea itself, we excluded all participants reporting use of tetracycline or isotretinoin or reporting use of antibiotics for acne or rosacea. Third, we further adjusted for diagnosis of depressive symptoms and UV index of

residence at age 30 years.[2, 3] Fourth, we excluded all participants with history of other common autoimmune diseases. Fifth, a lag analysis was conducted by excluding IBD cases identified in the first follow-up period. Sixth, we restricted the participants to Whites in a secondary analysis, as Whites reported a higher rate of rosacea. Seventh, we also conducted an analysis restricting follow-up between 1991 and 2005, as the question about rosacea diagnosis was assessed in 2005 and not updated afterwards.

For the analysis of tetracycline use, we also conducted further analyses. First, we conducted subgroup analysis by duration of tetracycline use (0, <1, or ≥1 year), categorized based on the distribution, as only 10.5% of participants reported a duration of 1 or more years. Linear trend analysis was conducted to calculate the *P* for trend. Second, we excluded all cases reporting a history of rosacea or acne to address whether the association was mostly independent of the disease. Third, a lag analysis was conducted by excluding IBD cases identified in the first follow-up period.

Interaction analyses

Smoking has been associated with risk of IBD in different patterns for Crohn's disease (CD) and ulcerative colitis (UC). Analyses in the Nurses' Health Study (NHS) and NHS II found that current and former cigarette smoking is associated with an increased risk of CD[4]. By contrast, a history of former smoking was associated with an increased risk of UC and no such association for current smoking[4]. Although limited studies are available for smoking and risk of rosacea, a similar pattern as the association with UC has been indicated previously, which reported that rosacea is a disease of non-smokers[5, 6]. We examined the statistical interaction between rosacea and smoking on risk of CD and UC respectively by using likelihood ratio test, comparing the -2

LOG L in the Cox regression model with the interaction terms to the model without the interaction terms. Similarly, we examined the statistical interaction between tetracycline use and smoking on risk of CD and UC. To further clarify whether personal history of rosacea and tetracycline use interacts on the risk of CD and UC, a third interaction analysis was conducted.

All above interaction analyses did not yield significant findings. We tested the interaction between rosacea and smoking but did not find significant interactions for CD (P_{int}=0.56) or UC (P_{int}=0.52). We did not observe significant statistical interactions between tetracycline use and smoking (P_{int}=0.28 for CD and 0.45 for UC). The interaction between tetracycline use and rosacea was not statistically significant either (P_{int}=0.77 for CD and 0.27 for UC), which again supports an independent role of tetracycline use and rosacea on risk of CD in our study.

Supplementary Table 1. Collection time of information on main exposure and outcome assessment in the cohort

	Questionnaire year
Main exposure	
Lifetime history of rosacea	2005
Ever use of tetracycline	1993
Duration of use of tetracycline	1993
Main outcome	
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	Biennially from 1989

Supplementary Table 2. The diagnosis age of incident Crohn's disease (CD) cases during the follow-up according to personal history of rosacea

	n	Mean (SD)	Median (Inter-quartile range)
CD without rosacea	138	45.2 (7.4)	45.4 (9.7)
CD with Rosacea	11	51.1 (5.3)	50.9 (6.7)

Supplementary Table 3. Personal history of rosacea and risk of incident Crohn's disease in sensitivity and secondary analyses

	Person-years	Cases	Multivariable-adjusted HR[†]
Additionally adjusting for severe teenage acne			
No rosacea	1,786,216	138	Ref (1.00)
Rosacea	70,371	11	2.19 (1.15-4.18)
Excluding those reporting history of severe teenage acne			
No rosacea	1,663,026	131	Ref (1.00)
Rosacea	63,103	11	2.45 (1.28-4.69)
Excluding those using tetracycline or isotretinoin, or antibiotics for acne or rosacea			
No rosacea	1,681,680	129	Ref (1.00)
Rosacea	48,052	9	2.43 (1.22-4.84)
Additionally adjusting for depressive systems and UV index			
No rosacea	1,786,216	138	Ref (1.00)
Rosacea	70,371	11	2.19 (1.15-4.17)
Excluding those with other major autoimmune diseases			
No rosacea	1,748,840	130	Ref (1.00)
Rosacea	67,808	11	2.36 (1.24-4.51)
Restricting to Whites only			
No rosacea	1,657,571	132	Ref (1.00)
Rosacea	67,887	10	2.04 (1.04-4.00)
Excluding cases identified in the first follow-up period			
No rosacea	1,594,595	128	Ref (1.00)
Rosacea	56,688	8	2.06 (0.98-4.34)
Restricting the follow-up between 1991 and 2005			
No rosacea	1,275,836	110	Ref (1.00)
Rosacea	33,176	8	2.56 (1.21-5.44)

[†]Adjusted for age, BMI, alcohol consumption, physical activity, physical examination, multi-vitamin use, smoking status, oral contraceptive use, menopausal status and menopausal hormone therapy, use of NSAIDs as well as use of medications including tetracycline, isotretinoin and antibiotics.

Supplementary Table 4. The diagnosis age of incident Crohn's disease (CD) or ulcerative colitis (UC) cases during the follow-up according to ever use of tetracycline

	n	Mean (SD)	Median (Inter-quartile range)
Crohn's disease			
Never use tetracycline	56	47.8 (7.5)	47.1 (8.5)
Ever use tetracycline	70	45.7 (6.4)	45.5 (9.1)
Ulcerative colitis			
Never use tetracycline	88	45.9 (7.0)	46.1 (9.1)
Ever use tetracycline	97	47.2 (6.4)	47.7 (8.8)

References to Supplementary Data

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