Higher Sun Exposure is Associated With Lower Risk of Pediatric Inflammatory Bowel Disease: A Matched Case-control Study

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See "To Prevent Inflammatory Bowel Disease in Children, Let the Sunshine in?" by Brenner and Sylvester on page 137.

ABSTRACT

Objectives: The incidence of pediatric inflammatory bowel disease (IBD) is increasing worldwide. Ecological studies show higher incidence in regions at higher latitude or lower ambient ultraviolet radiation; individual-level associations with sun exposure have not been assessed.

Methods: We recruited children (0–17 years) with IBD from 2 large hospitals in Melbourne, Australia. Control participants were recruited from the day surgery unit of one of the same hospitals. Questionnaires provided data on demographics, past sun exposure, the likelihood of sunburn (skin sensitivity) or tanning following sun exposure, use of sun protection, physical activity, and parental smoking and education. Grandparent ancestry was used to determine participant ethnicity. Cases and controls were matched on age and sex. We used conditional logistic regression to test the association between being an IBD case and past sun exposure at different ages, adjusted for a range of other factors.

Results: After matching, n = 99 cases and n = 396 controls were included in the analysis. In multivariable analysis, for each 10 min increment in leisure-time sun exposure in summer or winter there was a linear 6% reduction in the odds of having IBD ($P = 0.002$). Results were similar in sensitivity analyses including only the most recently diagnosed cases, only Caucasian cases and controls, only those with symptom onset within the year before study entry, or additionally adjusted for age or physical activity.

Conclusions: Higher sun exposure in the previous summer or winter was associated with a reduced risk of having IBD. There are plausible pathways that could mediate this effect.

Key Words: epidemiology, sun exposure, vitamin D

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What Is Known

- The incidence of pediatric inflammatory bowel disease is increasing.
- Ecological studies have shown an inverse association with ambient levels of ultraviolet radiation.
- The causes of pediatric inflammatory bowel disease are not well defined.

What Is New

- Higher past sun exposure is associated with lower odds of having inflammatory bowel disease.
- The association with sun exposure appears to be linear and is apparent when analyses are restricted to the most recently diagnosed, or within Caucasian populations only.

Inflammatory bowel disease (IBD) is uncommon in childhood, but 15 to 25% of all cases are diagnosed before age 20 years (1). The incidence of pediatric IBD is increasing over time (2). This may be partly because of improvements in diagnostic methods, but changing environmental exposures may also be important (3).

Both genetic and environmental factors are implicated in the risk of pediatric IBD, possibly working through changes in the gut microbiome and immunological pathways [reviewed in (4)]. Environmental risk factors for IBD include living at a higher latitude (2), urban living (5), higher socioeconomic status (6), lack of exposure to relatively harmless enteric microorganisms in infancy (7), and exposure to cigarette smoke (8).

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PAID Consortium: Pediatric AutoImmune Disease Consortium.

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The 2 main types of IBD, Crohn disease (CD) and ulcerative colitis (UC), have different clinical characteristics, and possibly different etiologies. We and others have shown that the incidence of pediatric CD increases with increasing distance from the Equator (at least in the Northern Hemisphere) (2,9) and in association with living in a location with a greater number of months where the average daily ultraviolet (UV) radiation was lower than a threshold (1488 kJ/m^2) (2). These findings suggest a link between incidence of childhood IBD and exposure to UV radiation or an associated factor, such as vitamin D. There are not yet any studies investigating, at the individual level, whether greater exposure to UV radiation is associated with a reduced risk of IBD onset.

Here we extend our previous work (2) to report the results from a matched case-control study investigating individual-level sun exposure and risk of IBD in children under 18 years of age, living in Melbourne, Australia.

METHODS

Study Population

Case participants were ages 0 to 17 years and diagnosed with IBD using clinical, histological, and radiological criteria, according to the guidelines of the Gastroenterology Society of Australia (10). They were recruited from 2 large hospitals in Melbourne, Victoria, Australia (latitude 37.7°S, average monthly maximum UV Index 2 in winter [June to August] and 10 in summer [December to February]) (11) from 2010 to 2013.

Control participants were ages 0 to 17 years and born in the state of Victoria. They had no prior diagnosis of any IBD-related disease and no family history of IBD. They were recruited from the day surgery unit of one of the hospitals involved in case recruitment.

Diagnosis of Inflammatory Bowel Disease

Medical records provided data on the date of symptom onset, and of IBD diagnosis, and the type of IBD (ie, CD, UC, or indeterminate IBD [IIBD]) for cases, and the reason for day surgery for controls.

Parents (or guardians) of the participating children completed questionnaires providing data on sun exposure and related variables, as well as demographic factors (age, sex, ancestry), physical activity, and parental smoking and education.

Sun exposure was measured with questions on time in the sun in summer and winter (separately) on weekends and holiday at ages 0 to 2 years, 3 to 5 years, 6 to 10 years, and 11 to 15 years; and time in the sun in the last summer and winter (separately) on weekdays, weekends, and during holidays (recorded in categories of <1 hour/day [with additional categorization of none, some but less than $^1/_2$ hour; $^1/_2$ to 1 hour], 1-2 hours/day, 2-3 hours/day, 3–4 hours/day, ≥4 hours/day). These questions have been previously validated in children against objective measures of sun exposure (12,13). Leisure-time (weekends and holidays) is preferable to weekdays as this is the time of the greatest variability in sun exposure, with weekday sun exposure often prescribed by work and/or school timetables.

Covariates

Ancestry of the child's natural grandparents (British/Irish, European, Asian, Aboriginal or Torres Strait Islander, Do not know, Other), reported separately for maternal and paternal grandparents;

Sun sensitivity, based on the question: "How does your child's skin react when your child sits in the sun in the middle of the day, for the first time in summer, without sunscreen?" (response categories: never burn, burn after more than 2 hours, burn after 1–2 hours, burn after $^1/_2$-1 hour, burn within $^1/_2$ hour).

Tanning, based on the question: "At the end of summer or after a 2-week holiday in the sun, what kind of tan would your child have?" (response categories: practically no tan, a light tan, a medium tan, a dark tan);

Sun protection, based on the question (separately for summer and winter): "When outside in summer (winter), how often would your child use sunscreen or be "covered up" during the following age groups? – 0–2 years, 3–5 years, 6–10 years, 11–15 years?" (response categories: never or rarely, occasionally, most of the time, always or almost always).

Physical activity, measured as the frequency and duration (how often, and how many hours or minutes) of vigorous physical activity per week in the past 3 months when the child was well (before developing disease for cases): not at all, less than once, once, 2 to 3 times, 4 to 6 times, every day; and, none, <30 minutes, 30 to 60 minutes, 1 to 2 hours, 2 to 3 hours, 3 to 6 hours, >6 hours;

Smoking: number of cigarettes smoked per day for mother and father separately and for the mother during the pregnancy with the participant child (nil, 1–10, 11–20, >20);

Education: the highest education achieved, separately for mother and father (did not complete secondary school, completed secondary school, trade certificate or similar, university qualification).

Data Management

Due to the disparity in the age distribution of cases and controls, we matched cases by sex and age at interview (within 3 months to age 8 years; within 6 months for ≥8 years) to as many controls as possible (from 1 : 1 to 1 : 24). For dates of diagnosis, where the exact day and/or month were missing (39% of days and 15% of months and days), we assigned the 15th for the day and June for the month. For example, 15th June 2012 was assigned as the date of diagnosis if only 2012 was provided for "date of diagnosis." Where the date of diagnosis was completely missing, but the date of symptom onset was available, we used the median days from symptom onset to the date of diagnosis for those with data on both variables (median = 216 days), added to the date of symptom onset, to impute the date of diagnosis. We used the date of diagnosis to determine the age group at diagnosis (and thus the time in the sun in that age group) as well as in the sensitivity analysis including only those most recently diagnosed (see below).

Sun exposure: We considered "time in the sun" as a categorical variable within each age group (collapsing categories to <1 hour, 1–2 hours, 2–3 hours, and ≥3 hours) and also as a continuous variable for leisure-time sun exposure in the last summer (and winter) by assigning the mid-point in minutes to each category (eg <$^1/_2$ hour per day = 15; $^1/_2$ to 1 hour per day = 45) and averaging across responses for holidays and weekends.

We collapsed categories for covariates to 2 or at most 3 categories to ensure sufficient numbers in each category and to preserve degrees of freedom.

Ethnicity was categorized as "Caucasian" if all grandparents were of Australian, British, Irish, or European ancestry, and otherwise "non-Caucasian/Mixed."

Sun sensitivity was collapsed to 3 categories: never burn or burn after 2 hours, burn after 1–2 hours, burn within 1 hour.

Tanning was collapsed to 2 categories: no tan or a light tan, a medium or dark tan.

Sun protection was collapsed to 3 categories: never, rarely or occasionally; most of the time; always/almost always. Data for the 0 to 2 years age group (summer) were used in the analysis as these were the most complete, and there was a high correlation with sun protection for other age groups in those with data available: 3–5 years: Spearman rho = 0.78, $P < 0.001$; 6–10 years: Spearman rho = 0.64, $P < 0.001$; 11–15 years, Spearman rho = 0.41, $P < 0.001$).

Physical activity: We combined frequency and duration to derive a 3-category variable of low (low frequency and low duration), moderate, and high (high frequency and high duration).

Smoking was categorized as a dichotomous variable of smoking/not smoking for each of mother, father, and smoking when pregnant.

Education was collapsed to 3 categories: secondary school or below; trade certificate or other, university qualification.

Statistical Analysis

Descriptive data are presented as frequencies (percentages) for categorical variables, and as mean and standard deviation (SD) or median, quartile 1, and quartile 3 (Q1, Q3) for continuous variables, according to whether the distribution was normally or nonnormally distributed. We first tested the univariate associations between each of the covariates and case-control status, using conditional logistic regression to take account of the matching by age and sex. We used Mann-Whitney *U* and Kruskal-Wallis tests for the univariate associations between *sun exposure* (as defined above) and each of the covariates in the control group, to identify potential confounders. We used a Spearman correlation to test inter-relationships between the covariates.

We modelled the association between being a case with IBD (outcome of interest) and sun exposure (exposure of interest) using univariable and multivariable conditional logistic regression. Covariates were included in the multivariable analysis based on a P value of <0.1 for both an association with the outcome and with the exposure (ie, a potential confounder). Where variables were collinear with similar P values, we selected the variable with the least number of missing values. In the main analysis, we generated an additional category of "missing" for each covariate to retain as much data in the analysis as possible. We undertook analyses stratified by sex and conducted several sensitivity analyses: restricting the dataset to those who had nonmissing data on all covariates; those with diagnosis within the previous year; those with symptom onset within the previous year; Caucasian only, additionally adjusting for age and sex, and additionally adjusting for physical activity.

Results are reported as odds ratios (ORs), adjusted ORs (aORs), and 95% confidence intervals (95% CI). Statistical analyses were performed with Stata 15.1 (StataCorp 2017. Stata Statistical Software, Release 15 College Station TX, StataCorp LP). A P value of <0.05 was considered statistically significant.

ETHICS APPROVAL

The study was approved by the Human Research Ethics Committees of the Victorian Department of Human Services, the Royal Children's Hospital, Melbourne, and the Australian National University. Parents/guardians gave written informed consent on behalf of each participating child before participation in the study.

RESULTS

After matching on age and sex there were n = 99 cases and n = 396 controls (Table 1). CD was the most common diagnosis (63.9%). Cases and controls were both primarily of Caucasian ancestry. Use of sun protection at age 0 to 2 years, physical activity, and father's education were not significantly different between cases and controls. Cases were less likely than controls to have a sunburn within 1 hour of sun exposure but more likely to have no tan or a light tan after a 2-week holiday in the sun. The prevalence of smoking was low in parents of both cases and controls; however, both fathers and mothers (including during pregnancy) of cases were less likely to currently smoke than for controls. Mother's education was significantly associated with case/control status, with the main difference between the groups the proportion having a trade certificate.

Table 2 shows the sun exposure for cases and controls within different age groups, in the summer and winter before interview, and in the age group corresponding to the date of diagnosis. The most complete data were for younger ages and for sun exposure in the previous summer or winter (younger cases and their matched controls do not provide responses for the older age categories). Cases tended to have lower sun exposure particularly with older age group, but the trend across sun exposure categories was statistically significant only for time in the sun at 11 to 15 years and for leisure-time sun exposure in the previous summer or winter. In the subset of participants (n = 66 cases, n = 108 controls) who had data across all 4 age-groups (ie, cases 11 years and older), the univariate association with sun exposure strengthened with increasing age (Table 2B). In order to retain as large a sample size as possible, the remainder of the analyses focused on sun exposure in the previous summer and winter.

We next explored the associations between recent summer and winter leisure-time sun exposure and the covariates in the control study population (Supplementary Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B650*). Tanning ($P = 0.001$, $P = 0.06$ for summer and winter, respectively) and use of sun protection at age 0 to 2 years ($P = 0.01$, $P = 0.05$ for summer and winter, respectively), but not sun sensitivity, were significantly associated with leisure-time sun exposure in the previous summer or winter. The children of mothers who smoked had higher leisure-time sun exposure in the previous summer ($P = 0.03$) and winter ($P = 0.04$), compared with those whose mothers did not smoke. Neither the mother's education nor the father's education, or the child's physical activity were associated with leisure-time sun exposure in the previous summer or winter (all $P > 0.1$).

We next assessed the correlation between covariates within the control group (see Supplementary Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/B650*). As might be expected sun sensitivity was inversely correlated with tanning (rho −0.23, $P < 0.0001$). Mother's education was inversely correlated with smoking (mother, rho = −0.29, $P < 0.0001$; father, rho = −0.23, $P < 0.0001$; smoking in pregnancy, rho = −0.23, $P < 0.0001$). Mother's smoking was highly correlated with father's smoking (rho = 0.46, $P < 0.0001$) and smoking during pregnancy (rho = 0.58, $P < 0.0001$). We thus selected the minimum set of covariates for multivariable analysis to include only one of the highly correlated pair (s), based on the covariate with the least amount of missing data, in addition to the criterion of $P < 0.1$ in univariate analyses of the associations with both case/control status (the outcome) and leisure-time sun exposure in the previous summer or winter (the exposure). Multivariable models thus included adjustment for tanning and mother's cigarette smoking.

Table 3 shows the results of the univariable and multivariable conditional logistic regression models for the association between leisure-time sun exposure in the previous summer and winter and being an IBD case. After adjustment, every additional 10 minutes of leisure-time sun exposure in the previous summer or winter was associated with a 6% reduction in the odds of being an IBD case (aOR = 0.94. 95% CI 0.91–0.98 for both). Figure 1 shows the adjusted ORs for categories of summer (a) and winter (b) leisure-time sun exposure, showing that the relationship is relatively linear (summer, P[trend] = 0.005; winter, P[trend] = 0.01). In models stratified by sex, the association with leisure-time sun exposure

TABLE 1. Characteristics of cases (n = 99) and age- and sex-matched controls (n = 396)

Characteristic	Cases	Controls	*P*
Age at interview (years)*, median (Q1, Q3)	13.2 (10.9, 15.5)	9.3 (6.4, 12.9)	
Sex, n (%)			
Male	51 (51.5)	257 (64.9)	
Female	48 (48.5)	139 (35.1)	
Ethnicity, n (%)			0.84
Caucasian	68 (75.6)	281 (75.9)	
Non-Caucasian/mixed	22 (22.4)	89 (24.1)	
Sun sensitivity, n (%)			0.03
Never burn or burn after 2 hours	32 (36.4)	97 (26.8)	
Burn after 1 to 2 hours	27 (30.7)	81 (22.4)	
Burn within 1 hour	29 (32.9)	184 (50.8)	
Tanning, n (%)			0.04
No tan or a light tan	45 (45.5)	138 (36.1)	
A medium or dark tan	54 (54.5)	244 (63.9)	
Sun protection (ages 0-2 years), n (%)			0.75
Never/rarely or occasionally	12 (13.2)	39 (12.4)	
Most of the time	22 (24.2)	101 (32.2)	
Always/almost always	57 (62.6)	174 (55.4)	
Physical activity, n (%)			0.23
Low	27 (30.0)	60 (20.1)	
Moderate	35 (38.9)	152 (50.8)	
High	28 (31.1)	87 (29.1)	
Mother cigarette smoking, n (%)			0.007
No	74 (81.3)	272 (70.5)	
Yes	17 (18.7)	114 (29.5)	
Father cigarette smoking, n (%)			0.01
No	69 (81.2)	232 (70.3)	
Yes	16 (18.8)	98 (29.7)	
Mother smoking when pregnant, n (%)			0.03
No	77 (85.6)	295 (76.8)	
Yes	13 (14.4)	89 (23.2)	
Mother's education, n (%)			0.003
Secondary school or less	38 (41.8)	121 (31.3)	
Trade cert or other	22 (24.2)	158 (40.8)	
University qualification	31 (34.1)	108 (27.9)	
Father's education, n (%)			0.10
Secondary school or less	23 (26.7)	89 (26.4)	
Trade cert or other	35 (40.7)	166 (49.3)	
University qualification	28 (32.6)	82 (24.3)	

P value is for the univariate conditional logistic regression (matched on age and sex) comparing cases and controls for each variable. *P* values are not recorded for the difference between cases and controls in age and sex, as cases and controls are matched on age and sex. Q1, Q3 = quartile 1, quartile 3. Numbers not adding to the total N represent missing data; university qualification = bachelor, postgraduate degree/postgraduate certificate or diploma.

*The difference in median age at date of interview between cases and controls relates to the greater number of controls matched to younger cases compared with those who were older.

was similar for boys (summer, aOR = 0.95, 95% CI 0.91–0.99, $P = 0.02$; winter, aOR = 0.94, 95% CI 0.89–0.99, $P = 0.02$) and girls (summer, aOR = 0.93, 95% CI 0.86–0.99, $P = 0.03$; winter, aOR = 0.95, 95% CI 0.89–1.02, $P = 0.16$). Additional adjustment for age did not alter the association (summer, aOR = 0.94, 95% CI 0.91–0.98, $P = 0.002$; winter: aOR = 0.94, 95% CI 0.91–0.98, $P = 0.006$).

Supplementary Tables 3 and 4 (Supplemental Digital Content, *http://links.lww.com/MPG/B650*) show the results of the first 2 sensitivity analyses. In the restricted data set containing only age- and sex-matched controls with complete data on the variables included in the adjusted analysis the results were very similar to those for the larger model. That is, greater leisure-time sun exposure in the previous summer (aOR = 0.93, 95% CI 0.90–0.97, $P = 0.001$) or winter (aOR = 0.94, 95% CI 0.90–0.98, $P = 0.004$) was associated with a reduced risk of being an IBD case. In the sensitivity analysis restricting to the 38 cases with diagnosis in the year before participation in the study and their matched controls (Supplementary Table 4, Supplemental Digital Content, *http://links.lww.com/MPG/B650*), the results were very similar with some attenuation of the effect size, likely because of the smaller sample size (summer, aOR = 0.96, 95% CI 0.91–1.02, $P = 0.21$; winter, aOR = 0.94, 95% CI 0.88–1.00; $P = 0.06$). We further restricted the analysis to the 24 cases (with 93 matched controls) whose symptom onset was within the year before participation in the study. In univariate analyses, greater leisure-time in the previous summer (OR = 0.96, 95% CI 0.89–1.03, $P = 0.22$) or winter (OR = 0.92, 95% CI 0.84–1.00, $P = 0.05$) were associated with reduced odds of IBD (note that multivariable analysis was not possible because of the small sample size). Restricting to only

TABLE 2. Sun exposure of cases and age- and sex-matched controls

A	Summer			Winter		
	Cases, % (n)	Controls, % (n)	*P* (trend)	Cases, % (n)	Controls, % (n)	*P* (trend)
0-2 years (hours/day)			0.58			0.95
<1	38.2 (34)	36.4 (116)		48.9 (44)	43.7 (138)	
1 to 2	38.3 (34)	38.9 (124)		38.9 (35)	42.1 (133)	
2 to 3	12.4 (11)	17.2 (55)		8.9 (8)	9.2 (29)	
≥3	11.2 (10)	7.5 (24)		3.3 (3)	5.1 (16)	
3-5 years (hours/day)			0.93			0.13
<1	10.2 (9)	5.6 (17)		27.0 (24)	14.6 (44)	
1 to 2	36.4 (32)	36.1 (110)		46.1 (41)	47.2 (142)	
2 to 3	31.8 (28)	34.8 (106)		19.1 (17)	26.6 (80)	
≥3	21.6 (19)	23.6 (72)		7.9 (7)	11.6 (35)	
6-10 years (hours/day)			0.07			0.05
<1	6.9 (6)	2.8 (7)		17.2 (15)	9.8 (23)	
1 to 2	25.3 (22)	17.2 (43)		39.1 (34)	31.4 (74)	
2 to 3	28.7 (25)	36.0 (90)		24.1 (21)	33.9 (80)	
≥3	39.1 (34)	44.0 (110)		19.5 (17)	25.0 (59)	
11-15 years (hours/day)			0.01			0.006
<1	11.0 (8)	0.9 (1)		19.2 (14)	12.5 (13)	
1 to 2	20.6 (15)	17.4 (19)		41.1 (30)	23.1 (24)	
2 to 3	28.8 (21)	26.6 (29)		17.8 (13)	31.7 (33)	
≥3	39.7 (29)	55.1 (60)		21.9 (16)	32.7 (34)	
Age group at diagnosis (hours/day)			0.29			0.08
<1	9.3 (7)	11.7 (33)		17.3 (13)	21.8 (61)	
1 to 2	26.7 (20)	29.7 (84)		46.7 (35)	33.2 (93)	
2 to 3	30.7 (23)	26.5 (75)		17.3 (13)	26.8 (75)	
≥3	33.3 (25)	32.2 (91)		18.7 (14)	18.2 (51)	
Previous summer or winter during leisure time, median (Q1, Q3) minutes/day	150 (90, 210)	210 (150, 270)	<0.001	90 (90, 150)	150 (90, 210)	0.001

B	Summer		Winter	
	OR (95% CI)	*P*	OR (95% CI)	*P*
0-2 years*	1.00 (0.68, 1.49)	0.98	1.00 (0.66, 1.51)	0.99
3-5 years*	0.80 (0.53, 1.22)	0.30	0.70 (0.44, 1.10)	0.12
6-10 years*	0.70 (0.45, 1.08)	0.10	0.62 (0.40, 0.97)	0.03
11-15 years*	0.62 (0.40, 0.96)	0.03	0.57 (0.38, 0.86)	0.008

Part A of the Table shows sun exposure for all cases and controls at different ages (including the age group at diagnosis) and in the summer or winter before participation in the study, and tests the difference between cases and controls. Part B shows the univariate odds ratio of being a case, per category (hours per day) increase in sun exposure for the subset of cases and matched controls with data for all age groups (n = 66 cases; n = 108 controls). OR is the univariate odds ratio from a conditional logistic regression model for the per category increment in sun exposure in the relevant age group (categories are <1 hour [reference], 1-2 hours, 2-3 hours, ≥3 hours). CI = confidence interval; OR = odds ratio.

*Per category increase

Caucasian participants (n = 62 cases with n = 216 matched controls), greater leisure-time in the previous summer (aOR = 0.96, 95% CI 0.91–1.01, *P* = 0.10) or winter (aOR = 0.93, 95% CI 0.88–0.98, *P* = 0.01) were associated with reduced odds of IBD. Throughout these analyses, although adjusting for tanning as a potential confounder, it is of note that darker tan (a consequence of greater recent sun exposure) was consistently associated with lower risk of IBD. Additional adjustment for physical activity attenuated the effect estimate for leisure-time sun exposure in the previous summer (aOR = 0.95, 95% CI 0.92–0.99, *P* = 0.02) or winter (aOR = 0.96, 95% CI 0.92–1.00, *P* = 0.05). The effect estimate for physical activity was not significant (moderate: aOR = 0.78, 95% CI 0.37–1.64, *P* = 0.51; high: aOR = 0.95, 95% CI 0.43–2.10, *P* = 0.90 compared with low). The models with and without physical activity were not significantly different (Likelihood ratio test *P* = 0.92).

DISCUSSION

In this case-control study of pediatric IBD, we found that for a small increment in sun exposure on weekends and holidays in summer or winter—an extra 10 minutes—there was a 6% reduction in the odds of being an IBD case. The association appeared to be relatively linear. This is further supported by the finding that achieving a darker tan after a 2-week holiday, including when the analyses were restricted to Caucasians only, was associated with reduced odds of being an IBD case. The effects remained significant in subgroup analyses, mainly for winter sun exposure. The association appeared to be stronger with increasing age, possibly reflecting a cumulative dose effect.

A key strength of this study is that all cases were diagnosed using the same diagnostic procedures and a uniform set of criteria. Further, many of the cases were included in this study shortly after

TABLE 3. Univariable and multivariable analysis for the association between recent leisure time sun exposure (per 10 minute increment) and being an inflammatory bowel disease case (n = 99 cases; 396 controls; winter: n = 95 cases; 387 controls)

	Crude OR	CI (95%)	*P* value	Adjusted OR*	CI (95%)	*P* value
Summer time in sun	0.93	0.90–0.97	<0.001	0.94	0.91–0.98	0.002
Tanning						
No tan or a light tan	Reference			Reference		
A medium or dark tan	0.61	0.38–0.99	0.05	0.96	0.39–2.40	0.98
Mother cigarette smoking						
No	Reference			Reference		
Yes	0.45	0.24–0.82	0.01	0.70	0.35–1.40	0.31
Winter time in sun	0.94	0.90–0.97	0.001	0.94	0.91–0.98	0.005
Tanning						
No tan or a light tan	Reference			Reference		
A medium or dark tan	0.63	0.39–1.03	0.06	0.67	0.40–1.10	0.11
Mother cigarette smoking						
Nonsmoker	Reference			Reference		
Smoker	0.47	0.26–0.87	0.02	0.55	0.29–1.02	0.06

CI = confidence interval; OR = odds ratio.
*Adjusted for the other factors listed in the table.

their diagnosis with IBD. Control participants were recruited from the day surgery unit of the main hospital from which the cases were recruited, that is, a similar catchment area. In this situation, hospital controls are likely to provide a valid estimate of the effect (14), but may underestimate the odds ratio compared with using population controls (15). The procedures for data collection were identical for cases and controls, minimizing the risk of measurement bias. The major limitation of the study was that past sun exposure was recalled by parents, risking recall error. It seems unlikely that this was differential between cases and controls, given that low sun exposure is not a recognized risk factor for IBD; if there is bias, it is most likely a bias toward a null result. The study used questions for past sun exposure that had been previously validated in children (12,13).

Our results support a protective effect of higher levels of sun exposure on the development of IBD. This is consistent with ecological studies (2), but does not delineate the possible causal pathway. That is, immune modulation that reduces the risk of IBD could occur through improvement in UV-induced vitamin D status, or through other changes that occur following UV irradiation of the skin [reviewed in (4)].

There is now recognition that UV irradiation of the skin (and possibly the eyes) has profound effects on systemic immunity (16). The overall effect is very similar to that associated with vitamin D—upregulation of innate immunity and suppression of adaptive immunity, particularly Th1 and Th17 (pro-inflammatory) pathways, and upregulation of T-regulatory and B-regulatory cells (17), and modulation of the microbiome [reviewed in (4)]. Our results suggest that recent sun exposure, or perhaps cumulative exposure over several years, is of particular importance. This is similar to findings in another autoimmune disease, multiple sclerosis (18).

We did not have data on vitamin D status, and cannot test whether the apparent protective effect of greater sun exposure is UV- or vitamin D-mediated. In a previous Australian study, children with IBD (n = 78, mean age 12.6 years) (19) had a mean concentration of 25-hydroxyvitamin D (25(OH)D, the usual measure of vitamin D status) of 71.2 nmol/L (based on review of

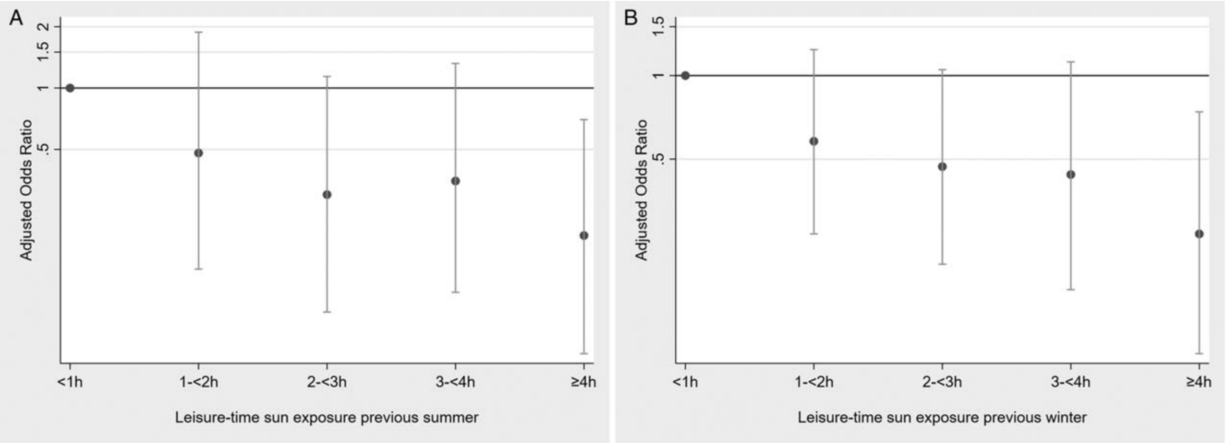

FIGURE 1. Adjusted odds of being a pediatric inflammatory bowel disease case in association with sun exposure (during weekends and holidays) during the (A) summer and (B) winter before study participation. Adjusted odds ratios for a multivariable model with adjustment for tanning and mother's smoking.

hospital records), which is similar to that for the 12 to 17 years age group in the national Australian Health Survey (69.0 nmol/L) (20). In both studies, 4% had levels <30 nmol/L. Other studies comparing 25(OH)D levels in children with and without IBD from comparable populations have had conflicting results. For example, Veit et al (21) found no difference in 25(OH)D levels between adolescents with CD, UC, and healthy controls (HC) (mean 25(OH)D: CD 61.7, UC 53.3, HC 65.3 nmol/L, $P = 0.20$) in a US study, with these levels not too dissimilar to those in an older study of a similar age group and location, but without a HC comparison group (mean 25(OH)D: CD 50; UC 56 nmol/L) (22).

In a recent meta-analysis of 11 case-control studies (761 cases, 540 controls) (23), adult patients with IBD had 64% higher odds of vitamin D deficiency (defined as 25(OH)D $\leq$50 nmol/L) compared with controls ($P = 0.0001$). The equivalent result for pediatric studies was an OR of 1.36 (95% CI 0.91–2.04, $P = 0.14$), based on 177 cases and 413 controls. All of the included studies were small and from higher northern hemisphere locations (latitudes 40°N, 42°N, and 60°N); the strongest effect appeared to be for UC compared with CD (23). It is not clear whether vitamin D deficiency is a cause or a consequence of the disease, and conflicting results from trials of vitamin D supplementation have not resolved this question (24).

We undertook a number of sensitivity analyses to attempt to rule out reverse causality, that is that case children had low sun exposure because of their diagnosis of IBD. Our sensitivity analyses were somewhat limited by the small sample size, such that we considered diagnosis in the previous year as ''recent'' diagnosis. In univariate analysis, the protective effect of higher sun exposure was seen when only those with symptom onset in the year before participation were included in the analysis; multivariable analysis could not be performed because of the small sample size.

CONCLUSIONS

The analyses presented here show that a modest increase in recent sun exposure was associated with a reduced risk of pediatric IBD. We were unable to explore the mechanism of this effect, and the possibility that it may be mediated by vitamin D. These findings add to growing evidence that higher sun exposure (or vitamin D) is associated with reduced risk of some autoimmune diseases (25); if replicated, this may provide an avenue toward prevention or reduction in incidence. Of course, any advice to increase sun exposure would need to be weighed against the known risks of sun exposure, particularly in childhood, for skin cancers such as melanoma.

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