


# Early lifecycle UV-exposure calibrates adult vitamin D metabolism: Evidence for a developmentally originated vitamin D homeostat that may alter related adult phenotypes

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## Abstract

**Objectives:** Within the Developmental Origins of Adult Disease (DOHaD) model, early life environmental exposures can confer a long-term legacy on human health. This mechanism may be adaptive or maladaptive depending on lifestyle circumstances. This article examines the role of first trimester UV-exposure on late-life vitamin D levels, and potentially related adaptive and maladaptive phenotypes (height and osteoporosis respectively).

**Methods:** Six hundred and forty nine subjects were examined for vitamin D<sub>2</sub> and D<sub>3</sub> (HPLC) and height (stadiometer). Osteoporosis was assessed with an extensive medical history questionnaire.

**Results:** Solar irradiance over the first 90 days postconception correlated positively with late-life vitamin D<sub>3</sub> ( $R^2 = .0140$ ;  $P = .0082$ ;  $\beta = .1075$ ), but not vitamin D<sub>2</sub> levels. It also correlated positively with female adult height ( $R^2 = .170$ ;  $P = .0103$ ;  $\beta = .1291$ ) and negatively with the occurrence of female osteoporosis ( $P = .0495$ ). All data were adjusted for age and gender as appropriate (unadjusted data also provided). From a contemporary perspective, vitamin D levels varied significantly according to season of blood sampling as might be predicted ( $P = .0009$ ).

**Conclusions:** Increased solar irradiance/UV exposure during the first trimester of pregnancy calibrates adult vitamin D metabolism, which is an important hormone in maintaining calcium balance. This may explain how very early lifecycle UV exposure can influence skeletal development (adult height) and modify risk for the skeletal degenerative disorder osteoporosis. The data demonstrate humans are tuned to the world (exposome) in ways we have not yet fully considered, and which are entrained at the earliest phase of the lifecycle.

## 1 | INTRODUCTION

The Developmental Origins of Adult Disease (DOHaD) paradigm suggests that early life nutritional exposures, combined with subsequent changes in diet and lifestyle in adulthood, can

result in enhanced risk of chronic degenerative disorders. Much of this focus on later life disease has centered on birth weight and growth in early postnatal life, as well as on the availability of protein and energy during these critical developmental windows (Christian & Stewart, 2010).



Considerable attention has also been focused on micronutrient status during the earliest phases of human life, particularly in the context of B-vitamins and epigenetic methylation, with attention given to the long-term consequences on late-life disease phenotypes (Glier, Green, & Devlin, 2014; Lucock et al., 2015). Folate and vitamin B12 are critical for *de novo* methyl group production (Beckett, Veysey, Lucock, & Joubert, 2017; Crider, Yang, Berry, & Bailey, 2012), a crucial metabolic step in the regulation of gene expression (Kader & Ghai, 2017). For example, methylation of the IGF2AS locus remains altered 20 years following very low preterm birth weight, indicating that altered in utero B-vitamin-related methylation may link very low birth weight to subsequent adult cardiovascular disease risk (Wehkalampi et al., 2013). Additionally, iron and zinc deficiency may reduce IGF1 activity and thus fetal growth (Allen, 2001; MacDonald, 2000), and have broader influences on the DOHaD, while vitamin A is also considered important within the DOHaD paradigm. These kinds of associations build upon the early ideas of Hales and Barker (2001). Their “Thrifty Phenotype” hypothesis postulated that malnutrition affecting mother or fetus can modify developmental biology of the unborn child in a way that prepares it for survival in an environment in which resources are likely to be limited—hence generating a thrifty phenotype. Sometimes referred to as the Barker Hypothesis, the paradigm suggests that early-life metabolic/epigenetic adaptations aid in utero survival by selecting an appropriate trajectory of growth in response to environmental cues (dietary exposure). That is to say, the thrifty phenotype adapts the fetus for its potential adult nutritional environment in the longer term. It has been suggested that problems arise when this adaptive mechanism generates a trajectory that is not matched to the postnatal environment, for example an environment that reflects the typical 21st century obesogenic lifestyle (Lucock, Martin, Yates, & Veysey, 2014).

Vitamin D nutrigenetics have also been examined in the context of the DOHaD framework. In one important study, early-life nutrition correlated to reduced lumbar spine bone mineral density in later life, a finding entirely consistent with the DOHaD paradigm (Dennison et al., 2001). Additionally, we recently demonstrated that duration of early-life light exposure and strength of recent irradiance, along with latitudinal genetic factors, influence degree of vitamin D receptor (VDR) gene methylation consistent with this epigenetic phenomenon being a molecular adaptation to variation in ambient light exposure (Beckett, Jones, et al., 2017). This suggests that vitamin D may be a critical component in epigenetic phenomena, but also raises an important question: what is the relative importance of vitamin D<sub>3</sub> photosynthesized in our skin vs vitamin D<sub>2</sub> taken in in our diet—moreover, do early life environmental exposures to UV have a long-term legacy on vitamin D metabolism and status? Little work has been done on very early lifecycle nondietary-related environmental cues

in the formation of adaptive/nonadaptive adult phenotypes. The UV-vitamin D relationship provides an ideal model to examine this within a DOHaD framework.

In order to investigate whether first trimester UV exposure might influence vitamin D<sub>2</sub> and/or vitamin D<sub>3</sub> levels later in life, we examined an established surrogate measure of UV exposure (Foukal, Frohlich, Spruit, & Wigley, 2006; Davis & Lowell, 2018; Frohlich & Lean, 2004; NASA SORCE, n.d.) during the first 90 days of gestation, linking this to vitamin D levels and potential vitamin D-related phenotypes after the age of 65 years. The two phenotypic outcomes examined were adult height, and occurrence of osteoporosis, both related in part to vitamin D/calcium homeostasis.

## 2 | METHODS

### 2.1 | Subjects and sample collection

Six hundred and forty nine volunteers from the cross-sectional Retirement Health and Lifestyle Study (RHLS), Central Coast, New South Wales, Australia (65–95 years; mean 77.67 years; SD ± 6.96 years; 287 males and 362 females) were assessed for blood vitamin D<sub>2</sub> and/or vitamin D<sub>3</sub> levels.

Volunteers provided written informed consent, and ethics approval was obtained from the University of Newcastle Human Research Ethics Committee (ref no. H-2008-0431) and the Northern Sydney Central Coast Health Human Research Ethics Committee (ref no. 1001-031M). More complete details of the study population and design have been reported previously (Olliver et al., 2016; Rose et al., 2016).

### 2.2 | Plasma calcidiol (25[OH]D<sub>3</sub>) and ercaldiol (25[OH]D<sub>2</sub>)

Both vitamers (D<sub>2</sub>, and D<sub>3</sub> along with total plasma vitamin D) were ascertained using an isocratic HPLC-UV method first described by Turpeinen, Hohenthal, and Stenman (2003).

### 2.3 | Photoperiod at conception

Photoperiod on the presumptive day of conception (minutes) was calculated via the Online- Photoperiod Calculator V 1.94 L (Lammi, © 1996-2008 [Lammi, 1996]). The model assumes that a pregnancy was full term and lasted exactly 9 months.

### 2.4 | Solar irradiance (solar cycle activity)

Sunspot activity as a surrogate measure of solar activity/irradiance (total, average and maximal\*) has been recorded for 90 days postconception (broadly equating to the first trimester of gestation) (Lucock, Yates, et al., 2014). Solar activity was ascertained via the Royal Greenwich

Observatory—USAF/NOAA Sunspot Database (<http://solarscience.msfc.nasa.gov/greenwch.shtml>). \*Total (ie, cumulative) solar irradiance over first 90 days of life (postconception), average solar irradiance over first 90 days of life (postconception), and maximal solar irradiance achieved on any given day over first 90 days of life (postconception) were ascertained for each study subject, and are based on the presumptive time of conception using sunspot data aligned with the specific day/month/year of conception.

An alteration in the number of sunspots (as measured by the occluded area of the sun visible from Earth in units equating to millionths of a hemisphere) associated with an approximate 11.1 year sunspot cycle predicts the amount of solar radiation hitting Earth (Foukal et al., 2006; Lucock, Yates, et al., 2014). As with Photoperiod, the presumptive time of conception in this model assumes pregnancy lasts exactly 9 months, although with both measures, the presumptive time of conception reflects a narrow periconceptional window that will include implantation and very early embryogenesis.

Figure 1 shows the total solar irradiance (sunspot activity) from 1900 to 2010. The range for the date of birth of study subjects is given, and demonstrates that our cohort was born over a period that covered three complete solar cycles.

## 2.5 | Clinical/descriptive phenotypes

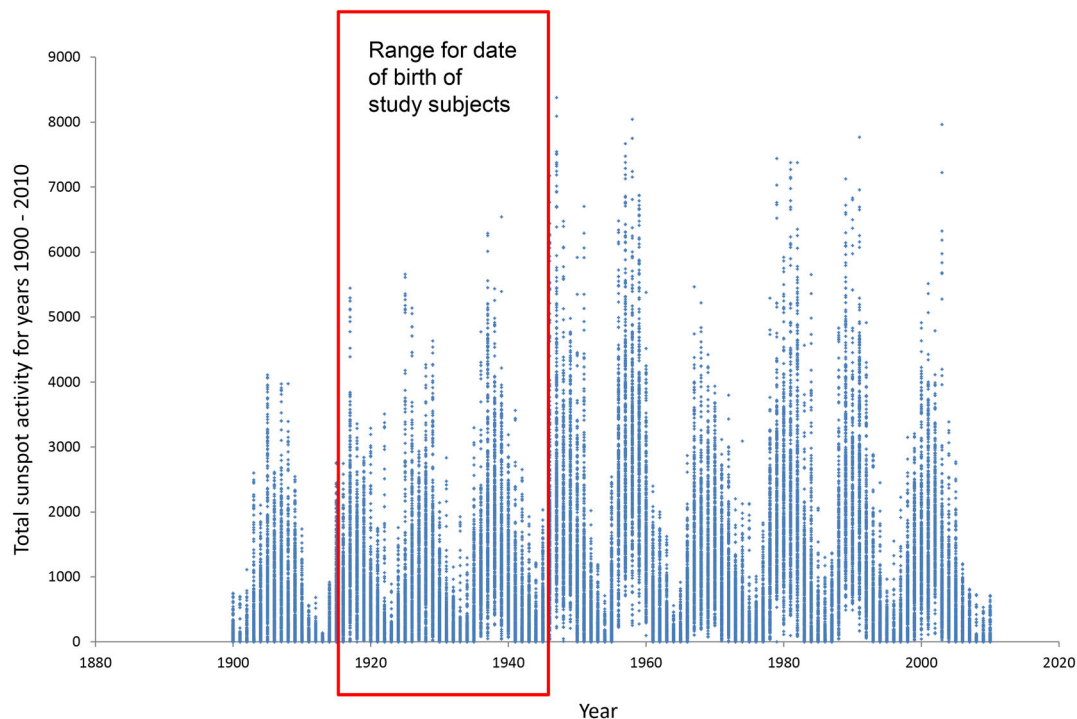
1. Anthropometric measurements including height were taken by a research project officer according to World

Health Organization (WHO) recommendations (Luepker, Evans, McKeigue, & Srinath Reddy, 2004). Height was ascertained using a portable stadiometer (design no. 1013522, Surgical and Medical Products, Australia). Two height measurements were recorded to the nearest 0.1 cm to calculate the average height for each individual.

2. The occurrence of an osteoporosis diagnosis was established following an extensive medical history questionnaire. Data were available for the following subjects: of 273 males, 31 had osteoporosis (11.4%); of 341 females, 138 had osteoporosis (40.5%).

## 2.6 | Statistics

Statistical analysis was carried out using JMP (version 11; SAS Institute Inc., Cary, North Carolina). Association between key variables and related parameters were assessed on an a priori basis, and were explored using either standard least squares, or, where categorical data were examined, logistic regression analysis that fits the cumulative response probabilities to the logistic distribution function of a linear model using maximum likelihood.  $P < .05$  provided a significance marker for effect. All statistical analyses were performed adjusting for age and gender as required. ANOVA, descriptive statistics such as mean, SE of mean and number of observations are reported as required, and where relevant, the standardized beta value is provided for slope. As an



**FIGURE 1** Total sunspot activity measured between 1900 and 2010, including the period evaluated in the present study, which covered three complete solar cycles

example, the regression model used would typically be *phenotype = solar irradiance, age, sex*.

### 3 | RESULTS

#### 3.1 | Total, average and maximal sunspot activity (solar irradiance) for the first 90 days postconception correlates with late-life photosynthesized vitamin D<sub>3</sub> level, but not dietary vitamin D<sub>2</sub> level

Table 1 demonstrates that late-life vitamin D<sub>2</sub> level does not significantly correlate with any of the three indices of solar irradiance experienced early in the lifecycle, or with photoperiod at conception. This is true for unadjusted data, and data adjusted for age and gender. However, by contrast, later life photosynthesized vitamin D<sub>3</sub> does show a significant, positive correlation with total, average and maximal solar irradiance experienced in the first 90 days of gestation, although no such relationship occurred with photoperiod at conception. The relationship between total vitamin D and solar irradiance/photoperiod did not achieve significance.

Figure 2 shows the nature of this relationship; when early lifecycle solar irradiance is plotted by adult vitamin D<sub>3</sub> quartile (dependent variable), it is clear those individuals who received higher levels of solar irradiance during their first 90 days post-conception experience higher levels of adult vitamin D<sub>3</sub>. This is true for total solar irradiance, average solar irradiance and maximal solar irradiance, and suggests that a “time-delayed” dose-response relationship exists in all three cases.

#### 3.2 | Total, average and maximal sunspot activity (solar irradiance) for the first 90 days postconception correlates with female adult height

Table 1 also demonstrates that adult height attained by females shows a significant, positive correlation with total and average solar irradiance, but not maximal solar irradiance (adjusted data). However, data unadjusted for age show a significant, positive correlation for all three indices of solar irradiance.

Figure 3 shows that those females who received higher levels of solar irradiance during their first 90 days post-conception experience a greater ultimate adult height (based on height quartile), and that this relationship holds true for all indices of solar irradiance. As with vitamin D<sub>3</sub>, height exhibits a dose-response relationship with all three measures of solar irradiance. However, the relationship with height is slightly different in that it shows greater linearity than with vitamin D<sub>3</sub> level. A significant relationship between solar irradiance and height was not observed for male subjects.

#### 3.3 | Total, average and maximal sunspot activity (solar irradiance) for the first 90 days postconception predicts osteoporosis in adult females

Table 1 demonstrates that in females, but not males, both total and average solar irradiance significantly predict risk for osteoporosis (adjusted for age). Results suggest that increased early-life solar irradiance protects against late-life osteoporosis. Figure 4 shows this graphically.

The only significant relationship with photoperiod at conception was for unadjusted adult height. However, in considering this, one needs to recognize that gender itself (adjusted for age), is influenced by photoperiod at conception ( $P = .0324$ ,  $n = 636$ ) this may therefore have bearing on the result for adult height, and has been described elsewhere (Navara, 2009). Solar irradiance did not influence gender.

In order to confirm a contemporary link between blood vitamin D level and the environment, ANOVA was performed to demonstrate whether any significant variation in vitamin D level occurred by season of blood sampling;  $P = .0009$  for total vitamin D. Figure 5 shows the changing vitamin level by season, and that maximal levels are present during the summer months.

### 4 | DISCUSSION

#### 4.1 | Overview

The data presented here are novel, yet fit well with the DOHaD paradigm. In examining the data, it is clear that environmental exposure at the earliest phase of the lifecycle (including embryogenesis) may potentially have a long-term influence that extends across the entire life span. Not only does our surrogate measure of UV exposure early in life appear to calibrate late-life vitamin D metabolism, but also it influences ultimate height and risk for osteoporosis—adaptive and maladaptive phenotypes respectively. The nature of these relationships fits a logical a priori framework in which increased UV might be expected to enhance vitamin D metabolism, lead to positive calcium balance, optimize skeletal development and minimize skeletal degenerative conditions. The data presented reflect this statement well; however, while data support a DOHaD model, it is particularly interesting to speculate on why such a temporally disparate set of events might exist.

#### 4.2 | Ideas on how UV may act as an early-life environmental cue with long-term effect

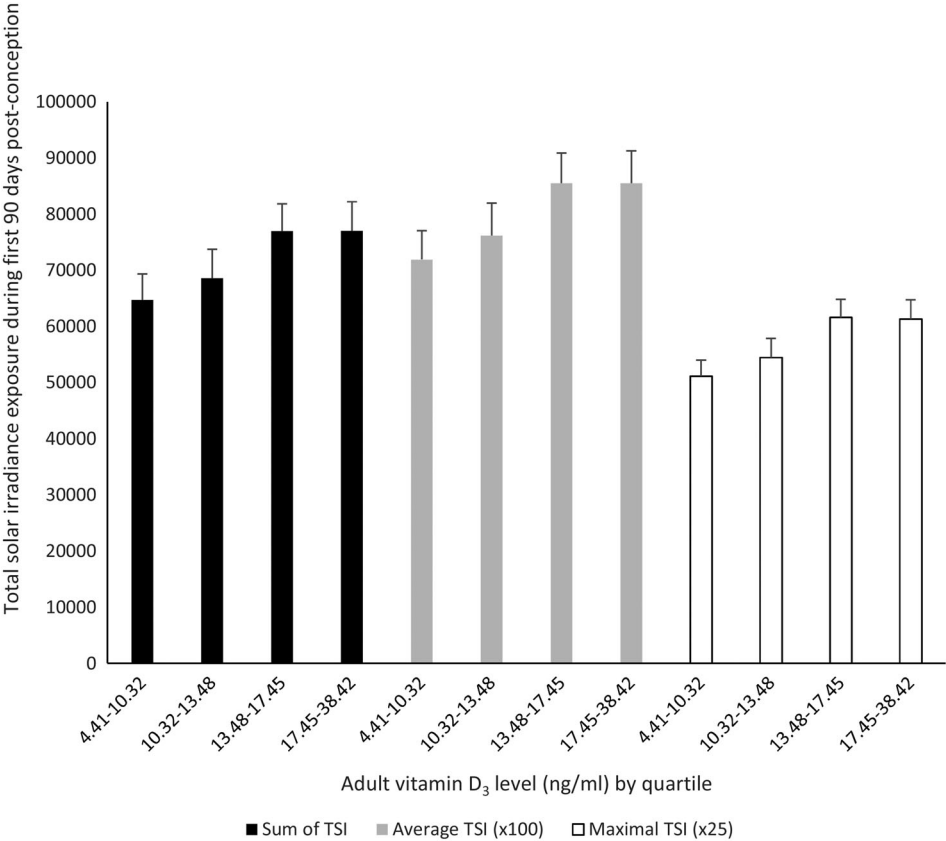
There are two main points to consider. Firstly, vitamin D homeostasis is critical for developmental processes during early pregnancy (Hahn et al., 2006), and given its importance in calcium metabolism, it plays a major role in fetal

**TABLE 1** Correlation of (i) early life (first 90 days postconception) solar irradiance and (ii) photoperiod at conception, with late life vitamin D<sub>2</sub>, D<sub>3</sub> and total vitamin D levels, and related phenotypic outcomes; where appropriate, data adjusted for age and gender; slope = standardized beta value

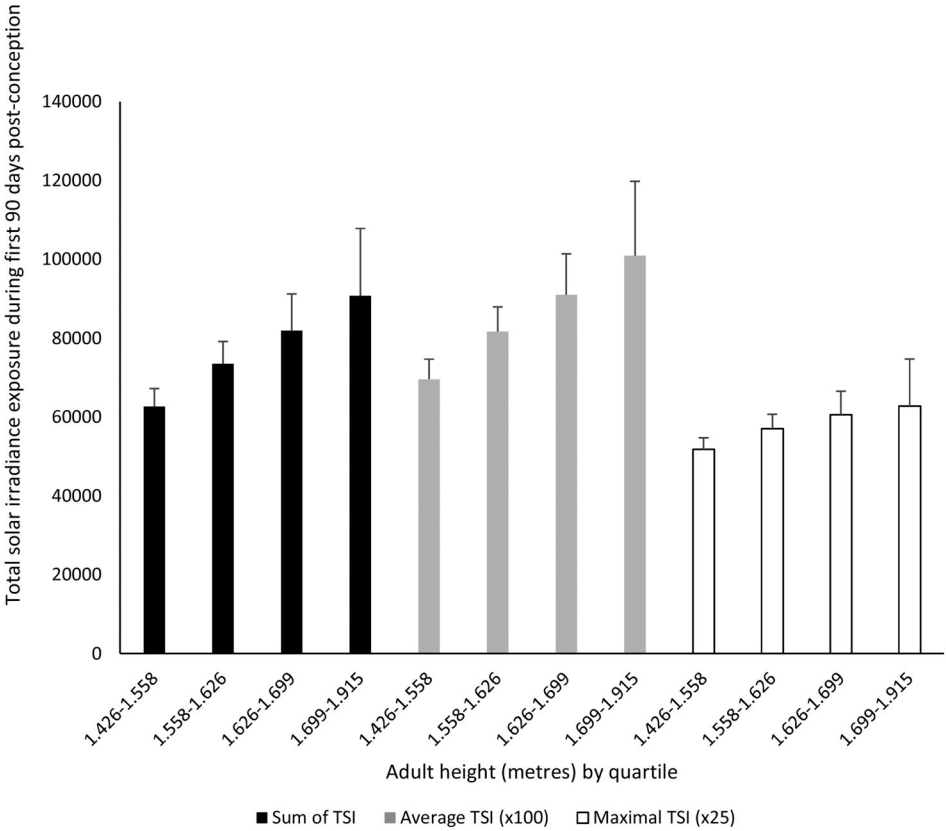
	Total solar irradiance	Average solar irradiance	Maximal solar irradiance	Photoperiod (min) at conception
Vitamin D <sub>2</sub> ( <i>adjusted for age &amp; gender</i> ) <sup>a</sup>	NS	NS	NS	NS
Vitamin D <sub>3</sub> ( <i>adjusted for age &amp; gender</i> )	$R^2 = .0142$ ; $P = .0082$ ; slope = 0.1075; SE = 0.0000; $n = 610$	$R^2 = .0142$ ; $P = .0084$ ; slope = 0.1075; SE = 0.0003; $n = 610$	$R^2 = .0179$ ; $P = .0024$ ; slope = 0.1235; SE = 0.0001; $n = 610$	NS
Total vitamin D ( <i>adjusted for age &amp; gender</i> )	NS	NS	NS	NS
Adult height (all) ( <i>adjusted for age &amp; gender</i> )	NS	NS	NS	NS
Adult height (all) ( <i>unadjusted</i> )	NS	NS	NS	$R^2 = .0126$ ; $P = .0063$ ; slope = 0.1120; SE = 0.0000; $n = 593$
Adult height (male) ( <i>adjusted for age</i> )	NS	NS	NS	NS
Adult height (male) ( <i>unadjusted</i> )	NS	NS	NS	NS
Adult height (female) ( <i>adjusted for age</i> )	$R^2 = .1695$ ; $P = .0103$ ; slope = 0.1291; SE = 0.0000; $n = 336$	$R^2 = .1695$ ; $P = .0103$ ; slope = 0.1291; SE = 0.0000; $n = 336$	NS	NS
Adult height (female) ( <i>unadjusted</i> )	$R^2 = .0232$ ; $P = .0052$ ; slope = 0.1523; SE = 0.0000; $n = 336$	$R^2 = .0232$ ; $P = .0052$ ; slope = 0.1523; SE = 0.0000; $n = 336$	$R^2 = .0119$ ; $P = .0456$ ; slope = 0.1091; SE = 0.0000; $n = 336$	NS
Osteoporosis ( <i>adjusted for age &amp; gender</i> )	NS	NS	NS	NS
Osteoporosis ( <i>unadjusted</i> )	$R^2 = .0065$ ; $P = .0301$ ; $n = 614$	$R^2 = .0065$ ; $P = .0301$ ; $n = 614$	$R^2 = .0074$ ; $P = .0210$ ; $n = 614$	NS
Osteoporosis (male) (* = <i>adjusted for age and *** = unadjusted for age</i> )	*NS **NS	*NS **NS	*NS **NS	*NS **NS
Osteoporosis (female) (* = <i>adjusted for age and *** = unadjusted for age</i> )	* $R^2 = .0176$ ; $P = .0495$ ; $n = 341$ ** $R^2 = .0092$ ; $P = .0393$ ; $n = 341$	* $R^2 = .0176$ ; $P = .0495$ ; $n = 341$ ** $R^2 = .0092$ ; $P = .0393$ ; $n = 341$	*NS **NS	*NS **NS

Note: Adult height refers to current height, although a small loss in height may have potentially occurred due to the aging process.  
<sup>a</sup>A lack of significance remains for unadjusted data.



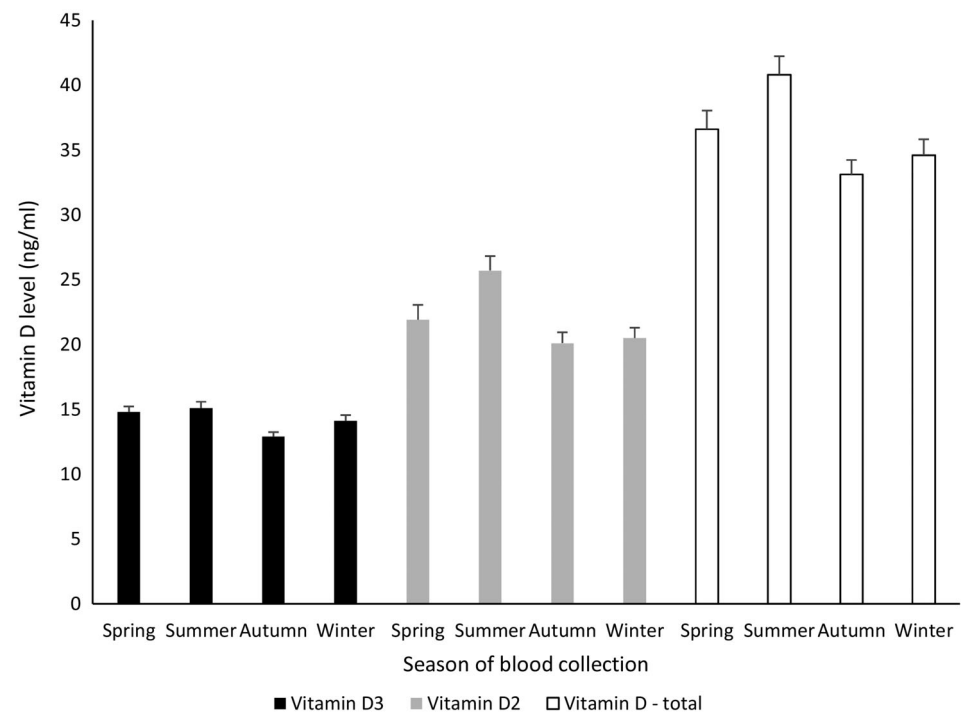
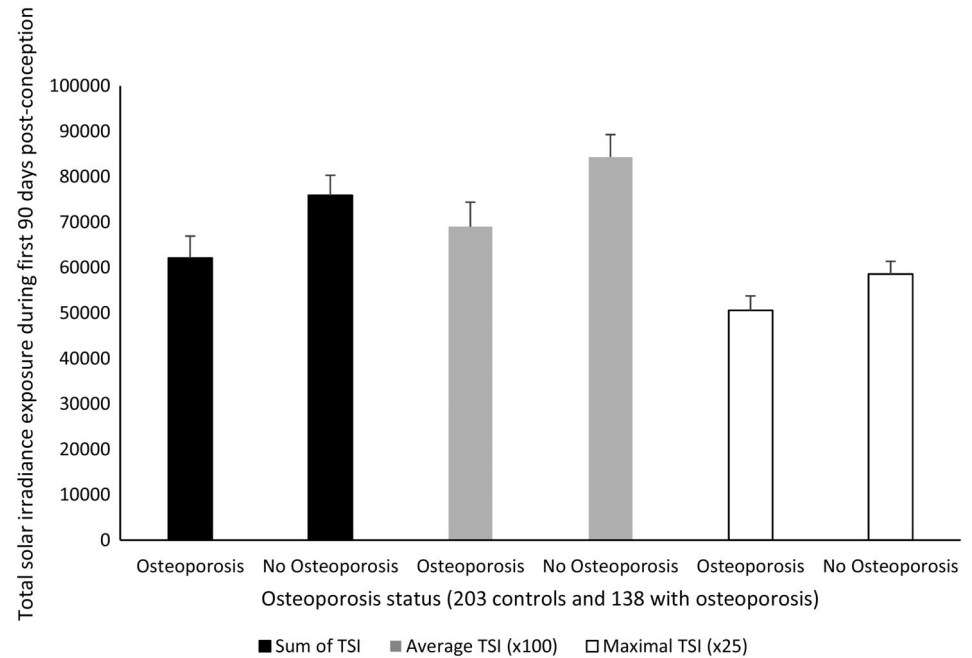


**FIGURE 2** Vitamin D<sub>3</sub> level (by quartile) in adulthood as dependent variable vs total solar irradiance (TSI) exposure during first trimester of life (all subjects)



**FIGURE 3** Height (by quartile) in adulthood as dependent variable vs total solar irradiance (TSI) exposure during first trimester of life (females)

**FIGURE 4** Osteoporosis status in adulthood as dependent variable vs total solar irradiance (TSI) exposure during first trimester of life (females)



**FIGURE 5** Contemporary data: Vitamin D level vs season of blood collection (all subjects)

bone health (Olausson, Laskey, Goldberg, & Prentice, 2008), with fetal ossification beginning very early at around post-conception week 7. Environmental cues at this point could, therefore, conceivably affect later skeletal phenotype. Secondly, and certainly more speculatively, given that our data fit a model that correlates with phenotypic adaptation upon early-life exposure to high UV, and since high UV is historically correlated to elevated skin pigmentation density, individuals with dense pigmentation may need to respond to UV more aggressively in synthesizing vitamin D<sub>3</sub> to ensure adequate levels are achieved.

In other words, changes during embryogenesis might work synergistically with the UV environment to tailor vitamin D<sub>3</sub> photosynthesis to skin phototype—justifying the proposition of a developmentally originated homeostat.

The focus in the present article has been on photosynthesis of vitamin D<sub>3</sub> in human skin; however, vitamin D<sub>2</sub> is also subject to photosynthesis. Although in the case of vitamin D<sub>2</sub>, it is photosynthesized by the grass that dairy cattle consume, and so contemporary UV exposure may link into human vitamin status according to milk consumption (Jakobsen & Saxholt, 2009;

Japelt & Jakobsen, 2013). This phenomenon may in part explain why both D vitamers show seasonal variation (Figure 5).

### 4.3 | Sunspot activity as a surrogate measure of UV exposure

The application of solar irradiance (sunspot activity) as a proxy measure for UV exposure is useful. Solar eruptions on the surface of the sun can lead to an efflux of charged particles capable of affecting satellites, human communication networks, and power grids. This is well established, and has led to much interest in how these solar events impact human infrastructure, although by comparison, there is a paucity of information relating to the effects on human biology. Although it may appear counter-intuitive, the total solar irradiance increases with sunspot activity (Frohlich & Lean, 2004), and is a balance between sunspot-related magnetic forces that shield the solar plasma, and highly energetic faculae that surround sunspots. During phases of high sunspot activity, there is an elevated flux of charged particles emitted from the solar surface, equating with a greater overall UV and total radiation output. In addition, high-energy solar protons influence Earth's magnetosphere, propagating geomagnetic storms that align with the 11.1-year sunspot cycle, affecting the entire planet (Kay, 2004).

The longer wavelengths of solar radiation emitted (UV-A) are better at penetrating both atmospheric ozone and human skin (Lucock, Yates, et al., 2014). However, shorter wavelength insolation such as vitamin D producing UV-B, responds to changes in the plage network (sunspot groupings linked by intense magnetism) and faculae, collectively areas where solar temperatures are much higher (Fligge & Solanki, 2000; Kane, 2002; Rottman, 2007). With this in mind, solar irradiance is likely to be relevant to both vitamin D stability/synthesis and photodegradation. Indeed, it is reported that vitamin D<sub>3</sub> photo-synthesized in the skin by the action of UV-B can be degraded by UV-A after only 10 minutes of nontropical sun, although the rate of loss in winter is lower (Webb, DeCosta, & Holick, 1989; Webb & Holick, 1988).

In light of this, we looked at the relationship between total surface UV irradiance (Mw/m<sup>2</sup>/nm) at 305 nm received over the 6 weeks prior to blood sampling, and vitamin D<sub>3</sub> levels (Lucock et al., 2017). This was the closest wavelength to optimal for skin photosynthesis of vitamin D<sub>3</sub> that was available as a dataset. We examined this according to the season of blood sampling. Although data are not presented in the results section for the sake of brevity, a significant positive corollary exists in spring ( $P = .0023$ ;  $R^2 = .053$ ;  $\beta = +.2296$ ), while in all other seasons, either no relationship (summer and winter), or a significant negative corollary exists (autumn:  $P < .0001$ ;  $R^2 = .301$ ;  $\beta = -.5486$ ). This would seem to support the above assertion that vitamin D

levels are a balance of UV-related photosynthesis and photodegradation.

One of the most interesting and relevant studies of recent years supports the value of examining solar energy in this way, but generated a conclusion (reduced life expectancy) that one might argue conflicts with the present findings, while still supporting the underlying tenet that solar energy by some mechanism alters the epigenome at birth (Davis & Lowell, 2018). However, the effects of early-life solar energy on later life outcomes are likely to be manifold, not least given the pleiotropic influence of vitamin D (see below), so we do not feel there is necessarily any conflict between these two studies. Both draw attention to the importance of a novel environmental factor early in the lifecycle.

### 4.4 | Vitamin D and pleiotropic effects on human adaptive biology

Vitamin D is a steroid hormone more than it is a vitamin, and like many hormones it plays a central role in phenotypic plasticity, modifying gene expression and phenotypic outcomes in response to environmentally originated cues. Pleiotropic effects for vitamin D<sub>3</sub> are well established, and partly stem from its role as a ligand for the vitamin D receptor (VDR). This nuclear receptor activates a large number of target genes, including those related to calcium binding proteins calbindin-D28k, found in the kidney, and calbindin-D9k, found in the intestine. Other notable VDR transcriptional targets include bone matrix proteins osteopontin (bone sialoprotein I) and osteocalcin, which are produced by osteoblasts and which help maintain bone matrix integrity (Bortman, Folgueira, Katayama, Snitcovsky, & Brentani, 2002). Importantly, these various calcium-binding proteins in bone, intestine, and kidney are critical for regulated calcium metabolism, and may well be involved in the mechanism that underscores the UV-vitamin D mediated phenomena described here, and which clearly influence ultimate adult height and osteoporosis, a maladaptive clinical phenotype. This idea becomes even more tenable when one considers that early response genes (c-fos) and growth factors are also directly regulated by the VDR (Bortman et al., 2002). In fact, 2276 genomic positions are occupied by the vitamin D<sub>3</sub> liganded VDR, with 229 genes having altered expression profiles in response to vitamin D (Ramagopalan et al., 2010).

Ultimately, the importance of vitamin D in the present and wider contexts is reinforced by the fact that regulation of the vitamin D system is a bidirectional process whereby epigenetic modifications regulate vitamin D signaling, while vitamin D itself contributes to the maintenance and integrity of the epigenome (Fetahu, Hobaus, & Kallay, 2014). This, along with pleiotropy, goes a long way in explaining the huge impact vitamin D has in health and disease. However, of equal importance is the critical link to UV as an



environmental cue for vitamin D homeostasis. Of all vitamins that play a part in the DOHaD paradigm, vitamin D must surely be one of the front-runners.

All organisms, including humans, can modulate phenotype as a response to environmental challenge. This provides a pivotal dogma in the life sciences. Certain environmental factors and hence selection pressures are highly dynamic. UV exposure is a good example as it varies according to latitude, season, solar/sunspot cycle, and time of day. This means that variable UV exposure is possible at critical phases of the lifecycle; the two timeframes of arguably greatest relevance to the data presented here being embryogenesis and later during the adolescent growth spurt. It is for this reason that it is important for humans to maintain a degree of phenotypic plasticity, and not to possess overly rigid phenotypes. Such adaptive plasticity allows us to respond to environmental cues in a flexible way during these critical early life events. While outcomes can be positively adaptive, such as optimal skeletal development (height), it could also be maladaptive if diet or related environmental factors are in short supply during these critical early-life events. We suggest that this may explain the present findings in relation to osteoporosis.

It seems clear from the present data that vitamin levels and skeletal biology are more sensitive to early-life solar irradiance in females than in males. This may well be related to other yet undefined hormone related effects.

Season/month of birth have previously been related to health outcomes (Foster & Roenneberg, 2008), with one article concluding that risk of immune-mediated diseases is significantly influenced by season of birth, suggesting gestational UV-B exposure and vitamin D production might be key factors predisposing to immune-mediated disorders (Disanto et al., 2012). We therefore believe that, given the present data, the early-life effect of environmental influences/flux would seem to be an area of human biology worth more intensive study.

## 4.5 | Limitations

While the current findings are interesting, they remain largely correlative, with relatively low  $R^2$  values. Hence, our findings do not definitively link cause and effect. However, the dose-response nature of the findings are compelling, and focus thinking on whether developmentally originated, UV enhanced-vitamin D metabolism might influence long-term calcium balance, and hence skeletal integrity. Indeed, it is recognized that maternal cells can affect the fetal epigenome, with cells migrating through the placenta to influence the maternal immune system, which is strongly modulated by vitamin D (Moffett, Chazara, & Colucci, 2007; Ostrand-Rosenberg et al., 2017).

While we examined photoperiod on the presumptive day of conception, and largely excluded this as a key factor, there are other important seasonally derived confounding elements such as temperature, altitude, ozone depletion, disease, and diet that could potentially interact with the effect of UV exposure during the periconceptional period (Lucock & Leeming, 2013). Additionally, one cannot rule out the secular trend in height as a potential confounder for any link between early life total solar irradiance and ultimate height. Nevertheless, we would argue that UV exposure is probably the major component within the vitamin D system of relevance to our findings.

We have no information on personal activity levels/time spent outdoors, clothing, etc., so could not build this into our model. We also suggest that future studies should examine whether the phenomena described here are influenced by key genetic factors related in particular to vitamin D metabolism.

## 4.6 | Conclusions

Data indicate that an increased UV exposure early in gestation may partially recalibrate adult vitamin D metabolism, presumably leading to improved calcium balance, optimizing skeletal development (height), and minimizing the risk of skeletal degenerative conditions like osteoporosis.

Ultimately, humans are tuned to the world in ways that we have, to date, failed to take full account of. Future research needs to examine how our early biology is adapted to (or by) a range of key environmental factors. In particular, we believe that environmental perturbations such as UV flux during gestation impact the epigenome via the photosensitivity of key vitamins (vitamin D, folate, etc.), and can engender legacy effects that span the full lifecycle (Beckett, Jones, et al., 2017; Fetahu et al., 2014; Lucock & Leeming, 2013). Other UV sensitive loci are also likely to be involved, and therefore this whole area needs further investigation. Ultimately, it seems that we are, indeed, shaped by our environment. Unraveling the role of gene-environment interactions in the present context should prove particularly fascinating.

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## CONFLICT OF INTEREST

The authors have no conflict of interests.

## ETHICS

Informed consent was obtained prior to participation under University of Newcastle Human Research Ethics Committee approval number H-2008-0431, and the Northern Sydney Central Coast Health Human Research Ethics Committee (ref no. 1001-031M).

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