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# Pregnancy outcome and ultraviolet radiation; A systematic review

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# Pregnancy outcome and ultraviolet radiation; A systematic review

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## ARTICLE INFO

## ABSTRACT

*Background:* Season and vitamin D are indirect and direct correlates of ultraviolet (UV) radiation and are associated with pregnancy outcomes. Further to producing vitamin D, UV has positive effects on cardiovascular and immune health that may support a role for UV directly benefitting pregnancy.
*Objectives:* To investigate the effects of UV exposure on pregnancy; specifically fetal growth, preterm birth and hypertensive complications.
*Methods:* We conducted a systematic review of Medline, EMBASE, DoPHER, Global Health, ProQuest Public Health, AustHealth Informit, SCOPUS and Google Scholar to identify 537 citations, 8 of which are included in this review. This review was registered on PROSPERO and a. narrative synthesis is presented following PRISMA guidance.
*Results:* All studies were observational and assessed at high risk of bias. Higher first trimester UV was associated with and improved fetal growth and increased hypertension in pregnancy. Interpretation is limited by study design and quality. Meta-analysis was precluded by the variety of outcomes and methods.
*Discussion:* The low number of studies and risk of bias limit the validity of any conclusions. Environmental health methodological issues are discussed with consideration given to design and analytical improvements to further address this reproductive environmental health question.
*Conclusions:* The evidence for UV having benefits for pregnancy hypertension and fetal growth is limited by the methodological approaches utilized. Future epidemiological efforts should focus on improving the methods of modeling and linking widely available environmental data to reproductive health outcomes.

## 1. Introduction

The developmental origins of health and disease are well established, with birthweight, gestational length and geography of birth linked to general health outcomes in both childhood and later life (Barker, 1995; Barker, 2000; Godfrey and Barker, 2000). An association between preterm birth, low birth weight and season has been suggested, with immune, infectious, vitamin D and hormonal pathways implicated (Beltran et al., 2013; Chodick et al., 2009). However using meteorological season as the exposure variable in epidemiology has intrinsic limitations. Season is not just a meteorological phenomenon, but has associated with it biological, psychological and behavioral effects (Weinberg et al., 2015) affecting conception rates, pregnancy

numbers and characteristics of the mothers which can confound reproductive outcomes. Analytical techniques to address this include considering a 'fetus at risk' approach and within-mother modeling which have been used to demonstrate 'seasonal' outcome differences may be attributable to confounding (Beltran, 2013; Curie, 2013; Weinberg et al., 2015).

Nevertheless, the association of pregnancy outcome with season is intriguing. Ultraviolet (UV) radiation is central to season and varies temporally and geographically (Lucas et al., 2006; Porojnicu et al., 2007). Solar UV is made up of three components determined by wavelength; UVA, UVB and UVC. The total UV spectrum encompasses wavelengths between 290 and 400 nm (nm) with UVA wavelengths between 315–400 nm and UVB between 290–315 nm. The main

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determinant of UV exposure on the ground is solar zenith angle which is determined by calendar date as well as factors such as altitude, the degree of cloud cover and proximity to the coast as well as behavioral determinants including time spent outdoors, clothing and sun cream use (Cherrie et al., 2015).

In the general health of adults, higher rates of cardiovascular disease mortality are associated with less available sunlight, winter season and increasing latitude (Brøndum-Jacobsen et al., 2013; Fares, 2013; Fleck, 1989; Wong, 2008). In pregnancy increased UV exposure is associated with reduced multiple sclerosis and schizophrenia in the adult offspring (Staples et al., 2010). Furthermore, in meta-analysis low vitamin D concentration, a surrogate marker of low sunlight exposure is associated with low birth weight [odds ratio (OR) 1.52 (CI 1.08, 2.15)], preterm birth [OR 1.58 (CI 1.08, 2.31)], pre-eclampsia [OR 2.09 (CI 1.50, 2.90)] and gestational diabetes [OR 1.38 (CI 1.12, 1.70)] (De-Regil et al., 2016; Wei et al., 2013). However, a number of vitamin D oral supplementation trials in pregnancy have been completed and the results have been mixed. The Cochrane Systematic Review includes 15 small RCTs with meta-analysis demonstrating moderate quality evidence for effects of vitamin D supplementation alone on preterm birth with RR 0.36 (95%CI 0.14, 0.93) and low birth weight ( < 2500 g) with RR 0.40 (95%CI 0.24, 0.67). However, combining vitamin D with calcium appeared to increase the risk of preterm birth and the final conclusion by the author's is that more rigorous data is required before recommending routine supplementation (De-Regil et al., 2016).

Other biologically plausible pathways exist that support the potential for an association between UV and pregnancy outcomes that is independent of the vitamin D pathway. For example, clinical research has shown that sunlight, specifically UVA, has a direct effect on vascular health by reducing blood pressure through the release of nitric oxide stores from the skin (Liu et al., 2014). A 20 min UVA exposure in healthy adults reduced mean arterial pressure by 3.50 mmHg (SD 0.73 mmHg, p0.0004) and diastolic blood pressure by 4.90 mmHg (SD 0.70 mmHg, p < 0.05) (Liu et al., 2014). Animal models also demonstrate beneficial effects of UVA on the immune and metabolic systems; mice fed a high fat diet gained 40% less weight when exposed to UV (p < 0.05) and had less metabolic derangement with lower fasting glucose, insulin and less glucose intolerance (Geldenhuys et al., 2014; Hart PH 2011) and Hart and Finlay-Jones (2011) summarizes the complex interactions between the innate and adaptive immune system and UV (Hart PH 2011). These systems are integral to pregnancy and moderation of these could underlie an association between UV and pregnancy outcome.

We hypothesize that UV radiation could influence maternal and perinatal outcomes. The aim of this study was to systematically review the literature on the relationship between UV radiation and singleton pregnancy outcomes, including birthweight, gestational length, preterm birth and hypertensive complications. A secondary aim was to review methods used to measure, quantify, estimate and apply available environmental data quantifying UV radiation at the Earth's surface and health outcomes specific to pregnancy. Understanding the environmental factors associated with pregnancy outcomes has implications for obstetric, environmental and public health research as well as improving clinical outcomes.

## 2. Methods

The review protocol was developed with peer review and registered on the Prospero Database of Systematic Reviews on 12 June 2015. It can be accessed at http://www.crd.york.ac.uk/PROSPERO/index.asp and the unique digital object identifier (DOI) 10.15124/CRD42015020367. Two authors Lauren Megaw (LM) and Tom Clemens (TC) undertook the review, with a third author Sarah Stock (SS) available to resolve conflict.

### 2.1. Eligibility criteria

We included studies that examined a relationship between pregnancy outcome and UV radiation exposure. Singleton pregnancies, with a gestation longer than 20 weeks were considered. The primary outcomes of interest were birth weight, gestational length perinatal mortality and hypertensive disorders of pregnancy including pregnancy induced hypertension(PIH), pre-eclampsia and eclampsia.

A measure of exposure to UV radiation had to be reported. These included direct measures of solar radiation or insolation, or an indirect measure such as sunshine or sunlight hours. We included prospective and retrospective studies and the search was conducted in August 2015 and repeated in March 2016 and included studies since 1946. English language studies only were included in this review as translational services were not available and 1 study was excluded on these grounds. Environmental factors such as food availability, infectious diseases and physical work requirements vary with season; these can confound studies focusing on pregnancy outcomes. To reduce this risk, only studies based in high-income countries, where the seasonal variation in these factors is less, were considered in this review.

### 2.2. Information sources

We searched MEDLINE (1946–2015), EMBASE (1980–2015 week 40), Database of promoting health effectiveness reviews (DoPHER 2006 – 2015), Global Health (1973 – 2015), ProQuest Public Health (1938–2015), AustHealth Informit (1985–2015), Google Scholar, Google and SCOPUS (1960–2015). We also hand searched citation lists of relevant articles. The majority of the search was performed in August 2015 and the last database was searched on 6th October 2015.

### 2.3. Search

A systematic search was developed with librarian support and search terms included pregnancy, ultraviolet radiation, sunlight, sunshine, insolation, solar, clear skies, pregnancy outcome, perinatal mortality, stillbirth, preterm birth, prematurity, low birth weight, small for gestational age, hypertension, pre-eclampsia, eclampsia, gestational hypertension. Full search strategy for Medline included in Appendix A.

### 2.4. Study selection

Title and abstracts were screened for duplication and language eligibility by LM and TC. Correspondence, editorials and those that did not include a reference to pregnancy and any environmental factor were excluded. Full text review was performed on the remaining studies by LM and TC independently to assess against eligibility criteria with discussion to resolve any discrepancies.

### 2.5. Data collection

A data collection form was developed and used by both authors for data extraction from the studies. This was based on previously published data extraction methods by the Agency for Healthcare and Research Quality (AHRQ) (Seida and DD Hartling, 2013). It was agreed upon by the second author and used by both authors for data extraction. Investigator data was sought from one study.

### 2.6. Data items

The data items extracted from the paper include title, author, journal of publication, year of publication, location and timing of study, type of study, exposure variable, method of measurement, outcome reported and method of measurement, population characteristics, inclusion and exclusion criteria, statistical method, confounders and adjustment and main results. Separate data extraction was done for each outcome.

### 2.7. Risk of bias

All included studies are observational environmental health studies. Risk of bias was assessed for each health outcome in each study using both the NRSI-ACROBAT tool developed by Cochrane for non-randomized studies and the Newcastle Ottawa Scale. Consideration of the quality and method of ascertainment of the environmental exposure was undertaken however no formal tool exists to score bias related to hazard exposure measurement methods within this study design. We followed the guidance in the WHO Guidance document 'Evaluation and use of epidemiological evidence for environmental health risk assessment' (WHO, 2000). Data relevant to study quality and design was extracted independently by both authors and consensus reached regarding final assessment. Publication bias was not able to be formally assessed by funnel plot due to the low number of studies and heterogeneity of outcomes.

### 2.8. Data synthesis

A narrative synthesis of the data is employed in this review with a discussion of limitations due to bias due to the small number of studies, PRISMA guidance is followed (Moher et al., 2009). The different outcomes measured and methods of estimating exposure are varied to an extent meta-analysis was not possible.

### 2.9. Role of the funding source

LM is funded by NHS Lothian as a Clinical Research Fellow and TC is funded by the Medical Research Council (MRC) through the Farr Institute. The funding bodies had no input into design or conduct of this systematic review.

## 3. Results

### 3.1. Study selection

Our search identified 537 non duplicate records. Title and abstract were screened against inclusion and exclusion criteria after which 45 articles were identified for full text review, 1 of which was unavailable from the library or corresponding author (Fig. 1). 44 studies underwent full text review and 36 were excluded; 9 for not referencing an outcome

of interest, 8 for having no measure of the exposure of interest, 19 for containing neither outcome nor exposure. 1 study was excluded during data extraction, as it included no measure of the exposure. 1 study was undertaken in Turkey, which is classified as an "upper-middle-income country" by the World Bank. Author discussion resolved to include this study. This left 7 original studies that are included in the review; 4 considered birth weight, 2 considered hypertension and 1 considered both preterm birth and birth weight outcomes. The study characteristics are summarized in Table 1.

### 3.2. Quality assessment

All papers were at moderate to serious risk of bias with agreement between the NOS and ACROBAT-NRSI tool (Sterne et al., 2014). Both tools assessed the Pereira paper at the least risk of bias and the Thayer (2014) paper at the most. Due to the low number of identified studies, all those that met inclusion are considered in the narrative review below, with their weaknesses addressed within the review. The generally low quality highlights the need for further well designed studies in this area to address these weaknesses. This is summarized in Table 1.

### 3.3. Exposure assessment

Information regarding the source of the exposure variable used in each study had limitations. The administrative agency responsible for collection and maintenance of the data was identified, however only 3 papers (Algert et al., 2010; Pereira et al., 2012; Tran et al., 2015) described the geographic location that their exposure variable was measured at. The quality of the description of the measured exposure also varied.

Across the studies, hazard exposure measures were aggregated in time using a variety of methods to allow pregnancy specific analysis. Direct measurement of UV exposure at an individual level although possible with UV monitors was not present in any of these studies. Environmental factors vary both spatially and temporally, and most papers captured the temporal change well. Spatial variability was less well accounted for and it is unclear if this was due to a lack of actual variation in the exposure variable, the variability not being measured or the analysis not incorporating spatial variability. For example, Thayer (2014) considered all births in the US and used a state based measure
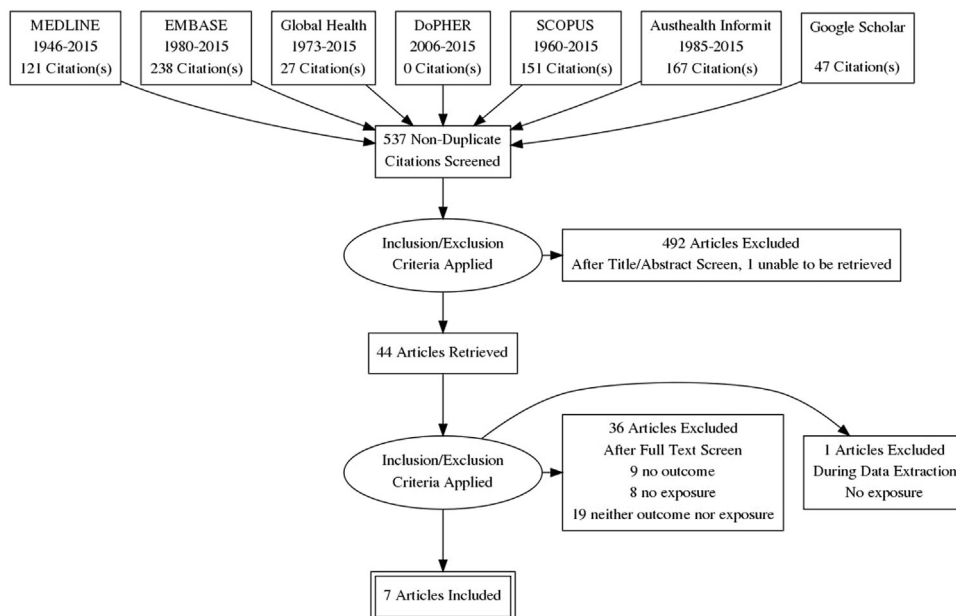


**Fig. 1.** : Article selection flow diagram.

**Table 1**
Study characteristics.

| REFERENCE, Year of publication | COUNTRY AND PERIOD | STUDY DESIGN | OUTCOME | INCLUSION/ EXCLUSION | UV | DATA SOURCE | NOS | POPULATION SIZE | ADJUSTMENT VARIABLES |
|---|---|---|---|---|---|---|---|---|---|
| Algert et al. (2010) | Australia, New South Wales 2001–2005 | Cohort | Primary: pregnancy hypertension (PH) Secondary: Pre-eclampsia (PE), early PE | Inc: All births in NSW Exc: multiple pregnancy superimposed PE | Monthly means of daily solar radiation | Midwives Data Collection (MDC) Admitted Patients Data Collection (APDC), Bureau of Meterology | 5 | n = 424 732 Total PH not included PE = 11 910 early PE = 1339 | Nil |
| Elter et al. (2004) | Turkey, Marmara 1992–2003 | Cohort | Mean birth weight for gestational week | Exc: Multiples and < 36/40 | Daily duration of sunlight | Maramara University Hospital database Turkish State Meteorological Service | 7 | n = 3333 | age, parity, fetal sex, route of delivery |
| Pereira et al. (2012) | Australia, Perth 1998–2006 | Cohort | SGA, Proportion of optimal birth weight (POBW) | Exc: births <33/40 | Sunlight hours | Midwifery notification system, Bureau of meterology, Department of Environment and Australian Bureau of Statistics | 8 | n= 147 357 | GDM, diabetes, pre-eclampsia, indigenous status, married/single, smoking, socioeconomic characteristics, |
| Thayer et al. (2014) | United States, 2007 | Cross sectional | Incidence rate of PTB by state, Incidence rate of LBW | Inc: Singleton births to non-hispanic mothers Exc: Induced births | Annual UV Index for State of birth | Centre for Disease Control and Prevention, National Oceanic and Atmospheric Association | 5 | Total n = 2 825 620 Black = 603 478 White =1 222 142 | State level confounders: Smoking rates, socioeconomic features, obesity rates |
| Tran et al. (2015) | France, Yvelines Region 2008–2011 | Case cohort | Severe Pre-Eclampsia (SPE) | Inc: All births Cases coded for SPE Exc: Multiple pregnancies Birth >41/40 | Solar hours Solar radiation (MJ/m−2) | Maternité en Yvelines et Périnatalité Active (MYPA), French Meteorological Agency | 6 | n=63 633 SPE = 526 | Mat age, single mother, smoking, parity, previous preterm, previous caesarean section. |
| Tustin et al. (2004) | New Zealand, Dunedin 1999–2003 | Cohort | Mean birth weight and gestational length | Inc: All births at maternity hospital Exc: < 38 weeks, multiples | Mean daily sunshine | Public birth records and National Institute of Water and Atmospheric Research | 6 | n=7036 T1 = 903 T2 = 955 | Nil |
| Waldie et al. (2000) | New Zealand, Dunedin 1967–1978 | Cohort | Mean monthly birth weight and mean monthly birth length | Inc: All births at maternity hospital Exc: Nil | Mean monthly sunshine hours | Public birth records and New Zealand Meteorological Service | 6 | n=20 021 | Smoking |

SPE – severe pre-eclampsia, mat age – maternal age, PH –pregnancy hypertension, PE - pre-eclampsia, PTB – preterm birth, LBW – low birth weight, UV – ultraviolet, SGA – small for gestational age, POBW – proportion of optimal birth weight, GDM – gestational diabetes.

of the annual 'UV index'; in 45 out of 50 states this was obtained from only one site.

Spatial variability in UV exposure arises from a number of factors including geography, latitude, urbanicity and proximity to the ocean (Cherrie et al., 2015). Not incorporating spatial variability may introduce a bias towards the null hypothesis if the spatial aggregation does not capture the mean for that geographical area. In commenting on the spatial scale of the UV measurement and the potential for measurement error introducing bias, only Pereira described the spatial location of the exposure monitor. This location at Perth airport, 20 km inland was extrapolated to represent the average exposure of the individuals birthing in a large metropolitan area that is a narrow coastal corridor and a catchment area for pregnant women over a 2 529 875 square kilometers area. However given the lack of variance in a flat, mostly suburban, mid latitude location, it is likely that any resulting bias may have a limited effect and bias towards the null. Elter, Tustin and Waldie described a regional variable obtained from a meteorological institute averaged and applied this average to the individuals – a method less likely to introduce bias as it is more representative of the area. All studies applied this to births delivered in their region of interest, not taking in to account residence outside the region of the measure.

Significant heterogeneity was evident between the study outcomes and exposures, precluding meta-analysis. Results are summarized by outcome in Table 2.

### 3.4. Fetal growth and UV exposure

5 identified studies had an indicator of fetal growth as an outcome. All studies utilized government birth notification systems to determine their outcomes. Various direct birth weight measures were used by 3 of the studies (Thayer, 2014; Tustin and Hayne, 2004, Waldie, 2000) and measures adjusted for gestational length were used by 2 (Elter et al., 2004; Pereira et al., 2012). Different methods of UV measurement and timing of exposure were also considered. The incidence of low birth weight (LBW, < 2500 g) and its correlation with the annual average UV index was considered by Thayer (2014) in a cross sectional study of the United States. Outcomes were stratified by black and white births and the results showed that higher annual average UV index for the state of birth was associated with both higher rates of LBW overall, and higher racial disparity (see Table 2).

Tustin and Hayne (2004) and Waldie (2000) both presented the association between mean birth weight and mean sunshine hours finding positive results between higher first trimester sunlight and birth weight. Waldie (2000) used spectral analysis to compare fluctuations in mean monthly birth weights with fluctuations in mean monthly sunshine hours and showed that the pattern of these fluctuations was similar with peak birth weight correlating with a peak sunshine period during the first trimester (Waldie et al., 2000). Tustin and Hayne (2004) aimed to test the first trimester sunlight exposure hypothesis further, and compared 903 births exposed to either peak or trough sunshine hours in the first trimester and found an increase in birth weight of 67.9 g (p < 0.05) when the first trimester occurred in a period of peak sunshine hours (Tustin and Hayne, 2004).

Pereira (2012) and Elter (2004) both considered birth weight outcomes adjusted for gestational length in large administrative birth cohorts and found no significant association between sunlight hours and adjusted birth weight (Elter et al., 2004; Pereira et al., 2012). Pereira (2012) considered ORs of small for gestational age (SGA) – defined as a birth weight less than the 10th centile for the gestational week, as well as calculating the proportion of optimal birth weight (POBW) for 140 000 births in Western Australia and Elter (2004) compared the individual birth weight to the mean birth weight for the gestational week of birth to produce a multiple of the mean value (MoM) for 3333 births in Turkey and also found no significant effects.

The exposure variable in both studies was a single site of regional

measurement of sunlight hours, which was aggregated in time to calculate mean trimester values that were then applied to each pregnancy for analysis (Elter et al., 2004; Pereira et al., 2012). Both studies also examined and adjusted for other pregnancy and meteorological variables (see Table 2).

Potential confounders of the birth weight – sunlight/UV relationship were only modeled, at the individual level in the Pereira (2012) and Elter (2004) papers. Confounders at a state level were considered in the Thayer (2014) paper including deprivation and smoking rates. Waldie (2000) and Tustin and Hayne (2004) both assumed a random distribution of pregnancy confounders and did not adjust their data.

### 3.5. Preterm birth and UV

An association between gestational length and UV was reported in just 1 study. Thayer (2014) assessed the association between UV and preterm birth (PTB) rates in the United States utilizing a similar methodology to its LBW comparison. Similarly it found that PTB incidence increased as the annual average UV index increased in both black and white women with the PTB rate of black women in the northern states 14.7% vs 18.4% in the southern states, (p < 0.0001) and for white women 9.9% northern states and 11.9% southern states (p=0.001) (Thayer, 2014). The strong positive association reported between the state UV index and indicators of poverty in the United States limit the applicability of this finding (Thayer, 2014).

### 3.6. Hypertension and UV

2 studies examined the relationship between the hypertensive complications of pregnancy and UV with methodological similarities borne out of the hypothesis that first trimester timing of peak exposure was critical to developing hypertensive complications. Algert (2010) used an Australian retrospective cohort of 424 732 pregnancies and demonstrated that higher 1st trimester and lower 3rd trimester solar radiation were strongly correlated with a higher risk of pregnancy hypertension (Algert et al., 2010). The strength of correlation in this study was similar for both time points with r +/−0.67 (Algert et al., 2010).

Tran (2015) used a case-cohort study to investigate the outcome of severe pre-eclampsia incidence in France with 526 cases from 63 000 births and found small but non-significant effects of higher trimester 1 solar radiation on the risk of severe pre-eclampsia (OR 1.04, 95%CI 0.99–1.09, Table 2) (Tran et al., 2015).

Both studies used direct measures of UV from their respective regional government collected data measuring solar radiation at ground level in megajoules per meter squared and calculated estimates for a period of time around conception and trimester one; Algert (2010) used one site and Tran used the daily average of 2 (Algert et al., 2010; Tran et al., 2015). UV data was linked temporally to the first trimester of each individual pregnancy to determine exposure. This design around assumption introduces a significant risk of confirmatory bias in interpretation.

## 4. Discussion

### 4.1. Summary of evidence

This review is the first systematic review focusing on the effects of UV for birth outcomes and pregnancy complications. We demonstrate a paucity of studies despite multiple biologically plausible pathways, readily available measures of the environmental exposure of interest, intense interest in vitamin D testing and supplementation and evidence of seasonal effects on immune gene expression (Dopico et al., 2015; Pérez-López et al., 2015). Despite a limited number of studies, the review is suggestive of a potential increase in fetal growth when the first trimester occurs in a period of higher UV availability and higher rates

**Table 2**
Study results by clinical outcome.

| Study, year of study | Outcome | Results | Discussion |
|---|---|---|---|
| **FETAL GROWTH** | | | |
| 1 Thayer, 2007 | Incidence rate of LBW by state (< 2500 g) | States with higher amounts of UV had higher rates of LBW in black and white women – LBW black women northern states 9.3% vs 12.1% in southern states (p < 0.0001), white women northern states 4.9% vs 5.8% southern states (p=0.002) <br> States with higher UV had a higher disparity between black and white LBW rates (β 0.007 (SE 0.002) p =0.002) <br> LBW disparity also correlated strongly with poverty rate, Gini co-efficient, latitude, temperature and obesity (β 0.34, 0.40, −0.61, 0.61, 0.35 respectively (p < 0.05).. | Difficult to separate effect of UV from the social confounders that correlate with it in the US |
| 2 Pereira, 2009 | SGA (Odds ratios) <br> POBW (proportion of optimal birth weight) | Effect sizes for sunlight exposure were small and non significant SGA sunlight (h) adjusted OR trimester1 1.02 (CI 0.98, 1.05), pregnancy 1.01 (CI 0.98, 1.03) | No significant effects seen for exposure to sunshine hours. Setting has year round high levels of sunshine (10th centile = 8.49, 90th = 9.07 h) |
| 3 Elter, 2004 | MoM individual birth weight to gestational week mean | Daylight hours not associated with birth weight in stepwise regression and effect size not reported | No association |
| 4 Tustin and Hayne (2004) | Mean birth weight | Peak sunshine in T1 associated with higher term birth weight. Effect size difference in birth weight of peak vs trough sunshine 67.9 g, p < 0.05.. <br> No sig effect in trimester 2 or 3 of peak vs trough sunshine or temperature | Assumed distribution of maternal and pregnancy characteristics randomly distributed. |
| 5 Waldie, 2000 | Mean monthly birth weight | Monthly means of birth weight and length varied with the same frequency as sunshine hours. Spectral analysis showed peak birth weight lagged peak sunshine hours by 6–9 months. | Trimester 1 effect of higher sunshine hours |
| **PRETERM BIRTH** | | | |
| 1 Thayer, 2007 | Incidence rate of preterm birth by state (< 37/40) | States with higher amounts of UV had higher rates of PTB in black and white women – PTB black women northern states 14.7% vs 18.4% southern states (p < 0.0001), for whites 9.9% in northern states vs 11.9% southern states (p = 0.001) <br> State with higher UV had a higher disparity between black and white PTB rates [β 0.006 (SE 0.003) p = 0.03] <br> PTB disparity also correlated strongly with the Gini co-efficient, latitude and temperature [β 0.36, −0.48, 0.44 respectively (p < 0.05)] | Difficult to separate effect of UV from the social confounders that correlate with it in the US |
| **BLOOD PRESSURE** | | | |
| 1 Tran, 2014 | Severe Pre-eclampsia | Small increases in rates of severe pre-eclampsia with increased solar duration and minimum temperatures in early pregnancy <br> OR and 95% C.I.s: <br> Solar duration 1.04 (0.99–1.09) <br> Minimum temperature 1.03 (1.01–1.05) | Increased trimester 1 solar hours associated with small inc OR of severe PE |
| 2 Algert, 2010 | ICD–10 code pregnancy hypertension (PH) <br> Secondary: Pre-eclampsia (PE), eclampsia | Mean PH rates by month of conception range: <br> 7.3% (May) – 8.9% (Oct) <br> Correlation between solar radiation and month of conception r= +0.67 <br> Opposite for 7 months post conception <br> Early PE correlation r= −0.51 (p=0.09 (non sig)) | Pregnancy hypertension rates vary by month of conception by up to 1.5%. <br> Higher solar radiation at conception had higher PH rates and inverse correlation for trimester 3 <br> Non significant trend towards less severe pre-eclampsia with higher T1 solar radiation |
| 3 Rylander, 2011 | Eclampsia | OR and 95% C.I.s <br> 'Winter' 1.9 (1.4–2.5) <br> 'Not winter' 1.0 (ref) | Approx doubling of risk of eclampsia in winter. |

MoM – multiples of the mean, PTB – preterm birth, UV – ultraviolet, US – United States of America, β – Beta co-efficient, LBW – low birth weight, SGA – small for gestational age, PH – pregnancy hypertension, PE – pre-eclampsia.

of hypertensive complications of pregnancy when the first trimester occurs during a period of higher UV availability.

In this review, fetal growth effects of UV are inconsistent and the methodological limitations and heterogeneity makes interpreting the findings difficult. That fetal growth may be effected by UV exposure is supported by a review of the vitamin D and pregnancy data showing a consistent association between early and mid pregnancy deficiency and fetal growth restriction (Pérez-López et al., 2015; Wei et al., 2013). The 2 studies set in Dunedin, New Zealand demonstrated benefits of higher first trimester sunlight, however neither Elter (2004) nor Pereira (2012) demonstrated any effect in lower latitude Turkey or Australia respectively (Elter et al., 2004; Pereira et al., 2012; Tustin and Hayne, 2004; Waldie et al., 2000).

In the adult health domain of cardiovascular disease the effect of UV is established; lower UV correlates with higher blood pressure and seasonal and latitudinal patterns of hypertension distribution are common in prospective observational studies (Fares, 2013; Hart and Finlay-Jones, 2011; Law and Morris, 1998; Xu et al., 2013). For pregnant women, hypertension is common complicating up to 10% of pregnancies and being a significant contributor to maternal and neonatal morbidity and mortality and its incidence is increasing (Gongora and Wenger, 2015). The nitric oxide (NO) pathway outlined by Liu (2014) of UV exposure generating NO release from the skin has relevance for pregnancy as NO is a central signaler in the vascular adaptation to pregnancy as well as promoting fetal growth and uterine quiescence (Leiva et al., 2016; Sladek et al., 1997). Nitrate donors such as l-arginine, sildenafil and isosorbide mononitrate are in clinical use to prevent preeclampsia and fetal growth restriction (Chan et al., 2016; Johal et al., 2014). The immediate and short lived nature of this effect could underpin the temporal relationship demonstrated in the 2 studies that considered hypertensive complications – lower UV in the third trimester correlated with increased incidence of hypertensive complications (Algert et al., 2010; Tran et al., 2015). Presumably the immediacy of maternal effect overwhelms any earlier benefit accrued during placentation.

### 4.2. Limitations

The one study examining gestational length and UV is limited substantially by its design and conclusions cannot be drawn on this outcome (Thayer, 2014) however given the pathways of UV effect discussed in this review, investigating preterm birth as an outcome is warranted and deserves consideration in future research.

Temperature and sunlight correlate closely and Beltran (2014) presented a comprehensive systematic review of meteorology and pregnancy (Beltran 2014). However this review focuses primarily on UV to assess the studies that have been done and their methodological strengths and limitations to guide future research.

Future work needs to consider the issues around exposure measurements and application as well as outcome ascertainment. Birth outcomes are prone to bias as birth numbers across the year are not constant and neither are mothers with many social attributes of mothers being patterned seasonally. Methodologies to minimize these biases have been utilized in other epidemiological research – a 'fetus at risk' approach would take in to account fluctuations in pregnancy numbers that may bias preterm birth rates; adjusting for individual maternal characteristics that influence gestational length and growth; application of the exposure around the conception time point rather than birth reduces misclassification bias and undertaking a 'within-mother' analysis could be considered (Curie, 2013; Weinberg et al., 2015).

The rigorous application of inclusion and exclusion criteria capture the strategies used to measure and model UV. Ideally exposure measurement aims to incorporate both spatial and temporal variation to reduce exposure misclassification in observational studies. Temporal variation includes both the variation in the exposure and method of analysis. In this review, except for Thayer (2014) all studies used a method of analysis that utilized monthly averages modeled into

trimester blocks increasing the strength of findings in those studies. Temporal variation of the UV exposure variable differed between latitudes affecting the power of the study to find small effects. This effect is also evident in the seasonal birth data at different latitudes. The Pereira (2011) and Tustin and Hayne (2004) studies highlight this difference – mid latitude Perth had a 40 min sunlight hours variation while low latitude Dunedin had a 10 h peak-trough difference (Elter et al., 2004; Pereira et al., 2012).

In contrast, Thayer (2014) utilized the annual average of the UV index of the state of residence losing both the temporal change in the exposure and the timing of the exposure substantially limiting its findings (Thayer, 2014).

Few of the studies examined exposures that varied between relatively small geographical areas. This is potentially important as other environmental exposures, such as air pollution, and their associated epidemiological effects for birth outcomes have been shown to be sensitive to whether or not higher resolution spatial variation is incorporated into exposure estimates. For example, studies that rely on a static monitor with high temporal resolution typically show lower effect estimates than those based on exposures derived from land-use regression models or other mapping techniques (Dibben and Clemens, 2015). The degree of this bias towards the null hypothesis depends on the extent to which the monitor captures the average exposure for the individual exposures being estimated. In the case of air pollution which can vary extensively over relatively small areas, static monitors rarely capture this average concentration level because they are often used to determine adherence to regulatory thresholds and are therefore sited in hotspot locations rather than areas that are representative of the wider area. Exposure to UV generally varies less within smaller areas when compared with air pollution and so is unlikely to suffer the same degree of bias towards the null when relying on temporal and seasonal exposure variation but nevertheless there remains a possibility that effect sizes may have been under-estimated (Dadvand et al., 2011).

Finally, sun related behavior, both individual and cultural, while not captured in the administrative datasets used to generate these studies is more likely to be randomly distributed (Dadvand et al., 2011; Lucas et al., 2006). This feature limits the validity of the results in ecological studies investigating UV exposure (Dadvand et al., 2011; Lucas et al., 2006; Sedgwick, 2014).

### 5. Conclusion

Optimizing the pregnancy environment is vital to the health of future generations. Considering sunlight as an explanatory environmental variable is of central public health concern as the prenatal vitamin D supplementation trials continue to demonstrate limited benefit in pregnancy. This systematic review of the effects of ultraviolet radiation on singleton pregnancy outcomes identified only 7 studies that considered UV as an explanatory variable. These were methodologically diverse and of low quality we conclude there is insufficient evidence regarding the question of the effects of UV on pregnancy outcomes. There may be beneficial effects of UV on blood pressure and fetal growth and this justifies further exploration. Future research should focus on spatial and temporal modeling and corresponding mechanistic work in human and animal models to improve our understanding and public health advice.

### Conflict of interest

Nil to declare.

## Appendix A

**FULL MEDLINE SEARCH STRATEGY**.

 1. Exp Pregnancy/
 2. Pregnan*.tw
 3. Gravid*.tw
 4. Or/1−3
 5. Exp Ultraviolet rays/
 6. (Ultraviolet adj2 light).tw
 7. Sunshine.tw
 8. Sunlight.tw
 9. Daylight.tw
10. Day length.tw
11. Bright light.tw
12. Clear skies.tw
13. Insolation.tw
14. Solar.tw
15. Or/5−14
16. 4 and 15
17. Exp Pregnancy outcome/
18. Pregnancy outcome.tw
19. Stillbirth.tw
20. Intrauterine.tw
21. F? etal death.tw
22. (F? etal adj2 death).tw
23. (F? etal adj2 demise).tw
24. Live born.tw
25. Twins.tw
26. Multiple pregnan*.tw
27. Singleton*.tw
28. Anomal*.tw
29. Exp Fetal death/
30. Exp Pregnancy, multiple/
31. Exp Twins/
32. Exp Birth weight/
33. (Birth adj2 weight).tw
34. Birthweight.tw
35. Birth length.tw
36. Small for gestational age.tw
37. SGA.tw
38. Ponderal index.tw
39. Intrauterine growth restriction.tw
40. Growth retardation.tw
41. (F? etal adj2 growth).tw
42. Exp Fetal growth retardation/
43. Exp Infant, Small for Gestational Age/
44. (Infant adj2 weight).tw
45. Exp Pre-eclampsia/
46. Exp Hypertension, pregnancy induced/
47. Pregnan* adj2 hypertensi$.tw
48. Pregnancy induced hypertension.tw
49. (Gestation$ adj2 hypertensi*).tw
50. Pre? eclamp*.tw
51. Eclamp*.tw
52. Tox$emia.tw
53. (Proteinuri* adj3 hypertensi*).tw
54. exp Premature Birth/
55. exp Infant, Premature/
56. exp Obstetric labor, premature/
57. exp Gestational age/
58. Prematur*.tw
59. Gestation* length.tw
60. Gestation period.tw
61. Pre? term.tw
62. Post? term.tw

63. Prolonged pregnancy.tw
64. Early term.tw
65. Late term.tw
66. (Maturity adj2 chronological).tw
67. Chronologic f$etal maturity.tw
68. (Age adj2 f? etal).tw
69. (Age adj2 gestation*).tw
70. or/17–69
71. exp animals/not humans.sh
72. 16 and 70
73. 72 not 71

## Appendix B. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2017.02.026.

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