Variation in incidence of paediatric Crohn's disease in relation to latitude and ambient ultraviolet radiation: a systematic review and analysis

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Conflict of Interest:

None declared.

Source of funding:

Ms. Holmes is supported by an ANU Australian Postgraduate Award (APA). Dr Xiang is supported by a NHMRC Centre of Research Excellence in Sun and Health Postdoctoral Fellowship. Prof Lucas is supported by a NHMRC Career Development Fellowship.

Word Count: 3,168

Abstract

Background

Paediatric Crohn's disease (CD) is a lifelong, debilitating and costly disease. In previous studies, CD incidence increased with higher geographic latitude in the Northern Hemisphere. This may indicate a role for lower vitamin D status as a risk factor for CD. Analysis of worldwide incidence of paediatric CD has not been previously reported.

Methods

We undertook a systematic review of population-based studies reporting incidence of paediatric CD and published between 2003 and 2013. Included studies had well-defined diagnostic criteria for CD, evidence of high case ascertainment, reported incidence according to age group and provided a specific location. Average daily ambient ultraviolet radiation (UVR) for each location was derived from satellite data. Negative binomial regression was used to assess the association between paediatric CD incidence and latitude and ambient UVR, adjusting for the study year.

Results

28 papers provided 39 incidence data points. Incidence of paediatric CD increased with higher latitude, and in association with a greater number of months where the average daily UVR was lower than a previously published threshold of 1.488kJ/m^2. Incidence of paediatric CD increased over calendar time.

Conclusions

After applying rigorous quality assessment criteria, and including only population-based studies, there was a modest increase in incidence of paediatric CD with higher latitude and

greater number of months with low ambient UVR. Reporting using non-consistent diagnostic criteria and age groups, with poorly defined geographic locations, makes it difficult to compare data across different studies.

Key words

Paediatric Crohn's disease, Incidence, Ultraviolet radiation, Vitamin D, Epidemiology

Introduction

Crohn's disease (CD) is an immune-mediated inflammatory bowel disease (IBD) that affects people of all ages. The incidence of CD appears to be increasing in both children[1, 2] and adults.[3] When the disease begins in childhood, it tends to run a more severe course, has a greater impact on the quality of life[4] and imposes a higher economic burden than does adult-onset disease.[5] Treatment costs for CD in the United States alone are estimated at $3.6 billion annually and the cost is approximately 18% higher for individuals under 20 years of age than it is for adults aged 20 to 39 years of age.[5]

The aetiology of CD remains unknown but probably involves a combination of genetic susceptibility, exposure to environmental risk factors, and alterations in the gut microbiome that stimulate an inflammatory response.[6] Although a wide range of environmental risk factors have been proposed to increase the risk of CD, findings have been generally inconsistent. For example, both rural living[7] and urban dwelling[8] have been shown to be risk factors, in separate studies.

Several studies have shown that in the Northern Hemisphere, the incidence of CD increases with increasing distance from the equator, i.e. higher latitude, even over quite a small latitudinal span.[9-13] Furthermore, two studies in France found that higher residential sun exposure was associated with a lower risk of CD in adults.[12, 14] These findings have been interpreted as indicating that low vitamin D status may be a risk factor for CD, since sun exposure of the skin is the primary source of vitamin D in many regions of the world. The data are however not completely consistent, with some studies showing no variation in incidence/prevalence with increasing latitude.[15-17] These inconsistent findings may reflect heterogeneity in the disease across different regions or at different times, or variations in

study methods, including diagnostic criteria, the study sampling frame, i.e. population-based or not, sampling, and the completeness of case ascertainment.

In order to further examine this issue, we conducted a systematic review of paediatric CD incidence in relation to latitude and ambient levels of ultraviolet radiation (UVR) in studies in both the Northern and Southern Hemispheres. We used rigorous assessment of study quality to select studies for inclusion in our analyses to ensure the validity of our findings.

Materials and Methods

Literature search

We systematically searched PubMed for articles in English published between 2003 and 2013. Keywords used were: ("Crohn's disease" OR "inflammatory bowel disease") AND "incidence" AND ("paediatric (pediatric)" OR "children") (for specific search strategies, see Supplementary material 1). We also searched the database of "related articles" cited in PubMed next to each abstract, reference lists of primary original studies and checked review articles for further relevant studies.

This search strategy returned 1239 articles. Perusal of the titles and abstracts of these papers led to the retention of 58 relevant papers. Twelve papers were excluded after the full text examination due to insufficient data, and thirty-seven papers were retained for full quality assessment (Figure 1).

Quality Assessment

Three independent reviewers (RL, FX and AH) scored the 37 retained papers using quality assessment criteria (Supplementary material 2) for five components of the study methodology: CD diagnostic criteria; study sampling frame; study location definition; study year; incidence data report method. Each component was graded as an A (good), B (sufficient) or C (insufficient) by each reviewer. Discrepancies were discussed and agreement achieved by consensus. Any paper receiving one or more C grades was excluded. This resulted in the exclusion of nine papers, leaving 28 papers for inclusion in the final analysis (Table 1).

Data Extraction

For each eligible paper the following information was extracted and recorded: first author, study year or median year of study period (if the study years were an even number the higher of the two median years was recorded), catchment area of the study population, and crude CD incidence rates (age group- and sex specific incidence rates, or combined male and female paediatric CD incidence rates and age group used to define "paediatric", depending on availability). CD incidence data were extracted from the main text and/or tables and/or figures. Where incidence rates were reported graphically only, Image J[1] was used to derive the relevant data. Latitude and longitude coordinates for the catchment area were assigned in a Geographic Information System (GIS).

Exposure data

The average daily surface ambient UVR levels were estimated for each catchment area and study year with GIS, using two databases: the "Ingrid" web-based data library (2000-2004)[18] and the NASA OMI data (2005-2012).[19] The resolution (one grid cell) of the satellite data was 1° latitude and 1.25° longitude. For studies conducted over large geographic regions, i.e., more than one grid cell, the ambient UVR was calculated as the average ambient UVR for all grid cells (e.g. national data from a country with wide latitude, such as Italy). For those studies which were conducted over several years, the ambient UVR was calculated as the average ambient UVR for those years.

1 ImageJ is image processing software that is analyses different image formats, developed by the National Institute of Health.

Paediatric CD incidence data

The definition of "paediatric" ranged widely across studies, from 0-14 to 0-19 years. The most consistent age group was "under 18 years" (i.e., 0-17) without separation of incidence rates by sex. As such, we converted all of the incidence data to this grouping (i.e., combined male and female incidence for under 18 years of age), using DISMOD II[2]. The detailed imputation process is described in Supplementary material 3. In brief, studies with both detailed age group-specific CD incidence rates and population data available (the reference study) were used to provide the pattern of incidence rates across different paediatric age groups. A study from New Zealand[20] was used as the reference study for studies in the Southern Hemisphere, and one from Denmark[21] was used as the reference study for studies in the Northern Hemisphere. Where the incidence rate for an under 18 years age group was not reported by a study (the target study), this was imputed using the data available in the target study and the pattern of incidence according to age group that was presented in the reference study.

Data Analysis

There was considerable over-dispersion of the data, and violation of the distribution assumption in a Poisson model that the variance equals the unconditional mean. Thus, the more generalised negative binomial regression was used to model the relationship between the CD incidence and latitude or ambient UVR. Because incidence is reported to be increasing over time, we adjusted all models for the year of the study.

[2] DISMOD II is a program that estimates parameters of diseases that are unknown, by iteration, based on those data that are available (incidence, prevalence, remission rate, case fatality etc.) for various age groups.

Two sensitivity analyses were conducted. The first used data only from studies in Europe and the second used data only from studies reporting incidence for the under 18 years age group (i.e. without imputed incidence data).

$P \leq 0.05$ was considered to be statistically significant. Statistical analyses were performed using Intercooled Stata 9 (StataCorp 2005. Stata Statistical Software, Release 9 College Station TX, StataCorp LP).

Results

A total of 28 papers were identified that met the inclusion and quality assessment criteria. These provided 39 data points: 4 (10%) in North America (including Canada), 31 (79%) in Europe, 3 (8%) in Australasia and 1 (3%) in the Middle East (Table 1). The CD incidence data were collected between 2000 and 2008 (publications from 2003-2013).

The incidence of CD (per 100,000 person-years) for the under 18 years age group (including imputed data) varied considerably across different geographic locations in the Northern Hemisphere from 0.6 per 100,000 in Poland (average annual daily UVR: 1.62 kJ/m^2)[22] to 9.9 per 100,000 in North Stockholm County, Sweden (average annual daily UVR: 1.19 kJ/m^2).[23] The only data available from the Southern Hemisphere were from Australia and New Zealand.

We first modelled the association between latitude and the incidence of paediatric CD (Table 2a). For a ten degree increase in latitude there was a significant increase in annual paediatric CD incidence of 0.23 new cases per 100,000 population. We next examined the association between ambient UVR and incidence of paediatric CD (Table 2b). There was a modest, but not statistically significant, decrease in the incidence of paediatric CD with increasing average annual daily ambient UVR levels.

We further explored the association between ambient UVR and CD incidence using average UVR for mid-winter and for mid-summer (Table 3a). There was no significant association between CD incidence and either mid-winter or mid-summer ambient UVR.

Nerich and colleagues reported decreasing CD incidence with increasing ambient UVR up to a threshold of 1.488 kJ/m^2[10] with no further change in incidence at UVR levels above this. We were unable to demonstrate a similar association in our data, and there was no evidence of a non-linear association between mid-winter ambient UVR and CD. However, we did find that there was a modest increase in CD incidence of 0.08 cases per 100,000 for every additional month where the daily UVR was lower than 1.488 kJ/m^2 (Table 3b).

Sensitivity analyses

There was no significant association between CD incidence and latitude or ambient UVR when the analyses were restricted to studies from Europe, or to those that reported incidence for the under 18 years age group (i.e., without imputation of incidence data) (Table 2a and b). In all cases, the direction of effect was the same as in the full analysis, but of smaller magnitude. Further investigation of this attenuation of effect showed that the data from two studies[23, 24] was highly influential. Both were conducted in at a high latitude location (Northern Stockholm County, Sweden) and the imputed CD incidence were the highest among all studies that required imputation.

Within studies that reported CD incidence for the under 18 year group, when adjusting for ambient UVR, there was modest increase in CD incidence with calendar year; in the examination of CD incidence in relation to number of months with daily UVR lower than 1.488 kJ/m^2, both greater number of months and more recent study calendar year were associated with significantly higher CD incidence (Table 3b).

Discussion

In this systematic review of the published literature on the incidence of paediatric CD, with inclusion of only population-based studies that used well-defined diagnostic criteria and high case ascertainment, there was an increase in CD incidence with higher latitude and a decrease with higher ambient UVR, although the latter was not statistically significant. We further investigated an association of paediatric CD with summer and winter UVR, and according to a previously published threshold of ambient UVR. In all cases there was an inverse association with disease incidence, but only the analyses in relation to months where UVR was below a threshold reached statistical significance, i.e. an 8% increase in incidence for each additional month of lower ambient UVR.

The main strengths of this work include firstly, that we have confined our analysis to data from paediatric age groups only. This provides a more homogeneous sample than occurs when data from adults and children are combined, and reduces the range of potential risk exposures. For example, children are unlikely to be smokers and have had fewer opportunities for microbial exposure. Studying the disease in children only may then give a clearer aetiological signal. Secondly, all of the studies used here were population-based, with high case ascertainment and thus some confidence in the accuracy of the incidence data. The studies were of high quality methodologically and provided sufficiently detailed data for inclusion in these analyses. Thirdly, although for three world regions (North America, Australasia and the Middle East) there were few studies and those included here may not adequately represent the true situation in the full regions, the data from Europe alone are representative of a relatively broad latitudinal range of locations from Italy (42°S) to Finland (62°N) and an ambient UVR range from 0.9 kJ/m^2 (Finland) to 2.6 kJ/m^2 (Italy). This allows for reasonably robust, although mainly high latitude, results for this area. Our analyses were

limited by the lack of sufficient suitable data to allow a full assessment of the global pattern of disease distribution. Further, as an ecological study, providing population-level analyses of the association between incidence and an environmental factor, this study did not provide individual-level data on the personal doses of UVR or potential confounding factors such as ethnicity. Indigenous populations in Canada and New Zealand are reported to have lower rates of CD than the European populations in the same region.[20, 25] Both skin type and sun exposure behaviour vary according to ethnicity and may alter the link between ambient UVR and received UVR dose,[26] while ethnicity may modify the link between measured vitamin D status and some health outcomes.[27]

Due to the lack of consistent age groupings used to report CD incidence, imputation of the incidence rate was required for more than half of the included studies (21 out of 39). The imputation process using DISMOD II was based on the assumption that the population structure and the pattern of CD incidence across age groups were the same for the reference study and the target study. Furthermore, only one reference study (i.e., study that has both CD incidence for all age groups and official data on the population structure for the catchment area) was available for each Hemisphere; thus the pattern of CD incidence according to age group for the target study was established based on the single reference study. This has inevitably led to a lack of precision in the imputed incidence data, and thus the estimates of the effect size.

Our finding of a small but significant increase in the incidence of paediatric CD with increasing latitude concurs with the results from some previous studies in adults,[9, 11-13, 28] that were mainly confined to smaller regions where the populations are likely to have been

relatively genetically similar, compared to the analysis undertaken here. The greater genetic and cultural diversity of the populations included in our analysis may explain the low estimate of effect we obtained. Nevertheless, a latitude gradient was not present in our subgroup analyses of only European studies.

Several other studies in adult populations have not demonstrated a latitude gradient,[1, 5, 16, 17] and in our results, the association between paediatric CD incidence and levels of ambient UVR was not statistically significant. Here we confined the included studies to those published since 2003. There is some evidence to suggest that the incidence of CD is increasing more rapidly in developing countries[29] that are often at low latitude, compared to more developed countries. This could lead to a weakening of an association between latitude and/or ambient UVR levels. A weakening of the latitude gradient over time is reported for multiple sclerosis, another autoimmune disease, within the Nurses Health Studies,[30] where the incidence in the southern states has increased more rapidly than in the northern US states, possibly due to decreasing sun exposure in the South.[30]

Alternative explanations for the weak association with latitude seen here, in comparison to previous studies, and the lack of association with ambient UVR is that there was insufficient study power to demonstrate a real gradient, or that previous findings were spurious, related to inadequate control for study quality. Here we used strict inclusion criteria to ensure only studies with population-based case ascertainment, using well-defined diagnostic criteria and with a clear-cut population-at-risk, were included, providing some confidence in our findings.

The modest decrease in CD incidence with increasing ambient UVR was not statistically significant for average daily ambient UVR over the whole year, or for summer or winter

UVR. We explored the latter because the amplitude of the seasonal variation in UV-B radiation (that is required for vitamin D synthesis) is increased with increasing latitude.[31] At high latitudes, vitamin D synthesis is not possible during the winter months, when UV-B levels are very low. This analysis is similar to that examining whether there is a threshold of ambient UVR above or below which there is a stronger association with CD incidence.

An association between sun exposure and/or vitamin D and risk of CD is biologically plausible. Both vitamin D (the active form) and exposure of the skin to UVR cause systemic suppression of Th-1 immune function and upregulation of T regulatory cells, that could decrease the inflammatory pathways leading to CD (for review, see[32]). Furthermore, vitamin D status may be able to influence the intestinal microbiome through upregulation of antimicrobial peptides such as cathelicidin, and more effective elimination of pathogenic microbes (for review, see[33]). In addition, there is a range of other factors related to latitude that could have importance for CD incidence and any latitude gradient, including patterns of migration from areas of high risk to areas of low risk and vice versa, and dietary factors, which also may be changing over time (e.g. becoming more homogeneous with globalisation).

Vitamin D deficiency is common in both children[34, 35] and adults[36, 37] who are diagnosed with CD. However, in most studies it is not clear whether vitamin D deficiency was associated with increased risk of CD, or that having the disease led to vitamin D deficiency. Clinical trials of vitamin D supplementation in people with inflammatory bowel disease are currently underway, but to date, most trials of vitamin D supplementation in people with autoimmune diseases have not resulted in clinical improvements.[38] It is important to note however, that the

risk factors for disease activity post-diagnosis may not be identical to those for disease incidence.[39]

It is worth noting the challenges in combining data from different studies. The studies included varied in the data provided, particularly in the availability of age-specific data and sufficient data to fully assess the completeness of case ascertainment. The sizes of the study areas and underlying populations and the number of cases, and thus the robustness of the incidence estimates, were also highly variable. These factors could lead to over- or under-estimation of the true incidence and affect the precision in our estimates. Furthermore, there was a scarcity of published population-based studies from Central and South America, Eastern Europe, Africa and Asia.

Ideally, the incidence data would derive from population-based samples from well-defined catchment areas with data on the underlying population and the incident cases reported according to narrow, or standard, age groupings. Diagnosis would use standardized case definitions and there would be evidence of complete or nearly complete case ascertainment. Registry data, appropriately validated and with prospective data collection,[40] would provide an alternative to repeated incidence studies, and have the advantage of consistent and comparable data collection. The lack of consistency in these key elements of the published data may well explain the inconsistency in the findings for an association between CD and latitude.

Global comparisons may help to provide aetiological clues to this debilitating disease. But, in reality, there are few data on which to establish comparisons and to observe trends in the

incidence of CD. Furthermore, its relative rarity, globally, limits our ability to define temporal and spatial trends, with estimates from small region data collection likely to be unstable. Despite the limitations of this study, the results are suggestive of latitudinal variation in CD incidence that could be plausibly caused by the biological effects of exposure to UVR or vitamin D. It also highlights some of the issues which limit the collection, analysis and reporting of CD epidemiological data. The long-term significance of UVR exposure and vitamin D for paediatric CD patients is unknown at present and merits further study, given that these would be inexpensive and safe potential therapeutic options.

Acknowledgements:

We are indebted to Ivan Hanigan for his assistance with derivation of the ambient UVR according to location, using Geographic Information System.

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Table 1 Summary of studies satisfying the inclusion criteria and included in analyses

Reference	Study year	Catchment area of population	Age group (Years)	M &F[a] combined incidence (per 100,000)	M&F combined imputed incidence	Average daily ambient UVR* (kJ/m^2)	Study region	Latitude	Quality Assessment
Abramson [41]	2001	14 North Californian Counties, USA	0-17	2.7		3.38	1	38.28° N	ABBBA
Ahmed [42]	2000	Cardiff and Vale, South Wales, UK	0-15		3.6	1.42	2	51.48° N	AAABB
Al Qabandi [43]	2002	Kuwait	0-14		1.53	4.35	4	29.17° N	AAABB
Benchimol [44]	2005	Ontario, Canada	0-17	6.6		1.65	1	50.00° N	AABAA
Castro [45]	2000	Italy	0-17	5.62		2.56	2	43.78° N	AABAB
	2001	Italy	0-17	4.68		2.46	2	43.78° N	AABAB
	2002	Italy	0-17	5.24		2.42	2	43.78° N	AABAB
	2003	Italy	0-17	6.48		2.61	2	43.78° N	AABAB
Grieci [46]	2004	South West Ontario, Canada	0-17	6.01		1.64	1	43.00° N	ABBBB
Henderson [47]	2006	Scotland	0-15		4.7	1.18	2	56.00° N	AABBA
Hildebrand [24]	2000	Northern Stockholm County, Sweden	0-15		8.4	1.16	2	59.70° N	AAABB
Hope [48]	2005	Ireland	0-15		2.51	1.34	2	53.00° N	AABAB
Jakobsen [49]	2003	Eastern Denmark	0-14		3.1	1.35	2	55.80° N	AAAAB
Jakobsen [50]	2008	Futen & Aarhus, Eastern Denmark	0-14		3.2	1.49	2	55.80° N	AAABB
Karolewska-Bochenek[22]	2004	Poland	0-18		0.6	1.62	2	51.78° N	AABBA
Kolek [51]	2000	Moravia Czech Republic	0-15		2.02	1.76	2	49.50° N	AAAAB
	2001	Moravia Czech Republic	0-15		4.44	1.57	2	49.50° N	AAAAB
Lehtinen [16]	2000	Finland	0-17	7.37		0.99	2	60.98° N	AAAAB
	2001	Finland	0-17	7.21		0.92	2	60.98° N	AAAAB
	2002	Finland	0-17	9.74		1.15	2	60.98° N	A AAAB
	2003	Finland	0-17	9.1		1.03	2	60.98° N	AAAAB
Malaty [52]	2000	Texas, USA	0-17	1.33		3.58	1	31.00° N	AAABB

Malmborg [23]	2003	Northern Stockholm County, Sweden	0-15		9.91	1.19	2	59.70° N	AAABB
Orel [53]	2003	Western Slovenia	0-18		2.88	2.20	2	45.30° N	AABBB
Ott [54]	2005	Oberfalz, Germany	0-15		2.24	1.70	2	49.30° N	ABBBB
Perminow [55]	2002	Akershus, Norway	0-15		2.05	1.15	2	60.00° N	BBABB
Perminow [56]	2006	Oslo and Akershus, Norway	0-18		6.8	1.16	2	60.00° N	AAABB
Pozler [57]	2000	Czech Republic	0-14		1	1.66	2	50.08° N	ABBAB
	2001	Czech Republic	0-14		1.26	1.50	2	50.08° N	AAAAB
Sincic [58]	2002	Primorsko-goranska, Croatia	0-14		8.18	2.05	2	45.45° N	ABABB
Turunen [59]	2000	Southern Finland	0-17	1.9		1.06	2	60.18° N	ABBAB
	2001	Southern Finland	0-17	2.6		1.00	2	60.18° N	ABBAB
	2002	Southern Finland	0-17	3.6		1.16	2	60.18° N	ABBAB
	2003	Southern Finland	0-17	2.6		1.05	2	60.18° N	ABBAB
Van der Zaag-loonen [60]	2000	Netherlands	0-17	2.1		1.39	2	52.37° N	AABBB
Vind [21]	2004	Copenhagen, Denmark	0-15		3.29	1.40	2	55.68° N	AAABB
Yap [61]	2003	New Zealand	0-14		1.9	2.54	3	39.07° S	ABBAB
Gearry [20]	2005	Canterbury, New Zealand	0-17	13.1		2.37	3	43.60° S	AAAAA
Wilson [62]	2007	Greater Geelong, Australia	0-14		6.0	2.95	3	38.15° S	AAAAB

[a] Male and female data combined

[b] Study region 1= North America and Canada; 2= Europe; 3=Australia and New Zealand; 4= Middle East

*Abbreviation: USA: United States of America; UK: United Kingdom; UVR: ultraviolet radiation

Table 2a) Association between CD incidence rates and latitude, with adjustment for study year

b) Association between CD incidence rates and ambient UVR with adjustment for study year

	All studies* (n=39)		**Studies from Europe** (n=31)**		**Studies reporting incidence data for <18 years age group (n=18)**	
a)	Coefficient (95% CI) R^2=2.9%	P value	Coefficient (95% CI) R^2=2.9%	P value	Coefficient (95% CI) R^2=2.9%	P value
Latitude (10°)	**0.23 (0.02, 0.44)**	**0.03**	0.17 (-0.09, 0.43)	0.19	0.15 (-0.05, 0.36)	0.19
Hemisphere						
Northern	Reference category				Reference category	
Southern	0.52 (-0.23, 1.26)	0.18	-		0.68 (-0.06, 1.43)	0.07
Study year (Year)	0.03 (-0.06, 0.12)	0.53	0.00 (-0.10, 0.10)	0.10	0.13(-0.01, 0.27)	0.08
b)	R^2=1.5%		R^2=0.1%		R^2=7.2%	
Ambient UVR (kJ/m^2)	-0.19 (-0.45, 0.07)	0.62	-0.10 (-0.53, 0.33)	0.65	-0.06 (-0.37, 0.25)	0.69
Study year (Year)	0.05 (-0.04, 0.14)	0.29	0.00 (-0.10, 0.11)	0.97	**0.17 (0.05, 0.30)**	**0.007**

Abbreviations: CI: Confidence interval; n: number; UVR: ultraviolet radiation

* Model included latitude, hemisphere and study year.

** Model included ambient UVR and study year.

Table 3a) Association between CD incidence rates and mid-winter and mid-summer average daily ambient UVR with adjustment for study year

b) Association between CD incidence rates and number of months of the year where the average ambient UVR was less than 1.488 kJ/m^2

	All studies (n=39)		**Studies from Europe (n=31)**		**Studies reporting incidence data for <18 years age group (n=18)**	
a)	Coefficient (95% CI) R^2=1.6%	P value	Coefficient (95% CI) R^2=0.1%	P value	Coefficient (95% CI) R^2=7.6%	P value
Winter UVR (kJ/m^2)	-0.41 (-0.95, 0.13)	0.14	-0.20 (-1.43, 1.03)	0.65	-0.28 (-1.06, 0.50)	0.69
Study year (Year)	0.04 (-0.05, 0.13)	0.36	0.00 (-0.11, 0.11)	0.99	**0.17 (0.04, 0.30)**	**0.01**
	R^2=1.4%		R^2=0.4%		R^2=9.1%	
Summer UVR (kJ/m^2)	-0.10 (-0.26, 0.05)	0.18	-0.08 (-0.30, 0.13)	0.43	-0.12 (-0.28, 0.05)	0.18
Study year (Year)	0.06 (-0.03, 0.15)	0.22	0.01 (-0.10, 0.11)	0.90	**0.20 (0.07, 0.32)**	**0.003**
b)	R^2=2.4%		R^2=0.1%		R^2=13.4%	
No. of months (n)*	0.08 (0.01, 0.15)	0.05	0.06 (-0.03, 0.16)	0.19	**0.09 (0.02, 0.06)**	**0.02**
Study year (Year)	0.05 (-0.04, 0.14)	0.27	0.01 (-0.10, 0.11)	0.98	**0.19 (0.07, 0.31)**	**0.002**

Abbreviations: UVR: ultraviolet radiation; CI: Confidence interval; n: number

Table 3a) Winter UVR: Average daily ambient UVR in January for study areas in Northern Hemisphere; Average daily ambient UVR in July for study areas in Southern Hemisphere.

Summer UVR: Average daily ambient UVR in July for study areas in Northern Hemisphere; Average daily ambient UVR in January for study areas in Southern Hemisphere.

Table 3b) *No. of months: Number of months with average daily ambient UVR less than 1.488 kJ/m^2