The seasonality of preterm birth in a British cohort: A time-series investigation

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Numerous Originals in Colour

ABSTRACT

Preterm birth is the leading cause of neonatal and infant mortality in developed countries. The risk of preterm birth has been reported to vary by season in several countries, including Japan and the USA. Discovering the reasons for such variations may contribute toward our understanding of preterm birth aetiology and enable the development of more effective interventions.

Using time-series data from the St Mary's Maternity Information System (SMMIS) from 1988 to 2000, I have been able to demonstrate that the probability of preterm birth varies by season in northwest London, Hertfordshire and Bedfordshire. The incidence of preterm birth was consistently higher during winters than during summers, with a 10% increase in risk of being born preterm in winter when compared with summer (RR 1.10, 95% CI 1.07 to 1.14). The seasonality appeared to be largely due to births that occurred later during the preterm period (i.e., 32 to less than 37 weeks of gestation) rather than earlier preterm births (i.e., 24 to less than 32 weeks of gestation).

My primary hypothesis was that this seasonal variation might be explained by climatic effects, including air pollution. I also investigated the possibility that infections, known to be a cause of some cases of preterm labour, might vary in a way that was associated with the risk of preterm birth. Regression techniques were used to investigate whether the seasonal variation in preterm births was explained by any short-term associations with various meteorological, air pollution or infection factors.

Other aspects of preterm birth, such as the type of clinical presentation and births necessitated by maternal pre-eclampsia were also investigated as potential mediators. Possible associations on the day of birth, cumulative effects from up to six weeks before birth and effects from exposure around the time of conception were investigated. To check for possible effect modification, each model was also stratified by maternal age, maternal ethnicity, sex of the fetus, gestational age of preterm birth, and parity.

The findings from the analysis of short-term associations confirmed the complexity of the pattern of preterm birth. While associations with some meteorological factors, influenza and PM_{10} were found, these did not appear to explain the seasonal pattern of preterm birth proportions that was observed. Nor was the seasonal pattern of pre-eclampsia or pregnancy-induced hypertension strong enough to explain more than a small proportion of the seasonal pattern of medically indicated preterm births. My findings did support, however, the theory that there are different causative mechanisms between early and late preterm birth. I also found that the seasonal patterns and associations varied between different ethnic groups.

My study has for the first time established a seasonality of preterm births in a British cohort and used a novel method for investigating and dissecting the multiple intersecting pathways that lead to preterm birth. In the current era, when climate change is widely predicted, it is important to study the impact this may have on our health. There is a need to develop methods to assess the potential impact of environmental factors on our well-being, and in particular, reproductive health. Further research related to understanding the mechanisms driving the seasonal pattern of preterm birth is warranted and could prove important in future efforts to prevent or reduce preterm birth and its related consequences.

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ABBREVIATIONS

BV	bacterial vaginosis
CI	confidence interval
g	grams
hrs	hours
IUGR	intrauterine growth restriction
mb	millibars
MeSH	medical subject heading
mm	millimetres
No	number
O_3	ozone
OR	odds ratio
PET	pre-eclampsia toxaemia
PIH	pregnancy induced hypertension
PM_{10}	particulate matter with a diameter of less than 10 micrometres
ppb	parts per billion
ROM	rupture of the membranes
RR	risk ratio
SMMIS	St Mary's Maternity Information System
UK	United Kingdom
WHO	World Health Organization

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INTRODUCTION

Preterm birth in developed countries remains one of the largest contributors to mortality in the neonatal period and infancy and morbidity in later life. Babies born between 32 to 36 weeks of gestation, which account for the majority of all preterm births, are still approximately three to 15 times more likely to die within the first year of life compared with babies born at term.[1]

Although much is known about the incidence and burden of preterm labour, the biological mechanisms of preterm birth are not well understood and as yet, the primary prevention of preterm birth is not possible. Indeed, it may be that rather than prevention, a reduction of preterm birth and amelioration of its consequences are more practicable approaches to the problems caused by preterm birth. An important step in reducing preterm birth and its consequences however, is likely to lie in furthering our understanding of the complex and often inter-related pathways that lead to preterm birth. One way in which this can be accomplished is to expand our knowledge of how environmental factors affect or interact with biological mechanisms that lead to preterm birth.

For example, it may be that a 'dose-response' relationship of exposure to an adverse environmental factor results in preterm birth or it may be that the effect results from cumulative exposure (to one or several factors) or the mechanism may involve both of these pathways. Differential adaptation by mothers from different ethnic groups may result in different responses to similar exposures, or an exposure may be associated with spontaneous but not medically indicated preterm births. Effects of environmental exposures may also be mediated through various biological pathways for births at different stages in the preterm period.

Seasonality is reported to exist for several reproductive outcomes in both developed and developing countries. It has been reported for term births, stillbirths, multiple births, ectopic pregnancies, mean birthweight and low birthweight.[2-8] A seasonality of preterm birth has been reported in Japan and the USA and several developing countries, but remains relatively unexplored.

Understanding preterm birth seasonality and what is driving it can provide important clues to the aetiology of preterm birth. Practically speaking, even if the potential mediators of preterm birth seasonality remain elusive, knowing in which seasons to expect more preterm births, or the months during which the risk of preterm birth is higher, has significant implications for planning the delivery of health care services and for the pregnant women themselves.

Prior to investigating the factors that drive preterm birth seasonality, it is obviously necessary to establish the existence of seasonality within a particular population. A conceptual framework of the potential mechanisms should also be constructed to guide any exploratory research. This will help to explain any findings within a consistent and plausible paradigm.

This research was essentially split into two components:

1. Establishing seasonal patterns
2. Establishing any short-term associations

The thesis is structured such that the reader may wish to proceed in one of two ways. Both suggested approaches begin with reading the Background and Research Hypothesis chapters (Chapters 1 and 2, respectively). The Background chapter discusses the importance of understanding preterm birth seasonality and presents the results of a systematic review on the seasonality of preterm birth which was conducted to help create the conceptual framework for this study. The chapter also reviews the complex and heterogeneous nature of preterm birth and demonstrates that consistent methodologies to assess short-term associations between various environmental factors and preterm birth are lacking. The chapter concludes with a discussion of the determinants of preterm birth in relation to seasonality.

Chapter 2 presents the research hypotheses and specific objectives as well as the conceptual framework on which this research was based. The study objectives are presented in the context of the assumptions on which the study was based namely, that births that occur earlier during the preterm period are the result of different mechanisms compared with births that occur later during the preterm period. Thus, any effect of meteorological factors on later preterm births would be as a 'trigger' to the early onset of the normal physiological process, whereas any effects on earlier preterm births would most likely be operating through pathological mechanisms. In addition, known determinants of preterm birth that demonstrate a seasonal pattern may be acting to contribute to the seasonality of preterm birth.

After Chapter 2, rather than reading the thesis straight through, readers who are less familiar with time-series and regression analysis methodologies may prefer to read the Methods chapter (Chapter 3) up to section 3.6.1 and then move directly to the first results chapter (Chapter 4) in which the seasonal pattern of preterm birth in this cohort is established. After Chapter 4, the reader should return to complete reading the Methods chapter before continuing on to the second and third Results chapters (Chapters 5 and 6, respectively).

For a person who is already familiar with modelling techniques, reading through the Methods chapter in its entirety before proceeding to the Results should be relatively straightforward. Beginning with a description of the study sample, the Methods chapter defines each of the exposure variables before describing the analysis used to determine seasonality and assess any short-term associations.

The second Results chapter (Chapter 5) examines any short-term associations with the various meteorological, air pollution, and infection exposure variables that might explain the seasonal pattern observed. The chapter includes a sensitivity analysis based on births that occurred in the hospitals located closest to the monitoring stations.

In the third Results chapter (Chapter 6), an alternative approach to the analysis is presented. Using fetuses-at-risk as the denominator, the results were compared with results from the analyses that were conducted using preterm birth proportions (using the total number of daily births as the denominator). This chapter also covers a separate analysis of preterm births based on clinical presentation and investigates the seasonality of pregnancy-related hypertensive disorders.

The final chapter (Chapter 7) begins by summarising the main findings from this study and placing them in the context of previously published work. Possible biological mechanisms are explored before the strengths and limitations of the study are discussed. The chapter concludes with a discussion on the implications and future directions of this research.

The ultimate goal of this research was to determine whether any pattern of preterm birth seasonality existed in Britain, and if so, to determine what potentially causative factors might be associated with this pattern.

1. BACKGROUND

An understanding of the antecedent factors associated with preterm birth is valuable for its prediction and may provide vital clues to its aetiology. This chapter discusses the importance of establishing whether or not a seasonality of preterm births exists in the UK and presents the results of a systematic review on the seasonality of preterm birth. The second part of this chapter considers the determinants of preterm birth in relation to seasonality.

1.1 Defining preterm birth

Preterm birth occurs in about 5-7% of all live births in the majority of developed countries,[9 10] the most notable exception being the United States, where it accounts for about 12% of all births.[11] It is defined by the World Health Organization (WHO) as any delivery, regardless of birthweight, that occurs before 37 completed weeks (<259 days) from the first day of the last menstrual period.[12] A gestation of less than 24 weeks is commonly accepted as the lower limit for viability; births at gestations less than this are generally classified as miscarriages or stillbirths rather than preterm births.[a] [13] There are, of course, anomalous cases where babies are born alive at 23 weeks of gestation or younger and are subsequently classified as a neonatal death or survive into adulthood. Although the routine collection of gestational age data for live births does not occur at a national level in the United Kingdom (UK) or England,[9 14] estimates derived from local rates place the overall preterm birth rate at about 7%.[15] This means that approximately 45,600 babies are born preterm each year in England and Wales.[b]

It is important to distinguish between preterm birth and low birthweight. Historically, the term 'premature' was used to define, for the purposes of vital statistics, babies who were born weighing 2,500g or less.[16] It is now recognised that a baby may be born with low birthweight (currently defined as birthweight less than 2,500g) because it was born too early, its growth was restricted *in*

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[a] The law in England and Wales (Section 41 of the Births and Deaths Registration Act 1953) was amended by the Stillbirth Definition Act in 1992.
[b] Calculated from the average number of live births occurring in England and Wales from 1988 to 2003 as reported by the Office for National Statistics, Historical Series FM1, Vol No's 13, 18, 28, 29, and 30-32.

utero, or a combination of both.[17] Subsequently, the term 'premature' has been replaced with the terms 'low birthweight' and 'preterm'.[18]

Furthermore, while many low birthweight infants may be preterm, not all preterm births result in low birthweight. It has been reported that more than 60% of preterm infants may weigh 2,500g or more.[19] Approximately two thirds of babies born weighing less than 2,500g are also preterm[9] and compared with full term low birthweight babies, preterm low birthweight babies are at greater risk of morbidity, mortality and disability.[20 21] In general, the risk of neonatal mortality and morbidity is inversely proportional to gestational age.[22 23 24]

It has been advocated that perinatal health assessment may be improved by replacing the use of low birthweight, where possible, by measures that differentiate between the distinct processes of preterm birth and restricted fetal growth.[25] Although babies may be born both preterm and growth restricted,[26] many studies have demonstrated that the risk factors associated with intrauterine growth restriction (IUGR) may differ from those associated with preterm birth.[17 27 28 29 30] These findings provide justification for considering preterm birth and IUGR as separate outcomes.

1.2 Consequences of preterm birth

Preterm birth in developed countries is one of the largest contributors to mortality in infancy and morbidity in later life. In Britain, for example, preterm birth accounts for up to 85% of neonatal mortality among normally formed infants.[31 32 33] In the past 20 years however, there has been a consistent upward trend in the survival of preterm infants and more than 90% of babies born after 30 weeks of gestation can now be expected to survive.[32 34] Despite these encouraging statistics, babies born between 32 to 36 weeks of gestation, who account for the majority of all preterm births, are still approximately three to 15 times more likely to die within the first year of life compared with babies born at term.[1] Preterm births have also been reported to be on the increase in countries such as the United States and Canada.[35 36 37]

In addition, complications associated with preterm birth survival remain a significant problem. Even a relatively small increase in the risk of morbidity at the higher preterm gestations may have a substantial impact on the attributable risk of morbidity (i.e., the risk of morbidity that can be attributed to being born preterm) because of the large numbers of babies affected. In a review of outcomes among surviving preterm infants, 20% to 50% were found to have at least one major disability, including impaired mental development, cerebral palsy, blindness, or deafness.[38] Studies also indicate possible long-term sequelae from being born preterm. These included lower educational achievement, decreased motor and cognitive functioning and increased behavioural disorders, such as attention-deficit/hyperactivity disorder, when compared with children who were born at term.[39 40 41 42 43 44 45]

Although much is known about the incidence and burden of preterm labour, the biological mechanisms of preterm birth are not well understood. Many modifiable risk factors have been identified, but interventions directed toward these risk factors have not been effective in the prevention or reduction of preterm birth. Most preterm births continue to occur without any known cause.[30 19] Unsuccessful efforts to reduce the incidence of preterm birth have included, but are not limited to, risk factor assessment to identify women at high risk for preterm birth,[46] bed rest,[47 48] uterine activity monitoring,[49] tocolysis[50] and treatment of vaginal infections.[51 52 53] Risk factor assessment has proved to have limited sensitivity and specificity for the prediction of preterm birth, however, ultrasonography for measuring cervical length and fetal fibronectin testing have had better (although still limited) success predicting preterm birth and in identifying women at high risk for preterm birth.[54 55 56 57 58]

1.3 The importance of seasonal variation

Biometeorology is the science of atmospheric phenomena such as climate, seasons, and weather and their effects on living organisms.[59] 'Climate' refers to the regular pattern of weather conditions of a particular place.[60] A 'season' can be defined as a part of the year that is distinguished by its type of particular weather.[60] 'Weather' is defined as the condition of the atmosphere at a certain place and time with reference to meteorological factors such as temperature, presence of rain, and sunshine.[60] Thus, the climate dictates the seasons of a particular geographic region and the weather determines both the climate and season.

Seasonality is reported to exist for several reproductive outcomes in both developed and developing countries including term births, stillbirths, multiple births, ectopic pregnancies, birthweight and low birthweight.[2-8] The seasonality of preterm birth has been reported, but remains relatively unexplored. An investigation of preterm birth seasonality can answer the following important questions:

- Are there seasons or months when more preterm births occur?
- Are there seasons or months when the risk of preterm birth is greater or less than others?

The answers to these questions have the potential to facilitate the effective delivery of health care services and assist carers of pregnant women in the assessment of an individual's risk of preterm birth. Following on from an investigation of seasonality, an exploration of factors that might be driving the seasonality can contribute toward understanding the aetiology of preterm birth.

The following studies conducted in the Gambia illustrate how seasonal patterns in a reproductive outcome (in this case, birthweight) may be explained through associations with seasonally changing factors. In the Gambia, food stores are depleted each wet season which extends from June to October. It was suggested that the decrease in average birthweight observed in babies born during the wet season was associated with nutritionally deficient maternal diets which were the result of the depleted food stores that occurred during this time each year.[61] Subsequently, a randomised controlled trial of supplementation during pregnancy compared with supplementation after pregnancy found that antenatal supplementation was effective in increasing birthweight.[62] The seasonal pattern of birthweight among babies born to women who received the supplementation during pregnancy was dramatically altered, with average birthweight found to be still increasing in June, whereas formerly, before supplementation, a sharp decrease had been observed. Furthermore, a study of mortality in the Gambia found that babies born during the wet season are 10 times more likely to die prematurely in young adulthood than babies who are born in the dry season.[63] These studies demonstrate not only the importance of seasonal influences and the profound impact they can have but also the value of investigating seasonal patterns of reproductive outcomes as this knowledge can effectively inform successful interventions.

As an indication that a seasonal pattern of preterm birth may exist in developed countries, various studies have demonstrated seasonal patterns of the duration of gestation. In Sweden, a study using data from the Swedish Birth Registry analysed all births between 20 and 48 weeks gestation together (including stillbirths past 28 weeks, early neonatal deaths and congenital abnormalities, n=427,581), found that the average duration of pregnancy exhibited a yearly seasonal pattern.[64] Over a five year period (1976 to 1980), the mean gestational age was 281 days with a consistent shortening in winter (December) and lengthening of gestational duration in summer (August). The differences in mean gestational duration from December to August ranged from 0.5 to 1.5 days over the study period. Below the age of 35, parous women had slightly shorter gestations than nulliparous women (up to 0.6 days difference) and women who were 35 years or older tended to have, on average, gestational durations 2 days shorter than those who were younger.

Another study on the seasonal pattern of mean gestational age was conducted in Japan.[65 66] Using vital statistics data from 1974 to 1983 (n=7,675,006 live singleton births; no restriction on an upper or lower limit of gestational age for inclusion was specified) and time series analysis to calculate seasonal indexes, this population exhibited its shortest mean gestational periods in the winter (December- January) like the mothers in the Swedish study. However, the longest gestational periods were observed in autumn (October), not in summer (August) as for the Swedish population. Further geographic analysis revealed that the amplitude for seasonal variation appeared to be more pronounced in the northern areas compared with the southern areas.

In Finland during the 1950s, a study that used data from all Finnish maternity hospitals (1957 to 1958) combined with data from a university maternity centre (1951 to 1960) found that a higher proportion of prolonged gestations (41+ weeks) occurred during the months with the highest amount of sunshine (May to October) compared with the darker part of the year (November to April).[67] When stratified by region (south, east and north Finland), this trend was only significant in the southern part of the country, where, interestingly, the day/night differences are *less* accentuated than in the north.

These studies support the existence of a seasonal pattern of gestational duration and as preterm birth is defined by gestational duration, it follows that preterm birth may also exhibit seasonal variation. The identification of a seasonal pattern of preterm birth may disclose important information and help to clarify markers that predict preterm birth.

As each of these three studies included preterm births in their analysis, it is possible that an underlying seasonal pattern of preterm birth contributed to the seasonal variation observed in gestational age. As with the lack of nutrition and its effect on birthweight in the Gambian study, it is possible that the meteorological factors of a particular season are associated with a risk factor for preterm birth, which subsequently contributes to a seasonal pattern of preterm birth. Alternatively, specific meteorological conditions, or changes in meteorological conditions, may trigger an early onset of parturition. A systematic literature review was conducted to discover whether previous seasonality of preterm birth had been reported and if so, what factors have been investigated or put forth to explain it.

1.4 Seasonality of preterm birth: Systematic literature review

In accordance with guidance from the UK National Health Service Centre for Reviews and Dissemination,[68] on which the methods of this review were based, efforts were made to locate any existing reviews on preterm birth seasonality by searching the Medline, Embase and Cochrane Library databases. None were found. Therefore, a systematic review of published literature in peer-reviewed journals was performed on the Medline, Popline, and Embase databases in May 2002. The review was updated in May 2005. The purpose of the systematic literature review was twofold. The first purpose was to answer the question: Does a seasonality of preterm birth exist? If so, in what countries has it been documented and what pattern(s) have been observed? The second purpose was dependent upon the existence of preterm birth seasonality. If any studies on the seasonality of preterm birth were located, the hypotheses that were suggested to explain the seasonal patterns (or lack thereof) were used to aid in the development of a conceptual framework for this study.

The review was restricted to studies that defined preterm birth by length of gestation (rather than by birthweight). Free text terms with wild cards and related medical subject headings (MeSH) established by each database were used. Keywords and phrases were categorised into two groups (Table 1.1). Terms within each group were combined using the '*or*' operator to remove any duplicates before combining both groups using the '*and*' operator to locate any relevant articles. All MeSH terms were exploded with all subheadings.

Table 1.1: Search strategy for systematic literature review.

Group 1: Preterm birth	**Group 2: Seasonality**
Free text terms	*Free text terms*
prematur*	climat*
gestation*	season*
pre?term	weather*
MeSH terms	*MeSH terms*
gestational age/	climate/
Infant, Premature/	Seasons/
Labor, Premature/	Weather/
	time factors/

Studies from developed and developing countries were included. Studies were excluded if they did not meet the following criteria:

- Report proportions or probabilities of preterm birth or gestational age data from which proportions or the risk of preterm could be calculated, by defined periods of time (e.g., by months or 'seasons')

- Span a study period of at least one year or compare data from different seasons within a year
- Be written in English

The relationship between preterm birth and low birthweight is complex because although they are separate outcomes, the processes are not mutually exclusive. It is not uncommon for authors to continue to use these terms interchangeably or for studies to use low birthweight as a proxy for preterm birth. Therefore, supplementary searches using the MeSH terms, *Infant-Very-Low-Birth-Weight* and *Infant-Low-Birth-Weight*, were also conducted to ensure that no preterm birth studies were inadvertently missed.

To maximise the chances of identifying all published studies on the seasonality of preterm birth, the references of included studies were examined to locate further articles that may have been missed, and the subject headings of all articles included in the review were scrutinised to determine if the search strategy required modification.

The initial search that was conducted in May 2002 returned 1569 citations, of which 141 full references were retrieved in order to more fully assess compliance with the inclusion criteria. Six articles fulfilled the criteria and were included in the review.[69-74] Using the same search strategy, the databases were searched again in May 2005, including any articles published in peer-reviewed journals since 2001. A further two articles[75 76] were included from 2,610 identified in the updated search. Both were from studies conducted in developing countries.

In total, the review incorporated seven studies, published in eight papers. Three of the studies were from developing countries (1 from Bangladesh, 1 from Zimbabwe, and 1 from the Gambia) and four were from developed countries (3 from the USA, 1 from Japan).

Using standard appraisal questions,[77] criteria were established a priori for assessing the quality of each study that met the inclusion criteria. To this end, specific information extracted for each study included information on research design, the study population, and the definitions of preterm birth and seasonality that were provided (Table 1.2). Although two of the articles were from the same study group and used the same data set for analysis,[69 70] both articles were included because the different aspects of preterm birth seasonality that were addressed were deemed as relevant to this research.

Table 1.2: Summary of studies found for the systematic review on the seasonality of preterm birth.

Study	Study design	Population	Methods	Outcomes	Results	Comments
Matsuda S, Kahyo H., 1992[69]	Cross-sectional; Secondary data analysis	All live, singleton infants born in Japan (n=7,665,006) from 1979 to 1983	Time-series analysis with proportions of preterm births by month Seasonal index calculated by dividing observed monthly frequency by corresponding yearly average Seasons: Spring (Mar-May); summer (Jun-Aug); autumn (Sep-Nov); winter (Dec-Feb) **Preterm birth defined as less than 37 weeks gestation as reported on vital statistic records**	Plots of time-series over 5 years for proportion of preterm births Seasonal indices of proportion of preterm births, stratified by parity and sex	Proportion of preterm births showed upward trend over 5 years Male primips: peaks in Jun and Dec, troughs in Mar and Sep/Oct Female primips: peaks in Jul and Dec/Jan, troughs in Mar and Oct Male multips: peaks in Aug and Dec, troughs in May and Oct Female multips: peaks in Aug and Dec/Jan, troughs in May and Oct	In discussion, suggest length of gestation may be governed by climatic factors i.e., onset of labour may be the result of direct or indirect factors which trigger a physiological response. Also suggest that risk factors associated with preterm births may be seasonal and this may govern part of seasonal periodicity in pt births
Matsuda S, Kahyo H., 1998[70]	Cross-sectional; Secondary data analysis	All live singleton infants born in Japan (n=7,665,006) from 1979 to 1983	Box-Jenkins analysis (ARIMA model) with proportions of preterm births applied for each of 47 prefectures Specifies only that regional differences in climate vary considerably from subarctic to tropical zones (latitude: 45 degrees N to 25 degrees N)	Plots of time-series over 5 years for proportion of preterm births in each prefecture Correlation between occurrence of preterm birth and mean summer (Jun to Aug) and	Winter peak dominant in northern prefectures; summer peak dominant in southern prefectures Average seasonal index of winter preterm birth negatively correlated with mean winter temp (r= -0.424, p<0.01); average seasonal index of summer preterm births was positively correlated with mean summer temperature (r=0.543, p=<0.01)	No stratification by sex or parity as previous analysis showed no differences Authors suggest that climate-related factors as associated with occurrence of preterm birth

Study	Study design	Population	Methods	Outcomes	Results	Comments
			Seasonal index calculated by dividing observed monthly frequency by corresponding yearly average **Preterm birth defined as less than 37 weeks gestation as reported on vital statistic records**	winter (Dec to Feb) temperature of each prefecture		
Keller CA, Nugent RP., 1983[72]	Cross-sectional; Secondary data analysis	N= 402,540 singleton births of white residents from 1967-1973 in Minnesota, USA	To avoid possible bias produced by season of conception of seasonal pattern of births, probability of various events among those (estimated) to be at risk were calculated. Number of pregnancies at risk was considered to be the total number of babies born each month for each gestational age band over the corresponding number of fetuses *in utero* each month **Preterm birth defined as live or stillbirth at 29-37 weeks gestation, as reported on birth certificates**	Probability of preterm birth by month per 1000 fetuses at risk	All pregnancy outcomes for each gestational group showed same seasonal pattern ie, seasonal pattern not likely to be due to factors present during season of conception, but rather to factors related to season of delivery. Seasonal pattern for each year over the 7 years was similar. Peak for probability of a preterm birth around Aug (approx 59.8 preterm births per 1000) and Dec-Jan (approx 58.7 preterm births per 1000) Low periods (troughs) in spring (April, approx 55.5 per 1000) and fall (Oct, 57.2 per 1000). Total spread from peak to trough reported to be 8%.	Artifactual, biologic and meteorlogic influences discussed to explain seasonal pattern. Artifactual: seasonal pattern of conception (an effect which the author's analysis by fetuses-at-risk accounts for). Biologic: seasonal association found in study was independent of month of birth by parity, maternal age, edu status, and legitimacy. Strongest suggestion is for seasonal pattern of genital infections and pregnancy outcomes

Study	Study design	Population	Methods	Outcomes	Results	Comments
Cooperstock M, Wolfe RA., 1986[71]	Cross-sectional; secondary data analysis	n= 928 live, preterm and n=3651 term births from 1959 to 1966 at 12 universities in northern USA (i.e, Oregon, Minnesota, Pennsylvania, New York, Massachusetts, Rhode Island) and southern (i.e., Maryland, Virginia, Tennessee and Louisiana)	Term births were at 40 weeks of gestation Pregnancies 'at risk' for preterm birth each month derived from number of 40 wk gestations that were in utero at 27th to 35th weeks on the middle day of each month in order to adjust preterm rates for normal seasonal variation in fertility The number of preterm births each month was divided by the mean number of preterm births/month **Preterm birth defined as live born between 27 to 35 weeks of gestation as calculated from menstrual dates**	Yearly variation of preterm birth overall and then stratified by maternal age, socioeconomic index, geographic location, marital status, and race (white vs. black)	Peak in September (144%) and trough in May (64%) for preterm births (adjusted for seasonal variation in fertility) Differences in demographic strata found: single vs. married, $\chi^2 = 6.8$, 2df, p = 0.03 and socioeconomic status $\chi^2 = 13.9$, 6df, p=0.03 When stratified, those less than 22 years old, those with socio economic status less than index =3.6, those living in southern states and those not married did not display a seasonal trend for preterm birth	In discussion, suggest that seasonal co-factors such as infection, allergens, endocrinologic phenomena, environmental toxins, nutritional parameters, and sexual activity influence patterns of preterm birth. Also suggest that modes of preterm birth onset, such as preterm labour, pPROM, chorioamnionitis, or bleeding may be selectively induced by seasonal events.
Konte JM, Creasy RK, Laros RL, 1988[73]	Cross-sectional	All women who delivered from May 1983 to June 1985 from 4 counties in northern California, USA recruited between 21 to24 weeks gestation (n=9296)	Preterm birth proportions for each May to October period and for each November to April period compared **Preterm birth defined as occurring between 140-259 days gestation as a result of spontaneous preterm labour or spontaneous**	Spontaneous preterm birth proportions for different parts of the year	No difference in spontaneous preterm birth proportions between May to October when compared with April to November	This analysis was conducted in the discussion section of the paper and no numbers from the comparison were provided. The number of births was lower in all Nov to Apr periods.

Study	Study design	Population	Methods	Outcomes	Results	Comments
			rupture of the membranes, except when delivery was indicated for maternal or fetal reasons unrelated to preterm labour or preterm labour treatment			
Hort KP, 1987[74]	Cross-sectional	All live singleton babies born in 1983 or 1984 at a rural hospital in Bangladesh (n=1772)	Gestational age of babies below 2kg assessed within first two days by Dubowitz method Year divided into four seasons: Winter (Dec-Feb), Summer (Mar-May), Monsoon (Jun – Aug), Autumn (Sep- Nov) **Preterm birth defined as <35 weeks of gestation**	Percent of preterm births (from among total births) during each season	Winter: 3.6% Summer: 5.5% Monsoon: 6.0% Autumn: 8.3%	This study assessed gestational age in babies that were below 2000g only. This is likely to underestimate the percentages of preterm births. The authors also mention that most births in this area still occur in the villages and only women who can come to the hospital or those with complicated pregnancies are likely to deliver in hospital.
Rayco-Solon P, Fulford AJ, Prentice AM, 2005[76]	Cross-sectional; secondary data analysis	All live births with gestational age and birthweight data not missing from 3 villages in the Gambia (n=1916) from 1976 to 2003	Seasonality of preterm birth proportions by month Fourier terms used to control for seasonality of birth and preterm birth by month Annual rainy season from July to November **Preterm birth defined as <37 weeks of gestation as assessed**	Plot of monthly preterm birth proportions Logistic regression to assess dependence on seasonality of births	Proportion of preterm births showed an annual pattern with two peaks (July and October) Likelihood ratio χ^2 = 20.07, 6df, p = 0.003 for dependence on season of birth	Authors suggest seasonality of external environmental risk factors associated with preterm birth as potential precipitating factors for the seasonality of preterm birth

Study	Study design	Population	Methods	Outcomes	Results	Comments
			by the Dubowitz scoring system			
Friis H, Gomo E, Nyazema N, Ndhlovu P, Krarup H, Kaestel P, Fleisher-Michaelson K, 2004[75]	Cross-sectional; secondary analysis of RCT data on micronutrient supplementation	Women between 22 and 36 weeks of gestation registering fro antenatal care at a maternity hospital in Harare, Zimbabwe from 1996 to 1997 who agreed to be included in the RCT (n=1106)	Harare has a tropical climate with four seasons: early dry (June to August), late dry (September to November), early rainy (December to February) and late rainy (March to May) Logistic regression analysis **Preterm birth defined as <37 weeks of gestation as measured from first day of last menstruation or by fundus height**	Effects of season of birth on gestational length (late rainy season used as reference group)	Odds ratios (OR): • **Early dry: OR 2.9, 95% CI 1.65 to 5.2** • Late dry: OR 0.94, 95% CI 0.51 to 1.72 • Early rainy: OR 1.38, 95% CI 0.75 to 2.52	Authors only discussed potential predictors of gestational length in general terms, not specifically in relation to preterm birth

The two articles from the same group of researchers were based on a cross-sectional, retrospective study conducted in Japan of all live births from 1979 to 1983 (n=7,665,006).[69 70] Length of gestation was described on vital statistic records in one week intervals. Using time-series analysis, yearly patterns in the monthly proportion of preterm births (less than 37 weeks gestation) was calculated and stratified initially by parity (first birth vs subsequent births) and also by infant gender.[69] The same months from each year over the study period were combined for the analysis so that results were presented over one 12 month period.

The authors reported that spring in Japan occurs from March to May, summer from June to August, autumn from September to November and winter from December to February. In addition, a rainy season, which lasts from June to July, precedes a typhoon season which affects the south western part of the country from August to October.

Among first births, the proportion of preterm births was highest in winter (December to January) and again in summer for both boys (June) and girls (July). The preterm birth proportions were lowest in spring (March) and autumn (September to October) for both boys and girls. Similar to first births, there was a higher proportion of preterm births among subsequent births in winter (December to January) and again in summer, although slightly later than for first births (August for both male and female babies).

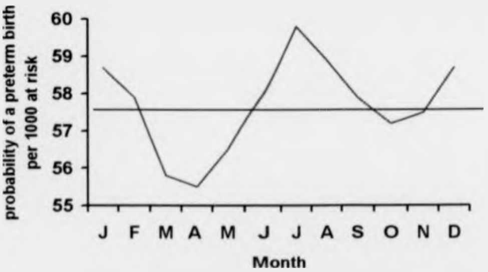
In the discussion, in order to explain the observed yearly pattern, the authors suggested that the onset of labour may be governed by climatic factors that directly or indirectly 'trigger' a physiological response in pregnant women (e.g., temperature, day length, barometric pressure, etc). The authors also suggested that risk factors associated with preterm birth may exhibit seasonal patterns and that this may contribute to a seasonal pattern of preterm births. The authors concluded that the increase in preterm births seen in the winter was due to different causes than the increase observed in the summer because when examined for skewness and kurtosis, the distributions of gestational age differed between the two seasons.

In the second Japanese article, Matsuda & Kahyo examined the geographic differences in the yearly pattern of preterm births and evaluated the association with temperature.[70] The yearly pattern of preterm birth was analysed by time-series separately for each of the 47 prefectures that stretch north to south for 3000 km on the islands that comprise Japan. They found that the winter peak (December to January), reported earlier for all of Japan,[69] dominated in the northern prefectures and that the summer peak (June and July) dominated in the southern prefectures, suggesting a possible association between the seasonal patterns and latitude.

In a multiple regression analysis, mean winter temperature was found to be negatively correlated with the mean winter proportion of preterm births ($p<0.01$) and mean summer temperature was found to be positively associated with the mean summer proportion of preterm births. This association remained after controlling for health and socio-economic variables (average maternal age, subsequent/first birth ratio, infant mortality rate, total fertility rate, population density, per capita income per prefecture, and number of hospital beds and doctors per 100,000 inhabitants). A possible explanation for this finding is that the risk for preterm birth increases whenever the temperature deviates from an 'optimum' range (likely to be between 15 to 25 °C); thus both very cold and very hot weather may act as a stressor on the mother (stress is generally acknowledged to increase the risk of preterm birth[78 79 80 81]). As before, the authors concluded that climate-associated factors may be related to the occurrence of preterm birth and that the factors were most likely different between summers and winters.

Two studies from the United States also analysed secondary data to establish a yearly pattern of preterm delivery.[71 72] For the majority of the United States, spring occurs from March to May, summer from June to August, autumn from September to November and winter from December to February. In the first study, which was cross-sectional, Keller and Nugent used gestational age from birth records to calculate probabilities from 402,540 singleton live and stillbirths in Minnesota from 1967 to 1973.[72] Probabilities were differentiated from proportions by using the total number of fetuses *in utero* at risk rather than the total number of births in a given month as the denominator. As in the Japanese study, the same months for each year were combined and results were presented as an average for each month of the year. Gestational groups (29 to 33, 34 to 37, 38 to 42, and 43+ weeks) were assessed separately but as two of the groups showed the same pattern (29 to 33 and 34 to 37 weeks), they were combined (29 to 37 weeks) for the rest of the analysis. The highest probabilities were seen in winter and summer and the lowest in spring and autumn (Figure 1.1).[c] The authors suggested that the similar seasonal pattern observed across the various gestational age groups indicated that the observed pattern was most likely due to factors present at the time of birth rather than factors present at conception.

Figure 1.1: Probability of a preterm birth among white singleton deliveries in Minnesota from 1967 to 1973. Probability was highest in winter and summer months (July and August: 59.8 preterm births per 1000 pregnancies at risk; December and January: 58.7 preterm births per 1000 pregnancies at risk) and lowest in spring and autumn (April: 55.5 preterm births per 1000 deliveries; October: 57.2 preterm births per 1000 deliveries).



In the discussion, the authors examined artifactual, biological and meteorological influences as possible etiologic factors. Artifactual effects, such as influence due to yearly variation in conception rates, were argued to have been eliminated as the methods used in the analysis looked at probabilities, rather than proportions, of preterm births. The authors referred to month of birth by parity, maternal age, educational status and legitimacy in the Minnesota population as 'biological influences' and stratified analysis by these factors demonstrated no consistent differences. Therefore, any factor contributing to

[c] Taken from Keller CA, Nugent RP. Seasonal patterns in perinatal mortality and preterm delivery. Am J Epidemiol 1983;118(5):689-98

the yearly probability of preterm birth was suggested to do so independently of its relationship to these risk factors. However, the authors did not specify how these variables were analysed (i.e., strata were not defined) or which differences were investigated. Temperature, sunlight and moisture are mentioned in the context of yearly variation in human endocrine function, but no data were available to relate cyclic hormonal variation to adverse reproductive outcomes. The authors concluded that the yearly rise and fall of preterm birth risk was consistent with an infectious disease aetiology, specifically genital infections. This is because some genital infections have been related to an increased risk of preterm birth and have also been shown to have a seasonal distribution.

In the second US study, using data from the Collaborative Perinatal Project, Cooperstock and Wolfe analysed the seasonality of all live preterm births (n=928) from 56,000 pregnant women from 12 universities in 10 different states from 1959 to 1966.[71] Preterm birth was defined as birth between 27 and 35 weeks of gestation. An additional 3,651 term births were used to adjust for seasonal variation in fertility. For each month, the number of preterm births was divided by the mean number of preterm births each month. Using this fraction, preterm births were found to vary from 64% in spring (May trough) to 144% in autumn (September peak). A smaller peak was also seen in winter (January) at about 109%. The data were stratified by five demographic variables, maternal age, socioeconomic status and geographic location, marital status, and age to examine their influence on the yearly pattern of preterm birth. Maternal age greater than 21 years, higher socioeconomic status, married women and women living in the northern areas of the country showed seasonal patterns of preterm birth but younger women, women from lower socioeconomic status, unmarried women and women who lived in southern states did not.

In another American study, preterm birth rates from May to October were compared with rates from November to April for 1983 to 1985 in a northern Californian population.[73] The data were collected as part of an intervention project which attempted to identify women at high-risk for preterm birth and thereby target the use of tocolytic therapy. Preterm birth was defined as occurring between 140 to 259 days (i.e., 20 to 37 weeks). The study did not include indicated or iatrogenic preterm births and unlike the previous four studies cited in this review, no seasonal variation was demonstrated in the spontaneous preterm birth proportions between these two periods. Because it is a coastal state, California is an area of the United States that experiences anomalous climatic patterns. In particular, in the San Francisco Bay area where this study was conducted, the climate is mild all year round with an average temperature of 11 degrees Celsius in January rising to about 20 degrees in July. There is virtually no rain from June to the end of September. The comparison between the two periods covered a large span of time. This may have resulted in any seasonal patterns being masked or undetected.

The exclusion of indicated or iatrogenic preterm births may also have had an impact on the lack of pattern observed. The previous four studies did not mention exclusion of medically indicated preterm births when reporting a seasonality of preterm birth. The proportion of preterm births that are medically indicated is high and rising,[82 83] and a seasonality of medically indicated preterm births may be subject to different mechanisms than spontaneous preterm births.

Among developing countries, if a relationship between preterm birth and seasonality exists, it is likely to be due to factors different from those that operate in developed countries. For example, seasonal patterns in nutritional status and maternal weight loss have been implicated as factors responsible for the seasonal pattern of low birthweight in developing countries.[84 85] These factors, however, are unlikely to play a large role in developed countries where seasonal food shortages are no longer prevalent and overall nutrition is generally good but where seasonality of low birthweight still exists.

This systematic review found three developing countries in which a seasonal pattern of preterm birth was reported. In the first study, all live, singleton births in a rural hospital in Bangladesh in 1984 were included.[74] Although any birth that occurred at less than 35 weeks of gestation was defined as preterm, mothers in this study could rarely offer accurate information on gestational duration and only babies who weighed less than 2.0kg were assessed for gestational age. Gestational age was assessed using the Dubowitz method (external characteristic assessment of the newborn) within 2 days after birth. Four seasons were defined: winter (December to February), summer (March to May), monsoon (June to August), and autumn (September to November). The total number of births each season was used as the denominator and the lowest proportion of preterm births occurred during winter (3.6%), followed by summer (5.5%) and the monsoon season (6.0%). The highest proportion of preterm births was observed in autumn (8.3%). The authors did not discuss possible factors responsible for the seasonal variation in preterm births observed.

Another study was conducted in The Gambia and consisted of all live births in three villages from 1976 to 2003.[76] Preterm births were defined as occurring before 37 weeks of gestation as assessed by the Dubowitz scoring system. The annual pattern was that preterm birth proportions were highest twice a year: in July and again in October. The rainy, or 'hungry', season in The Gambia extends from July to November each year. Using logistic regression, the authors demonstrated that the seasonality of preterm births was dependent on the season of birth, and suggested that mechanisms related to the seasonality of risk factors for preterm birth might explain the seasonality of preterm birth proportions (e.g, malarial infections in pregnant women).

In the final study that was located in this systematic review, data from a randomised controlled trial (RCT) on micronutrient supplementation conducted in Harare, Zimbabwe, was analysed for predictors of gestational duration.[75] Harare was reported to experience four seasons which were defined as early dry (June to August), late dry (September to November), early rainy (December to February) and late rainy (March to May). Preterm birth was defined as occurring before 37 weeks of gestation as calculated from the first day of the last menstrual cycle or estimated by fundal height prior to delivery. Although the annual pattern of preterm birth seasonality was not reported, the risk of preterm birth was found to vary by seasons. Using the late rainy season as the referent group, births in the early dry season were three times more likely to be preterm (Odds ratio 2.9, 95% confidence interval 1.65 to 5.2). The authors did not extend the discussion beyond potential explanations of determinants of shorter gestation generally, and did not speculate on possible seasonal mechanisms for an increased risk of preterm birth.

In the American studies that reported a seasonal pattern, the highest incidence of preterm births was observed in the late summer months (July- September). In Japan, a higher proportion of preterm births was also observed in the summer months (June-August). In both Japan and the USA, the seasonality of preterm birth proportions demonstrated a bimodal annual pattern with two peaks each year. All three studies from developing countries reported a seasonal pattern of preterm births, using their own definitions of seasons. Only one study, conducted in the USA, reported no seasonal variation in preterm births. Conflicting or slightly varying results are most likely related to geographical, cultural and socio-economic differences between the populations studied.

Overall there were five countries in which a seasonal pattern of preterm birth was reported. This is a small number compared with the number of reports on the seasonality of birthweight or low birthweight. It is possible that the seasonality of preterm births has been investigated elsewhere, but no seasonality was found and therefore the results were not subsequently published. Studies have shown that publication is indeed affected by the study outcome and that studies with significant results are more likely to be published.[86 87 88] Publication bias is of concern in this systematic review. The only study reporting no seasonality that was located was a study that mentioned this result in its discussion section only.[73] This may be because studies that have not found a seasonal pattern are less likely to be published or are published under a different heading, as was the case with the study mentioned above (which was published as a preterm birth prevention project).

Another limitation of this systematic review was that it only considered studies that were written in English. Previous studies have identified drawbacks and potential bias due to excluding studies written in other languages.[89 90] For example, one study found that in German speaking countries, the results of clinical trials were more likely to be published in English language journals if the results were significant and in German language journals if the results were not significant.[89] On the other hand, a more recent study reported that while examining only a portion of the evidence available may introduce bias, that in fact, language restricted systematic reviews did not result in biased findings.[91]

The results of this systematic review suggest that a seasonality of preterm births does exist and that in developed countries, the pattern is annual with the highest proportions occurring twice a year: once in summer and again in winter. One reason that only relatively few reports of preterm seasonality exist in the literature (compared with low birthweight) may be because of the complex and poorly understood aetiology of preterm birth. The results of the studies support the likelihood that numerous factors are contributing to the seasonality of preterm birth. The aims of this study were to establish the seasonal pattern of preterm birth proportions in a British cohort and to assess whether the effect of various external environmental variables could explain any seasonal patterns observed. Two hypotheses suggested by the above studies were used to construct the conceptual framework (see Chapter 2) for this research:

1) there is a possibility of a direct 'triggering' of a physiological response in pregnant women that is governed by climatic factors and,
2) risk factors associated with preterm birth may exhibit seasonal patterns and this may contribute to a seasonal pattern of preterm births.

The remainder of this chapter reviews the potential role of various meteorological factors that may 'trigger' preterm birth and considers the potential mediating role of air pollutants and influenza A, as well. The role of established risk factors for preterm birth and their potential relationship to preterm birth seasonality is also discussed.

1.5 Meteorological factors and the initiation of labour

Aspects of weather which have previously been implicated in triggering the onset of labour include changes in barometric pressure and an increased heat humidity index, though the findings have not always been consistent.[92-96]

Anecdotally, it has been said that the number of women who go into labour increases after sudden changes in meteorological conditions such as drops in barometric pressure. Indeed, in one cross-sectional, retrospective study of 162 women who were at 36 weeks gestation or more in Texas, USA,[92] the overall number of labour onsets was significantly increased in the 24 hours following a drop in barometric pressure when compared with the 24 hours before (n=96 vs. n=66, $\chi^2 = 5.56$, p=0.02).

In another American cross-sectional study, records of childbirth in 1984 from Kentucky were retrospectively reviewed and the relationship between the onset of labour and barometric pressure was evaluated by superimposing the time of onset of labour onto a graph depicting the rise and fall of barometric pressure as a function of time.[97] Statistically more frequent onsets of labour occurred in the crest regions but no significant relationship between barometric pressure and the time of birth was reported. This study did not report any significance tests from their analysis and the number of women included in the study was also not specified.

One study was located that reported no association between the onset of labour and days of low barometric pressure among 2,404 deliveries in Massachusetts, USA.[93] This cross-sectional, retrospective study was conducted from October 1993 to October 1994 and restricted to births in which labour occurred after 37 weeks, but before 42 weeks of gestation, and did not include births by caesarean section, induction, or those that used tocolysis or involved maternal transport. Not only was the probability of a spontaneous onset of labour found not to be significantly different on the 122 days with the lowest average barometric pressure (t-test p value=0.26), but also, three-hour periods of falling barometric pressure were significantly less likely to be followed by onset of labour when compared with increasing or other three-hour pressure changes ($\chi^2 = 8.08$, $p<0.005$).

Curiously, another cross-sectional American study conducted in Texas found a positive association between labour onset and low pressure when using data on pregnant women from 1978 to 1979, and then reported an inverse association using data from the same study site, but a few years later (i.e., 1987 to 1992).[98 99] While reporting the approximate number of people that the hospital from which the cohort came from usually served, there was no mention in either publication of how many women were actually included in the study. The authors acknowledged the discrepancy in their findings and stated, 'There appears to be no explanation for this inconsistency'.[98]

It may be that the conflicting findings of all these studies were due to the inconsistent methodologies that were used, but the methodological quality in many of the studies was also poor (see Appendix 1). Whatever the reason, the inconsistencies demonstrate the need for a standardisation of analytical techniques to help to clarify whether any relationship between preterm birth and changing barometric pressure exists. None of the studies examined the effect of barometric pressure on labour onset before term and none utilised time-series methods for analysis.

Another aspect of weather that has been previously cited in the literature as having an association with the onset of labour is heat stress.[94 95] A cross-sectional study in New York examined four periods which were selected by obtaining daily heat-humidity indexes[d] and calculating seven day averages for a one year period (1993 to 1994).[94] Period A comprised the coldest 7 days of winter (15-21 Jan 1994, index 25), period B was the warmest 7 days of winter (4-10 Mar 1994, index 42.7), C=coolest 7 days of summer (15-21 Sep 1994, index 63.3), and D=hottest 7 days of summer (7-13 Jul 1993, index 79.5). The rates of preterm labour and preterm birth were then calculated for each period using the number of patients at risk as denominator (those with gestational ages 20 to 36 weeks inclusive). Using a test for linear trend, a significant positive association was found between the preterm labour rate and the heat humidity index ($p<0.002$). The preterm birth rate, however, was not statistically significantly different although it exhibited a similar trend ($p<0.29$). In the discussion, the authors suggest that intervening variables, such as intravenous

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[d] The heat-humidity index combines measurements of temperature and humidity to determine how hot the weather 'feels'.

therapy to interrupt labour or medications to inhibit labour, may account for this finding.

In a follow-up study of 11,792 singleton vaginal births from Illinois, USA, no evidence to support an association between shortened gestation and increased maximum apparent temperature was found.[95] However, whereas the previous study investigated preterm birth and preterm labour, this study used mean gestational age and did not restrict inclusion to preterm births. It is possible that any effect of temperature on preterm births was masked by a lack of effect on term births. Thus, a possible association between increased temperature or humidity and preterm birth is not ruled out by the results of this study.

As preterm birth has been shown to vary seasonally in the USA[72 71] and temperature varies seasonally, an analysis of any association between the two should take into account the seasonal variation in at least one of the variables. Otherwise, any relationship found may be attributable to similarities in the seasonal patterns rather than a true association between the two variables. Conversely, any relationship *not* found may be due to dissimilarities in the seasonal patterns. In particular, with the above studies on heat exposure, both studies assumed a linear relationship across all seasons with preterm birth. However, previous studies have shown that while a positive linear association may exist in summer, an inverse relationship can appear in winter. As with the studies on barometric pressure, a time-series design, which can account for any long term seasonal variation, will help to establish whether an independent short-term association between preterm delivery and temperature exists.

1.6 Risk factors for preterm birth that vary seasonally

In addition to a meteorological factor potentially triggering the early initiation of labour, preterm birth seasonality may be driven by associations with risk factors for preterm birth that are known to have their own seasonal variation. Air pollution, infections and hypertensive disorders of pregnancy have all been shown to vary seasonally as well as increase the risk of preterm birth.[100-105]

1.6.1 Air pollution (time-series versus spatial analysis)

A positive association between air pollution and preterm birth has been reported previously in China,[106] Croatia,[107] the USA,[108 109 110] Canada,[111] Lithuania,[112] Taiwan[113-118] and the Czech Republic.[119] One study conducted in Sweden[120] found no association between preterm birth or very preterm birth and air pollution.

Many of the studies, including the Swedish study which reported no association, utilised a methodology in which the risk of preterm birth in areas of high exposure was compared with areas of low exposure.[113-118 120] Other studies grouped preterm births across exposure categories according to pollutant concentrations to compare levels of risk[112 111] or assessed the risk of air pollution as a continuous exposure using linear regression.[109 119] Only two studies used a time-series design,[108 106] and only one of these assessed exposure across time, rather than at an individual level.[108] With the exception of this one study, previous studies using spatial distributions of air pollution between individuals have required adjustment for confounding factors, such as maternal smoking and socio-economic status. For an outcome such as preterm birth, however, such methodologies are unable to account for the many risk factors that remain unknown.[30 19]

Time-series regression is commonly used for other outcomes of environmental epidemiological research, such as in air pollution and mortality and temperature and mortality studies.[121 122 123] Because of the particular strength of this analytical technique that allows adjustment for the influence of any known and unknown risk factors that vary across individuals, but not within individuals, over short periods of time, a time-series design was used in this study to find any short-term associations between preterm birth and seasonally varying exposures, such as ambient air pollution, that may explain any seasonality of preterm birth.

1.6.2 Infections (and the severity of preterm birth)

One well-established and modifiable risk factor associated with preterm birth that has been widely researched is infections. Both maternal systemic and genital tract infections have been implicated in the aetiology of preterm birth.[124 33 125 126] Despite the fact that results from trials using various drugs to treat vaginal infections have not resulted in a lowering the risk of preterm birth, [51 52 53] studies on the association between infections and preterm birth have continued to yield valuable information on other aspects of the epidemiology of preterm birth. An important example of this is the association between infections and early preterm birth. Infections have been shown to be present in most cases where births have occurred before 30 weeks of gestation.[33] One study found that women who reported a sexually transmitted infection or bacterial vaginosis (BV) early in pregnancy were two to three times more likely to be hospitalised for preterm labour between 24 and 32 weeks (Odds ratio (OR) 1.8, 95% confidence interval (CI) 1.1 to 3.0 for sexually transmitted infection; OR 2.6, 95% CI 1.7 to 4.1 for BV).[127] No increased risk with reporting a sexually transmitted infection or bacterial vaginosis was found among women who were hospitalised for preterm labour between 33 to 37 weeks of gestation. Thus, while infection is strongly correlated to births occurring between 24 and 32 weeks of gestation, it appears to have a much less important role in the initiation of labour between 33 and 37 weeks. The frequency of genital tract infections, such as gonorrhoea and Chlamydia, has been reported to follow a seasonal pattern and systemic infections, such as influenza, are also known to be seasonal.[101 128 129 130 131 132] As such, infections may be an important mediating variable in explaining any seasonality that occurs for preterm birth between 24 and 32 weeks of gestation.

1.6.3 Hypertensive disorders (and the clinical presentation of preterm birth)

Because preterm birth appears to have heterogeneous causes, it has been suggested that that any study which aims to advance our understanding of its aetiology should assess spontaneous and medically indicated preterm births separately.[19 133 134] Spontaneous preterm birth is reported to account for 50% of all preterm births,[83] with low-risk populations tending to have higher proportions of preterm birth presenting in spontaneous labour (range 28% to 64%).[133]

Several studies have assessed preterm birth by separating women into groups defined by each of the processes that lead to preterm birth. These studies have found that the magnitude of an association with a particular risk factor for preterm birth can vary depending on whether the mother presented in spontaneous preterm labour or whether the preterm birth was medically indicated. Furthermore, although some factors were associated with preterm birth regardless of the clinical classification, other factors were associated with medically indicated but not spontaneous preterm births and vice versa.[135 136 137] Differential rates of neonatal morbidity and mortality by clinical presentation of preterm birth have also been reported.[82]

With differing risk factors and outcomes associated with the clinical classification of preterm birth, it follows that any seasonal variation observed may also differ between spontaneous and medically indicated preterm births. For example, one study found that an increased risk of spontaneous preterm birth with infections, specifically bacterial vaginosis, was associated a parallel decreased risk for medically indicated preterm births.[138] Within this paradigm, one might expect to see infections as a mediating factor for seasonality among spontaneous preterm births, but not medically indicated preterm births.

Along the same lines, one of the most frequently cited reasons for medically indicated preterm births are hypertensive disorders in pregnancy.[137 139] Pre-eclampsia and pregnancy-induced hypertension have been reported to vary seasonally.[102 103 104 105] If, therefore, medically indicated preterm births are found to demonstrate a seasonal pattern, these two conditions would be likely candidates as mediating factors.

1.7 Other determinants with respect to seasonality

Although the mechanisms that lead to preterm birth remain elusive, a variety of predictors for preterm birth have been identified.[140 17 19] Some risk factors, such as cocaine use, carry small aetiological fractions making them unlikely to be quantitatively important mediators. Among established risk factors, many are unlikely to vary seasonally, such as maternal ethnicity and the sex of the fetus. While such factors are unlikely to vary seasonally, they remain important in furthering our understanding of preterm birth aetiology. One of the strongest identified risk factors for preterm birth is a prior history of preterm birth.

Although not modifiable, a previous history of preterm birth is one of the most consistent clinical risk factors associated with preterm birth. The risk of preterm birth after a prior preterm birth increases as the number of prior preterm births increases. When studying all singleton births in Norway from 1967 to 1973, Bakketeig et al. found that the risk of a subsequent preterm birth was 14.3% if the first birth was preterm, and that this risk increased to 28.1% for the third pregnancy if both prior births were preterm.[141] The attributable risk, or the percentage reduction in preterm birth that could be expected if this risk factor was removed from the population, was 12.3% and 19.3% for second and third preterm births, respectively. Therefore, the effect of a prior preterm birth is substantial and may influence any preterm birth seasonality observed.

Differences in preterm birth rates have also been found between maternal ethnic groups. Although we have yet to gain an understanding of why these differences occur, studies have consistently reported Black women to be at highest risk for preterm birth. In one London-based study of 122,400 pregnancies with a spontaneous onset of labour, Patel and colleagues[142] found that preterm birth proportions were highest among Black mothers at 7.6%, followed by Asian mothers at 6.5%. White European mothers had the lowest proportions of preterm birth at 5.1%. They also reported that the median gestational age for birth among Black and Asian women was 39 weeks, compared with 40 weeks for white European women. Patel and colleagues suggested that the shorter median gestational duration in Black and Asian women may be due to earlier fetal maturation, potentially influencing the definition of term and preterm (i.e. earlier maturation at the same gestational age may mean that a Black or Asian baby born at 36 weeks is not actually 'premature' in the functional sense). Another English study, conducted in Birmingham, further supports the hypothesis that ethnic differences in preterm birth rates exist in the UK.[143] Aveyard et al. found an increased risk of preterm birth (less than 37 weeks of gestation) among Afro-Caribbean mothers (adjusted OR 1.22, 95% CI 1.07 to 1.41), but not among African or Asian mothers, when compared with white mothers. An increased risk for African mothers was only seen for preterm births at less than 28 weeks of gestation (OR 4.02, OR 1.60 to 10.12). When an extra week of 'maturity' was added to the gestational age of an African baby, most of the racial differential remained unexplained (OR 3.21, 95% CI 1.15 to 8.90). Thus, while maternal ethnicity does not vary seasonally, it is clear that ethnic differences in preterm birth exist. Ethnic differences in preterm birth seasonality may expand our understanding of how environmental and genetic factors interact to contribute to this disparity.

Other factors that demonstrate varying risks for preterm birth include maternal age and the sex of the fetus. A higher rate of spontaneous preterm birth has been reported to occur among male fetuses[144] [145] and both younger and older mothers (35+ years) have been reported to carry a higher risk of preterm birth.[146] While maternal age and the sex of the fetus may not vary seasonally, potential differences in preterm birth seasonality across maternal age strata or between male and female fetuses may help to clarify our understanding of how environmental factors interact to influence the difference in risk between groups.

Other risk factors, such as the quality of antenatal care and socio-economic status, and some that could be argued to vary seasonally, such as access to antenatal care and stress or depression, were not considered in this study (see Methods, section 3.6.3.1).

Multiple births account for nearly a third of preterm births[124] and approximately half of all twin births are born preterm.[146] Although multiple births have been reported to vary seasonally,[3] the aetiology of preterm birth in the case of multiple births is thought to differ from that of singleton preterm births. Therefore, it follows that any seasonality of multiple births is likely to be due to factors that are different from factors that might be driving a seasonal pattern of singleton preterm births (see Methods, section 3.2.3).

1.8 Summary

Preterm birth is the single most important problem to overcome if the outcome of pregnancy in developed countries is to improve. Investigating the seasonality of preterm birth may provide new insights that will be useful in understanding, targeting and limiting the risk of preterm birth.

In my systematic review of the literature, most studies from both developing and developed countries reported a seasonal pattern of preterm birth. In developed countries, among the studies that reported a seasonality, proportions or probabilities of preterm births were highest twice a year; once in summer and again in winter. No British studies investigating the seasonality of preterm birth were located.

Among the studies that were found, the authors often suggested correlations with particular aspects of weather as a possible mechanism for the seasonal pattern observed. This raises the question of whether seasonality might be a proxy for other potential exposures, that is, the risk of preterm birth may be linked to the seasonal patterns of a risk factor. There may also be some aspect of meteorological factors that act to physiologically trigger an early initiation of labour.

Previous studies on the association between barometric pressure or temperature and preterm birth report inconsistent methodologies and results. In general, there was a lack of *a priori* hypotheses of how meteorological factors might influence preterm birth proportions. In addition, although there is considerable literature on the effects of air pollution on various adverse reproductive outcomes in relation to fetal growth restriction or low birthweight, studies on the potential effects of air pollution on preterm birth are scarce and use mostly spatial exposure analysis that is subject to confounding by individual risk factors.[147 148 149] Thus, although there is some indication of the associations one might expect in a time-series study of these factors in relation to preterm birth, there is much that remains unclear or unknown.

Other factors that might influence a seasonal pattern of preterm births include seasonality of infections and the seasonality of pregnancy related hypertensive disorders. The seasonality of these risk factors were discussed in the context of the severity of preterm birth and the clinical presentation of preterm birth, respectively.

Although risk factors that are unlikely to vary with season have also been identified for preterm birth, the seasonal pattern of preterm birth may be modified by some of these, such as maternal ethnicity, sex of the fetus and maternal age.

The seasonal patterns of preterm birth may disclose important information and help to clarify markers that predict preterm birth. Establishing a seasonality of preterm birth may have important implications for the delivery of health care. By disentangling the heterogeneous aetiology of preterm birth through an investigation based on its seasonality, it is hoped that specific factors that may be amenable to intervention will be identified.

2. STATEMENT OF RESEARCH HYPOTHESIS & OBJECTIVES

This chapter summarises the rationale and conceptual framework for the research presented in this thesis. The main hypothesis is stated and the specific objectives of the study are listed by whether they were part of the exploratory or hypothesis driven analysis.

2.1 Exploratory and hypothesis driven research

While certain aspects of this study were hypothesis driven, much of the research was inevitably exploratory in nature because of the limited prior knowledge in this area. Where possible, guidance was taken from previously published work. Studies that reported a seasonal pattern of preterm birth,[72 69 70] suggested the following:

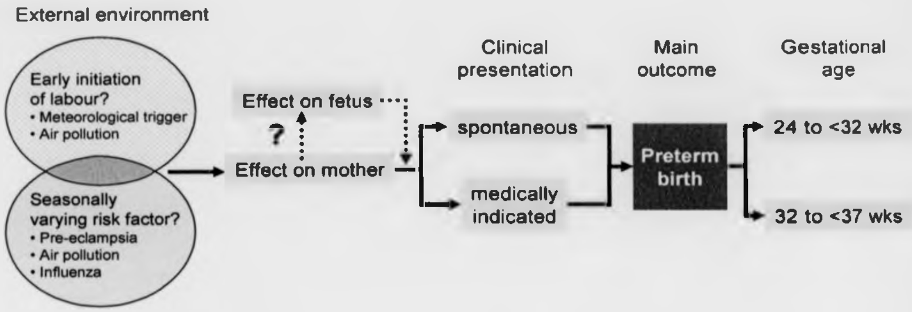
- the variation may be due to an early 'triggering' of the physiological onset of labour in pregnant women produced by climatic factors,
- any observed seasonality is most likely due to factors present at the time of birth rather than factors present at the time of conception, and that
- risk factors associated with preterm birth may exhibit seasonal patterns and that this may contribute to a seasonal pattern of preterm births.

Hence, the main hypotheses of this research was (Figure 2.1):

1. **There is a seasonal pattern of singleton preterm birth proportions in England.**
2. **The seasonal pattern can be explained, in part, by exposure around the time of birth to environmental factors that vary seasonally.**
3. **Other aspects of preterm birth, such as the type of clinical presentation, may have a seasonal pattern that may explain some of the seasonal variation in preterm birth.**

There was less guidance available on specific aspects of the analysis such as the best method to establish the associations that might explain a seasonal pattern of birth. Once the seasonal pattern of preterm birth was established in the study cohort, initial exploratory analysis was used to uncover consistent plausible findings from the data that could be used to explain the pattern observed. In some areas, the result was that additional hypotheses of interest were raised through the course of the analysis and some of these were investigated further.

Figure 2.1: Framework for study hypothesis.



2.2 Objectives

2.2.1 Hypothesis driven

A known seasonal pattern of preterm births may provide a previously unexplored route for the reduction and prevention of morbidity and mortality as well as having important implications with regard to the delivery of health care. After establishing the seasonality of preterm birth, this study sought to determine some of the potential factors that might explain a seasonal pattern of preterm birth, as well as elucidate the pathways and mechanisms through which the seasonal pattern was occurring. This is conceptualised in Figures 2.2 and 2.3.

1. Establish a seasonal pattern of preterm birth in a British cohort. Seasonal patterns of preterm birth have been observed and reported in Japan and the USA.[69 71 72] The first objective of this study was to identify any seasonal pattern in the proportion of live, singleton preterm births in a British cohort from 1988 to 2000.

2. Establish any associations between preterm birth proportions and exposures that may vary seasonally as well.

- *An association between preterm birth proportions and daily mean temperature?*

  Although it has been postulated that heat stress may increase uterine contractility,[150] it is unclear whether an association between daily mean temperature and preterm birth exists. One study investigated the effect of short-term heat stress on length of gestation and reported no association.[95] Another study found that the rate of preterm labour increased significantly with an increasing heat-humidity index. [94] The second objective of this study was to investigate whether any short-term associations between daily mean temperature and preterm birth proportions might help to explain the seasonality of preterm birth proportions in this cohort.

- *An association between preterm birth proportions and daily mean barometric pressure or the largest daily drop in barometric pressure?*

  The results and methodologies of studies investigating an association between barometric pressure and labour onset have varied widely.[92 93 97 98 151-153] Amongst these studies, an association between the onset of labour and barometric pressure was anticipated within 0 to 24 hours. Any short-term associations between daily mean barometric pressure or the largest daily drop in barometric pressure in this study were therefore anticipated to occur with exposure on the day of birth or within the three days before birth, although cumulative exposure for up to six weeks before birth was also investigated.

- *An association between preterm birth proportions and any other meteorological variables?*

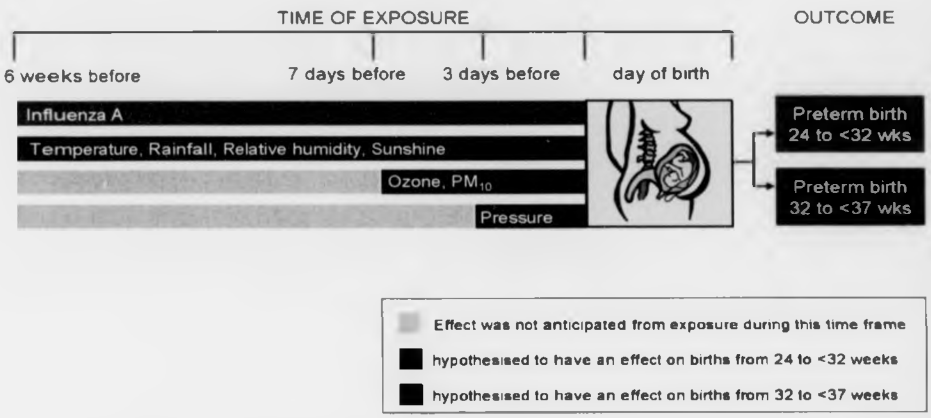
  While hypothesis driven, this particular objective could also be considered an exploratory component of the research. In addition to temperature and barometric pressure, daily hours of sunshine, daily amount of rainfall, and daily mean relative humidity were investigated for any short-term associations with preterm birth proportions. No previously published studies on the possible effect of these exposures on preterm births were located. Guidance on anticipated findings therefore, relied on results from studies on related outcomes, such as the duration of gestation and birthweight.[67 154]

- *An association between preterm birth proportions and daily mean levels of ambient ozone or particulate matter with a diameter of less than ten micrometres (PM_{10})?*
  Previous studies on preterm birth and air pollution that have utilised spatial analysis have reported associations between particulate matter and an increased risk for preterm birth.[106 109 119] For ambient ozone levels however, studies using spatial analysis have found little evidence of an increased risk for preterm birth.[109 111] Using a time-series design to remove the influence of individual confounding factors that do not change over short periods of time, (e.g. socio-economic status), the data were analysed for associations between preterm birth proportions and daily levels of ambient ozone and PM_{10}. Any effects of ambient air pollution on preterm birth were anticipated from exposure on the day of birth or from cumulative exposure during the week before birth,[108] but potential effects from cumulative exposure from up to six weeks before birth were also investigated.
- *An association between preterm birth proportions and weekly influenza A counts?*
  Studies have demonstrated an association between preterm labour and systemic maternal infections, such as pneumonia.[125] Therefore, time-series regression methods were also used to investigate whether the seasonal variation of influenza A counts in London might explain any of the seasonal variation in preterm birth proportions.

3. Investigate any differences in exposure-outcome associations by the gestational age (severity) of preterm birth.

This study assumed that preterm birth between 32 and less than 37 weeks was due to an early initiation of normal physiological mechanisms, whereas preterm birth from 24 to less than 32 weeks was much more likely to be due to pathological mechanisms (e.g., infections or other maternal or fetal complications). Differences in exposure outcome associations were assessed separately for preterm births occurring between 32 and less than 37 weeks and preterm births occurring between 24 to less than 32 weeks (Figure 2.2).

Figure 2.2: Hypothesised short-term associations.



4. Examine the seasonal pattern of preterm birth and outcome-exposure associations by parity (nulliparous versus parous women) to assess the potential effect of repeated sampling in this dataset.
As each record in this dataset represented a pregnancy, any woman who had more than one child while living in the study area was likely to be included in the dataset multiple times. Thus there was a potential for correlations among pregnancies contributed by the same woman, especially among those who had experienced a prior preterm birth.[155 141 19 156 157] To investigate bias due to repeat sampling, analysis was stratified by parity (nulliparous and parous) and examined for differences. Any differences found were also considered in the context of differences in susceptibility to the effect of the exposures by parous versus nulliparous women.

5. Investigate any differences in seasonality and outcome-exposure associations when analysed using the number of fetuses at risk rather than preterm birth proportions.

It is well-known that the number of births vary seasonally.[3-5 8 158-162] For this reason, using the number of preterm births was not feasible and the majority of the analysis in this study used preterm birth proportions (i.e., dividing the number of preterm births on any given day by the total number of live births on that day). It has been argued, however, that using proportions includes births that are not at risk for preterm birth and that this may any affect any associations found. Therefore, a fetuses-at-risk approach was also conducted whereby the denominator was redefined as the number of on-going pregnancies at 24 to less than 37 weeks for each index day.

6. Assess any effect of proximity of hospital of birth to monitoring station.

The nature of an ecological study is that individual levels of exposure cannot be assessed. Instead, this study relied on independent measurements for ambient air pollution and meteorological variables from monitoring stations and collection sites. A sensitivity analysis was conducted to detect any effect the location of the monitoring and collection sites, in relation to the hospital of birth, may have had on the results of the analysis.

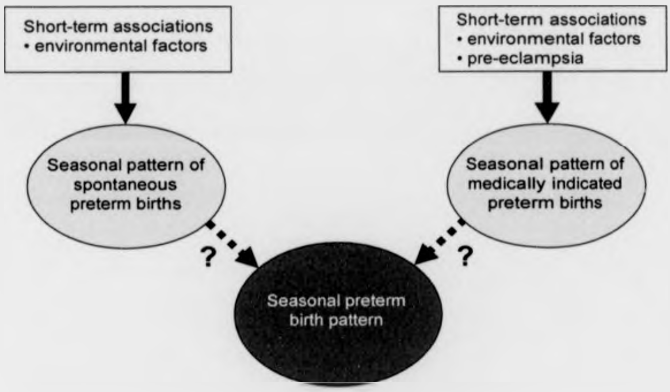
7. Establish the seasonal pattern of other antenatal complications related to preterm birth and assess how these factors may be contributing to the seasonal pattern of preterm birth proportions.

- *A difference by the clinical presentation of preterm birth?*
  It was hypothesised that if both spontaneous and medically indicated preterm births exhibited seasonal patterns, that these patterns may not only be different from one another, but also that different factors may be driving each respective pattern. In addition, by examining the seasonality of spontaneous and medically indicated preterm births separately, the relative

contribution of each process to the overall pattern of preterm birth could be better determined (Figure 2.3).

- *A contribution by the seasonal pattern of pre-eclampsia (PET)?* Previous studies have reported seasonal patterns for pre-eclampsia[102 103 104 105] and it is also known to be related to preterm birth.[10 124 19] One objective of this study was to determine if PET in this cohort displayed any seasonality and if so, whether this was contributing to any seasonal pattern observed in medically indicated preterm birth proportions.

Figure 2.3: Other potential mediators.



2.2.2 Exploratory analysis

This section lists only the a priori aspects of the exploratory analysis. It was anticipated that the initial exploration covered by these objectives would uncover plausible findings and explanations that would lead to further hypothesis generation and analysis.

1. ***Investigate various windows of exposure.***
   - *Is there a particular window around the time of birth during which an exposure is most likely to manifest its effect on preterm birth proportions?*

Because the effect of air pollutants and meteorological factors could be cumulative and there was a possibility of a latent period between exposure and effect, varying windows of exposure of up to six weeks before birth were analysed.

- *Does exposure at the time of conception have an effect on preterm birth proportions?*

  Interpretation of the results in one study on preterm birth seasonality led the authors to suggest that the variation observed was most likely due to factors present at the time of birth.[72] Studies investigating air pollution and preterm birth, however, have reported significant associations of particulate matter air pollution and preterm birth at the beginning of pregnancy.[109 119] Therefore, this study also considered the possibility of exposure effects at the time of conception.

2. Assess potential interaction by some of the known risk factors for preterm birth, including maternal age, maternal ethnicity, and the sex of the fetus.

It is interesting to note that one study in which a seasonal pattern of preterm birth was reported found that the seasonal pattern existed only for specific socio-economic subgroups.[71] The Japanese study conducted by Matsuda et al.[69] also found that stratifying by the sex of the fetus and by parity altered the yearly periodicity of preterm birth. Because it is known that the risk of preterm birth differs by maternal ethnicity[143] and the sex of the fetus,[144 145] the possibility that the effect of the exposures investigated differed according to whether a preterm fetus is male or female or according to the ethnic background of the mother was investigated. Analysis was also stratified by maternal age to investigate whether any exposure effects were modified by this factor.[136 162]

3. METHODS

In this chapter, the study design is discussed, the datasets and outcome and exposure variables are described and the methods used for analysis are presented. The analysis consisted of two main parts: determination of the seasonal pattern of preterm birth proportions and the use of time-series regression techniques to identify any short-term associations that might explain any seasonal pattern observed in preterm birth proportions.

3.1 An ecological study design

Daily time-series data were used to establish the seasonal pattern of preterm birth proportions in a northwest London cohort and to investigate any short-term associations between preterm birth proportions and various exposures through the formulation of a statistical regression model. It was hypothesised that any short-term associations with environmental factors that also vary seasonally may help to explain any seasonal pattern of preterm birth proportions. Further exploration of what may be influencing or contributing to the seasonal pattern of preterm birth proportions was conducted by investigating the seasonal pattern of other factors related to preterm birth, such as pre-eclampsia.

The majority of the analysis was based on daily proportions of preterm birth as the main outcome variable. Individual level data (pregnancy records) were collapsed so that the final dataset contained one record for each day during the study period (Figure 3.1). As such, exposure measurements were also assigned on the basis of time (day) and place (proximity to weather or pollution monitoring station) rather than measurements made in individuals.

Figure 3.1: Illustration of how data were collapsed for analysis such that each day during the study period represented a unit of observation.

Original Data: Each record represents a birth

Date	Preterm?
Jan 1	Yes
Jan 1	No
Jan 1	No
Jan 1	No
Jan 2	No
Jan 2	Yes
Jan 2	Yes
Jan 3	No
Jan 3	No
Jan 3	Yes
Jan 3	No
Jan 3	No
Etc.	

Prepared for analysis: Each record represents a day during the study period

Date	No. preterm	Total births	Daily %
Jan 1	1	4	25
Jan 2	2	3	66
Jan 3	1	5	20
Etc.			

3.2 The birth cohort: St Mary's Maternity Information System

3.2.1 Background and geographical coverage

The St Mary's Maternity Information System (SMMIS) is a widely used computer information system in obstetrics. First designed and piloted in 1984,[163] SMMIS has been used in the majority of maternity units located in the former North West Thames health region since 1988. The boundaries of this region were defined by the Regional Health Authorities that existed in England until 1994 and covered northwest London, Hertfordshire and Bedfordshire (Figure 3.2). The region had a population of 3.5 million, a wide variety of ethnic groups, and included rural areas, suburbs and metropolitan areas. There were approximately 50,000 births per year to its residents, of which 86% took place in maternity units in the region, 13% in maternity units in other regions and 1% at home.[164]

Figure 3.2 Study area: Northwest London, Hertfordshire, and Bedfordshire

Participating hospitals used SMMIS to collect data on every pregnancy booked at the unit, as well as homebirths if the midwife was linked to a hospital in the region (Table 3.1). About 40,000 pregnancies were added to the database each year and each pregnancy was followed prospectively from the first antenatal clinic visit until the file was closed 28 days after birth. For women who were transferred to other centres or who experienced spontaneous abortion, an 'antenatal-only' record completion program was used.

Table 3.1: Hospitals in the area formerly covered by the North West Thames region and the years of their participation in SMMIS.

Hospital name	Years
Ashford	1988-1996
Barnet General	1997-2000
Bedford	1988-2000
Central Middlesex	1988-1994, 2000
Chelsea and Westminster*	1995-1999
Ealing	1988-1994
Edgware General**	1988-1996
Hemel Hempstead†	1988, 1992-2000
Hillingdon	1988-2000
Lister (Stevenage)	1988-2000
Luton and Dunstable	1988-2000
Northwick Park	1988-2000
QE2 (Welwyn Garden City)	1988-2000
St Albans	1988-1991
St Mary's, Paddington	1988-2000
Watford General	1988-2000
West London*	1988-1994
West Middlesex	1988-2000
Westminster*	1988 only

* *West London and Westminster merged to form Chelsea and Westminster in 1995.*
** *Moved the majority of the maternity unit to Barnet General; currently a small midwife-led unit.*
† *Closed for renovations for 3 years; women went to Watford General during this time.*

3.2.2 How the data in SMMIS were collected

Based within each unit, SMMIS data were collected at an individual level as part of routine clinical practice and, in the majority of cases, entered directly into a computer by a midwife or trained clerk. Programmed checks were in place to reduce the likelihood of implausible values. For example, the system would not accept a date of birth of 30 February and for gestational ages less than 24 weeks or higher than 43 weeks the user was prompted for confirmation. Each year, the data from each unit were centrally collated and stored on a secure private network at the Department of Epidemiology and Public Health at Imperial College School of Medicine (located at St Mary's Hospital, London).

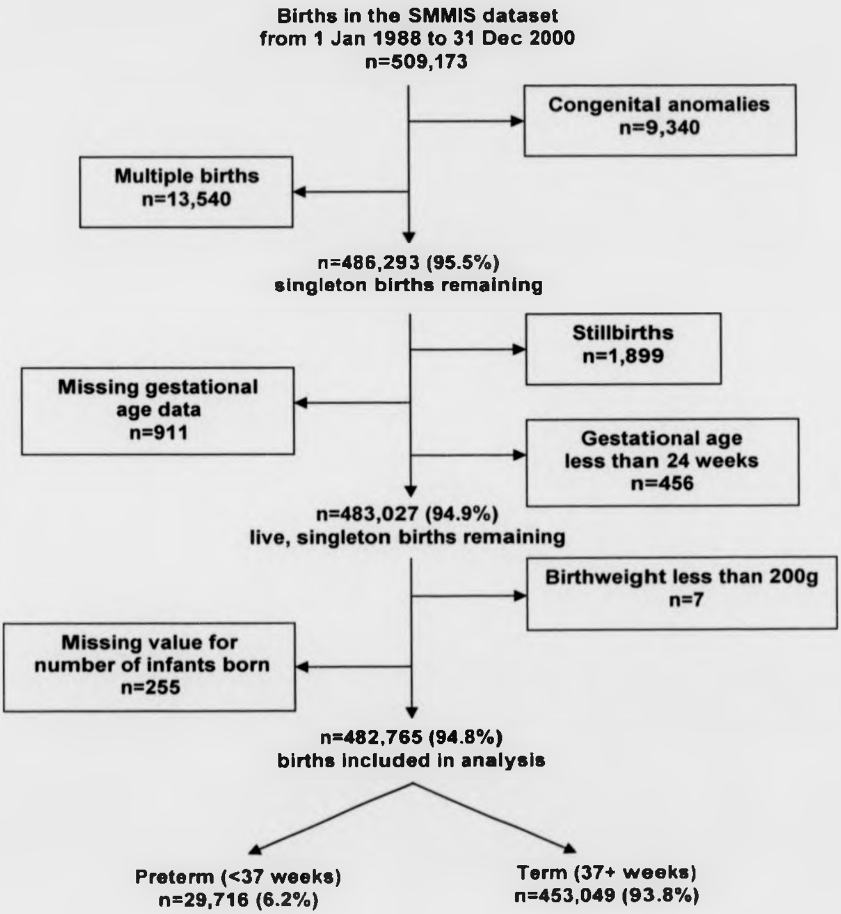
Two separate studies have confirmed the reliability of the data in SMMIS. In one study, maternity records were sampled at three units and 17 fields from the SMMIS dataset were selected for comparison.[165] A high level of agreement was found between the selected SMMIS fields and the equivalent variables abstracted from the maternity records. Eleven of the 17 fields exhibited 95% agreement or better across the three units sampled, including the variables for method of onset of labour, mode of delivery, live or stillborn, delivery date, birthweight, and parity. For categorical fields, Cohen's Kappa was also calculated and ranged between 0.71 to 1.0 among the variables with 95% or higher agreement. Gestational age exceeded 80% agreement across the three units sampled. A few years later, another study on computerised maternity data collection systems in England concluded that SMMIS (and other systems) contained high quality data that "...could be used to provide reliable population based clinical data on mothers and children for public health and epidemiological purposes".[166]

3.2.3 Description of the study population

There were 509,173 births in the SMMIS dataset from 1 January 1988 to 31 December 2000 that progressed far enough to have a birthweight recorded. Only live, singleton births between 24 and 44 weeks of gestation and weighing more than 200g were included in this analysis. In addition, congenital anomalies (n=9340) were excluded from the analysis because any effect of meteorological, pollution or infection related factors on preterm birth was likely to be outweighed by the influence of this high risk medical condition on the pregnancy. Similarly, multiple births (n=13,540) were not included because this places a mother at much higher risk for preterm birth than the general pregnant population[167] and the postulated causes for preterm birth in the case of multiple births (e.g., distended uterus) are likely to far outweigh any effect of meteorological, pollution or infection related factors. Stillbirths (n=1899) were excluded as its aetiology differs from that of preterm births. Although the removal of stillbirths resulted in a significantly lower overall mean of preterm birth proportions (6.16% vs. 6.35%, $\chi^2 = 16.1$, $p < 0.001$), the removal of stillbirths did not appear to alter the seasonal pattern of preterm births (Appendix 2).

After the exclusion of birth records that had missing data for gestational age (n=911), a gestational age of less than 24 weeks (n=456), a birthweight less than 200g (n=7), or missing data for the number of infants born (n=255), 482,765 live, singleton births remained for analysis (Figure 3.3). These were used to calculate preterm birth proportions for each day during the study period (n=4749 days).

Figure 3.3: Reasons for exclusion from analysis



3.3 Variable definitions

3.3.1 Outcomes

The seasonal variation of births is well-established.[3-5 8 158-161] To account for the seasonality of births, the primary outcome used in this study was the daily *proportion* of preterm births, which was calculated using the total number of live births for each day as the denominator. There were 4,749 days during the study period (1 January 1988 to 31 December 2000). In accordance with the definition provided by the WHO, any birth that occurred at less than 37 weeks of gestation (i.e., less than 259 days) was considered preterm.[12] A birth was classified as very preterm if it occurred at less than 32 weeks of gestation (i.e., less than 224 days).[168] Although not internationally defined, 24 weeks (i.e., 168 days) is commonly accepted as a lower limit for preterm birth[13] and is also the lower boundary for preterm live birth registration in the UK.[9] Therefore, for this study, a birth that occurred between 24 and less than 37 weeks of gestation was preterm and term if it occurred at 37 weeks or later (i.e., 259 days or more).

The daily numbers of preterm and very preterm births were derived from estimates of gestational age which were measured from the first day of the last menstrual period. In the case of an irregular menstrual history or uncertain dates, the best antenatal assessment, taking dates, menstrual cycle and ultrasound scan(s) into account was recorded in SMMIS. Gestational age was expressed in days and in completed weeks in the dataset. This meant that a birth occurring between 259 to 265 days, inclusive, after the onset of the last menstrual period was considered to have occurred at 37 or more completed weeks of gestation and would not have been classified as preterm.[169]

3.3.2 Other antenatal outcomes

It was hypothesised that other complications or factors related to preterm birth may vary seasonally and that this seasonality might explain some of the seasonal pattern exhibited by preterm birth proportions. Therefore, the seasonal pattern of the clinical presentation of preterm birth (spontaneous or medically indicated) and pre-eclampsia were also examined. If seasonality was evident, then the outcome was investigated for short-term associations with the various exposures.

For clinical presentation, preterm births were classified as spontaneous if resulting from spontaneous labour onset and spontaneous rupture of the membranes, or a spontaneous labour that began before an artificial rupture of the membranes. All other preterm births were classified as medically indicated. The daily proportions of spontaneous and medically indicated preterm births were calculated using the total number of live births for each day as the denominator.

For the SMMIS database, a spontaneous labour onset was defined as "regular, painful, unstimulated uterine contractions with a frequency of greater than 1:10 recorded by the mother".[169] Membranes were considered ruptured if amniotic fluid could be seen in the vagina and this was defined as spontaneous if it occurred without surgical intervention. Artificial rupture was the surgical rupture of the membranes.[169] There were a small number of records that had the same time of labour onset as time of artificial rupture of the membranes on the day of birth (n=4700). These, and births with missing data for type of onset of labour or of rupture of the membranes (n=6,845), were excluded from any analyses that included these variables.

A pre-defined variable that existed in the SMMIS dataset was used for analysing the seasonality of pre-eclampsia toxaemia (PET). It was derived from several other variables in the dataset including blood pressure at booking, persistent proteinuria (defined as at least two consecutive mid-stream urine specimens, in the absence of infection, with proteinuria) and highest blood pressure, and only considered women who presented for antenatal care at or before 20 completed weeks of gestation. For this variable, women were coded as: normotensive, kidney disease, essential hypertension, pregnancy-induced hypertension (PIH), PET and essential hypertension leading to PET. PET was defined as having a diastolic[e] blood pressure at booking of less than 90 mm Hg, the highest diastolic blood pressure during the antenatal period rising to 90 mm Hg or more, and persistent proteinuria. PIH was similarly defined but without proteinuria. PET and PIH as well as all pregnancies that were not normotensive were investigated for any temporal or seasonal pattern. In addition, pregnancies with PET that led to a preterm birth were also investigated for seasonality.

There were 165,799/482,765 individual records (34.3%) that had missing data for the PET variable. Many of these were the result of incomplete reporting by particular hospitals during particular years. Therefore, any hospital that had more than 70% of the values missing for the PET variable for any given year was dropped from any analysis using this variable for that year (n=29,644 records dropped from five different hospitals- see Appendix 3 for complete listing). The remaining 140,246 records with missing data were also excluded from any analysis using this variable. This left 312,875 records to be analysed, of which 299,178 pregnancies (95.6%) were classified as normotensive. Due to the small number of pregnancies complicated by PET (n=2,158/312,875), there were only 1,714/4,749 days (36%) with at least one case of PET (range 0-4). Therefore, this analysis was conducted at a monthly rather than daily level.

3.3.3 Effect modifiers

Male fetuses,[144 145] younger women and older women,[136 162] and black women[143] have been reported to be at higher risk for preterm birth. To investigate potential interaction by these factors, analyses were stratified by fetal sex (male and female), maternal age (<25 years, 25 to 34 years and 35+ years), and maternal ethnicity (white European, black and Asian).

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[e] Due to lack of storage space on computers when SMMIS was first developed, only diastolic pressure was recorded.

From 1988 to April 1995, maternal ethnicity was classified by the midwife conducting the booking (first antenatal check). Since April 1995, it has been self-classified by the women themselves. For this study, black women were those who were identified or who identified themselves as black African, black Caribbean or black 'Other'. Asians included Indian, Pakistani and Bangladeshi women. Births from women who did not self-classify themselves as white, black or Asian were excluded from the maternal ethnicity stratified analysis (n=37,414). Records with missing data for maternal ethnicity (n=13,623) were also excluded from this particular analysis.

Maternal age at the time of booking was categorised as <25 years, 25 to 34 years and 35 years or older. These groups were chosen to conform to standard groupings and to reflect similar levels of preterm birth risk among those within each group. Women aged 46 and older were excluded from the analysis due to very small numbers (n=203) and a very sharp increase in preterm birth proportions in this group. Records with missing data for maternal age were also excluded from this particular analysis (n=4,413). Similarly, records that were missing data on the sex of the fetus were excluded from the analysis that stratified by male and female (n=5).

3.3.4 Bias

Another factor associated with a higher risk of preterm birth is a previous preterm birth.[155 19 141 156 157] As each record in SMMIS represented a birth, a woman was included in the dataset each time she gave birth within the study area. Thus, there was a danger of bias from repeated sampling of the same woman, especially if the woman had already given birth to a preterm baby and was therefore at higher risk than the general population to deliver preterm again. To control for this, analysis was also stratified by parity, comparing seasonal patterns and associations among nulliparous women with those of parous women. Any differences by parity could also indicate differences in susceptibility to the effect of an exposure. Records for which data on parity was missing were excluded from this analysis (n=70).

3.4 Exposure data

3.4.1 Climate

Daily time-series data were obtained for maximum and minimum temperature, amount of rainfall, and amount of sunshine for the period 1 January 1988 to 31 December 2000. Hourly time-series data were obtained for relative humidity and mean barometric pressure for the same period. All meteorological data were obtained from the UK Met Office through the British Atmospheric Data Centre (BADC)[f] using the Heathrow airport collection site (Appendix 4a).

Six daily variables were used in the analysis to examine possible associations between weather and preterm birth proportions:

- mean temperature (°C)
- amount of rainfall (mm)
- amount of sunshine (hours)
- mean relative humidity (%)
- mean barometric pressure (millibars- hereafter referred to as mb)
- largest drop in barometric pressure (mb)

Daily mean temperatures were derived by averaging the daily maximum and minimum values. Daily mean relative humidity and barometric pressure were derived by averaging the 24 hourly values for each day. The largest daily drop in barometric pressure was derived to investigate whether a change in weather conditions might precipitate preterm birth thereby influencing its seasonal pattern. This variable was calculated using the hourly values of barometric pressure. If there was no drop in barometric pressure for an entire 24 hour period, the value for the day was 0.

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[f] Available online at http://badc.nerc.ac.uk/home/. Last accessed on 14 May 2005.

Missing values for any day were either imputed by averaging the values on either side of the day on which the value was missing or, where possible, obtained from another data file format from the same collection site. There was one missing value for relative humidity (on 21 September 1992) which was imputed by averaging the values on 20 and 22 September 1992. For rainfall, daily data were missing for the years 1996 to 1998. These data were derived from a data file reporting twice daily rainfall measurements. There were no missing values for any day for temperature, sunshine, and barometric pressure.

3.4.2 Air pollution

To investigate the relationship between daily preterm birth proportions and air pollution, daily tirne-series data were obtained for mean ambient levels of ozone and levels of particulate matter with a diameter of less than 10μm (PM_{10}). Ozone was measured in parts per billion (ppb) and PM_{10} was measured in mass units of micrograms per cubic metre ($\mu g/m^3$). The data on air pollutants are collected through an automated network that has various sites around the UK and were obtained from the UK National Air Quality Archive.[9]

In general, adverse heath effects due to ozone exposure are considered to be independent of those due to PM_{10}.[100] Particulate matter consists of airborne particulates that are largely derived from common combustion processes (e.g., car engines, manufacturing and power generation, and burning of biomass) and are therefore fairly ubiquitous and readily penetrate indoors. When there is a layer of cold air above a layer of warmer air, also called an 'inversion layer', pollutants may become trapped and this may result in high concentrations of PM_{10} during winters. Ozone, however, is unlike other air pollutants in that it is not emitted directly into the atmosphere. It is the result of a reaction between nitrogen dioxide, hydrocarbons and sunlight. As sunlight serves as the catalyst for the reaction, high levels of ozone are usually found on hot, sunny days. Current British objectives, or what current legislation

[9] http://www.airquality.co.uk/archive/index.php. Last accessed 14 May 2005.

considers acceptable in light of what is known about the effect of various air pollutants on health and the environment, state that[h]:

- 50 μg/m^3 of PM_{10} should not be exceeded more than seven times per year
- the annual mean of PM_{10} should not exceed 40 μg/m^3
- the eight hour running mean of ozone should not exceed 50 ppb

For ozone, two monitoring sites were used: London Bridge Place and Bloomsbury. Bloomsbury was also the monitoring site used for PM_{10}. PM_{10} and ozone measurements from the Bloomsbury monitoring site were not available from 1988 to 1991 inclusive. Ozone measurements from London Bridge Place were not available for 1988, 1989 and 2000. Due to the large number of consecutive days for which data were missing, it was not possible to impute these values and therefore, days with missing values for air pollution were dropped from the analysis.

The collection and monitoring sites for meteorological and air pollution data were chosen to maximise the period which the data covered and data completeness while maintaining maximal proximity to the location of the hospitals in which the births in the SMMIS data set occurred. (see Appendix 4 for map of location of monitoring sites with rings indicating 5 and 10 miles radius)

3.4.3 Influenza

Initially, it was anticipated that data on sexually transmitted infections that have been shown to have a seasonal variation[128-132] could be analysed for short-term associations with preterm birth proportions. These data, however, were not available at daily, weekly or monthly intervals for London. The smallest timeframe for which the data were available was quarterly.

[h] From the UK National Air Quality Archive (www.airquality.co.uk), last accessed 2 August 2005

Therefore, another seasonally varying infection, albeit systemic, for which data were available was influenza. Daily counts of influenza A & B for the London area were obtained from laboratory reports to the Communicable Disease Surveillance Centre at the Health Protection Agency Centre for Infections (formerly the Public Health Laboratory Service).[1]

There were 698/4749 days (14.7%) during the study period on which at least one case of influenza A was reported. The daily range was zero to 12 cases. Due to the very small numbers of daily counts and many days with zero influenza A cases (n=4051 days), the data for influenza A were aggregated by week for analysis, rather than by day.

There were a total of 4445/4749 days (93.6%) for which there were zero cases of influenza B. The number of counts on the remaining days (n=304 days) ranged between zero and eight, with a total of 385 cases of influenza B during the study period. The total number of cases over the 13 years was too small to analyse with sufficient power and the RNA virus effect of influenza B was felt to be sufficiently different from influenza A as to justify not conflating the two variables. Therefore, influenza B counts were not included in the analysis.

[1] Located at 61 Colindale Avenue, London NW9 5EQ, United Kingdom.

3.5 Summary of variables

The following table lists all the variables used in this study and provides a short description of each.

Table 3.2: Summary of outcomes, exposures and other variables used in this study

Variable	Description
Outcomes	
Preterm birth	proportions and by fetuses at risk
Very preterm birth	proportions
Exposures	
Ozone	daily mean ambient level in ppb
PM_{10}	daily mean ambient level in $\mu g/m^3$
Temperature	daily mean °C
Sunshine	hours/day
Rainfall	mm/day
Barometric pressure	daily mean in mb
Barometric pressure	largest daily drop in mb
Relative humidity	daily mean %
Influenza A	weekly counts
Other antenatal outcomes	
Pre-eclampsia	monthly proportions
Clinical presentation	spontaneous or medically indicated proportions
Effect modifiers	
Mother's age	<25, 25 to 34, 35+ years
Sex of fetus	male, female
Mother's ethnicity	Black, white European, Asian
Bias	
Parity	nulliparous, parous

3.6 Analysis

3.6.1 Determining seasonality

Initially, proportions of preterm birth were examined using a chi-squared analysis to identify any differences by season. Seasons were defined by months with each season occurring over three months such that:

Spring = March, April and May

Summer = June, July, and August

Autumn = September, October, and November

Winter = December, January and February.

Visual inspection of any seasonal patterns was achieved by plotting preterm birth and very preterm birth proportions. This was necessary to determine the existence of any trend or between year variations for the purposes of building the model. As the number of daily values over the 13 years were too numerous to create a plot that could be visually inspected in a meaningful way, the number of preterm births each week were divided by the total number of births each week to produce weekly proportions. These were plotted to identify any seasonal patterns and any overall increasing or decreasing trend in preterm birth proportions across the 13 years.

If a similar pattern appeared in corresponding seasons for successive years, the data were plotted in one 52 week period to improve recognition of any yearly pattern. This was done by combining the corresponding week of each year into one weekly average for the 13 year period. To emphasise any regularity in the series, moving averages were used to remove some of the random variation. This technique acted to 'smooth' the data by moving through each point in the dataset and replacing it with the average of the value itself plus the values on either side of it. The number of values on either side to be included in the average was specified such that a moving average of five included the value itself plus two values on either side of the data point and a moving average of 19 included the value itself plus nine values on either side of the data point. The aim was to select a moving average span that removed enough short-term noise to allow for the detection of any long term patterns or trend that may be of interest. Moving average spans between five and 19 were used for the weekly proportions and weekly averages of preterm birth proportions.

In addition to overall preterm birth proportions, the same method was used to establish seasonal patterns of:

- preterm birth by gestational age (24 to less than 32 weeks and 32 to less than 37 weeks)
- preterm birth by parity

- preterm birth by sex of the fetus
- preterm birth by mother's ethnicity
- preterm birth by mother's age
- preterm birth using fetuses at risk as the denominator
- the clinical presentation of preterm birth

To determine whether yearly patterns were apparent for the exposure variables, each one was plotted across a 365 day period. For each plot, the values on any given day were averaged across all 13 years and any annual patterns were noted.

3.6.2 Using a fetuses-at-risk approach

It may be argued that if the magnitude of the association between outcome and exposure is small, the use of proportions for preterm births may mask any effect as the analysis is 'diluted' by the inclusion in the denominator of those births that were not at risk of being preterm. That is, by definition, any fetus that survives *in utero* beyond 37 weeks of gestation is no longer at risk for preterm birth. Yet, using preterm birth proportions with all live births on any given day as the denominator precluded any opportunity to analyse only the fetuses that were actually at risk for preterm birth separately.

It has also been reported that the number of conceptions and the number of births vary by season.[8 160 4 158 161 170 171] A seasonality of conceptions may conceivably drive a seasonality of preterm birth proportions. In particular, if preterm birth rates were constant and conceptions were seasonal, a seasonality of preterm birth proportions would be entirely attributable to the seasonality in conceptions (see Appendix 5 for further explanation of possible effect of seasonality of conceptions). A fetuses-at-risk approach, however, calculates its denominator prospectively thereby accounting for any seasonality of birth or conceptions. A seasonal pattern of preterm births by fetuses at risk that was also similar to the seasonality of preterm birth proportions would indicate that despite any potential contribution from the seasonality of conceptions, other mediating factors for the seasonality of preterm birth remain to be found.

Thus, findings from the analysis using preterm birth proportions were compared to the results of an analysis using fetuses at risk. A pregnancy was considered a 'at risk' if it was between 24 (168 days) and less than 37 weeks (259 days) of gestation on the day of interest (index day). This meant that for each index day, all ongoing pregnancies between 24 and less than 37 weeks were included in the denominator. The result was that preterm birth probabilities, rather than preterm birth proportions, were now being analysed. Results from this analysis were reported per 1000 pregnancies at risk each day.

As preterm birth was defined as a dichotomous variable (i.e., preterm birth or not), this analysis assumed equal risk for each pregnancy regardless of whether it occurred at 25 weeks or 35 weeks of gestation.

A model was run for each exposure using daily probabilities for preterm birth. These results were compared with results from the corresponding model that used daily preterm birth proportions and exposure values from the day of birth. Any inconsistency between any two models for the same exposure would suggest a need for further investigation of the possible effect that either analytical approach had on the results. If the relationship presented in both models for each exposure was similar, the results found using preterm birth proportions was considered robust and any potential 'dilution' effect due to the inclusion of births not at risk of being preterm was considered minimal.

3.6.3 Associations between outcome and exposures: Time-series regression

3.6.3.1 The basics of time-series analysis

Time-series regression techniques were used to evaluate any associations between the daily proportions of preterm birth and various exposure variables. Time-series statistical methods divide the variation of a series into any trend, seasonal variation, other cyclic change, and remaining irregular fluctuations. By doing this, any incidental associations between the outcome (preterm birth) and exposure (meteorological factor, air pollution, or influenza) that exist because of similar time-dependent patterns could be identified and accounted for. This approach allowed any long-term or slow changes (e.g. demographic shifts) over time to be controlled for while the short term effects of the exposure of interest was examined against an adjusted baseline.

In practical application, this particular advantage of time-series analysis meant that the existence of unspecified confounders which may vary with time will be accounted for in the analysis. In particular, as changes at the population level (such as an increase in the pregnancy rate) occur gradually over a period of months or years rather than days or weeks, time-series analyses operate on the assumption that day-to-day changes within the population are unlikely to occur. As such, while factors that vary rapidly with time may potentially confound any associations found, individual level factors such as socio-economic status, which does not vary markedly over time, was unlikely to play a confounding role in the analysis. Specifically, the potential confounding effect of variables that may demonstrate longer term seasonality (but are not likely to change dramatically in the short-term), for which no data were available, such as the quality of antenatal care, access to antenatal care and stress or depression, was accounted for. Thus, with the study population acting as its own control and other long-term time-dependent patterns accounted for, the remaining irregular fluctuations, which represented the effect of any relevant exposure and that of random error, could be investigated further.

The time-series data of preterm birth proportions were approximately normally distributed with a slight skew to the right. Although the Kolmogorov-Smirnov test for normality indicated deviation from normality (p<0.001), for large datasets such as this one, such tests are known to be very sensitive to any departure from normality.[172 173] Confirmation of this was found by inspecting the Kolmogorov coefficient which was close to zero (0.03), indicating little evidence of asymmetry. In addition, the histogram showed that the departure from normality was modest and therefore unlikely to influence the results of the analysis (Appendix 6). Therefore a normal distribution was assumed and because the analysis was based on proportions (and not counts), Gaussian regression techniques were employed. As such, the resultant coefficient represented an absolute change in preterm birth proportions, e.g., a coefficient of 0.02 would be interpreted as: preterm birth proportions increased by 0.02% for every unit increase in the exposure.

When fetuses at risk were modelled, binomial error was specified. In this case, the coefficient represented the log odds which can take any positive or negative values, whereas proportions were constrained to lie between 0 and 1. The anti-log was reported for all coefficients from the binomial analysis. Thus, the results from any binomial analysis were interpreted as how much the likelihood of preterm birth changed with each unit change in the exposure, i.e., a coefficient value of greater than one indicated an increased risk of preterm birth and coefficient values less than one indicated a decreased risk.

3.6.3.2 Creating a core model

An association between preterm birth proportions and an exposure may be confounded by the fact that they both have similar trends or seasonal patterns. This meant that any observed associations may be partly due to the seasonal pattern of daily preterm birth proportions being similar to the seasonal pattern exhibited by the particular exposure of interest rather than any causal underlying relationship between the two variables.

Therefore, it was necessary to 'remove' the seasonality from at least one of the variables before adding the other variable to the model. In this study, the core model consistently 'removed', or adjusted for, any seasonality and trend in the outcome variable before adding the exposure variable to the final model. Any associations found after this adjustment could then be investigated further for its possible role in driving the seasonal pattern of preterm birth proportions.

To account for the seasonality of preterm birth proportions, a parametric approach was used as part of a generalised linear model.[174] Fourier terms (a combination of sine and cosine waves, also called 'harmonics') were used to recreate a consistent seasonal pattern.[175] The number of harmonics determined how closely the original signal was reproduced with one paired harmonic (e.g., one sine and one cosine term) reproducing a yearly pattern, two paired harmonics reproducing half-yearly cycles, etc. The optimal number of paired harmonics was determined by assessing 1) the significance of each harmonic and 2) the deviance of the model, a decrease in deviance representing a better 'fit'. As each harmonic added another degree of freedom to the model, a decrease in deviance by more than 3.84 (chi square value for 1 degree of freedom at the p = 0.05 level) for any harmonic added indicated a significantly better fit for the model. Fourier terms up to the 8^{th} harmonic (paired) were found to provide the best fit for the core model.

An indicator, or 'dummy' variable, was used to adjust for the significant variation in preterm birth proportions between the years (see Table 4.2 in Results Part I). Although a seven day pattern was not evident for preterm birth proportions in this cohort (see Table 4.2 in Results Part I), neonatal mortality and births have been shown to exhibit distinct seven day cycles and holiday patterns.[4 176 177] Therefore, in keeping with a conservative modelling methodology, indicator variables were included to adjust for day of week and holiday effects in preterm birth proportions.

It is also possible for specific events to have a 'one-off' effect on the seasonal pattern or trend displayed by preterm birth proportions. Several such potential factors were identified during the study period. These included:

- A change in the defined upper limit of spontaneous abortions from less than 28 to less than 24 weeks of gestation in October 1992
- A flu epidemic at the end of 1989
- A heat wave in the summer of 1995

Relevant indicator variables to control for these events were included, as necessary.

A comparison plot of the observed and predicted values was used to assess the fit of the model (Appendix 7). A time series plot of the residuals (i.e., the difference between the actual and predicted values) was also examined to ensure that the core model was appropriate (Appendix 8). A good fit was demonstrated by a plot of residuals that was randomly distributed with no discernable pattern. Finally, the residuals of the core model were plotted against the predicted values. This plot revealed any model inadequacies as gaps in residuals for given ranges of the predicted values or as vertically clumped bands (Appendix 8).

Once the core model was built with adjustment for between year variation, seasonal confounders, and other cyclic changes in the outcome variable, the short term effects of each exposure variable could be examined by adding it to the model. A separate model was generated for each exposure. Models for each exposure were also stratified by the severity of preterm birth, sex of the fetus, maternal ethnicity, and maternal age to identify any effect modification by these factors. In addition, a separate model for each exposure was stratified by parity to discern any potential sampling bias in the study cohort. Models for daily hours of sunshine, daily mean relative humidity and daily mean levels of ambient ozone were also run with and without control for daily mean temperature. To avoid making assumptions about the shape of the relationship between daily mean temperature and preterm birth proportions, temperature was represented using cubic spline terms in these models (see section 3.6.4 below).

3.6.4 The shape of the outcome-exposure relationship: Graphs

At first, scatterplots were generated to get an idea about the shape of the outcome-exposure relationship. Then cubic spline terms were used to summarise the basic relationship of a preterm birth-exposure association by 'smoothing' to allow graphical inspection. Smoothing was achieved by dividing each exposure series into equal intervals. Within each interval, a cubic function was used to describe the association between preterm birth proportions and the exposure, and the cubic functions were constrained to join at the ends of each interval. Each interval was joined by a 'knot' with the number of knots determining the level of smoothing. Fewer knots resulted in a smoother curve. The appropriate number of knots for each exposure model was assessed by both visual inspection and by using Akaike's Information Criterion (AIC).

The AIC is a fit statistic that aids with model selection. As it is subject to a penalty term that increases as the number of parameters in the model increases, the AIC assesses whether additional complexity is worthwhile while preventing over-fitting. In this way, determination of an appropriate model using the AIC helps to strike a balance between the need for a parsimonious model (i.e., one that uses as few parameters as possible) and one that is too simple and may therefore fail to detect any effects.[178]

Thus, complex relationships between preterm birth proportions and any exposure could be modelled without making assumptions about the shape of the potential association. Within these relationships, if a linear association was apparent, the threshold, or 'ends' of this segment could be estimated and a 'linear term' could be generated.

To identify the best fitting threshold, maximum likelihood was used. Regressions were repeated after varying the visually identified threshold by one unit until the best fitting model, defined by the lowest deviance and AIC, was found. Once the best fitting threshold was found, the cubic spline values that were used for smoothing were replaced by the actual values of the exposure of interest for the linear segment identified. The resulting coefficient of the linear regression then represented the percent change in preterm birth proportions per unit change in a given measure of the exposure variable above, below or within the threshold specified.

3.6.5 Delayed effects and effects at the time of conception

Conceivably, the effects of weather, air pollution or influenza on preterm birth may manifest themselves at any time during a pregnancy. As previously published studies did not provide consistent consensus, this study hypothesised that the effect of any given exposure may manifest itself on the day of birth, sometime before the day of birth or around the time of conception.

3.6.5.1 Exposure on the date of conception

Dates of conception were calculated for individual level data by subtracting backwards from the date of birth using the gestational age in days, and then subtracting an additional 14 days to allow for the convention that conception is assumed to occur on the 14^{th} day of gestation (day 0 being the first day of the last menstrual period). The data were then collapsed as before so that each record represented one day during the study period (see Methods, section 3.1), but this time by using the estimated dates of conception instead of the dates of birth. Preterm birth proportions therefore, now used the number of births conceived on any given day as the denominator rather than the number of babies born on any given day. Because the dates of conception were calculated backwards from the date of birth, dates of conception for the final year of the study period, 2000, began to taper off around March. Therefore, all records from the year 2000 were excluded from this analysis leaving 4,383 days (or 624 weeks) during the study period.

The optimal number of Fourier terms to control for seasonality in preterm birth proportions by conception was assessed and the addition of indicator variables to control for public holidays and day of week and between year variations created the core model. A separate model was run for each exposure. As with the models investigating effects around the time of birth, cubic splines were initially used in lieu of the actual values of the exposure variable to aid in summarising any potential non-linear relationships with preterm birth. For any relationship found, linear segments were isolated using maximum likelihood to identify the optimal threshold point(s), if necessary. The cubic spline values were subsequently replaced with the original exposure values so that the resultant coefficient from the regression analysis represented the change in *the proportion of conceptions resulting in a preterm birth* per unit change in a given measure of the exposure variable.

3.6.5.2 Exposure before birth

While the original time-series data for exposures represented values on the day of birth and could be added directly into a model, the investigation of a possible exposure effect sometime before the day of birth required the calculation of lags and was necessarily exploratory. Therefore, a wide range of lags were investigated for each exposure. Lag terms were calculated by averaging the values of an exposure over a specified time (e.g., three days before birth or one week before birth) and then adding that term to the model in lieu of the exposure value on the day of birth (lag 0). When a lag term greater than zero was added to a model, any associations between preterm birth proportions and the exposure of interest were then assumed to represent a cumulative, linear effect over the timeframe chosen. With temperature, for example, an averaged weekly lag of 2 weeks, would average the values of temperature for the 14 days before birth for each day during the study period and any associations with preterm birth proportions would be attributed to exposure to daily mean temperature during those two weeks.

Initially, an exploration of averaged weekly lags during the three months before birth provided was conducted. For the week before birth, averaged daily lags were examined. This provided an indication for which lags should be incorporated in the model for each exposure.

The lags chosen for presentation in this analysis were ultimately determined by the magnitude of association observed at each lag for each variable and were constrained by the number of harmonics that were included in the core model. As the number of harmonics corresponded to the lowest wavelength produced, the eight harmonics used for the core model in this study indicated a wavelength of about 6.5 weeks (i.e., 1/8 of a year). This meant that lagged analysis in the final models was constrained to a maximum of about six weeks before birth as any patterns or trends beyond six weeks were adjusted for in the core-model.

Lagged analysis on the models stratified by severity of preterm birth, parity, sex of the fetus, maternal ethnicity, and maternal age were only conducted in the case where an initial lagged association between the exposure being investigated and preterm birth proportions was found.

For the comparative analysis by fetuses at risk, associations at lag 0 were investigated. For the other antenatal outcomes related to preterm birth, exploratory lagged analysis was conducted for 3 days, one week, and four weeks, in addition to the effects on the day of birth (lag 0).

3.6.6 Dealing with autocorrelation

A particular feature of time-series data is that they are correlated through time and not independent. Autocorrelation (or 'serial correlation') refers to the non-independence of exposure measurements from one day to the next, and to a slightly lesser extent, the day after that, etc. with the strength of the correlation diminishing each successive day. This meant, for example, that a high temperature on any particular day would be likely to indicate a similarly high temperature on the day directly before or after that day. The temperature two days before and two days after will continue to be strongly correlated but less so than the day directly before and after. The temperature 15 days later will be much less dependent on what the temperature was 15 days earlier. Associations between daily preterm birth proportions and the time-series exposure data were likely to be affected by autocorrelation.

To check for serial correlation, the residuals of each model were inspected using the partial autocorrelation function (PACF). A PACF describes the autocorrelation of a time-series at consecutive lags while correcting the value of each lag for the previous lags. Significant positive partial autocorrelation coefficients indicated remaining autocorrelation and were accounted for by including the appropriate number of autoregressive terms in the model. An autoregressive term is a linear function of the preceding values or values.[179] The appropriate number of autoregressive terms was determined by how many days or 'lags' the PACF indicated were still serially correlated. For example, if significant autocorrelation existed at lag 1 and at lags 4 and 5, autoregressive terms up to the fifth lag would be generated and included in the model. After inclusion of the autoregressive terms, the PACF was run again to ensure all autocorrelation was accounted for. If autocorrelation still existed, the process was repeated until none remained. Negative autocorrelation indicated over-fitting of the model (i.e., the inclusion of unnecessary seasonal terms). No autocorrelation was found in the core model (Appendix 9). Autocorrelation was systematically checked as each exposure was added to the core model and controlled for, as necessary.

3.6.7 A sensitivity analysis

One of the limitations of an ecological study is imprecise exposure assessment as each mother is assumed to be exposed to the same extent. In particular, with air pollution variables, it has been suggested that where a significant association between air pollution and increased risk for preterm birth has been reported, these effects were no longer apparent when women who lived further than 10 miles from the monitoring station(s) were included in the analysis (personal communication, B. Ritz, August 2004).

A sensitivity analysis was conducted to detect what effect the location of the monitoring sites in this study may have had on the results of the analysis. Because the data in SMMIS were made non-attributable before it was received for analysis in this study, neither the mother's place of residence nor place of work was available. This necessitated the use of the hospital of birth as a proxy. All births that occurred in the hospitals located furthest from the air pollution and weather monitoring stations (Edgware General, Barnet, Bedford, Hemel Hempstead, Lister, Luton and Dunstable, QE II, St Albans, and Watford General) were excluded (Appendix 4) and the model for each exposure variable was re-run and compared with the models from the initial analysis which included births from all hospitals. Any differences in effect from exposure on the day of birth were assessed.

All analysis was carried out using Stata, version 8.2 (StataCorp LP, Texas, USA).

3.7 Ethical approval

The data used for this study were non-attributable as they were abstracted from the original data set at St Mary's Hospital in London, UK, with all identifiers removed to preserve the confidentiality of the mothers and babies. General ethical approval was obtained to use non-attributable data from SMMIS for epidemiological studies from the Local Research Ethics Committee at St Mary's Hospital, London, UK (Appendix 10).

Ethical approval for this specific study was obtained from the London School of Hygiene and Tropical Medicine Ethics Committee as well as the ethics committee at St Mary's Hospital (Appendix 11 & 12).

3.8 Chapter summary

Weekly proportions of preterm births in the SMMIS dataset were plotted to determine if there was any seasonal pattern. Once the seasonality of preterm birth proportions was established, regression techniques were used to uncover any potential associations with various environmental exposures to which the seasonality of preterm birth proportions could be attributed.

Because of the possibility that the outcome as well as the exposure variable could exhibit a seasonal pattern, it was necessary to control for seasonality in at least one of the series (either outcome or exposure) if short-term associations were to be investigated. This was because if any two series show a seasonal pattern, correlations could be attributed to the similarities in cyclic variation rather than a true relationship between the variables. Therefore, a core model was created in which seasonal variation, between year and day of week variations, one-off effects and public holidays were adjusted for in the outcome variable. Exposures were added to the core model to identify any remaining short-term associations.

A model was created for each meteorological, air pollution and infection exposure variable by adding the exposure to the core model. Cubic spline terms were generated for each exposure variable to allow for graphical inspection of potentially non-linear associations with preterm birth proportions. Within any outcome-exposure relationship, if linear associations were present, the best-fitting threshold was identified, the spline terms replaced with the actual values of the exposure within this threshold and the association quantified. Models were fitted to examine not only the effect of each exposure on the day of conception and the day of birth, but also for up to 6 weeks before the preterm birth. Analysis was stratified by sex of the fetus, maternal age, and maternal ethnicity to investigate potential interaction and also by parity to examine any effects of repeat sampling in the dataset. Sensitivity analysis was conducted to detect any effect of the proximity of the mothers (by hospital of birth) to the air pollution and climate monitoring stations. The potential effect of using daily preterm birth proportions as the unit of analysis was assessed through comparison with an analysis by fetuses at risk.

Efforts were also made to understand what factors might be contributing to the seasonal pattern of preterm birth proportions by examining the seasonality of other endpoints related to preterm birth, such as spontaneous and medically indicated preterm birth proportions and pre-eclampsia. These models were fitted to examine the effect of each exposure on the day of birth, 3 days before birth, one week before birth and four weeks before birth.

4. RESULTS PART I: EMERGING SEASONALITY

Descriptive statistics for the SMMIS and exposure datasets and the seasonal patterns exhibited by each outcome and exposure are presented in this chapter. Results of the investigation to determine what factors might be driving the preterm birth seasonality observed in this cohort are presented in the next chapter (Results Part II).

4.1 Background characteristics of SMMIS births

Among the 482,765 singleton, live births in the SMMIS dataset from 1 January 1988 to 31 December 2000, 29,716 (6.16%) were born before 37 weeks of gestation (see Methods, section 3.2.3). The proportion of very preterm births (24 to less than 32 weeks) was 0.87% (4202/482,765). There were 4,749 days during the study period and an average of 101.7 (range 52 to 148) births on each of those days, of which an average of 6.3 (range 0 to 17) were preterm and 0.88 (range 0 to 5) were very preterm. There were 13 days (0.27%) on which no preterm births occurred (or were recorded) in the study area.

There was strong evidence (Table 4.1) of an association between preterm birth and:

- sex of the fetus
- maternal ethnicity
- maternal age

Male fetuses were 13% more likely to be born preterm than female fetuses (risk ratio (RR) 1.13, 95% confidence interval (CI) 1.11 to 1.16); Black mothers were 71% more likely to give birth to a preterm infant when compared with white mothers (RR 1.71, 95% CI 1.64 to 1.78); Asian mothers were 30% more likely to give birth to a preterm infant when compared with white mothers; and younger and older mothers were more likely to have a preterm baby when compared with mothers aged 25 to 34 years (RR 1.24, 95% CI 1.21 to 1.28 for mothers <25 years old and RR 1.22, 95% CI 1.18 to 1.26 for mothers 35 years and older). These associations indicated an interaction with preterm birth, thereby providing support for stratified analysis by these factors (see Methods, section 3.3.3).

Although there were fewer medically indicated births, a significantly larger proportion of these were likely to be preterm (Table 4.1). Births that were medically indicated were 66% more likely to be delivered preterm than spontaneous births (RR 1.66, 95% CI 1.62 to 1.70). There was also strong evidence of an association between parity and preterm birth (Table 4.1). Children who were born to first-time mothers were 15% more likely to be preterm than children who were born to parous women (RR 1.15, 95% CI 1.13 to 1.18). Whether or not the seasonal pattern of preterm birth proportions varied with the clinical presentation of preterm birth or by parity was investigated in Results Part III and in section 4.3, respectively.

Temporal trends in preterm birth proportions were also evident. The proportion of preterm births varied significantly over the years. The proportions also varied significantly by month, which was suggestive of a seasonal variation (Table 4.2). Terms to adjust for between year variations and day of week variations in preterm birth proportions were included in the design of the core model (see Methods, section 3.6.3.2).

Table 4.1: Characteristics of births in the SMMIS dataset (n=482,765), 1988 to 2000, using chi square to check for differences in preterm birth proportions between groups

	No. of births (%)	% preterm	χ^2 (degrees of freedom), p
*Parity**			
Nulliparous	212,799 (44.1)	6.64	
Parous	269,896 (55.9)	5.77	χ^2 (1) = 157.2, p < 0.001
*Ethnicity***			
White European	340,079 (78.8)	5.63	
Black	28,942 (6.7)	9.63	
Asian	62,707 (14.5)	7.29	χ^2 (2) = 911.3, p < 0.001
Clinical presentation†			
Spontaneous	350,063 (74.3)	5.14	
Medically indicated	121,157 (25.7)	8.51	χ^2 (1) = 0.002, p < 0.001
Sex of fetus††			
Male	247,188 (51.2)	6.54	
Female	235,572 (48.8)	5.75	χ^2 (1) = 128.7, p < 0.001
Maternal age‖			
<25 years	111,399 (23.3)	6.99	
25 to 34 years	304,646 (63.7)	5.62	
35+	62,104 (13.0)	6.83	χ^2 (2) = 334.4, p < 0.001

* *70 records were excluded due to missing data on parity*
** *All other ethnicities (n=37,414) and records with missing data on ethnicity (n=13,623) were excluded*
† *11,545 records with missing data or same time of labour onset and ROM were excluded*
†† *5 records were excluded due to missing data on sex of fetus*
‖ *Mothers aged 46 and older (n=203) and records with missing data on maternal age (n=4413) were excluded*

Table 4.2: Temporal patterns of the SMMIS dataset (n=482,765), 1988 to 2000, using chi square to check for differences in preterm birth proportions between time periods.

	No. of births (%)	% preterm	χ^2 (degrees of freedom), p
Year			
1988	35,444 (7.34)	6.76	
1989	37,929 (7.86)	6.35	
1990	39,931 (8.27)	6.11	
1991	40,052 (8.30)	6.26	
1992	40,201 (8.33)	6.43	
1993	39,543 (8.19)	6.11	
1994	40,242 (8.34)	5.92	
1995	35,476 (7.35)	6.08	
1996	36,003 (7.46)	6.04	
1997	35,502 (7.35)	6.10	
1998	36,048 (7.47)	5.86	
1999	33,467 (6.93)	6.01	
2000	32,927 (6.82)	5.98	χ^2 (12) = 45.81, $p < 0.001$
Month			
January	39,289 (8.14)	6.83	
February	36,705 (7.60)	6.29	
March	40,537 (8.40)	6.19	
April	39,330 (8.15)	6.04	
May	41,883 (8.68)	5.97	
June	41,327 (8.56)	5.96	
July	42,633 (8.83)	5.99	
August	41,711 (8.64)	5.83	
September	41,487 (8.59)	5.60	
October	40,725 (8.44)	6.08	
November	38,470 (7.97)	6.53	
December	38,668 (8.01)	6.66	χ^2 (11) = 96.57, $p < 0.001$
Day of week			
Sunday	58,957 (12.21)	6.32	
Monday	68,992 (14.29)	6.03	
Tuesday	71,139 (14.74)	6.16	
Wednesday	72,900 (15.10)	6.08	
Thursday	73,481 (15.22)	6.14	
Friday	73,748 (15.28)	6.19	
Saturday	63,548 (13.16)	6.20	χ^2 (6) = 5.63, $p < 0.47$ χ^2 (1) = 2.98, $p < 0.09$*

* *conducted for weekdays versus the weekend*

4.2 Background characteristics and seasonality of exposures

4.2.1 Climate

The monthly and seasonal means of daily measures for the climate exposure variables from Heathrow station from 1988 to 2000 are presented in Table 4.3. Graphs of the seasonal pattern for each climate exposure variable are presented in Figure 4.1. Unsurprisingly, mean daily temperature and the mean daily hours of sunshine had strong seasonal patterns that were positively correlated over the entire study period (Spearman's rho (ρ) = 0.40). Mean daily relative humidity also showed a clear seasonal pattern that was inversely correlated to both mean daily temperature (ρ = -0.43) and mean daily hours of sunshine (ρ = -0.73) over the entire time-series (n=4749 days).

The monthly range of daily mean temperatures was between 5.76 and 18.74 degrees Celsius, a variation of only about 13 degrees between winter and summer (Table 4.3). Similarly, the monthly range of daily rainfall did not show much variation, ranging from 1.04mm to 2.16mm.

More than half of the days during the study period (n=2595 days or 55%) had no rainfall at all. There were 164 days (3.5%) when the recorded daily amount of rain was greater than 10mm. Although graphical inspection revealed no discernable annual pattern for the mean amount of daily rainfall (Figure 4.1), when investigated by season (Table 4.3) it became apparent that the highest amount of daily rainfall occurred in the autumn, followed by winter.

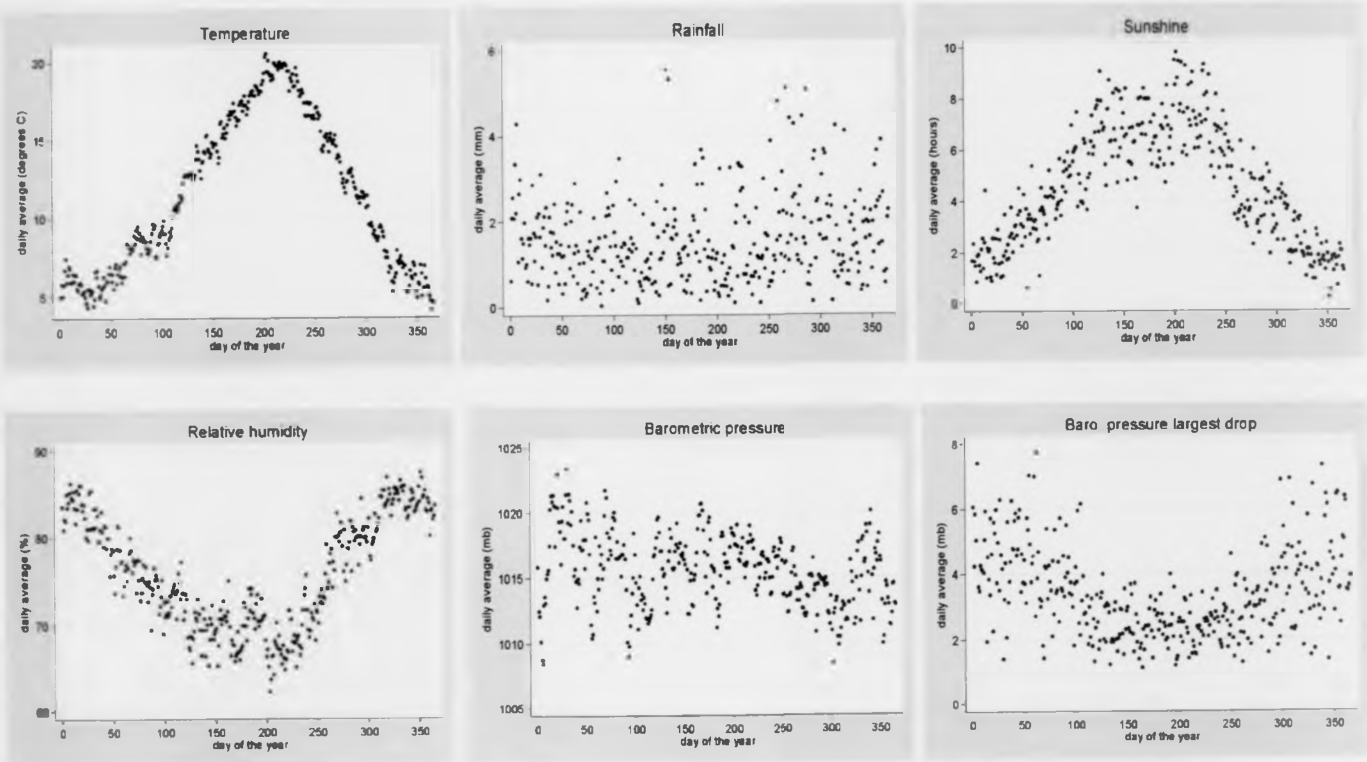
The largest daily drop in barometric pressure appeared to have a more distinct seasonal pattern than the daily mean barometric pressure (Figure 4.1). Drops in barometric pressure grew gradually larger from the summer to winter months (Table 4.1).

Table 4.3 Monthly, seasonal, and percentile distributions of mean daily measures for climate exposure variables used in analysis, 1988 to 2000 (n=4749 days).

	Daily mean temperature (°C)	Daily rainfall (mm)	Daily sunshine (hrs)	Daily mean relative humidity (%)	Daily mean barometric pressure (mb)	Largest daily drop in pressure (mb)
Month						
January	5.76	1.81	1.86	83.45	1017.15	4.47
February	6.00	1.45	2.88	79.46	1016.66	4.69
March	8.20	1.04	3.75	75.62	1017.14	3.84
April	9.59	1.62	5.41	73.18	1013.36	3.18
May	13.66	1.30	7.04	69.32	1016.73	2.49
June	16.12	1.52	6.61	69.44	1016.40	2.44
July	18.63	1.26	7.16	69.31	1016.41	2.36
August	18.74	1.42	7.16	68.93	1016.18	2.44
September	15.52	1.98	4.87	75.51	1014.70	2.74
October	11.80	2.16	3.96	79.49	1013.63	3.58
November	7.83	1.64	2.52	84.20	1013.66	3.81
December	5.88	1.78	1.64	83.88	1014.82	4.40
*Season**						
Spring	10.49	1.32	5.40	72.70	1015.77	3.17
Summer	17.85	1.40	6.98	69.23	1016.33	2.41
Autumn	11.71	1.93	3.77	79.73	1013.99	3.38
Winter	5.88	1.69	2.10	82.35	1016.20	4.52
Percentile						
25	7.15	0	0.40	68.76	1009.26	0.80
50	11.25	0	3.80	76.62	1016.42	2.00
75	15.90	1.40	7.70	83.84	1022.80	4.10
Range	-5.5, 27.4	0, 61.80	0, 15.7	41.74, 99.86	959.65, 1044.34	0, 37.30

* *spring = Mar, Apr, and May; summer = Jun, Jul, and Aug; autumn = Sep, Oct and Nov; winter = Dec, Jan and Feb*

Figure 4.1 Annual pattern of climate exposure variables by daily mean.



4.2.2 Air pollution

Monthly and seasonal means of daily levels and percentiles of distribution of the air pollution exposure variables are presented in Table 4.4. Data from the London Bridge Place monitoring station were available for 10 of the 13 study years, from 1990 to 1999, and data from the Bloomsbury monitoring station were available for nine of the 13 study years, from 1992 to 2000. Daily mean ambient levels of ozone from the London Bridge Place monitoring station were higher than at the Bloomsbury monitoring station for all months (Table 4.4). This was reflected in the break down by season, as well.

Graphical presentation of the seasonal patterns of ozone and PM_{10} is found in Figure 4.2. The highest levels of ambient ozone occurred during the spring and summer for both monitoring stations, almost double the levels seen in autumn and winter (Table 4.4). This is most likely attributable to the fact that sunlight serves as a catalyst in the production of ozone. Graphical inspection of the graph for daily ambient PM_{10} levels revealed no obvious annual pattern (Figure 4.2) although inspection by season indicated that the lowest levels of ambient PM_{10} occurred during winter (Table 4.4).

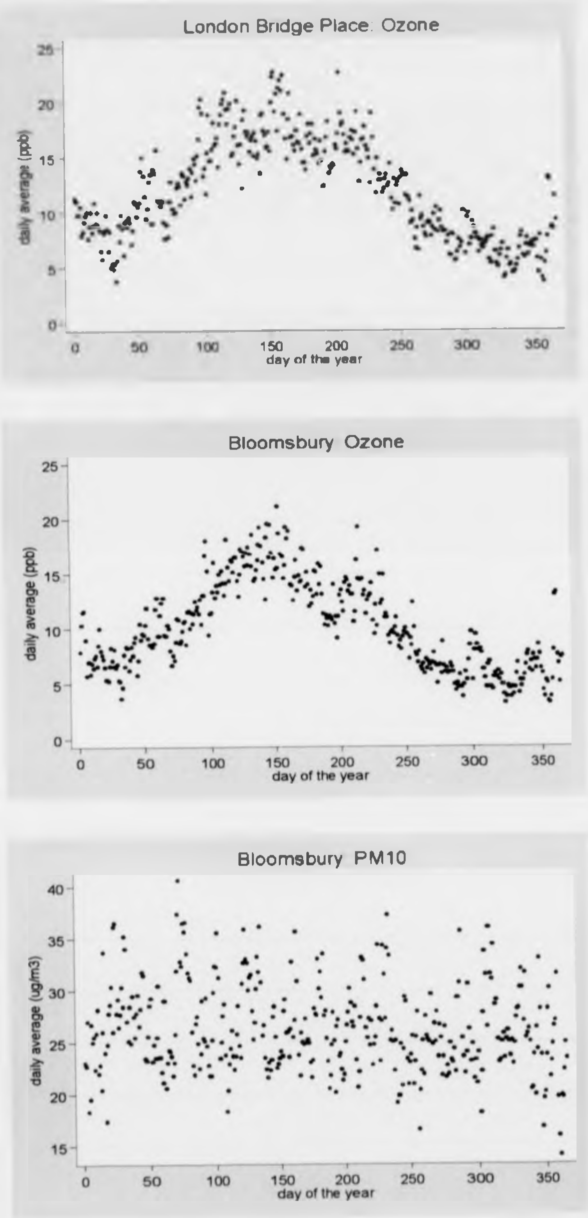
The daily mean ambient levels of ozone from both monitoring stations were positively correlated with daily mean temperature (Spearman's rho (ρ) = 0.48 for London Bridge Place and ρ = 0.42 for Bloomsbury).

Table 4.4: Monthly, seasonal and percentile distributions of daily mean levels for ambient ozone (O_3) and PM_{10}.

	Bloomsbury*		London Bridge Place**
	PM_{10} ($\mu g/m^3$)	**O_3 (ppb)**	**O_3 (ppb)**
Month			
January	26.39	7.26	8.52
February	27.08	8.33	9.64
March	28.12	10.26	11.80
April	26.09	14.30	16.90
May	27.47	16.61	16.87
June	27.10	15.15	17.86
July	25.49	12.40	16.02
August	26.37	11.97	14.44
September	24.75	7.82	10.21
October	25.20	6.44	8.07
November	27.29	5.18	6.31
December	23.30	6.64	7.29
Season†			
Spring	27.24	13.71	15.04
Summer	26.33	13.18	16.07
Autumn	25.73	6.49	8.15
Winter	25.57	7.39	8.49
Percentile			
25	18	5	6
50	23	9	11
75	31	14	16
Range	7, 103	1, 45	1, 48

** data only available from 1992 to 2000.*
*** data only available from 1990 to 1999.*
† spring = Mar, Apr, and May; summer = Jun, Jul, and Aug; autumn = Sep, Oct and Nov; winter = Dec, Jan and Feb

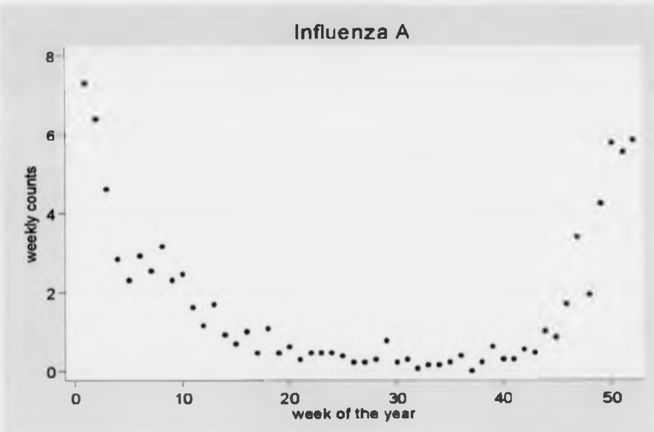
Figure 4.2: Annual pattern of air pollution exposure variables by daily mean.



4.2.3 Influenza A

Data on daily influenza counts in London were available from the Communicable Disease Surveillance Centre for 1988 to 2000. Despite using summed weekly counts in lieu of daily counts for influenza A, a substantial proportion of weeks still had 0 cases (56.5%). An additional 115 weeks (17%) that had only one case of influenza A reported. The maximum number of influenza A cases reported for any one week during the entire study period was 36 and this occurred during the influenza epidemic at the end of 1989. Influenza A displayed a distinct seasonal pattern each year with the most counts occurring during winter weeks and the fewest counts occurring during summer weeks (Figure 4.3).

Figure 4.3: Annual pattern of influenza A by weekly counts.



4.3 Seasonality of preterm birth proportions

When plotted by weekly proportions (Figure 4.4a), a pattern emerged in which preterm birth proportions were similar for corresponding seasons in successive years; consistently highest during the winter and lowest during the summer. A very gradual overall decrease in preterm birth proportions over the 13 years was also evident although there was also a considerable amount of variation between the years. To get a better idea of the annual pattern, preterm birth proportions were plotted as a composite of all 13 years over a 52 week period (Figure 4.4b).

As the pattern of preterm birth proportions appeared consistent for each year, the data were combined into seasons for comparison. There was strong evidence of an association between preterm birth proportions and seasons (χ^2=53.8, p< 0.001, 3 degrees of freedom). Using summer as the referent group, babies whose birthdates were in winter were 11% more likely to be born preterm (Table 4.5).

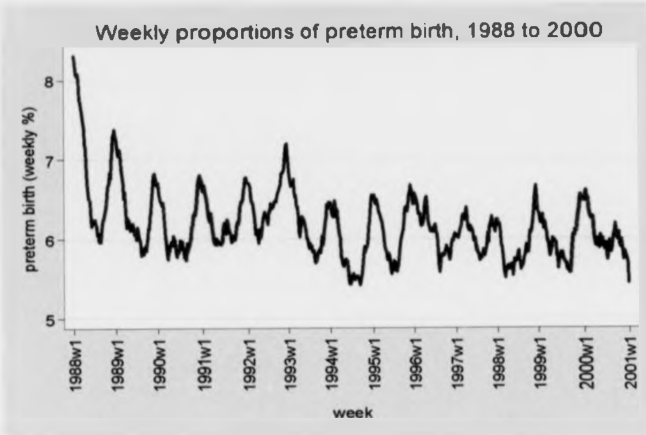
Table 4.5: Daily preterm birth proportions by season*

	Preterm %	Risk ratio	95% CI
Spring	6.07	1.02	0.99 to 1.06
Summer**	5.93	1	-
Autumn	6.06	1.02	0.99 to 1.05
Winter	6.60	**1.11**	**1.08 to 1.15**

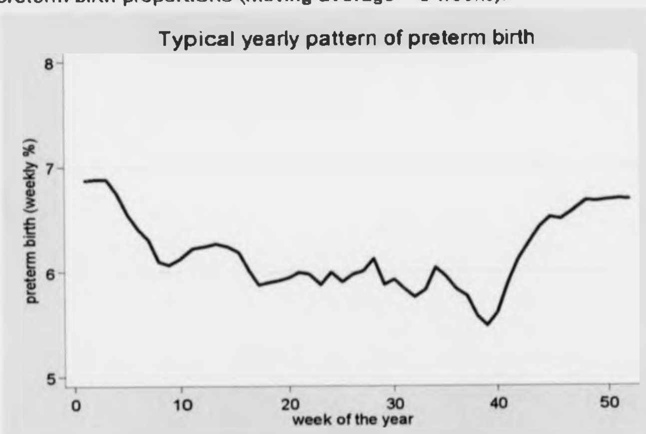
** spring = Mar, Apr, and May; summer = Jun, Jul, and Aug; autumn = Sep, Oct and Nov; winter = Dec, Jan and Feb*
*** referent group*

Figure 4.4 Seasonal pattern of weekly preterm birth proportions in SMMIS.

a) Over 13 years (moving average[1] = 17 weeks).



b) Collapsed into one 52 week period; the 'typical' or 'averaged' yearly pattern of weekly preterm birth proportions (moving average = 5 weeks).



[1] Please see Methods, section 3.6.1 for an explanation on moving averages and why they were used

When separated by gestational age, weekly proportions of preterm births occurring between 32 to less than 37 weeks continued to exhibit a consistent seasonal pattern during each of the study years (Figure 4.5a). Therefore, all years were combined so that the annual pattern, with a winter peak and summer low, could be more clearly identified (Figure 4.5b). No discernable or consistent seasonal pattern emerged over the years for the weekly proportions of preterm births occurring between 24 and less than 32 weeks (Figure 4.5c).

When weekly preterm birth proportions were stratified by parity to examine any differences among parous and nulliparous women (see Methods, section 3.3.4), a seasonal pattern that followed a similar pattern each year of the study period was more apparent among parous women (Figure 4.6a). This pattern was consistent with the pattern observed for all preterm births, with a peak during the winter months and a trough during the summer months (Figure 4.6b). The seasonal pattern of weekly preterm birth proportions among nulliparous women was not as consistent, nor as pronounced, as that seen in parous women. In particular, there were several years for which no summer trough was distinct for preterm births among nulliparous women (i.e., 1991-1993, 1999; Figure 4.6a). When displayed over one 52 week period however, the seasonal pattern of preterm birth proportions among nulliparous women could be seen more clearly (Figure 4.6b).

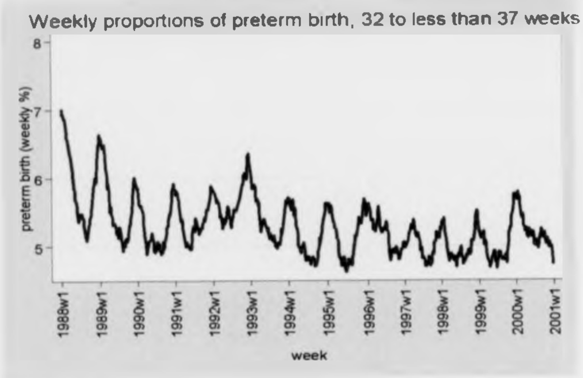
The seasonality of weekly preterm birth proportions among both male and female babies, a potential effect modifier (see Methods, section 3.3.3), exhibited a consistent pattern for each of the study years (Figure 4.7a). Similarity to the overall pattern of weekly preterm birth proportions could be seen when the data were combined into one 52 week period (Figure 4.7b).

When stratified by mother's ethnicity, another potential effect modifier, no clear consistent seasonal pattern for each year could be identified for weekly preterm birth proportions among Asian mothers or Black mothers (Figure 4.8a). For all three maternal ethnic groups, there was an anomalous pattern from January to March 1995 due to missing values in the maternal ethnicity variable. This may have been due to the change in definitions and self-classification that came into effect in April 1995. Notwithstanding this anomalous time period, the yearly pattern exhibited by weekly preterm birth proportions among white mothers was consistent for each year from 1988 to 2000. The yearly pattern corresponded fairly well with the pattern observed for all weekly preterm births proportions, except that the higher winter values extended further into the beginning of the year (Figure 4.8b).

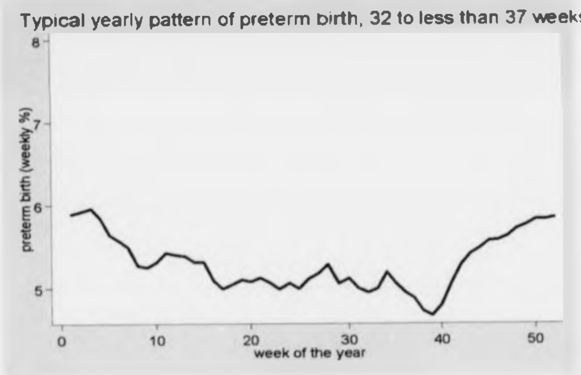
Another potential effect modifier was maternal age. Weekly preterm birth proportions to mothers who were younger than 25 years did not display any recognisable, consistent pattern each year (Figure 4.9a). Preterm births to older mothers (35 years or older) and to mothers between the age 25 to 34 years demonstrated a seasonality that was consistent each year. This annual pattern had its lowest values during the summers and was highest during the winter (Figure 4.9b).

Figure 4.5 Seasonal pattern of weekly preterm birth proportions by severity

a) At 32 to less than 37 weeks, over 13 years (moving average of 17 weeks used)



b) At 32 to less than 37 weeks, in one 52 week period (moving average of 5 weeks used)



c) At 24 to less than 32 weeks, over 13 years (moving average of 17 weeks used)

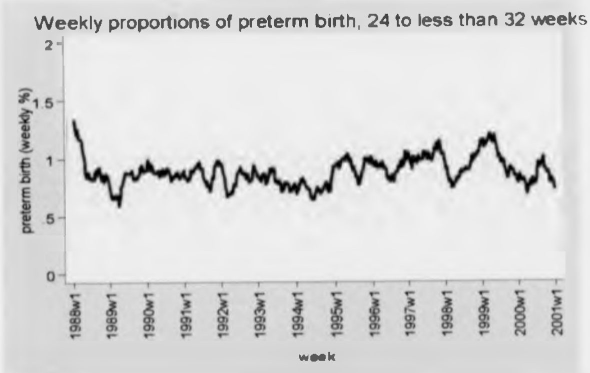
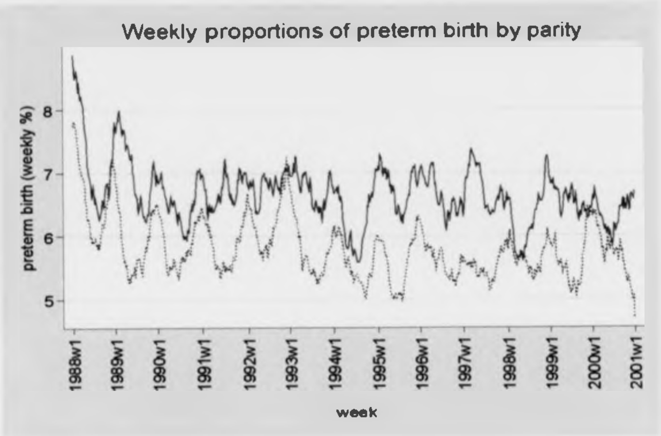


Figure 4.6 Seasonal pattern of weekly preterm birth proportions by parity.

a) This graph showed that parous women (dotted line) demonstrated a more consistent seasonal pattern over each year of the study period than did nulliparous women (solid line) (moving average of 19 weeks used).



b) When collapsed into one 52 week period, however, both nulliparous (solid) and parous (dotted) women demonstrated a yearly pattern of preterm birth proportions (moving average of 5 weeks used).

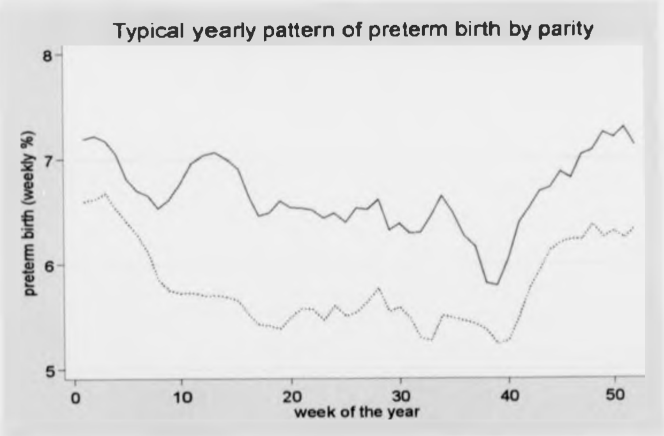
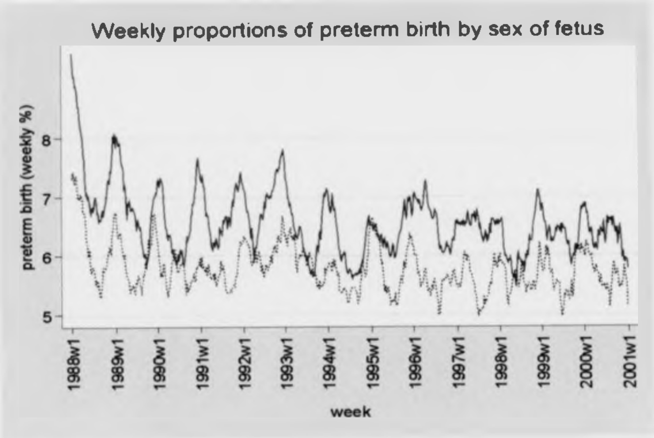


Figure 4.7: Seasonal pattern of weekly preterm birth proportions of male (solid line) and female (dashed line) fetuses.

a) Over 13 years (moving average of 17 weeks used)



b) In one 52 week period (moving average of 5 weeks was used)

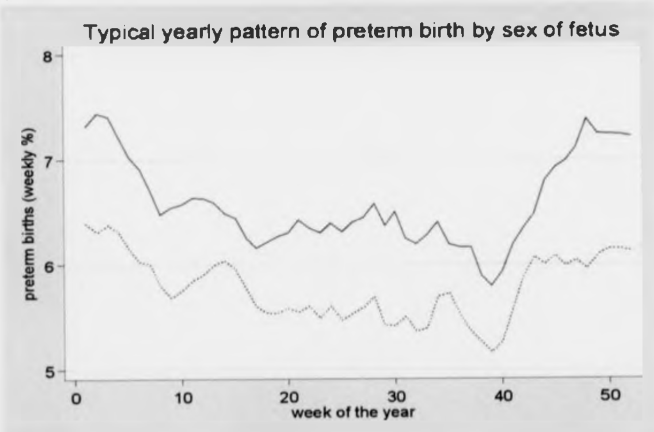
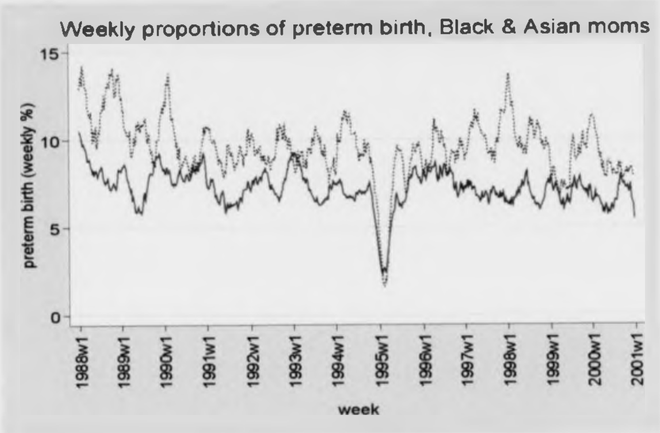


Figure 4.8 Seasonal pattern of weekly preterm birth proportions by maternal ethnicity.

a) Neither Black (dotted line) nor Asian mothers (solid line) demonstrated a consistent seasonal pattern over the 13 years (moving average of 17 weeks used).



b) Collapsed into one 52 week period, the 'typical' yearly pattern of preterm birth proportions to white mothers (moving average of 5 weeks used).

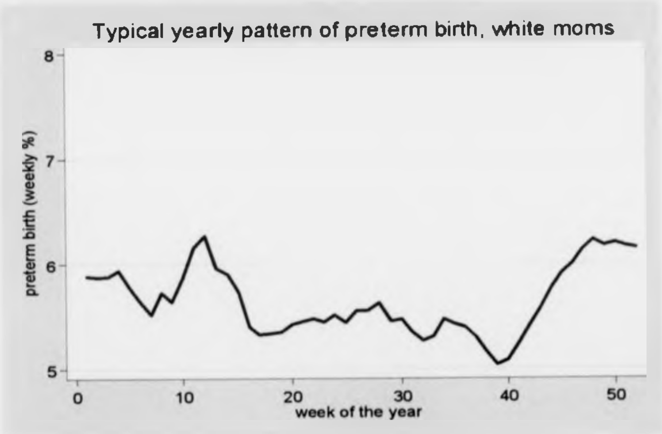
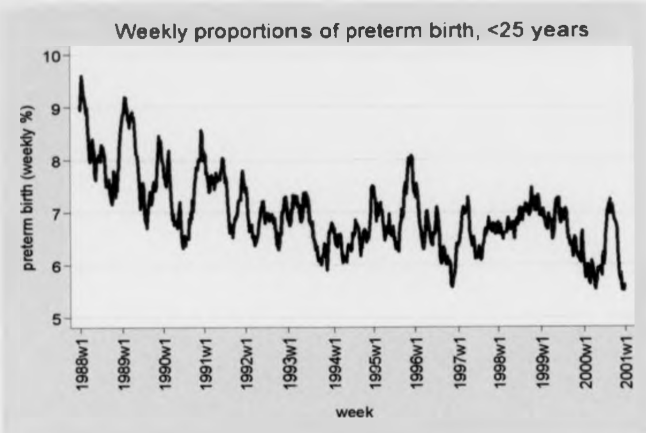
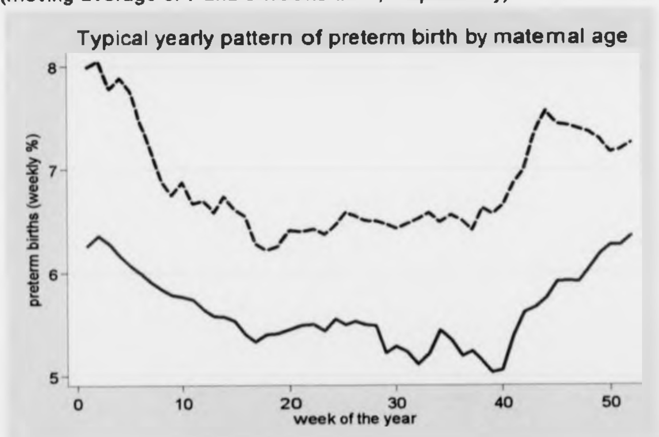


Figure 4.9: Seasonal pattern of preterm birth proportions by maternal age

a) No consistent seasonal pattern could be recognised for mothers younger than 25 years (moving average of 5 weeks used).



b) Collapsed into one 52 week period; the 'typical' yearly pattern of preterm birth proportions to mothers older than 35 years (dashed line) and for mothers aged 25 to 34 years (solid line) (moving average of 7 and 5 weeks used, respectively).



4.4 Chapter summary

Evidence of an association between preterm birth proportions and sex of the fetus, maternal ethnicity, and maternal age was found, indicating potential interaction with these factors. Male fetuses were more likely to be born preterm than female fetuses. Black and Asian mothers were more likely to have a preterm baby when compared with white mothers. Older (35+ years) and younger (less than 25 years) mothers were more likely to have a preterm baby than mothers who were aged between 25 and 34 years old. An increased risk of preterm birth was also observed in nulliparous women when compared with parous women.

There was significant between year variation in preterm birth proportions, with a slight downward trend over the 13 years.

The proportions of preterm births by month were suggestive of a seasonal pattern. The association between preterm birth proportions and seasons was confirmed when babies born in winter were found to be 11% more likely to be preterm when compared with babies born in summer.

The majority of the daily exposure variables appeared to be highly seasonal and some were strongly correlated to daily mean temperature. The range of monthly means for daily mean temperature and amount of daily rainfall indicated that the study area is subject to a temperate climate.

The seasonality of preterm birth proportions was clearly established with the highest proportions occurring during winter and the lowest proportions occurring during the summer. When analysed further however, notable differences emerged. Younger mothers (age less than 25 years), preterm births occurring between 24 and less than 32 weeks, to women less than 25 years old and to Black or Asian women did not appear to adhere to any consistent seasonal pattern that could be identified yearly or by any other time interval. On the other hand, preterm births occurring between 32 and less than 37 weeks, to women aged 25 to 24 years or 35 years and older, and to white women exhibited the same seasonal pattern each year, with highest proportions in the winter and lowest proportions in the summer.

There did not appear to be any difference in preterm birth seasonality when investigated by the sex of the fetus or by parity. Preterm birth proportions in both male and female fetuses occurred consistently higher during winter and lower during summer each year. The same pattern was observed for both nulliparous and parous women. This indicated that any factor(s) influencing the seasonality of preterm birth did so independently of its relationship to parity and sex of the fetus.

5. RESULTS PART II: OUTCOME- EXPOSURE ASSOCIATIONS

Having established that proportions of preterm births in the SMMIS dataset were consistently higher in winters than in summers, the next step was to uncover any associations that might help to explain what was driving this pattern. To ensure that any correlations found were not due to similar existing trends between the outcome and exposure, each exposure was added to a core model in which the seasonality of preterm birth proportions was controlled for. This chapter presents findings from the regression analysis on short-term associations between preterm birth proportions and exposure to various environmental variables on the day of birth and at various times before birth, including the time of conception. A sensitivity analysis, based on the proximity of the hospital of birth to the air pollution and weather monitoring stations, is also presented.

5.1 Meteorological exposures

5.1.1 Associations with daily mean temperature

A scatter plot of the crude, or unadjusted, relationship indicated a potential increase in monthly preterm birth proportions as average monthly temperatures decreased (Figure 5.1a). The relationship between daily preterm birth proportions and exposure to daily mean temperature on the day of birth was summarised using cubic spine terms[k] (Figure 5.1b). The relationship observed was as anticipated since the daily proportions of preterm births were observed to be at their lowest during summers when temperatures were at their highest.

To remove any correlations that might be due to existing similar seasonal patterns and to facilitate investigation of any short term relationships, daily preterm birth proportions were adjusted for public holidays, seasonality, and day of week and between year variations in the core model. Cubic spline terms for daily mean temperature were then added

[k] Please see Methods, section 3.6.4 for an explanation of smoothing splines used in this analysis.

to the model. Daily mean temperature on the day of birth (lag 0) appeared to have little or no effect on daily proportions of preterm birth (Figure 5.2a). To quantify any temperature effect at this lag, one linear term across the whole range of values for daily mean temperature (i.e., the actual values for daily mean temperature) was added to the model in lieu of the cubic splines. Regression analysis indicated that preterm birth proportions on the day of birth were not significantly related to any degree (°C) change in temperature (coefficient (β)[l]= -0.02%, 95% confidence interval (CI): -0.04 to 0.01).

Nor were any associations apparent when the combined effect of daily lags up to one week or the combined effect of weekly lags up to six weeks were investigated in lieu of exposure on the day of birth.[m] (Figure 5.2b).

When stratified by gestational age groups corresponding to the severity of preterm birth, daily mean temperature on the day of birth had little or no effect on the daily proportion of preterm births occurring between 32 and less than 37 weeks (β= -0.01%, 95% CI -0.03 to 0.02; Figure 5.3a). At 24 to less than 32 weeks, however, an inverse relationship emerged. As the shape of the relationship was essentially linear (Figure 5.3b), the temperature splines were again replaced by one linear term, consisting of the whole range of actual daily mean temperature values, to quantify the association. The proportion of preterm births that occurred between 24 to less than 32 weeks of gestation increased by 0.01% (95% CI 0.01 to 0.02) with each degree decrease in daily mean temperature on the day of birth.

There was evidence of effect modification when the temperature model was stratified by maternal ethnicity. As each relationship appeared to be relatively linear (Figure 5.4), any effect of temperature was quantified by

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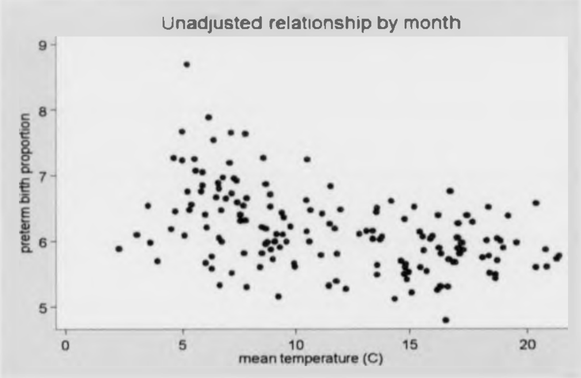
[l] The β, or coefficient, represented the percent change in preterm birth proportions per unit change in exposure and was interpreted as, "for each degree decrease daily mean temperature, preterm birth proportions increased by 0.02%", where the '-' sign indicated an inverse relationship.
[m] For an explanation of averaged lags please see Methods, Section 3.6.5.2

replacing the cubic splines with one linear term consisting of the whole range of actual daily mean temperature values. For exposure on the day of birth, preterm birth proportions among white mothers were found to increase by 0.05% (95% CI 0.01 to 0.08) with each degree decrease in daily mean temperature (Figure 5.4a). In contrast, preterm birth proportions among Asian mothers increased by 0.09% (95% CI 0.01 to 0.17) with each degree increase in daily mean temperature on the day of birth (Figure 5.4b). Daily mean temperature on the day of birth or at any other lag investigated did not significantly affect preterm births proportions among black mothers (β= -0.13%, 95% CI -0.26 to 0.01; Figure 5.4c).

When preterm births were stratified by parity, sex of the fetus and by maternal age, no differences in relationship were found. Each model for each stratum indicated little or no relationship between exposure to daily mean temperature on the day of birth and preterm birth proportions.

Figure 5.1: Unadjusted relationship between preterm birth proportions and mean temperature.

a) Using monthly means for preterm birth proportions and daily mean temperature.



b) Using daily preterm birth proportions and daily means for temperature, the crude relationship (thick red line) was smoothed using cubic splines (95% CI = thin grey lines).

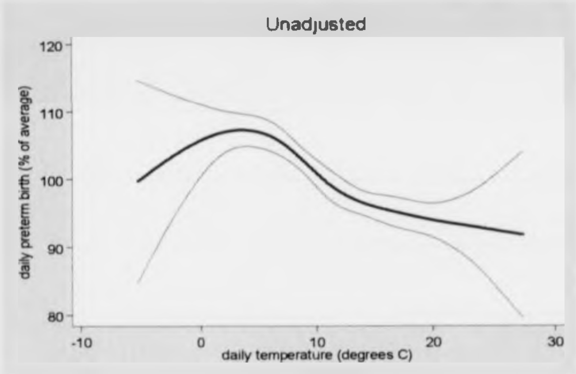
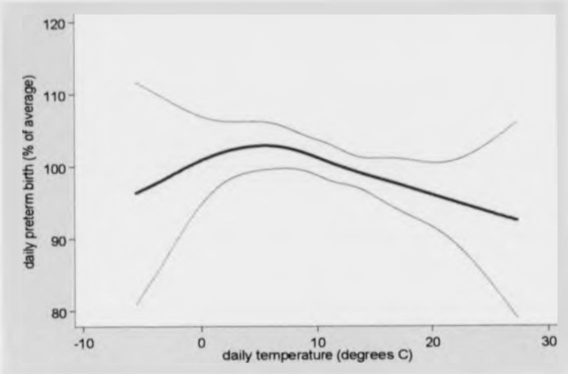


Figure 5.2: Adjusted relationship (thick red line) between daily preterm birth proportions and daily mean temperature (95% CI = thin grey lines).

a) Although exposure to higher temperatures on the day of birth (lag 0) appeared to be related to lower proportions of preterm birth, this association did not reach statistical significance.



b) The relationship shown here indicated no apparent effect of cumulative exposure to temperature during the six weeks before birth

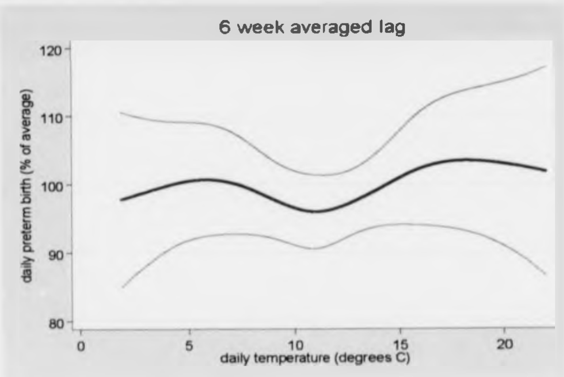
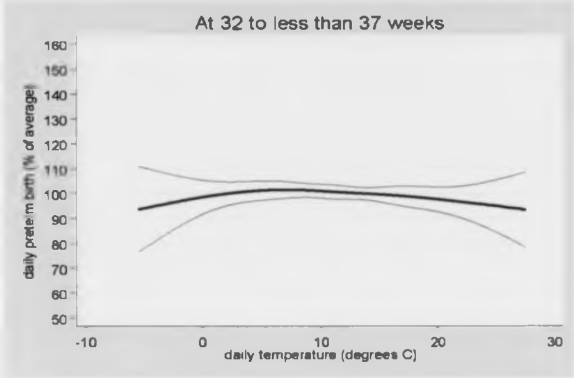


Figure 5.3: Adjusted relationship between daily preterm birth proportions and exposure to daily mean temperature on the day of birth (thick red line), stratified by severity of preterm birth (95% CI = thin grey lines).

a) This graph showed that temperature had little or no effect on preterm birth proportions occurring between 32 to less than 37 weeks



b) When this relationship was quantified, preterm birth proportions occurring between 24 to less than 32 weeks increased by 0.01% (95% CI 0.01 to 0.02) with each degree decrease in daily mean temperature on the day of birth.

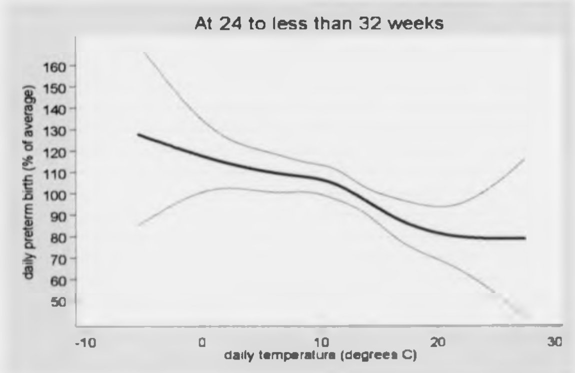
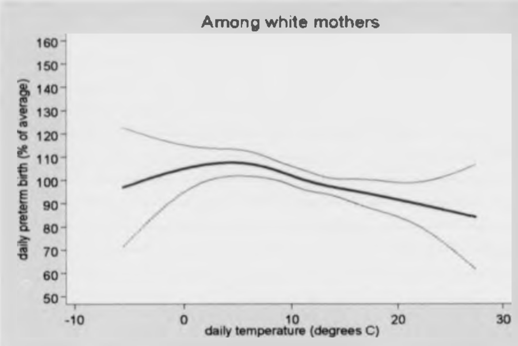
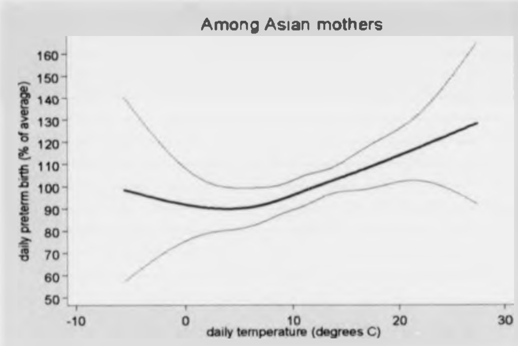


Figure 5.4 Adjusted relationship between daily preterm birth proportions and exposure to daily mean temperature on the day of birth (thick red line), by maternal ethnicity (95% CI = thin grey lines).

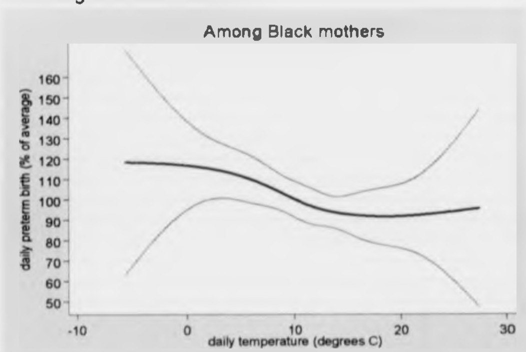
a) When the relationship for white mothers was quantified, preterm birth proportions increased by 0.05% (95% CI 0.01 to 0.08) with each degree decrease in daily mean temperature.



b) When the relationship for Asian mothers was quantified, preterm birth proportions increased by 0.09% (95% CI 0.01 to 0.17) with each degree increase in daily mean temperature.



c) This graph showed that temperature had little or no effect on preterm birth proportions occurring to Black mothers



5.1.2 Associations with hours of daily sunshine

Similar to the scatter plot for average monthly temperature, the unadjusted scatter plot of the average amount of daily sunshine per month suggested an inverse relationship with monthly preterm birth proportions (Figure 5.5a). This was expected since daily mean temperature and hours of sunshine were positively correlated (see Results Part I, section 4.2.1). The relationship was then plotted at a daily level using cubic splines for smoothing (Figure 5.5b). Because the relationship appeared straightforwardly linear, one term across the range of daily sunshine values was used in lieu of the cubic splines to quantify the crude, inverse relationship. Preterm birth proportions were found to decrease by 0.03% (95% CI 0.01 to 0.04) with each hour increase in exposure to sunshine on the day of birth.

After adjustment for public holidays, seasonality, and day of week and between year variations in preterm birth proportions (i.e., the core model), exposure to sunshine on the day of birth showed little or no association with preterm birth proportions (β= 0.01%, 95% CI -0.01 to 0.03; Figure 5.6a). In addition to the core adjustment for the above factors, cubic spline terms to adjust for daily mean temperature were added to the model.[n] After adjustment for daily mean temperature, exposure to sunshine on the day of birth continued to show little or no association with preterm birth proportions (β= 0.02%, 95% CI 0.00 to 0.04).

The lack of apparent association persisted until about four weeks before birth when the combined effect of exposure to sunshine over this time began to produce a different shape to the outcome-exposure relationship. At this four week averaged lag, the shape of the relationship indicated a threshold for a potential linear association between preterm birth proportions and sunshine at less than three hours per day (Figure 5.6b). Indeed, using maximum likelihood and varying the

[n] Please refer to Methods, section 3.6.3.2, last paragraph, for an explanation of why cubic spline terms were used to control for daily mean temperature.

threshold by one hour each time, a threshold at three hours resulted in the best-fitting model. The cubic splines for daily sunshine were removed and a linear term was fit for hours of daily sunshine below this threshold. Preterm birth proportions were found to decrease by 0.34% (95% CI 0.09 to 0.58) for each hour decrease in daily sunshine below three hours. Results were similar when control for daily mean temperature was added to the model (β= 0.33%, 95% CI 0.08 to 0.58). The effect below a threshold of three hours of sunshine per day continued to be seen through exposure during the six weeks before birth (β= 0.44%, 95% CI 0.15 to 0.73; Figure 5.6c); this result included control for daily mean temperature and was nearly identical to results from the model that did not control for temperature. According to measurements taken at the Heathrow weather monitoring station, 45% of days during the study period had 3 hours of sunshine or less.

There was evidence of effect modification when the model was stratified by severity of preterm birth, sex of the fetus and maternal age. A similar relationship to the above was found for preterm births that were male, to mothers aged 25 to 34 years and that occurred between 32 to less than 37 weeks of gestation; although little or no relationship was apparent on the day of birth (at lag 0), a different shape emerged with exposure during the four weeks before birth. The graphical output for each of these strata was almost identical to that of Figure 5.6b, indicating a threshold for a potential outcome- exposure relationship at less than three hours of sunshine per day. Proportions of preterm births that occurred between 32 and less then 37 weeks, among male fetuses and among mothers aged 25 to 34 years decreased with each hour decrease in exposure to daily sunshine below three hours (Table 5.1). In contrast, three or less hours of sunshine per day had little or no effect on proportions of preterm births occurring between 24 to less than 32 weeks, female preterm birth proportions and preterm birth proportions among older (35+ years) and younger mothers (less than 25 years). Again, in those strata where an effect was seen, the effect continued with exposure up to six weeks before birth (Table 5.1). As results with and without control for temperature were very similar, only results including control for temperature were presented.

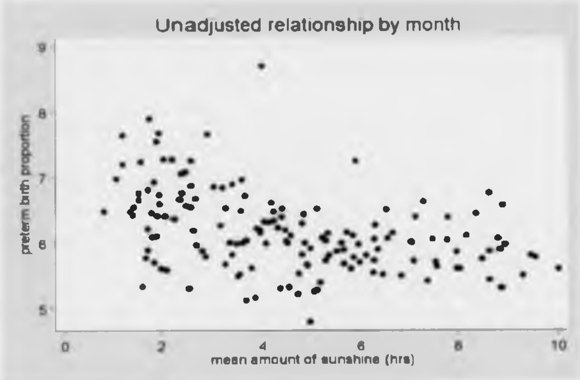
The stratified models for preterm births to parous and nulliparous women demonstrated no differences; both showed little or no relationship with exposure to sunshine on the day of birth or at any lag investigated, with and without control for daily mean temperature.

When stratified by maternal ethnicity, an association between hours of sunshine and daily preterm birth proportions was observed among white, but not black or Asian mothers. A separate model was generated for each stratum, at each lag, and in no case did the significance of the results differ when splines to control for daily mean temperature were included.

Exposure on the day of birth resulted in a decrease in preterm birth proportions among white mothers by 0.04% (95% CI 0.01 to 0.07) for every hour decrease in daily sunshine (Figure 5.7a). For exposure during the four weeks before birth, graphical inspection revealed a potential linear relationship below a threshold of seven hours of daily sunshine (Figure 5.7b). Repeated regression, varying the threshold of daily sunshine amount by one hour each time, confirmed that a threshold at seven hours provided the best fit. Linear terms above and below this threshold were created and replaced the spline terms in the model. Using a four week averaged lag, preterm birth proportions among white mothers decreased by 0.21% (95% CI 0.05 to 0.36) per hour decrease in daily sunshine below a threshold of seven hours. The association below this threshold continued when lags of five and six weeks were investigated. Using a combined lag of six weeks in the model, preterm birth proportions among white mothers decreased by 0.22% (95% CI 0.07 to 0.37) with each hour decrease in daily sunshine below seven hours (Figure 5.7c). Preterm birth proportions among black and Asian mothers exhibited little or no apparent relationship with daily hours of sunshine when the combined effect of weekly lags was investigated.

Figure 5.5: Unadjusted relationship between preterm birth proportions and hours of sunshine

a) Using monthly means for preterm birth proportions and hours of sunshine each day.



b) Using daily preterm birth proportions and hours of sunshine each day, the crude relationship (thick red line) was smoothed using cubic splines (95% CI = thin grey lines).

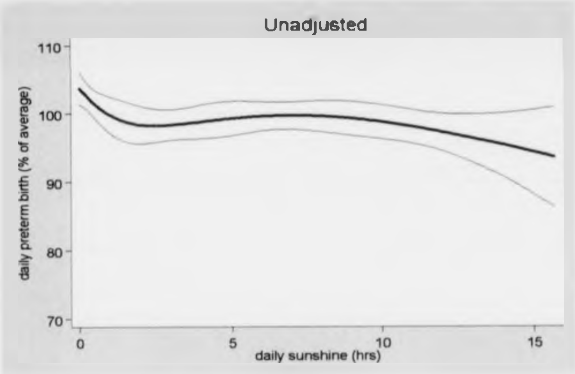
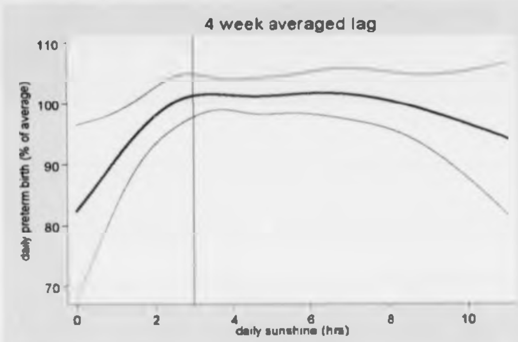


Figure 5.6 Adjusted relationship (thick red line), including control for daily mean temperature, between daily preterm birth proportions and hours of sunshine each day (95% CI = thin grey lines).

a) This graph indicated little or no relationship with exposure to sunshine on the day of birth.

b) The relationship shown here indicated a potential linear effect, below three hours, of cumulative exposure to sunshine during the four weeks before birth.



c) The shape of the relationship persisted with cumulative exposure to sunshine up to six weeks before birth.

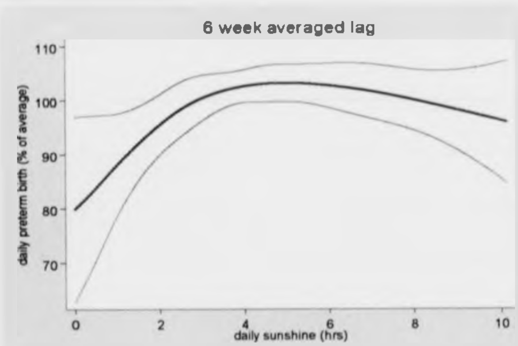


Table 5.1: Adjusted stratified models, for cumulative exposure occurring four or six weeks before birth, below a threshold of three hours.

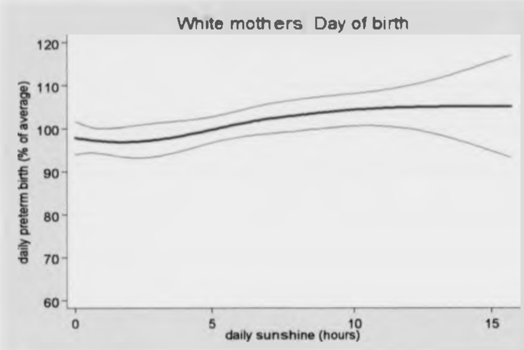
	Decrease in preterm birth proportions per hour decrease in daily sunshine, below 3 hours*			
	4 wks before**	**95% CI**	**6 wks before****	**95% CI**
Severity				
24 to <32 weeks	0.01%	-0.10 to 0.11	0.09%	-0.03 to 0.21
32 to <37 weeks	**0.36%**	**0.11 to 0.61**	**0.41%**	**0.12 to 0.70**
Sex of fetus				
Male	**0.61%**	**0.25 to 0.97**	**0.78%**	**0.37 to 1.20**
Female	0.05%	-0.30 to 0.40	0.09%	-0.32 to 0.49
Maternal age				
35+ years	-0.05%	-0.80 to 0.70	0.56%	-0.32 to 1.44
25-34 years	**0.54%**	**0.24 to 0.84**	**0.56%**	**0.21 to 0.91**
<25 years	-0.11%	-0.66 to 0.43	0.52%	-0.59 to 0.69

** Includes control for public holidays, seasonality, day of week and between year variations, and daily mean temperature.*

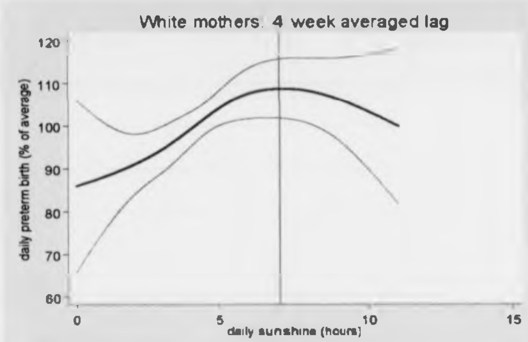
*** The coefficient should be interpreted as an absolute decrease in preterm birth proportions per hour decrease in exposure to daily sunshine.*

Figure 5.7: Adjusted relationship (includes control for daily mean temperature) between daily proportions of preterm births and exposure to sunshine (thick red line) among white mothers (95% CI = thin grey lines).

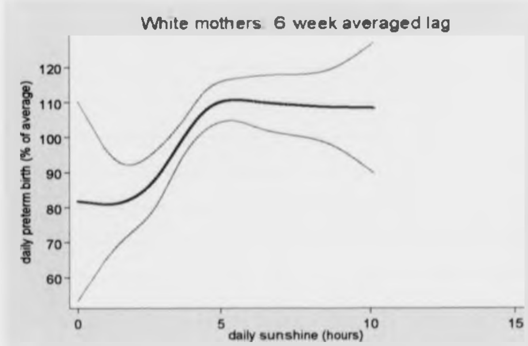
a) This graphed showed that exposure on the day of birth had an essentially linear relationship with preterm birth proportions among white mothers across the whole range of sunshine values.



b) The relationship shown here indicated a potential linear effect, below seven hours, of cumulative exposure to sunshine during the four weeks before birth for white mothers.



c) The shape of the relationship persisted with cumulative exposure to sunshine up to six weeks before birth for white mothers.



5.1.3 Associations with amount of daily rainfall

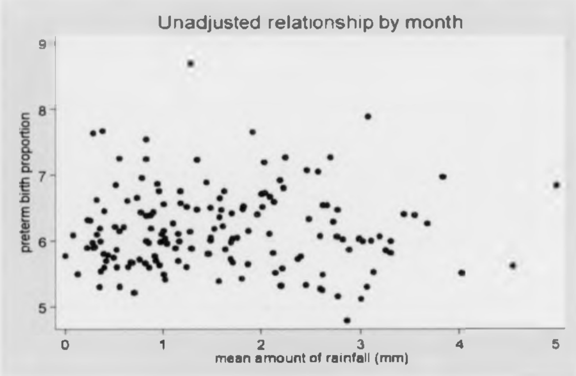
The scatter plot of crude relationship between monthly preterm birth proportions and mean amount of daily rainfall each month did not reveal any obvious potential associations (Figure 5.8a). When summarised at a daily level using cubic spline terms, the unadjusted model exhibited a flat, linear relationship (Figure 5.8b). Using a linear term across the range of daily rainfall values in lieu of the smoothing splines, regression analysis confirmed the lack of any association (β= 0.00, 95% CI -0.02 to 0.02).

In the adjusted model, daily preterm birth proportions were controlled for public holidays, seasonality, and day of week and between year variations. Exposure to rainfall on the day of birth showed little or no relationship with daily preterm birth proportions (Figure 5.9). The lack of association was confirmed using regression using a single linear term across the range of rainfall values which replaced the spline terms in the model (β= 0.01%, 95% CI -0.01 to 0.02). When the combined effect of daily lags up to one week and the combined effect of weekly lags up to six weeks were investigated, the lack of apparent association persisted. Thus, only lag 0 was investigated in any of the stratified models.

When stratified by sex of the fetus, maternal age, severity of preterm birth, maternal ethnicity, and parity, there were no differences between the models for each stratum. All models demonstrated results consistent with little or no association between preterm birth proportions and exposure to rainfall on the day of birth.

Figure 5.8: Unadjusted relationship between preterm birth proportions and amount of daily rainfall.

a) Using monthly means for preterm birth proportions and amount of daily rainfall.



b) Using daily preterm birth proportions and daily rainfall amount, the crude relationship (thick red line) was smoothed using cubic splines (95% CI = thin grey lines).

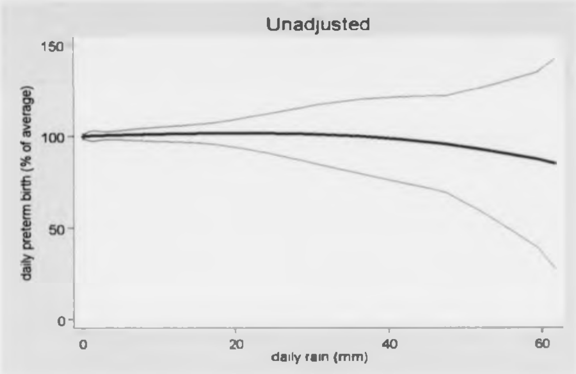
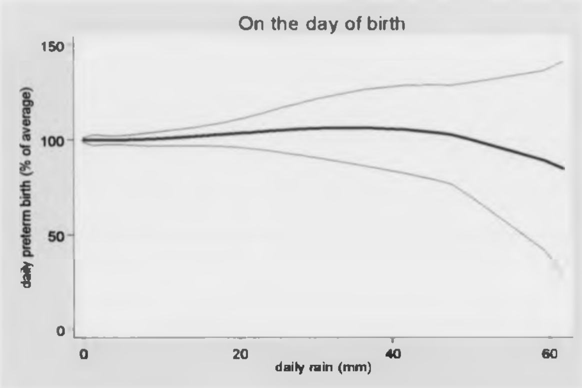


Figure 5.9: Adjusted relationship (thick red line) between daily preterm birth proportions and amount of daily rainfall at lag 0 (95% CI = thin grey lines).



5.1.4 Associations with daily mean barometric pressure

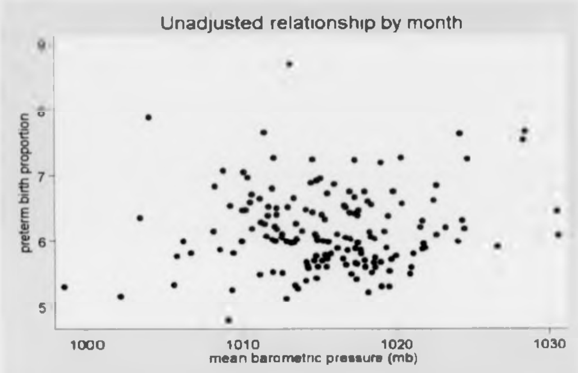
The initial scatterplot did not reveal any obvious crude relationship between monthly preterm birth proportions and the monthly average of daily mean barometric pressure (Figure 5.10a). Spline terms were used to summarise the relationship at a daily level which suggested possible linear associations at the higher and lower values of daily mean barometric pressure (Figure 5.10b).

After adjustment for public holidays, seasonality, and day of week and between year variations in preterm birth proportions, the relationship with daily mean barometric pressure appeared flat and linear for exposure on the day of birth (Figure 5.11a). Because there were few days with very high or very low daily mean barometric pressure, there were wide confidence intervals where potential linear relationships had been seen at these values in the unadjusted model. Assuming a linear relationship across the range of barometric pressure values, the spine terms were replaced by one linear term in the model and little or no association was found (β= 0.00, 95% CI 0.00 to 0.01). The investigation of the combined effect of daily lags up to one week and the combined effect of weekly lags up to six weeks, in lieu of lag 0 in the model, did not alter the shape of the flat relationship (Figure 5.11b & 5.11c).

The analysis was repeated after preterm birth proportions were stratified by severity of preterm birth, maternal ethnicity, parity, sex of the fetus and by maternal age. A separate model was generated for each strata and no differences were found. Each model demonstrated little or no relationship with exposure to rain on the day of birth.

Figure 5.10: Unadjusted relationship between preterm birth proportions and mean barometric pressure.

a) Using monthly means for preterm birth proportions and daily mean barometric pressure.



b) Using daily preterm birth proportions and daily means for barometric pressure, the crude relationship (thick red line) was smoothed using cubic splines (95% CI = thin grey lines).

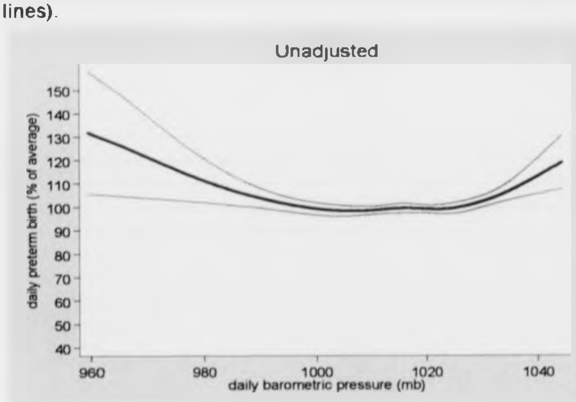
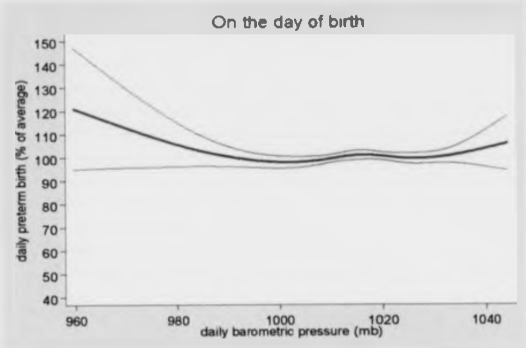
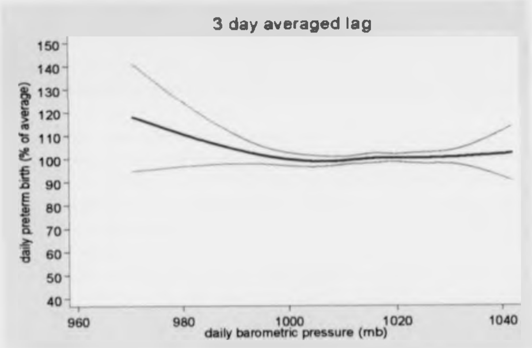


Figure 5.11: Adjusted model of daily preterm birth proportions and daily mean barometric pressure on the day of birth.

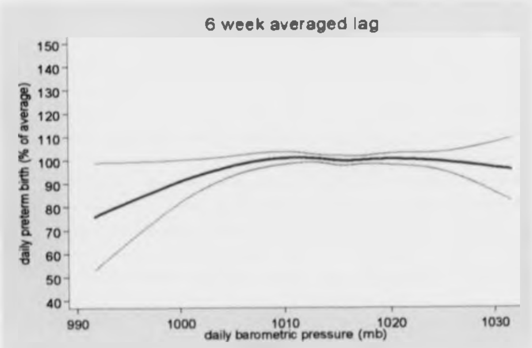
a) This graph indicated little or no relationship with exposure to barometric pressure on the day of birth.



b) The graph shown here indicated no apparent effect of cumulative exposure to barometric pressure during the three days before birth.



c) The graph shown here indicated no apparent effect of cumulative exposure to barometric pressure during the six weeks before birth.



5.1.5 Associations with largest daily drop in barometric pressure

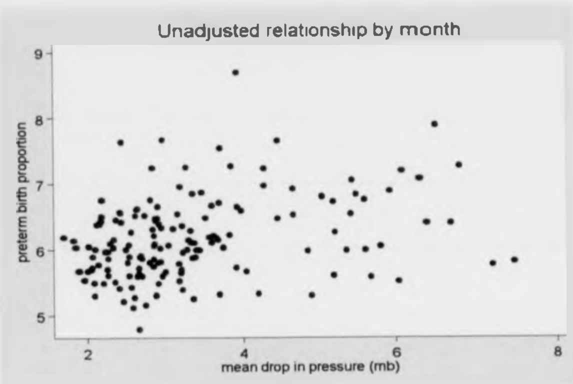
When the largest daily drop in barometric pressure was averaged by month and plotted against monthly preterm birth proportions without adjusting for any other factors, a positive relationship could be seen although most of the scatter was concentrated around the lower left hand corner of the plot (Figure 5.12a). When summarised using cubic splines and daily values for the largest drop in barometric pressure and preterm birth proportions, however, the relationship appeared flat and linear (Figure 5.12b). There were wide confidence intervals due to few days with large drops in pressure which may account for the discrepant findings in the unadjusted graphs. Replacing the spline terms with one linear term made up of the range of barometric pressure values, regression analysis confirmed the lack of any association in the unadjusted model (β= 0.01%, 95% CI -0.01 to 0.02).

After the model was adjusted for public holidays, seasonality, and day of week and between year variations in preterm birth proportions, exposure to a large barometric pressure drop on the day of birth had little effect on preterm birth proportions (β = -0.01%, 95% CI -0.03 to 0.01; Figure 5.13a). The shape of the relationship varied little and little or no relationships were apparent when the combined effect of daily lags up to one week and the combined effect of weekly lags up to six weeks before birth were investigated in lieu of exposure on the day of birth (Figure 5.13b).

Stratified analysis by severity of preterm birth, maternal ethnicity, parity, sex of the fetus and by maternal age demonstrated little or no evidence of effect modification. There were no differences between models of each stratum; each model showed little or no association with exposure to a drop in barometric pressure on the day of birth.

Figure 5.12: Unadjusted relationship between preterm birth proportions and largest drop in barometric pressure.

a) Using monthly means for preterm birth proportions and the largest daily drop in barometric pressure.



b) Using daily preterm birth proportions and the largest daily drop in barometric pressure, the crude relationship (thick red line) was smoothed using cubic splines (95% CI = thin grey lines).

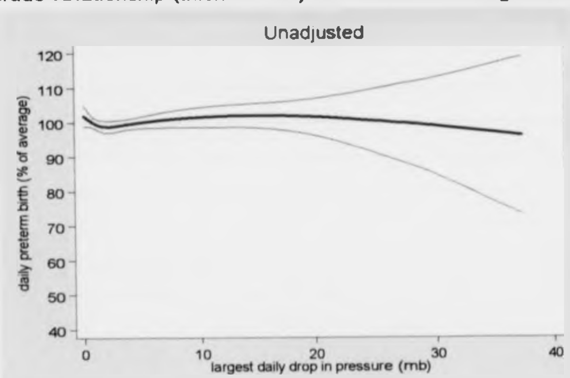
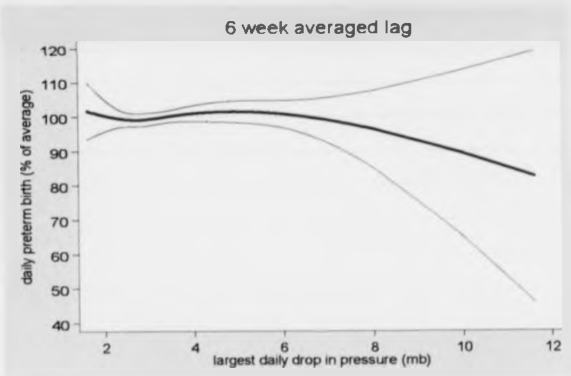


Figure 5.13: Adjusted relationship (thick red line) between daily preterm birth proportions and the largest daily drop in barometric pressure (95% CI = thin grey lines).

a) This graph indicted little or no effect of exposure to a drop in barometric on the day of birth

b) The relationship shown here indicated no apparent effect of cumulative exposure to drops in barometric pressure during the six weeks before birth.



5.1.6 Associations with daily mean relative humidity

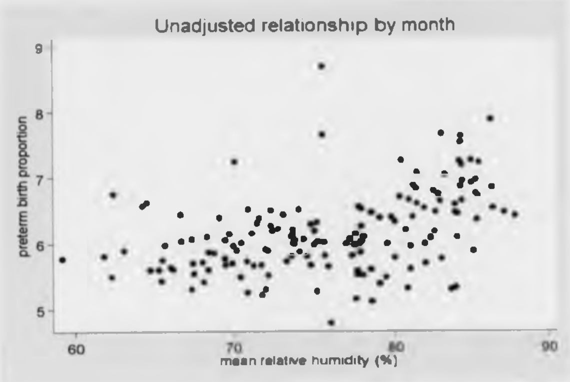
In the scatter plot of the crude relationship between monthly mean preterm birth proportions and monthly means of relative humidity, a positive correlation was evident (Figure 5.14a). Using cubic splines to smooth the relationship at a daily level, the positive relationship, which appeared linear, could be seen more clearly (Figure 5.14b). The cubic splines were replaced with a linear term consisting of the range of actual relative humidity values on the day of birth and preterm birth proportions increased by 0.02% (95% CI 0.01 to 0.02) with every percentage increase in mean relative humidity.

After preterm birth proportions were adjusted for public holidays, seasonality, and day of week and between year variations, however, little or no relationship between daily preterm birth proportions and exposure to relative humidity on the day of birth remained (β= 0.00, 95% CI -0.01 to 0.01; Figure 5.15a). Using spline terms to adjust for daily mean temperature in the model did not alter this finding (β= 0.00, 95% CI -0.01 to 0.01). The shape of the relationship remained essentially the same when the combined effect of daily lags up to one week and the combined effect of weekly lags up to six weeks were investigated in lieu of exposure on the day of birth (Figure 5.15b).

Stratifying preterm birth proportions by severity of preterm birth, maternal ethnicity, parity, sex of the fetus and by maternal age, and generating a model for each stratum, did not produce any differences. All models demonstrated little or no relationship between preterm birth proportions and exposure to relative humidity on the day of birth.

Figure 5.14 Unadjusted relationship between preterm birth proportions and mean relative humidity

a) Using monthly means for preterm birth proportions and daily mean relative humidity



b) Using daily preterm birth proportions and daily mean relative humidity, the crude relationship (thick red line) was smoothed using cubic splines (95% CI = thin grey lines).

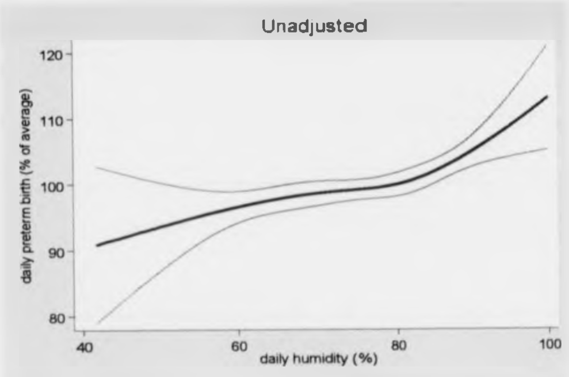
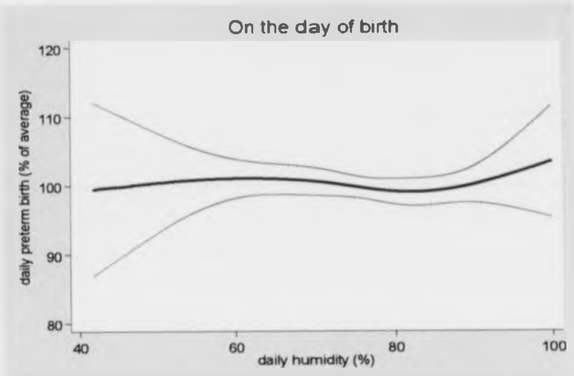
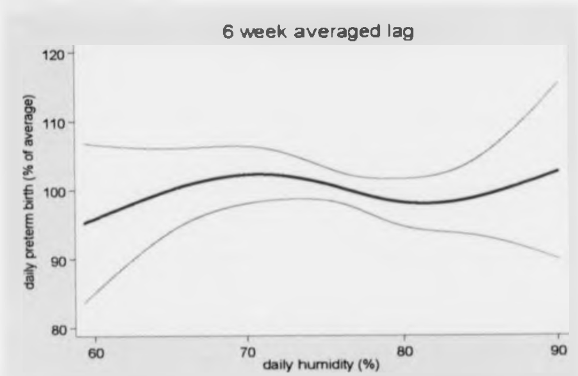


Figure 5.15: Adjusted relationship (thick red line), including control for daily mean temperature, between daily preterm birth proportions and daily mean relative humidity (95% CI = thin grey lines).

a) This graph indicated little or no relationship with exposure to relative humidity on the day of birth.



b) The lack of relationship persisted with cumulative exposure to relative humidity up to six weeks before birth.



5.2 Air pollution exposures

5.2.1 Associations with ozone

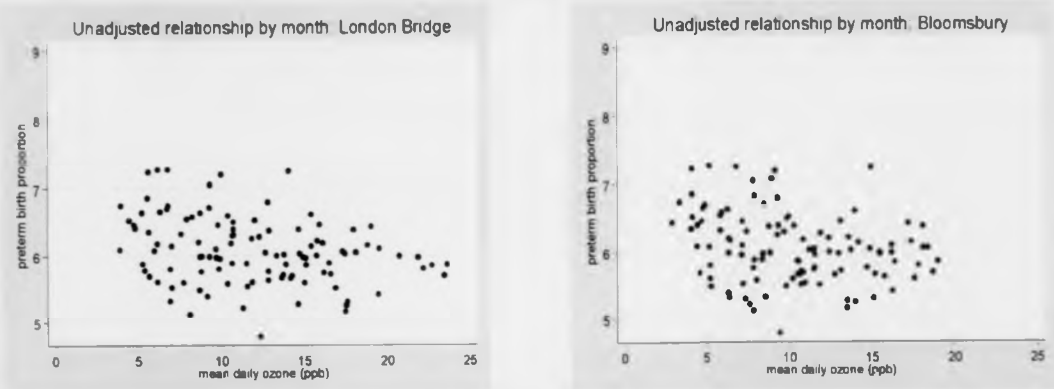
Monthly preterm birth proportions were plotted against mean daily levels of ambient ozone that were averaged by month for each monitoring station. For both the Bloomsbury and London Bridge Place monitoring station, graphical inspection of the crude relationship in the scatter plots indicated a potential inverse association between preterm birth proportions and ambient ozone levels (Figure 5.16a); monthly proportions of preterm birth appeared to decrease as the monthly mean of daily ozone levels increased. The data from both monitoring stations were then summarised at a daily level using cubic splines (Figure 5.16b). The inverse relationship appeared strongest at the lower values of mean ambient ozone, below about 10ppb per day, after which the relationship seemed to level out. Replacing the spline terms with one linear term across the range of ozone values, there was little or no association between preterm birth proportions and mean levels of ambient ozone (β = 0.02%, 95% CI 0.00 to 0.03 for London Bridge Place and β = -0.01%, 95% CI -0.02 to 0.00).

After controlling for public holidays, seasonality, and day of week and between year variations in preterm birth proportions, exposure to ambient ozone on the day of birth demonstrated fairly flat relationships with preterm birth proportions, with wide confidence intervals at higher mean ozone levels (Figure 5.17). The wide confidence intervals above 30ppb were due to few days having mean ambient ozone levels this high. A single linear term using the range of values for ozone replaced the spine terms in the model for quantification. Little or no association was apparent for exposure to ambient ozone on the day of birth (β= 0.00, 95% CI -0.01 to 0.02 for London Bridge Place and β= 0.01%, 95% CI -0.01 to 0.02 for Bloomsbury). Results were similarly non-significant when cubic splines to control for daily mean temperature were included in the models (β= 0.01%, 95% CI -0.01 to 0.02 for London Bridge Place and β= 0.01, 95% CI 0.00 to 0.03 for Bloomsbury).

For ambient levels of ozone as measured at either monitoring station, core adjusted models using cumulative daily exposure up to one week or cumulative weekly exposure up to six weeks also showed little or no relationship to daily preterm birth proportions, with or without splines to control for daily mean temperature. The shape of the relationship for exposure during the six weeks before birth remained similar to that seen for exposure on the day of birth (Figure 5.18).

Adjusted models were run for preterm birth proportions that were stratified by maternal age group, sex of the fetus, severity of preterm birth, maternal ethnicity and parity. There was no evidence for potential interaction as the models for each stratum were similar. This was true for models using measurements of ambient ozone from either of the two monitoring stations, with or without splines to control for daily mean temperature. Overall, there was little or no association between exposure to ambient ozone and preterm birth proportions.

Figure 5.16 Unadjusted relationship between preterm birth proportions and means of daily ozone levels.
a) Using monthly means for preterm birth proportions and daily levels of ozone.



b) Using daily preterm birth proportions and daily mean levels of ambient ozone, the crude relationship (thick red line) was smoothed using cubic splines (95% CI = thin grey lines).

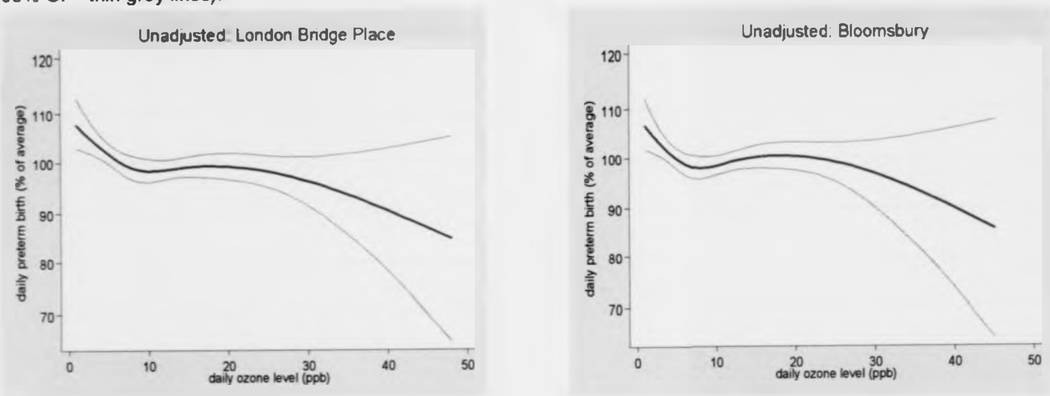


Figure 5.17: Adjusted relationship (thick red line), including control for daily mean temperature, between daily preterm birth proportions and exposure on the day of birth to daily mean levels of ambient ozone, as measured at two different monitoring stations (95% CI = thin grey lines).

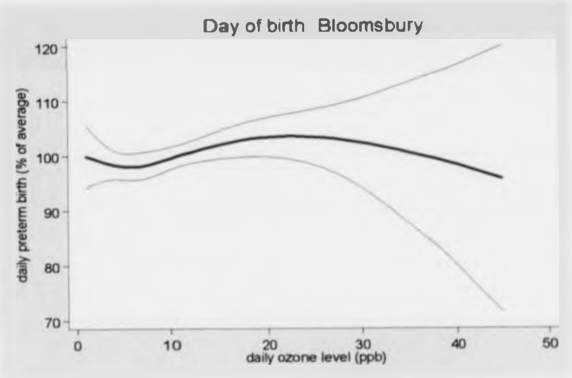
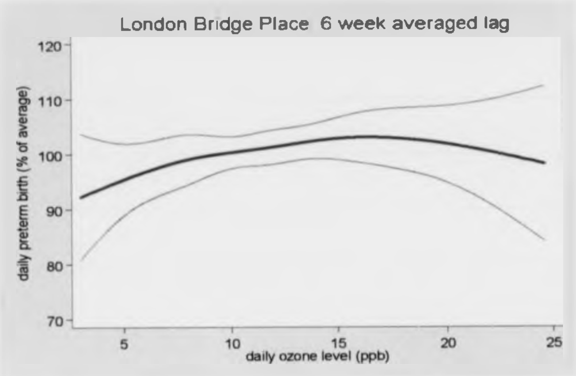
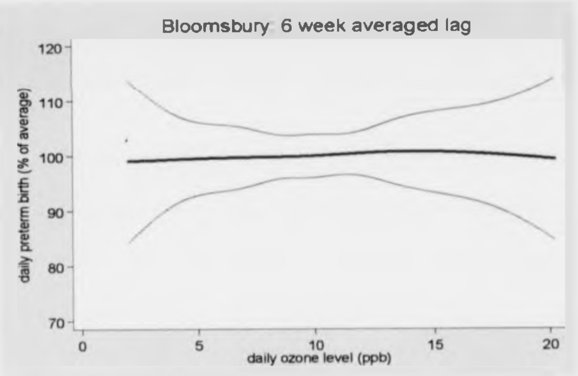


Figure 5.18 Adjusted relationship (thick red line), including control for daily mean temperature, between daily preterm birth proportions and cumulative exposure during the six weeks before birth to daily mean levels of ambient ozone, as measured at two different monitoring stations (95% CI = thin grey lines).





5.2.2 Associations with PM_{10}

There was no relationship that was immediately apparent in the unadjusted scatter plot of monthly preterm birth proportions and daily mean PM_{10} levels by month (Figure 5.19a). Summarised using spline terms, graphical inspection of the crude relationship at a daily level appeared flat and linear (Figure 5.19b).

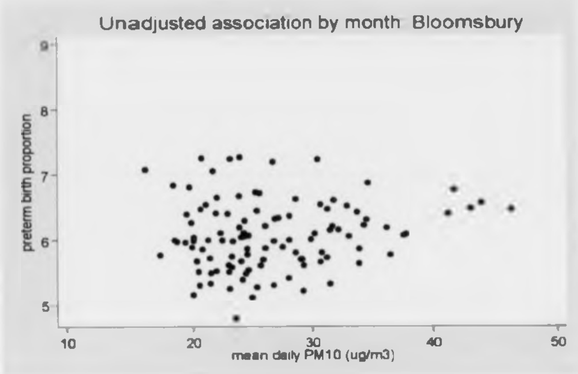
Preterm birth proportions were adjusted for public holidays, seasonality, and day of week and between year variations. The shape of the relationship remained similar to that seen in the unadjusted model (Figure 5.20a). As the relationship appeared linear across the range of PM_{10} values, one linear term was used to replace the spline terms in the model to quantify the association. There was little or no association between daily preterm birth proportions and exposure on the day of birth to ambient PM_{10} (β= 0.00, 95% CI -0.01 to 0.01).

With the exception of wider confidence intervals, there was little change in the shape of the relationship when the effect of combined daily lags up to one week and the effect of combined weekly lags up to six weeks were examined in the adjusted model (Figure 5.20b).

When preterm birth proportions were stratified by severity of preterm birth, male or female birth, maternal age groups, maternal ethnicity or parity, the PM_{10}-preterm birth relationship did not reveal any associations in any model for any strata.

Figure 5.19: Unadjusted relationship between preterm birth proportions and mean ambient levels of PM_{10}.

a) Using monthly means for preterm birth proportions and daily mean levels of ambient PM_{10}.



b) Using daily preterm birth proportions and daily mean ambient PM_{10}, the crude relationship (thick red line) was smoothed using cubic splines (95% CI = thin grey lines).

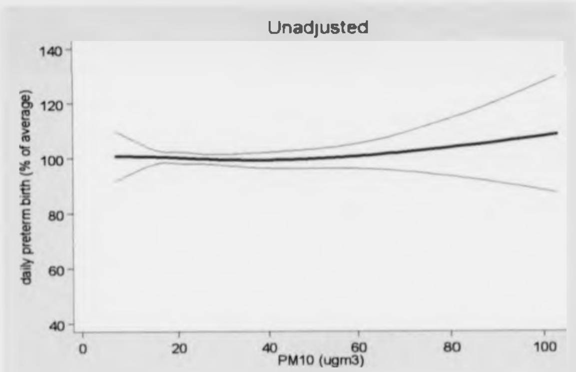
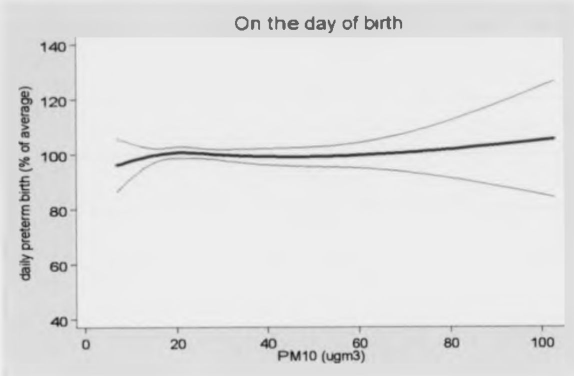
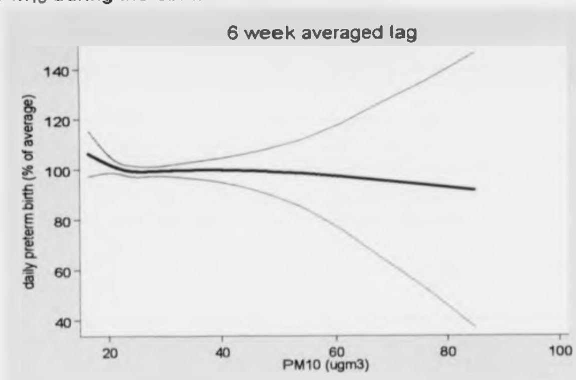


Figure 5.20: Adjusted relationship (thick red line) between daily preterm birth proportions and daily mean ambient PM_{10} levels (95% CI = thin grey lines).

a) This graph indicated little or no effect after exposure to PM_{10} on the day of birth



b) The relationship shown here indicated no apparent effect of cumulative exposure to ambient PM_{10} during the six weeks before birth.



5.3 Influenza A exposure

During the study period, 85% of the days (4051/4749) had zero cases of influenza A and a further 10% (495/4749) had only one case per day. Using monthly totals for influenza A counts, 43% of the months still had only one influenza case or less (43/156 months were 0, 24/156 were 1), rendering it difficult to interpret any potential relationship from the scatter plot (Figure 5.21a).

As 95% of the days during the study period had one or zero cases of influenza A recorded, splines were not included in the model. Instead, a linear plot of the crude relationship between daily preterm birth proportions and exposure to influenza A on the day of birth was initially generated. Daily preterm birth proportions increased by 0.05% (95%CI 0.03 to 0.08) with every additional case of influenza A each day (Figure 5.21b).

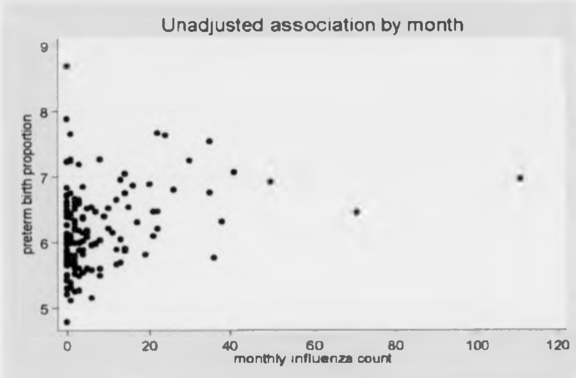
Due to the large number of days with 0 or only one count of influenza A, the data were aggregated by week for the adjusted analysis (see Methods, section 3.4.3). After controlling for seasonality and between year variations in weekly preterm birth proportions, the association with exposure to influenza A during the week of birth persisted but did not retain significance (β= 0.01, 95% CI -0.02 to 0.03; Figure 5.22). Lagged analysis was conducted for averaged weeks two to six weeks before birth with a separate model for each lag (n=5 models). The incorporation of lag terms in the model did not return any significant associations.

When weekly preterm birth proportions were stratified by maternal ethnicity and adjusted for seasonality and between year variations, a significant effect of exposure to influenza A during the week of birth was found. Weekly preterm birth proportions among white mothers increased by 0.05% (95% CI 0.01 to 0.08) with each additional case of influenza A each week. There was no significant association between weekly influenza counts and weekly preterm birth proportions among black or Asian mothers (β= 0.05, 95% CI -0.09 to 0.18

and β= 0.03, 95% CI -0.05 to 0.11, respectively). Nor were any significant associations apparent in any of the other stratified models.

Figure 5.21: Crude linear relationship between preterm birth proportions and influenza A counts.

a) Using monthly means for preterm birth proportions and the sum of influenza counts for each month.



b) The crude relationship (thick red line) using daily preterm birth proportions and daily influenza A counts (95% CI = thin grey lines).

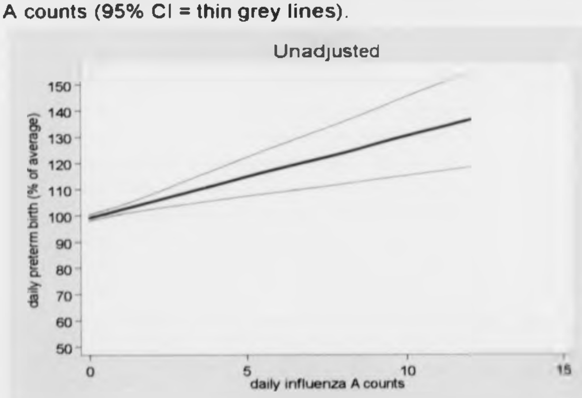
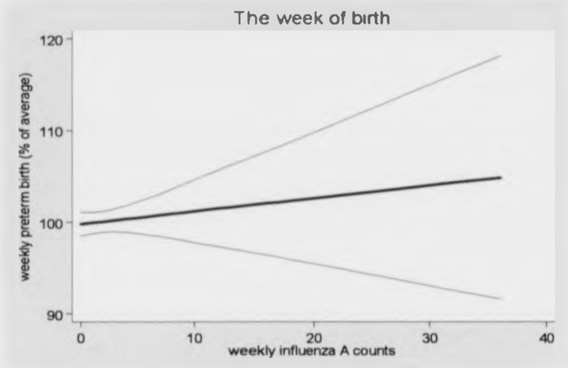


Figure 5.22 Adjusted relationship* (thick red line) between weekly preterm birth proportions and weekly counts of influenza A (95% CI = thin grey lines).



* *adjusted for seasonality and between year variations in weekly preterm birth proportions*

5.4 Effects around the time of conception

In addition to around the time of birth, it was hypothesised that an exposure may manifest its effect around the time of conception thereby influencing the seasonal pattern of preterm birth.[o] By subtracting backwards from the date of birth using gestational age in days, the dates of conception were estimated so that any potential effect of the exposure variables around this time on preterm birth proportions could be assessed. For this analysis therefore, the number of births conceived on any given day during the study period served as the denominator, and the coefficient from the regression analysis now represented the change in *the proportion of conceptions resulting in a preterm birth* per unit change in a given measure of the exposure variable.

Daily preterm birth proportions were adjusted for public holidays, seasonality, and day of week and between year variations. A separate model was then run for each meteorological variable by adding the values from the day of conception for each variable to the adjusted core model. Using spline terms to smooth the graphical outputs, little or no relationship was apparent between the proportion of conceptions resulting in a preterm birth and exposure to any of the meteorological variables on the day of conception (Figure 5.23). For each model, the spline terms were removed and replaced with a single linear term to

[o] For an explanation on associations on the date of conception please see Methods, section 3.6.5.1

quantify the association. The linear terms spanned the range of actual values on the day of conception for each exposure. Regression confirmed that little or no association existed between daily preterm birth proportions and exposure to any of the meteorological variables on the day of conception (Table 5.2). Results were similar when spline terms to control for daily mean temperature were included in the sunshine and relative humidity models.

Similarly, each air pollution exposure was added to a core model in which preterm birth proportions were adjusted for public holidays, seasonality, and day of week and between year variations. Little or no relationship with exposure to ambient ozone or PM_{10} on the day of conception was seen (Figure 5.24). Again, adding control for daily mean temperature to the ozone models had little effect. A single linear term consisting of the range of actual values for each air pollution exposure on the day of conception was added to each model in lieu of the spline terms to quantify the lack of effect (Table 5.2).

Influenza A was analysed using weekly counts and weekly proportions of preterm births. Because 72.4% of weeks had only one (110/624 weeks) or no cases (342/624 weeks) of influenza, spline terms were not used to smooth the relationship as the similarity in values resulted in terms being dropped from the analysis due to collinearity. After controlling for seasonality and between year variations in weekly preterm birth proportions, little or no relationship could be seen between exposure to influenza A during the week of conception and weekly proportions of preterm birth (Figure 5.25). Regression confirmed the lack of any association (β= -0.01, 95% CI -0.03 to 0.02).

Figure 5.23 Adjusted relationship (thick red line) between the proportion of conceptions that resulted in a preterm birth and exposure to meteorological exposures on the estimated day of conception (95% CI = thin grey lines). Models for hours of daily sunshine and daily mean relative humidity included control for daily mean temperature.

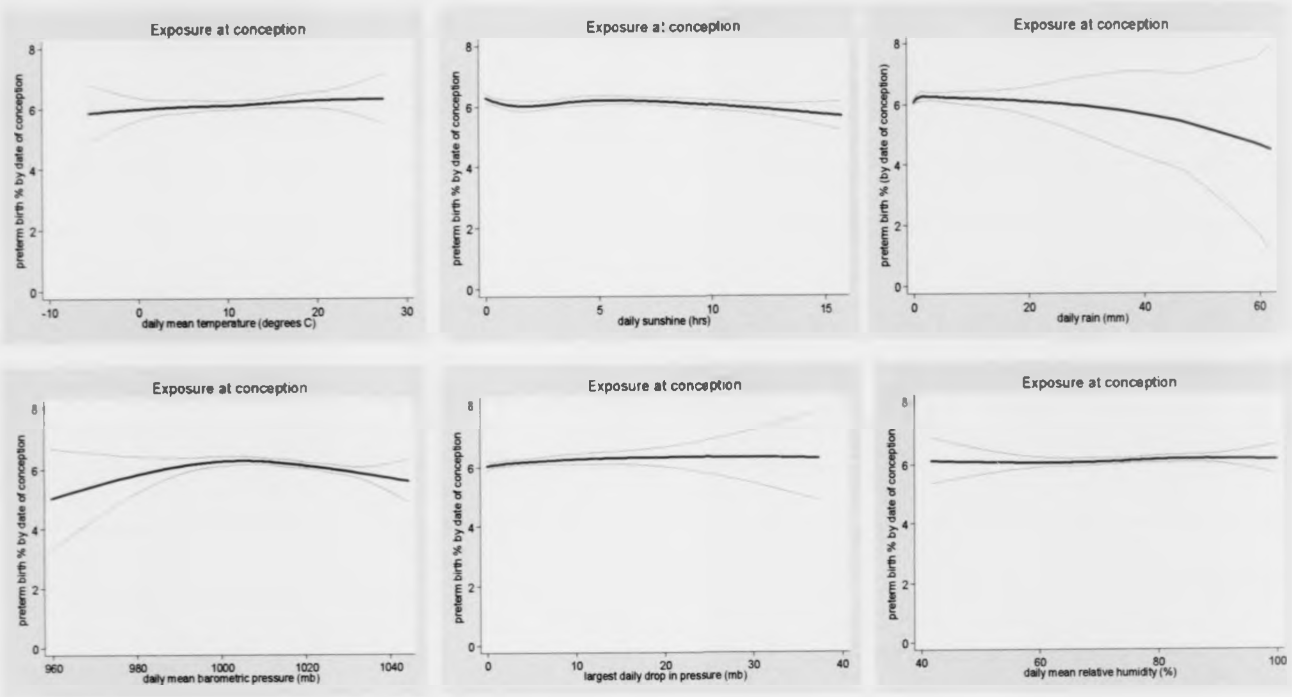


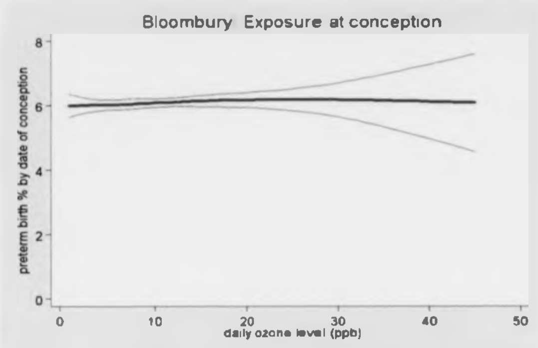
Table 5.2: Adjusted regression analysis investigating effect of exposure on the estimated day of conception.

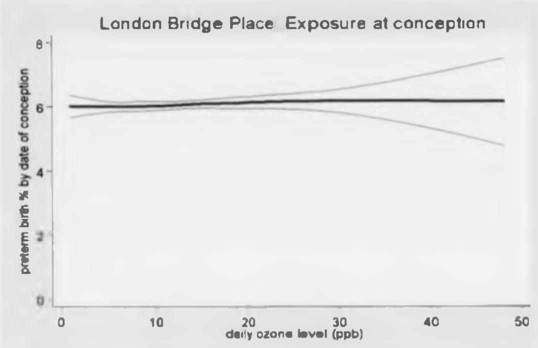
Exposure	% change in proportion of preterm birth*	95% CI
Meteorological		
Daily mean temperature (°C)	0.01	-0.01 to 0.04
Hours of daily sunshine†	-0.02	-0.04 to 0.00
Amount of daily rain (mm)	0.00	-0.02 to 0.02
Daily mean barometric pressure (mb)	-0.01	-0.02 to 0.00
Largest daily drop in pressure (mb)	0.02	0.00 to 0.03
Daily mean relative humidity† (%)	0.01	0.00 to 0.01
Air pollution		
Daily ambient ozone (ppb), Bloomsbury†	0.01	-0.01 to 0.03
Daily ambient ozone (ppb), London Bridge Place†	0.01	-0.01 to 0.02
Daily ambient PM_{10} ($\mu g/m^3$)	-0.01	-0.02 to 0.00

* *The values in this column represent the coefficient or 'β' and should be interpreted as an absolute increase in the proportion of conceptions resulting in a preterm birth per unit increase in exposure. Negative signs indicate an inverse association*

† *includes control for daily mean temperature with splines*

Figure 5.24 Adjusted relationship (thick red line) between the proportion of conceptions resulting in a preterm birth and exposure to air pollution variables on the estimated day of conception (95% CI = thin grey lines). The models of ozone included control for daily mean temperature.





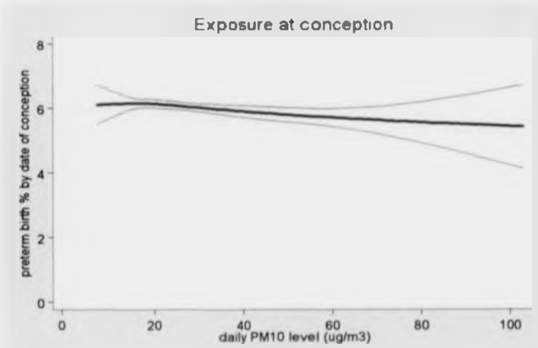
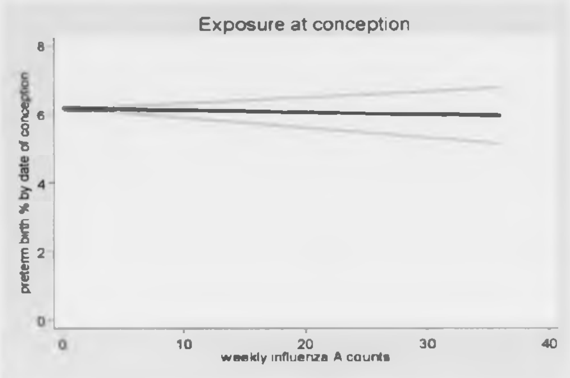


Figure 5.25: Adjusted relationship (thick red line) between the weekly proportion of conceptions resulting in a preterm birth and exposure to influenza A counts during the week of conception (95% CI = thin grey lines).



5.5 Sensitivity analysis

To assess the potential effect of imprecise exposure assessment, a sensitivity analysis was undertaken. Models for each exposure were re-run after removing the births that occurred in the hospitals furthest from the air pollution and weather monitoring stations from the dataset (see Methods, section 3.6.7). The hospitals from which births were included or excluded and their respective distribution of births and preterm births is shown in Table 5.3.

Table 5.3: The hospitals from which births were included or excluded in the sensitivity analysis and their distribution of births and preterm births

Hospital name	Number of births (% of total*)	Number preterm (% of births)
Included		
Ashford	13,783 (2.9)	739 (5.4)
Central Middlesex	14,704 (3.0)	1,054 (7.2)
Chelsea and Westminster**	28,722 (5.9)	1,844 (6.4)
Ealing	15,894 (3.3)	921 (5.8)
Hillingdon	41,886 (8.7)	2,553 (6.1)
Northwick Park	42,897 (8.9)	2,734 (6.4)
St Mary's, Paddington	37,178 (7.7)	2,814 (7.6)
West Middlesex	28,324 (5.9)	1,578 (5.6)
Westminster	1,036 (0.2)	107 (10.3)
Excluded		
Barnet General & Edgware General†	35,911 (7.4)	2,262 (6.3)
Bedford	29,490 (6.1)	1,616 (5.5)
Hemel Hempstead‡	26,978 (5.6)	1,354 (5.0)
Lister (Stevenage)	34,891 (7.2)	2,357 (6.8)
Luton and Dunstable	52,444 (10.9)	3,609 (6.9)
QE2 (Welwyn Garden City)	32,298 (6.7)	1,731 (5.4)
St Albans	8,023 (1.7)	380 (4.7)
Watford General	38,306 (7.9)	2,063 (5.4)

* *of 482,765 total births*
** *Includes births from West London which merged to form Chelsea and Westminster in 1995.*
† *Moved the majority of the maternity unit to Barnet General; currently a small midwife-led unit.*
‡ *Closed for renovations for 3 years; women went to Watford General during this time.*

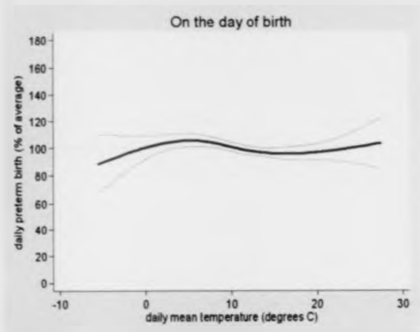
As previously, a separate model was generated for each exposure variable which was added only after preterm birth proportions were adjusted for public holidays, seasonality, and day of week and between year variations. The models for sunshine and relative humidity also included adjustment for daily mean temperature.

The exclusion of births that occurred in hospitals furthest from the monitoring stations appeared to have little or no effect on the majority of preterm birth-exposure relationships. The shape of the relationship between preterm birth proportions and most of the meteorological exposures was similar to results obtained from the adjusted models that included births from all hospitals (Figure 5.26). The shape of the relationship for rainfall on days that received more than 40mm was unreliable as it was generated by data from 5 days only. For each model, the spline terms were removed and replaced with a single linear term to quantify the association. The linear terms spanned the range of actual values on the day of birth for each exposure. Regression confirmed that little or no association existed between daily preterm birth proportions and exposure to any of the meteorological variables on the day of birth (Table 5.4).

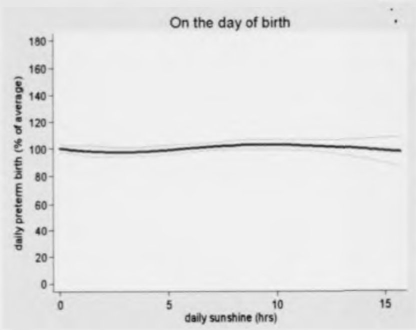
Similar to the meteorological exposures, there were no discernable differences in the general shape of the relationship between daily preterm birth proportions with exposure to mean ambient ozone on the day of birth when births from the furthest hospitals were excluded (Figure 5.27). For ambient PM_{10} however, there appeared to be a threshold for a linear association with preterm birth proportions at the lower daily mean levels. Using maximum likelihood and varying the level of PM_{10} by one $\mu g/m^3$ each time, 21 $\mu g/m^3$ was found to be the change-point that resulted in the model with the best fit. A linear term below this threshold was fit and added to the model in lieu of the spline terms. By excluding the births that occurred in the hospitals that were located furthest from the air pollution monitoring stations, a small effect from exposure to ambient PM_{10} on the day of birth could be seen. Preterm birth proportions decreased by 0.05% (95% CI 0.01 to 0.11) for every $\mu g/m^3$ decrease in the daily mean level of ambient PM_{10} below 21 $\mu g/m^3$. The associations for ozone were quantified using regression after replacing the spline terms with a linear term that spanned the range of actual values on the day of birth (Table 5.4).

Figure 5.26 Adjusted relationship (thick red lines) between daily preterm birth proportions and exposure on the day of birth to meteorological variables, after exclusion of the births that occurred at hospitals located furthest from weather monitoring stations (95% CI = thin grey lines). Graphs of daily sunshine and daily mean relative humidity included control for daily temperature.

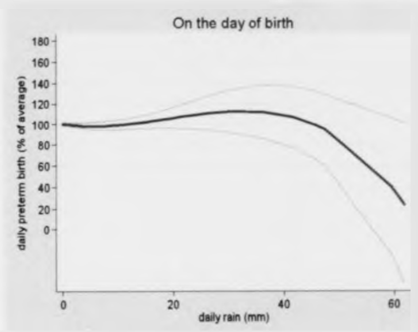
The location of the corresponding graph from the analysis using births from all hospitals is listed below the graph for each exposure



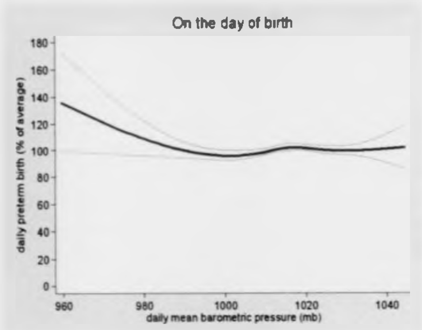
p. 117 (Figure 5.2a)



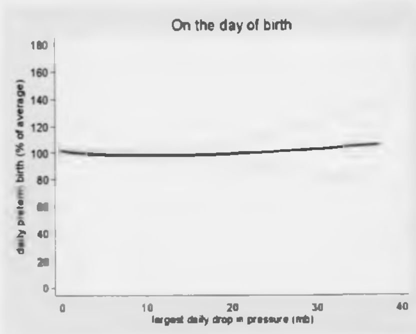
p. 124 (Figure 5.6a)



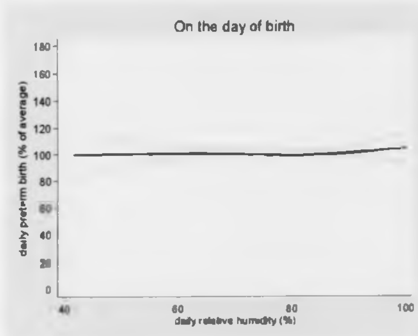
p. 129 (Figure 5.9)



p. 131 (Figure 5.11a)



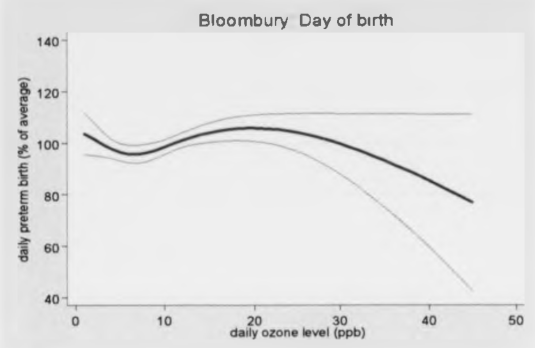
p. 134 (Figure 5.13a)



p. 137 (Figure 5.15a)

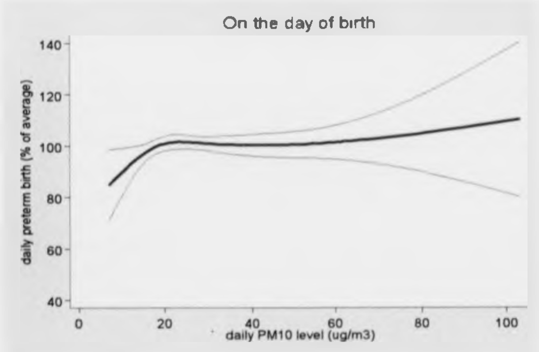
Figure 5.27: Adjusted relationship (thick red lines) between daily preterm birth proportions and exposure to air pollution variables on the day of birth, after exclusion of births occurring in hospitals located furthest from the monitoring stations (95% CI = thin grey lines). The graphs of ozone include control for daily mean temperature.

The location of the corresponding analysis using births from all hospitals is listed next the graph for each exposure.



p. 141 (Figure 5.17)

p. 141 (Figure 5.17)



p. 145 (Figure 5.20a)

Table 5.4: Adjusted regression analysis investigating effect of exposure on the day of birth on daily preterm birth proportions after excluding births that occurred in hospitals located furthest from the meteorological and air pollution monitoring stations.

Exposure	% change in preterm birth proportions*	95% CI
Meteorological		
Daily mean temperature (°C)	-0.02	-0.06 to 0.01
Hours of daily sunshine†	0.02	-0.01 to 0.04
Amount of daily rain (mm)	0.00	-0.03 to 0.02
Daily mean barometric pressure (mb)	0.00	-0.01 to 0.01
Largest daily drop in pressure (mb)	-0.01	-0.03 to 0.01
Daily mean relative humidity† (%)	0.00	-0.01 to 0.01
Air pollution		
Daily ambient ozone (ppb), Bloomsbury†	0.02	-0.01 to 0.05
Daily ambient ozone (ppb), London Bridge Place†	0.00	-0.03 to 0.02

* *The values in this column represent the coefficient or 'β' and should be interpreted as an absolute increase in preterm birth proportions per unit increase in exposure. Negative signs indicate an inverse association.*
† *includes control for daily mean temperature*

5.6 Chapter summary

After preterm birth proportions were adjusted for seasonality, public holidays, and between year and day of week variations, several associations with various meteorological, air pollution, and infection variables were found.

A small effect from exposure to daily mean temperature on the day of birth was seen with preterm birth proportions occurring between 24 and less than 32 weeks of gestation; proportions of very preterm births decreased as daily mean temperature increased. There was also evidence that the effect of daily mean temperature varied by maternal ethnicity. Whereas the proportion of preterm births among white mothers decreased with increasing daily mean temperatures, they increased with increasing temperature among Asian mothers. Daily mean temperature did not appear to affect the proportion of preterm births among black mothers.

Although little or no association was evident with exposure to sunshine on the day of birth, cumulative exposure during 4 or more weeks before birth appeared to have an effect on preterm birth proportions. There was a threshold effect where preterm birth proportions increased with increasing hours of daily sunshine until three hours a day. With more than three hours of sunshine per day, the cumulative effect of exposure to sunshine during four or more weeks before birth plateaued and remained flat. When preterm birth proportions were stratified by sex of the fetus, maternal age, the severity of preterm birth, and by maternal ethnicity, differences between strata were found in the cumulative effect of exposure to sunshine. Proportions of preterm births among male fetuses, mothers aged 25 to 34 years, and those preterm births which occurred between 32 and less than 37 weeks of gestation increased with each hour increase in exposure to daily sunshine below three hours a day. For maternal ethnicity, an effect was only seen among white mothers with exposure on the day of birth. With cumulative exposure during the four weeks before birth, the effect was stronger but only observed below a threshold of seven hours per day.

An association between weekly influenza counts and weekly preterm birth proportions was found at lag 0 among white mothers only. The weekly proportion of preterm births among white mothers increased as the weekly number of influenza cases increased.

Little or no associations were seen when exposure on the estimated day of conception was analysed.

When the births that occurred in the hospitals located furthest from the monitoring stations were removed from the analysis, an effect from exposure to ambient PM_{10} on the day of birth emerged. Daily preterm birth proportions increased with increasing levels of daily mean ambient PM_{10} below a threshold of 21 $\mu g/m^3$, above which the relationship remained flat and unchanged. New particle objectives for the area of greater London have set an objective of lowering the annual mean of PM_{10} to 20 $\mu g/m^3$ by 31 December 2015.[p]

Analysis of the remaining variables (daily rainfall amount, daily mean barometric pressure, largest daily drop in barometric pressure, daily mean relative humidity, and daily mean levels of ambient ozone) established little or no association with daily preterm birth proportions. Possible mechanisms and the biological plausibility of how the associations that were established might help to explain the seasonal pattern of preterm birth is considered in the Discussion.

[p] From the UK National Air Quality Information Archive (www.airquality.co.uk) last accessed 30 March 2005

6. RESULTS PART III: FURTHER INVESTIGATIONS

To account for the seasonality of births in the SMMIS dataset, preterm birth proportions were used for the majority of this study. From an epidemiological perspective, however, it could be argued that a fetuses-at-risk approach should be used for this analysis (see Methods, section 3.6.2). The first part of this chapter presents the results from a comparative analysis of any short-term associations using fetuses at risk, in lieu of preterm birth proportions.

For the second part of this chapter, it was hypothesised that some of the seasonal pattern of preterm birth proportions displayed by this cohort might be explained by antenatal complications that are related to preterm birth. Preterm birth proportions were therefore separated into spontaneous or medically indicated and the seasonality of each examined. Short-term associations with the various environmental exposures were investigated as potential predictors of the seasonal pattern and additionally, a seasonality of pre-eclampsia (and other pregnancy-related hypertensive disorders) was investigated as a possible explanation for the seasonality observed in medically indicated preterm birth proportions.

6.1 A comparative analysis by fetuses at risk

6.1.1 Seasonality of preterm birth probability

Just as for daily preterm birth proportions, variation between the years could be seen when daily probabilities were calculated (Table 6.1). There were similar temporal patterns by month, with the highest preterm birth risk occurring during the winter months. The lowest risk, however, was slightly earlier than when analysed using proportions. Rather than during the summer months as for proportions, the lowest risk of preterm birth was observed during the spring months.

Table 6.1: Temporal patterns of preterm birth probability per 1000 fetuses at risk.

	Probability of preterm birth*
Year	
1988	0.72
1989	0.70
1990	0.67
1991	0.69
1992	0.72
1993	0.67
1994	0.68
1995	0.68
1996	0.67
1997	0.67
1998	0.65
1999	0.68
2000	0.81
Month	
January	0.73
February	0.68
March	0.66
April	0.64
May	0.65
June	0.67
July	0.68
August	0.66
September	0.68
October	0.72
November	0.76
December	0.76

** per 1000 fetuses at risk*

The lower risk during spring was confirmed when the data were combined by seasons for comparison (Table 6.2). Babies had a 10% higher risk of being born preterm in autumn and winter when compared with spring.

Table 6.2: Daily preterm birth probabilities by season.†

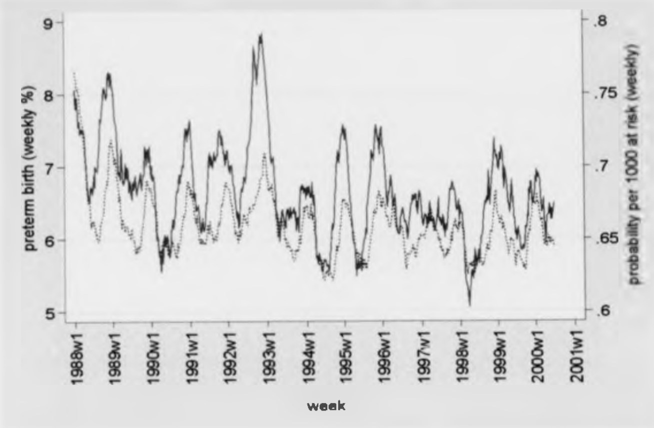
	Probability*	**Risk ratio**	**95% CI**
Spring**	0.65	1	-
Summer	0.67	1.03	0.99 to 1.06
Autumn	0.72	**1.10**	**1.07 to 1.14**
Winter	0.72	**1.10**	**1.07 to 1.14**

† spring = Mar, Apr, and May; summer = Jun, Jul, and Aug; autumn = Sep, Oct and Nov; winter = Dec, Jan and Feb
** per 1000 fetuses at risk*
*** referent group*

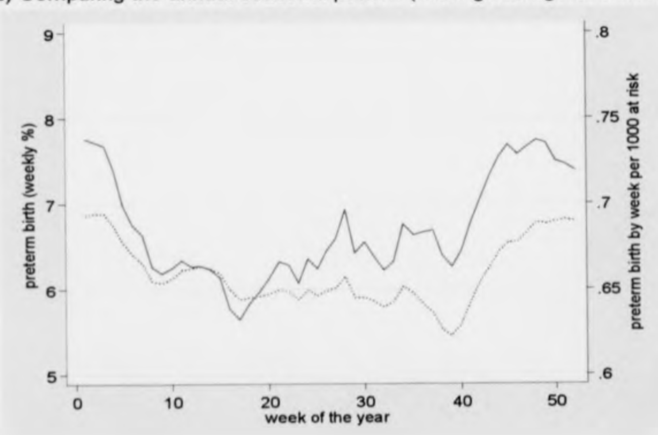
Notwithstanding the earlier occurrence of the lowest risk, the seasonal pattern between weekly preterm birth proportions and probabilities were comparable and both were fairly consistent over the 13 year study period (Figure 6.1a). When the weekly values are collapsed into one representative 52 week period, the earlier occurrence of the lower risk in spring can be seen more clearly (Figure 6.1b). The lowest probability of preterm birth occurred about 20 weeks earlier and the risk was increasing at the same time that preterm birth proportions were at their lowest.

Figure 6.1: Comparative plot of the seasonal pattern of weekly preterm birth proportions (dotted line) and probabilities (solid line).

a) Comparing seasonal patterns over the 13 year study period, each year separately (moving average of 17 and 21 weeks used, respectively).



b) Comparing the annual seasonal pattern (moving average of 5 weeks used).



6.1.2 Associations between probabilities and exposures

By using all births on any given day as the denominator for preterm birth proportions, births that were no longer at risk for being preterm were included in the analysis. To assess whether the inclusion of these births may have acted to mask or dilute the effect of any of the exposures, the adjusted models using overall daily preterm birth proportions were compared with adjusted models using a prospectively calculated daily probability of preterm birth as the outcome (see Methods, section 3.6.2). Fetuses at risk were modelled using a binomial error structure such that the parameter estimates from the regression analysis now represented log odds ratios, which were converted to odds ratios for presentation in these results.

Preterm birth probabilities per 1000 fetuses at risk were adjusted for public holidays, seasonality, and day of week and between year variations in the core model. Using the adjusted core model, a separate binomial model was generated for each exposure variable by adding the relevant spline terms (for graphical inspection) or the actual values of the exposure on the index day as linear terms (for quantification of association). Little or no relationship was evident between the daily probability of preterm birth and exposure to any of the following meteorological exposures on the index day:

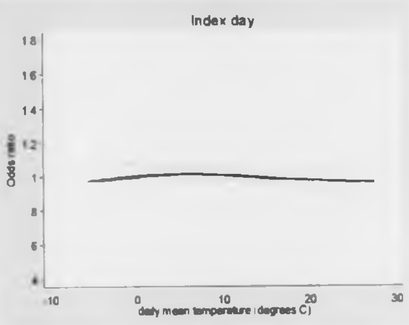
- daily mean temperature
- the daily amount of rainfall
- daily mean barometric pressure
- the largest drop in barometric pressure
- hours of sunshine each day
- daily mean relative humidity

Models for hours of sunshine each day and daily mean relative humidity were also generated with splines to control for daily mean temperature but the shape of the relationship remained essentially unchanged. The relationships demonstrated in all the probability models were comparable to those seen in the models using daily preterm birth proportions (Figure 6.2). As the shapes of the adjusted relationships were all generally flat across the whole range of exposure values, one linear term replaced the spline terms in each model to quantify the associations (Table 6.3).

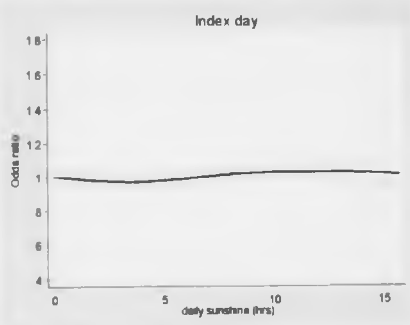
Similarly, little or no relationship was observed between the daily probabilities of preterm birth and exposure on the index day to any of the air pollution variables, after public holidays, seasonality, and day of week and between year variations were adjusted in the core model. Nor did the addition of splines to control for daily mean temperature in the ozone models have any discernable effect. The shape of each relationship was consistent with that seen with the analysis by daily preterm birth proportions (Figure 6.3). The relationships appeared linear across the range of values for each exposure. Therefore, the spline terms in each air pollution exposure model were replaced with one linear term consisting of the actual daily mean values of the pollutants on the index day for quantification of the association (Table 6.3).

Figure 6.2: Adjusted relationship (thick red line) between meteorological exposures and daily preterm birth probability per 1000 fetuses at risk (95% CI = thin grey lines). The plots for sunshine and relative humidity included control for daily mean temperature.

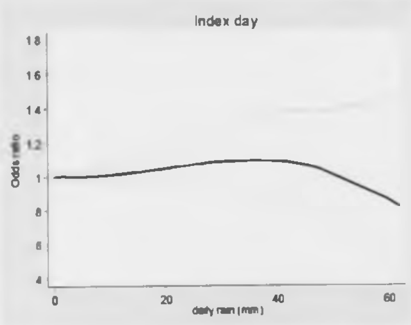
The location of the corresponding analysis using daily preterm birth proportions is listed below the graph for each exposure.



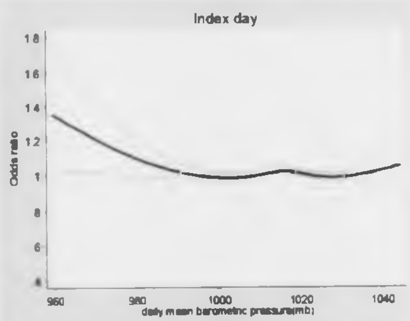
p. 117 (Figure 5.2a)



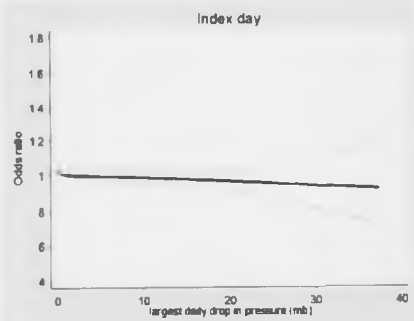
p. 124 (Figure 5.6a)



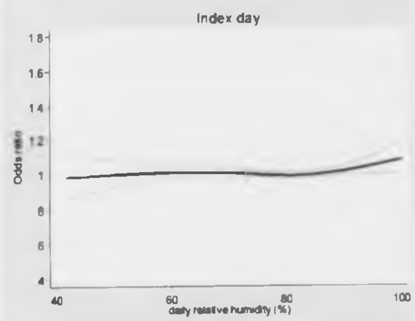
p. 129 (Figure 5.9)



p. 131 (Figure 5.11a)



p. 134 (Figure 5.13a)



p. 137 (Figure 5.15a)

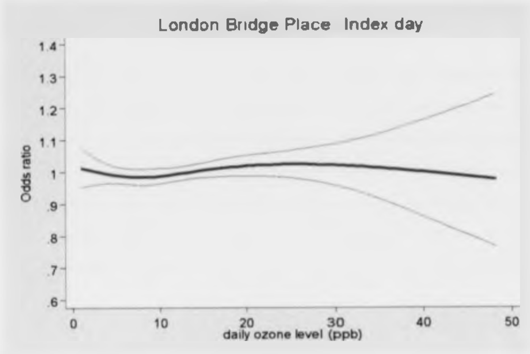
Table 6.3: Adjusted binomial regression analysis investigating the effect of exposure on the day of birth (index day) on daily preterm birth probability per 1000 fetuses at risk.

Exposure	OR*	95% CI
Meteorological		
Daily mean temperature (degrees C)	1.00	0.99 to 1.00
Daily sunshine (hrs)**	1.00	1.00 to 1.01
Daily rainfall (mm)	1.00	1.00 to 1.00
Daily mean barometric pressure (mb)	1.00	1.00 to 1.00
Largest daily drop in barometric pressure (mb)	1.00	0.99 to 1.00
Daily mean relative humidity (%)**	1.00	1.00 to 1.00
Air pollution		
Daily mean ozone (ppb), Bloomsbury**	1.00	1.00 to 1.01
Daily mean ozone (ppb), London Bridge Place**	1.00	1.00 to 1.00
PM_{10} ($\mu g/m^3$), Bloomsbury	1.00	1.00 to 1.00

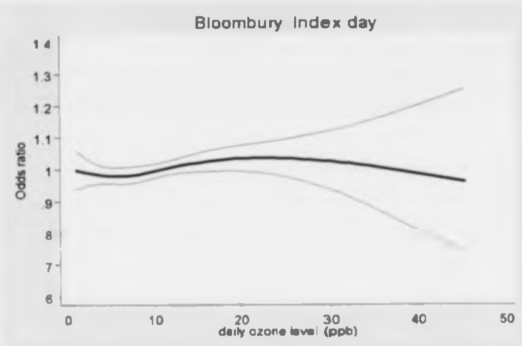
** odds ratio*
*** includes control for daily mean temperature*

Figure 6.3 Adjusted relationships (thick red line) between air pollution exposures and daily preterm birth probability per 1000 fetuses at risk (95% CI = thin grey lines). The graphs of ozone included control for daily mean temperature.

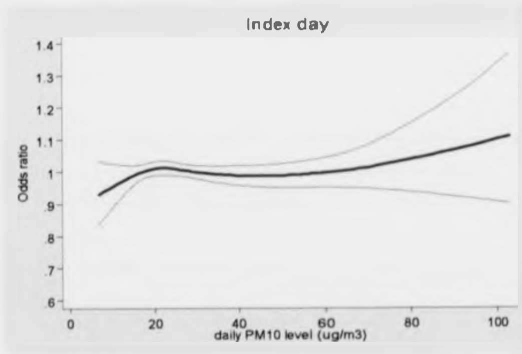
The location of the corresponding analysis using daily preterm birth proportions is listed next to the graph for each exposure.



p. 141 (Figure 5.17)



p. 141 (Figure 5.17)



p. 145 (Figure 5.20a)

6.2 Investigating by preterm birth subtypes

6.2.1 Seasonality of spontaneous and medically indicated preterm births

Several studies have shown that some risk factors for preterm birth may differ by subgroups of preterm birth, such as those that occur after medical intervention compared with those that occur spontaneously.[82 83 133-135 137 139 180] To assess the effect of the aetiologic heterogeneity of preterm birth, the seasonality of medically indicated preterm births and spontaneous preterm births were examined. Records with missing data for type of labour onset or for type of membrane rupture were excluded from this analysis (n=6,845) as were records that had the same birthdate and the same time for onset of labour and artificial rupture of the membranes (n=4700). This left 471,220 births for inclusion in this analysis. Of these births, 17,985 (3.82%) were preterm due the spontaneous occurrence of labour and 10,312 (2.19%) were medically indicated preterm births.

Daily proportions were calculated for spontaneous and medically indicated preterm births using the total number of births each day as the denominator (Table 6.4). There were 628 days (13.2%) for which there were no medically indicated preterm births and 121 days (2.5%) for which no spontaneous preterm births were recorded.

Table 6.4 Break down by preterm birth subtype*

	Spontaneous	Indicated
Mean number of preterm births each day (range)**	3.79 (0-13)	2.17 (0-9)
Mean daily proportion	3.84 (0-13.33)	2.19 (0-9.88)

** 11,545 records were dropped due to missing values or because they had the same time of onset of labour and artificial rupture of the membranes*
*** An average of 99.23 births occurred each day during the study period*

The lowest proportions of preterm birth by either classification occurred during the summers and the highest proportions occurred during the winters (Table 6.5). These seasonal differences were more than would be expected by chance (χ^2 (3) = 11.19, p = 0.01 for medically indicated preterm births and χ^2 (3) = 43.64, p < 0.001 for spontaneous preterm births). Babies born in winter were 10% and 12% more likely to be born preterm than babies born in summer, for medically indicated and spontaneous preterm births, respectively (Table 6.5).

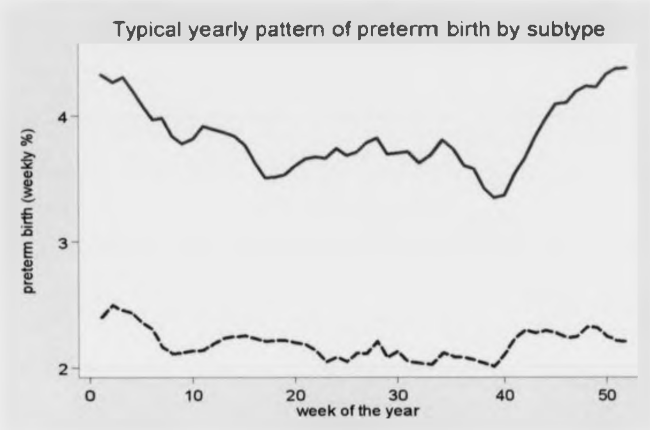
Table 6.5 Daily preterm birth proportions by subtype by season*

	Spontaneous %	**RR† (95% CI)**	**Indicated %**	**RR† (95% CI)**
Spring	3.72	1.00 (0.96, 1.05)	2.19	1.05 (0.99, 1.10)
Summer**	3.70	1	2.09	1
Autumn	3.72	1.01 (0.97, 1.05)	2.19	1.05 (0.99, 1.11)
Winter	4.15	**1.12 (1.08, 1.17)**	2.29	**1.10 (1.04, 1.16)**

* *spring = Mar, Apr, and May; summer = Jun, Jul, and Aug; autumn = Sep, Oct and Nov; winter = Dec, Jan and Feb*
** *referent group*
† *risk ratio*

When plotted by weekly proportions over the 13 year study period, the seasonality exhibited by both medically indicated and spontaneous preterm birth proportions was consistent for each year. Therefore, both were plotted in one representative 52 week period to enable better identification of the yearly pattern (Figure 6.4). Visual inspection confirmed a slightly higher magnitude of increase in proportions in winters for spontaneous preterm births than for medically indicated preterm births.

Figure 6.4. Seasonality of preterm birth proportions by clinical presentation; spontaneous (solid line) and medically indicated (dashed line). A moving average of 5 weeks was used for both.

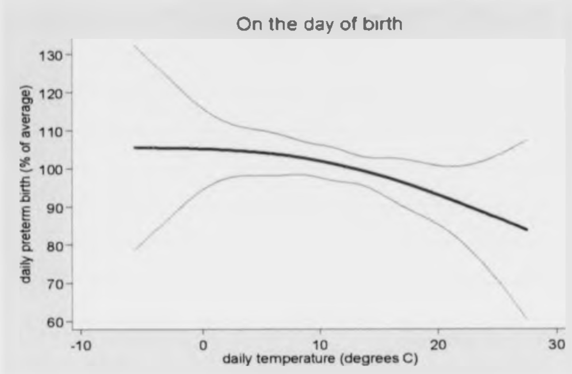


6.2.2 Associations with meteorological exposures

Two core models were created: one for medically indicated preterm birth proportions and one for spontaneous preterm birth proportions. In both, preterm birth proportions were adjusted for public holidays, seasonality, and day of week and between year variations. Daily mean temperature at lag 0 was added to each of the core models. Little or no relationship between exposure to daily mean temperature on the day of birth and either daily proportions of spontaneous preterm births or medically indicated preterm births was apparent (Figures 6.5a & 6.5b). The lack of association was confirmed with regression analysis in which the smoothing splines were replaced with the actual values of daily mean temperature on the day of birth (Table 6.6). As the relationship on the graph appeared to be essentially linear, there was no obvious need to investigate a potential change-point. When the values for daily mean temperature on the day of birth were replaced with averaged lagged values to investigate possible relationships with exposure 3 days, one week and one month before the day of birth, no significant associations were observed (Table 6.6).

Figure 6.5 Adjusted relationship (thick red line) between daily medically indicated and spontaneous preterm birth proportions and exposure to daily mean temperature on the day of birth (95% CI = thin grey lines).

a) This graph showed that exposure to daily mean temperature had little or no effect on preterm birth proportions that were medically indicated.



b) This graph showed that exposure to daily mean temperature had little or no effect on spontaneous preterm birth proportions.

Table 6.6 Adjusted regression analysis investigating the effect of cumulative exposure to daily mean temperature by preterm birth subtype.

	% change in preterm birth proportions (95% CI)*	
	Spontaneous	***Indicated***
Exposure time		
Day of birth	0.00 (-0.02 to 0.02)	0.00 (-0.01 to 0.01)
3 days**	-0.01 (-0.03 to 0.02)	-0.01 (-0.03 to 0)
1 week**	0.00 (-0.03 to 0.03)	-0.02 (-0.04 to 0)
4 weeks**	0.02 (-0.03 to 0.07)	-0.01 (-0.05 to 0.02)

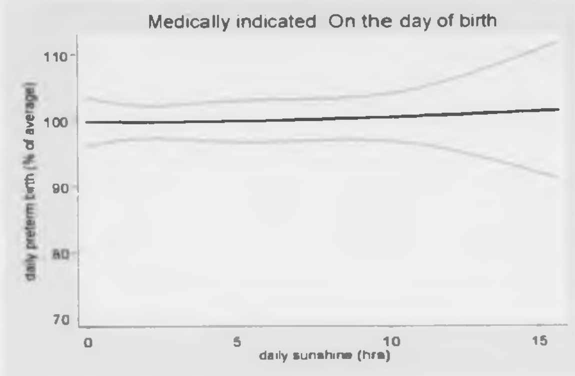
* *The values in these columns represent the coefficient, or 'β' and should be interpreted as an absolute increase in preterm birth proportions per degree increase in daily mean temperature. A negative coefficient indicated an inverse association.*
** *averaged lags for the time prior to birth*

Similarly, when the values for daily hours of sunshine on the day of birth were added to each of the adjusted core models, no relationship with either spontaneous or medically indicated preterm birth proportions could be seen (Figures 6.6a & 6.6b). As the relationships again appeared not only flat, but also linear, one linear term across the range of daily sunshine values was added to the model in lieu of the spline terms to quantify the association (β = 0.01%, 95% CI 0 to 0.03 for spontaneous; β = 0.0, 95% CI -0.01 to 0.01 for medically indicated).[q] For medically indicated preterm birth proportions, a lack of association persisted with cumulative exposure to daily sunshine during and up to three days (β = -0.01%, 95% CI -0.02 to 0.01), one week (β = -0.01%, 95% CI -0.04 to 0.02) and one month (β = 0.0, 95% CI -0.05 to 0.04) before the day of birth. For spontaneous preterm birth proportions, although there was a persistent lack of association with cumulative exposure three days (β = 0.0, 95% CI -0.02 to 0.03) and one week (β = 0.0, 95% CI -0.03 to 0.04) before birth, the relationship changed with cumulative exposure in the four weeks before birth (Figure 6.7). Using maximum likelihood to identify the optimal threshold to fit a linear term, spontaneous preterm birth proportions were found to decrease by 0.25% (95% CI 0.05 to 0.45) for every hour decrease in daily sunshine below three hours.

[q] All results from the regression analysis for associations with daily sunshine include control for daily mean temperature.

Figure 6.6 Adjusted relationship (thick red line), including control for daily mean temperature, between daily medically indicated and spontaneous preterm birth proportions and exposure to daily hours of sunshine on the day of birth (95% CI = thin grey lines).

a) This graph showed that exposure to hours of daily sunshine had little or no effect on preterm birth proportions that were medically indicated.



b) This graph showed that exposure to hours of daily sunshine had little or no effect on spontaneous preterm birth proportions.

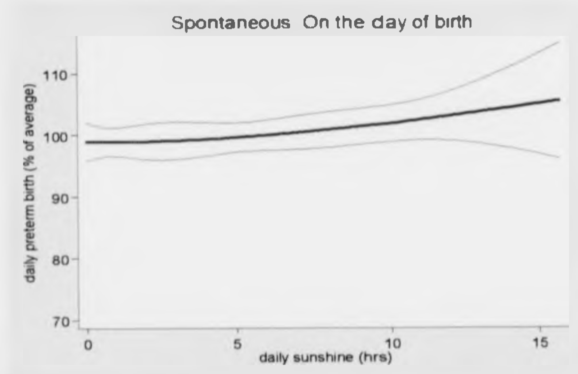
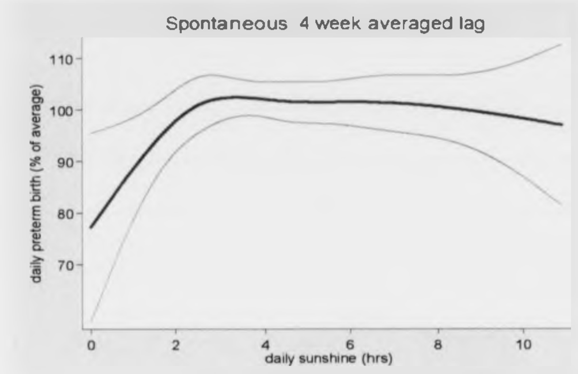


Figure 6.7: Adjusted relationship (thick red line), including control for daily mean temperature, between daily medically indicated and spontaneous preterm birth proportions and cumulative exposure to daily hours of sunshine during the four weeks before birth (95% CI = thin grey lines).



Using the adjusted core models, separate models were generated for daily amount of rainfall, daily mean barometric pressure, the largest daily drop in barometric pressure and daily mean relative humidity. The relationships with exposure on the day of birth were summarised using cubic spline terms. Little or no relationship was apparent with exposure to any of these variables on the day of birth (Figures 6.8 to 6.11). Each of these relationships was quantified using regression techniques after replacing the spline terms in the models with a linear term that represented the full range of values for each respective variable on the day of birth (Table 6.7). Investigation of averaged lags in a similar manner at three days, one week and four weeks before birth also did not produce any significant associations (Table 6.7).

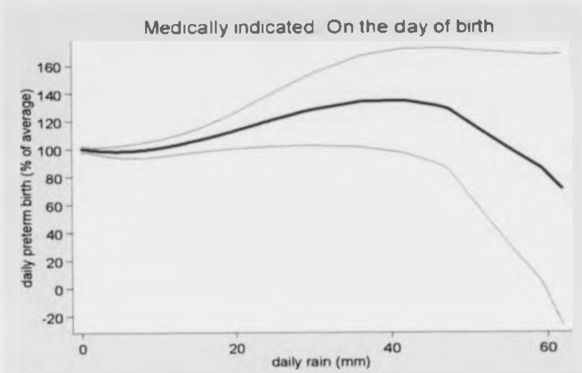
Table 6.7: Adjusted regression analysis investigating the effect of various exposures at various lags on preterm birth proportion by subtype.

	% change in preterm birth proportions (95% CI)*	
Daily exposure**	**Spontaneous**	**Indicated**
Rainfall (mm)		
Day of birth	0.0 (-0.02 to 0.01)	0.01 (-0.01 to 0.02)
3 days	0.0 (-0.02 to 0.03)	0.01 (-0.01 to 0.02)
1 week	0.01 (-0.02 to 0.04)	0.01 (-0.02 to 0.03)
4 weeks	-0.02 (-0.08 to 0.04)	0.04 (0 to 0.09)
Mean barometric pressure (mb)		
Day of birth	0.0 (-0.01 to 0.01)	0.0 (0 to 0.01)
3 days	0.0 (-0.01 to 0.01)	0.0 (0 to 0.01)
1 week	0.0 (-0.01 to 0.01)	0.0 (0 to 0.01)
4 weeks	0.0 (-0.01 to 0.01)	0.0 (-0.01 to 0)
Largest drop in pressure (mb)		
Day of birth	-0.01 (-0.02 to 0)	0.0 (-0.01 to 0.01)
3 days	0.01 (-0.02 to 0.03)	-0.01 (-0.03 to 0)
1 week	0.02 (-0.02 to 0.05)	0.0 (-0.03 to 0.03)
4 weeks	0.01 (-0.06 to 0.07)	0.05 (0 to 0.09)
Mean relative humidity (%)†		
Day of birth	0.0 (-0.01 to 0)	0.0 (0.0 to 0.01)
3 days	0.0 (-0.01 to 0.01)	0.01 (0.0 to 0.01)
1 week	0.0 (-0.01 to 0.01)	0.01 (0.0 to 0.02)
4 weeks	-0.01 (-0.03 to 0.01)	0.01 (-0.01 to 0.02)

** The values in these columns represent the coefficient, or 'β' and should be interpreted as an absolute increase in preterm birth proportions per unit increase in exposure. A negative coefficient indicated an inverse association.*
*** The values for 3 days, one week, and four weeks represented averaged lags for the specified time prior to birth.*
† Also included adjustment for daily mean temperature.

Figure 6.8 Adjusted relationship (thick red line) between daily medically indicated and spontaneous preterm birth proportions and exposure to amount of daily rainfall on the day of birth (95% CI = thin grey lines).

a) This graph showed that exposure to amount of daily rainfall had little or no effect on preterm birth proportions that were medically indicated.



b) This graph showed that exposure to amount of daily rainfall had little or no effect on spontaneous preterm birth proportions.

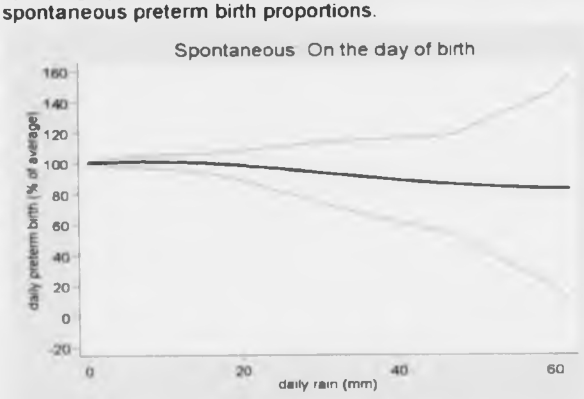
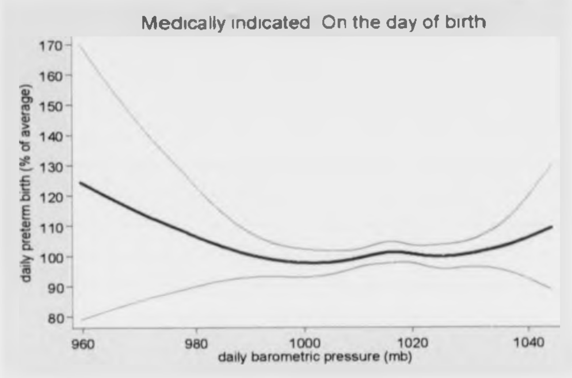


Figure 6.9 Adjusted relationship (thick red line) between daily medically indicated and spontaneous preterm birth proportions and exposure to mean barometric pressure on the day of birth (95% CI = thin grey lines).

a) This graph showed that exposure to daily mean barometric pressure had little or no effect on preterm birth proportions that were medically indicated.



b) This graph showed that exposure to daily mean barometric pressure had little or no effect on spontaneous preterm birth proportions.

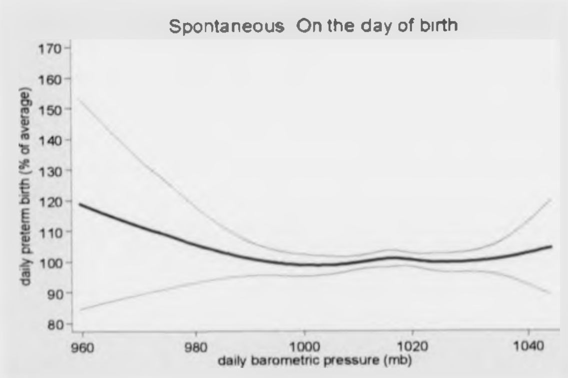
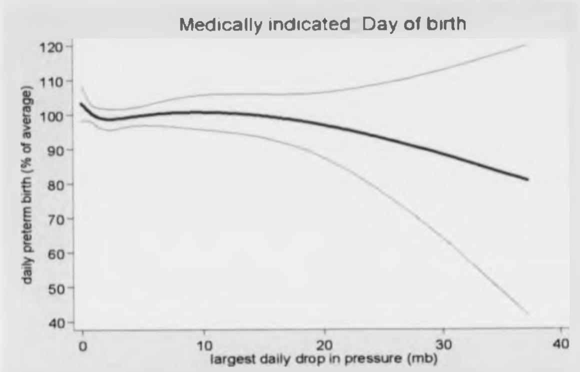


Figure 6.10 Adjusted relationship (thick red line) between daily medically indicated and spontaneous preterm birth proportions and exposure to the largest daily drop in barometric pressure on the day of birth (95% CI = thin grey lines).

a) This graph showed that exposure to the largest daily drop in barometric pressure had little or no effect on preterm birth proportions that were medically indicated



b) This graph showed that exposure to the largest daily drop in barometric pressure had little or no effect on spontaneous preterm birth proportions.

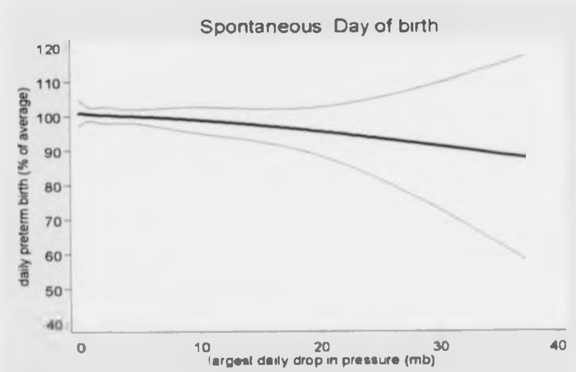
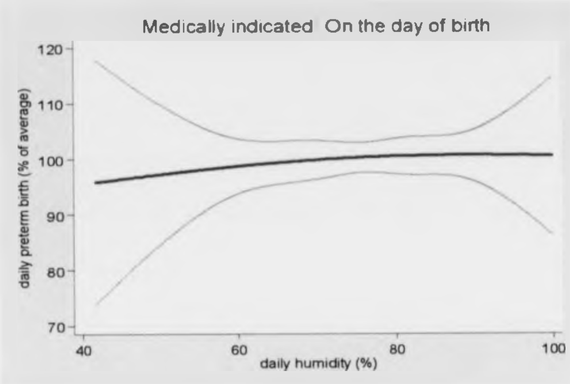
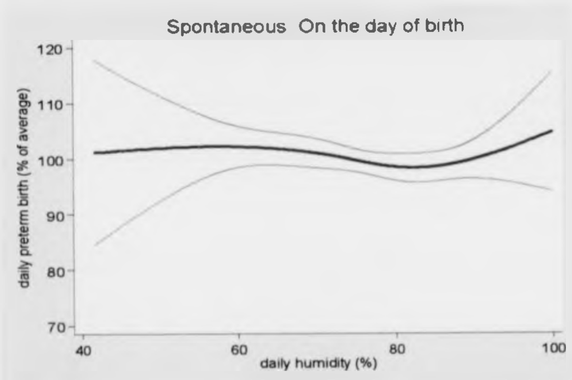


Figure 6.11: Adjusted relationship (thick red line) between daily medically indicated and spontaneous preterm birth proportions and exposure to daily mean relative humidity on the day of birth (95% CI = thin grey lines).

a) This graph showed that exposure to daily mean relative humidity had little or no effect on preterm birth proportions that were medically indicated.



b) This graph showed that exposure to daily mean relative humidity had little or no effect on spontaneous preterm birth proportions.



6.2.3 Associations with air pollution exposures

Again, two core models were created, one for medically indicated preterm birth proportions and one for spontaneous preterm birth proportions. Both were adjusted for seasonality, public holidays, and day of week and between year variations before any air pollution exposures were added to the model. Ozone models were adjusted for daily mean temperature, as well.

When daily mean ambient ozone levels at lag 0 were added to the core models, spline terms were used to summarise the relationship. Little or no relationship with either medically indicated or spontaneous preterm birth proportions could be seen (Figures 6.12 & 6.13). By replacing the spine terms in each preterm birth subtype model with one linear term across the range of daily ozone values at lag 0, the lack of association was quantified (Table 6.8). Similarly, investigation at other lags did not produce any significant associations (Table 6.8).

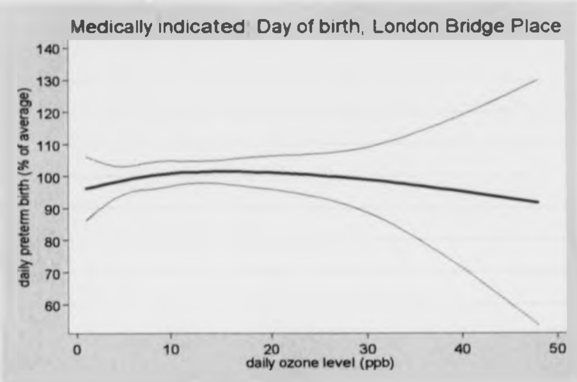
Table 6.8: Adjusted regression analysis, including control of daily mean temperature, investigating the effect of ambient ozone exposure at various lags on preterm birth proportions by subtype

	% change in preterm birth proportions (95% CI)*	
Daily mean exposure**	**Spontaneous**	**Indicated**
Ozone (ppb) at London Bridge		
Day of birth	0.0 (-0.01 to 0.02)	0.0 (-0.01 to 0.01)
3 days	0.01 (-0.01 to 0.03)	0.0 (-0.01 to 0.02)
1 week	0.01 (-0.01 to 0.03)	0.0 (-0.02 to 0.02)
4 weeks	0.02 (-0.02 to 0.05)	0.01 (-0.02 to 0.04)
Ozone (ppb) at Bloomsbury		
Day of birth	0.01 (0 to 0.03)	0.0 (-0.01 to 0.02)
3 days	0.01 (-0.01 to 0.03)	0.0 (-0.02 to 0.01)
1 week	0.02 (0.0 to 0.05)	-0.01 (-0.03 to 0.01)
4 weeks	0.01 (-0.04 to 0.05)	0.01 (-0.02 to 0.05)

** The values in these columns represent the coefficient, or 'β' and should be interpreted as an absolute increase in preterm birth proportions per unit increase in exposure. A negative coefficient indicated an inverse association.*
*** The values for 3 days, one week, and four weeks represented averaged lags for the specified time prior to birth.*

Figure 6.12 Adjusted relationship (thick red line) between daily proportions of medically indicated and spontaneous preterm births and exposure to daily mean levels of ambient ozone on the day of birth (95% CI = thin grey lines).

a) This graph showed that exposure to daily mean levels of ambient ozone, as measured at London Bridge Place, had little or no effect on medically indicated preterm birth proportions.



b) This graph showed that exposure to daily mean levels of ambient ozone, as measured at London Bridge Place, had little or no effect on spontaneous preterm birth proportions.

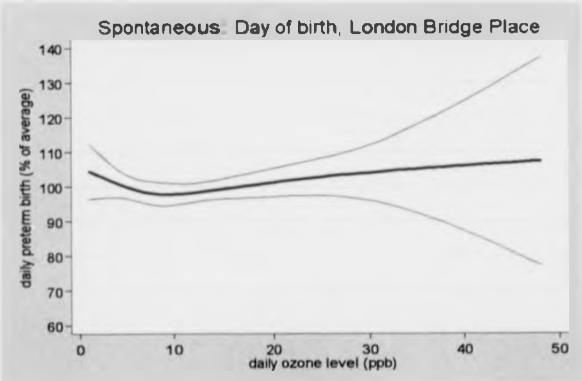
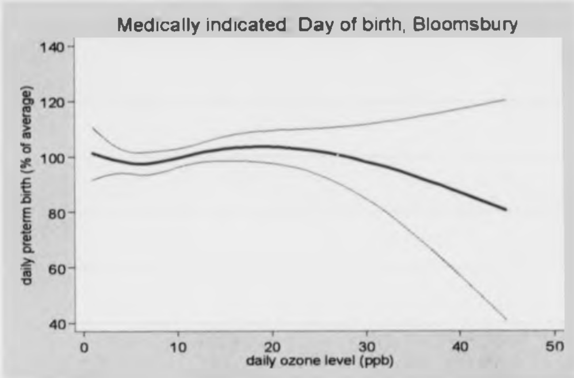
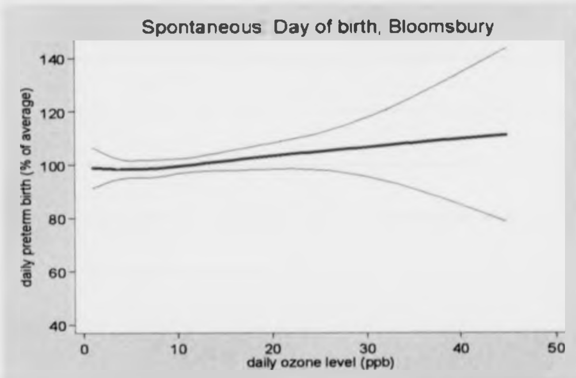


Figure 6.13: Adjusted relationship (thick red line) between daily proportions of medically indicated and spontaneous preterm births and exposure to daily mean levels of ambient ozone on the day of birth (95% CI = thin grey lines).

a) This graph showed that exposure to daily mean levels of ambient ozone, as measured at Bloomsbury, had little or no effect on medically indicated preterm birth proportions.



b) This graph showed that exposure to daily mean levels of ambient ozone, as measured at Bloomsbury, had little or no effect on spontaneous preterm birth proportions.



When daily mean levels of ambient PM_{10} at lag 0 were added to the core models, spline terms were again used to summarise the relationship. Again, little or no relationship with either medically indicated or spontaneous preterm birth proportions could be seen (Figure 6.14). By replacing the spine terms in each subtype model with one linear term across the range of daily PM_{10} values at lag 0, the lack of association was quantified (β = 0, 95% CI -0.01 to 0.01 for indicated and β = 0, 95% CI -0.01 to 0.01 for spontaneous). Using the same process to investigate associations at other lags did not produce any significant results (Table 6.9).

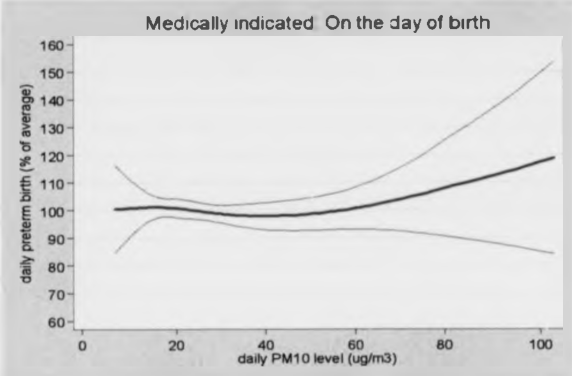
Table 6.9 Adjusted regression analysis investigating the effect of ambient PM_{10} exposure at various lags on preterm birth proportions by subtype.

	% change in preterm birth proportions (95% CI)*	
Daily mean exposure**	**Spontaneous**	**Indicated**
PM ($\mu g/m^3$) at Bloomsbury		
Day of birth	0.0 (-0.01 to 0.02)	0.0 (-0.01 to 0.01)
3 days	0.01 (-0.01 to 0.03)	0.0 (-0.01 to 0.02)
1 week	0.01 (-0.01 to 0.03)	0.0 (-0.02 to 0.02)
4 weeks	0.02 (-0.02 to 0.05)	0.01 (-0.02 to 0.04)

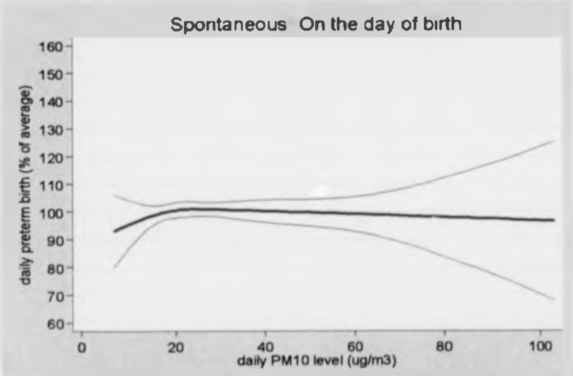
** The values in these columns represent the coefficient, or 'β' and should be interpreted as an absolute increase in preterm birth proportions per unit increase in exposure. A negative coefficient indicated an inverse association.*
*** The values for 3 days, one week, and four weeks represented averaged lags for the specified time prior to birth.*

Figure 6.14: Adjusted relationship (thick red line) between daily proportions of medically indicated and spontaneous preterm births and exposure to daily mean levels of ambient PM_{10} on the day of birth (95% CI = thin grey lines).

a) This graph showed that exposure to daily mean levels of ambient PM_{10}, as measured at Bloomsbury, had little or no effect on medically indicated preterm birth proportions.



b) This graph showed that exposure to daily mean levels of ambient PM_{10}, as measured at Bloomsbury, had little or no effect on spontaneous preterm birth proportions.

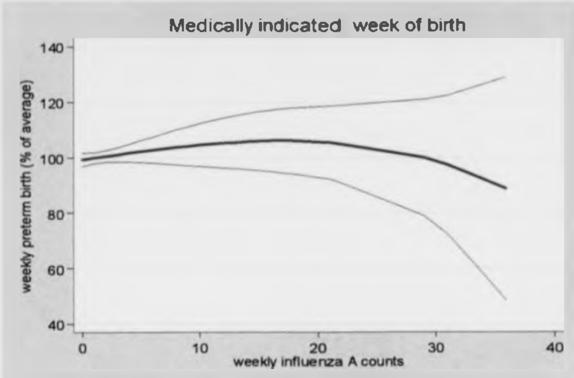


6.2.4 Associations with influenza A

The analysis for influenza A was conducted at a weekly (n=676 weeks), rather daily (n=4749 days), level due to the high percentage (85%) of days with zero counts (4051/4749). Two core models were created: one for medically indicated preterm birth proportions and one for spontaneous preterm birth proportions. In both core models, preterm birth proportions were controlled for seasonality and between year variations before the exposure variable was added. Spline terms were used to summarise the relationship between preterm birth proportions by subtype and influenza A counts during the week of birth (Figure 6.15). As both graphs revealed an essentially linear relationship across the range of influenza A counts, the spline terms were replaced in both models by one linear term. Using regression to quantify the relationship, no association was found (β= 0, 95% CI 0.0 to 0.02 for indicated and β= 0, 95% CI -0.02 to 0.02 for spontaneous). An averaged lag of four weeks was also investigated for an association with either medically indicated or spontaneous preterm birth proportions (Figure 6.16). When quantified, the association was not significant (β= 0.01, 95% CI -0.01 to 0.03 for indicated and β= -0.01, 95% CI -0.03 to 0.01 for spontaneous).

Figure 6.15 Adjusted relationship (thick red line) between weekly proportions of medically indicated and spontaneous preterm births and exposure to weekly influenza A counts during the week of birth (95% CI = thin grey lines).

a) This graph showed that exposure to weekly influenza A counts had little or no effect on medically indicated preterm birth proportions.



b) This graph showed that exposure to weekly influenza A counts had little or no effect on spontaneous preterm birth proportions.

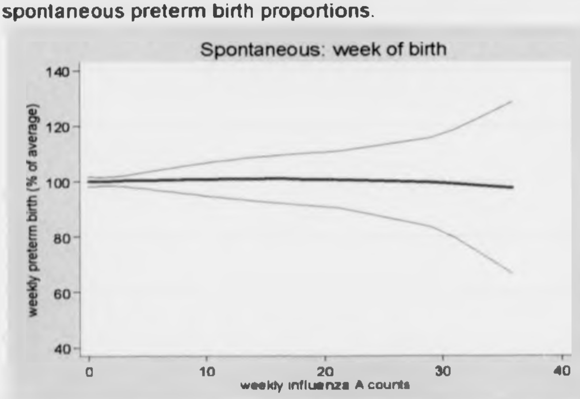
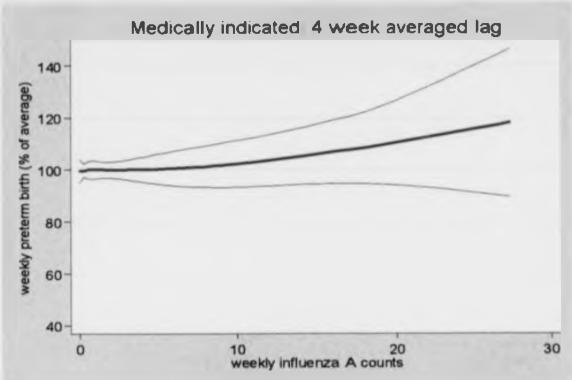
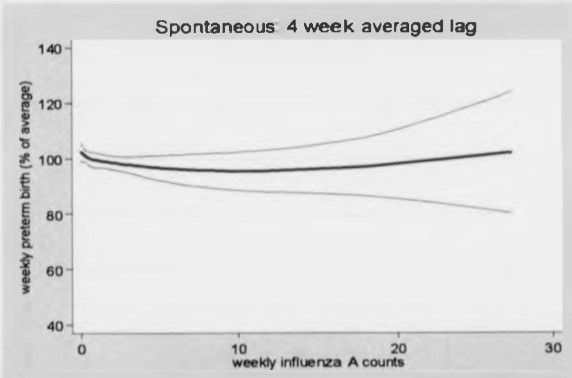


Figure 6.16: Adjusted relationship (thick red line) between weekly proportions of medically indicated and spontaneous preterm births and cumulative exposure to weekly influenza A counts during the four weeks before birth (95% CI = thin grey lines).

a) This graph showed that cumulative exposure to weekly influenza A counts during the four weeks before birth had little or no effect on medically indicated preterm birth proportions.



b) This graph showed that cumulative exposure to weekly influenza A counts during the four weeks before birth had little or no effect on spontaneous preterm birth proportions.



6.3 Seasonality of hypertensive disorders

Although medically indicated preterm birth proportions demonstrated a clear seasonal pattern, little or no association with any of the environmental exposures was apparent. Therefore, we also investigated pre-eclampsia and the related condition of pregnancy-induced hypertension as a possible mechanism to help explain the seasonal pattern of medically indicated preterm birth proportions that was observed. Pre-eclampsia (PET) and pregnancy-induced hypertension have both been reported to have an annual seasonal pattern[103 105] and over a quarter (25.7%) of medically indicated preterm births in this cohort had a diagnosis of pre-eclampsia or pregnancy-induced hypertension (PIH).

To determine the seasonality of PET and PIH in this cohort, months were used as the unit of analysis, rather than days. This was because only 36% of days (1714/4749) had at least one pregnancy diagnosed with PET and there were only 888 days (18.7%) on which at least one preterm birth with a diagnosis of PET occurred (range 0 to 3). Proportions were calculated using the total number of births each month as the denominator. The overall monthly mean proportion of pregnancies with pre-eclampsia resulting in a preterm birth was 0.31%. When the corresponding month of each year was combined, the lowest proportions for PET and for the proportions of preterm birth with a diagnosis of PET occurred in July and August (Table 6.10). There was variation between the months, but a distinct yearly periodicity was not evident (Figure 6.17).

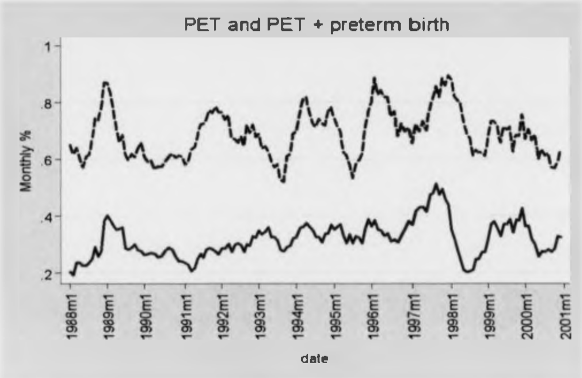
Table 6.10: The distribution of monthly means of pregnancies with PET, pregnancy-induced hypertension (PIH), all non-normotensive pregnancies combined and pregnancies with pre-eclampsia resulting in a preterm birth.

	PET %	PET & preterm	Non-normotensive	PIH %
January	0.79	0.34	4.75	3.24
February	0.69	0.29	4.58	3.11
March	0.75	0.36	4.68	3.13
April	0.68	0.31	4.55	3.13
May	0.70	0.31	4.56	3.06
June	0.69	0.32	4.29	2.84
July	0.57	0.25	4.13	2.86
August	0.59	0.26	4.01	2.77
September	0.74	0.37	4.25	2.84
October	0.68	0.29	4.05	2.68
November	0.71	0.36	4.38	2.88
December	0.70	0.31	4.36	2.90

Figure 6.17: Graphical distribution of mean proportions, by month, of pregnancies that had pre-eclampsia and resulted in a preterm birth.

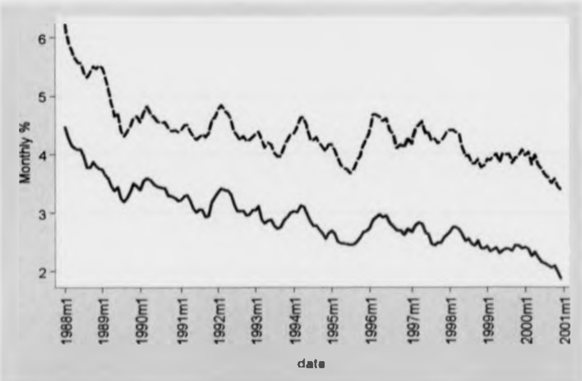
Similarly, when each year of the study period was plotted separately, no consistent pattern over any time interval could be identified for pregnancies with pre-eclampsia or for pregnancies with pre-eclampsia that resulted in a preterm birth (Figure 6.18).

Figure 6.18: No consistent seasonal pattern could be identified for pre-eclampsia (dashed line) or for pre-eclamptic pregnancies that resulted in a preterm birth (solid line). A moving average of 3 weeks used.



The same was true for pregnancy-induced hypertension and for when all the pregnancies in the SMMIS dataset that were not normotensive were grouped together; no consistent pattern over any time interval could be identified during the study period (Figure 6.19).

Figure 6.19: No consistent seasonal pattern could be identified for monthly proportions of pregnancy-induced hypertension (solid line) or when all pregnancies that were not normotensive were grouped together (dashed line). A moving average of 3 months was used.



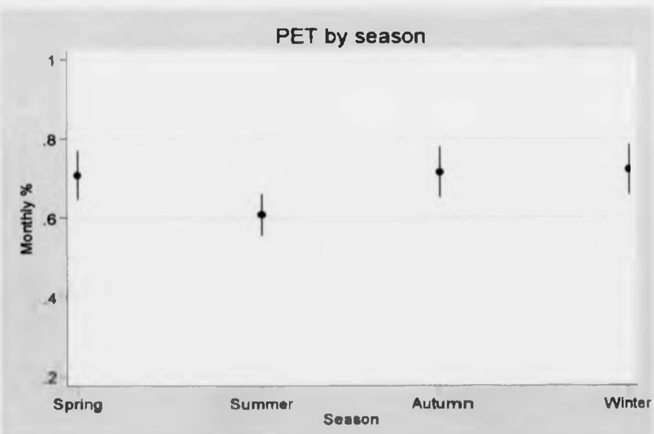
Differences emerged, however, when PET and PIH pregnancies were grouped by season. When grouped by season, the lowest proportions of PET pregnancies were in summer and the highest proportions were in winter (Table 6.11 and Figure 6.20). Proportions of medically indicated preterm births were similarly lowest in summer and highest in winter (Table 6.5). The lowest proportions of PIH pregnancies occurred in autumn, although proportions in summer were only 0.7% higher (Table 6.11). Pregnancies were significantly more likely to be diagnosed with PET by the time of birth in every other season than summer. Pregnancy-induced hypertension was more likely in spring and winter when compared with autumn.

Table 6.11: Monthly PET and PIH proportions by season.*

	PET %	RR† (95% CI)	PIH %	RR† (95% CI)
Spring	0.71	**1.15 (1.02, 1.30)**	3.11	**1.11 (1.05, 1.17)**
Summer	0.62	1**	2.82	1.01 (.095, 1.07)
Autumn	0.71	**1.15 (1.02, 1.30)**	2.80	1**
Winter	0.73	**1.18 (1.05, 1.34)**	3.09	**1.10 (1.04, 1.17)**

** spring = Mar, Apr, and May; summer = Jun, Jul, and Aug; autumn = Sep, Oct and Nov; winter = Dec, Jan and Feb*
*** referent group*
† risk ratio

Figure 6.20: Monthly means of pre-eclampsia proportions by season, with 95% confidence intervals.



When pregnancies with pre-eclampisa that resulted in a preterm birth were considered, the lowest proportions were again seen in summer (Table 6.12). The largest difference in proportions was 0.6% and occurred from summer to autumn. Preterm births in pregnancies diagnosed with PET were 23% more likely to occur in autumn when compared with summer. An increased risk of being born preterm in winter was not observed.

Table 6.12: Monthly proportions of pregnancies that were diagnosed with PET and subsequently resulted in a preterm birth, by season.*

	PET & preterm birth %	RR† (95% CI)
Spring	0.33	**1.21 (1.01, 1.44)**
Summer	0.28	1**
Autumn	0.34	**1.23 (1.03, 1.46)**
Winter	0.31	1.14 (0.95, 1.37)

** spring = Mar, Apr, and May; summer = Jun, Jul, and Aug; autumn = Sep, Oct and Nov; winter = Dec, Jan and Feb*
*** referent group*
† risk ratio

6.4 Chapter summary

A comparison of seasonality and short-term associations using a fetuses-at-risk approach was conducted. While the lowest risk of preterm birth appeared to occur earlier than the lowest proportion of preterm births, no differences in short-term associations were found; there was little or no effect of any exposures on the day of birth on the daily probability of preterm birth.

Preterm birth proportions were separated into medically indicated and spontaneous preterm births. Regardless of the type of delivery, the highest likelihood of preterm birth occurred in winter. For spontaneous preterm birth proportions, a threshold for an effect at less than three hours of sunshine per day was found. It is likely, therefore, that the similar association with daily sunshine exposure that was seen when using overall preterm birth proportions (see Results Part II, section 5.1.2) was attributable to spontaneous, and not medically indicated, preterm births.

In an attempt to uncover what might be driving the seasonal pattern of medically indicated preterm birth proportions, the seasonality of various hypertensive disorders of pregnancy were investigated. As previous studies have reported seasonal variation in pre-eclampsia and pregnancy-induced hypertension,[105 103] it was thought that a seasonality of these conditions, which account for over a quarter of medically indicated preterm births, might explain at least part of the annual variation of medically indicated preterm births. When plotted by month, however, pregnancies with pre-eclampsia that resulted in a preterm birth did not indicate any clear seasonality. Similarly, when pre-eclampsia and pregnancy-induced hypertension monthly proportions were examined, distinct seasonal patterns were not evident.

When grouped by season, however, PET and PIH proportions were lowest in summer and autumn, respectively. The seasonal proportions indicated a greater likelihood of PET at the time of birth in spring, autumn and winter and a greater likelihood of PIH in spring and winter. When pregnancies with pre-eclampsia that resulted in a preterm birth were investigated, a higher likelihood of preterm birth was found in spring and autumn when compared with summer, but not in winter when the highest likelihood of medically indicated preterm births occurred.

Thus, while an annual pattern of pre-eclampsia could be seen when analysed by season, and this pattern corresponded to the pattern observed for medically indicated preterm births, a seasonality in PET could not be identified at a monthly level. This suggested that any seasonal pattern of PET (as diagnosed by the time of birth) was only weak at best and therefore unlikely to be contributing to the seasonal pattern of medically indicated preterm births. This conclusion was further supported when the highest likelihood of pregnancies with pre-eclampsia to result in a preterm birth occurred in autumn rather than in winter as would be expected if this condition was to be implicated as a mechanism for driving the seasonality of medically indicated preterm births.

7. DISCUSSION

This chapter sets out the main findings from this research, places the results in the context of previously published studies, and discusses the possible mechanisms through which a seasonal pattern of preterm births is occurring. Limitations of the study design and implications for the future are also discussed.

7.1 Main findings

Preterm birth proportions in the SMMIS dataset displayed a distinct seasonal pattern that was consistent each year over the study period. Preterm birth proportions were lowest in summers and highest during winter. In the winter months (i.e., December, January and February), babies were 11% more likely (Risk Ratio = 1.11, 95% confidence interval (CI) 1.08 to 1.15) to be born preterm when compared with summer births (i.e., those with birthdates in June, July, August). Although preterm birth proportions were also higher in the autumn than in the summer, this association did not reach statistical significance. The seasonality appeared to be driven by the proportions of preterm births that occurred between 32 and less than 37 weeks of gestation, rather than by preterm births that occurred between 24 and 32 weeks of gestation. This suggested that any potential mechanisms were ones that 'triggered' an early initiation of the normal labour process rather than being pathological in nature, which was in keeping with this study's main hypothesis.

When analysed using a fetuses-at-risk approach, the seasonal pattern was similar but the lowest risk of preterm birth came slightly earlier, in spring (i.e., March, April and May), rather than in summer. There was a significantly higher risk of being born preterm in autumn (i.e., September, October and November) when spring was used as the referent season (Risk Ratio (RR) = 1.10, 95% CI 1.07 to 1.14), that was not seen when the data were analysed using preterm birth proportions (RR = 1.02, 95% CI 0.99 to 1.05, using summer as the referent season). The significantly higher risk in winter was seen regardless of whether the data were analysed using proportions or probabilities (RR = 1.10, 95% CI 1.07 to 1.14 for probabilities).

The seasonal pattern of preterm birth proportions was affected by maternal age, ethnicity and parity. After stratification by these variables, a clear and consistent annual seasonal pattern was observed with proportions of preterm births among White mothers, who had the lowest risk of preterm birth, but not among Black or Asian mothers. The seasonal pattern was also seen with proportions of preterm births to mothers aged 25 to 34 years and for mothers who were 35 and older, but not among preterm birth proportions to mothers younger than 25 years. Both parous and nulliparous women demonstrated a seasonal pattern of preterm birth proportions, although the pattern among parous women was more consistent over the 13 years studied. Both male and female preterm births demonstrated similar annual seasonal patterns. With the exception of older mothers (aged 35 and older), it appeared that groups with a higher risk for preterm birth (i.e., Black and Asian mothers and mothers younger than 25 years) did not demonstrate a consistent seasonal pattern. Although a seasonal pattern was seen among preterm births to older mothers, this result should be interpreted with caution due to small numbers in this group.

Short-term associations with preterm birth proportions were seen with daily mean temperature, hours of daily sunshine and weekly influenza A counts. An association with ambient PM_{10} was seen only when births occurring in the hospitals located furthest from the air pollution and weather monitoring stations were removed from the analysis. No differences in short-term effects from exposure on the day of birth were found when the results of the analysis based on preterm birth proportions were compared with results from the fetuses-at-risk analysis.

A small effect of daily mean temperature was seen among very preterm birth proportions (gestational age between 24 and less than 32 weeks). Very preterm birth proportions decreased by 0.01% (95% CI 0.01 to 0.02) with each degree increase in daily mean temperature on the day of birth. Daily mean temperature on the day of birth also appeared to have a different effect among White, Asian and Black pregnancies. While preterm birth proportions among white mothers increased by 0.05% (95% CI 0.01 to 0.08) with each degree increase in daily mean temperature, they decreased by 0.09% (95% CI 0.01 to 0.17) for each degree increase in daily mean temperature among Asian mothers. No significant effect of daily mean temperature was seen for preterm birth proportions among Black mothers.

With cumulative exposure during the four weeks before birth, a 0.34% (95% CI 0.09 to 0.58) increase in preterm birth proportions per hour increase in daily sunshine below 3 hours was also observed. Rather complicatedly, this was interpreted as: pregnant women who were exposed to an average of three hours or less of daily sunshine during the four weeks before birth had an increased risk of preterm birth with each hour increase in daily sunshine below three hours. Controlling for daily mean temperature in this model improved the overall fit of the model (according to the deviance) and the results remained statistically significant, with preterm birth proportions increasing by 0.33% with each hour increase in daily sunshine (95% CI 0.08 to 0.58). In the stratified models, the effect of sunshine was seen among male preterm birth proportions, proportions of preterm births that occurred between 24 to less than 32 weeks of gestation, preterm birth proportions among White mothers and among mothers that were between 25 to 34 years old. Preterm birth proportions in these groups decreased with each hour decrease in daily sunshine below three hours with cumulative exposure in the four to six weeks before birth. This effect of daily sunshine was seen for proportions of preterm births that were the result of spontaneous labour, but not medically indicated preterm births.

An effect of weekly influenza A counts was seen among White mothers only. Among White mothers, weekly preterm birth proportions increased by 0.05% (95% CI 0.01 to 0.08) with each additional weekly case of influenza A.

Although no effect of daily mean levels of ambient PM_{10} was observed when all births were included in the analysis, when births that occurred in the hospitals located 10 or more miles away from the monitoring stations were removed, preterm birth proportions increased by 0.05% (95% CI 0.01 to 0.11) with each $\mu g/m^3$ increase in the daily mean level of ambient PM_{10}.

When it was apparent that much of the seasonality in preterm birth proportions could not be explained by short-term associations with the environmental exposures investigated in this study, further analyses to uncover potential mechanisms were conducted. Due to the complex aetiology of pathways purported to lead to preterm birth, it has been argued that both aggregating as well as separating into spontaneous and medically indicated preterm births are justified approaches for research in this field.[138]

In this study, it was hypothesised that the environmental exposures studied were more likely to have an effect on spontaneous, rather than medically indicated, preterm birth proportions. Somewhat surprisingly, when separated by whether they occurred spontaneously or were medically indicated, both preterm birth subtypes demonstrated a strong seasonal pattern. The association with daily sunshine at a lag of 4 weeks appeared to be driven by spontaneous preterm birth proportions. The seasonality of pre-eclampsia and pregnancy-induced hypertension was investigated as a possible explanation for the seasonality of medically indicated preterm birth proportions. As only a weak seasonal pattern could be detected for both pre-eclampsia and pregnancy-induced hypertension, however, it was concluded that neither were likely to be substantial contributors to the seasonal pattern of medically indicated preterm births.

7.2 Interpretation of findings

Although the results from this study are consistent or compatible with previous studies on the seasonality of preterm birth, the larger challenge was consideration of the short-term findings within the larger context of biological plausibility. The rationale behind this study was that one or more of the exposures investigated might trigger the activation of the mechanisms leading to an early initiation of the normal labour process or that factors that have short-term associations with preterm birth may exhibit a seasonal pattern, thereby driving the seasonal pattern of preterm birth. Early activation may be due to an effect of the exposure on the mother or the fetus or both.

7.2.1 In the context of findings from other studies

While the seasonal pattern exhibited by the preterm birth proportions was similar to that exhibited when analysed by probabilities, the seasonality of preterm births in the SMMIS dataset differed from previously reported seasonal patterns of preterm birth in developed countries. In both Japan and the United States (USA), a six monthly pattern of preterm births was observed.[69 70 71 72] In addition to higher proportions or probabilities of preterm births in the winter, higher proportions and probabilities were also observed in the summer or autumn in the Japanese and American cohorts. This summer or autumn increase was not apparent in the SMMIS study population. In fact, it was during this time of year that preterm birth proportions were at their lowest.

A likely reason for the difference in seasonality of preterm birth proportions between this British cohort and the American and Japanese cohorts is the temperate climate of England compared with the more extreme temperatures experienced throughout Japan and in the majority of the USA. The mean summer temperature from the Heathrow monitoring station was 17.9 °C for the study period. In a study of geographical differences of the seasonal pattern of preterm birth proportions, Matsuda et al. reported mean summer temperatures for all 47 prefectures in Japan (June to August), ranging from 19.5 °C to 27.4 °C.[70] The authors reported that while the general pattern of preterm birth proportions had a peak in the summer and a peak in the winter, the summer peak became more prominent in the southern prefectures, where the highest summer temperatures occur. In the northern prefectures, the summer peak was much smaller. This suggests that a positive association between temperature and preterm birth may only exist above a certain threshold that is not typically reached by the English climate. Thus it is possible that no summer peak was observed in the SMMIS preterm birth seasonality because pregnant women in the study area were not exposed to the high temperatures needed to observe an effect. As more recent SMMIS data become available, future work may like to include an investigation of associations during the 2003 heatwave in southern England to either support or refute this theory.

Similar to the findings from this study, Matsuda & Kahyo found that a comparable seasonality was exhibited by both male and female preterm birth proportions.[69] Matsuda & Kahyo also found that the seasonal pattern for both nulliparous and parous women was comparable when the five year study period was averaged across one 12 month period. In this study, the averaged seasonal pattern over one 52 week period was similar for both parous and nulliparous women.

After stratification by variables which demonstrated varying risk for preterm birth between groups, preterm birth seasonality was no longer apparent among Black or Asian mothers and to mothers younger than 25 years. Using a chi-squared analysis, these were the groups that had significantly higher proportions of preterm births in the SMMIS dataset (see Results I, section 4.1). This suggested that the smaller numbers in these groups did not allow detection of a seasonal pattern or that the factors responsible for the early initiation of parturition in these high risk groups override or were greater than the factors driving the seasonal pattern of preterm birth. The study by Cooperstock and Wolfe[71] similarly found that younger mothers (21 years or less) and mothers from lower socio-economic status, i.e., groups of women at higher risk for preterm birth, did not show consistent seasonal preterm birth patterns. Therefore, the elucidation of the mechanisms behind the seasonality of preterm birth in groups at higher risk for preterm birth may not have as much potential to provide benefit as for the lower risk groups since the seasonality in these higher risk groups is likely to be obscured by other factors contributing to preterm birth.

Daily mean temperature (within the range experienced in the UK) did not appear to offer a strong explanation for preterm birth seasonality. Among mild preterm birth proportions (gestational age between 32 and less than 37 weeks), little or no short-term association between and daily mean temperature was found. As suggested earlier in this section, it may be that exposure to high temperatures are associated with an increased risk for preterm birth but that the temperate climate in Britain does not reach the required threshold to pose a significant risk to pregnant women. It may also be, however, that an association between temperature and births that occur later in the preterm period simply does not exist at any threshold. Consistent with the results from this study, one American study that reported an association between increasing temperature and preterm labour[94] found that the association with temperature was no longer significant when using preterm births as the outcome. Another study found no evidence of an association between the length of gestation and heat stress.[95]

One of the strongest associations found in this study was with exposure to daily sunshine at least four weeks before birth. Although the association was seen only for spontaneous preterm births and not for medically indicated preterm births, it did not correspond well with the seasonal pattern of preterm births. The season in which most days with less than three hours of sunshine are likely to occur is winter and during winter, the proportions of preterm birth were at their highest. Preterm birth proportions, however, were found to decrease with each hour decrease in daily sunshine, suggesting that this association would be responsible for lowering preterm birth proportions in winter, if it was indeed a contributing factor to preterm birth seasonality.

A study from New Zealand investigated sunshine as a factor that might account for seasonal variation in gestational age in full term infants and found no association with exposure during any trimester.[84] As with the seasonal patterns in preterm birth proportions, when investigating associations with climatic factors, differences between countries may be attributed to the distinct meteorological conditions of each geographical area to which the people are exposed. While nearly half of the days during the SMMIS study period had 3 hours of sunshine or less, there was no month in the New Zealand study (from 1999 to 2002) that experienced a daily average of less than 4 hours of sunshine. Thus, in fact, not only was it impossible for the New Zealand study to investigate an association below a threshold of three hours of sunshine per day, but also, the results from the New Zealand study are consistent with the findings from this study which found no association above this threshold.

Due to the exploratory nature of this study where many associations were investigated, one might expect that some of the findings are due to chance. Given the consistency of this particular association across various strata (e.g. white mothers and mothers aged 25 to 34 years), however, this seems unlikely. It seems more likely that preterm birth proportions do indeed increase with increasing sunshine below a threshold of three hours but that this is a relatively small effect that does not greatly influence the high proportions of preterm birth generally seen in winter.

This study found no association between daily mean barometric pressure or the largest daily drop in barometric pressure and preterm birth proportions. Previous studies have investigated the possibility of an association between barometric pressure and the onset of labour at or near term, rather than for preterm births. Because this study assumed, however, that an effect of barometric pressure would be to trigger an early initiation of the normal labour process during the preterm period, results from these studies were considered relevant for providing context for the findings of this study. Unfortunately, the results and methodologies of previously published studies varied widely making it difficult to draw conclusions about the potential effect of barometric pressure on labour onset. In addition, the quality of most studies was poor, either failing to report the number of subjects included or omitting clear explanations of methodology and results (see Appendix 1). While one study reported an association between fewer labour onsets and drops in barometric pressure during the three hours before birth,[93] other studies reported an increase in the number of labour onsets after a drop in barometric pressure[92] or an association with the most labour onsets occurring when pressure was at its highest.[97] The unreliable methodologies and inconsistent findings of these studies suggests a need for standardisation of analytical techniques, which this study hopes to provide. Using time-series data and regression techniques which controlled for any potential long term seasonal trends in at least one of the variables of interest, combined with the power provided by a large dataset, the lack of any short-term association between preterm birth and barometric pressure in this study was considered a robust finding.

While this study found a small positive association with weekly influenza A counts and preterm birth proportions among White mothers, these results were not consistent with the findings of a case-control study of perinatal outcomes amongst pregnant women who were hospitalised during eight consecutive influenza seasons in the United States.[181] In fact, among all Black and White pregnant women hospitalised and diagnosed with pneumonia or influenza, no significant difference in preterm labour or preterm birth was detected. Because the study was conducted in a high risk population, however, the results may not be representative of what was occurring in the general pregnant population. Indeed, hospitalised subjects were found to be less likely to be Black when compared with the source population. In the SMMIS study sample, the seasonal occurrence of influenza A, combined with the evidence of an association between influenza A and preterm births to White mothers, appeared to provide at least a partial explanation for the seasonal pattern of preterm birth proportions that was seen among white mothers. The results for preterm births among Black and Asian mothers should be interpreted with caution as the numbers in this group were quite small. For example, there were 100 days during the study period that had no births to Black mothers and 2,646 days (56%) where the preterm birth proportion was 0.

The association between daily mean levels of ambient PM_{10} and preterm birth proportions found in this study was consistent with previous reports in the literature. One study that reported an increased risk of preterm birth with exposure to PM_{10} used individual estimates of maternal exposure to ambient pollution based on data from monitoring stations.[109] The study was therefore subject to confounding by individual level risk factors whereas the present study design had the advantage of removing the effect of such individual level confounders because time (i.e. days), rather than an individual, was used as the unit of measure. A more recent study, which used a time-series design similar to the one used in this study, also found an increased risk with exposure to PM_{10} during the two days before birth.[108] Regardless of study design, both of these studies reported an increased risk from exposure to PM_{10} similar to the association found in this study. The consistency of this association in different environments and using different study designs lends increasing certainty to possibility that maternal exposure to ambient PM_{10} during pregnancy increases the risk of preterm birth.

The association with PM_{10} in this study was apparent only when women who gave birth in a hospital located within a 10 mile radius of the monitoring stations were included in the analysis. This finding is perhaps unsurprising considering the limitation of having to rely on monitoring station measurements for exposure assessment. Notwithstanding other limitations related to imprecise exposure assessment (see section 7.3.5), it has been argued that higher ambient air pollution levels do indeed translate to higher individual level exposure.[149] Nevertheless, the representativeness of estimates from monitoring station to surrounding areas is difficult to judge though it follows logically that the estimates will be more imprecise the further one gets from the monitoring station. A previous study was unable to find an association with PM_{10} when women who lived further than 10 miles from the monitoring stations were included in the analysis (unpublished results, B. Ritz, August 2004). In addition, differences in city and suburban pollution levels are to be expected; the further one travels from central London, the less pollution one might expect.

With regards to daily mean levels of ambient ozone, no associations with preterm birth proportions were found. Two other studies also found no evidence of an association between preterm birth and ambient levels of ozone.[109 111] Again, these two studies used designs that were subject to confounding by individual level risk factors. The consistency of the results across varying study designs, however, lends further support to the lack of association between exposure to ambient ozone and preterm birth.

The seasonality of pre-eclampsia and of pregnancy-induced hypertension was explored as possible predictors of the seasonality that was observed in medically indicated preterm birth proportions. The seasonality of pre-eclampisa has been relatively well-explored in other countries, although no reports on its seasonality in Britain were located. Despite hypotheses that PET or PIH seasonality is driven by an association with hot or humid weather, the results of previously published studies have not consistently confirmed this association, nor have studies consistently demonstrated that PET or PIH exhibits seasonality.[105 182 104 102 103 183 184 185] Reports exist for both developed[104 105 185 182] and developing countries[102 103 183 184] that indicate conflicting results regarding whether a seasonality of PET or PIH exists. A small effect size may be one reason for the many conflicting reports in the literature. One of the strengths of the SMMIS dataset, however, is the power provided by the large sample size to detect small associations, if they exist. An annual variation in PET proportions was apparent in this dataset when the proportions were grouped by seasons, but not by month, indicating weak seasonality.

7.2.2 Biological plausibility

While a general conceptual framework existed, much of this analysis was exploratory since the aetiology of preterm birth is not well understood and data on a wide range of explanatory factors were available. The conceptual framework for this study was developed in accord with previously published research on the exposures that were investigated and on preterm birth aetiology. It made several specific assumptions about biological plausibility:

1. any effects of meteorological factors would be to 'trigger' an early initiation of the normal labour process and therefore would be more likely to be seen with preterm births from 32 to less than 37 weeks of gestation,
2. any effects of the air pollution or influenza A exposures would be as risk factors for preterm birth that vary seasonally, thereby influencing the seasonal pattern of preterm birth,
3. an effect of influenza A would be more likely to be seen with preterm births from 24 to less than 32 weeks of gestation, and
4. differences in effect would be seen when stratified by potential modifiers that were decided *a priori*: maternal ethnicity, fetal sex, and maternal age.

Although differences in effect were seen by maternal age, sex of the fetus and by maternal ethnicity, this study provided little evidence for the other three assumptions that were made. At the same time, the findings from this study did not necessarily refute these assumptions. This section discusses possible mechanisms through which the findings might be operating and which do not contradict the concept of the framework.

While the seasonality of preterm birth proportions was more clearly evident among later preterm births (32 to less than 37 weeks of gestation) when compared with earlier preterm births (24 to less than 32 weeks of gestation), associations with the exposures investigated did not appear to contribute to this seasonality. Although earlier preterm births did not appear to demonstrate any consistent annual pattern across the 13 years, a linear association was found where decreasing daily mean temperature was associated with small increases in preterm birth proportions. The theory that cold exposure *in utero* may have a direct effect on the physiological development of the fetus may explain the inverse association found between earlier preterm births and temperature.

Animal studies have shown that maternal adaptation to cold exposure beneficially alters fetal growth and results in increased birth weight.[186] If the maternal response to cold exposure in humans was to increase birthweight, the synchronisation of fetal maturation and birth that leads to the determination of gestational age could conceivably result in an earlier birth due to earlier maturation of the fetus. A review on the thermal environment and birthweight, however, found no studies investigating either chronic or acute cold stress in relation to human pregnancy.[187]

In contrast, a recent study of British women aged 60 to 79 years found a higher prevalence of cardiovascular disease and increased insulin resistance among those born during the coldest months[188] suggesting an adverse developmental effect of cold exposure during pregnancy which could lead to preterm birth. One possible pathway suggested by Murray et al.,[6] purports that colder temperatures result in reduced blood flow between the uterus and placenta, restricting fetal growth. The restriction of fetal growth may, in turn, lead to preterm birth.

The potential effect of cold exposure on early preterm births through any mechanism, however, is acknowledged to be quite small. As no seasonal pattern of early preterm births was apparent, it may be concluded that the association with cold exposure was either not strong enough to result in consistent increases in winter or that other factors have a larger role in determining the risk of early preterm births in this cohort. Nevertheless, the seasonality in later but not earlier preterm births and the differences in short-term associations that were found between the two groups support the fundamental assumption upon which the specific assumptions of the conceptual framework were based, that is, that causative mechanisms for preterm birth depend, at least to some extent, on when during the preterm period a birth occurs.

A positive association with cumulative exposure to an average of three hours of daily sunshine or less during the four weeks before birth was found for early, but not later preterm births. While a positive association with daily sunshine may seem counterintuitive at first, upon further inspection, one realises that this effect of sunshine on early preterm births will occur predominantly during the winter months. This is because over the entire 13 years, only 88 to 115 days had three hours of sunshine or less during the summer months. There were 2175/4749 days (45%) during the study period that had three hours of sunshine or less and 61% of these (1325/2175 days) occurred during the winter months or in the months on either side of the winter season. The effect that was found was only for pregnant women who had been exposed to an average of three hours or less of daily sunshine in the four weeks prior to birth. Therefore, it was unlikely that this effect would have occurred very often in summer. Indeed, even in winter, when 'nocturnal' periods are longest and the majority of increase in early preterm births due to sunshine would be likely to occur, the effect is likely to be small.

Both term and preterm labour have been shown to begin more frequently during the night.[189 190] This suggests that labour onset may be modulated in some way by photoperiod, either through the diurnal rhythm of hormone activation, such as oxytocin,[191] or the nocturnal predominance of uterine contractions[192] that may result in the onset of labour. Different patterns of labour onset between winter and summer nights have been reported.[190] If longer periods of 'night' are also associated with a greater frequency of preterm labour onsets, it may be that exposure to sunshine subsequently plays some role in determining the length of labour or the timing of birth, thus driving the association found in this study. Like many issues with preterm birth, the relationship with sunshine appears to be complex. It was observed for spontaneous, but not medically indicated, preterm births. This suggests that whatever the mechanism, it is most likely a physiological response.

There were also differences in associations found with maternal ethnicity. The association with daily sunshine was apparent among white but not Black or Asian mothers. The difference in effect by maternal ethnicity may be due to differential adaptation to sunshine. For example, in the case of rickets, it has been found that while people from the entire range of skin colour are capable of synthesising vitamin D with exposure to ultraviolet light, people with darker skin require greater exposure to synthesise the same amount as a lighter skinned person.[193] Along the same line of reasoning, it may be that the darker colour of Asian and Black skin somehow confers a protective effect against sunshine when compared with white women.

In addition to differences in susceptibility, adaptation may result in diverse outcomes from the same exposure among different ethnic groups. In one study on the effect of environmental pollutants on birth outcomes in inner city minority populations, exposure to polycyclic aromatic hydrocarbons (a common airborne urban pollutant) resulted in lower birthweight and smaller head circumference among African Americans but not among Dominicans.[194] Variation in response to the effect of an exposure due to cultural adaptation provides an explanation for the different directions of association that were found for daily mean temperature and preterm birth when stratified by maternal ethnicity.

On the other hand, the association with influenza that was found only with preterm births to white mothers, and not among black or Asian mothers, may be relate to issues of sample size. One limitation of this study was that the only infection exposure studied was influenza. The influenza counts were based on the general population of London and were from laboratory reports. This meant that as a proxy, not only were the numbers undoubtedly underestimates of how many people in the population actually suffered from the flu, but also that numbers for the population were applied to a female pregnant population. There were also a large number of days on which either zero or one case of flu was reported, necessitating the use of weekly, rather than daily, units of measure. When the sample was then further divided by maternal ethnicity, white mothers comprised the largest group. In light of these limitations, it is perhaps unsurprising that a small effect of weekly influenza A counts was seen only among preterm births to white mothers. Furthermore, ethnic differences in seeking medical help may mean that lab-based estimates of influenza counts are a better indicator for a white, rather than a non-white, population subgroup.

Although a large and increasing body of epidemiological evidence exists to implicate particulate matter air pollution and its adverse effects, the mechanisms through which this is occurring has remained elusive, not just for pregnancy-related outcomes, but for other health-related outcomes as well.[195] It is possible that air pollution acts to exacerbate or increase pre-existing conditions, such as maternal asthma, subsequently increasing the risk of preterm birth.[196 197] Another possibility is that maternal systemic infections and air pollutants operate through similar as well as interacting pathways leading to preterm birth. For example, air pollution may act to increase the susceptibility of a pregnant woman to systemic infections.[198] An inflammatory response in the mother due to infection or as a result of exposure to particulate matter may then increase blood viscosity.[199] If the increase in blood viscosity resulted in reduced blood flow to the placenta, fetal growth may be restricted, resulting in preterm birth. Alternatively, the release of inflammatory cytokines may stimulate prostaglandin production, which stimulates uterine contractions and the release of metalloproteases, which act to rupture the membranes.[33] It is also possible that rather than mediating its effect through the mother, air pollution passes across the placenta and affects fetal growth more directly.

It was anticipated that the findings from this study would support the assumptions of the conceptual framework that was used. Instead, however, the findings from this study confirmed the complexity of the preterm birth issue. While the findings can be interpreted within a biological construct that complements the original hypothesis of the study, further work to aid the understanding of how preterm birth seasonality is mediated is warranted. Disentangling the mechanisms responsible for the existing ethnic variation in preterm birth seasonality and the related short-term associations may help reduce the ethnic disparity in preterm birth. These findings represent only the beginning of a large body of exploratory work that can contribute to the understanding of the heterogeneous aetiology of preterm birth.

7.3 Strengths and limitations

7.3.1 Study design

One strength of this study was the consistency of results that were obtained using different approaches for analysis. Conducting the analysis using preterm birth proportions as well as by fetuses-at-risk added assurance that the findings were robust. By using two methods of analysis, one could also rule out the possibility that the seasonality of preterm birth proportions was being driven solely by a seasonality of conceptions. If, for example, the risk of preterm births was constant, a seasonality of conceptions would make it appear seasonal. In this study, however, the design of the fetuses-at-risk analysis, which used denominators that were prospectively calculated, accounted for any seasonality of conceptions. Using both approaches (i.e., proportions and fetuses-at-risk), similar patterns of preterm birth seasonality were observed. Thus while a seasonality of conceptions may indeed contribute to the seasonal pattern of preterm birth proportions, the seasonality of preterm birth probabilities suggested that other mediating factors must also exist.

The time-series methodology was also a strength of this study as it allowed the investigation of exposure effects while controlling for the potential influence of known and unknown individual level risk factors that are not likely to vary over the short-term. Using other study designs, the majority of research on meteorological or air pollution effects has been subject to inadequate control for confounding by individual risk factors that could potentially affect any findings of a relationship with preterm birth.

In addition, the large size of the SMMIS dataset and the long period of time that it covered permitted detection of potentially small effects that undersized studies may not have the power to detect. As the data were routinely collected and covered a wide geographical area, this population-based study was not likely to have been subject to the selection biases that may arise when recruiting a patient population.

Finally, as this study used an ecological study design, it should be remembered that the generalisability of the results do not apply at an individual level, but may have implications for regulation and health policy at the population level. The findings from this study could be enhanced with similar studies conducted in different regions of the UK.

7.3.2 Subjectivity of model building

One potential drawback of general linearised models is that their creation and generation represents a series of steps during which a combination of diagnostic criteria and personal opinion come into play. While some of the diagnostic criteria are statistically based, others require judgement by the person who is analysing the data. This judgement is subjective and will vary depending on the experience and knowledge of the analyst. A good model is said to be one that is parsimonious as well as encompassing a reasonable scope, where 'scope' refers to the range of conditions over which the outcome is generalisable.[200]

If one continuously added parameters to a model, one would eventually obtain a perfectly fitting model. This, however, does not help to simplify or clarify the relationship(s) one seeks to identify. A useful model therefore, requires a parsimonious selection of parameters so that the data or outcome(s) remain interpretable, and any confounders (known or unknown) are adequately controlled. Under this principle, the inclusion of unnecessary extra parameters should be avoided. This means that despite thorough checks of the model fit using residuals and other statistics, the final determination of how many parameters to include in any model may vary from one modeller to the next. As this was largely an exploratory study in which we were seeking consistent, plausible findings, the modelling methodology was conservative and only parameters that were deemed necessary were included.

7.3.3 Gestational age assessment

As with all studies on preterm birth, the measurement of gestational age can be problematic. Before the 1980s, gestational age was recorded primarily through maternal recall of the date of the last menstrual period (LMP). Not only is there an inherent lack of precision in this method due to individual variation in the interval between the first day of the menstrual period and conception, but recalled dates may also be inaccurate or menstrual cycles irregular. Furthermore, it has been suggested that errors in estimation of gestational age by LMP may be systematic, in particular, with a tendency to overstate the duration of gestation.[201 202]

More recently, the uptake of early ultrasound has resulted in various algorithms combining the use of LMP and ultrasound measurements of crown-rump length, biparietal diameter, or head circumference to estimate gestational age.[203] One of the consequences of using different methods to estimate gestational age is that the rates of preterm births may vary substantially depending on which algorithm is used. Early ultrasound scans appear to reduce gestational age estimates when compared with LMP dating and may result in 13-20% higher rates of preterm birth.[118 204]

The SMMIS dataset used LMP when available and certain and no consistently specified algorithm was used when LMP was not available or uncertain. Instead, the 'best antenatal assessment' was made using available ultrasound scans. The systematic tendency to overestimate gestational age when using LMP may have resulted in an underestimate of preterm births in this dataset. However, this was likely to be offset by an overestimate of preterm births from ultrasound estimates.

This study was restricted to preterm births between 24 to 44 weeks of gestation so that implausible gestational durations would be excluded from the analysis. Misclassification was still a concern, however, as inconsistencies between hospitals in methods for estimating gestational age by week have been shown to affect preterm birth estimates by up to 10%.[205] To avoid such misclassification in this study, days of gestation, rather than weeks, were used to dichotomise the outcome (i.e., less than 259 days).

7.3.4 Unit of observation

The unit of observation in this dataset was a pregnancy and therefore any woman who had more than one child in the SMMIS area was included in the dataset two or more times. This may have resulted in bias due to correlations among pregnancies contributed by the same woman, especially as women who have had a prior preterm birth are more likely to experience another.[141] As it was not possible to identify women in this dataset, analysis could not be restricted to only one pregnancy from each woman. To account for this, the analysis was stratified by parity (i.e. first pregnancies were separated from second and any other subsequent pregnancies) to determine any effect of possible bias in sampling. Although parous women appeared to demonstrate a more consistent seasonal pattern across the study years than nulliparous women, no differences in short-term associations between nulliparous and multiparous women were found.

7.3.5 Exposure assessment[r]

The reliance on measurements from routine monitoring stations for meteorological and air pollution factors was a limitation in this study. Although a time-series design precludes the inclusion of each pregnant woman's exposure to any factor, the extrapolation from data that were obtained from outdoor monitoring stations is not likely to accurately represent individual levels of exposure. While the result of such exposure misclassification would be more likely to bias the findings towards null,[206 207] some have argued that exposure measurement error may also account for any associations found.[208]

A study on the effects of particulate matter on other outcomes systematically tested what effect the relationship between personal exposure and ambient exposure might have on study findings.[208] While the results suggested that exposure misclassification did not account for any associations found, the authors concluded that more studies were needed for confirmation of these conclusions. In a review of ambient air pollution and pregnancy outcomes,[149] the authors suggested that evidence from studies showing higher levels of pollution biomarkers in maternal blood and placentas in areas with higher levels of ambient pollution indicated that ambient levels do indeed correspond to individual level exposures.

Many factors may contribute to differences between area wide and individual level exposures for both air pollution and meteorological variables. Spatial distributions of air pollutants may not be homogeneous within an area (e.g., some argue that ozone is less localised when compared with PM_{10} which has many point sources) and a pregnant woman may spend much of her time indoors (indoor sources of air pollution may also contribute to exposure, further contributing to the difference[209]) or somewhere distant from the monitoring station. The potential effect of this was demonstrated by the sensitivity analysis

[r] For discussion on limitations of influenza exposure assessment, please refer to section 7.3.2 on biological plausibility.

conducted for this study. Using the hospital of birth as a proxy, a positive association with PM_{10} was only seen when women giving birth in the hospitals located furthest from the monitoring stations were excluded from the analysis. Additionally, air pollutants may interact with each other and this was not addressed in this study.

Specifically with regards to meteorological factors, cultural adaptations may result in imprecise exposure assessment. For example, a pregnant woman may spend most of her time indoors in air conditioning when it is hot during the summers and in a heated house (or work) when it is cold during winters. Actions that act to negate the effects of outdoor weather are presumably prevalent in British culture and these may counteract any effect of meteorological factors on preterm birth. On the other hand, sunny days may encourage more pregnant women to go outdoors and this action would act to overestimate the size of any associations found. The reader is urged to bear in mind the potential effect of cultural adaptations to weather phenomena when interpreting the findings from this study.

7.3.6 Time of exposure

The critical period of exposure to meteorological, air pollution and infectious agents during pregnancy has not been established. In general, the duration of pregnancy is 40 weeks. It has been hypothesised that susceptibility to environmental effects *in utero* may occur only during sensitive and brief periods during development.[210] Others suggests that potential adverse effects may have their largest impact during times of rapid growth of the fetus, such as between 20 to 32 weeks after conception.[45] The analysis in this study was limited to the period six weeks before birth and at the time of conception and other windows of exposure were not controlled for in our analysis.

Realistically, environmental exposures may manifest their effect(s) in a least two different ways. First, a relatively immediate effect could result in an early birth soon after exposure or from short-term exposure at some other period during the pregnancy. Second, a cumulative effect after a longer period of exposure throughout (or at various times during) the pregnancy may result in an early birth. Results from this and previous studies on air pollution indicate that both types of effects may actually be occurring. For example, two studies found a significant association between ambient particulate matter and preterm birth with exposure during the period of 7 days to six weeks before birth.[109 106] The effect found in one of the studies[106] represented a cumulative exposure. Similarly, in this study, the association found between sunshine and preterm birth proportions was only apparent with a four week cumulative effect. In contrast, another study found no association between exposure during the third trimester and particulate matter but reported a significantly increased risk for preterm birth with exposure during the first trimester.[119]

Complicating the situation even further is the potential for exposure at different times during gestation to have different effects. For example, in a study of ambient temperature and birthweight,[85] mean temperature during the first trimester was inversely associated with birthweight whereas mean temperature during the third trimester was positively associated with birthweight.

Furthermore, controlling for exposure during other periods of gestation is problematic since the inclusion of explanatory variables that are highly correlated in a model can have undesirable consequences, such as predicting unstable results.[174]

Continued research into the critical periods of exposure during pregnancy will aid understanding of the biological mechanisms through which air pollution, weather factors and infections may be having an effect on preterm birth. Issues of whether there is a potential for long-term exposures to accumulate and thereby have an effect should also be addressed.

7.4 Implications

Many international organisations are now warning against the potential impact that climate change will have on human health.[211] That the climate is indeed rapidly changing is demonstrated by the fact that nine of the warmest years on record in Europe have occurred since 1989 and by reconstructions that show unprecedented warming in the last decade.[212] It is predicted that more intense, more frequent and longer lasting heatwaves will occur during the second half of the 21st century.[213] A change in temperature and other meteorological factors in Britain could mean a change in their impact on preterm birth. In addition, as air pollution and influenza demonstrate seasonal patterns based on climatological conditions, climate change may impact their effect on preterm birth patterns, as well. Therefore, the establishment of methods to assess the potential impact of meteorological factors on our well-being, and in particular, reproductive health, are essential. This study provides a relatively unexplored model for dissecting the multiple intersecting pathways that lead to preterm birth.

For the formulation of air pollution standards, awareness of the exposure-response relationship will be important for the determination of what is considered acceptable. Safe thresholds and knowledge about the potential effects of individual pollutants are needed to inform policy in this area. The current national objective for Britain is not to exceed ambient PM_{10} levels of 40 $\mu g/m^3$ and to achieve levels of PM_{10} below 20 $\mu g/m^3$ by the end of 2015.[214] This study found a positive association between PM_{10} and preterm birth proportions below a threshold of 21 $\mu g/m^3$, indicating that potentially toxic effects of ambient particulate matter at levels below current national guidelines have been identified.

Establishing the seasonal pattern of preterm births can also be useful for the organisation of health care service delivery. Hospitals could ensure that more specialised medical staff and neonatal care resources are on hand in preparation for the larger proportion of preterm births that occur during the winter months, thereby potentially reducing morbidity and mortality due to preterm birth. The investigation of preterm birth seasonality and its mediators may also assist with the future assessment of risk of preterm birth by contributing toward the understanding of the aetiology preterm birth.

7.5 Future work

This design of this study was based on suggestions of mediating factors for a seasonal pattern of preterm birth taken from previously published studies. While associations with some meteorological factors, influenza and PM_{10} were found, these did not appear to explain the seasonal pattern of preterm birth proportions that was observed. Nor was there a strong seasonal pattern of pre-eclampsia or pregnancy-induced hypertension that might explain the seasonal pattern of medically indicated preterm births. Additional studies on other potential mediating factors that might explain the seasonal pattern of preterm birth are warranted. Investigation of seasonally varying risk factors for which routinely collected or monitored data are not available, in particular, sexually transmitted infections such as Chlamydia and gonorrhoea, may require longitudinal studies for data collection.

The findings from this research raised questions that could be investigated in future studies, the findings of which may help to clarify what is driving the seasonal pattern of preterm births. Further exploration along these lines could have important implications for epidemiology and clinical practice, including for example, contributing to the identification of pregnant women who are most at risk or who are most susceptible to the effects of pollution. Further analysis in this area, based on the findings from this study, could address following questions:

- Is the seasonal pattern of preterm birth gradual? That is, does it gradually become more pronounced later in the preterm period if split into further gestational age categories?
- Similarly, is the seasonal pattern of preterm birth between spontaneous and indicated preterm births gestation dependent?
- What is the seasonal pattern of time of rupture of the membranes and how might this contribute to the seasonal pattern of preterm birth?
- Does the seasonal pattern of preterm birth vary by latitude within Britain?

- What associations might be found with a stratified analysis of exposures around the time of conception? Are there any differences from the findings of exposure around the time of birth (e.g. an influenza effect by ethnicity, a temperature effect by ethnicity, or a temperature effect by severity of preterm birth?)
- Does the effect of PM_{10} (from sensitivity analysis) differ by ethnicity?
- Can the effect of PM_{10} (from sensitivity analysis) be seen for both spontaneous and medically indicated preterm births?
- Is the association of PM_{10} stronger when only births from hospitals within a five mile radius of the monitoring stations are analysed?
- Do the ethnic differences in the association with daily mean temperature exist for both early and later preterm births?
- Do the ethnic differences in the association with influenza exist for both early and later preterm births?
- Can the seasonal pattern of pre-eclampsia or pregnancy-induced hypertension be explained by a seasonal pattern of blood pressure? Or, is warmer weather associated with decreased blood pressure levels at booking?

7.6 Conclusions

A distinct seasonal pattern among preterm birth proportions in the SMMIS dataset has been established. In this British cohort, it appeared to be driven by preterm births that occurred from 32 to less than 37 weeks and the highest proportions were demonstrated once a year during the winter months. A similar seasonal pattern was found using a fetuses-at-risk approach and also when preterm birth proportions were split by subtype (medically indicated and spontaneous). Although other developed countries that have reported seasonal preterm birth patterns have observed two yearly peaks, one in summer as well as in winter, the lack of a summer peak in this study may be due to the temperate British climate which does not reach as high temperatures as the United States or Japan.

Environmental events may disrupt developmental processes, leading to adverse outcomes. Given the relative lack of a priori knowledge of how meteorological factors might influence preterm births, however, an exploratory approach was taken. It was hypothesised that meteorological factors may act to trigger an early onset of the normal labour process. Alternatively, other factors, such as air pollution, influenza and hypertensive disorders of pregnancy, which have been previously shown demonstrate seasonal patterns and are risk factors for preterm birth, were also investigated as potential mediators of preterm birth seasonality. To gain an understanding of how any potential mediators might be operating, analysis was also stratified by maternal age, maternal ethnicity, sex of the fetus and severity of preterm birth.

While not many associations at the broader levels were found, more were found in the stratified models, indicating a complexity of preterm birth aetiology and suggesting differing effects by ethnicity, in particular. Direct evidence to support the assumptions on which the conceptual framework of this study was based was not found, however, nor did the findings contradict the assumptions made. For example, the results support the theory that different causative mechanisms for early versus late preterm birth exist. Biological explanations for the findings included mechanisms that interacted with the different exposures, such as exposure to air pollution leading to an increased susceptibility to infection.

The strengths of the study were based on the sample size and study design. Limitations included imprecise exposure assessment, the need for clarification of the critical window(s) for exposure, estimations of gestational age and the subjectivity that is inherent in modelling methodologies. Nevertheless, with predictions of climate change and its potential effects on our health, an investigation of the effects of weather, air pollution and infections on preterm birth seasonality remain relevant. The findings from this study raise important questions, the answers of which can have implications for clinical practice and future epidemiological studies on preterm birth.

Appendix 1. Table of studies on barometric pressure and labour onset.

Paper	Population	Methods	Period of exposure	Outcomes	Results	Comments
Noller KL et al, 1996[93]	All women admitted with onset of spontaneous labour at term (37 or more wks and <42 wks) from Oct 1993 to Sep 1994 in hospital in Massachusetts, USA (n=2,435)	**Cross-sectional** Daily mean barometric pressure calculated from hourly measurements Each of 8760 hours of the year categorized by changes in the preceding 3 hour (continuous rise, continuous fall, or other) and compared using chi- square The expected number of onsets of labour for each day during the study year was calculated by developing a model for the probability of labour occurring at a given gestational age	Time of labour onset and 3 hours before labour onset	Onsets of labour occurring during lowest yearly tercile of pressure (n=122 days) compared to onsets of labour from other 2 terciles (n=243 days) using t-test χ^2 to test that number of labour onsets associated with falling pressure in the preceding 3 hour period is what would be expected χ^2 to test that number of labour onsets associated with rising pressure in the preceding 3 hour period is what would be expected	P=0.26 for tercile with days of lowest mean barometric pressure v other 2 terciles* Continuously falling pressure v all others, χ^2=8.087, 1df, p<0.005; fewer labour onsets than expected Continuously rising pressure v all others, χ^2=0.00, 1df, p>0.97 ** sample size not large enough to detect a difference less than 5.7% with power of 80% at alpha=0.05*	
King EA et	N=162 pregnant	**Cross- sectional**	0- 24 hours prior to	Occurrences of	13 occurrences of	**Only the number of**

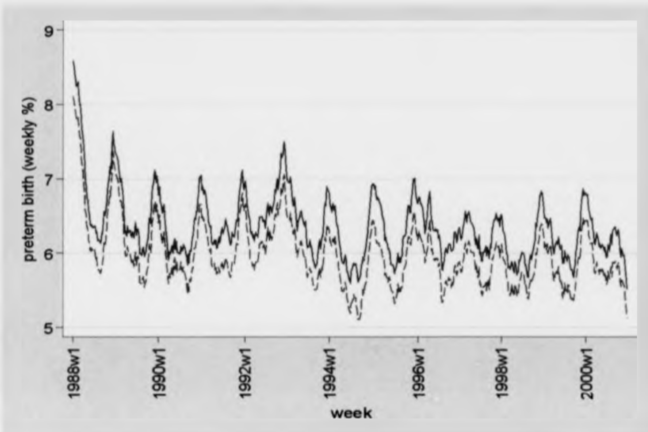
Paper	Population	Methods	Period of exposure	Outcomes	Results	Comments
al, 1997[92]	women presenting with spontaneous onset of labour at >36 wks, within 48hrs surrounding a 'significant' drop in barometric pressure, in tertiary care hospital in Texas, USA in 1992	Hourly barometric pressure data obtained and a drop of 0.06 inches Hg within 1 hour defined as 'rapid fall' For identified times of 'rapids falls' in pressure, incidence of onset of labour (with or without PROM) 24 hrs after fall in pressure (n=96) compared with incidence 24hrs before fall (n=66) in pressure	onset of labour	'rapid falls during 1992 χ^2 to determine whether there are more occurrences of onset of labour after barometric pressure drop than before*	'rapid drops' but one excluded due to overlapping in one 24 hr period **χ^2 = 5.556, p = 0.02**	**cases was known, i.e., the number of pregnant women who did not experience onset of labour was not reported, so unclear how chi-square was calculated**
Trapasso LM & Yurchison MJ, 1988[97]	In Kentucky, USA, all birth during 1984 from one medical centre	**Cross-sectional** Hourly barometric pressure data plotted and divided into 'ascending limbs, crests, descending limbs, troughs and level areas' The time of onset of labour for each birth superimposed on plotted pressure	Time of onset of labour (defined as 3cm of cervical dilation)	χ^2 plots with pressure curves superimposed with onset of labour times	**Significance tests from analysis not presented** but 'available upon request' More labours occurred in crest regions- **y and x axis of graph not labelled**; unclear how times of labour were plotted (n=16 dots representing onset of labour on graph)	**Number of births included not reported**

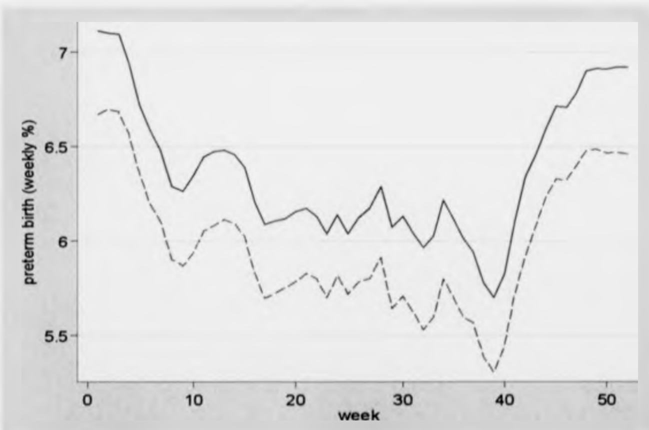
Paper	Population	Methods	Period of exposure	Outcomes	Results	Comments
		curve χ^2 analysis for each region of barometric pressure and labour onsets				
Driscoll DM & Merker DG, 1984[99]	Women between 38 and 42 weeks of gestation presenting with their 'first' uterine contractions at a hospital in Texas, USA from 1978 to 1979	**Cross-sectional** Pressure at 6am and 'pressure change from previous day' **(how this was derived was not explained)** Data for mean number of labour onsets compared for warm (Apr to Sep) and cool (Oct to Mar) seasons and between terciles	Day of 'first' uterine contractions	Ratio of mean daily onsets to the mean daily onsets for a tercile to that season	For the lowest tercile of pressure at 6am, the mean number of onsets per day was 1.12 times the mean daily onsets in winter, p = 0.02 No other results appeared to be statistically significant	**Number of births included not reported**
Driscoll DM, 1995[98]	Information from delivery records at a hospital in Texas, USA from Oct to Mar of 1987 to 1992	**Cross-sectional** Comparison of weather on days in which 7 or more onsets of labour occurred (and the day before and the day after) using the number of onsets that would be expected if	**Not specified**	χ^2	Mean daily onset rate 82%, p<0.05, for days with low pressure (n=38 days)	**Number of births included not reported**

Paper	Population	Methods	Period of exposure	Outcomes	Results	Comments
		onsets were in proportion to the number of days the particular weather event occurred over all days				

Appendix 2. Seasonal pattern of preterm birth proportions with (blue solid) and without (red dotted) stillbirths.

The removal of stillbirths from the dataset did not alter the seasonal pattern of preterm birth proportions.



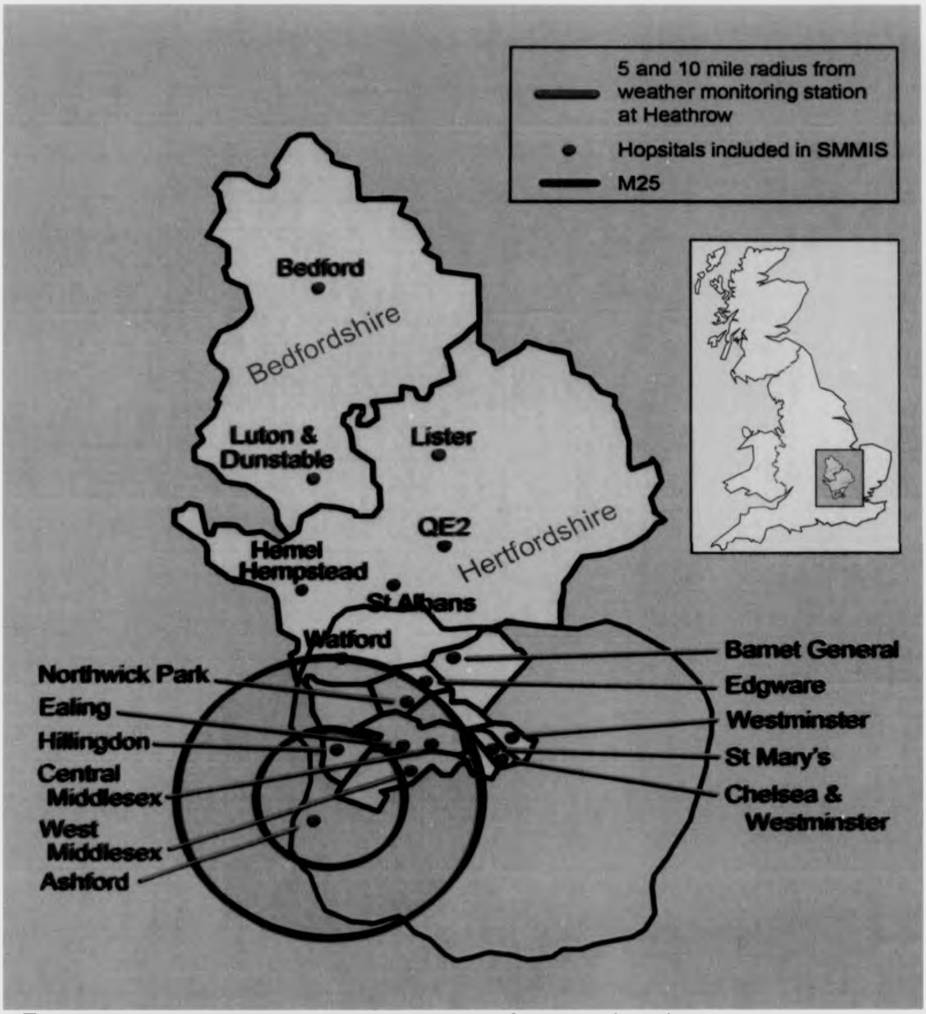


Appendix 3. List of hospitals and the years from which births were dropped for the pre-eclampsia analysis.

All births from the following hospitals were dropped for the years specified as they had more then 70% of the values for the pre-eclampsia variable missing.

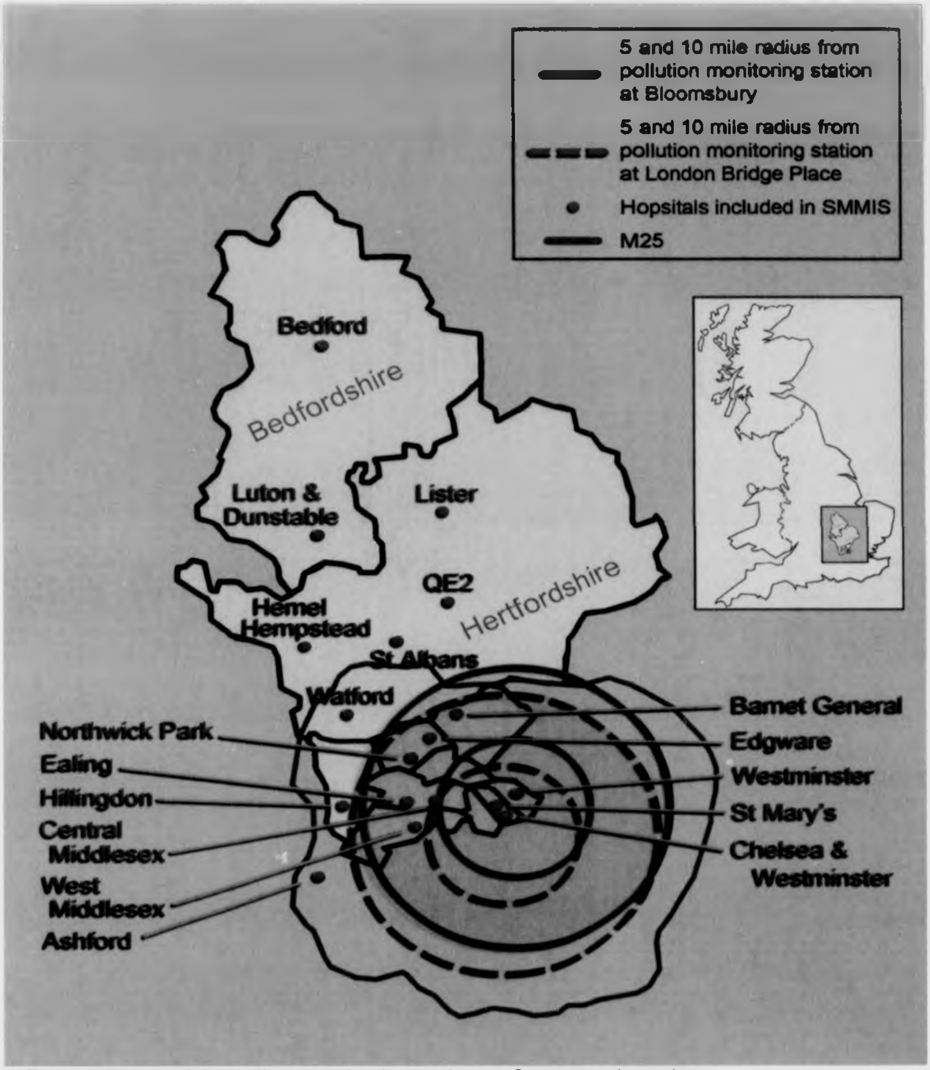
Hospital	Years omitted	Missing data (%)	Births
Barnet General & Edgware General	1994 - 2000	15596 (86.7)	17995
St Alban's	1988	587 (71.7)	819
Ashford	1988 - 1992	6443 (82.6)	7803
West Middlesex	2000	1781 (100)	1781
West London & Chelsea & Westminster	1999	1146 (92.0)	1246
Total number of births dropped			**29,644**

Appendix 4a. Hospitals located within a 10 mile radius of the weather monitoring station.*



* *The M25 roughly indicates the boundary of greater London*

Appendix 4b. Hospitals located within a 10 mile radius of the air pollution monitoring stations.*



** The M25 roughly indicates the boundary of greater London*

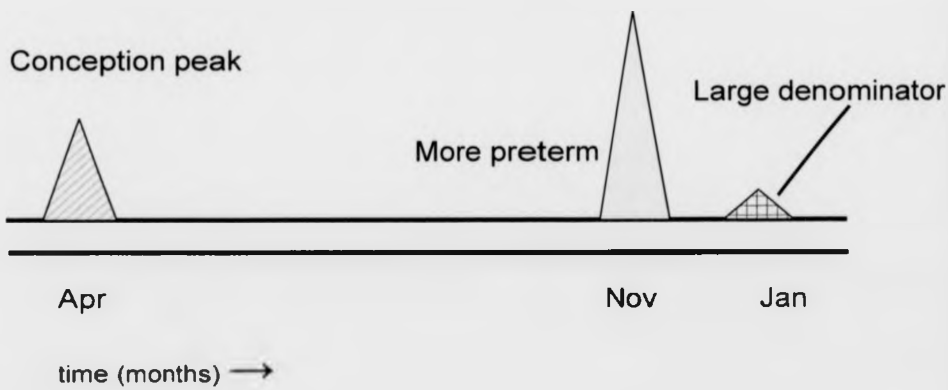
Appendix 5. Possible effect of seasonality of conceptions.

To illustrate how a seasonality of conceptions may influence the seasonality of preterm birth the following example is provided.

For simplicity, months are used as the unit of time and the proportion of preterm births is assumed to be constant at 20% for each month. The number of conceptions is also assumed to be constant for every month (n=10) except April (n=100). Preterm births are assumed to occur at 7 months and term births (for this example, all other births) at nine months.

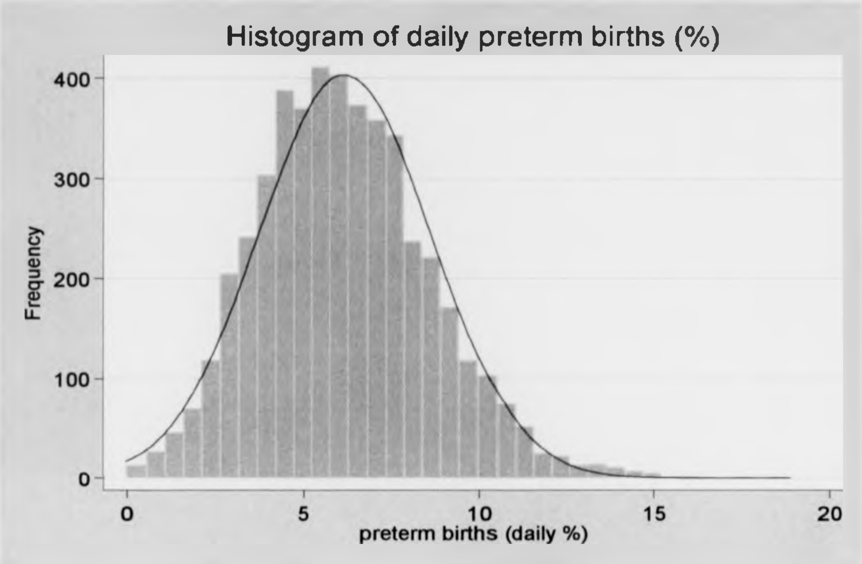
Because the proportion of preterm births is constant at 20%, in the months with 10 conceptions, the result will be 8 births nine months later and 2 preterm births seven months later. For April, however, there will be 80 births in nine months later (Jan) and 20 preterm births seven months later (Nov).

The denominator, or total number of births, in January will therefore be 82 (80 births + 2 preterm births from June) and the total number of births November will be 28 (8 births from March + 20 preterm births from April) while for all other months, the denominator remains constant at 10 total births. The resultant proportions of preterm birth will then be 2.4% for January (2/82), 71% (20/28) for November and 20% (2/10) for all other months.



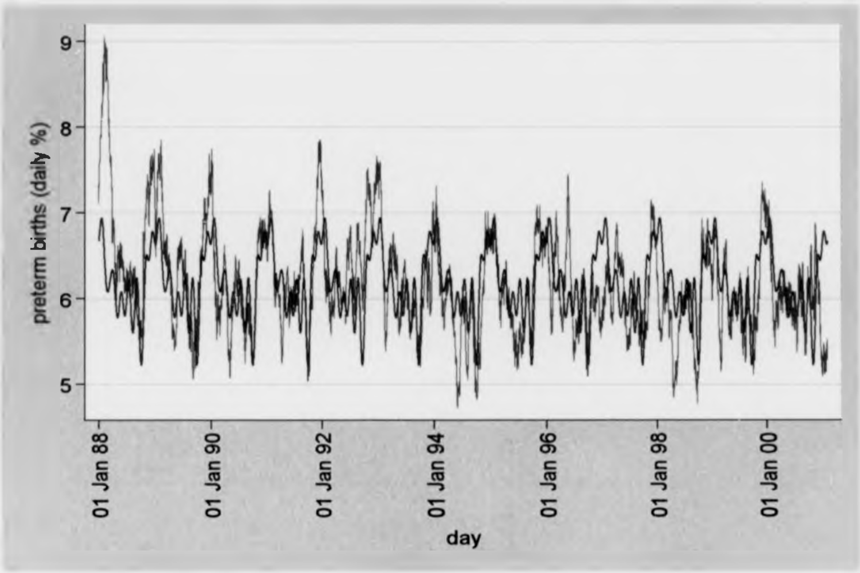
Appendix 6. Distribution of preterm birth proportions.

Histogram of daily preterm birth proportions showing that the departure from normality is modest and unlikely to affect the results of the analysis.



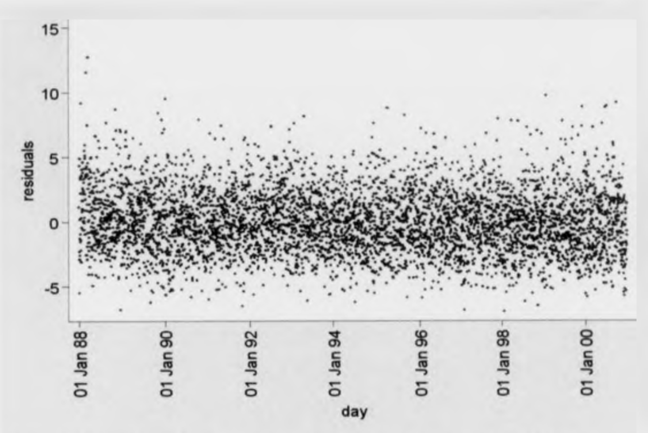
Appendix 7. Observed versus predicted plots.

Checking the model fit: A plot of observed (red) and fitted (blue) values using a moving average of 35 for the observed values.

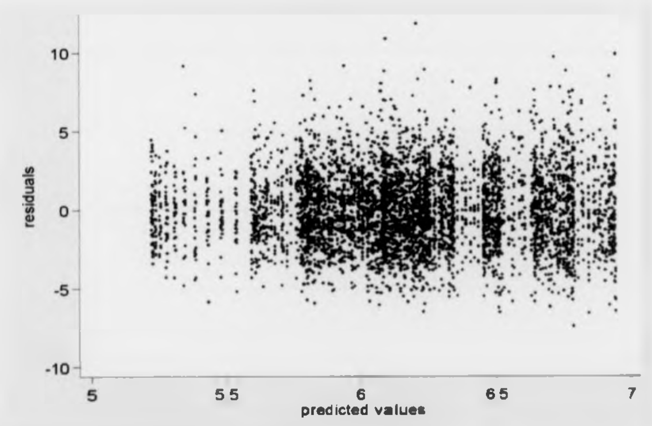


Appendix 8. Residuals.

Checking the model fit: Plots of the residuals (difference between the observed and fitted values).



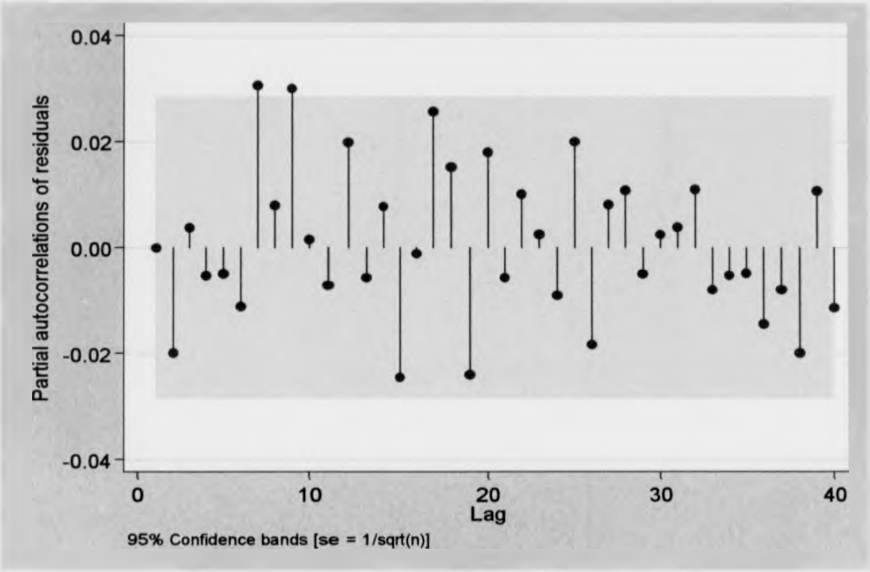
Residual time-series showing no consistent pattern.



Residuals against fitted values.

Appendix 9. Partial autocorrelation function (PACF).

PACF showing that any autocorrelation has been adequately controlled for in the model.



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Appendix 10. General ethical approval.

St Mary's NHS
NHS Trust
Local Research Ethics Committee, R&D Office
Mailbox 121, St Mary's Hospital, 41 Praed Street, London, W2 1NY
Tel No: 020 7886 6514: Fax No: 020 7886 1529
Email: Ros.Cooke@st-marys.nhs.uk

Prof. P Steer,
Academic department of Obstetrics and Gynaecology,
Faculty of Medicine, Imperial College London,
Chelsea and Westminster Hospital,
369 Fulham Road,
London SW10 9NH.

9 December 2002.

Dear Professor Steer

Non-attributable St Mary's Maternity Information (SMMIS) Data Set

The Ethics Committee has considered your request to continue to use this data set, even though specific consent for use of the data has not been obtained from the patients to whom it relates, and to publish the aggregated results of analysis of the data.

We understand that the major reason that for obtaining patient consent would be impractical, is that SMMIS contains details of almost 500,000 births going back almost 15 years. You have pointed out that identifying the addresses of all the women having the earlier births after all this time would be almost impossible; the logistics and cost of writing to all 500,000 would be prohibitive. We also understand that the core dataset (with some identifiers, such as postcode) is housed only on the private network of the Department of Epidemiology and Public Health under very secure conditions and is not normally used for analysis. Analysis for clinical benchmarking (for example, examining the risk of preterm birth associated with multiple pregnancy) and for hypothesis generation (for example, examining the relationship of maternal haemoglobin concentration with birth weight) is done entirely on the pseudo-anonymised data set held by the members of the SMMIS project group.

We understand that the collection and analysis of the SMMIS data at Imperial College has always been notified to the ethics committee at St Mary's Hospital, (who have given specific approval for studies requiring attributable data). We are aware that the data collection is done by a company called Ciconia and has the full approval of all the clinicians of the seventeen maternity units contributing to the database. You have informed us that there is a National User Group to whom reports are made at regular intervals. It is attended by representatives (data guardians) of all the contributing units. Data individual to each unit is fed back annually, and comparative (non-attributable) data is also fed back on request. Each maternity unit has a Maternity Services Liaison Group containing patient/user representatives and information is often fed back to them at their request. No concerns have ever been expressed by these groups about the way the data is used. Use of the data is overseen by a Committee that comprises Professor Elliott, yourself and Dr J Chapple.

We also understand that you are applying for exemption under Section 60 of the Health & Social Care Act for maintenance and development of the core data set.

I am now writing to confirm that St Mary's Local Research Ethics Committee approves:

(a) the publication of aggregated data derived from the non-attributable data set:

(b) the continuing use of the non attributable data set for clinical benchmarking and hypothesis generation.

The results of your application for Section 60 exemption for the further development of the core database should be forwarded to myself, as Chairman of this Committee. We would also like to receive copies of all papers to be published from the non-attributable data set at submission stage. Analysis and publication should continue to be supervised by the Committee (Professors Elliott, Steer and Chapple). The importance of maintaining confidentiality at all times should continue to be stressed.

Yours sincerely

Dr Rodney Rivers
Chairman of LREC

Appendix 11. Ethical Approval from the London School of Hygiene and Tropical Medicine.

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

ETHICS COMMITTEE

APPROVAL FORM
Application number: **953**

Name of Principal Investigator	Sue Lee
Department	Infectious and Tropical Diseases
Head of Department	Professor Hazel Dockrell

Title: **Seasonal Variation of Preterm Birth in a Developed Country**

Approval of this study is granted by the Committee.

Chair T.W Meade ....
Professor Tom Meade

Date 17. 3. 2003. ....

Approval is dependent on local ethical approval having been received.

Any subsequent changes to the consent form must be re-submitted to the Committee.

Appendix 12. Ethical approval from St Mary's Hospital.

EC No: 02.122
R&D No: 02/X0220E
Registered Date: 17.10.02

St Mary's NHS
NHS Trust
Local Research Ethics Committee, R&D Office
Mailbox 121, St Mary's Hospital, Praed Street, London, W2 1NY
Tel No: 020 7886 6514: Fax No: 020 7886 1529
Email: Ros.Cooke@st-marys.nhs.uk

November 1, 2002

Ms Sue Lee
LSHTM, ITD/IDEU
Kepple Street
London WC1E 7HT

Dear Ms Lee

Seasonal Variation of Preterm Birth
EC No: 02.122 R&D No: 02/X0220E

On behalf of the members I am pleased to say that St Mary's Local Research Ethics Committee (LREC) discussed the above project at their meeting on 31 October 2002. The following grid shows the documents reviewed.

Research documents approved	Original date	Decision date
LREC application form	17.10.02	01/11/2002
Addition of Prof Steer to be link at St Marys	31.10.02	01/11/2002

The members of the Committee present agreed there is no objection on ethical grounds to the proposed study, I am therefore happy to give you the favourable opinion of the committee in accordance with the ICH Good Clinical Practice Guidelines.

This decision is given on the understanding that the research team will observe strict confidentiality over the medical and personal records of the participants. It is suggested that this be achieved by avoidance of the subject's name or initials in the communication data. In the case of hospital patients, using the hospital record number can do this; in general practice, the National Insurance number or a code agreed with the relevant GP

Chairman's initials

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