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Mini Review

"I see the light": The role of seasonal photo period in the development of immune regulation, a potential explanation for the latitude gradient of autoimmunity and allergy

Margaret S. Clark[1,*]

[1]Australian Latitude Immune Study, Melbourne, Australia

*Author for correspondence:
Email: mclark@comcen.com.au

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Evidence for a Latitude Gradient for Autoimmune Disease and Allergy

Prevalence of common autoimmune diseases such as multiple sclerosis (MS), type 1 diabetes, rheumatoid arthritis, and inflammatory bowel disease and allergies such as food allergies or eczema affect approximately 20% of the human population. However, prevalence of autoimmunity and allergy is not uniform latitudinally from the equator to the poles of the globe. Epidemiological studies demonstrate the prevalence of autoimmunity and allergy increases with increasing latitude, with higher prevalence towards the north in the northern hemisphere or the south in the southern hemisphere [1]. The prevalence of MS (an autoimmune disease of the central nervous system) is up to ten times the risk in people who grew up in northern Canada (latitude 41°–83° North) compared to equatorial zones [2]. This latitude gradient is not due to genetic disparity and has been demonstrated to be associated with factors occurring during childhood. In Australia, where there is a large range of latitude (10°–43° South) the prevalence of MS is higher for people who grew up in the south of the country compared to the north [3–5]. In New Zealand (latitude 29°–52° South), the association of latitude of childhood domicile and development of MS is observed until the age of twelve [6] showing the link is due to factors in childhood. The incidence of type 1 diabetes up to the age of 15 demonstrates variation between high and low latitudes [1,7]. The prevalence of rheumatoid arthritis and inflammatory bowel disease has been demonstrated to be higher in higher latitudes compared to southern latitudes in the US, with the effect also associated with location of residence during childhood [8,9]. There was no significant effect of latitude for systemic lupus erythematosus, a disease that can be aggravated by sunlight [10].

The prevalence of allergy demonstrates a similar latitudinal gradient to autoimmunity. The risk of acquiring eczema as an 8–9 year-old is at least twice that for those who live in the south of Australia compared to the north [11]. Moreover, the risk of having a peanut allergy is 6 times greater for 8–9 year-olds who reside in the south of Australia compared to the north [11]. Additionally, prescription of EpiPens and admission to emergency for anaphylaxis for infants 0–4 years old and children, was shown to be significantly higher in both the south of Australia and the south of Chile (latitude 17°–56° South) compared to the north [12,13].

The increased risk of autoimmune disease and allergy with growing up at higher latitudes has been linked to decreased sunlight exposure [3–5,14–17] whereby daylight length and ultraviolet light (UV) are significantly reduced at high latitudes in winter. Progression to a greater level of disability in MS is associated with lower UV exposure as children and teenagers, as seen in a multi-nation study [18]. In Norway and Italy, the risk of MS is associated with decreased sunlight exposure during childhood and early adolescence [19,20]. Low levels of Vitamin D were previously thought to be involved in predisposition to MS [21–23] and allergy [12] however studies have demonstrated that the development of disease is most likely independent of vitamin D [24,13]. Some studies have also demonstrated that the development of MS is even independent of UV [25]. A study in Western Australia demonstrated that male fetus *in utero* in the third trimester and the baby boys in their first year of life who resided in areas with the highest quartile of ambient erythemal UV radiation had approximately a 40% reduced risk of type 1 diabetes [26]. The study did not measure time spent outdoors and it may not be that high UV alone is responsible, indeed high UV levels correlate with brighter intensity of visible light spectrum and increased infrared radiation. Light intensity, photoperiod (the number of daylight hours of the visible light spectrum), and near infrared radiation vary with latitude and can also influence the immune system [27,28] and most likely play a role in disease predisposition.

Association of Regulatory T-cells with Disease and Sunlight Exposure

The immune system normally protects us from disease however in the cases of autoimmunity and allergy, the mechanisms which keep the immune system in check against over-reaction have been weakened or disrupted, resulting in inflammation and disease. Regulatory controls which normally suppress unwanted reactions of the immune system against self or antigens, include the production and activation of regulatory T-cells which prevent inappropriate actions of effector T-cells. Regulatory T-cells are present from as early as *in utero* and expand during the childhood developmental years [29,30]. These cells are highly relevant to disease such that reduced T-regulatory cell levels and function have been observed in MS [31–38] and allergy [39–41]. T-regulatory cells help prevent unwanted immune reactions by both soluble mediators and surface binding co-stimulatory molecules [42]. It has been observed that B regulatory cells are also implicated in controlling autoimmunity [43] and allergy [44].

A link between decreased sunlight exposure and reduced regulatory T-cell activity could provide an explanation for the latitude gradient of predisposition to autoimmunity and allergy. Indeed, we demonstrated that the circadian circulation of T-regulatory cells (the egress from lymph nodes out into the periphery) is reduced in winter in pubescent girls and their mothers who lived at a moderately high latitude in the southernmost part of Australia where the daylight length is six hours less in winter than in summer (winter photoperiod 9 hours light: 15 hours dark) [45]. In the UK, it has also been demonstrated that the levels of T-regulatory cells are lowest mid-winter and highest in summer (winter photoperiod 8:16 hours) in adult males and are associated with cortisol levels [46]. Circadian migration of T-cells from lymph nodes is mainly dependent on cortisol [47–51], a circadian and a circannual hormone, which is influenced by daylight length. Sunlight can affect T-regulatory cell levels *in utero* as demonstrated in a study whereby T-regulatory cell levels in mothers and the umbilical cord of newly born infants were positively associated with vitamin D levels, a marker of sunlight exposure [52] but not a driver of T-cell circulation. Vitamin D is not a circannual hormone and the results from a study investigating season and T-regulatory cells, suggest that is not involved in seasonal circadian variation in T-regulatory cell circulation [53]. Vitamin D levels are more of a surrogate or general indication of sun and UV exposure.

It is conceivable that during winter at high latitudes, fewer naïve (untrained) T-regulatory cells are produced and released into circulation in developing children, and thus fewer cells transition to memory T-regulatory cells. That is, there are fewer T-regulatory cells in circulation which have been trained to assist in controlling unwanted immune reactions against self-antigen and foreign antigen. The circulation of T- cells is associated with cortisol levels [47], therefore changing levels of cortisol with season will result in changing levels of T-regulatory cells. Lower levels of trained regulatory cells could potentially lead to reduced ability to suppress attack against self-tissue by effector T-cells when the body is under stress. Combined with specific genetic predisposition, this could potentially pre-dispose an individual to autoimmune disease. In the case of allergy, the hygiene theory or extent of prior exposure to allergens combined with fewer available T-regulatory cells could potentially lead to an over-reaction to allergens.

In our study we also made the observation that T-helper 17 cell (Th17) levels in adults are associated with the amount of time spent outside in the recent summer (but did not vary between summer and winter) [45], suggesting that the levels of these cells could be influenced directly and transiently by the amount of direct sunlight. Th17 levels are much higher in adults, so children may not necessarily demonstrate this association. Previous studies have shown that successful treatment with UV light in patients with psoriasis is associated with lowered Th17 levels [54], suggesting that Th17 levels are more likely influenced by UV and not photoperiod. It appears that different mechanisms are acting on T-regulatory cells and Th-17 cells, but it is the photoperiod during childhood that is influencing how T-regulatory cells develop.

Evidence of the Effect of Photoperiod on Immunity

Studies of the effect of photoperiod on the immune system in animal models have elucidated the finding that photoperiod alone can have significant effects on immune cell levels and function. The advantage of animal models, for example, rodents or swine, is that UV light can be eliminated and only the length of the visible light spectrum can be manipulated to determine the effect of short day or long day, as in summer and winter. Experiments in nocturnal species such as Siberian hamsters have demonstrated differences in immune reactivity in different photoperiods [55–59]. Swine has a similar circadian rhythm and immune system to humans and being diurnal are more appropriate to study than say rodents [60]. Short day photoperiod, the winter equivalent, was demonstrated to be associated with higher total leukocytes, Natural Killer cells, γδ T cells, naïve Th cells, and monocytes levels in blood in swine, and leukocyte levels were associated with cortisol levels, the circadian hormone [27]. Photoperiod has also been shown to influence the immune status of pregnant sows and their piglets, that is total white blood cell number, neutrophil to T-cell ratio and proliferation

responses to concanavalin and Lipo-polysaccharide, with cortisol levels influenced by short or long length photoperiod [61]. These studies provide support for the notion that predisposition to allergy and autoimmunity can start as early as *in utero* and is influenced by photoperiod via circadian hormones such as cortisol. The mechanism by which the photoperiod and cortisol can influence immune cell frequency and function, in simplistic terms, is via the hypothalamic-pituitary-adrenal (HPA) axis whereby the detection of light through the eyes transmits neural signals to pineal gland which regulates the release of cortisol. As discussed, cortisol regulates the circulation of T-cells and influences the function of immune cells.

The effect of photoperiod on B-cell numbers and function is less well understood. In a mouse model the number of circulating B-cells was found to be increased, along with T-cell numbers in a short day photoperiod compared to a long day photoperiod [62]. In contrast the memory B-cell mediated antibody response was reduced in Siberian hamsters in a short day photoperiod [63]. In relation to the effect of photoperiod on cytokine action, the response to lipopolysaccharide injected into hamsters was studied and in the short day photoperiod decreased levels of interleukin (IL)-6 and IL-1beta were observed with reduced length of infection symptoms due to the reduced levels of these pro-inflammatory cytokines [64]. In a similar study of squirrels, short day photoperiod was associated with reduced levels of the inflammatory cytokines C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), and IL-6, and increased levels of IL-2, and this was associated with daylength dependent melatonin levels [65]. Caution must be used when interpreting results of photoperiod effects in rodent models to human responses as rodents are nocturnal. However, melatonin has been demonstrated to be synthesized by lymphocytes, and to regulate IL-2 and the IL-2 receptor [66]. In addition, IL-2 influences differentiation of immature T-cells to T-regulatory cells [67] and this may occur via phosphotyrosine linked signaling [68] thereby demonstrating a mechanism for the effect of photoperiod on the immune system and immune regulation. That is, long day photoperiod may both influence the number of T-regulatory cells being produced and selected in the thymus, as well as the number of T-regulatory cells in circulation and being trained against antigen.

Seasonal changes in the immune system have also been observed at the gene expression level, with the expression of 4,000 genes in white blood cell varying according to season [69]. Epigenetic changes leading to gene expression can potentially be influenced by light and season.

Sunlight Can Act on the Immune System via Different Mechanisms

It is likely that the human body has evolved to develop redundancies to utilize the various wavelengths of sunlight to its immunological advantage, and to align with the seasons for energy conservation and breeding. It would make sense that the body has different pathways to optimize sunlight with multiple mechanisms to harness the different wavelengths emitted by the sun to maximize immune health particularly during harsher seasons such as winter. Photoperiod, that is the length of exposure of visible light in a diurnal pattern, and the circadian control of levels of regulatory immune cells by cortisol has been discussed. Transient intense sun exposure may also be utilized to boost or help regulate the immune system in addition to the effects due to photoperiod. That is, a brief but high intensity sun exposure can assist in immune regulation via a different pathway to photoperiod. For example, a burst of high UV radiation via the skin may provide short term anti-inflammatory effects. It is well established that UV has multiple health benefits and has immune effects via dendritic cells and antigen presenting cells and has previously been comprehensively reviewed [70] and is not the scope of this paper. It is also feasible that during periods of high UV radiation there is also higher luminosity (lux) of visible light which may influence the immune system. Green-blue light spectrum are the main wavelengths that control circadian rhythm via transmission through the eyes and the HPA axis, and therefore a transient increase in that wavelength could influence the effects of photoperiod on the immune system [71]. Bright light can change cortisol levels and mood [72], therefore it is conceivable that a burst of strong bright visible light can influence the immune system. In addition, it is established that blue light via an artificial source can affect the immune system via the skin and improve allergic conditions via the release of nitric oxide [73]. Near infra-red radiation also has positive effects via the production of melatonin and anti-oxidative properties which could contribute to lower inflammation [28]. The reduction in risk of autoimmunity and allergy associated with greater sunlight exposure may be due to a combination of factors: long daylight photoperiods (with T-regulatory cells circulating in sufficiently high levels for most of the year), exposure to UV light, high intensity blue light and near infra-red, all of which can modify the immune system and provide health benefits.

How Much Sunlight Do We Need? Evidence from Epidemiology Studies

Autoimmune diseases and allergies give rise to economic cost as well as personal suffering. Understanding the relationship between early life sun exposure and disease risk is a means to developing preventative strategies against disease. Early sunlight exposure is a balance between avoiding skin cancer and allowing the immune system to develop normal regulatory mechanisms. Developed countries such as Australia have guidelines for safe sun exposure to avoid sunburn whilst still obtaining normal vitamin D levels, but we do not have recommendations for minimal amounts of sunlight exposure to prevent allergy and autoimmunity. Epidemiological studies, although not controlled trials, provide an insight into sunlight dosage to avoid disease. One study demonstrated that infants who were diagnosed with eczema had had an average of 7 minutes of outdoor exposure between the hours of 11 am and 3 pm in the first 3 months of life compared to children without eczema who had had an average of 20 minutes exposure (it's noted that the standard deviation of times was high) [17]. Thus, as little as 13 minutes exposure at a time of higher sunlight intensity may help reduce the risk of allergy but exposure at this time of day carries risk.

Studies of childhood sun exposure and MS risk also provide some insight into how much sunlight is necessary to reduce disease risk. In a cohort of children with MS it was observed that those who spent at least one hour outside on the weekend in summer had an 80% lower risk of MS [74]. Another study demonstrated that sun seeker behavior versus sun avoidance and spending time outside in early life was associated with 75% reduction in risk of disease as an adult [20], but the study did not provide specific exposure times. In a large retrospective study of nurses, it was observed that spending more than nine hours outside per week in summer (an average of just over an hour per day, or >4 hours outside on weekends) in conjunction

with optimal UV levels was associated with an approximately 50% reduction in risk [75]. In an Australian control study of people with MS, it was found that adults who recalled having spent at least one hour outside daily in winter (compared to <1 hour) between the ages of six and 10 years were likely to have a 50% reduced risk of MS [76].

From these studies, a general approximation for the dosage of time required to spend outdoors during childhood to reduce disease risk by at least 50%, would be to go outside for at least one hour daily in summer, and one hour in winter. Protection can potentially increase up to 80% with increased time spent outside with more sun exposure, but the exact amount of time that affords maximum protection is not known. Spending more time outside as a child will reduce the risk of disease. Obviously, the UV index needs to be considered when spending time outside to avoid sunburn and skin cancer. In countries where there is a high UV index it is recommended to go outside when UV index is below 3, usually early morning or late in the day. For the best time of day see the Sun smart global UV app, or alternatively people can go outside and sit in the shade or use sun protection strategies such as sunscreen, clothing and a broad brimmed hat. Decreasing the risk of allergy and autoimmunity is possible without increasing the risk of skin cancer, as just 'seeing' light without being in direct sunlight, for example sitting in the shade, is sufficient to influence the immune system.

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