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Lower regional and temporal ultraviolet exposure is associated with increased rates and severity of inflammatory bowel disease hospitalisation

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SUMMARY

Background
In the northern hemisphere, the incidence of inflammatory bowel diseases (IBD) has a north–south gradient, suggesting a link between ultraviolet (UV) exposure or vitamin D status and the pathogenesis of IBD.

Aim
To test the association of UV exposure with the rates and severity of IBD hospitalisation.

Methods
We conducted a retrospective nationwide analysis of 649 932 Crohn's disease (CD), 384 267 ulcerative colitis (UC), and 288 894 297 non-IBD hospitalisations in the US between 1998 and 2010. Mean UV exposure was assigned to each hospitalisation using surface measures from the National Oceanic and Atmospheric Administration. Relative rates across UV exposures were estimated for IBD hospitalisations, prolonged hospitalisations, bowel surgeries and deaths.

Results
Among IBD patients, lower UV exposures had increased hospitalisation rates for CD (217.8 vs. 182.5 per 100 000 overall hospitalisations with low and very high UV, respectively; P trend <0.001) and UC (123.2 vs. 113.8 per 100 000; P trend = 0.033). Low UV groups had greater relative rates of prolonged hospitalisations [CD: 1.13, 95% confidence interval (CI) 1.07–1.19; UC: 1.21, 95% CI 1.13–1.30], bowel surgeries (CD: 1.24, 95% CI 1.16–1.32; UC: 1.21, 95% CI 1.09–1.33), and CD deaths (CD: 1.76, 95% CI 1.14–2.71; UC: 1.24, 95% CI 0.92–1.67). Among non-IBD patients, low UV was associated with prolonged hospitalisations (1.09; 95% CI 1.07–1.11) and deaths (1.13; 95% CI 1.09–1.17), but not bowel surgeries (1.01; 95% CI 0.99–1.03).

Conclusions
Lower ultraviolet exposure is associated with greater rates of hospitalisation, prolonged hospitalisation and the need for bowel surgery in IBD. This trend for bowel surgery was not seen with non-IBD encounters.

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INTRODUCTION

The inflammatory bowel diseases (IBD), whose major forms include Crohn's disease (CD) and ulcerative colitis (UC), are chronic gastrointestinal disorders characterised by dysregulated intestinal inflammation.[1] Etiologies that increase the risk of IBD include genetic risk profiles and poorly defined environmental factors, although the specific immediate causes of IBD remain unknown.

Vitamin D is a fat-soluble secosteroid traditionally known for its role in calcium and phosphorus homoeostasis. More recently, vitamin D has been found to possess immunomodulatory properties,[2–5] and hypothesised to play a role in IBD pathogenesis. Although there is no direct evidence that vitamin D deficiency contributes to increased IBD incidence or severity in humans, epidemiological studies have revealed a latitudinal gradient of IBD incidence; that is, more northern geographical regions where populations receive less ultraviolet (UV) exposure and synthesise less vitamin D have higher incidences of IBD. The European Collaborative Study on Inflammatory Bowel Disease found higher overall incidence rates for both CD and UC among northern centres, even after adjusting for tobacco use and college education.[6] French and Scottish studies also showed within-country north–south gradients of CD, but not UC.[7, 8] In a study of sunlight exposure and IBD risk, Nerich *et al.* found a significant association between average regional UV exposure and CD incidence.[9] A latitudinal gradient was similarly observed among women enrolled in the US-based Nurses' Health Studies I and II.[10] Moreover, a separate analysis of the Nurses' Health Study that modelled vitamin D levels based on dietary intake and physical activity revealed an inverse correlation between estimated vitamin D levels and risk of developing CD.[11]

Given the empiric role of vitamin D in immunomodulation and its association with IBD incidence, it is conceivable that vitamin D status may similarly influence disease severity. IBD murine models with VDR (vitamin D receptor)-knockout experience more severe colitis than wild-type mice,[12, 13] while exogenous administration of vitamin D or an analogous VDR agonist ameliorates symptoms.[14, 15] Although clinical studies in humans have also shown a relationship between measured vitamin D levels and IBD severity,[16, 17] a key limitation of these cross-sectional analyses is reverse causation; that is, it remains unclear whether low vitamin D levels aggravate IBD or whether intestinal malabsorption in the setting of active IBD leads to vitamin D deficiency. In this case, UV exposure is a stronger determinant of vitamin D status than dietary intake or oral supplementation.[18, 19]

To examine the relationship between UV exposure and IBD severity, we used UV surface data from the National Oceanic and Atmospheric Administration (NOAA) and hospitalisation information from the Nationwide Inpatient Sample (NIS) from 1998 to 2010. We further compared the relationship between UV exposure and severity among non-IBD patients to confirm whether the associations were specific to IBD and not general trends in hospitalisation outcomes. We hypothesised that low UV exposure would be associated with increased rates of hospitalisations and disease severity in IBD patients, but not necessarily in non-IBD patients.

METHODS

UV exposure

Daily UV radiation data were collected from the NOAA for 57 cities throughout the continental US, Alaska, and Hawaii between 1998 and 2010. Ground-based UV exposure was calculated by NOAA using a validated radiative transfer model that accounts for regional and temporal ozone, sun–earth distance, solar zenith angle, and altitude;[20, 21] cloud cover was estimated from satellite-based ozone data, while surface albedo was kept constant at 5%. Tropospheric pollution and haze were not considered in the UV index. We quantified UV exposure for each hospitalisation as the UV index (one unit equals a noontime erythemal dose of 25 mW/m^2) for the corresponding month (averaged UV over all days of the month), year, and hospital location (state level). UV exposures were then stratified according to rounded UV index thresholds defined by the World Health Organization: low (0–2), moderate (3–5), high (6–7) and very high (8 and above).[22] Admission month was not available for Florida, so UV exposure could not be assigned to hospitalisations in this state.

Hospitalisation data

The NIS is the largest database of hospitalisations in the US. The NIS is generated annually as part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ). The database samples approximately 1000 nonfederal, short-term, acute care hospitals, while excluding psychiatric, substance abuse, and short-term rehabilitation facilities.[23] The sampled hospitals comprise

approximately 8 million annual in-patient records and represent over 39 million hospitalisations per year. The authors obtained permission from AHRQ to access the NIS data set and used it according to HCUP guidelines (www.hcup-us.ahrq.gov/team/NationwideDUA.jsp). This study protocol (NA83700) was approved by the Institutional Review Board of the Johns Hopkins University School of Medicine.

The NIS was analysed for all hospitalisations between 1998 and 2010. Diagnoses and types of procedures were based on ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) codes in primary and secondary diagnosis or procedure positions. IBD hospitalisations were defined as those with a corresponding discharge code for CD (ICD-9-CM code 555) or UC (ICD-9-CM code 556) in the primary and a secondary diagnosis positions, while non-IBD hospitalisations included those without an ICD-9-CM code 555 or 556 in any diagnosis position. Records without an available admission month (n = 54 835 records) and states with ≥10% missing race information for a particular year (n = 156 718 records from 19 states) were excluded. Information of interest included demographical data (age, sex and race), types of abdominal surgery, in-patient or peri-hospitalisation mortality, hospitalisation characteristics (admission month, year and length of stay) and hospital-specific features (state, bed size). The Charlson–Deyo comorbidity index is an aggregate severity score of comorbid diagnoses, designed for use with administrative data and based on the presence of 17 medical conditions, such as cardiovascular disease, chronic pulmonary disease, liver disease, diabetes and malignancy. The comorbidity index was calculated for each hospitalisation according to published diagnostic criteria.[24, 25]

IBD severity

Hospitalisation severity outcomes were assessed among IBD hospitalisations. These outcomes of interest included rates of CD or UC hospitalisation, prolonged hospitalisation, need for bowel surgery and death. A prolonged hospitalisation was defined as the top quartile length of stay among all hospitalisations, which is equivalent to >7 days. Bowel surgery comprised incisions, excisions, anastomoses and other therapeutic interventions of the intestinal tract (ICD-9-CM procedural codes 45.0, 45.3–46.2, 46.4–46.5, 46.7, 48.3–48.6). CD-related surgeries included bowel resections and proctectomies (45.5–45.9, 48.4, 48.61–48.65). UC-related surgeries included partial or total colectomies, and proctectomies (45.7–45.8, 45.92–45.95, 48.4, 48.61–48.65). Only procedures associated with IBD were included in these categories.

Severity in non-IBD hospitalisations

To compare hospitalisation trends for IBD and other disorders, hospitalisations rates were also calculated for cirrhosis (ICD-9-CM code 571.5), cardiovascular disease (430–438), chronic obstructive pulmonary disease (490–505, 506.4) and diabetes mellitus (250.0–250.7). To assess whether UV-associated trends observed with IBD-related surgeries among IBD hospitalisations are unique or suggestive of general surgical practice patterns, we evaluated the rates of bowel surgery and common surgeries unrelated to IBD, including cholecystectomies (ICD-9-CM 51.2) and appendectomies (ICD-9-CM 47.0–47.1), in non-IBD hospitalisations.

Potential confounders

Age, sex, race, Charlson–Deyo comorbidity index, admission type and hospital size were included as potential confounders of hospitalisation severity. Race was categorised as White, Black or other. Admission types included emergent or urgent, elective and other admissions. Hospital size is thought to influence the volume and complexity of IBD cases encountered in a particular hospital.[26] Hospital size was pre-assigned in NIS based on the number of beds as 'small', 'medium' or 'large' according to approximately one-third cutoff points for each size category within a given region, urban or rural location, and teaching status combination. We considered urban location and teaching status as potential confounders, but did not ultimately include them in the model because of their strong associations with hospital size.

Statistical analysis

All aggregate data were analysed using survey procedures that accounted for the complex sampling design of the NIS. The sampling weights provided with NIS generally permit calculation of national estimates, and require that at least one observation per sampled hospital be included in the analysis for correct variance estimation.[27] Disease severity was measured among IBD and non-IBD hospitalisations. Rates of CD or UC hospitalisations were calculated over all-cause hospitalisations within each UV exposure group. Poisson regression was used to estimate relative rates of prolonged hospitalisation, abdominal surgeries and death according to UV exposure. Multivariable models adjusted for age, gender, race,

Charlson–Deyo comorbidity index and hospital size. Variance estimations were done with Taylor series linearisation. *P* for trend was calculated to assess for a dose–response pattern of severity outcomes across UV exposures. Statistical significance was defined as a two-sided α of less than 0.05. Statistical analyses were performed using SAS 9.3 (Cary, NC, USA) and Stata SE 12.1 (College Station, TX, USA).

Sensitivity analysis

We performed a sensitivity analysis of our case definition to understand the robustness of our findings by defining IBD hospitalisations using all diagnostic positions rather than the first two diagnostic positions.

RESULTS

Hospitalisation characteristics

The study population included 289 928 496 hospitalisations in the US between 1998 and 2010. Of these hospitalisations, there were 649 932 for CD and 384 267 for UC (Table 1). The median age at hospitalisation was 40.7 years [interquartile range (IQR) 28.1–55.1] for CD and 46.1 years (IQR 30.2–64.1) for UC. For both CD and UC, there were slightly more females and the majority of patients were White, which was comparable with non-IBD hospitalisations.

Rates of hospitalisations

The rates of CD and UC hospitalisations were greatest in the lowest UV index group and had a statistically significant decline with increasing UV exposure (Figure 1). For CD, the low and moderate UV index groups had 217.8 [95% confidence interval (CI) 216.8–218.8] and 203.8 (95% CI 202.9–204.7) hospitalisations per 100 000 overall hospitalisations, compared with the very high UV group rate of 182.5 (95% CI 181.4–183.6). The *P* for trend was <0.001. For UC, the low and moderate UV groups had 123.2 (95% CI 122.5–124.0) and 119.3 (95% CI 118.6–119.9) hospitalisations per 100 000 residents, compared with the very high UV group rate of 113.8 (95% CI 112.9–114.7; *P* for trend = 0.033).

Bowel surgeries

Overall, bowel surgeries in CD were significantly more common in the low [relative rate (RR) 1.24; 95% CI 1.16–1.32], moderate (RR 1.18; 95% CI 1.11–1.26) and high (RR 1.17; 95% CI 1.09–1.24) UV index groups, compared with the very high UV group. Lower UV exposures had a significant trend for more bowel surgeries (*P* for trend <0.001) (Figure 2a). For CD-related bowel resection, a similar trend was noted across UV groups: low (RR 1.29; 95% CI 1.20–1.38); moderate (RR 1.22; 95% CI 1.13–1.31); high (RR 1.20; 95% CI 1.12–1.29) (*P* for trend <0.001) (Figure 2b). Similar to CD patients, overall bowel

Table 1 | Demographics of Crohn's disease, ulcerative colitis and non-IBD hospitalisations

	Crohn's disease	Ulcerative colitis	Non-IBD
Hospitalisations (*n*)	649 932	384 267	288 894 297
Median age (IQR)	40.7 (28.1–55.1)	46.1 (30.2–64.1)	53.9 (31.3–72.7)
Female (%)	376 637 (58.1)	205 906 (53.8)	172 271 721 (59.8)
Race (%)			
White	517 788 (81.9)	292 569 (78.8)	189 651 855 (67.8)
Black	69 069 (10.9)	32 946 (8.9)	38 296 620 (13.7)
Other	45 005 (7.1)	45 963 (12.4)	51 963 642 (18.6)
Charlson–Deyo Index (%)			
0	526 474 (81.0)	296 425 (77.1)	165 811 790 (57.4)
1–2	111 281 (17.1)	75 339 (19.6)	91 533 838 (31.7)
≥3	12 178 (1.9)	12 503 (3.3)	31 548 668 (10.9)
Admission type (%)			
Emergent/urgent	460 630 (79.2)	243 725 (75.2)	168 803 647 (72.0)
Elective	120 728 (20.8)	80 285 (24.8)	65 351 789 (27.9)
Other	101 (0.0)	33 (0.0)	217 712 (0.1)
Hospital size (%)			
Small (1–249 beds)	85 131 (13.2)	46 673 (12.2)	38 736 810 (13.5)
Medium (25–449 beds)	165 985 (25.6)	98 189 (25.6)	78 112 071 (27.1)
Large (45–450 + beds)	396 040 (61.2)	238 187 (62.2)	171 125 893 (59.4)

IQR, interquartile range.

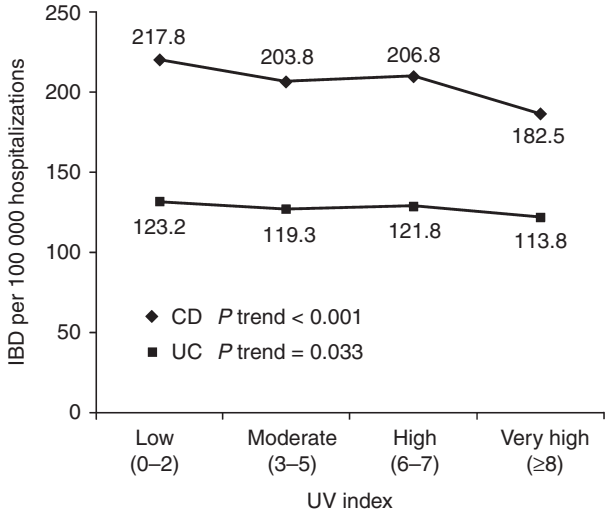

Figure 1 | Rates of Crohn's disease and ulcerative colitis hospitalisations according to UV exposure. Low UV exposures are associated with higher rates of CD and UC hospitalisations. Rates were calculated as the number of CD or UC hospitalisations over all-cause hospitalisations.

surgeries for UC were also more common in the low (RR 1.21; 95% CI 1.09–1.33), moderate (RR 1.15; 95% CI 1.06–1.24) and high (RR 1.14; 95% 1.05–1.25) UV index groups, with a significant trend across UV exposures (*P* for trend <0.001). This observation was consistent with relative colectomy rates in the low (RR 1.35; 95% CI 1.15–1.58), moderate (RR 1.24; 95% CI 1.09–1.42) and high (RR 1.22; 95% CI 1.06–1.40) UV groups. There was a significant trend of increasing colectomy rates with lower UV exposures (*P* for trend <0.001). UV exposure did not influence rates of other abdominal surgeries unrelated to IBD, including cholecystectomies (CD: *P* for trend = 0.184; UC: *P* for trend = 0.746) or appendectomies (CD: *P* for trend = 0.919; UC: *P* for trend = 0.435) (Figure 3).

Length of stay

Inflammatory bowel disease patients in the low UV index group were more likely to have prolonged hospitalisations (>7 days) than those in the very high UV index group (Figures 2c). The trends were statistically significant for both CD (*P* for trend <0.001) and UC (*P* for trend <0.001).

Death

In-patient mortality was greater in the low UV indices compared with the very high UV indices for CD (RR 1.76; 95% CI 1.14–2.71; *P* for trend = 0.046; Figure 2d). Although in-patient mortality rates for UC were statistically similar in the low (RR 1.24; 95% CI 0.92–1.67), moderate (RR 1.16; 95% CI 0.87–1.55) and high (RR 1.08; 95% CI 0.79–1.48) UV index groups (*P* for trend = 0.110), the point estimates steadily increased across UV exposures.

Severity of non-IBD hospitalisations

When analysing rates of non-IBD hospitalisations, there was no significant trend across UV exposures for cardiovascular disease (*P* for trend = 0.098) and diabetes mellitus (*P* for trend = 0.500). Hospitalisation rates for cirrhosis had a significant trend in hospitalisation rates (*P* for trend = 0.007), but with decreasing hospitalisations at lower UV exposures; this is the inverse of the trend observed with IBD. Chronic obstructive pulmonary disease shared a similar directional trend of hospitalisation rates as IBD along UV exposures (*P* for trend <0.001). For the other surrogates of disease severity, the low UV indices compared with the high UV indices had higher rates of prolonged hospitalisations (RR 1.09; 95% CI 1.07–1.11) and deaths (RR 1.13; 95% CI 1.09–1.17). Trends were also significant for increasing rates of prolonged hospitalisations (*P* for trend <0.001) and deaths (*P* for trend <0.001) with lower UV exposures. In contrast to IBD hospitalisations, lower UV indices among non-IBD hospitalisations did not increase rates of overall bowel surgeries (*P* for trend = 0.931) and bowel resections (*P* for trend = 0.441). There was a significant decline in rates of cholecystectomies (*P* trend < 0.001) and appendectomies (*P* for trend < 0.001) with lower UV exposures for non-IBD hospitalisations (Figure 3).

Sensitivity analysis

When examining hospitalisations for CD or UC using all diagnosis positions, similar trends were observed as in the primary analyses. Among CD hospitalisations, low UV exposure was associated with more prolonged hospitalisations (*P* for trend = 0.004), overall bowel surgeries (*P* for trend <0.001), bowel resections (*P* for trend <0.001) and deaths (*P* for trend = 0.001). For UC hospitalisations, low UV exposure was also associated with more prolonged hospitalisations (*P* for trend = 0.015), overall bowel surgeries (*P* for trend = 0.038), colectomies (*P* for trend = 0.007), but not deaths (*P* for trend = 0.068).

DISCUSSION

We found that low UV exposure is associated with increased IBD hospitalisation rates and severity. IBD hospitalisation rates, prolonged hospitalisation and bowel surgery were consistently greater in the lower UV indices

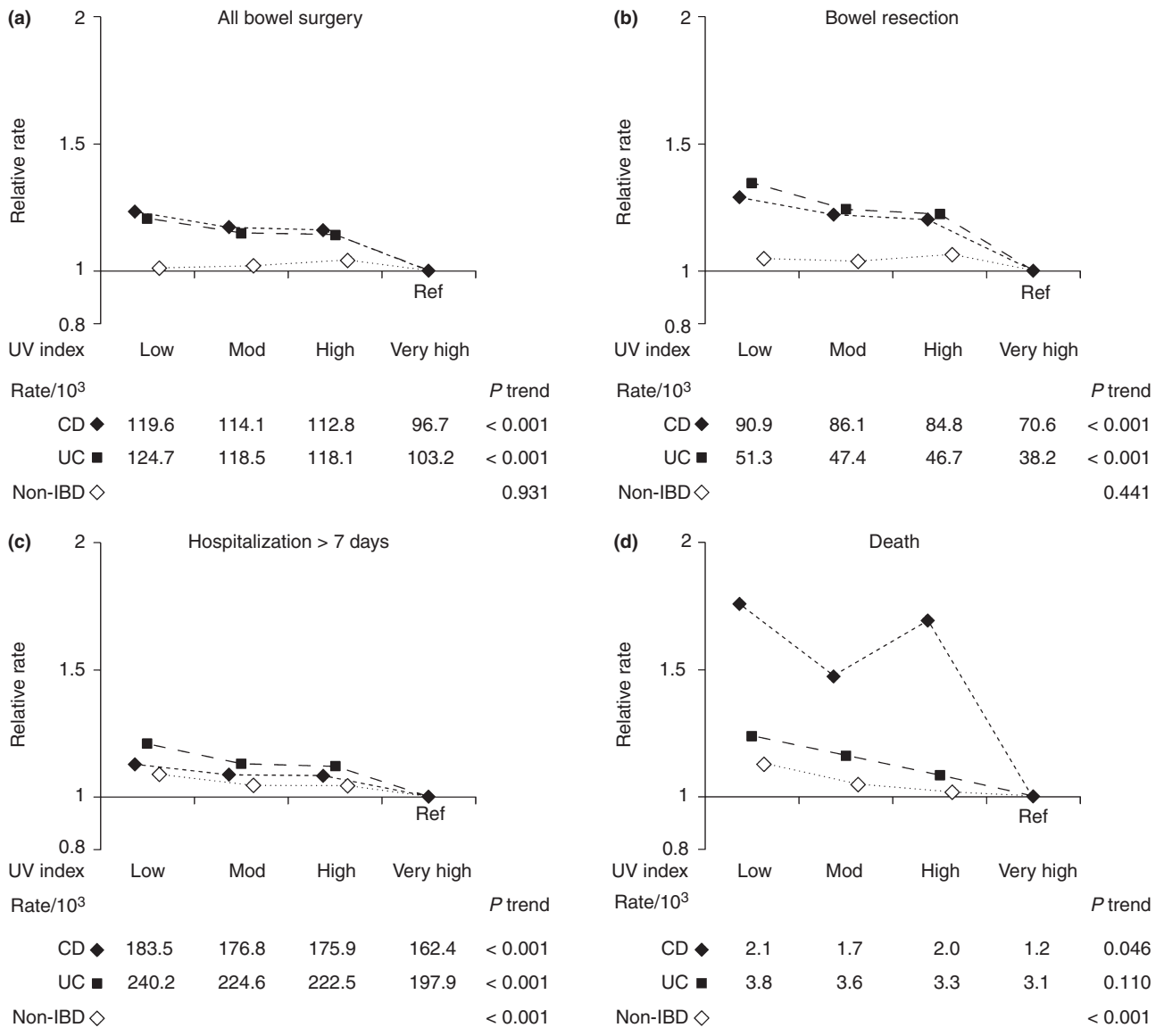

Figure 2 | Rates of hospitalisation severity and death according to UV exposure. Low UV exposures are associated with increased rates of Crohn's disease and ulcerative colitis severity outcomes: (a) all bowel surgeries; (b) bowel resection; (c) prolonged hospitalisation (length >7 days) and (d) death. For non-IBD hospitalisations, low UV exposures are not associated with rates of all bowel surgeries and bowel resection, but are associated with prolonged hospitalisation and death.

for both CD and UC. Mortality rates were low with small differences across UV exposures, but there was a significant increase in mortality with lower UV exposure for CD and a trend towards significance for UC.

These findings are consistent with some, but not all, prior epidemiological data that showed a north–south gradient relationship with IBD incidence.[6, 8–10, 28] Studies in France and Scotland found associations with CD, but not UC.[8, 9] On the other hand, analogous epidemiological studies in all of Europe and the US detected a north–south gradient for both CD and UC, albeit a weaker association for UC.[6, 10] A possible explanation for this discrepancy is the shorter latitudinal breadth in the French and Scottish studies than their US and pan-European counterparts, which would affect their ability to detect the weaker association for UC.

As UV exposure is a strong determinant of vitamin D status,[18, 19] the observed effects of UV exposure on IBD hospitalisations and severity may be mediated by vitamin D. *In vitro* and animal data have demonstrated vitamin D

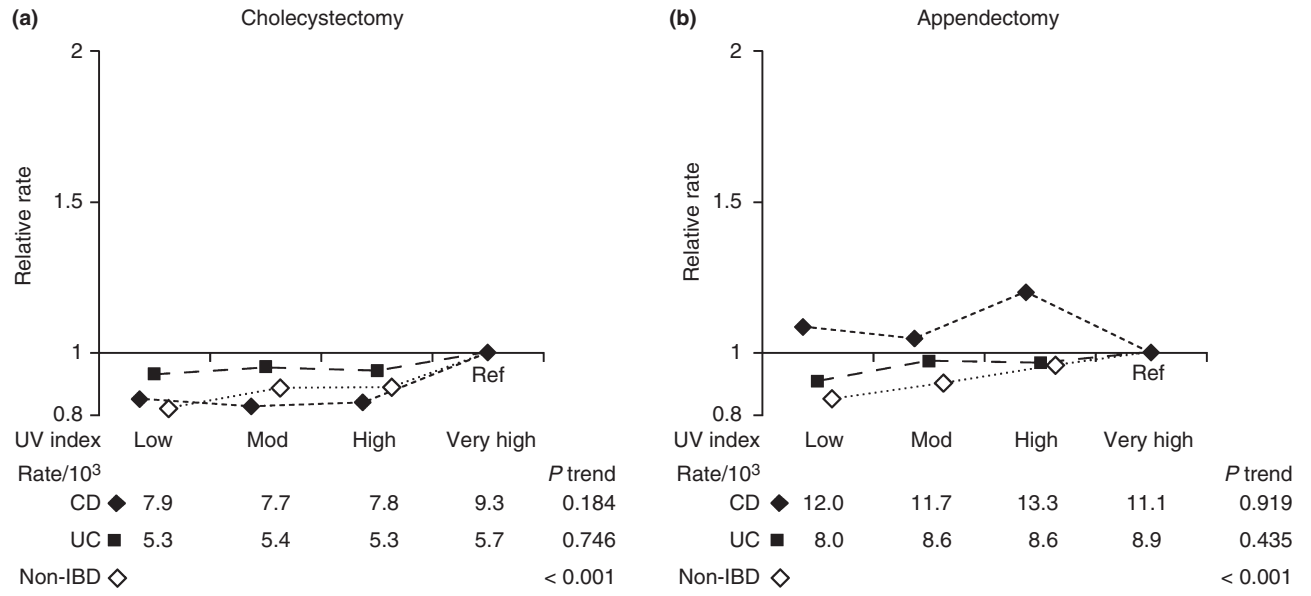

Figure 3 | Rates of other abdominal surgeries according to UV exposure. Low UV exposures are associated with decreased rates of cholecystectomies and appendectomies for non-IBD hospitalisations, but not for Crohn's disease or ulcerative colitis.

to possess immunomodulatory properties through several mechanisms. In monocytes, 1,25-dihydroxyvitamin D (1,25-$[OH]_2D$) suppresses toll-like receptor expression and leads to a diminished inflammatory response to antigenic stimulation.[29] Vitamin D also downregulates expression of pro-inflammatory cytokines, such as interleukin (IL)-2, IL-6, IL-17, interferon-γ and tumour necrosis factor-α (TNF-α), in favour of anti-inflammatory proteins, such as IL-10, transforming growth factor-β (TGF-β) and cytotoxic T-lymphocyte antigen 4 (CTLA-4).[29–32] In the trinitrobenzene sulphonic acid-treated IBD mouse model, 1,25-$(OH)_2D$ administration shifts the T helper (Th) 1/Th17 profile to Th2 and regulatory T cells.[32] Additional VDR knockout in the IL-10-deficient IBD mouse model leads to severe and accelerated IBD.[33–35] Vitamin D-sufficient mice do not develop IBD symptoms, while vitamin D-deficient mice manifest diarrhoea, wasting disease, and subsequent death.[14] These findings are bolstered by studies that identified variable genotype associations of VDR and DBP (vitamin D binding protein) polymorphisms with CD or UC; in particular, a recent genome wide association study found an IBD association at a polymorphism (rs11168249) adjacent to the VDR gene.[36–40]

Large administrative databases have been used to examine the relationship between UV exposure and other conditions expected to be associated with UV exposure, latitude and vitamin D. For instance, studies that linked UV data to the Surveillance, Epidemiology, and End Results (SEER) database and state cancer registries (New York, New Jersey, Illinois, California, Texas, and Florida) found higher UV indices to be associated with an increased risk of melanoma.[41, 42] In a separate study using the Model Reporting Area for Blindness Statistics and the National Health and Nutrition Examination Survey data sets, regions with greater sunlight exposure were found to have higher cataract-to-control ratios for persons aged 65 years or older.[43] Similarly, an analysis of multiple sclerosis prevalence in the US and Canada showed a strong inverse correlation between UV index and multiple sclerosis distribution.[44] A large case–control study also found that high vitamin D levels were associated with lower risk of multiple sclerosis.[45]

There are several strengths of this study, including the method of measuring UV, measure of disease severity, and use of control outcomes to help rule out practice variation unrelated to IBD. First, in measuring UV exposure, we employed data that were derived using a validated model to estimate ground-level UV exposure, thus providing an additional layer of specificity than satellite-based sensors. The model incorporates several factors, including regional and temporal sun–earth distance, solar zenith angle, ozone, cloud cover and altitude. In addition to the use of ground-based UV estimations, our methods combined regional and temporal measures to account for seasonal and weather-pattern variations in UV exposure; this contrasts from other studies

that only evaluated geographical latitude to indirectly infer UV exposure. Geographical latitude is a less specific indicator of UV exposure due to seasonal variations in UV exposure that do not strictly follow a latitudinal gradient.[46] Second, unlike other studies which could only measure the relationship between UV or latitude and IBD incidence or prevalence, this study was able to also evaluate IBD severity during hospitalisation as an outcome, given its much larger sample size. Third, we explored severity outcomes in non-IBD hospitalisations to assess whether geographical or surgical practice patterns contributed to our observations of UV exposure and IBD-related outcomes. Prolonged hospitalisations and deaths were increased with low UV exposures in the non-IBD hospitalisations, so it remains unclear how much of the similar observations among IBD hospitalisations is due to increased IBD severity across UV exposures or due to general hospitalisation trends. Nonetheless, in contrast to IBD-specific hospitalisations, UV exposures in non-IBD hospitalisations did not influence rates of bowel surgeries, bowel resections and colectomies. Moreover, rates of other abdominal surgeries unrelated to IBD, including cholecystectomies and appendectomies, were not influenced by UV exposure among IBD hospitalisations. These findings further reinforce our observation that low UV and higher bowel surgery rates is a unique, and not random, phenomenon in IBD hospitalisations.

There are several limitations of this study. First, our analyses were constrained by data available in a large administrative database that includes information about hospitalisations. The data set does not identify when multiple hospitalisations occurred within a single individual and does not have complete information on potential confounders, such as smoking, medication use or readmissions. However, for confounding to occur there needs to be a relationship between the confounder and disease. Although smoking is strongly associated with CD and UC, there is no evidence that smoking is associated with day-to-day variability in UV, despite potential regional differences in smoking rates. Similarly, we were unable to identify a known confounder strongly associated with both UV and IBD or IBD outcomes that is likely to change our inference. Second, an inherent limitation in administrative databases is the completeness and accuracy of ICD-9 coding for IBD, comorbidities or procedures. Although the codes used in this study have not been validated with the NIS, we selected codes that were either validated in other databases or based on reasonable codes used in clinical practice.[25, 47] Third, some records had to be excluded due to missing admission time or race data, which did not permit us to calculate national estimates using weighted data. We were nonetheless still able to use weighted regression analyses to make technically valid comparisons among UV groups, provided we include at least one observation from each sampled hospital for correct variance estimation.[27]

In conclusion, our findings demonstrate at the population level an association between low UV exposure and increased IBD hospitalisation rates and severity. Although the precise mechanism for UV effect on IBD is currently unknown, a proposed mediator for this relationship is vitamin D. There is a growing body of evidence that vitamin D is involved in IBD pathogenesis and disease severity. Measurement of vitamin D levels on the individual level and genotyping of IBD risk genes related to vitamin D are needed to further elucidate the mechanisms and gene–environment interactions of this relationship.

AUTHORSHIP

Guarantor of the article: Berkeley N. Limketkai.

Author contributions: BNL, TMB, SRB and SMH participated in study concept and design, data interpretation, drafting and critical revision of the manuscript. BNL and SMH participated in data acquisition and statistical analyses. BNL, TMB, SRB and SMH provided administrative, technical and material support. SMH provided study supervision. All authors approved the final version of the manuscript.

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