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Higher sun exposure in the first trimester is associated with reduced preterm birth

Citation for published version:

Lauren, M, Clemens, T, Daras, K, Weller, RB, Dibben, C & Stock, SJE 2021, 'Higher sun exposure in the first trimester is associated with reduced preterm birth: a Scottish population cohort study using linked maternity and meteorological records', *Frontiers in Reproductive Health*.
<https://doi.org/10.3389/frph.2021.674245>

Digital Object Identifier (DOI):

[10.3389/frph.2021.674245](https://doi.org/10.3389/frph.2021.674245)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Frontiers in Reproductive Health

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

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23 **Keywords: sunlight, ultraviolet radiation, preterm birth, pregnancy, cohort,**

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27

28 **Abstract:**

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

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

36 Methods: We performed a population-based data-linkage study of 556 376 singleton births
37 (in 397,370 mothers) at or after 24 weeks gestation, in Scotland between 2000-2010.

38 Maternity records were linked to available sun exposure from meteorological records, by
39 postcode. Logistic regression analysis was used to explore the relationship between available
40 sunshine and preterm birth at less than 37 weeks gestation. Exploratory analyses included a
41 subgroup analysis of spontaneous and indicated preterm births and a sibling analysis in sib-
42 pairs discordant for preterm birth.

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

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

56

57

58

59 **Introduction**

60

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

66

67 Sunlight is a component of the natural environment that is necessary for human health (3).

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

79

80 Only one US based study has explored preterm birth rates and sunlight exposure however,
81 this study did not address whether UV light exposure influenced preterm birth or low
82 birthweight, but aimed to assess whether variation in UV light–induced vitamin D synthesis

83 might contribute to racial disparities in birth outcomes in the United States, using statewide
84 estimates. To specifically examine the effects of available sunlight on preterm birth requires
85 consideration of exposure periods and individual level adjustment of other maternal data.
86 Using high granularity environmental data applied to an individual pregnancy allows
87 modeling of overall risk related to sun availability and modeling of exposure periods. As
88 latitude increases, the variation offered by larger alterations in length of day over the calendar
89 year offer a natural experiment in which to examine effects of available sun exposure.
90 Scotland has high-quality maternity data, and high latitude with variability in sunshine both
91 across and between years, making it an ideal place to study the effects of available sunshine
92 on pregnancy. The objective of this population cohort study was to determine whether there
93 is an association between available sunlight and preterm birth by linking geographically
94 mapped sunlight data to pregnancy and birth records.

95

96 **Methods**

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

102

103 *Study population*

104 We used the Scottish Morbidity Record 02 (SMR02) which records information on all women
105 admitted to Scottish maternity hospitals (11). It contains information on maternal and infant
106 characteristics, clinical management, and obstetric complications (11). During the period
107 studied this does not include homebirths, but these are less than 2% of all Scottish births and

108 ethnicity was poorly (<40%) recorded in the 2008-9 review (11). Regular detailed quality
109 assurance of the SMR02 is performed, the 2008-9 review is most relevant to this dataset and
110 this report confirmed the completeness (>90%) and accuracy of the fields we used in this study
111 (11).

112

113 *Inclusion and exclusion criteria*

114 We extracted data from SMR02 data on all liveborn infants born in Scotland between Jan 1,
115 2000, and Dec 31st 2010, inclusive. We restricted our analysis to singleton births at or beyond
116 24 weeks gestation as a feature of the SMR02 database (11). We excluded births with
117 congenital anomalies. We also excluded cases based on *a priori* thresholds of plausibility.
118 Births were excluded if gestational length was more than 46 weeks, birth weight greater than
119 7000g or less than 350g and maternal age less than 13 years. Finally, we excluded women with
120 missing gestation at birth, parity, smoking status or who we could not link with available
121 sunshine exposure.

122

123 *Definitions*

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

130

131 The mean daily sunlight exposure was calculated for each trimester, and a whole pregnancy
132 for each individual woman. We did not use data on available sun exposure during third

133 trimester of pregnancy, because most preterm births occur during the third trimester which
134 complicates the exposure duration of available sunlight during this period. To represent
135 cumulative sunlight exposure, a value was calculated for the mean of trimester 1 and 2 to
136 represent this called ‘average trimester 1 and 2’ exposure.

137

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

142

143 Postcodes of residence, which are highly geographically specific, were used to link to
144 meteorological data in 5 x 5km grid squares, generated from two sources - the UK
145 Meteorological (Met) office (13) and EUMETSAT (14) . The Met office is the United
146 Kingdom’s weather observation and prediction service funded under the Department for
147 Business Innovation and Skills (13). Met office data is freely available including monthly
148 average sunlight hours over a grid of Scotland with each grid value referencing a 5x5km surface
149 area of Scotland. EUMETSAT includes geostational meteorological satellites covering Europe.
150 Included within freely available EUMETSAT data is the Meteosat series of satellites, which
151 provide daily values for surface solar insolation at a spatial resolution of 1 degree of latitude
152 and longitude. Met office and Meteosat data were combined to provide mean sunlight hours a
153 day for each 5 x 5 km grid square across Scotland, for every day of the exposure period (1st
154 January 1999 to 31st December 2010).

155

156 *Potential Confounders*

157 We took a first principles approach to identifying confounders of the sunlight and preterm birth
158 relationship utilizing directional acyclic graphs (DAGs) to determine our primary modeling
159 approach (Supplementary Figure 1). Available sunlight and pregnancy outcome are at low risk
160 of confounding using this approach, as very little is deterministically associated with available
161 sunlight. We considered adjustment for season of conception as available sunlight in the
162 northern latitudes is highly correlated with season and season of conception has been variably
163 associated with preterm birth). However, it is likely that season acts as a proxy for seasonal
164 reproductive behaviour, variation in temperature, the burden of winter influenza, seasonal
165 changes in pollen counts and particulate air pollution all of which have the potential to be
166 mediated by available sunlight. We also note the approach recommended by Weinberg et al,
167 who demonstrated that if measures of social confounding are available, preferentially modeling
168 these instead of utilizing season as a surrogate is more analytically rational (12). As such our
169 primary logistic regression model did not include season of conception, but did include
170 sociodemographic variables including maternal age at birth (categorized as ≤ 18 , 19-29, 30-34,
171 35-39, ≥ 40 years of age), smoking in pregnancy (yes/no), parity and socioeconomic deprivation
172 (derived from Scottish Index of Multiple Deprivation (SIMD) Quintiles, allocated by postcode
173 (15). (model 1). We did include season of conception in an additional model (model 2)
174 recognizing the potential for over adjustment in this model. We defined season of conception
175 meteorologically with December-February as winter, March-May as spring, June-August as
176 summer and September-November as autumn.(15)

177

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

182

183 *Statistical Analysis*

184 For descriptive statistics of continuous variables, we used mean and standard deviation (sd)
185 for normally distributed data, and median and interquartile range (IQR) for non-parametric
186 data. Categorical data were presented as percentages with 95% confidence Intervals (CI). We
187 modelled odds ratios of preterm birth using logistic regression, before and after adjustment
188 for confounders. p values lower than 0.05 were taken to be statistically significant.

189

190 *Sensitivity analysis*

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

197

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

205

206 *Subgroup analysis*

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

209

210 All analyses were done with Stata (version 14).

211

212 **Results**

213

214 Between Jan 1, 2000, and Dec 31, 2010 there were 553 791 live singleton births recorded in
215 Scotland. Of these births, we excluded 81 417 (figure 1). The analysis cohort consisted of
216 472 374 births to 395 588 mothers. Of these births 32 958 (6.0%) were preterm. The
217 characteristics of the cohort are described in Table 1, stratified by quartile of available sun
218 exposure in trimester 1.

219

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

226

227 *Relationship between available sun exposure and preterm birth*

228 Available sun exposure in trimester 1 of pregnancy was inversely associated with preterm
229 birth in univariable and multivariable models with evidence of a dose dependent effect (Table
230 2). Compared to the lowest quartile of exposure, the highest quartile of exposure was
231 associated with a reduced odds ratio (OR) of preterm birth of 0.90 (95% Confidence Interval
232 (CI) 0.88 – 0.94 p <0.01) on univariable analysis with a small attenuation of effect size in the

233 adjusted models but a persistent significant dose dependent protective effect (model 1 OR
234 0.91 (95% CI 0.87, 0.93 p <0.01)) (Table 2). However, available sun exposure in trimester 2
235 was not associated with preterm birth OR 1.02 (OR 0.99, 95% CI 1.06 p 0.12). The average
236 trimester 1 and 2 exposure had a weakened but similar effect to the trimester 1 exposure,
237 confirming the persistence of the trimester 1 effect regardless of trimester 2 with the highest
238 quartile of exposure associated with a reduced OR of preterm birth of 0.95 (95% CI 0.92,
239 0.99 p0.01) and in the adjusted model 1 OR 0.96 (95% CI 0.93, 1.0 p0.04). The results were
240 unchanged controlling for within mother effects (Supplementary Table 2). Using linear
241 regression for gestational length, increasing available sun exposure was associated with
242 increasing gestational length with the highest exposure quartile of exposure β Coefficient
243 0.07 (95% CI 0.05-0.08 p<0.01) (Supplementary Table 3).

244

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

247

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

251

252

253 **Discussion**

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

258

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

273

274 As explored in our DAG (Supplementary Figure 1) sunlight availability is an environmental
275 exposure variable that is quite protected from confounding and measurement error bias as this
276 is unlikely to be introduced by satellite data. Our main potential confounder is season of
277 conception which represents a clustering of biological, social, behavioral and environmental
278 factors rather than a discrete entity. In methodological reproductive work, numbers of
279 conceptions and therefore births vary by season which may account for some of the observed
280 seasonal variation in gestational length - utilizing season of conception as we have done
281 rather than season of birth accommodates this (17, 18). Adjusting for measurable aspects of
282 'season' – such as markers of deprivation and behavior – reduces 'seasonal' variation in
283 preterm birth outcomes - in Weinburg's work in Norway (17), adjusting for season of

284 conception and maternal characteristics ameliorated seasonal variation in gestational length.
285 Curie (18) took a ‘within mothers’ sibling design approach to address seasonal variation in
286 birth outcomes – specifically gestational length and birth weight – and showed that even
287 adjusting within siblings, a May conception (or spring in the northern hemisphere) remained
288 associated with a shorter gestational length and hypothesized that this may be attributable to
289 seasonal influenza.

290

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

297

298 Season of conception has been previously associated with preterm birth and in a London
299 cohort winter birth was associated with a 10% increased risk of preterm birth (19) . However,
300 whether this observation was due to a biological pathway or due to potential methodological
301 limitations of the study is unclear. Weinberg (17) demonstrated that seasonal influences on
302 preterm birth are weakened by taking a ‘fetus at risk’ approach. This is because assessment of
303 preterm birth that does not include consideration of the population of fetuses at risk will bias
304 the data to appear as though more preterm births occur at a time when more women are
305 pregnant – ie a greater number of fetuses are at risk. Adjusting for season of conception
306 ameliorates this bias. Weinberg(17) also demonstrated that seasonal effects on preterm birth
307 are stronger in unplanned rather than planned conceptions. Unplanned pregnancy, smoking,
308 low levels of education and non-married status are risk factors for preterm birth and also bias

309 pregnancy dating by recalled last menstrual period (LMP). Weinberg (17) concluded that is
310 measures of social confounding are available, preferentially modeling these instead of
311 utilizing season as a surrogate is more analytically rational. We have followed this approach
312 within our study.

313

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

330

331 This large epidemiological study increases our understanding of the protective effect of early
332 pregnancy sunlight on gestational length in a high latitude country. As preterm birth remains
333 the leading contributor to neonatal death understanding environmental influences opens novel

334 research pathways to investigate strategies to reduce preterm birth and hence childhood
335 morbidity and mortality.

336

337 Conclusion:

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

344

345

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- 415

417 Captions

418 Figure 1: Inclusion and exclusion flow chart for study population

419

420

421