High Residential Sun Exposure Is Associated With a Low Risk of Incident Crohn's Disease in the Prospective E3N Cohort

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Background: Vitamin D insufficiency has been suggested to be associated with high risk of Crohn's disease (CD). In France, where food fortification is limited, the major source of vitamin D is through sun exposure. The aim of this work was to analyze the relationship between residential sun exposure and the risk of incident CD or ulcerative colitis (UC).

Methods: The E3N cohort consists of women living in France, aged 40 to 65 years and free of major diseases at inclusion in 1990. Among the 91,870 women included in the study, we identified 123 incident cases (45 CD, 71 UC, and 7 indeterminate colitis). To assess residential sun exposure, we used a database containing mean daily ultraviolet radiation (UVR) dose for each French county. The relationship between residential sun exposure and risk of incident inflammatory bowel diseases was explored using Cox models.

Results: Higher levels of residential sun exposure were associated with a significant decreased risk of CD (hazard ratio [HR] for the third versus the first tertile of UVR dose, 0.49; 95% confidence interval (CI), 0.23–1.01; P for trend = 0.04), but not of UC (HR, 1.21; CI, 0.61–2.11). In women with available data on dietary vitamin D intake, we observed a lower risk of CD with higher residential UVR (HR, 0.29; 95% CI, 0.11–0.80; P for trend = 0.01). Dietary vitamin D intake was neither associated with the risk of CD (HR, 0.41; 95% CI, 0.14–1.24; P for trend = 0.14) nor UC (HR, 1.61; CI, 0.61–4.23).

Conclusions: In this prospective cohort of women, high residential sunlight exposure was associated with decreased incidence of CD, but not UC.

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Key Words: cohort study, sun exposure, Crohn's disease, vitamin D, ultraviolet radiation

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) characterized by an abnormal composition of the intestinal microbiota and a deregulated activation of cellular immunity within the intestines.[1] During the past 2 decades, there have been substantial progress in genetics of IBD, and 163 predisposing loci have been identified.[2] Environmental factors also play a crucial role in the etiology of IBD. Tobacco, antibiotics, and diet are the best documented of these factors.[3,4] Geographical variation in the incidence of IBD may be a clue to other environmental risk factors.[5] There are indeed large differences in CD and UC incidence across regions and countries. A gradient of increasing risk of IBD with latitude has been demonstrated in different countries.[6–9] Variations in the level of ultraviolet radiation (UVR) exposure could account for this gradient. In a recent work, we described an ecological association between regional level of UVR and incidence of CD in a nationwide study using an administrative data set.[10] However, in this study, it was impossible to control for other lifestyle factors, such as tobacco, physical exercise, and vitamin D intake. Therefore, the aim of this study was to investigate the possible relationships between residential sun exposure, dietary vitamin D intake, and the risk of subsequent IBD in a well-defined prospective cohort of women followed up for more than 15 years, with appropriate adjustment for a number of salient factors.

POPULATION AND METHODS

E3N ("Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale") is a prospective cohort study conducted in France to assess hormonal and dietary risk factors for the most common diseases, especially cancer, in women. Details of the cohort have been described extensively elsewhere.[11,12]

In brief, the cohort was established in 1990 and consisted of 98,995 women living in France, aged 40 to 65 years at baseline and insured by a national health plan mainly covering teachers.[11] Physical activity, reproductive factors, use of hormonal treatments,

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tobacco consumption, anthropometric measurements, skin color, personal history of disease, family history of cancer, and other factors were recorded in self-administered questionnaires completed approximately every 24 to 36 months up to 2005. Each questionnaire inquired about the occurrence of personal medical events (cancers, chronic diseases, or hospitalizations). All study subjects signed an informed consent form, in compliance with the rules of the French National Commission for Computed Data and Individual Freedom from which we obtained approval.

Identification of IBD Cases and Noncases

Cases were first identified through the questionnaires, where the women checked the item "Crohn's disease" or "ulcerative colitis." Cases were identified up to the latest questionnaire in 2005. A further validation was performed with a subsequent questionnaire filled by their physician (gastroenterologist or general practitioner) to confirm IBD diagnosis. Two of the authors (P.J. and F.C.) reviewed all the cases for final classification: CD, UC, or indeterminate chronic colitis.[12]

Among the entire cohort, 458 women checked the item CD or UC on the self-administered questionnaire. After investigation, including contact with the general physician and/or gastroenterologist, we validated the diagnosis of IBD in 194 women and excluded IBD in 264 cases (mainly IBS). Among the 194 IBD cases, 123 women were diagnosed as having IBD after enrollment in the cohort.

Residential Sun Exposure

The metropolitan French territory is divided administratively into 94 counties, which differ in size (from 105 to 10,000 km^2) and in population (from 74,234 to 2,561,800 inhabitants).

County of residence was obtained for all participants at inclusion in the cohort and at each subsequent questionnaire. Information on county of residence at baseline was linked to a database containing mean daily erythemal doses (UVR in kJ/m^2 per day) in French metropolitan counties, which we obtained from the Joint Research Centre of the European Commission.[13]

The database covers the period from January 1984 to August 2003, with UVR maps covering Europe with a spatial resolution of 0.05°. UVR doses were estimated by a satellite-derived mapping algorithm that has been previously described.[13] Briefly, UVR doses were obtained by interpolation in a validated look-up table using the UV specification code of the radiative transfer model package (version 13), the entries of which are solar zenith angle, total column ozone amount, cloud liquid water thickness, near-surface horizontal visibility, surface elevation, and UV albedo. Both satellite (Meteosat) and nonsatellite (synoptic observations, meteorological model results, and digital elevation model) data were exploited to assign values to the influencing factors. UVR doses were constructed by numerical integration of the dose rate estimated at half-hourly intervals from, and including, the local solar noon (for each pixel from the full-resolution satellite images). The quality of the satellite-derived estimates has been assessed at several sites in Europe with usually good relative difference between the satellite estimates and the measured ground erythemal daily doses and small bias (<3%).[14]

For this study, we considered residential sun exposure (i.e., mean daily UVR dose in the county of residence at inclusion) for each woman over the period 1984 to 1989 (i.e., before the inclusion into the cohort). We calculated tertiles of UVR dose, both at inclusion using data from the 1990 questionnaire (for the analysis based on the whole cohort) and at baseline using data from the 1993 diet questionnaire. No data were available on individual recreational sun exposure. We included in the analyses only those women who consistently lived in the same county throughout the study period.

Dietary Data Collection

Dietary data were collected once, between June 1993 and July 1995, using a 2-part questionnaire. The first part contained questions on the usual amounts and frequency of consumption of food items from the various food groups, whereas the second included qualitative questions specifying individual food items within the food groups. The questionnaire was used to assess the consumption of 208 food items and beverages and the recipes used to prepare them. It was accompanied by a booklet of photographs illustrating portion sizes. Both the questionnaire and the booklet have been validated.[15] The diet history questionnaire was sent to 95,644 women, with 2 reminders to nonresponders; 74,531 questionnaires were available for analysis. The mean daily intake of nutrients was assessed using a food composition table derived from the French national database.

Physical Activity

Assessment of habitual physical activity at baseline was based on questions on the usual distance walked daily, the average number of stairs climbed daily, the average amount of time spent weekly doing light household activity and heavy household activity, and the average amount of time spent weekly doing moderate recreational activity and vigorous recreational activity. A recreational physical activity score was estimated by multiplying the metabolic equivalent task (MET) of walking and moderate and vigorous recreational activities by their frequency and duration. A value of 3 METs for walking and 6 METs and 9 METs for moderate and vigorous recreational activities, respectively, was assigned, according to the Compendium of Physical Activities.[16]

Skin Complexion

At baseline, E3N participants were asked to report their skin color with a higher level of detail, using 6 categories: albino, very fair, fair, medium, dark, and very dark (Table, Supplemental Digital Content 1, http://links.lww.com/IBD/A341).

Statistical Analysis

The association between residential sun exposure and risk of IBD was analyzed for all incident IBD cases and separately for CD and UC using Cox proportional hazards regression models

with age as the time scale. Age at diagnosis of IBD or at censoring date was used as end-of-study time variable. Two analyses were performed: the first on the whole cohort after excluding 6985 women with incomplete data and 140 prevalent IBD cases, and the second restricted to women who completed a dietary questionnaire in 1993. Among the women with dietary data, those with extreme values (in the bottom and top 1%) of the ratio between energy intake and energy required (computed after taking into account age, weight, and height) were excluded (n = 1364). In addition, 4654 women who had reported cancer diagnosis before responding to the dietary questionnaire, 112 women who changed county of residence during follow-up were excluded, thus leaving 67,572 women for the dietary analysis. Dietary vitamin D intake was included in the model as tertiles of intake.

Models were adjusted for body mass index at baseline (continuous), physical activity at baseline (i.e., MET per hour during a week: weekly energy expenditure), smoking status at baseline (former/never/current), menopausal hormone therapy use (ever/never), level of education as a proxy for socioeconomic status, and skin complexion in 2 categories: (1) fair skin including (albino/very fair/fair) and (2) dark skin: including (medium/dark/very dark).

Results were presented as the mean, SD or median, interquartile range (IQR) for continuous variables and N (%) for categorical variables. In survival analyses, we computed hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical tests were 2-sided and P values < 0.05 were considered statistically significant. Analyses were performed using the SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Among the 91,870 women included in this study, 123 incident cases of IBD occurred (45 CD, 71 UC, and 7 indeterminate chronic colitis) during a mean follow-up of 13.1 years. Among the 67,572 women who completed the dietary questionnaire, 77 cases of IBD occurred during a mean follow-up of 10.4 years. The characteristics of IBD cases and noncases are displayed in Table 1. The mean age at diagnosis of IBD was 54.4 years (SD, 7.0) for UC and 53.8 years (SD, 6.9) for CD, and the median duration of follow-up before diagnosis was 7.1 years (IQR, 7.1). The median (IQR) daily residential UVR doses for CD, UC, and non-IBD cases were, respectively, 1.51 (0.22), 1.60 (0.33), and

TABLE 1. Characteristics of CD, UC, and Noncases

	UC (N = 71)	CD (N = 45)	Noncases (N = 91,747)	*P*
Age at inclusion, mean (SD), yr	47.4 (6.2)	46.9 (6.0)	49.3 (6.6)	0.003
Age at diagnosis, mean (SD), yr	54.4 (7.0)	53.8 (6.9)	—	
Median follow-up duration before diagnosis (IQR range)	7.0 (3.34–10.63)	6.90 (4.38–9.80)	—	
Tobacco smoking at baseline, %				
Never	51.3	54.3	56.3	0.73
Past	30.3	26.1	28.9	
Current	28.6	19.6	14.6	
University degree, %	94.8	89.1	71.4	0.25
Hormonal treatments, %				
Ever use of MHT	68.4	73.9	66.1	0.48
Ever use of oral contraceptives	60.5	63.0	60.1	0.90
Physical activity at baseline, %				
Inactive	38.2	34.8	39.0	
Moderately active	39.5	26.1	31.7	
Active	22.3	39.1	29.3	
Skin Color*				0.05
Light skin, N (%)	46 (64.7)	32 (71.1)	52,674 (57.5)	
Dark skin, N (%)	24 (33.8)	13 (28.9)	37,183 (40.5)	
Missing	1	—	1890 (0.02)	
Daily UVR dose in county of residence at inclusion (kJ/m^2), median (IQR)	1.60 (0.33)	1.51 (0.22)	1.59 (0.28)	0.02

	UC (N = 43)	CD (N = 30)	Noncases (N = 67,499)
Vitamin D intake, N, mean (range)	113.4 (25.7–304.1)	93.2 (18.4–252)	104.9 (0.1–647.2)

*Skin color was grouped into 2 categories: light skin included people with fair to median skin type and dark skin included people with olive to black skin type.

TABLE 2. Relationship Between Daily Residential Sun Exposure and Risk of IBD in the E3N Cohort Study (n = 91,870)

			Age-adjusted Model				Multiadjusted model*			
			Mean Daily UVR Dose Exposure in County of Residence at Inclusion (kJ/m^2)				Mean Daily UVR Dose Exposure in County of Residence at Inclusion (kJ/m^2)			
	Cases	Noncases	<1.51 HR	1.51–1.75 HR (95% CI)	≥1.75 HR (95% CI)	*P* Trend	<1.51 HR	1.51–1.75 HR (95% CI)	≥1.75 HR (95% CI)	*P* Trend
IBD	123	91,747	1	0.76 (0.49–1.17)	0.79 (0.52–1.21)	0.27	1	0.77 (0.50–1.19)	0.79 (0.52–1.21)	0.28
UC	71	91,747	1	0.97 (0.54–1.76)	1.17 (0.67–2.03)	0.58	1	1.01 (0.56–1.85)	1.21 (0.69–2.11)	0.51
CD	45	91,747	1	0.58 (0.29–1.17)	0.50 (0.24–1.04)	0.05	1	0.57 (0.28–1.16)	0.49 (0.23–1.01)	0.04

*Adjusted for body mass index at baseline (continuous), physical activity at baseline (weekly energy expenditure, continuous), smoking status at baseline (former/never/current), menopausal hormone therapy use (ever/never), and level of education.

1.59 (0.28) kJ/m^2 per day. At baseline, the annual daily doses of UVR for each tertile were defined as follows: <1.51, 1.51 to 1.75, or >1.75 kJ/m^2 per day.

In a multivariable-adjusted model, the risk of incident CD was lower in the group of women who lived in counties with the highest UVR levels at inclusion (1.75 kJ/m^2 day) as compared with the lowest (1.51 kJ/m^2 per day) (HR, 0.49; 95% CI, 0.23–1.01; *P* for trend = 0.04). Additional adjustment for skin color did not change the association between UVR and the risk of CD (data not shown). There was no significant association between risk of UC and residential sun exposure (Table 2).

Dietary variables (vitamin D and calcium) were analyzed in women who completed the dietary questionnaire, including 30 cases of incident CD, 43 cases of incident UC, and 67,492 noncases (Table 3). In the cohort as a whole, participants had a quite low median dietary vitamin D intake: 94.8 IU/d (IQR, 61.6). Mean daily intakes of vitamin D were 59.2, 95.2, and 149.2 IU/d for the first, second, and third tertiles, respectively. The mean calcium intake in the cohort was 1050 g/d (SD IU/d 439).

In age-adjusted models, dietary vitamin D intake was not significantly associated with the risk of either CD (HR for the third versus the first tertile of vitamin D intake, 0.39; 95% CI, 0.12–1.20), or UC (HR, 1.78, 95% CI, 0.82–3.87), although point estimates for CD and UC significantly differed (*P* for homogeneity = 0.02). There was no significant relationship between calcium intake and the risk of either CD or UC. An additional analysis was performed adjusting for oral supplement use of vitamin D by a subset of women, which did not change the relation between vitamin D and risk of CD (data not shown).

When including both vitamin D intake and residential sun exposure in the model, the relationship between UVR dose and risk of CD was strengthened (HR, 0.29; 95% CI, 0.11–0.80; *P* for trend = 0.01), whereas the association with dietary vitamin D and incident CD remained nonsignificant (HR for the third versus the first tertile of vitamin D intake, 0.41; 95% CI, 0.14–1.24; *P* for trend = 0.14). The relation between UC, UVR, and dietary vitamin D remained nonsignificant in the multiadjusted model.

DISCUSSION

In this prospective cohort study, we describe an inverse association between risk of incident CD and residential UVR exposure in a French female population of medium age.

Our results confirm our previous study showing a North to South gradient of CD incidence in France.[6] They are in line with another prospective cohort study performed in the United States, where the authors found a decreased incidence of CD with latitude.[17] In this study, the HR for women residing at southern latitudes was 0.48 (0.30–0.77) for CD and 0.62 (0.42–0.90) for UC. We did not find any relation between UVR and risk of UC in this study or in our previous studies. The association between CD and latitude may be attributed to a direct immune effect of UVR or to variations in vitamin D synthesis.

TABLE 3. Multivariate Analysis of Residential Daily Sun Exposure, Dietary Vitamin D Intake, and Dietary Calcium Intake in Relation with CD Incidence in the E3N Cohort (n = 67,565)*

	Median Value	Cases	Noncases	HR (95% CI)	*P* Trend
CD					
Daily UVR (kJ/m^2)					0.01
<1.51	1.49	16	23,039	1 (reference)	
1.51–1.75	1.60	9	20,736	0.58 (0.26–1.31)	
>1.75	1.85	5	23,717	0.29 (0.11–0.80)	
Dietary vitamin D intake (IU/d)					0.13
<95.7	59.2	10	22,504	1 (reference)	
95.7–116.8	95.2	15	22,496	1.32 (0.59–2.99)	
>116.8	149.2	5	22,500	0.41 (0.14–1.24)	
Calcium intake (mg/d)					0.39
<844	696	9	22,500	1 (reference)	
844–1138	981	10	22,504	1.18 (0.48–2.93)	
>1138	1376	11	22,496	1.49 (0.60–3.68)	
UC					
Daily UVR (kJ/m^2)					0.77
<1.51	1.49	17	23,039	1 (reference)	
1.51–1.75	1.60	10	20,736	0.74 (0.31–1.78)	
>1.75	1.85	16	23,717	0.88 (0.39–2.01)	
Dietary vitamin D intake (IU/d)					0.38
<95.7	59.2	10	22,504	1 (reference)	
95.7–116.8	95.2	15	22,496	1.81 (0.72–4.60)	
>116.8	149.2	18	22,500	1.61 (0.61–4.23)	
Calcium intake (mg/d)					0.73
<844	696	15	22,500	1 (reference)	
844–1138	981	10	22,504	0.58 (0.22–1.51)	
>1138	1376	18	22,496	1.11 (0.49–2.52)	

*Adjusted for total energy intake, body mass index at baseline (continuous), smoking status at baseline (former/never/current), physical activity at baseline (weekly energy expenditure, continuous), menopausal hormone therapy use (ever/never), level of education, dietary vitamin D intake, calcium intake, and UVR daily dose.

There are many pieces of evidence about immunosuppression at the local UV-irradiated site (skin), but there remains some uncertainty about the potential mechanisms associated with UV-induced systemic immunosuppression. Indeed, some molecules activated by UVR might play a role in the regulation of the immune system.[18,19]

Two sources of vitamin D are available to humans: diet provides vitamin D mediated by chylomicrons, and the skin is the site of vitamin D synthesis through ultraviolet B radiation. Natural food sources of vitamin D are limited and mainly consist of fatty fish, eggs, and liver. Thus, vitamin D from ultraviolet B is essential. Under the action of UVR, the skin synthesizes pro-vitamin D3. The level of dermal absorption of radiation is directly correlated to the exposed surface and to skin pigmentation. A recent U.S. study examined vitamin D status in relation to risk of CD and UC. It showed a lower risk of CD but not of UC in patients with the highest quartile of predicted serum level of vitamin D and an inverse correlation between dietary vitamin D and risk of UC, but not of CD.[20] In France, food fortification is recent and very limited. The major source of vitamin D comes from endogenous synthesis through outdoor UV exposure. There was a nonsignificant trend for an inverse association between high dietary intake and risk of CD. The daily dietary intake of vitamin D in our cohort was quite low even in the high-intake group. Moreover, we had a lack of power in this subgroup analysis because only 5 subjects were in the highest tertile of vitamin D intake.

Several mechanisms involved in the relationship between vitamin D, sunshine, and gut inflammation have been documented. Vitamin D acts both on innate and acquired immunity.[21] The metabolic effect of vitamin D runs through the vitamin D receptor, whose gene is located on chromosome 12 (region q13-26) and for which many variants have been identified.[22] Some of these polymorphisms have been associated with CD in adult

populations.[23] It has been shown that vitamin D stimulates the expression of NOD2/CARD15 in monocytes and epithelial cells.[24] Finally, there is consistent evidence for an impact of UVR and vitamin D on lowering the risk of TH1-mediated autoimmune diseases, such as multiple sclerosis or type 1 diabetes.[25–28] These data add to the evidence that UVR and/or vitamin D may protect against CD. In this study, we found a yearly difference of 33 kJ/m^2 (33,000 J/m^2) between CD and noncases. This can be extrapolated as a difference of production of vitamin D of 1000 IU/d between CD and noncases assuming that only one-quarter of the body is exposed. Thus, this difference of 1000 IU/d is clinically relevant.[29]

The strengths of our study are the prospective collection of data, the high response rates at each questionnaire, the long follow-up of the cohort, the adjustment for several lifestyle factors, and the careful ascertainment of diagnosis of CD and UC. The low number of IBD cases in our study population (which may have induced a type 1 error in our main finding) and extrapolation of county of residence at inclusion to individual level of residential sun exposure are the main limitations of the study. Assessment of individual sun exposure levels in humans involves known challenges, and several studies have examined the question of the best assessment tool to use. Various collection systems exist and all have their advantages and drawbacks (e.g., prospective or retrospective questionnaires, skin sensors of sun exposure, etc).[30–32] Ground sensors are not available everywhere in France. However, in this study, we used data from satellite collection that have proven to be a reliable measurement of ground sunlight.[14] Although women living in the same county may have similar levels of residential UVR exposure, they may have very different levels of total sun exposure depending on their daily activities, and especially regarding the amount of outdoor sun exposure. We systematically adjusted our analyses for physical activity in an attempt to control for sun exposure during outdoor physical activity and thus reduce this potential bias. Besides, because report of residential sun exposure is unlikely to be differential between cases and noncases, a misclassification bias in this factor would likely underestimate our results. It can also be argued that the study population of women aged between 40 and 65 years does not reflect the peak age of diagnosis of CD, which is about 2 decades earlier. However, one study showed that the decreased incidence of CD with latitude is observed for residence at 30 years of age but not for residence at birth or at the age of 15 years.[17] This suggests that the protective effect of residential sun exposure may appear later and apply to middle-aged women only.

In conclusion, this study adds to the available evidence that residential sun exposure is associated with a decreased incidence of CD. Various level of sun exposure may well explain the North-to-South gradient of CD incidence. Vitamin D production through reasonable sunlight exposure may therefore reduce the risk of CD in high-risk populations. Future studies could investigate the relationship between UVR and the modulation of IBD in animal models of IBD and its interaction with vitamin D.

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Ethical approval: The French Commission for Computed Data and Individual Freedom (Commission Nationale Informatique et Libertés, CNIL) gave its ethical approval for the study.

Author contributions: P. Jantchou contributed to study design and implementation, data collection, design and implementation of the statistical analysis, interpretation of results, and drafting and review of the article. F. Clavel-Chapelon contributed to enrolment and follow-up of patients, design and implementation of the study, and review of the article. A. Racine and M. Kvaskoff contributed to drafting and review of the article. M. C. Boutron-Ruault contributed to design and implementation of the study, data collection, design and implementation of the statistical analysis, interpretation of results, and drafting and review of the article. All authors have reviewed the final submitted article and agreed with its contents.

REFERENCES

1. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med.* 2009; 361:2066–2078.
2. Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature.* 2012;491:119–124.
3. Hviid A, Svanström H, Frisch M. Antibiotic use and inflammatory bowel diseases in childhood. *Gut.* 2011;60:49–54.
4. Andersen V, Olsen A, Carbonnel F, et al. Diet and risk of inflammatory bowel disease. *Dig Liver Dis.* 2012;44:185–194.
5. Cosnes J, Gower-Rousseau C, Seksik P, et al. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology.* 2011;140: 1785–1794.
6. Nerich V, Monnet E, Etienne A, et al. Geographical variations of inflammatory bowel disease in France: a study based on national health insurance data. *Inflamm Bowel Dis.* 2006;12:218–226.
7. Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut.* 1996;39:690–697.
8. Armitage EL, Aldhous MC, Anderson N, et al. Incidence of juvenile-onset Crohn's disease in Scotland: association with northern latitude and affluence. *Gastroenterology.* 2004;127:1051–1057.
9. Sonnenberg A, McCarty DJ, Jacobsen SJ. Geographic variation of inflammatory bowel disease within the United States. *Gastroenterology.* 1991; 100:143–149.
10. Nerich V, Jantchou P, Boutron-Ruault MC, et al. Low exposure to sunlight is a risk factor for Crohn's disease. *Aliment Pharmacol Ther.* 2011;33:940–945.
11. Clavel-Chapelon F, van Liere MJ, Giubout C, et al. E3N, a French cohort study on cancer risk factors. E3N Group. Etude Epidemiologique aupres de femmes de l'Education Nationale. *Eur J Cancer Prev.* 1997;6: 473–478.
12. Jantchou P, Morois S, Clavel-Chapelon F, et al. Animal protein intake and risk of inflammatory bowel disease: the E3N prospective study. *Am J Gastroenterol.* 2010;105:2195–2201.
13. Verdebout J. A European satellite-derived UV climatology available for impact studies. *Radiat Prot Dosimetry.* 2004;111:407–411.

14. Mayer B, Seckmeyer G, Kylling A. Systematic long-term comparison of spectral UV measurements and UVSPEC modeling results. *J Geophys Res.* 1997;102:8755–8767.
15. van Liere MJ, Lucas F, Clavel F, et al. Relative validity and reproducibility of a French dietary history questionnaire. *Int J Epidemiol.* 1997;26 (suppl 1):S128–S136.
16. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc.* 2000;32:S498–S504.
17. Khalili H, Huang ES, Ananthakrishnan AN, et al. Geographical variation and incidence of inflammatory bowel disease among US women. *Gut*. 2012;61:1686–1692.
18. Hart PH, Gorman S. Exposure to UV Wavelengths in Sunlight Suppresses Immunity. To What Extent is UV-induced Vitamin D3 the Mediator Responsible? *Clin Biochem Rev.* 2013;34:3–13.
19. Norval M, Halliday GM. The consequences of UV-induced immunosuppression for human health. *Photochem Photobiol.* 2011;87:965–977.
20. Ananthakrishnan AN, Khalili H, Higuchi LM, et al. Higher pedicted Vitamin D status is associated with reduced risk of Crohn's disease. *Gastroenterology*. 2012;142:482–489.
21. Adams JS, Hewison M. Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. *Nat Clin Pract Endocrinol Metab.* 2008;4:80–90.
22. Ramagopalan SV, Heger A, Berlanga AJ, et al. A ChIP-seq defined genome-wide map of vitamin D receptor binding: associations with disease and evolution. *Genome Res.* 2010;20:1352–1360.
23. Xue LN, Xu KQ, Zhang W, et al. Associations between vitamin D receptor polymorphisms and susceptibility to ulcerative colitis and Crohn's disease: a meta-analysis. *Inflamm Bowel Dis.* 2013;19:54–60
24. Wang TT, Dabbas B, Laperriere D, et al. Direct and indirect induction by 1,25-dihydroxyvitamin D3 of the NOD2/CARD15-defensin beta2 innate immune pathway defective in Crohn disease. *J Biol Chem.* 2010;285:2227–2231.
25. Hyppönen E, Läärä E, Reunanen A, et al. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet*. 2001;358:1500–1503.
26. Sloka S, Grant M, Newhook LA. Time series analysis of ultraviolet B radiation and type 1 diabetes in Newfoundland. *Pediatr Diabetes.* 2008;9:81–86.
27. Sloka S, Grant M, Newhook LA. The geospatial relation between UV solar radiation and type 1 diabetes in Newfoundland. *Acta Diabetol.* 2010; 47:73–78.
28. van der Mei IA, Ponsonby AL, Dwyer T, et al. Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. *BMJ*. 2003; 327:316.
29. Macdonald HM. Contributions of sunlight and diet to vitamin D status. *Calcif Tissue Int.* 2013;92:163–176.
30. McCarty CA. Sunlight exposure assessment: can we accurately assess vitamin D exposure from sunlight questionnaires? *Am J Clin Nutr.* 2008;87:1097S–1101S.
31. Thieden E, Philipsen PA, Heydenreich J, et al. UV radiation exposure related to age, sex, occupation, and sun behavior based on time-stamped personal dosimeter readings. *Arch Dermatol.* 2004;140:197–203.
32. Yu CL, Li Y, Freedman DM, et al. Assessment of lifetime cumulative sun exposure using a self-administered questionnaire: reliability of two approaches. *Cancer Epidemiol Biomarkers Prev.* 2009;18:464–471.