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Title:

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Date:

2019-05-01

Citation:

Chiaroni-Clarke, R. C., Munro, J. E., Pezic, A., Cobb, J. E., Akikusa, J. D., Allen, R. C., Dwyer, T., Ponsonby, A. L. & Ellis, J. A. (2019). Association of Increased Sun Exposure Over the Life-course with a Reduced Risk of Juvenile Idiopathic Arthritis. *Photochemistry and Photobiology*, 95 (3), pp.867-873. <https://doi.org/10.1111/php.13045>.

Persistent Link:

<https://hdl.handle.net/11343/284814>

Article type : Research Article

Association of Increased Sun Exposure Over the Life-Course with a Reduced Risk of Juvenile Idiopathic Arthritis

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/php.13045](https://doi.org/10.1111/php.13045)

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ABSTRACT

Cutaneous sun exposure is an important determinant of circulating vitamin D. Both sun exposure and vitamin D have been inversely associated with risk of autoimmune disease. In juvenile idiopathic arthritis (JIA), low circulating vitamin D appears common, but disease-related behavioural changes may have influenced sun exposure. We therefore aimed to determine whether pre-disease sun exposure is associated with JIA. Using validated questionnaires, we retrospectively measured sun exposure for 202 Caucasian JIA case-control pairs born in Victoria Australia, matched for birth year and time of recruitment. Measures included maternal sun exposure at 12 weeks of pregnancy, and child sun exposure across the life-course pre-diagnosis. We converted exposure to UVR dose, and looked for case-control differences using logistic regression, adjusting for potential confounders. Higher cumulative pre-diagnosis UVR exposure was associated with reduced risk of JIA, with a clear dose response relationship (trend $p=0.04$). UVR exposure at 12 weeks of pregnancy was similarly inversely associated with JIA (trend $p=0.011$). Associations were robust to sensitivity analyses for pre-diagnosis behavioural changes, disease duration, and knowledge of the hypothesis. Our data indicate that lower UVR exposure may increase JIA risk. This may be through decreased circulating vitamin D, but prospective studies are required to confirm this.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is an autoimmune rheumatic disease affecting around 1 in 1000 children of European descent. It is defined as joint pain and swelling of unknown cause that persists for at least 6 weeks in a child 16 years of age or under (1). JIA is considered a complex disease, in which both genetics and environment contribute to susceptibility (2). While the genetic variants associated with JIA are

beginning to be uncovered (3), far less is known about the environmental components of disease risk (4).

Exposure to sunlight (ultraviolet radiation, UVR) has been examined as a potential environmental risk factor for a variety of autoimmune diseases (5). Cutaneous exposure to UVR leads to increased production of vitamin D₃ (25(OH)D₃) (6). It is circulating vitamin D that is often presumed to be the relevant mechanism through which UVR exposure leads to a change in autoimmune disease risk, but it is not the only possible pathway (7). Vitamin D has established anti-inflammatory and immunomodulatory properties (8, 9), including suppression of immune responses mediated by T cells; central to the development of autoimmune disease (8).

Both UVR exposure and levels of circulating vitamin D have been robustly associated with the autoimmune disease multiple sclerosis (MS). Seminal studies in Australia (10), followed later by meta-analysis of global data (11), demonstrate a clear increase in MS incidence with higher latitudinal gradient. Lower circulating vitamin D (12), and polymorphisms in vitamin D pathway genes (13, 14), have also been associated with MS. There are also multiple lines of evidence linking UVR and vitamin D to rheumatoid arthritis (RA), with which JIA shows phenotypic and genetic overlap (15, 16). Cumulative ultraviolet B exposure has been prospectively inversely associated with RA risk (17). There is also some evidence of association of RA with latitudinal gradient (18), of increased RA disease activity with lower circulating vitamin D (19-21), and of vitamin D supplementation with reduced RA recurrence (22).

Several studies have examined circulating vitamin D in children with JIA. A meta-analysis of 529 individuals across 14 studies, reported that vitamin D deficiency (as defined for adult populations, <50 nmol/l) is prevalent in JIA (23). However, this is not unexpected, since JIA is a physically disabling disease that is likely to reduce behaviours related to outdoor activity and thus exposure to sun. Therefore, it is difficult to determine whether vitamin D deficiency in JIA is a cause, or a consequence, of disease. Prospective studies that measure vitamin D prior to disease onset are needed to determine causality; however, the relative rarity of JIA in the population makes such an approach difficult. As an alternative, a recent study measured vitamin D in neonatal dried blood spots, but found no association between

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vitamin D at birth and later onset of JIA (24). No studies to date have been able to examine the association of JIA with vitamin D at other pre-disease life-course time-points.

An approach that does not require prospective vitamin D measurement is to consider UVR exposure across the life-course. Sun exposure is the main driver of circulating vitamin D (6), especially in countries such as Australia where fortification of foods with vitamin D is not commonplace (25). The relationship between sun exposure and circulating vitamin D is influenced by ambient UVR levels (determined by latitude, altitude, season and time of day), time in the sun, and sun protection factors (6). In a recent study of healthy children in Melbourne Australia, we reported that environmental factors (such as UVR exposure six weeks prior to interview) and phenotypic factors (such as skin colour) explained 28% and 21% of the variance in circulating 25(OH)D₃ respectively (26). Therefore sun exposure can be used as a measure of child circulating 25(OH)D₃ in our setting.

To understand the relationship between sun exposure and JIA risk, we used validated questionnaire instruments (26-29) to retrospectively collect information about sun exposure and associated factors across the life-course in children with and without JIA born in Victoria, Australia. We compared reported pre-disease UVR exposure between cases and controls both during specific age periods (including mother's exposure during pregnancy) and cumulatively.

MATERIALS AND METHODS

Participant population. Participants were drawn from the ChiLdhood Arthritis Risk factor Identification sTudY (CLARITY) (30). CLARITY is a collection of clinical, epidemiological and environmental data and biospecimens from children with JIA (cases), and from healthy children (controls). JIA cases were recruited at the Royal Children's Hospital (RCH), Melbourne, Victoria, Australia. All cases were aged between 0–18 years at recruitment, with paediatric rheumatologist-diagnosed onset of JIA by 16 years, using the ILAR criteria (31). Cases were defined as incident if recruited within six months of diagnosis, and prevalent if diagnosed more than six months prior to recruitment. Victorian-born controls aged 0–18 years were recruited

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from the day surgery unit at the RCH while attending for minor surgical procedures. All cases and controls were asked to provide a blood sample, and their parents were asked to complete an extensive questionnaire capturing epidemiological and environmental information, including on skin type and sun exposure (30). The Human Research Ethics Committee of the RCH approved the study. All study participants provided written consent.

Inclusion criteria. To minimise ethnicity-related differences in skin type, vitamin D synthesis and bioavailability (32), we selected only CLARITY cases and controls of self-reported Caucasian ancestry. Ancestry of the child's four grandparents was collected by questionnaire. Participants were considered to be Caucasian if all four grandparents were reported as Caucasian. If one or more grandparents were reported as non-Caucasian, or if data were missing for any grandparent, participants were excluded from the study.

To minimise latitude-related variability in UVR exposure, we restricted participant selection to children born in Victoria. To minimise discrepancies in recall and temporal community behavioural changes, and sun exposure window, we used a matched case-control design where each eligible case was matched to one eligible control on year of birth and closest possible recruitment date. Age matching also served to remove differences in cumulative sun/UVR exposure between groups that reflected differences in age.

Measurement of sun exposure. Components of the participant questionnaire regarding past sun exposure and skin reaction to sun were used to analyse the relationship between past sun exposure and JIA. These instruments have demonstrated validity and reliability in both adults and children, where they show strong correlation with objective measures of sun exposure and circulating vitamin D (26-29, 33). Maternal sun exposure at 12 weeks of pregnancy was also recorded because we have previously related this to autoimmune disease (34).

Parents were asked about the amount of time their child would normally have spent in the sun during weekends and holidays in winter and summer at ages 0–2, 3–5, 6–10, and 11–15 years, as well as the summer and winter preceding interview. Time in sun

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measures were categorised as <1, 1–2, 2–3, 3–4, and 4+ hrs per day. Where an answer of <1 hr per day was given, parents were asked to provide further detail as to whether this constituted no time in the sun, some, but less than ½ hour, or ½ to 1 hour.

Based on our expectation of a delay in the impact of sun exposure on the immune system (35), we considered only the sun exposure measures that preceded disease diagnosis by at least one year.

Cumulative sun exposure was determined by number of hours spent in the sun per day during summer or winter weekends and holidays across ages 0–2, 3–5, 6–10 and 11–15 years. Categories were converted into time in minutes as follows: None – 0 min; some, but less than half an hour – 15 min; half to 1 hr – 45 min; <1 hr – 30 min (if parents failed to provide further detail); 1 to 2 hrs – 90 min; 2–3 hrs – 150 min; 3–4 hrs – 210 min and ≥ 4 hrs per day – 270 min. Time in the sun in each category was multiplied by the number of years in the specific age category, and then added for each age group to get the total number of hours spent in the sun over the life-course.

To determine total UVR exposure, data were obtained for the monthly average of daily total UVR dose in standard erythemal doses for Melbourne, latitude 37.5°S, from the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA, personal communication). To account for differences in UVR strength in summer and winter, cumulative sun exposure for each time point was multiplied by the mid-summer or mid-winter average ambient UVR index over the years 1993–2011, for summer and winter respectively, and these values were added together. Total UVR dose was divided into quartiles for analysis.

The amount of time the mother would normally have spent in the sun during weekdays and weekends at 12 weeks of pregnancy with the participating child was also collected. Time in sun measures were categorised as <1, 1–2, 2–3, 3–4, and 4+ hrs per day.

We calculated the date when the mother was 12 weeks pregnant by subtracting the gestational age from the child's date of birth. We then determined the UVR index specific to the month and year of the pregnancy using ARPANSA data, and

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multiplied this by time in the sun at 12 weeks of pregnancy for weekdays or weekends (5/7 and 2/7 of average daily exposure respectively). Pregnancy UVR was divided into quartiles for analysis. To account for latitude related differences, pregnancy measures were only determined where pregnancy occurred in Victoria.

Measurement of skin phenotype. Parents were asked about how their child's skin reacts to the sun (tendency to burn, summer tan, lifetime sunburn, freckling; see Supporting Information file for details). The skin type of the participant was also objectively recorded as dark, olive, olive/medium, medium/fair, or fair, by the nurse during recruitment to the study, using a validated colour chart (36) for two-thirds of the sample.

Statistical analysis. We modelled the risk of JIA for the different measures of sun exposure. Pearson's correlation was used as a measure of linear association. ORs and 95% CIs were calculated using multivariate logistic regression. Tests for trend of categorical variables were undertaken by using a single predictor, taking category rank scores. Where exposure categories had no or low numbers, categories were merged.

All analyses were adjusted for age at recruitment and sex. For the childhood UVR multivariate model, mother's age at birth, mother's completion of high school education (as a measure of socioeconomic status used in this sample previously (30)) and mother's current smoking status were included in the model. Additional potential confounders were assessed by adjusting the analysis by the variable of interest and if the change in estimate was greater than 10% it was included in the multivariate analysis. The following covariates were assessed but were not included in the final model: number of siblings within six years of age (37); gestational age at birth; mother married at interview; mother hours in paid work; father smoked during pregnancy; parent had any autoimmune disease; parent had rheumatoid arthritis; number of days breastfed; tan at end of summer; reaction of skin to sun; and lifetime sunburns.

For the pregnancy UVR exposure multivariate model, mother's age at child's birth, mother's completion of high school education, and mother smoked during pregnancy

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were included in the model. The following covariates were tested as above but were not included in the final model: number of siblings within six years of age (37); gestational age at birth; mother married at interview; mother hours in paid work; mother had any autoimmune disease; mother had rheumatoid arthritis; number of days breastfed; mother tan at end of summer; mother reaction of skin to sun; and mother lifetime sunburns.

Where matched analyses were possible, we performed conditional logistic regression. Where missing covariates removed samples and consequently reduced available pairs we instead performed a frequency-matched analysis, and accounted for matching factors by adjusting for birth year and recruitment year.

Previously, we constructed two vitamin D genetic allele scores (26). The ‘Synscore’ included two SNPs at genes involved in vitamin D synthesis (*CYP2R1* rs10741657, *DHCR7* rs12785878) and the ‘Metscore’ included two SNPs involved in vitamin D metabolism (*CYP24A1* rs6013897, *GC* rs2282679). In our setting, Metscore and Synscore combined contribute to 11% of 25(OH)D₃ variation. We examined whether either of these scores modified our findings by assessing multiplicative interaction in a logistic regression model, and additive interaction using the Synergy Index (38).

All analyses were undertaken using StataMP V14 (StataCorp, College Station, Texas, USA). P-values < 0.05 were considered significant (39).

Sensitivity analyses. Sensitivity analyses were undertaken to evaluate potential bias. To assess bias introduced by disease-related behavioural changes, we excluded sun exposure for the 12 months preceding diagnosis. To assess recall bias due to knowledge of the hypothesis, we removed participants who reported belief that sun exposure is relevant to disease risk.

To assess bias due either to disease-length-related changes in recall of past sun exposure or in sun exposure behaviour, we assessed incident and prevalent cases separately.

RESULTS

Participant characteristics

Overall, we included 202 cases (72% female) and 202 controls (41% female) in the study. All participants were born in the state of Victoria between 1993 and 2011, and reported Caucasian ancestry. Characteristics of the participants are shown in Table 1.

Skin type characteristics were very similar between cases and controls (Supporting Information, Table S1). We used the sub-sample of children with skin type measured by a nurse (36) to further confirm ethnicity in relation to skin pigment. 0.5% cases and 0% controls were reported to have 'dark' skin. Furthermore, in our overall CLARITY hospital control population, 0.8% of self-reported Caucasians had nurse-reported dark skin, compared to 23% of non-Caucasians. Therefore, restriction to Caucasian ethnicity did appear to standardise for skin type.

Cumulative sun exposure over the life-course

An inverse association between total cumulative UVR exposure and JIA was observed (Table 2). There was a clear dose-response relationship, with greater total UVR exposure showing an increasingly protective association with JIA (test for trend $p=0.04$). The magnitude of the association was strengthened in the multivariate model. We did not observe an association between cumulative life-course time in sun for either summer or winter specifically, and JIA.

Total UVR accounts for the effect of differential sun behaviour between the seasons. Therefore the apparent inverse association of JIA with total UVR, but not minutes in sun per season, suggests that it is not outdoor time in itself, but actual UVR dose from the outdoor time, that is driving the association.

Sun exposure during specific age periods

We tested to see if the inverse association of total UVR exposure with JIA could be attributed to a specific age period. There was no evidence of significant association of JIA with sun time or cumulative UVR exposure for the age periods 0–2 years (Table S2), 3–5 years (Table S3), or 6–10 years (Table S4) specifically, although trends

towards lower JIA risk with higher sun/UVR exposure emerged for each age group. Due to small numbers we did not analyse the age period 11–15 years.

Our data suggested that the association between sun exposure and JIA was dependent on accounting for cumulative life-course UVR. We therefore proceeded to further investigate this relationship.

Sensitivity analyses

Based on the assumption that behavioural changes could have had an impact on outdoor time for cases up to 12 months before diagnosis, we calculated a censored life-course cumulative UVR exposure up until 12 months before diagnosis (this excluded cases diagnosed at ≤ 1 year of age, and their matched control) (Table S5). The patterns of association between JIA and cumulative UVR exposure were not materially altered in this analysis. Associations were of borderline significance (trend $p=0.058$), likely due to reduced sample size resulting in wider confidence intervals. Therefore, behavioural change in the 12 months prior to diagnosis is unlikely to be explain the JIA-cumulative UVR association.

We then tested whether knowledge of the hypothesis affected the association outcome by removing nine individuals whose parents had indicated a belief that low vitamin D was a possible cause of JIA. The significant inverse association remained (Table S6).

Time between diagnosis and recruitment (disease duration)

We considered whether a longer disease duration in prevalent cases might bias self-reported UVR exposure. A longer disease duration correlated with lower average UVR per year (Figure S1). When cases were stratified as incident or prevalent, the correlation was restricted to incident cases, driven mainly by individuals with disease duration of 0 months (recruited at diagnosis). There was no significant correlation for prevalent cases. Thus, there was no evidence that the longer disease duration in prevalent cases prior to interview altered study findings, but a recall bias associated with incident cases could not be fully excluded.

We therefore stratified the association analysis between cumulative UVR exposure and JIA by incident or prevalent cases. The inverse association was present for both
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strata, with ORs of a similar magnitude to the full sample, although associations did not reach statistical significance (Table S7). This is likely due to reduced sample size. The consistent direction of effect between incident and prevalent cases suggests that disease duration (longer or shorter) does not affect the association substantially.

Sun exposure at 12 weeks of pregnancy and JIA risk

To determine whether sun exposure during pregnancy is relevant to JIA risk, we tested for association between JIA and maternal weekday and weekend sun and UVR exposure at 12 weeks of pregnancy. To maximise sample size, we performed a frequency-matched analysis adjusting for year of birth and year of recruitment for all pregnancy sun exposure measures.

We found evidence of inverse association between maternal weekday time in sun at 12 weeks of pregnancy and JIA risk (Table 3), with a clear dose-response relationship (test for trend $p=0.011$). There were no significant associations for weekend time in sun, however, the direction of effect was consistently protective. For UVR exposure at 12 weeks of pregnancy, there was also evidence of inverse association with JIA risk (test for trend $p=0.031$). To consider the effect of season, we included season of birth in the multivariate models, and this did not materially alter the findings (although a significant dose response trend emerged for weekend time in sun, $p = 0.034$) (Table S8). Additionally, there was no evidence of association between season of birth and JIA in our sample (Table S9). These data suggest that prenatal sun behaviour differences are more important than season of birth itself.

Vitamin D allele scores

We examined the vitamin D allele scores (Synscore, Metscore) in cases and controls. Neither of them modified the UVR and JIA associations (Tables S10-S13).

DISCUSSION

Our study provides novel evidence that increasing cumulative UVR exposure over the pre-diagnosis life-course, and maternal UVR at 12 weeks gestation, is associated with reduced risk of developing JIA. Life-course and maternal UVR exposure exhibited a dose-response relationship with JIA, with increasing amounts of UVR exposure being

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increasingly protective for the disease. We used pre-diagnosis life-course measures of sun exposure, as opposed to post-diagnosis measures of circulating vitamin D, in an effort to establish a possible causal role for sun exposure/vitamin D in JIA risk.

We did not observe a significant association between time in the sun and JIA when we did not take into account UVR dose. This illustrates that the increased UVR exposure in summer relative to winter is important in the relationship between sun exposure and JIA. Also, it provides reassurance that UVR exposure, not outdoor time, is of importance. We did not find a significant association of JIA with time in sun or cumulative UVR for any particular post-natal age period, though consistently inverse directions of effect were apparent. This suggests that it is the cumulative UVR exposure prior to disease onset that is important in JIA. Consistent with this study, higher cumulative sun exposure prior to disease onset has been associated with decreased risk of MS (40) and RA (17).

We also observed a significant inverse association between JIA and both weekday sun exposure and UVR dose at 12 weeks of pregnancy. Interestingly, and in contrast to previous work (41), there was no association between JIA and season of birth, and when adjusted for season of birth, the association between JIA and UVR at 12 weeks of pregnancy remained. Our data are consistent with evidence that low maternal first trimester UVR exposure is associated with MS, independent of season of birth (34). Of note, for MS, there is temporal specificity in the prenatal UVR exposure, with the association being restricted to first trimester. We did not measure maternal sun exposure outside of first trimester, so could not further examine temporal specificity in JIA. However, a previous study that analysed serum 25(OH)D₃ levels at birth from newborn screening cards found no association with JIA (24), suggesting some temporal specificity. Future studies should determine whether first trimester sun exposure is a window of risk for JIA, or if it is a marker of overall pre- and post-natal sun exposure.

Our study had a number of strengths. Firstly, our restriction to individuals born in the state of Victoria avoided confounding due to latitude. Secondly, our ability to examine pre-disease sun exposure allowed us to avoid the issue of reverse causation, in which disease-related behavioural changes such as less time outdoors may lead to

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reduced circulating vitamin D in children with JIA, as reported by prior studies (23). This seems particularly likely for a debilitating disease such as JIA. By matching a control to each case by exposure window, we controlled for differences in cumulative sun exposure due to different ages of recruitment to the study. We also performed a number of sensitivity analyses to ensure the reliability and robustness of the association in the overall sample in relation to participant knowledge of the hypothesis, disease-related behavioural changes, and disease duration. These factors have not been dealt with in prior studies of vitamin D and JIA.

Limitations included that we were unable to directly measure circulating vitamin D across the pre-disease life-course. Although we collected participant blood post-diagnosis, measuring post-disease vitamin D is not a feasible way to gauge pre-disease vitamin D due to issues of reverse causation as discussed above. In our overall CLARITY sample, there is an average delay of seven months between parent-reported symptom onset and JIA diagnosis (unpublished data), so even those recruited at diagnosis are unlikely to reflect true pre-disease behaviour. We used sun exposure and vitamin D pathway gene allele scores as proxy measures of vitamin D status. Using such proxies introduces the possibility of missing a true association of an alternative factor that contributes to vitamin D status, or finding a false positive association due to confounding. While our sensitivity analyses served to minimise possible confounding, additional factors likely to be associated with past or current circulating vitamin D (for example vitamin D supplementation, sunscreen use) were not assessed. We did test for a number of potential confounders in this study, such as sibling exposure, which has previously been shown to be associated with risk of JIA in our sample (37). Nonetheless, it is important to recognise that epidemiological associations might reflect non-causal explanations and therefore further work should be done to confirm the identified associations. In addition, gene-environment interaction analyses should be re-conducted in larger studies to ensure that our null findings are not reflective of sample size.

We hypothesise that the mechanism through which sun exposure might attenuate JIA risk is through influence on circulating levels of active vitamin D ($1,25(\text{OH})_2\text{D}_3$), and its subsequent effect on the child immune system. $1,25(\text{OH})_2\text{D}_3$ has many and varied effects on almost all immune cell types, with anti-inflammatory and

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immunomodulatory consequences (42, 9). Of particular relevance to JIA, $1,25(\text{OH})_2\text{D}_3$ signalling represses the transcription of Th1 cytokine genes, driving T helper responses towards a more regulatory Th2 phenotype, thus suppressing Th1-driven autoimmune responses (9). Feasibly then, lower $1,25(\text{OH})_2\text{D}_3$, through reduced UVR exposure, could reduce suppression of autoimmune responses in JIA. However, it is important to acknowledge that UVR might impact JIA risk through vitamin D-independent pathways. Animal studies have demonstrated that UVR can induce immunosuppression in the absence of vitamin D receptor, or changes to circulating vitamin D (7). In humans, there is evidence that sun exposure and serum vitamin D act independently on risk of central nervous system demyelination (40). Such alternative pathways are yet to be elucidated.

This study has considered the association of life-course UVR exposure with overall JIA risk, that is, all JIA subtypes together. Our efforts to minimize confounding through careful participant selection and case-control matching limited the total number of cases available for analysis, and thus our ability to subdivide our sample by subtype. It is possible that subtypes may differentially associate with life-course UVR, and this should be considered in future studies.

In conclusion, we have demonstrated an inverse association between life-course sun exposure and JIA risk. Our data suggests that increased vitamin D via maternal cutaneous UVR exposure during pregnancy, and increased child cutaneous UVR exposure prior to diagnosis, protects against JIA. These findings require replication using other study designs including those with prospectively collected vitamin D and sun exposure measures. However, they do provide the first body of evidence that circulating vitamin D prior to disease onset may contribute to JIA risk. If these associations are confirmed, they will point to an environmental factor amenable to intervention that has potential to reduce risk of developing this debilitating childhood disease.

Acknowledgements

We thank the families who kindly participated in this study. We thank the research nurses and research assistants who undertook recruitment and data entry. We acknowledge support from the Australian National Health and Medical Research
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Council (NHMRC), the Australian Research Council (ARC), Arthritis Australia, Rebecca L Cooper Foundation, LEW Carty Charitable Fund, ANZ Medical Research and Technologies in Victoria Fund, Lynne Quayle Charitable Trust, The Victorian State Government Operational Infrastructure Support Program, and the Murdoch Children's Research Institute. JAE was supported by an ARC Future Fellowship. ALP was supported by NHMRC Senior Research Fellowships.

SUPPORTING INFORMATION

Additional Supporting Information is available in the online version of this article:

The Supporting Information file (Tables S1-S13, Figure S1) contains detailed methodological information on the measurement of skin type, and results tables and figures detailing skin type and skin reactivity of study participants, sun/UVR exposure association analyses at different age-groups, sensitivity analyses, and analyses stratified by vitamin D synthesis and metabolism genetic scores.

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Table 1. Characteristics of CLARITY cases and controls selected for analysis.

	Case	Control
Female; N (%)	145 (72)	83 (41)
Male; N (%)	57 (28)	119 (59)
Female to male ratio	2.6:1	1:1.4
Mean age; years (SD)	7.38 (4.29)	7.46 (4.21)
Born in Victoria; N (%)	202 (100)	202 (100)
Pregnancy in Victoria; N (%)	188 (94)	197 (98)
Caucasian; N (%)	202 (100)	202 (100)

Case Characteristics

Case type; N (%)

Incident	112 (55)	-
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Prevalent	90 (45)	-
JIA subtype; N (%)		
Oligoarticular	112 (55)	-
Polyarticular RF -ve	42 (21)	-
Polyarticular RF +ve	5 (2)	-
ERA	4 (2)	-
Psoriatic	6 (3)	-
Systemic	12 (6)	-
Undifferentiated	11 (5)	-
Missing	10 (5)	-
Age at diagnosis; mean years (SD)	5.11 (3.92)	-
Duration of disease; mean months (SD)	27 (38)	-
Minimum months	0	-
Maximum months	157	-

RF = rheumatoid factor; Duration of disease = time between disease diagnosis and recruitment

Table 2. Conditional logistic regression analysis for the association of cumulative sun exposure with JIA.

Sun exposure	N case/ control†	OR‡ (95%CI)	P value	AOR§ (95%CI)	P value
<i>Summer cumulative time in sun (mins)</i>					
0–999	149/145	1 (reference)	-	1 (reference)	-
1000–1999	39/42	0.84 (0.37–1.91)	0.69	0.72 (0.30–1.73)	0.46
2000+	14/15	1.32 (0.33–5.27)	0.69	0.96 (0.22–4.30)	0.96
Test for trend			0.90		0.74
<i>Winter cumulative time in sun (mins)</i>					
0–999	164/163	1 (reference)	-	1 (reference)	-
1000–1999	29/26	1.40 (0.63–1.09)	0.40	1.15 (0.47–2.82)	0.76
2000+	9/13	0.83 (0.22–3.10)	0.78	0.53 (0.12–2.28)	0.40
Test for trend			0.91		0.57
<i>Total UVR (quartiles)</i>					
1	60/41	1 (reference)	-	1 (reference)	-
2	45/57	0.36 (0.15–0.86)	0.021	0.27 (0.10–0.72)	0.0091
3	49/51	0.33 (0.11–0.96)	0.043	0.25 (0.08–0.82)	0.022
4	48/53	0.27 (0.07–1.04)	0.056	0.19 (0.04–0.85)	0.030
Test for trend			0.044		0.025

Summer and winter time in sun are total minutes in sun until age at diagnosis for case and matched control. Total UVR is cumulative summer or winter minutes in sun multiplied by mid-summer or mid-winter average UVR index over the years 1993–2011. Abbreviations: A, adjusted; CI, confidence interval; N, number; mins, minutes; OR, odds ratio.

† If either matched pair missing for a covariate factor the pair was dropped from analysis

‡ Adjusted for age at recruitment and sex

§ Adjusted for age at recruitment, sex, maternal age at birth, mother currently smokes and mother completed year 12 (proxy for SEIFA)

Table 3. Logistic regression analysis of association of sun exposure at 12 weeks of pregnancy with JIA.

12 weeks of pregnancy	N case/ control	OR† (95%CI)	P value	N case/ control	AOR‡ (95%CI)	P value
<i>Weekday time in sun (hrs)</i>						
<1	57/40	1 (reference)	-	56/40	1 (reference)	-
1–2	53/67	0.48 (0.27–0.86)	0.014	51/66	0.51 (0.28–0.96)	0.036
2+	17/36	0.30 (0.14–0.64)	0.0018	16/36	0.38 (0.17–0.85)	0.019
Test for trend			0.001			0.011
<i>Weekend time in sun (mins)</i>						
<1	26/17	1 (reference)	-	26/17	1 (reference)	-
1–2	58/57	0.55 (0.25–1.17)	0.12	55/56	0.48 (0.21–1.09)	0.08
2+	40/49	0.48 (0.21–1.07)	0.074	40/49	0.48 (0.20–1.14)	0.097
Test for trend			0.10			0.15

UVR§ (quartiles)

1	34/24	1 (reference)	-	34/24	1 (reference)	-
2	24/23	0.46 (0.19–1.10)	0.083	23/23	0.57 (0.22–1.47)	0.25
3	29/28	0.53 (0.23–1.21)	0.13	28/27	0.76 (0.31–1.87)	0.55
4	16/38	0.24 (0.10–0.57)	0.0012	16/38	0.32 (0.13–0.80)	0.014
Test for trend			0.0026			0.031

Abbreviations: A, adjusted; CI, confidence interval; hrs, hours; N, number; mins, minutes; OR, odds ratio.

† Adjusted for age at recruitment, sex, year of birth and year of recruitment

‡ Adjusted for age at recruitment, sex, year of birth, year of recruitment, maternal age at birth, mother currently smokes and mother completed year 12 (proxy for SEIFA)

§ Combined UVR exposure for weekend and weekday time in sun