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Higher sun exposure in the first trimester is associated with reduced preterm birth; a Scottish population cohort study using linked maternity and meteorological records

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Abstract:

Background: Preterm birth (birth at less than 37 weeks gestation) is the leading cause of death in children under five years old and prevention is a global public health issue. Seasonal patterns of preterm birth have been reported, but factors underlying this have been poorly described. Sun exposure is an important environmental variable that has risks and benefits for human health, but the effects of sun exposure on pregnancy duration and preterm birth are unknown.

Objectives: To determine the association between available sun exposure and preterm birth.

Methods: We performed a population-based data-linkage study of 556 376 singleton births (in 397,370 mothers) at or after 24 weeks gestation, in Scotland between 2000-2010. Maternity records were linked to available sun exposure from meteorological records, by postcode. Logistic regression analysis was used to explore the relationship between available sunshine and preterm birth at less than 37 weeks gestation. Exploratory analyses included a subgroup analysis of spontaneous and indicated preterm births and a sibling analysis in sib-pairs discordant for preterm birth.

Results: The rate of preterm birth was 6.0% (32 958/553 791 live births). Increased available sun exposure in the first trimester of pregnancy was associated with a reduced risk of preterm birth, with evidence of a dose response. Compared to the lowest quartile of sun exposure, the highest quartile of sun exposure was associated with a reduced odds ratio (OR) of preterm birth of 0.90 (95% Confidence Interval (CI) 0.88 – 0.94 p <0.01) on univariable analysis and OR 0.91 (95% CI 0.87, 0.93 p <0.01) after adjustment for second trimester sunlight exposure, parity, maternal age, smoking status and deprivation category. No association was seen between preterm birth and second trimester available sun exposure or combined first and second trimester exposure. Similar patterns were seen on sibling analysis and within both the indicated and spontaneous preterm subgroups.

Discussion: Available sun exposure in the first trimester of pregnancy is associated with a protective effect on preterm birth less than 37 weeks gestation. This opens up new mechanisms, and potential therapeutic pathways, for preterm birth prevention.

Introduction

Preterm birth (birth at less than 37 weeks gestation) is a leading cause of neonatal morbidity and mortality, and deaths in children under five years old worldwide (1). The contribution of environmental factors to preterm birth is not well studied, (2) however, understanding the impact of the natural environment on pregnancy may present novel pathways for intervention.

Sunlight is a component of the natural environment that is necessary for human health (3). Vitamin D production, nitric oxide production and activity of the immune system are all influenced directly by sunlight with implications for disease manifestation (4). These pathways are central to the establishment and maintenance of pregnancy, with the early pregnancy state establishing risk for later outcomes (5, 6). However, sun exposure in pregnancy remains mainly incidental and unconsidered. Although there have been relatively few studies, a systematic review of sun exposure and pregnancy outcomes found associations with fetal growth restriction, blood pressure and preterm birth rates (7, 8), with higher first trimester sunlight correlating with higher fetal birth weights and less hypertensive complications in the third trimester (8). The postulated mechanisms were related to vitamin D generation by sun exposure – deficiency of which in pregnancy is associated with low birth weight, preterm birth and hypertensive complications of pregnancy (9).

Only one US based study has explored preterm birth rates and sunlight exposure however, this study did not address whether UV light exposure influenced preterm birth or low birthweight, but aimed to assess whether variation in UV light–induced vitamin D synthesis might contribute to racial disparities in birth outcomes in the United States, using statewide estimates. To specifically examine the effects of available sunlight on preterm birth requires consideration of exposure periods and individual level adjustment of other maternal data. Using high granularity environmental data applied to an individual pregnancy allows modeling of overall risk related to sun availability and modeling of exposure periods. As latitude increases, the variation offered by larger alterations in length of day over the calendar year offer a natural experiment in which to examine effects of available sun exposure. Scotland has high-quality maternity data, and high latitude with variability in sunshine both across and between years, making it an ideal place to study the effects of available sunshine on pregnancy. The objective of this population cohort study was to determine whether there is an association between available sunlight and preterm birth by linking geographically mapped sunlight data to pregnancy and birth records.

Methods

The study was approved by the Privacy Advisory Service for National Services Scotland approval number PAC91/147. Data available for analysis were pseudo-anonymized and analyzed within a trusted research environment (the NHS Scotland Safe Haven). Findings are reported in accordance with RECORD checklist for observational studies using routinely collected health data(10).

Study population

We used the Scottish Morbidity Record 02 (SMR02) which records information on all women admitted to Scottish maternity hospitals (11). It contains information on maternal and infant characteristics, clinical management, and obstetric complications (11). During the period studied this does not include homebirths, but these are less than 2% of all Scottish births and ethnicity was poorly (<40%) recorded in the 2008-9 review (11). Regular detailed quality assurance of the SMR02 is performed, the 2008-9 review is most relevant to this dataset and this report confirmed the completeness (>90%) and accuracy of the fields we used in this study (11).

Inclusion and exclusion criteria

We extracted data from SMR02 data on all liveborn infants born in Scotland between Jan 1, 2000, and Dec 31st 2010, inclusive. We restricted our analysis to singleton births at or beyond 24 weeks gestation as a feature of the SMR02 database (11). We excluded births with congenital anomalies. We also excluded cases based on *a priori* thresholds of plausibility. Births were excluded if gestational length was more than 46 weeks, birth weight greater than 7000g or less than 350g and maternal age less than 13 years. Finally, we excluded women with missing gestation at birth, parity, smoking status or who we could not link with available sunshine exposure.

Definitions

Preterm birth was considered as a categorical variable, defined as birth before 37 weeks gestation. Ultrasound in the first half of pregnancy is routinely used in Scotland to determine gestational age(12). We imputed date of conception from date of delivery, minus gestational age at delivery plus two weeks. Trimester 1 we defined as the first 12 weeks of pregnancy from conception and trimester 2 as weeks 13 to 28. In the sensitivity analysis we also used completed gestational weeks as a continuous variable.

The mean daily sunlight exposure was calculated for each trimester, and a whole pregnancy for each individual woman. We did not use data on available sun exposure during third trimester of pregnancy, because most preterm births occur during the third trimester which complicates the exposure duration of available sunlight during this period. To represent cumulative sunlight exposure, a value was calculated for the mean of trimester 1 and 2 to represent this called 'average trimester 1 and 2' exposure.

We defined 'spontaneous preterm births as women who gave birth <37 weeks gestation who did not have an elective caesarean section or an induction of labour. We defined 'provider initiated' preterm births as women who gave birth <37 weeks gestation who had an elective caesarean section or an induction of labour.

Postcodes of residence, which are highly geographically specific, were used to link to meteorological data in 5 x 5km grid squares, generated from two sources - the UK Meteorological (Met) office (13) and EUMETSAT (14) . The Met office is the United Kingdom's weather observation and prediction service funded under the Department for Business Innovation and Skills (13). Met office data is freely available including monthly average sunlight hours over a grid of Scotland with each grid value referencing a 5x5km surface area of Scotland. EUMETSAT includes geostational meteorological satellites covering Europe. Included within freely available EUMETSAT data is the Meteosat series of satellites, which provide daily values for surface solar insolation at a spatial resolution of 1 degree of latitude and longitude. Met office and Meteosat data were combined to provide mean sunlight hours a day for each 5 x 5 km grid square across Scotland, for every day of the exposure period (1^{st} January1999 to 31^{st} December 2010).

Potential Confounders

We took a first principles approach to identifying confounders of the sunlight and preterm birth relationship utilizing directional acyclic graphs (DAGs) to determine our primary modeling approach (Supplementary Figure 1). Available sunlight and pregnancy outcome are at low risk of confounding using this approach, as very little is deterministically associated with available sunlight. We considered adjustment for season of conception as available sunlight in the northern latitudes is highly correlated with season and season of conception has been variably associated with preterm birth). However, it is likely that season acts as a proxy for seasonal reproductive behaviour, variation in temperature, the burden of winter influenza, seasonal changes in pollen counts and particulate air pollution all of which have the potential to be mediated by available sunlight. We also note the approach recommended by Weinberg et al, who demonstrated that if measures of social confounding are available, preferentially modeling these instead of utilizing season as a surrogate is more analytically rational (12). As such our primary logistic regression model did not include season of conception, but did include sociodemographic variables including maternal age at birth (categorized as ≤18, 19-29, 30-34, 35-39, ≥40 years of age), smoking in pregnancy (yes/no), parity and socioeconomic deprivation (derived from Scottish Index of Multiple Deprivation (SIMD) Quintiles, allocated by postcode (15). (model 1). We did include season of conception in an additional model (model 2) recognizing the potential for over adjustment in this model. We defined season of conception meteorologically with December-February as winter, March-May as spring, June-August as summer and September-November as autumn.(15)

For the ‘trimester 1’ and ‘trimester 2’ exposure models we adjusted for the alternative trimester of exposure – available sunlight exposure in the preceding trimester (for second trimester exposure) or subsequent trimester (for first trimester exposure) - for both model 1 and model 2. The ‘average trimester 1 and 2’ exposure was not adjusted for any other exposure variable.

Statistical Analysis

For descriptive statistics of continuous variables, we used mean and standard deviation (sd) for normally distributed data, and median and interquartile range (IQR) for non-parametric data. Categorical data were presented as percentages with 95% confidence Intervals (CI). We modelled odds ratios of preterm birth using logistic regression, before and after adjustment for confounders. p values lower than 0·05 were taken to be statistically significant.

Sensitivity analysis

We undertook the primary analysis described above and also controlled for within-mother effects using conditional fixed effects regression by using the national identifier (Community Healthcare Index [CHI] to identify mothers within the dataset. We also modeled available sun exposure with gestational age at delivery in completed weeks as a continuous variable using linear regression with univariate and multivariate models as described for the primary analysis.

We did a sibling analysis as a sensitivity analysis to explore the effect of any potential residual confounding. Mothers of both a term and preterm birth were identified and utilising conditional logistic regression with mother-level fixed effects we modelled the effect of difference in sun exposure between the pregnancies. In the sibling analysis we compared available sunlight exposure during pregnancy in sib-pairs discordant for preterm birth. We analysed the whole group, as well separate analyses to adjust for season of conception and for maternal age, smoking status, SIMD category and parity.

Subgroup analysis

In order to explore potential underlying mechanisms we performed a subgroup analysis of spontaneous preterm births <37 weeks and indicated preterm births < 37 weeks

All analyses were done with Stata (version 14).

Results

Between Jan 1, 2000, and Dec 31, 2010 there were 553 791 live singleton births recorded in Scotland. Of these births, we excluded 81 417 (figure 1). The analysis cohort consisted of 472 374 births to 395 588 mothers. Of these births 32 958 (6.0%) were preterm. The characteristics of the cohort are described in Table 1, stratified by quartile of available sun exposure in trimester 1.

Over the study period the mean sunlight exposure hours per day ranged from 1.59 in winter months to 6.71 hours in summer months (Supplementary Table 1). The annual distribution was unimodal with a summer peak. Variation in exposure between years was evident primarily to differences in available summer sunlight. An indication of spatial variation is given in Supplementary Figure 2 with a map showing variation in average trimester 1 exposure for births delivered in 2001 across 5 x 5 km areas in Scotland.

Relationship between available sun exposure and preterm birth

Available sun exposure in trimester 1 of pregnancy was inversely associated with preterm birth in univariable and multivariable models with evidence of a dose dependent effect (Table 2). Compared to the lowest quartile of exposure, the highest quartile of exposure was associated with a reduced odds ratio (OR) of preterm birth of 0.90 (95% Confidence Interval (CI) 0.88 – 0.94 p <0.01) on univariable analysis with a small attenuation of effect size in the adjusted models but a persistent significant dose dependent protective effect (model 1 OR 0.91 (95% CI 0.87, 0.93 p <0.01)) (Table 2). However, available sun exposure in trimester 2 was not associated with preterm birth OR 1.02 (OR 0.99, 95% CI 1.06 p 0.12). The average trimester 1 and 2 exposure had a weakened but similar effect to the trimester 1 exposure, confirming the persistence of the trimester 1 effect regardless of trimester 2 with the highest quartile of exposure associated with a reduced OR of preterm birth of 0.95 (95% CI 0.92, 0.99 p0.01) and in the adjusted model 1 OR 0.96 (95% CI 0.93, 1.0 p0.04). The results were unchanged controlling for within mother effects (Supplementary Table 2). Using linear regression for gestational length, increasing available sun exposure was associated with increasing gestational length with the highest exposure quartile of exposure β Coefficient 0.07 (95% CI 0.05-0.08 p<0.01) (Supplementary Table 3).

The sibling analysis included 9054 sibling pairs and showed an inverse relationship between preterm birth and sun exposure in the first trimester similar to the full cohort (Table 3).

This outcome was seen in the spontaneous and indicated preterm birth analysis with persistent dose dependent effect sizes for the inverse relationship between available sunlight in trimester 1 and preterm birth (Table 4 and 5).

Discussion

We found a robust association between available sunlight in the first trimester and a reduction in the risk of preterm birth. That this effect appears dose dependent, is minimally attenuated by increasing adjustment and is borne out in the sibling, spontaneous and indicated preterm birth subgroups all support the strength of this relationship.

Only one other study has examined sunlight and preterm birth risk. Thayer et al (16) in the United States investigated the role of sunlight in accounting for differences in preterm birth rates between white and non-Hispanic black populations. Their methodology used a state wide average measure of the UV index as the exposure variable and aggregated state wide data and found that as average annual UV increased, the disparity in preterm birth rates between white and non-Hispanic black women increased concluding that in the United States the socioeconomic factors co-vary with the UV index and that sunlight availability (which they considered an instrument for photosynthesis of Vitamin D) were not responsible for the race based disparities in preterm birth. Our methodology strives to refine the limitations of Thayer's study using highly granular environmental data in both space and time, linked at an individual level, alongside a less racially varied study population, which may account for our significantly different findings (8). That the effect of an annual average UV index alone does not overcome patterning of births related to social disparity, does not contradict our finding that available early pregnancy sunlight may be protective for preterm birth.

As explored in our DAG (Supplementary Figure 1) sunlight availability is an environmental exposure variable that is quite protected from confounding and measurement error bias as this is unlikely to be introduced by satellite data. Our main potential confounder is season of conception which represents a clustering of biological, social, behavioral and environmental factors rather than a discrete entity. In methodological reproductive work, numbers of conceptions and therefore births vary by season which may account for some of the observed seasonal variation in gestational length - utilizing season of conception as we have done rather than season of birth accommodates this (17, 18). Adjusting for measurable aspects of 'season' – such as markers of deprivation and behavior – reduces 'seasonal' variation in preterm birth outcomes - in Weinburg's work in Norway (17), adjusting for season of conception and maternal characteristics ameliorated seasonal variation in gestational length. Curie (18) took a ‘within mothers’ sibling design approach to address seasonal variation in birth outcomes – specifically gestational length and birth weight – and showed that even adjusting within siblings, a May conception (or spring in the northern hemisphere) remained associated with a shorter gestational length and hypothesized that this may be attributable to seasonal influenza.

We prefer the approach that season of conception is not a discrete entity, and adjusting for season in addition to maternal confounders is overadjustment that hypothetically would then attenuate effect. Our data supports this hypothesis, with an increasing reduction in effect size with addition of season of conception in to the model. That the effect remains, even if reduced in size, supports the strength of the relationship between first trimester sunlight and preterm birth.

Season of conception has been previously associated with preterm birth and in a London cohort winter birth was associated with a 10% increased risk of preterm birth (19) . However, whether this observation was due to a biological pathway or due to potential methodological limitations of the study is unclear. Weinberg (17) demonstrated that seasonal influences on preterm birth are weakened by taking a ‘fetus at risk’ approach. This is because assessment of preterm birth that does not include consideration of the population of fetuses at risk will bias the data to appear as though more preterm births occur at a time when more women are pregnant – ie a greater number of fetuses are at risk. Adjusting for season of conception ameliorates this bias. Weinberg(17) also demonstrated that seasonal effects on preterm birth are stronger in unplanned rather than planned conceptions. Unplanned pregnancy, smoking, low levels of education and non-married status are risk factors for preterm birth and also bias pregnancy dating by recalled last menstrual period (LMP). Weinberg (17) concluded that is measures of social confounding are available, preferentially modeling these instead of utilizing season as a surrogate is more analytically rational. We have followed this approach within our study.

It is biologically plausible higher sunlight availability in trimester 1 has downstream effects on gestational length and therefore preterm birth by improving implantation or early placentation. The determination of gestational length is complex and poorly understood, with maternal age, body mass index (BMI) and previous genetic predisposition interacting with intrinsic pregnancy factors (20). The essential component of sunlight, ultraviolet radiation, reduces blood pressure potentially by stimulating nitric oxide release and also modulates the immune system (4, 21, 22) – these are essential physiological mediators in the process of implantation, early placentation and thus tolerance of pregnancy (23-25). Subtle deficits in early placentation become apparent in later pregnancy and can manifest as both spontaneous and iatrogenic preterm birth due to the classic obstetric complications of pre-eclampsia and fetal growth restriction (25, 26). These conditions are placentally mediated and are significant contributors to iatrogenic preterm birth in either the fetal or maternal interest but often co-exist with spontaneous onset of preterm labour (25). That we see similar effects in both spontaneous and iatrogenic preterm birth models suggest a pathophysiological role for higher available sunlight promoting conditions for more favorable implantation or placentation and thus reducing preterm birth.

This large epidemiological study increases our understanding of the protective effect of early pregnancy sunlight on gestational length in a high latitude country. As preterm birth remains the leading contributor to neonatal death understanding environmental influences opens novel research pathways to investigate strategies to reduce preterm birth and hence childhood morbidity and mortality.

Conclusion:

In Scotland, higher environmental sunlight availability in the first trimester of pregnancy has significant dose dependent protective effects on preterm birth that are applicable to the whole singleton pregnancy population. This effect is seen in spontaneous and indicated preterm births, suggesting a likely early pregnancy effect on the maternal vascular and immunological adaptation to pregnancy. This opens novel research pathways to explore both mechanisms and interventions to reduce preterm birth.

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Captions

Figure 1: Inclusion and exclusion flow chart for study population