Ambient Air Pollution and Risk of Stillbirth in New Jersey

By

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ABSTRACT OF THE DISSERTATION

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Introduction

The purpose of this study was to examine the secular trends in the rates of stillbirth by race and ethnicity and to examine the risk of stillbirth with increase in ambient air pollution in each of the three trimesters of pregnancy and with short term increase in ambient air pollution.

Materials and Methods

We used New Jersey births and fetal deaths records linked to hospital discharge data for 1997-2005. Gestational age specific stillbirth rates were calculated by fetus at risk approach and Cox proportional hazard model was used to estimate the risk of stillbirth. We used logistic regression models to estimate the risk of stillbirth associated with incremental increase in ambient air pollution in each of the three trimesters. The association of transient increase in ambient air pollution with the risk of stillbirth was analyzed with a time stratified case crossover design using conditional logistic regression.

Results

The rate of stillbirth was 4.4 per 1000 total births (3.4 for white non-Hispanics, 7.9 for black non-Hispanics and 4.4 for Hispanics /1000 total births) in NJ for the period 1997 to 2005. The rates of stillbirth decreased only for white non-Hispanics but remained unchanged for other race/ethnicity groups. In the first trimester, increased risk of stillbirth was associated with interquartile range increase in $PM_{2.5}$ (OR 1.14, 95% CI, 1.00, 1.31) and NO_2 (OR 1.10, 95% CI, 1.00, 1.21) and SO_2 (OR 1.12, 95% CI, 1.00, 1.25) and with $PM_{2.5}$ (OR 1.20, 95% CI, 1.04, 1.37) in the second trimester and with SO_2 in both 2nd trimester (OR 1.21, 95% CI, 1.03, 1.29) and the 3rd trimester (OR 1.18, 95% CI, 1.00, 1.28). There was an increased risk of stillbirth for each interquartile range increase in 2nd day concentration of SO_2 (RR 1.12, 95% CI, 1.02-1.23) and CO (RR 1.20, 95% CI, 1.04-1.38).

Conclusion

We found an increased risk of stillbirth associated with increase in ambient air pollution in all three trimesters of pregnancy and with short term increase in ambient air pollution. Understanding the biological mechanism for the association of criteria pollutants with the risk of stillbirth merits attention.

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INTRODUCTION

Stillbirth, one of the most common adverse pregnancy outcomes is a major public health problem in the United States. Approximately 1 in every 160 deliveries ends in stillbirth, representing 60% of all perinatal mortality in the US[1]. The risk of stillbirth varies greatly by race and ethnicity groups and black non-Hispanics and Hispanics are more likely to have stillbirth than white non Hispanics[2].

There are several known risk factors for stillbirth including advanced maternal age, obesity, smoking, nuliparity and multiple gestations. Pregnancy complications associated with stillbirth include diabetes mellitus, hypertension, placental abruption and premature rupture of membranes[3,4]. Advance maternal age is an independent risk factor for stillbirth even after accounting for medical conditions that are more likely to occur in older women such as multiple gestation, hypertension, diabetes, and placental abruption all of which are associated with higher rates of stillbirth[4,5]. Hypertension and diabetes, the two most common medical conditions are associated with increased risk of stillbirth; there is two to five folds increased risk of stillbirth in women with diabetes[1].

There has been a large reduction in the rate of stillbirth in the second half of the 20th century (from 18.4 per 1000 total births in 1950 to 6.7 per

1000 births in 2000)[6] but the rate of decline has slowed down in the past twenty years and the rate of stillbirth was 6.2 per 1000 births in 2004[1]. The rates of stillbirth have shown differences by race and ethnicity and rates are higher for black non-Hispanics and Hispanics than for white non-Hispanics. The rate per 1000 total births was 4.98 for white non-Hispanics, 11.25 for black non-Hispanics and 5.43 for Hispanics in 2005[7]. The rate of stillbirth remained high in black women, even among those with adequate prenatal care. This disparity was attributed to higher rates of diabetes, hypertension, placental abruption, and premature rupture of membranes in black women[8].

Despite improvement in the rate of stillbirth, rate is still higher in the United States than in many other developed countries and there is persistent disparity in the rates of stillbirth by race and ethnicity groups. In addition to known risk factors, there may be other behavioral and environmental risk factors that need to be examined to understand persistent high rates of stillbirth.

Ambient air pollution is one of the environmental factors found to be associated with increase in morbidity and mortality in adults and children and has an association with adverse pregnancy outcomes. Several studies have reported association of criteria pollutants ($PM_{2.5}$, NO_2, SO_2, and CO) with adverse pregnancy outcomes including preterm birth, low birth weight and intrauterine growth restriction[9-18]. However the evidence for an association of ambient air pollution with fetal mortality is inconsistent[15,19,20] and only one study conducted in Sao Pãulo, Brazil reported an association of daily counts of stillbirth with ambient air pollution[20]. The period of gestation when the growing fetus is susceptible to the harmful effects of exposure to these pollutants remains to be determined. It is not clear if exposure during early gestation is harmful or exposure in late pregnancy leads to fetal demise.

To understand the secular changes and racial and ethnic disparities in the rates of stillbirth, we examined the trends in stillbirth by race/ethnicity groups and the risk factors of stillbirth using New Jersey birth and fetal death data from 1997 to 2005. The association of stillbirth was examined with increase in ambient air pollutants including particulate matter with an aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$), sulfur dioxide (SO_2), nitrogen dioxide (NO_2) and carbon monoxide CO in each trimester of pregnancy using New Jersey birth and fetal death data from 1998 to 2004. We also examined the association of stillbirth with transient, short-term exposure to increased levels of ambient fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3) air pollution. Effect modification of these associations by risk factors of stillbirth including pregnancy complications, such as placental abruption and premature rupture of membranes, was also examined.

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Abstract

Introduction

Stillbirth is the leading component of perinatal mortality in the Unites States and varies substantially by race and ethnicity. The purpose of this study was to examine the secular trends from 1997 to 2005 in rates of stillbirth by race/ethnicity and nativity of mothers and to determine risk factors for stillbirth.

Methods

We used New Jersey data for births and fetal deaths for the years 1997-2005, in which data from electronic birth certificates and fetal death certificates were linked to delivery hospital discharge data. Rates of stillbirth were calculated as number of stillbirth per 1000 total births and gestational age specific stillbirth rates were calculated as number of stillbirths per 1000 fetuses at risk at each gestational age. Cox proportional hazard model was used to estimate the risk of stillbirth associated with maternal and fetal risk factors and pregnancy complications.

Results

The rate of stillbirth was 4.4 per 1000 total births (3.4 for white non-Hispanics and 7.9 for black non-Hispanics and 4.4 for Hispanics /1000 total births) in NJ for the period 1997 to 2005. The rates of stillbirth decreased

from 3.8 in 1997 to 2.7 per 1000 total births in 2005 for white non-Hispanics but remained unchanged for other race/ethnicity groups from 1997 to 2005. The rate of stillbirth was higher for foreign born than US born women (4.8 vs. 4.1 /1000 total births). Adjusted relative risks for risk factors associated with stillbirth were, 1.3 (1.2-1.4) for maternal age 35 years and older, 1.9 (1.7-2.1) for black non-Hispanics, 2.8 (2.4-3.3) for no prenatal care, 40.2 (36.9-43.9) for placental abruption, 5.3 (3.4-8.2) for eclampsia, 3.5 (2.8-4.3) for diabetes mellitus and 1.7 (1.3-2.2) for preeclampsia. There was decrease in stillbirth in white non-Hispanics, in women with more than high school education, and in women with placental abruption over nine year period.

Conclusion

There is a decline in the rate of stillbirth but there are persistent racial disparities with highest rates of stillbirth for black non-Hispanics. In addition to known risk factors, environmental and behavioral risk factors need to be examined to understand the causes for racial disparity in the rate of stillbirth.

Introduction

Stillbirth is one of the most common adverse pregnancy outcomes and accounts for about half of all perinatal deaths and for more than a third of mortality from 20 weeks' gestation to one year of age[1]. The risk of stillbirth varies by race and ethnicity groups and black non-Hispanics and Hispanics are at higher risk of having a stillbirth than white non-Hispanics[2]. Other risk factors for stillbirth are advanced maternal age, obesity, smoking, primiparity, multiparity, and multiple gestations. Pregnancy complications associated with stillbirth include diabetes mellitus, hypertension, placental abruption, and premature rupture of membranes[3,4].

Although there was a large reduction in the rate of stillbirth in the second half of the 20th century from 18.4 per 1000 total births in 1950 to 6.7 per 1000 births in 2000 the rate of decline has slowed down in the past twenty years[5]. Rates of stillbirth have also shown differences by race and ethnicity[6] and rates were higher for black non-Hispanics and Hispanics than for white non-Hispanics. The rate per 1000 total births was 4.98 for white non-Hispanics, 11.25 for black non-Hispanics and 5.43 for Hispanics in 2004[6].

Despite improvement in the rate of stillbirth, rate is still higher in the United States than in many other developed countries and there is persistent disparity in the rates of stillbirth by race and ethnicity groups. To understand the secular changes and racial and ethnic disparities in the rates of stillbirth, we examined the trends in stillbirth by race/ethnic groups and the risk factors for stillbirth using New Jersey birth and fetal death data from 1997 to 2005. As New Jersey has large proportion of women born outside United States we also examined the rate of stillbirth by nativity of mothers for different race/ethnicity groups.

Materials and Methods

Data Sources & Study Population

For this study we used electronic birth certificate (EBC) records for live births and fetal death certificates linked to hospital delivery discharge records for the period between 1997 and 2005. The dataset was maintained by the Division of Family Health Services, New Jersey Department of Health and Senior Services (NJDHSS). We included all singleton births in New Jersey, between 20 and 42 completed weeks gestational age (141-294 days of pregnancy) with birth weight ≥500 g. We did not perform reviews of medical records or interviews of subjects.

Outcome & Risk Factors

Stillbirth was defined in NJ as death of the fetus prior to complete expulsion or extraction of a product of conception, where the fetus showed no signs of life such as breathing or beating of the heart, pulsation of umbilical cord, or definite movement of voluntary muscle[7]. The State of New Jersey requires all stillbirths at 20 or more completed weeks of gestation to be reported to NJDHSS.

From the linked dataset, we retained data on maternal and fetal characteristics and pregnancy complications. Maternal and fetal characteristics were mainly derived from birth and fetal death certificates while pregnancy complications were derived mainly from hospital delivery records. Maternal age was grouped as, < 25 years, 25-34 years, ≥ 35years, maternal race/ethnicity as white non-Hispanic, black non-Hispanic, other non-Hispanic, and Hispanic. Maternal level of education as high school or less and more than high school education, prenatal care initiation as either at any time during pregnancy or never. Self reported smoking during pregnancy as yes/no, and sex of the fetus as male / female. Birth weight after excluding those less than 500 g was grouped as 500-2499 g, 2500-3999 g and ≥ 4000 g. Gestational age was calculated in weeks from last menstrual period and date of birth using NCHS algorithm[8] and grouped as 21-24 weeks, 25-28 weeks, 29-32 weeks, 33-36 weeks and > 36 weeks. Clinical estimate of gestational age was used when data were missing to calculate the gestational age. We utilized both birth certificate (electronic birth certificate or fetal death certificate) and hospital discharge data to define pregnancy complications including chronic hypertension, pregnancy induced hypertension, diabetes mellitus, gestational diabetes, placental abruption, preeclampsia and eclampsia.

The ICD-9 or ICD-10 codes were used to classify cause of stillbirth noted on the fetal death certificates. Causes of death were aggregated into congenital defects, maternal medical conditions, pregnancy complications, placenta and cord complications, fetal conditions, others, and unspecified. Congenital malformations included any malformation or deformity of the fetus specified as cause of death. Maternal conditions included medical problems, injury, toxicity, infections, or any maternal condition unrelated to present pregnancy. Pregnancy complications included an indication of incompetent cervix, premature rupture of membranes, oligohydramnios, polyhydramnios, ectopic pregnancy or any malpresentation before labor. Any type of placental separation and hemorrhage, cord compression and cord prolapse and any abnormality or infection of membranes were included in complications of placenta and cord. Fetal conditions included alteration in fetal growth, injury or trauma, asphyxia or hypoxia, infections, hemorrhage and endocrine or metabolic conditions resulting in death of the fetus. All other conditions for stillbirth were combined in other causes of fetal death. If the death of fetus was given the ICD-9 or ICD-10 code for unspecified cause then the cause of death was unspecified.

Statistical Analysis

Trends in Rates of Stillbirth

We calculated annual rates of stillbirth as the number of stillbirths per 1000 total births (live births and stillbirths) for each year from 1997 to 2005. We defined the gestational age specific rate of stillbirth, calculated by using the fetuses-at-risk approach[9,10], as number of stillbirths per 1000 fetuses at risk at each gestational age. We computed this by dividing the number of stillbirths that occurred during each completed week of gestation by the number of ongoing pregnancies at the beginning of that specific gestational week. Gestational age at the date of delivery was used as a surrogate for the time of fetal death because the exact time of death of fetus was not available. We examined gestational age specific stillbirth rates in five gestational age groups: 21-24 weeks, 25-28 weeks, 29-32 weeks, 33-36 weeks, and > 36 weeks for non-Hispanic whites, non-Hispanic blacks, other non-Hispanics, and Hispanics separately. We used the Cochran Armitage trend test to examine the trends in rates of stillbirth over the nine year period.

Main Analyses

We used Cox proportional hazards model to estimate the unadjusted and adjusted risk of stillbirth associated with the known risk factors of stillbirth. The date to birth/fetal death was defined as the number of completed gestational weeks at the date of delivery. Indicator variables for maternal characteristics and pregnancy complications were included for adjusted analyses. Stratified analyses were used to determine the risk of stillbirth associated with the risk factors for white non-Hispanic, black non-Hispanic and Hispanics. All analyses were done using SAS v9.1 (®SAS Institute, Cary, NC).

Results

Study Population

There were 1,011,824 births in NJ from 1997 to 2005, of which 1,004,118 were live births and 7,706, were stillbirths. Of the 969,849 singleton births there were 6,879 stillbirths, giving a rate of 7.1 stillbirths per 1000 total births during the study period.

Rates of Stillbirth

The rate of stillbirth was 5,723/940,526 or 6.1 per 1000 total births after excluding those occurring beyond 42 weeks of gestation. After the exclusion of fetuses with birth weight less than 500 g, the rate of stillbirth in the study population was 4,025/937,709 or 4.3 per 1000 total births in NJ for the period 1997 to 2005.

Maternal and fetal characteristics associated with stillbirths and total births are shown in Table 1.The annual rate of stillbirth in all births and in those with birth weight ≥ 500 g in NJ from 1997-2005 are shown in Fig 1. The rates were 3.4 /1000 total births for white non-Hispanics, 7.9 /1000 total births for black non-Hispanics, 2.9 /1000 total births for other non-Hispanics and 4.4/1000 total births for Hispanics during nine year period. The annual rates of stillbirth for white, black and other non-Hispanics and for Hispanics are shown in Figure 2. There was reduction in the rates of stillbirth per 1000 total births from 4.4 in 1997 to 3.8 in 2005 (trend test 2.4 and $p < 0.05$). The rates decreased for white non-Hispanics ($p < .05$ for trend test) but remained unchanged for the other race/ethnicity groups.

In stratified analysis by maternal place of birth, foreign born white and black non-Hispanic mothers had higher rates of stillbirth than US born mothers. However, rates were similar between foreign born and US born

Hispanic mothers (Table 2). The annual rates of stillbirth by nativity of mothers from 1997 to 2005 are shown in Fig 3. There was decline in the rate of stillbirth for foreign born mothers over nine year period (trend test 3.6 and $p < .001$).

The gestational age-specific rates of stillbirth per 1000 fetuses at risk by race/ethnicity groups are shown in Figure 4. The fetus at risk approach showed that at all gestational age groups the rate of stillbirth was highest for black non Hispanics, intermediate among Hispanics and lowest among white non-Hispanics except for 21-24 weeks of gestation when white non Hispanics and Hispanics had the same rates. In all race/ethnicity groups gestational age specific stillbirth rates exhibited a U shaped relationship i.e. stillbirth rates were highest in the 21-24 weeks of gestation then the rates showed a decline up to 25-28 weeks of gestation and the rates increased again up to end of term. The peak increase started at 33-36 weeks of gestation.

Relative risks of stillbirth (with 95% CI) comparing mothers with and without factors complicating pregnancy were 25.7 (95% CI, 24.3-27.2) for placental abruption, 6.0 (95% CI, 4.1- 8.8) for eclampsia and 3.6 (95% CI, 3.0- 4.2) for diabetes mellitus. The risk of stillbirth was 20% (95% CI, 0.9-1.5) higher for chronic hypertension and 60% (95% CI, 1.4-1.8) higher for preeclampsia. Gestational diabetes was found to be protective for stillbirth with relative risk of 0.5 (95% CI, 0.4-0.6) and this protective effect was found in all gestational age groups when data were stratified by gestational age groups (data not shown).

The timing of fetal death was unknown for 20% of the cases of stillbirth (antepartum or intrapartum). In the remaining cases, antepartum deaths occurred in 88% of stillbirths and this proportion remained unchanged from 1997 to 2005 ($p > 0.05$ for trend test). The cause of death of fetus was not known in approximately one third of stillbirths. The complications of placenta and cord accounted for another third and other causes of stillbirths included congenital defects, maternal conditions, pregnancy complications, fetal conditions and other uncommon causes. However, the proportions of these causes of stillbirths showed little change from 1997 to 2005 (Table 3).

There was an increase in stillbirth in other non-Hispanic and Hispanic women, in women with less than high school education and no prenatal care in women with diabetes mellitus. There was decrease in stillbirth in white non-Hispanics, in women with more than high school education, and in women with placental abruption from 1997-2005 (Table 4).

The adjusted relative risk showed that maternal age 35 years and older, being black non-Hispanic, being Hispanic, absence of prenatal care, maternal education of high school or less and maternal smoking were the risk factors associated with stillbirth. Pregnancy complications associated with stillbirth were diabetes mellitus, preeclampsia, eclampsia and placental abruption. After excluding placental abruption from the model, the adjusted relative risk showed the same risk factors to be associated with stillbirth with difference in magnitude for some of the risk factors (Table 5). When stratified by race/ethnicity, the adjusted relative risk was similar to overall risk for most of the determinants of stillbirth with 10 to 20% difference in magnitude of effect (data not shown). However, there were certain factors with risk estimates more than 20% different from the overall risk by race/ethnicity. This included absence of prenatal care with adjusted relative risk of 4.0 (95% CI, 2.8-5.6) for white non-Hispanics and 3.6 (95% CI, 2.2-5.8) for Hispanics. Adjusted relative risk for eclampsia was 8.2 (95% CI, 3.8-17.8) for white non-Hispanics, 7.0 (95% CI, 4.0-12.3) for black non-Hispanics and 1.4 (95% CI, 0.3-5.7) for Hispanics. Adjusted relative risk was 49.3 (95% CI, 41.0-59.3) for placental abruption for Hispanics and 31.0 (95% CI, 26.4-36.4) for black non-Hispanics.

Discussion

There is a decrease in the rate of stillbirth from 1997 to 2005 in New Jersey but there are persistent racial differences and the rates are highest for black-non Hispanics during this period. The foreign born non-Hispanic women of all races have higher rates of stillbirth than US born women but foreign born and US born Hispanic women have the same rates. The risk factors associated with stillbirth are advanced maternal age, absence of prenatal care, diabetes mellitus and placental abruption which is found to be the most important risk factor for stillbirth. The trends in stillbirth with risk factors demonstrate decrease in stillbirth in white non-Hispanics, in women with more than high school education, and in women with placental abruption from 1997 to 2005. There is an increase in stillbirth in other non-Hispanics and Hispanics, in women with no prenatal care, in women with less than high school education and in women with diabetes mellitus.

The rate of stillbirth is much higher for black non-Hispanic women than for other race/ethnicity groups. The rate for black non-Hispanic women is 2.3 times higher than white non-Hispanic women and 1.8 times higher than Hispanic women and although there is a decrease in rates of stillbirth for white non-Hispanics the rates of stillbirth for black non-Hispanic women have not changed over time. The rates are found to be highest for black non-

Hispanics compared to white non-Hispanics and Hispanics at all gestational age groups when fetus-at-risk approach was used. This racial disparity in stillbirth may be due to factors that are reported in literature for contributing to higher rates in black women such as low level of maternal education, absence of prenatal care and higher prevalence of medical risk factors and pregnancy complications[2,11].

Rates of stillbirth by maternal nativity demonstrate higher rates for foreign born white and black non-Hispanic mothers than US born non-Hispanic mothers. The rates are similar between foreign born and US born Hispanic mothers. This is different from the lower fetal mortality rates reported by Kallan[12] for foreign born non-Hispanic blacks and Hispanics compared to those born in the United States using New Jersey vital statistics data from 1991-1998[12]. The annual rates of stillbirth by nativity of mothers show a sharp decline in rates of stillbirth for foreign born mothers after 2001 and the rates become similar to US born mothers but the reason for this decline is not clear.

Placental abruption is found in 26% of all stillbirths and adjusted relative risk is 40.2 (36.9-43.9). This is much higher than reported by Ananth et al (1999)[13], who found adjusted relative risk of 8.9 (95% CI, 6.0-7.2) and Smulian et al (2002)[14] who reported adjusted relative risk of 7.0

(95% CI, 6.8-7.2). There is a decrease in stillbirth in women with placental abruption from 32.4% in 1997 to 20.4% in 2005 and it may be possible that management of pregnancies with placental abruption has improved during this period and this may explain at least in part the decline in rates of stillbirth over time.

Other risk factors found to be associated with stillbirths are in agreement with those reported by previous studies. These include advanced maternal age, absence of prenatal care, diabetes mellitus, preeclampsia, and eclampsia[11,14,15]. Chronic hypertension and pregnancy induced hypertension are not found to be associated with the risk of stillbirth after adjusting for other risk factors. Diabetes mellitus is found to be associated with stillbirth with a relative risk of 3.5 (95% CI, 2.8-4.3) and there is an increase in stillbirth in women with diabetes mellitus from 1997 to 2005.

This is a population based study using New Jersey electronic birth certificate and fetal death certificate data linked with hospital discharge data from 1997 to 2005. In this study, we utilized both birth certificate (electronic birth certificate or fetal death certificate) and hospital discharge data to define pregnancy complications (chronic hypertension, pregnancy induced hypertension, diabetes mellitus, gestational diabetes, placental abruption, preeclampsia and eclampsia) as this has been shown to provide higher sensitivity and specificity than birth certificate or hospital discharge data alone[16,17]. There are certain limitations in our study as data are not available for pre-pregnancy body mass index and weight gain during pregnancy. As obesity is found to be a risk factor for stillbirth[18], there may be residual confounding due to missing information.

Fetal death certificates had specific cause of fetal death based on clinical assessment which may not be the true cause or the primary cause of death of the fetus. Large studies with accurate assessment of cause of death by autopsy would be necessary to correctly identify and classify the cause of death. This would help to identify the risk factors for different causes of death of fetus and to formulate strategies for prevention of stillbirth.

Conclusion

There is a decline in the rate of stillbirth but there are persistent racial disparities with highest rates of stillbirth for black non-Hispanics. In addition to known risk factors, environmental and behavioral risk factors need to be examined to understand the causes for racial disparity in the rate of stillbirth.

Table1: Characteristics Associated with Stillbirths and Total births in New Jersey 1997-2005

	Stillbirths*	Total Births*
Maternal Characteristics	4,025	933,258
	N (%)	N%
Maternal Age (years)		
<20	287 (7.3)	66,265 (7.1)
20-24	775 (19.8)	156,516(16.8)
25-29	899 (22.9)	236,396(25.3)
30-34	1,015 (25.9)	287,543(30.8)
35-39	723 (18.5)	154,661(16.6)
>40	221(5.6)	31,877(3.4)
Maternal Race		
White Non-Hispanic	1,694(42.3)	496,248(53.4)
Black Non-Hispanic	1175(29.3)	147,251(15.8)
Other Non-Hispanic	256(6.4)	87,143(9.4)
Hispanics	881(22.0)	199,377(21.4)
Maternal Education		
< High School	591 (14.6)	129,199(13.8)
High School Graduate	1,329 (32.9)	265,910(28.5)
>High School	2,105(52.5)	538,577(57.7)
Prenatal Care Initiation		
1st Trimester	2,497(72.0)	728,521(80.1)
2nd Trimester	539(15.5)	135,530(14.9)
3rd Trimester	143(4.1)	33,689(3.7)
Never	289(8.4)	11,853(1.3)
Smoking		
Yes	480 (14.0)	89,330(9.6)
No	2,946(86.0)	840,058(90.4)
Sex of the fetus		
Male	2,058(52.5)	479,276(51.3)
Female	1,862(47.5)	454,388(48.7)
Length of gestation (weeks)		
21 - 24	896(22.3)	2,234(0.2)
25 - 28	558(13.9)	5,711(0.6)
29 - 32	603(15.0)	14,888(1.6)
33 - 36	782(19.4)	77,614(8.3)
>36	1,186(29.4)	833,240(89.3)
Birthweight (gms)		
500-2499	2,424(69.4)	55,079 (5.9)
2500-3999	975(27.9)	783,238(83.9)
≥ 4000	96(2.7)	94,834(10.2)

*Numbers tabulated vary slightly because of missing data

Table 2: Stillbirths in New Jersey 1997-2005, by Maternal Race, Ethnicity and Nativity

Race/Ethnicity/Nativity	Stillbirth	Total Births	Rates/1000 births
White non-Hispanic			
US-Born	1,450	448,078	3.2
Foreign Born	244	49,266	5.0
Black non-Hispanic			
US-Born	865	117,889	7.3
Foreign Born	310	30,071	10.3
Other non Hispanic			
US-Born	19	8,153	2.3
Foreign Born	237	78,815	3.0
Hispanics			
US-Born	327	74,464	4.4
Foreign Born	554	125,509	4.4
Overall*			
US-Born	2,672	650,687	4.1
Foreign-Born	1,353	285,244	4.7

*Total number higher than all race/ethnicity data combined due to missing data for race/ethnicity

Table 3: Causes of fetal deaths by year in NJ 1997-2005 (N=4,025)

		Cause of Fetal Death						
Year	Fetal Deaths	Congenital Defects	Maternal Conditions	Pregnancy Complication	Placenta & Cord	Fetal conditions	Others	Unspecified
	N	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
1997	451	40(9)	26(6)	28(6)	141(31)	42(9)	43(10)	131(29)
1998	413	49(12)	27(7)	23(6)	129(31)	34(8)	31(7)	120(29)
1999	501	51(10)	24(5)	37(7)	162(32)	36(7)	29(7)	162(32)
2000	483	37(8)	27(6)	29(6)	157(33)	30(6)	41(7)	162(34)
2001	475	36(8)	25(5)	26(5)	157(33)	38(8)	36(8)	157(33)
2002	440	34(8)	29(7)	34(8)	121(28)	24(5)	25(5)	173(39)
2003	442	28(6)	22(5)	19(4)	151(34)	24(5)	19(5)	179(41)
2004	428	36(8)	21(5)	40(9)	141(33)	27(6)	16(5)	147(34)
2005	392	29(7)	21(6)	19(5)	130(33)	30(8)	36(9)	127(32)
Total	4,025	340(8)	222(6)	255(6)	1289(32)	285(7)	276(7)	1358(34)

Table 4: Secular Trends in Risk Factors of Stillbirths in NJ 1997-2005

	1997		2001		2005		(1997-2005)
	TB	SB	TB	SB	TB	SB	% Change
	102,860	451	105,075	475	103,597	392	
Risk Factors	%	%	%	%	%	%	TB (SB)
Age (years)							
<25	24.0	21.4	24.3	29.5	23.6	27.1	-1.8 (26.4)
25-34	58.1	55.1	55.5	51.6	55.3	49.4	-4.9(-10.2)
≥ 35	17.9	23.5	20.2	18.9	21.1	23.5	18.4 (0)
Maternal Race							
White Non-Hispanic	57.6	49.3	53.2	40.2	49.5	35.0	-14.0(-29.2)*
Black Non-Hispanic	17.0	29.0	15.8	32.6	14.6	27.3	-14.3(-5.9)
Other Non-Hispanic	7.4	3.4	9.7	7.2	10.6	7.4	43.8 (121.0)*
Hispanics	18.0	18.3	21.3	20.0	25.3	30.3	40.4(65.9)*
Maternal Education							
≤ High School	44.9	45.7	41.5	43.8	41.6	53.6	-7.4 (17.3)*
> High School	55.1	54.3	58.5	56.2	58.4	46.4	6.0 (-14.5)*
Prenatal Care							
Never	1.6	5.7	1.4	8.7	1.1	12.9	-32.8 (125.5)*
1st Trimester	81.0	78.8	79.7	71.9	78.5	66.2	-3.1 (-16.0)
2nd & 3rd Trimester	17.4	15.5	18.9	19.4	20.4	20.9	17.3 (35.0)
Smoking**	12.4	15.1	9.5	12.5	8.1	14.4	-34.4 (-4.8)
Birthweight (gms)							
500-2499	6.2	66.0	6.1	71.4	6.2	72.1	0 (9.2)
2500-3999	83.0	31.2	83.8	26.3	85.1	27.1	2.5 (-13.1)
≥ 4000	10.8	2.8	10.1	2.3	8.7	0.8	-19.3(-70.8)
Gestation(wks)							
21-24	0.34	23.5	0.30	20.4	0.30	24.0	-11.2(2.0)
25-28	0.68	12.6	0.68	15.0	0.60	13.8	-11.0 (9.0)
29-32	1.61	14.9	1.66	14.7	1.65	15.6	2.6 (4.7)
33-36	8.23	18.4	8.29	21.3	8.65	19.8	4.9 (8.1)
>36	89.14	30.6	89.07	28.6	88.80	26.8	-0.4 (-12.5)
Diabetes Mellitus	0.78	1.77	0.90	4.00	1.00	3.83	28.4 (115.7)*
Gestational Diabetes	4.28	1.77	5.10	2.11	6.34	1.53	48.1 (-13.7)
Eclampsia	0.13	0.44	0.12	0.63	0.13	0.51	1.0 (15.1)
Preeclamsia	3.04	3.10	2.62	5.05	2.97	3.83	-2.1 (23.3)
Placenta Abruption	1.15	32.37	1.07	25.26	1.09	20.41	4.7(-40.0)*
Chronic Hypertension	1.21	0.89	1.26	1.47	1.59	1.53	31.6(72.6)
PIH	6.13	5.54	6.15	8.00	6.86	6.6	12.0 (19.7)

* p-value < 0.05 ** % change from 1997 to 2004 due to missing data

Table 5: Unadjusted and Adjusted Hazard Ratio with 95% Confidence Interval for Risk Factors of Stillbirth

	Unadjusted HR	Adjusted HR	*Adjusted HR
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age (years)			
<25	1.2(1.1-1.3)	1.0(1.0-1.1)	1.0(0.9-1.1)
25-34	Ref		
≥ 35	1.3(1.2-1.4)	1.3(1.2-1.4)	1.4(1.3-1.6)
Maternal Race			
White Non-Hispanic	Ref		
Black Non-Hispanic	2.3(2.2-2.5)	1.9(1.7-2.1)	2.1(1.9-2.3)
Other Non-Hispanic	0.7(0.6-0.8)	0.8(0.7-1.0)	0.8(0.7-1.0)
Hispanics	1.0(1.0-1.1)	1.2(1.1-1.3)	1.2(1.1-1.3)
Maternal Education			
≤ High School	1.3(1.2-1.3)	1.1(1.0-1.2)	1.1(1.0-1.2)
> High School	Ref		
Prenatal Care			
Never	8.1(7.2-9.2)	2.8(2.4-3.3)	4.3(3.7-5.1)
Ever	Ref		
Smoking	1.6(1.4-1.7)	1.1(1.0-1.2)	1.3(1.1-1.4)
Gender			
Male	Ref		
Female	1.1(1.0-1.1)	1.0(1.0-1.1)	1.1(1.0-1.1)
Diabetes Mellitus	4.0(3.4-4.8)	3.5(2.8-4.3)	3.6(2.9-4.5)
Eclampsia	7.4(5.1-10.8)	5.3(3.4-8.2)	6.3(4.1-9.8)
Preeclamsia	1.9(1.6-2.2)	1.7(1.3-2.2)	2.2(1.7-2.8)
Placenta Abruption	42.4(39.5-45.5)	40.2(36.9-43.9)	*
Chronic Hypertension	1.3(1.0-1.7)	1.0(0.7-1.3)	1.0(0.7-1.3)
Pregnancy Induced Hypertension	1.3(1.1-1.4)	0.7(0.5-0.8)	0.7(0.6-0.9)

* Without placental abruption in the model

Figure 1: Rates of Stillbirth / 1000 Total Births in NJ 1997-2005

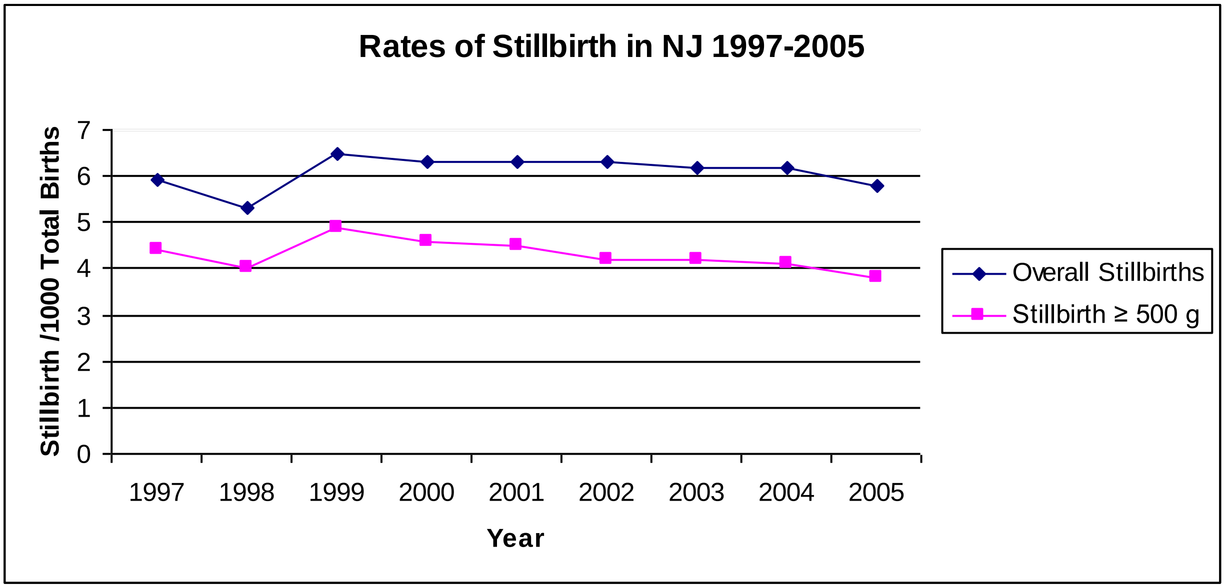


Figure 2: Rates of Stillbirth / 1000 Total Births in NJ 1997-2005 by Maternal Race/Ethnicity

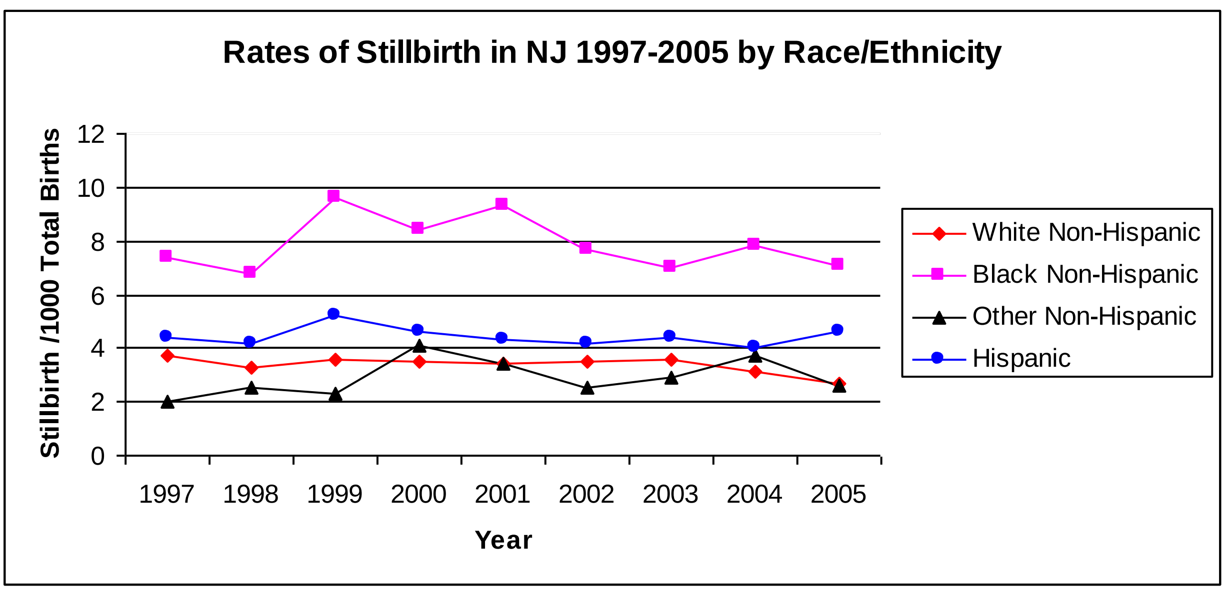


Figure 3: Rates of Stillbirth /1000 Total Births in NJ 1997-2005 by Maternal Nativity

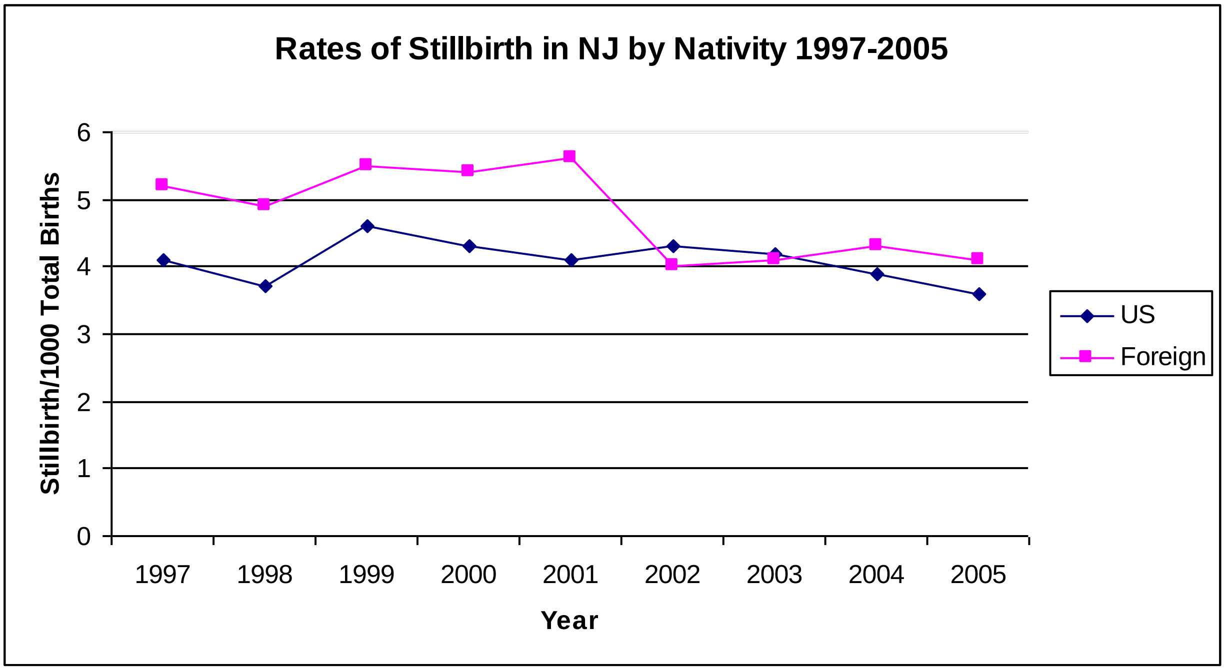
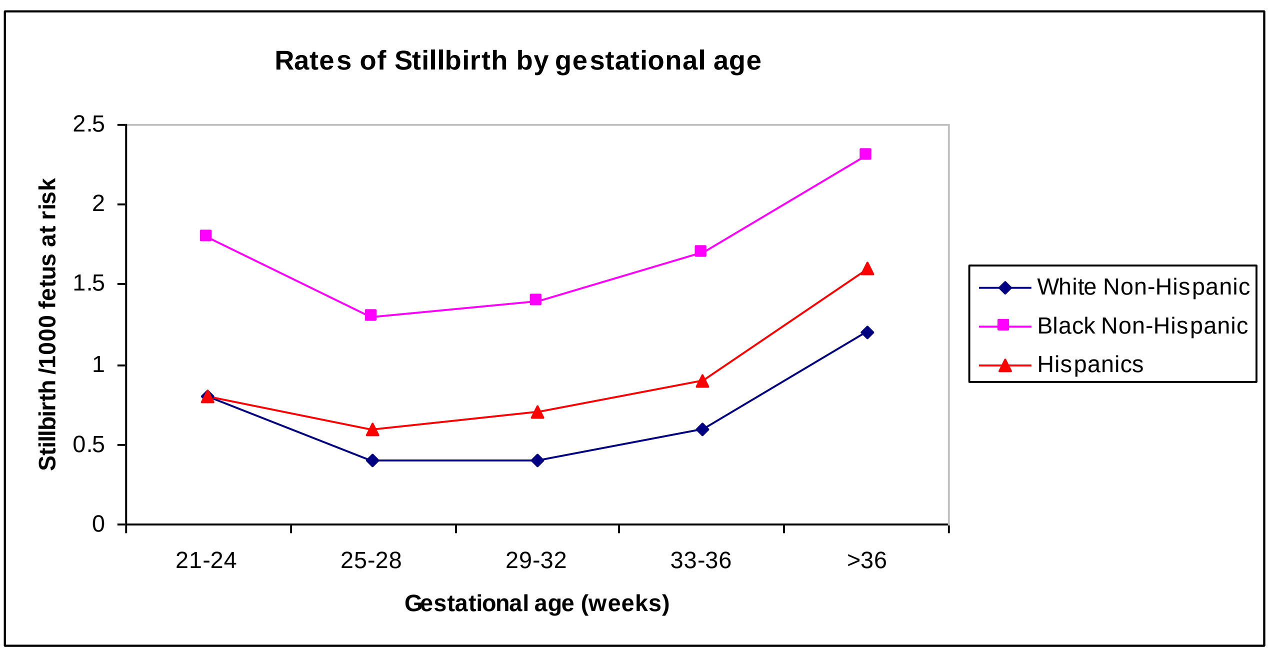


Figure 4: Gestational Age Specific Stillbirth Rates in NJ 1997-2005 by Race/Ethnicity using Fetus at Risk Approach



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Chapter II

Ambient Air Pollution and Risk of Stillbirth in New Jersey 1998-2004

Abstract

Introduction

Previous studies have reported inconsistent evidence regarding a possible association of stillbirth risk with ambient air pollution during pregnancy. Moreover, the association has not been examined in different periods of gestation. The objective of this study was to examine the risk of stillbirth associated with increased ambient air pollutant concentrations, including $PM_{2.5}$, SO_2, NO_2 and CO during the 1st, 2nd, and 3rd trimesters of pregnancy.

Methods

We used New Jersey electronic records of births and fetal deaths for the years 1998-2004 that were linked to hospital discharge data. For each birth we assigned concentration of air pollutants from a monitoring site within 10 km from the maternal residence as recorded on the birth certificate. We used logistic regression models to estimate the risk of stillbirth associated with incremental increase in the mean concentration of each pollutant in each of the three trimesters. Risk factors known to be associated with stillbirth such as maternal age, race/ethnicity, maternal education, prenatal care, smoking, a socioeconomic status (SES) neighborhood index (generated from census data for the census tract of the maternal residence at birth), as well as indicator variables for calendar month and year were included in all models.

Results

We observed increased risks of stillbirth associated with each 4 μg/m^3 increase in mean $PM_{2.5}$ concentration (14% increase, 95% CI, 1.00, 1.31), each 10 ppb increase in mean NO_2 concentration (10 % increase, 95% CI, 1.00, 1.21), and each 3 ppb increase in mean SO_2 concentration (12% increase, 95% CI, 1.00, 1.25) in the 1st trimester. Similarly we found increased risks of stillbirth associated with each 4 μg/m^3 increase in $PM_{2.5}$ (20% increase, 95% CI, 1.04, 1.37) in the second trimester, and with each 3ppb increase in mean SO_2 concentration in both the 2nd trimester (21% increase, 95% CI, 1.03, 1.29) and 3rd trimester (18% increase, 95% CI, 1.00, 1.28). We did not find increased risk of stillbirth associated with CO during any trimester.

Conclusion

We found an increased risk of stillbirth associated with incremental increase in $PM_{2.5}$ and NO_2, in early pregnancy and with incremental increase in SO_2 in all three trimesters of pregnancy in women living within 10 km of an air pollution monitoring station. Further studies are needed to confirm these findings and to understand the biological mechanism for the association of ambient air pollution and the risk of stillbirth.

Introduction

Over the past few years, several studies have examined the association between ambient air pollution and several adverse pregnancy outcomes including preterm birth[1-6], low birth weight[1,2,4,6-10] and intrauterine growth restriction[1,2,11]. In contrast, reports examining associations between ambient air pollution and stillbirth are limited[7,12,13,]. These studies were ecological studies and only one study conducted in Sao Pãulo, Brazil, reported an association in daily counts of stillbirth with ambient air pollutants[13]. Also unclear is the period(s) of gestation where the growing fetus is most susceptible to the harmful effects of ambient air pollution.

The objectives of this study were to (i) examine the association between the risk of stillbirth and the mean concentration of ambient air pollutants including particulate matter $\leq$ 25 µm, ($PM_{2.5}$), sulfur dioxide, SO_2, nitrogen dioxide, NO_2 and carbon monoxide, CO, during each trimester of pregnancy and (ii) examine effect modification of these associations by pregnancy complications such as placental abruption and premature rupture of membranes.

Materials and Methods

Data Sources & Study Population

We used electronic birth certificate (EBC) records for live births and fetal death certificates that were linked to corresponding hospital delivery discharge records for the period between 1998 and 2004. The dataset is maintained by the Division of Family Health Services, New Jersey Department of Health and Senior Services (NJDHSS). We included all singleton births in New Jersey, between 20 and 42 completed weeks gestational age (141-294 days of pregnancy) with birth weight ≥500 g.

Outcome & Risk Factors

Stillbirth was defined as the death of the fetus prior to complete expulsion or extraction of a product of conception, where the fetus showed no signs of life such as breathing or beating of the heart, pulsation of umbilical cord, or definite movement of voluntary muscle[14]. The State of New Jersey requires all stillbirths at 20 or more completed weeks of gestation to be reported to the NJDHSS.

Maternal and fetal characteristics were mainly derived from birth and fetal death certificates while pregnancy complications were derived mainly from hospital delivery records. Maternal and fetal variables were grouped based on the findings from the multivariate analyses for the risk factors of stillbirth. Maternal age was grouped as < 25 years, 25-34 years, ≥ 35 years, maternal race/ethnicity as white non-Hispanic, black non-Hispanic, other non-Hispanic, and Hispanics, maternal level of education as ≤ High school and > High school, prenatal care initiation at any time during pregnancy or never, and self reported smoking during pregnancy as (yes/no). Birth weight was grouped as 500-2499 g, 2500 to 3,999 g and ≥ 4000 g. Gestational age was grouped as 21-24 weeks, 25-28 weeks, 29-32 weeks, 33-36 weeks and > 36 weeks. Gestational age was calculated in weeks from the first day of last menstrual period (LMP) and date of birth using the NCHS algorithm[15]. The NCHS algorithm imputed the gestational age by assigning the week of gestation from previous completed record with similar race and birth weight in cases where date of LMP was missing but the record was complete for month and year. Clinical estimate of gestational age was used when data were missing for month, year or entire LMP and in cases where both the LMP and clinical estimates were missing, gestational age was said to be missing. We utilized both birth certificate (electronic birth certificate or fetal death certificate) and hospital discharge data to define pregnancy complications (chronic hypertension, pregnancy induced hypertension, diabetes mellitus, gestational diabetes, placental abruption, preeclampsia and eclampsia) as this has been shown to provide higher sensitivity and specificity than birth certificate or hospital discharge data alone[16,17].

Socioeconomic Status

To control for differences in socioeconomic status, we used a neighborhood summary index previously developed to investigate the relationship between area and individual level social position indicators [18]. For each subject we used the geocoded residential address to assign each subject to a census tract (using ArcGIS software). For this index, census tracts served as proxies for neighborhoods, with six variables extracted from the 2000 US Census for each census tract. These variables were: median household income, median home value, and proportion of households receiving interest, dividend or net rental income, percentage of adults ≥ 25 years of age with high school diploma, percentage of adults ≥ 25 years of age who completed college, and percentage of people employed in executive, management, or professional specialty occupation. A z-score for each variable for each census tract was estimated by using the mean and standard deviation of that variable for the total population of New Jersey. These z-scores were then summed to obtain the neighborhood score for a given census tract.

Matching of Birth Residence to Air Pollution Monitor

The latitude/longitude of each birth and fetal death residence (provided by live births and fetal death certificate) and the latitude/longitude of each air pollution monitor (provided online, NJDEP website) were used to calculate the distance from each maternal residence to the monitor. For each birth we assigned $PM_{2.5}$ concentration data from the closest monitoring station within 10 km of the maternal residence. All births whose maternal residence was > 10 km from the monitoring site were excluded from the PM2.5 analyses. We repeated this matching process, separately for NO_2, SO_2, and CO.

Ambient Air Pollutants

We used criteria pollutant measurements including particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO) made at monitoring stations across New Jersey during the study period (1998-2004).

All pollutant measurements by the NJ Department of Environmental Protection were retrieved from the United States Environmental Protection Agency website (US EPA)[19]. PM2.5 measurements were made every third day and there were hourly measurements for other pollutants including SO_2, NO_2 and CO. There were 25 monitoring sites for $PM_{2.5}$ with 20 sites making measurements every third day (one monitor had incomplete data and 4 monitors were making measurements every 6th day). There were eleven monitoring sites for nitrogen dioxide NO_2 and sixteen monitoring sites each for sulfur dioxide SO_2 and carbon monoxide CO in New Jersey.

Using the estimated date of conception, trimester specific mean concentrations of air pollutants for each of the three trimesters were calculated. If more than 30% of a pollutant's measurements for that trimester were not available we set that trimester specific pollutant concentration to missing. For example, for $PM_{2.5}$, 31 days of $PM_{2.5}$ measurements would be available for any given trimester. If values for more than 10 of these 31 days were not available, we set the mean trimester specific $PM_{2.5}$ concentration to missing. Trimester specific mean concentrations were then calculated for each pollutant in the following manner: the mean concentration for the first trimester was calculated as the mean of the first 93 days while the 2nd trimester was the mean of the next 93 days. The third trimester was the mean of the remaining 94 days of pregnancy. The average concentration of the three trimester specific mean pollutant concentrations was used as the mean concentration for the entire pregnancy.

Statistical Analysis

We used logistic regression models to estimate the risk of stillbirth associated with the mean concentration of the 1st trimester mean $PM_{2.5}$ concentration. Risk factors known to be associated with stillbirth like maternal age, race/ethnicity, maternal education, prenatal care, self-reported smoking and neighborhood index were included for adjusted analysis. There were seasonal variations in the mean concentrations of pollutants and changes in pollutants' concentrations over time from 1998 to 2004. Therefore, indicator variables for calendar month and year were included in the model to control for the potential confounding by time trends. From this model, the excess risk, and 95% confidence interval, for the mean pollutant concentration was then calculated. We then re-ran this model to examine the risk of stillbirth associated with increases in 2nd and 3rd trimester and whole pregnancy mean $PM_{2.5}$ concentrations and trimester specific and whole pregnancy CO, SO_2, and NO_2 concentrations. Two pollutant models were used to assess the risk of each pollutant after adjusting for other pollutants. Pearson correlation coefficient was used to evaluate correlation between trimester specific mean concentrations of pollutants and between each trimester and pollutant pair.

To investigate effect modification (for $PM_{2.5}$ only) indicator variables were used for risk factors of stillbirth including age (< 25 years, 25 to 35 years and > 35 years), race/ethnicity (white non-Hispanic, black non-

Hispanic, other non-Hispanic and Hispanics), maternal education (≤ High school, > High school) , prenatal care (ever or none), self reported smoking, placental abruption and premature rupture of membranes. An interaction term was included in the same model described for each risk factor with two levels (for example, $PM_{2.5}$ * placental abruption). For risk factors with more than two levels like age and race, an interaction term was added with contrast statement for each level in the same model (for example, for race, there were 3 interaction terms and 3 contrast statements in the model).

To evaluate the assumption of a linear concentration response, the continuous pollutants' concentrations for the entire pregnancy were replaced by indicator variables based on quintiles for $PM_{2.5}$, NO_2, SO_2, and CO in the same logistic regression model described above. Cochran Armitage trend test was used to test for trend. All analyses were done using SAS v9.1 (®SAS Institute, Cary, NC).

Results

There were 756,562 total singleton births including 5,381 stillbirths and 751,181 live births from 1998 to 2004 in New Jersey. After excluding births beyond 42 weeks of gestation and fetuses with birth weights less than 500 g, there were 718,974 births including 3,034 stillbirths. The annual rate of stillbirth between 20 and 42 weeks was 4.2 per 1000 total births.

After excluding those with maternal residence > 10 km from a monitoring site or with missing trimester specific mean air pollutant concentration there were 1,233 stillbirths available for $PM_{2.5}$ analyses, 1,175 stillbirths for NO_2 analyses, 1,223 stillbirths for SO_2 analyses, and1,228 stillbirths for CO analyses. There were 387,162 total births including 1,810 stillbirths in at least one pollutant specific analysis. Stillbirth rates were similar in these individual pollutant analyses ranging between 4.76 per 1000 total births for CO to 5.27 per 1000 total births for NO_2.

The distribution of births by risk factor category was similar in pollutant specific analyses/cohorts except for race, where the proportion of black non Hispanics was higher in the NO_2 cohort and proportion of Hispanics was higher in SO_2 cohort compared to other pollutants' cohorts (Table 1). Incidence of stillbirth was high in black non-Hispanics and low in white and other non-Hispanics. Women with stillbirth were less educated, less likely to have any prenatal care, and more likely to self report smoking during pregnancy, than mothers of live births. Less than a third of women with a stillbirth reached term gestation, and about three quarters of these had a birth weight less than 2500 g or more than 4000 g. In contrast, about 15% of total births were preterm and had a birth weight less than 2500 g or more than 4000 g (Table 1).

The mean concentration of $PM_{2.5}$ at the monitors with third day measurement was between 11.2 and 16.9 µg/m^3. The mean daily concentration of NO_2 was between11.0 to 38.0 ppb at the NO_2 monitors. The mean daily concentration of SO_2 in New Jersey was between 2.7 to 8.2 ppb at the monitors. The mean concentration of carbon monoxide ranged between 0.28 and 1.80 ppm at the monitors.

Subject specific mean exposure to $PM_{2.5}$ concentration for the whole pregnancy ranged from 6.5 to 20.8 µg/m^3. The range for NO_2 was 9.4 to 46.9 ppb, for SO_2 2.2 to 10.1 ppb, and CO 0.14 to 2.07 ppm (Table 2). The differences in mean and standard deviation for subjects' trimester specific pollutant concentrations for stillbirths and live births are shown in Table 3. The subjects' trimester specific mean concentrations for NO_2 and $SO_{2,}$ were higher for stillbirths than for live births for all three trimesters of pregnancy. Subject specific mean concentrations were higher for stillbirths in first trimester of pregnancy for $PM_{2.5}$ and in second and third trimesters for CO.

As shown in Table 4, there were high correlations between the trimester specific mean concentrations of NO_2 and CO, but not for $PM_{2.5}$ and SO_2. Subjects' trimester specific pollutant concentration correlation showed moderate correlation between trimester specific concentrations of CO and

NO_2 (correlation coefficient between 0.47-0.55) but not between other pollutants and trimesters pairs.

In unadjusted analyses, each 4 µg/m^3 increase in 1st trimester mean $PM_{2.5}$ concentration and each 0.4 ppm increase in 2nd and 3rd trimester mean CO concentrations were associated with an increased risk of stillbirth. There was an increased risk of stillbirth associated with each 10 ppb increase in mean NO_2 concentrations and each 3 ppb increase in SO_2 in all three trimesters (Table 5). After adjusting for known risk factors and neighborhood SES, each 10 ppb increase in mean concentration of NO_2 in 1st trimester and each 4 µg/m^3 increase in 1st and 2nd trimesters mean $PM_{2.5}$ concentration were associated with an increased risk of stillbirth. There was an increased risk of stillbirth with each 3 ppb increase in mean SO_2 concentration in all three trimesters of pregnancy. There was an increased risk of stillbirth with incremental increase in mean CO concentration in each trimester but the risk was not statistically significant (Table 5).

When mean concentrations of two pollutants for the entire pregnancy were included in the model simultaneously, the relative risk estimates for each pollutant were similar to the relative risk estimates from single pollutant models (Table 6). The risk of stillbirth associated with mean concentration of $PM_{2.5}$ over the entire pregnancy was not modified by maternal age, race ethnicity, level of education, prenatal care, maternal smoking, or placental abruption. There was an increased risk of stillbirth with $PM_{2.5}$ in the presence of premature rupture of membranes, but the association was not statistically significant (Table 7). Risk of stillbirth increased with increasing quintile of exposure over the entire pregnancy for each pollutant (Table 8).

Discussion

In this cohort of women living within 10 km of an air pollution monitoring station, increases in ambient air pollution levels were associated with an increased risk of stillbirth, after adjusting for known risk factors of stillbirth and a neighborhood level measure of socioeconomic status. Each interquartile range increase in $PM_{2.5}$ and NO_2 in the 1st trimester, and SO_2 in all three trimesters was associated with an increased risk of stillbirth. The risk estimates of stillbirth for any pollutant were similar but slightly lower in two pollutant models than single pollutant models. These increases in risk were independent of other pollutants, in an increasing concentration-response function. However, we did not observe effect modification of these associations by any risk factor for stillbirth including maternal age, race ethnicity, level of education, prenatal care, maternal smoking, placental abruption or premature rupture of membranes,.

Our findings are consistent with studies reporting a greater risk of adverse pregnancy outcomes including stillbirth associated with incremental increase in ambient air pollution. An association of ambient air pollution was reported with daily counts of intrauterine mortality in the city of Sao Pãulo, Brazil for fetuses over 28 weeks of gestation[13]. The study found an association of stillbirth with NO_2 (coefficient=0.0013/μg /m^3; $p < 0.01$) with 5 day moving average, mean of SO_2 on concurrent day (coefficient=0.0005/μg /m^3; $p < 0.10$) and with 3 day moving average for CO (coefficient=0.0223/ppm; $p < 0.10$). These associations exhibited a short time lag which was not over 5 days and the effect of trimester specific exposure to ambient air pollution was not examined for stillbirth.

Our study used a large cohort with linked data from birth/fetal death certificates and maternal hospital discharge records over a seven year period. Our findings demonstrate an increased risk of stillbirth with ambient air pollutants including $PM_{2.5}$, NO_2 and SO_2. The risk of stillbirth was associated with increases in NO_2 and $PM_{2.5}$ in early pregnancy and with SO_2 in all three trimesters. Although risk was not statistically significant with CO in any trimester and with $PM_{2.5}$ and NO_2 in late pregnancy, odds ratios for these pollutants in all three trimesters of pregnancy were greater than 1.0

supportting an association with stillbirth. Our findings of an association of stillbirth with early pregnancy $PM_{2.5}$ and NO_2 and all three trimesters of SO_2 may suggest long term effect of pollutants with homogeneous spatial distribution with little change in the concentrations of pollutants over large areas. For pollutants like CO with heterogeneous spatial distribution the long term or trimester specific mean concentration of pollutant may not be associated with stillbirth.

If this pollutant/stillbirth association is real, the biologic mechanism by which ambient air pollution may affect fetal survival is not clear and may differ between exposures during early and late pregnancy. Direct transfer of pollutants across placenta causing irreversible damage to the dividing cells of the growing fetus and hypoxic damage or immune mediated injury during critical periods of development are possible mechanisms that may lead to stillbirth. The period of gestation at the time of exposure may also be important in determining the effect of each individual pollutant, if in fact they operate differently. The transplacental exposure of fetus to ambient air pollutants at different periods of development may have different effects because of differences in exposure pattern and physiological maturity of the fetus[22,23]. Perhaps exposure to certain pollutants in early pregnancy is harmful for fetal survival, while other pollutants cause fatal damage in late pregnancy, and others are harmful throughout pregnancy. Our findings suggest that exposure to NO_2 and $PM_{2.5}$ may cause damage at early stages of fetal development that leads to later fetal death whereas exposure to higher levels of SO_2 may be harmful throughout pregnancy.

There are certain limitations in the methods for assignment of pollutants' concentrations in the study which may cause non-differential misclassification of exposure and underestimation of risk. We used maternal residence reported at birth to assign the pollutant concentration from the monitoring site within 10 km of the maternal residence. However, previous studies have reported that 12-33% of women move during pregnancy, 62% within the same municipality and maternal residence reported at birth may be different from maternal residence during pregnancy[20,21]. There may be mismatching of monitoring site if monitoring site was assigned based on maternal residence reported at birth but mother had changed residence during pregnancy. As this change of residence by mothers may be non-differential with respect to stillbirth, this exposure misclassification may have resulted in bias towards null and underestimation of risk. Finally, the possibility of residual confounding by socioeconomic or other differences between areas with more and less air pollution cannot be excluded.

Conclusion

We found an increased risk of stillbirth with increase in $PM_{2.5}$ and NO_2, in early pregnancy and with SO_2 in all three trimesters of pregnancy in women living within 10 km of an air pollution monitoring station. Our study confirms the findings of previous studies of an association of ambient air pollution with other adverse pregnancy outcomes but further studies are needed to define more clearly the roles of specific pollutants and to understand the biological mechanism.

Table1: Demographic Characteristics Associated with Singleton Stillbirths and Total Births of 20 to 42 wks of Gestation in New Jersey 1999-2004 for $PM_{2.5}$ and 1998-2004 for NO_2, SO_2 and CO

	$PM_{2.5}$		SO_2	
	Stillbirth	Total Births	Stillbirth	Total Births
Maternal Characteristics	N=1,233	N=254,240	N=1,223	247,487
	N (Rate)*	(%)	N (Rate)*	(%)
Maternal Age (years)				
< 20	97(4.5)	8.5	104(4.6)	9.2
20-24	279(5.6)	19.6	282(5.5)	20.8
25-29	264(4.0)	25.8	274(4.1)	26.8
30-34	279(3.9)	28.0	283(4.3)	26.7
35-39	215(5.7)	14.8	196(5.8)	13.6
>40	61 (7.4)	3.3	52 (7.2)	2.9
Maternal Race				
White Non-Hispanic	339(3.6)	36.8	344(4.0)	34.9
Black Non-Hispanic	498(8.6)	23.0	467(8.5)	22.2
Other Non-Hispanic	77(2.8)	11.0	75(2.8)	10.9
Hispanics	314(4.2)	29.2	332(4.2)	32.0
Maternal Education				
< High School	209(4.8)	17.3	229 (5.1)	18.1
High School	415(5.4)	30.5	446(5.5)	33.0
>High School	609(4.6)	52.2	548 (4.5)	48.9
Prenatal Care Initiation				
1st Trimester	750(4.0)	75.4	707(4.0)	73.9
2nd Trimester	183(4.1)	18.1	201(4.4)	19.2
3rd Trimester	51(4.5)	4.6	57(4.9)	4.9
Never	104(22.4)	1.9	109(23.3)	2.0
Self-reported Smoking				
Yes	164(7.5)	8.7	166(7.2)	9.3
No	1,106(4.3)	91.3	997(4.5)	90.7
Gestation (weeks)				
>20 ≤ 24	264(260.6)	0.4	248(244.6)	0.4
>24 ≤ 28	169(80.0)	0.8	183(88.1)	0.8
>28 ≤ 32	198(38.9)	2.0	202(40.7)	2.0
>32 ≤ 36	260(11.1)	9.3	245(10.8)	9.2
>36	342(1.5)	87.5	345(1.6)	87.6
Birthweight (gms)				
500-2499	805(44.0)	7.2	805(45.4)	7.2
2500-3999	290(14.0)	83.8	282(14.0)	83.9
≥ 4000	33(14.0)	9.0	30(14.0)	8.9

* per 1000 total births

Table1: Demographic Characteristics Associated with Singleton Stillbirths and Total Births of 20 to 42 wks of Gestation in New Jersey 1999-2004 for $PM_{2.5}$ and 1998-2004 for NO_2, SO_2 and CO

	NO_2		CO	
	Stillbirth	Total Births	Stillbirth	Total Births
Maternal Characteristics	N=1,175	222,929	N=1,228	N=257,909
	N (Rate)*	(%)	N (Rate)*	(%)
Maternal Age (years)				
< 20	98(4.7)	9.3	99(4.5)	8.6
20-24	256(5.7)	20.2	280(5.5)	19.7
25-29	251(4.3)	26.1	269(3.9)	26.5
30-34	273(4.5)	27.0	297(4.1)	27.8
35-39	201(6.3)	14.2	199(5.4)	14.3
>40	57(8.0)	3.2	54 (6.8)	3.1
Maternal Race				
White Non-Hispanic	290(3.9)	33.1	342(3.8)	35.5
Black Non-Hispanic	545(8.5)	28.7	463(8.5)	21.3
Other Non-Hispanic	70(2.8)	11.2	87(2.9)	11.8
Hispanics	263(4.4)	27.0	330(4.1)	31.4
Maternal Education				
< High School	197(5.0)	17.7	218(4.9)	17.3
High School	397(5.7)	31.2	437(5.4)	31.4
>High School	581(5.1)	51.1	573(4.3)	51.3
Prenatal Care Initiation				
1st Trimester	679(4.3)	74.0	720(3.8)	75.1
2nd Trimester	189(4.6)	19.0	195(4.2)	18.4
3rd Trimester	49(4.8)	4.8	55(4.7)	4.7
Never	108(22.5)	2.2	102(21.9)	1.9
Self-reported Smoking				
Yes	171(8.5)	9.0	151(6.9)	8.5
No	934(4.6)	91.0	1,011(4.3)	91.5
Gestation (weeks)				
>20 ≤ 24	258(252.9)	0.5	258(249.8)	0.4
>24 ≤ 28	164(80.2)	0.9	174(83.9)	0.8
>28 ≤ 32	196(41.2)	2.1	200(40.1)	1.9
>32 ≤ 36	229(10.8)	9.5	248(10.6)	9.1
>36	328(1.7)	87.0	348(1.5)	87.8
Birthweight (gms)				
500-2499	773(45.2)	7.7	806(44.5)	7.0
2500-3999	256(14.0)	83.7	284(13.0)	84.0
≥ 4000	28(15.0)	8.6	28(12.0)	9.0

* per 1000 total births

Table 2: Subject Specific Distribution of Pollutant Concentration by Trimester

Pollutants	Mean (SD)	10%ile	25%ile	Median	75%ile	90%ile
$PM_{2.5}$($\mu g/m^3$)						
Entire Pregnancy (N=250,032)	13.89(1.7)	11.8	12.8	13.9	15.0	16.0
Ist Trimester (N=224,990)	13.79(2.6)	10.4	11.9	13.7	15.6	17.2
2^{nd} Trimester (N=211,678)	13.80(2.6)	10.4	11.9	13.7	15.6	17.4
3^{rd} Trimester (N=197,106)	13.98(2.4)	10.8	12.3	14.0	15.7	17.1
NO_2(ppb)						
Entire Pregnancy (N=222,929)	25.29(7.4)	16.5	19.5	26.3	28.9	37.8
Ist Trimester (N=221,171)	25.22(7.7)	15.4	19.3	25.6	29.4	35.5
2^{nd} Trimester (N=212,398)	25.28(7.8)	15.4	19.2	25.7	29.6	36.8
3^{rd} Trimester (N=200,979)	25.34(7.9)	15.3	19.0	25.8	29.6	37.5
SO_2(ppb)						
Entire Pregnancy (N=247,487)	5.60(1.7)	3.8	4.4	5.2	6.5	8.2
Ist Trimester (N=245,425)	5.68(2.3)	3.0	3.9	5.3	7.0	8.8
2^{nd} Trimester (N=236,548)	5.63(2.3)	3.0	3.8	5.2	7.0	8.8
3^{rd} Trimester (N=224,501)	5.54(2.2)	3.0	3.8	5.1	6.9	8.5
CO (ppm)						
Entire Pregnancy (N=257,909)	0.932(0.31)	0.60	0.68	0.89	1.12	1.33
Ist Trimester (N=254,594)	0.920(0.32)	0.56	0.67	0.90	1.11	1.34
2^{nd} Trimester (N=243,465)	0.931(0.32)	0.56	0.68	0.91	1.13	1.35
3^{rd} Trimester (N=228,876)	0.935(0.32)	0.56	0.67	0.93	1.14	1.35

Table 3: Mean and Standard Deviation of $PM_{2.5}$, NO_2, SO_2 and CO for Stillbirths and Live Births

	Stillbirths	Live Births	
	Mean(SD)	Mean(SD)	p-value
Pollutants			
$PM_{2.5}$(μ/m^3)	N=1,233	N=253,007	
Entire Pregnancy	14.05(1.7)	13.89(1.7)	<0.0013
First Trimester	13.97(2.4)	13.79(2.6)	0.0168
Second Trimester	13.95(2.5)	13.80(2.6)	0.0782
Third Trimester	14.12(2.5)	13.98(2.4)	0.0719
NO_2(ppb)	N=1,175	N=221,754	
Entire Pregnancy	25.85(6.9)	25.29(7.4)	0.0089
First Trimester	25.86(7.3)	25.22(7.7)	0.0047
Second Trimester	25.86(7.3)	25.28(7.8)	0.0123
Third Trimester	25.89(7.4)	25.33(7.9)	0.0207
SO_2(ppb)	N=1,223	N=246,264	
Entire Pregnancy	5.77(1.7)	5.60(1.7)	0.0006
First Trimester	5.82 (2.3)	5.68 (2.3)	0.0330
Second Trimester	5.89 (2.3)	5.63 (2.3)	<0.0001
Third Trimester	5.68 (2.2)	5.54 (2.2)	0.0228
CO (ppm)	N=1,228	N=256,681	
Entire Pregnancy	0.945(0.31)	0.932(0.31)	0.1442
First Trimester	0.931(0.33)	0.920(0.32)	0.2408
Second Trimester	0.953(0.32)	0.931(0.32)	0.0183
Third Trimester	0.955(0.32)	0.935(0.32)	0.0351

Table 4: Pearson Correlation Coefficients for Subjects' Trimester Specific and Entire Pregnancy Pollution Concentration

Pollutant	$PM_{2.5}$				NO_2				SO_2				CO			
Trimester	1st	2nd	3rd	Preg	1st	2nd	3rd	Preg	1st	2nd	3rd	Preg	1st	2nd	3rd	Preg
$PM_{2.5}$																
1st	**1.00**	**0.00**	**0.12**		0.14	0.24	0.37		0.08	-0.05	0.41		0.26	0.18	0.26	
2nd	**0.00**	**1.00**	**-0.03**		0.25	0.14	0.25		0.17	0.09	0.00		0.35	0.25	0.18	
3rd	**0.12**	**-0.03**	**1.00**		0.34	0.26	0.13		0.43	0.22	0.11		0.24	0.37	0.26	
Pregnancy				**1.000**				0.336				0.286				0.346
NO_2																
1st	0.14	0.25	0.34		**1.00**	**0.87**	**0.77**		0.28	0.23	0.05		0.54	0.52	0.46	
2nd	0.24	0.14	0.26		**0.87**	**1.00**	**0.86**		0.07	0.28	0.24		0.46	0.54	0.52	
3rd	0.37	0.25	0.13		**0.77**	**0.86**	**1.00**		0.06	0.05	0.29		0.50	0.47	0.55	
Pregnancy				0.336				**1.000**				0.252				0.567
SO_2																
1st	0.08	0.17	0.43		0.28	0.07	0.06		**1.00**	**0.45**	**0.11**		0.40	0.37	0.19	
2nd	-0.05	0.09	0.22		0.23	0.28	0.05		**0.45**	**1.00**	**0.41**		0.24	0.41	0.35	
3rd	0.41	0.00	0.11		0.05	0.24	0.29		**0.11**	**0.41**	**1.00**		0.24	0.25	0.43	
Pregnancy				0.286				0.252				**1.000**				0.452
CO																
1st	0.26	0.35	0.24		0.54	0.46	0.50		0.40	0.24	0.24		**1.00**	**0.89**	**0.81**	
2nd	0.18	0.25	0.37		0.52	0.54	0.47		0.37	0.41	0.25		**0.89**	**1.00**	**0.88**	
3rd	0.26	0.18	0.26		0.46	0.52	0.55		0.19	0.35	0.43		**0.81**	**0.88**	**1.00**	
Pregnancy				0.346				0.567				0.452				**1.000**

Table 5: Unadjusted and Adjusted Odds Ratio with 95% Confidence Interval for Criteria Pollutants

		Unadjusted OR (95% CI)		*Adjusted OR (95% CI)
	N		N	
$PM_{2.5}$(4 µg/m^3)				
Pregnancy	250,032	1.24(1.09-1.42)	238,893	1.26(1.05-1.51)
First Trimester	224,990	1.12(1.02-1.23)	215,379	1.14(1.00-1.31)
Second Trimester	211,678	1.09(0.99-1.19)	202,459	1.20(1.04-1.37)
Third Trimester	197,106	1.10(0.99-1.23)	188,408	1.02(0.87-1.19)
NO_2(10 ppb)				
Pregnancy	222,929	1.11(1.03-1.19)	211,813	1.09(0.99-1.20)
First Trimester	221,171	1.11(1.03-1.20)	210,104	1.10(1.00-1.21)
Second Trimester	212,398	1.10(1.02-1.18)	201,782	1.08(0.98-1.18)
Third Trimester	200,979	1.09(1.01-1.18)	191,059	1.07(0.98-1.17)
SO_2(3 ppb)				
Pregnancy	247,487	1.19(1.08-1.31)	236,256	1.14(1.01-1.28)
First Trimester	245,425	1.08(1.01-1.16)	234,245	1.12(1.00-1.25)
Second Trimester	236,548	1.21(1.08-1.24)	225,805	1.21(1.03-1.29)
Third Trimester	224,501	1.13(1.01-1.19)	214,411	1.18(1.00-1.28)
CO(0.4 ppm)				
Pregnancy	257,909	1.05(0.98-1.13)	246,010	1.09(0.99-1.20)
First Trimester	254,594	1.04(0.97-1.12)	242,832	1.08(0.98-1.19)
Second Trimester	243,465	1.09(1.01-1.17)	232,222	1.09(0.99-1.20)
Third Trimester	228,876	1.08(1.01-1.16)	218,417	1.09(0.98-1.20)

* Adjusted for age, race/ethnicity, maternal education, prenatal care and smoking neighborhood SES and years and months

Table 6: Adjusted Odds Ratios with 95% CI for Risk of Stillbirth for Combined Models with One & Two Pollutants for Entire Pregnancy

			One Pollutant*	Two Pollutants
Pollutants	**IQR**	**N**	**OR (95% CI)**	**OR (95% CI)**
		Total Birth(Stillbirth)		
$PM_{2.5}$	4µg/m^3	153,881(717)	1.37(1.10-1. 73)	1.35(1.06-1.72)
NO_2	10 ppb		1.07(0.96-1.19)	1.03(0.92-1.15)
$PM_{2.5}$	4µg/m^3	136,970(633)	1.18(0.92-1.50)	1.14(0.88-1.47)
SO_2	3 ppb		1.11(0.95-1.30)	1.08(0.92-1.27)
$PM_{2.5}$	4µg/m^3	147,339(654)	1.14(0.90-1.45)	1.07(0.83-1.37)
CO	0.4 ppm		1.15(1.00-1.33)	1.14(0.98-1.32)
NO_2	10 ppb	145,656(664)	1.09(0.97-1.22)	1.05(0.93-1.19)
SO_2	3 ppb		1.26(1.08-1.48)	1.25(1.06-1.46)
NO_2	10 ppb	149,428(681)	1.07(0.95-1.20)	0.98(0.85-1.13)
CO	0.4 ppm		1.17(1.02-1.34)	1.18(1.01-1.38)
SO_2	3 ppb	218,095(937)	1.16(1.02-1.31)	1.14(0.98-1.31)
CO	0.4 ppm		1.08(0.98-1.18)	1.03(0.92-1.14)

* N different from Table 5 because only subjects with data from both pollutants were tabulated

Table 7: Effect Modification for the Risk of Stillbirth with PM2.5 for Entire Pregnancy

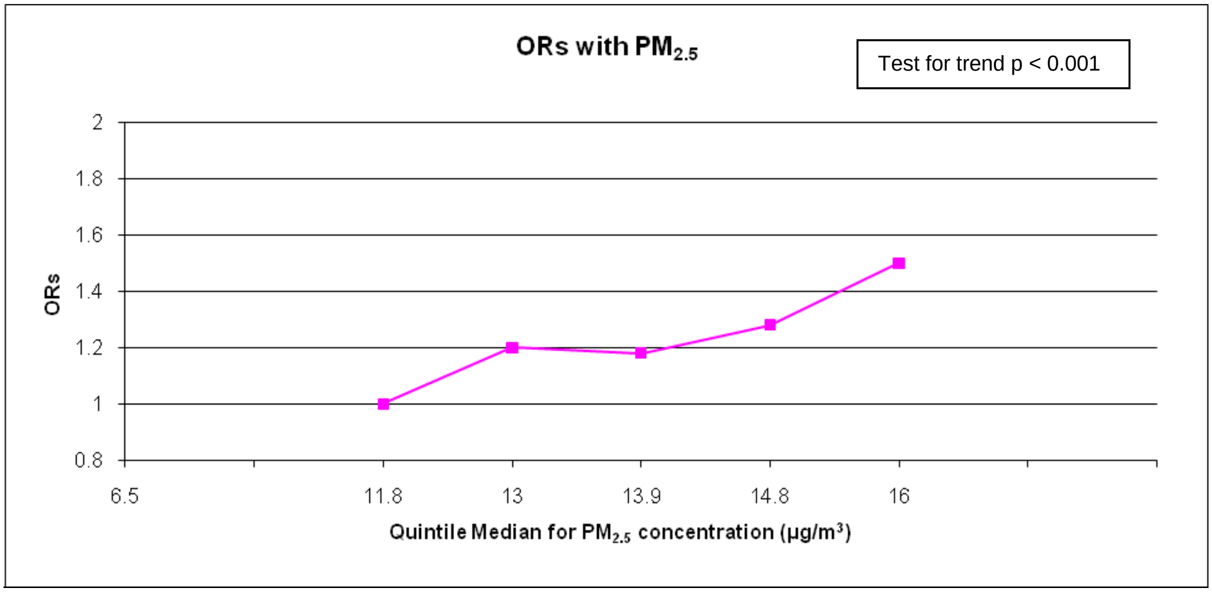
Risk Factors	**OR (95% CI)**	**p-value**
Maternal Age*		
< 25 Years	1.32(0.98-1.77)	0.067
25-34 Years	1.19(0.95-1.51)	
≥ 35Years	1.24(0.90-1.71)	0.182
Maternal Race**		
White non-Hispanics	1.44(1.09-1.91)	
Black non-Hispanics	1.29(0.97-1.73)	0.083
Other non-Hispanics	1.17(0.68-2.03)	0.572
Hispanics	1.07(0.79-1.46)	0.670
Maternal Education		
≤ High School	1.23(0.98-1.55)	0.078
> High School	1.32(1.05-1.67)	
Prenatal Care		
None	1.23(0.70-2.16)	0.481
Ever	1.22(1.03-1.45)	
Smoking		
Yes	1.23(0.80-1.91)	0.345
No	1.28(1.06-1.54)	
Placental Abruption		
with	1.15(0.83-1.61)	0.402
without	1.39(1.14-1.70)	
Premature Rupture of Membranes		
with	3.03(0.43-21.07)	0.266
without	1.26(1.06-1.51)	

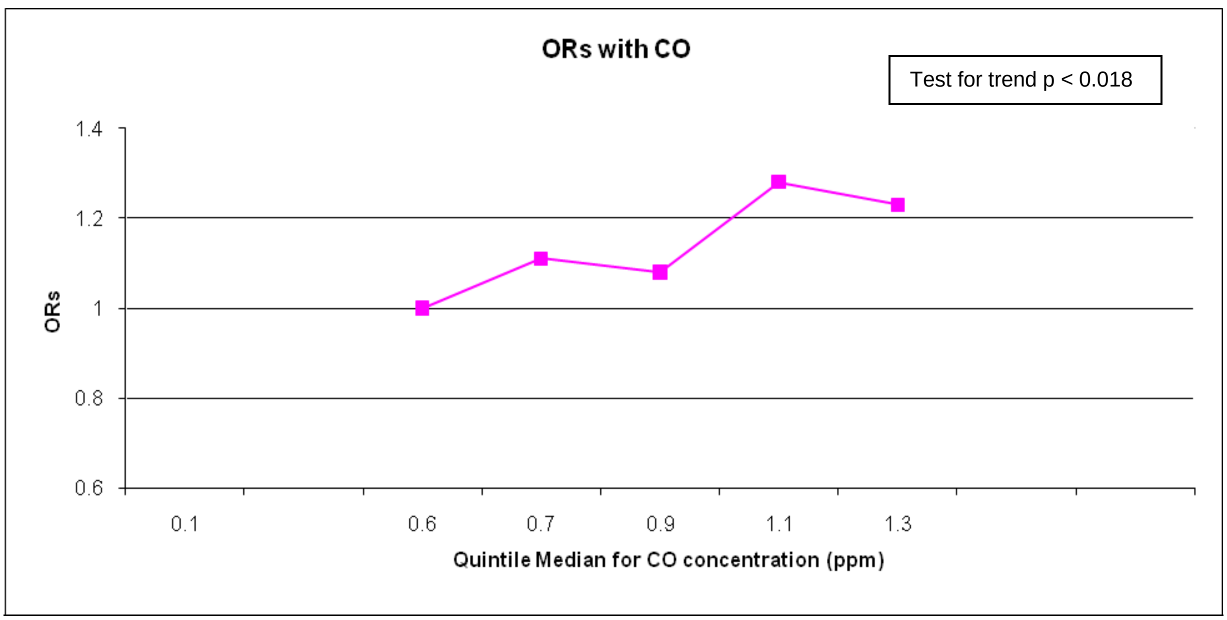
*p-values with interaction terms comparing with age 25-35 years
** p-value with interaction terms comparing with white non-Hispanics

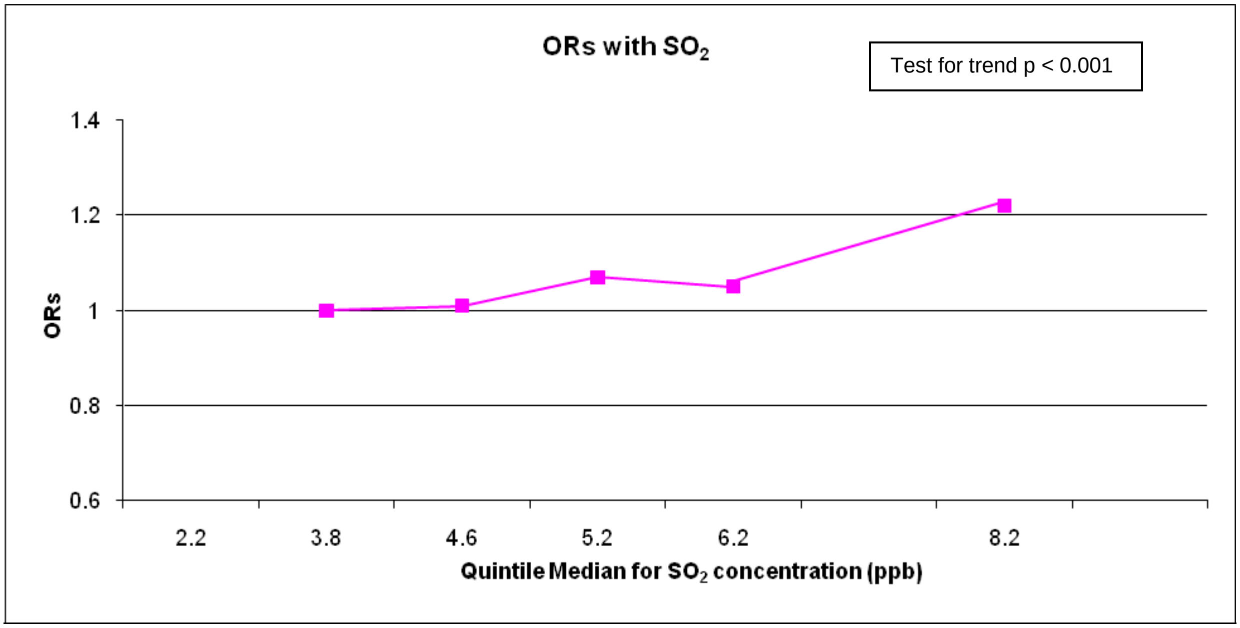
Table 8: OR with 95% CI for Risk of Stillbirth with Quintiles of Entire Pregnancy for $PM_{2.5}$, NO_2, SO_2 and CO

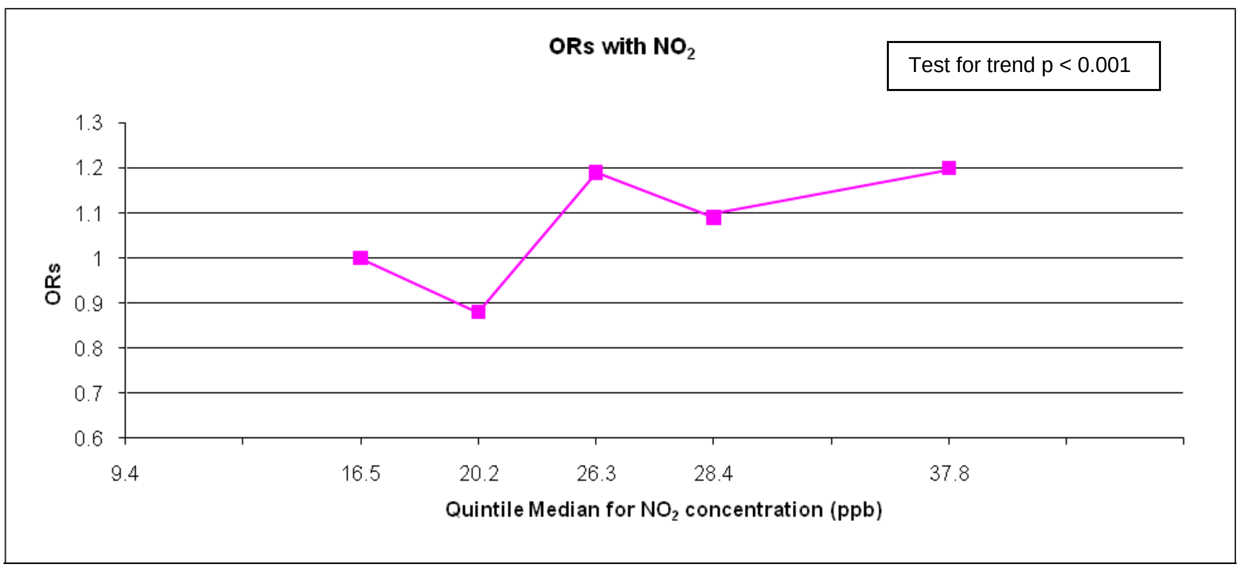
						Test for trend
Pollutants	1st Quintile	2nd Quintile (95% CI)	3rd Quintile (95% CI)	4th Quintile (95% CI)	5th Quintile (95% CI)	p-value
$PM_{2.5}$(μg/m³)	Reference	1.20 (0.96-1,50)	1.18 (0.94-1.47)	1.28 (1.02-1.62)	1.50 (1.18-1.90)	<0.001
NO_2(ppb)	Reference	0.88 (0.70-1.11)	1.19 (0.97-1.17)	1.09 (0.88-1.35)	1.20 (0.97-1.49)	0.0003
SO_2(ppb)	Reference	1.01 (0.81-1.25)	1.07 (0.87-1.33)	1.05 (0.85-1.31)	1.22 (0.99-1.51)	<0.0001
CO (ppm)	Reference	1.11 (0.90-1.37)	1.08 (0.87-1.34)	1.28 (1.04-1.56)	1.23 (0.97-1.57)	0.018

Figure: ORs for Risk of Stillbirth with Quintile Median of Entire Pregnancy for $PM_{2.5}$, NO_2, SO_2 and CO






ORs with SO_2
Test for trend $p < 0.001$
1.4
1.2
1
0.8
0.6
ORs
2.2
3.8
4.6
5.2
6.2
8.2
Quintile Median for SO_2 concentration (ppb)


ORs with NO_2
Test for trend $p < 0.001$
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
ORs
9.4
16.5
20.2
26.3
28.4
37.8
Quintile Median for NO_2 concentration (ppb)

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Chapter III

Short Term Effect of Ambient Air Pollution on the Risk of Stillbirth 1998-2004

Abstract

Introduction

An increase in risk of stillbirths has been reported with incremental increase in ambient air pollution. It is not clear however, if only prolonged exposure to air pollution during pregnancy is harmful, or if short term increases in ambient air pollution, late in pregnancy, are also associated with increased risk of stillbirth. The purpose of this study was to examine the short term effects of increased ambient air pollutant concentrations on the risk of stillbirth.

Methods

We used New Jersey data for fetal deaths linked to hospital discharge data for the years 1998-2004. For each stillbirth we assigned concentration of air pollutants from a monitoring site within 10 km from the maternal residence at the time of stillbirth. The association of ambient air pollution with the risk of stillbirth was analyzed with a time stratified case crossover design using conditional logistic regression.

Results

We found an increased risk of stillbirth associated with each 5.1 ppb increase in the mean SO_2 concentration (OR= 1.12; 95% CI, 1.02-1.23) and 0.57 ppm increase in mean CO concentration (OR =1.20; 95% CI, 1.04-

1.38) in the 2nd day before the stillbirth. The effect estimate of CO was greater in the presence of placental abruption but the effect estimates were smaller when other risk factors for stillbirth were present.

Conclusion:

We found an increased risk of stillbirth associated with increases in mean concentrations of SO_2, and CO few days prior to stillbirth. Our findings of fetal mortality with short term increase in ambient air pollution are consistent with previous studies reporting an increase in mortality including fetal death with short term increase in ambient air pollution.

Introduction

A number of studies have provided evidence of an association between ambient air pollution and all cause mortality, cardiovascular mortality and respiratory mortality[1-10]. The elderly, infants and children may be more susceptible to the harmful effects of ambient air pollution[4,11-13]. Several studies have also reported an association between ambient air pollution and adverse pregnancy outcomes including preterm birth[14-], low birth weight[14,15,17,19,21-24] and intrauterine growth restriction[14,15,25]. The evidence for an association between ambient air pollution and fetal mortality is inconsistent[15,26,27] with one study conducted in Sao Pãulo, Brazil reporting an association between daily counts of stillbirth with ambient air pollution[27]. The other two ecological studies, one conducted in Czech Republic[15] and other in Sweden[26] did not find an association of ambient air pollution with stillbirth.

The purpose of this study was to examine whether transient, short-term increases in levels of ambient air pollutants were associated with an increased risk of stillbirth. Specifically we used a time stratified case-crossover design to model the risk of still birth associated with exposure to particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3) in the few days before stillbirth (2 to

6 days before stillbirth). We also examined if the risk of stillbirth, associated with these acute increases in ambient air pollutants, was modified by the presence of placental abruption and premature rupture of membranes to explore the potential mechanism leading to fetal death.

Materials and Methods

Data Sources & Study Population

For this study we used New Jersey fetal death certificates that were linked to their corresponding hospital delivery discharge records from 1998 to 2004. The dataset is maintained by the Division of Family Health Services, New Jersey Department of Health and Senior Services (NJDHSS). We included all singleton deaths in New Jersey, between 20 and 42 completed weeks of gestation (141-294 days of pregnancy) with birth weight ≥500 g.

Outcome & Risk Factors

Stillbirth was defined in NJ as death of the fetus prior to complete expulsion or extraction of a product of conception, where the fetus showed no signs of life such as breathing or beating of the heart, pulsation of umbilical cord, or definite movement of voluntary muscle (NCHS). The

State of New Jersey requires all stillbirths at 20 or more completed weeks of gestation to be reported to NJDHSS.

From the linked fetal death certificates and hospital delivery discharge records dataset, we retained data on maternal and fetal characteristics and pregnancy complications. This included maternal age (years), race/ethnicity (white non-Hispanic, black non-Hispanic, other non-Hispanic and Hispanics), maternal education, prenatal care, smoking status, sex of the fetus, birth weight of fetus (grams) and gestational age of fetus (weeks), placental abruption and premature rupture of membranes.

Ambient Air Pollutants and Weather

Hourly measurements made by New Jersey Department of Environmental Protection were used for mean daily concentrations of criteria pollutants. All pollutants measurements by the NJ Department of Environmental Protection were retrieved from the United States Environmental Protection Agency website (US EPA)[28]. We used measurements from five monitoring sites for $PM_{2.5}$, nine monitoring sites for nitrogen dioxide NO_2, fourteen monitoring sites for sulfur dioxide SO_2, thirteen monitoring sites for CO and fifteen monitoring stations for ozone.

Matching of Birth Residence to Air Pollution Monitor and Weather Monitor

The latitude/longitude of each maternal residence at delivery (provided by fetal death certificate) and the latitude/longitude of each air pollution monitor and weather monitor were used to calculate distance from each maternal residence to the monitor. For each fetal death, we assigned mean concentration of air pollutants from the monitoring site within 10 km from the maternal residence. All fetal deaths whose maternal residence was > 10 km from the monitoring site were excluded from the analysis. The weather monitoring site closest to maternal residence at birth was used to assign weather measurement.

Mean daily concentrations of air pollutants were calculated from hourly measurements if $\geq$ 75% of a 24 hour period measurements were available. Otherwise the value was considered missing. For weather, hourly temperature and dew point measurements made at the Newark, Caldwell, Somerset, and Trenton airports during the study period were used. Mean daily temperature and dew point were calculated from hourly measurements if $\geq$ 75% of a 24 hour period were not missing. The 24 hour mean temperature and dew point measurements were then used to calculate a 24 hour mean apparent temperature[29] which is a measure of individual's perceived temperature given humidity. Daily pollutants' concentrations corresponding to the case and control periods were used for the analyses.

Study Design

The association of air pollution with stillbirth was analyzed using a time stratified case crossover design[30,31]. In this design, each subject contributes information as a case during the case period before the stillbirth and as matched control during control periods. As case periods and control periods are derived from the same subjects, potential confounding variables such as maternal characteristics like age and race and pregnancy complications are controlled by design and confounding variables that change over time like temperature and humidity are controlled in the analysis.

The case period for the study was defined as the two days prior to the day of stillbirth and control periods (3-4 per case) were selected by matching on weekday within same calendar month. For example, if case period was the second Friday of a calendar month then the control periods were all other Fridays of that same month. Two days prior to stillbirth was chosen as the case period because the fetus is not always delivered immediately after death and the average time between fetal death and spontaneous or induced delivery has been estimated to be 48 hours in the third trimester[32]. For all cases of stillbirth in all trimesters, the median time from death of the fetus until birth was estimated as 22 to 38 hours[33]. To test the assumption that mean concentration of pollutants 2 days before stillbirth was the optimal exposure for the risk of stillbirth, we conducted sensitivity analyses using the day before stillbirth as the case period.

Statistical Analysis

Using conditional logistic regression models, we estimated the risk of stillbirth associated with each interquartile range increase in the mean $PM_{2.5}$ concentration in two days before the stillbirth, after controlling for apparent temperature. Using the Akaike Information Criterion (AIC) to select the optimum lag time and degrees of freedom for apparent temperature, the mean apparent temperature on day two with one degree of freedom was included in the model. We then replaced the day 2 mean daily concentrations of $PM_{2.5}$ to estimate the risk of stillbirth associated with mean concentrations of pollutants for lag days 2 to lag days 6 (mean of 2-3, 2-4, 2-5, and 2-6 days) for each pollutant. The analysis was repeated for other pollutants including $NO_{2,}$ $SO_{2,}$ and CO and O_3. Risk estimates with 95% confidence interval were scaled to the interquartile range of each pollutant for each lag period. Two pollutant models were then used to estimate the risk of stillbirth associated with increases in each pollutant after adjusting for other pollutants.

We examined effect modification of the CO/stillbirth association by several factors including maternal age (< 25 years, 25 to 34 years and ≥ 35 years), race/ethnicity (white non-Hispanic, black non-Hispanic, other non-Hispanic and Hispanics), maternal education (≤ High school, > High school), prenatal care (ever or none), self reported smoking, placental abruption and premature rupture of membranes and season (winter=January, February and March; summer= July, August and September).

We conducted sensitivity analyses to estimate the risk of stillbirth with each interquartile range increase in the mean $PM_{2.5}$ concentration in one day before the occurrence of stillbirth defined as case period. The analysis was repeated for other pollutants including NO_2, SO_2, and CO and O_3. We then replaced the day 1 mean daily concentrations of pollutants to estimate the risk of stillbirth associated with mean concentrations of pollutants for lag days 1 to lag days 6 (means of day 1-2, 1-3, 1-4, 1-5, and 1-6 days). Risk estimates with 95% confidence interval were scaled to the interquartile range of each pollutant for each lag period. All datasets were constructed using SAS v9.1 (®SAS Institute, Cary, NC) and all analyses were done using R package version 2.9.1 (®.The R Foundation for Statistical Computing).

Results

There were 1,875 stillbirths from 1998 to 2004 in New Jersey after excluding births beyond 42 weeks of gestation and fetuses with birth weights less than 500 g. After excluding those with maternal residence > 10 km from a monitoring site, there were 689 stillbirths available for analyses with $PM_{2.5}$, 1,212 for NO_2, 1277 for SO_2, 931 for CO, and 1,079 for $O_{3.}$

Distribution of births by risk factor categories was similar in different pollutant cohorts except for race where the proportion of black non Hispanics was highest in the NO_2 cohort and lowest in the CO cohort and the proportion of women with no prenatal care was lowest in the CO cohort compared to other cohorts (Table1). About 60% of stillbirth occurred in women younger than 25 years or in women 35 years or older. Black non-Hispanic women had the highest proportion of stillbirths and a quarter of stillbirths occurred in Hispanics. More than half the women with stillbirth had high school or less education, and about one third initiated their prenatal care after the first trimester and 14% had self-reported smoking. About two thirds of stillbirths occurred before 36 weeks of gestation. About three quarters of the stillbirths had birth weight less than 2500 g or more than 4000 g (Table 1a).

During the study period the mean daily concentration of $PM_{2.5}$ from five monitors was15.0µg/m^3 for $PM_{2.5}$ (interquartile range was 9.4 µg/m^3). The mean daily concentration of NO_2 was 26.1 ppb (interquartile range was

16.4 ppb) and the mean daily concentration of SO_2 was 5.9 ppb (interquartile range was 5.0 ppb). Mean daily concentration was 0.88 ppm (interquartile range was 0.57 ppm) for CO and 23.6 ppb (interquartile range was 19.2 ppb) for O_3 (Table 2). There was modest correlation between the day 2 mean concentrations of NO_2, SO_2, and CO (r= 0.48 to 0.55), but the correlation was weak between $PM_{2.5}$ and other pollutants (r= 0.25 to 0.37). Ozone was negatively correlated with all pollutants but with $PM_{2.5}$ correlation was positive. With the exception of O_3, the correlation coefficients for mean concentrations of lag days 2 to 6 were smaller than the coefficients for lag day 2 mean concentrations for all pollutants (Table 3).

There was an increased risk of stillbirth for each interquartile range increase in NO_2, SO_2, and CO concentrations 2 days prior to stillbirth. For each interquartile range increase in SO_2 and CO concentrations for lag days 2-3 and lag days 2-4 there was an increased risk of stillbirth (Table 4). After adjusting for apparent temperature there was an increased risk of stillbirth for each interquartile range increase in SO_2 and CO concentrations in lag day 2 and lag days 2 -3. Each interquartile range increase in SO_2 concentration for lag days 2-4 was also associated with an increased risk of stillbirth (Table 5).

Because the interquartile range decreased as more days (e.g. days 2-6) were averaged to create the pollutant estimates, and because this introduces some non-comparability in the odds ratio estimates, we recalculated the odds ratios using a fixed interquartile range (Table 5a). The results are very similar to those shown in Table 5.

With day 1 defined as the case period, there was an increased risk of stillbirth only with SO_2 and CO but risk was not statistically significant with day 1 concentration of these pollutants. With each interquartile range increase in SO_2 in lag days 1 and 2, the OR was 1.11 (95% CI, 1.00-1.23); and in lag days 1-3, the OR was 1.13 (95% CI, 1.00-1.27); and in lag days 1-4, the OR was 1.14 (95% CI, 1.00-1.30). The OR was 1.16 (95% CI, 1.00-1.35) with each interquartile range increase in CO concentration in lag days 1 and 2 (data not shown).

When mean concentrations of two pollutants in lag day 2 were included in the model simultaneously, the risk estimates of stillbirth for each pollutant in two pollutant models were similar to the estimates from single pollutant models on the same subjects (Table 6). The effect modification of risk of stillbirth was estimated with mean concentration CO, as effect estimates of CO were higher than other pollutants. The risk of stillbirth associated with mean concentration of CO was not modified by maternal age, race ethnicity, level of education, prenatal care or maternal smoking.

However, risk of stillbirth was modified by placental abruption and risk was greater in women with placental abruption as compared to those without placental abruption (Table 7).

Discussion

In a cohort of women with stillbirth residing within 10 km of an air monitoring station there was an increased risk of stillbirth for each interquartile range increase in mean concentration of SO_2 and CO. There was an increased risk of stillbirth with odds ratios greater than 1.0 with increase in NO_2 and to lesser degree with $PM_{2.5}$ and O_3 few days prior to stillbirth but these associations were not statistically significant. The risk estimates of two pollutant models were similar to the risk estimates from single pollutant models on the same subjects. There was no effect modification of the association of CO with stillbirth by maternal age, race ethnicity, level of education, prenatal care, or maternal smoking but risk was modified by placental abruption.

Our findings of increased risk of stillbirth with short term increase in sulfur dioxide and carbon monoxide are consistent with a previous study reporting an association of higher daily fetal mortality with ambient air pollutants including nitrogen dioxide, sulfur dioxide and carbon monoxide[27].

The study of Pereira found an association of stillbirth with NO_2 (coefficient=0.0013/μg /m^3; $p < 0.01$) with 5 day moving average, mean of SO_2 on concurrent day (coefficient=0.0005/μg /m^3; $p < 0.10$) and with 3 day moving average for CO (coefficient=0.0223/ppm; $p < 0.10$). However, the study was ecological by design and did not control for potential confounding factors.

Our study was a large cohort study with linked data from fetal death certificates and maternal hospital discharge records over a seven year period. Our findings demonstrate an increased risk of stillbirth with ambient air pollutants including SO_2 and CO. Although risk was not statistically significant with other pollutants the odds ratios indicated an association of stillbirth with all pollutants including NO_2, $PM_{2.5,}$ and O_3. These findings suggest that short term increase in ambient air pollution may cause irreversible damage to the fetus leading to death. It may be possible that these pollutants lead to fetal death either directly by crossing the placental barrier or indirectly by hypoxic or immune-mediated injury. Association with SO_2 and CO may suggest that there may be harmful effect of short term increase in both traffic related pollutants and industrial pollutants on the fetus.

The risk of stillbirth with CO was higher in pregnancies complicated by placental abruption. As placental abruption is an independent risk factor of stillbirth and risk of stillbirth is several folds higher with premature separation of placenta it may be possible that ambient air pollution accelerates the pathological changes in the placenta susceptible to premature separation by direct transfer of pollutant across the placental barrier. Thus women with placental abruption are at higher risk of having a stillbirth with increases in ambient air pollution than those without it.

There are certain limitations in the methods for measurement and assignment of concentration of pollutants in the study which may cause non-differential misclassification of exposure and underestimation of risk. The mean daily concentrations of pollutants were assigned to all women with residence within 10 km from a monitoring site regardless of the time spent at other locations. This may not represent exposure for all women and there may be mismatching of monitoring sites if women spent time at locations other than at the residences reported at birth. As this mismatching may not be different for case and control periods this may result in non differential misclassification of exposure and underestimation of effect.

The mean concentrations of pollutants 2 days prior to stillbirth were used to estimate the risk of stillbirth. As the exact time of fetal death prior to delivery is not known and may vary at different times of gestation, pollutant concentration in day 2 may not be the optimum exposure to assess the risk of stillbirth. However, as pollutant concentration in day 2 was assigned to all stillbirths irrespective of gestational age, this may result in non differential misclassification of exposure and underestimation of risk.

Conclusion

We found an increased risk of stillbirth associated with increases in mean concentrations of SO_2, and CO few days prior to stillbirth. Our findings of fetal mortality with short term increase in ambient air pollution are consistent with previous studies reporting an increase in mortality and morbidity including stillbirth with short term increase in ambient air pollution.

Table1: Demographic Characteristics Associated with Singleton Stillbirths in New Jersey 1998-2004 for $PM_{2.5}$, NO_2, SO_2, CO and O_3

Maternal Characteristics	$PM_{2.5}$	NO_2	SO_2	CO	O_3
	N=689	N=1,212	N=1,277	N=931	N=1,079
	N (%)	N (%)	N (%)	N (%)	N (%)
Maternal Age (years)					
< 20	51(7.6)	99(8.5)	108(8.6)	68(7.4)	99(9.5)
20-24	141(21.0)	271(23.1)	294(23.6)	216(23.6)	236(22.6)
25-29	164(24.4)	261(22.3)	289(23.3)	203(22.2)	225(21.6)
30-34	159(23.7)	275(23.5)	290(23.4)	236(25.8)	253(24.3)
35-39	126(18.8)	209(17.8)	207(16.7)	148(16.3)	177(17.0)
>40	31(4.5)	57(4.8)	54(4.4)	43(4.7)	53(5.0)
Maternal Race					
White Non-Hispanic	175(25.8)	297(24.7)	361(28.4)	316(34.1)	332(30.9)
Black Non-Hispanic	276(39.8)	568(47.1)	482(37.9)	263(28.4)	418(38.9)
Other Non-Hispanic	49(7.4)	70(5.8)	81(6.4)	83(9.0)	70(6.5)
Hispanics	183(27.0)	270(22.4)	348(27.3)	265(28.5)	254(23.7)
Maternal Education					
< High School	119(17.6)	213(17.6)	238(18.6)	151(16.2)	198(18.4)
High School	229(33.2)	413(34.1)	467(36.6)	331(35.6)	374(34.6)
>High School	341(49.2)	586(48.3)	572(44.8)	449(48.2)	507(47.0)
Prenatal Care Initiation					
1st Trimester	401(67.0)	695(66.1)	740(66.2)	578(71.0)	633(66.8)
2^{nd} Trimester	103(17.2)	194(18.4)	206(18.4)	133(16.3)	183(19.3)
3^{rd} Trimester	32(5.4)	50(4.8)	59(5.3)	45(5.5)	42(4.4)
Never	62(10.4)	113(10.7)	113(10.1)	58(7.2)	90(9.5)
Self-reported Smoking					
Yes	84(12.9)	179(15.8)	173(14.3)	106(12.1)	155(15.3)
No	566(87.1)	956(84.2)	1036(85.7)	772(87.9)	855(84.7)
Gestation (weeks)					
>20 ≤ 24	144(20.9)	264(21.6)	254(20.0)	184(19.8)	226(21.0)
>24 ≤ 28	97(14.1)	166(13.7)	186(14.5)	125(13.4)	156(14.5)
>28 ≤ 32	112(16.3)	197(16.3)	206(16.1)	149(16.0)	168(15.6)
>32 ≤ 36	120(17.4)	241(20.0)	255(20.0)	189(20.3)	211(19.6)
>36	216(31.3)	344(28.4)	376(29.4)	284(30.5)	318(29.3)
Birthweight (gms)					
500-2499	442(71.6)	773(72.0)	825(71.4)	580(69.5)	685(72.0)
2500-3999	161(26.1)	273(25.4)	298(25.7)	236(28.3)	244(25.7)
≥ 4000	14(2.3)	27(2.5)	33(2.9)	18(2.2)	22(2.3)

Table1a: Maternal & Fetal Characteristics of Stillbirths Associated with any Criteria Air Pollutant in New Jersey 1998-2004

Maternal & Fetal Characteristics	Stillbirths (N=1,875)
	N(%)
Maternal Age (years)	
< 20	151(8.3)
20-24	411(22.5)
25-29	405(22.2)
30-34	451(24.7)
35-39	321(17.6)
>40	85(4.7)
Maternal Race	
White Non-Hispanic	581(31.1)
Black Non-Hispanic	692(37.1)
Other Non-Hispanic	122 (6.5)
Hispanics	472(25.3)
Maternal Education	
< High School	328 (17.5)
High School	631(33.7)
>High School	916(48.8)
Prenatal Care Initiation	
1st Trimester	1,125(68.5)
2nd Trimester	286(17.5)
3rd Trimester	78(4.8)
Never	150(9.2)
Self-reported Smoking	
Yes	250(14.1)
No	1,519(85.9)
Gestation (weeks)	
>20 ≤ 24	399(21.3)
>24 ≤ 28	263(14.0)
>28 ≤ 32	292(15.6)
>32 ≤ 36	370(19.7)
>36	551(29.4)
Birthweight (gms)	
500-2499	1,167(70.9)
2500-3999	436(26.5)
≥ 4000	43(2.6)

Table 2: Distribution of Criteria Pollutants for Case and Control Periods for Mean Concentration of Lag Day 2

	Case Periods							**Control Periods**						
Pollutants	N	10%ile	25%ile	Median	75%ile	90%ile	IQR	N	10%ile	25%ile	Median	75%ile	90%ile	IQR
$PM_{2.5}$(μg/m^3)	689	6.6	8.8	12.5	18. 2	27.0	9.4	2,341	6.3	8.6	12.3	18.8	25.8	10.1
NO_2(ppb)	1,212	11.6	17.3	25.2	33.7	41.8	16.4	4,126	11.3	16.4	24.0	32.6	41.3	16.2
SO_2(ppb)	1,277	1.6	2.8	4.8	7.8	11.8	5.1	4,338	1.7	2.9	4.6	7.4	11.0	4.5
CO(ppm)	931	0.42	0.56	0.74	1.13	1.52	0.57	3,195	0.40	0.53	0.75	1.07	1.47	0.53
O_3(ppb)	1,079	6.8	12.8	22.7	32.0	40.8	19.2	3,705	7.0	13.0	22.3	32.1	41.3	19.2

Table 3: Pearson Correlation Coefficients for Mean Pollution Concentration on Lag day 2 and Lag days 2-6

	$PM_{2.5}$ (N)	**NO_2** (N)	**SO_2** (N)	**CO** (N)	**O_3** (N)
Mean of lag day 2	**Mean of lag day 2**				
$PM_{2.5}$	**1.00** (689)				
NO_2	0.38(595)	**1.00** (1212)			
SO_2	0.32(586)	0.52 (836)	**1.00** (1277)		
CO	0.33 (426)	0.60 (529)	0.53(831)	**1.00** (931)	
O_3	0.32(498)	-0.41(849)	-0.31(767)	-0.34 (527)	**1.00** (1079)
Mean of lag days 2-6	**Mean of lag days 2-6**				
$PM_{2.5}$	**1.00** (719)				
NO_2	0.19 (625)	**1.00** (1245)			
SO_2	0.10 (617)	0.38 (865)	**1.00** (1296)		
CO	0.14 (452)	0.48 (555)	0.48 (863)	**1.00** (960)	
O_3	0.47 (528)	-0.33 (883)	-0.32 (794)	-0.29 (553)	**1.00** (1106)

Table 4: Unadjusted ORs with 95% Confidence Interval for Risk of Stillbirth with Criteria Pollutants

Pollutants	**N**	**Lag days**	**IQR**	**OR**	**95% CI**
$PM_{2.5}$(µg/m^3)					
	689	**2**	9.4	1.05	0.94-1.16
	700	**2,3**	8.4	1.02	0.91-1.13
	706	**2,3,4**	8.0	1.05	0.94-1.18
	714	**2,3,4,5**	7.5	1.07	0.95-1.20
	719	**2,3,4,5,6**	7.1	1.09	0.96-1.23
NO_2(ppb)					
	1,212	**2**	16.4	1.13	1.00-1.28
	1,232	**2,3**	13.6	1.11	0.99-1.26
	1,238	**2,3,4**	12.0	1.10	0.97-1.25
	1,241	**2,3,4,5**	12.2	1.06	0.92-1.23
	1,245	**2,3,4,5,6**	11.9	1.04	0.89-1.22
SO_2(ppb)					
	1,277	**2**	5.1	1.12	1.02-1.23
	1,288	**2,3**	4.7	1.12	1.01-1.24
	1,291	**2,3,4**	4.3	1.12	1.00-1.26
	1,295	**2,3,4,5**	4.2	1.07	0.94-1.22
	1,296	**2,3,4,5,6**	4.0	1.01	0.89-1.16
CO (ppm)					
	931	**2**	0.57	1.21	1.06-1.39
	943	**2,3**	0.53	1.18	1.02-1.37
	947	**2,3,4**	0.51	1.18	1.00-1.39
	954	**2,3,4,5**	0.49	1.09	0.99-1.20
	960	**2,3,4,5,6**	0.49	1.19	0.99-1.44
O_3(ppb)					
	1,079	**2**	19.2	0.99	0.85-1.15
	1,094	**2,3**	17.7	1.04	0.89-1.22
	1,098	**2,3,4**	17.8	1.03	0.86-1.23
	1,103	**2,3,4,5**	17.0	1.00	0.83-1.20
	1,106	**2,3,4,5,6**	17.4	1.01	0.82-1.24

Table 5: Adjusted ORs with 95% Confidence Interval for Risk of Stillbirth with Criteria Pollutants

Pollutants	**N**	**Lag days**	**IQR**	**OR**	**95% CI**
$PM_{2.5}$(μg/m^3)					
	689	**2**	9.4	1.06	0.94-1.20
	700	**2,3**	8.4	1.01	0.89-1.15
	706	**2,3,4**	8.0	1.07	0.93-1.22
	714	**2,3,4,5**	7.5	1.08	0.94-1.23
	719	**2,3,4,5,6**	7.1	1.10	0.96-1.25
NO_2(ppb)					
	1,212	**2**	16.4	1.12	0.99-1.27
	1,232	**2,3**	13.6	1.09	0.96-1.24
	1,238	**2,3,4**	12.0	1.07	0.94-1.23
	1,241	**2,3,4,5**	12.2	1.03	0.88-1.20
	1,245	**2,3,4,5,6**	11.9	1.01	0.85-1.19
SO_2(ppb)					
	1,277	**2**	5.1	1.12	1.02-1.24
	1,288	**2,3**	4.7	1.13	1.01-1.26
	1,291	**2,3,4**	4.3	1.14	1.01-1.28
	1,295	**2,3,4,5**	4.2	1.08	0.94-1.23
	1,296	**2,3,4,5,6**	4.0	1.02	0.89-1.17
CO (ppm)					
	931	**2**	0.57	1.20	1.04-1.38
	943	**2,3**	0.53	1.17	1.00-1.37
	947	**2,3,4**	0.51	1.17	0.98-1.40
	954	**2,3,4,5**	0.49	1.15	0.96-1.38
	960	**2,3,4,5,6**	0.49	1.18	0.96-1.44
O_3(ppb)					
	1,079	**2**	19.2	1.01	0.86-1.18
	1,094	**2,3**	17.7	1.06	0.90-1.26
	1,098	**2,3,4**	17.8	1.07	0.88-1.29
	1,103	**2,3,4,5**	17.0	1.03	0.85-1.25
	1,106	**2,3,4,5,6**	17.4	1.02	0.82-1.26

*Adjusted for lag day 2 apparent temperature with 1 df

Table 5a*: Adjusted ORs with 95% Confidence Interval for Risk of Stillbirth with Criteria Pollutants with Constant IQR for all Lag days

Pollutants	**N**	**Lag days**	**IQR**	**OR**	**95% CI**
$PM_{2.5}$(µg/m^3)					
	689	**2**	9.4	1.06	0.94-1.20
	700	**2,3**	9.4	1.02	0.88-1.17
	706	**2,3,4**	9.4	1.08	0.92-1.26
	714	**2,3,4,5**	9.4	1.10	0.93-1.30
	719	**2,3,4,5,6**	9.4	1.13	0.95-1.35
NO_2(ppb)					
	1,212	**2**	16.4	1.12	0.99-1.27
	1,232	**2,3**	16.4	1.11	0.95-1.30
	1,238	**2,3,4**	16.4	1.10	0.921.33
	1,241	**2,3,4,5**	16.4	1.04	0.84-1.28
	1,245	**2,3,4,5,6**	16.4	1.01	0.80-1.27
SO_2(ppb)					
	1,277	**2**	5.1	1.12	1.02-1.24
	1,288	**2,3**	5.1	1.14	1.01-1.28
	1,291	**2,3,4**	5.1	1.16	1.01-1.34
	1,295	**2,3,4,5**	5.1	1.09	0.93-1.28
	1,296	**2,3,4,5,6**	5.1	1.02	0.86-1.22
CO (ppm)					
	931	**2**	0.57	1.20	1.04-1.38
	943	**2,3**	0.57	1.18	1.00-1.40
	947	**2,3,4**	0.57	1.19	0.98-1.45
	954	**2,3,4,5**	0.57	1.18	0.95-1.46
	960	**2,3,4,5,6**	0.57	1.21	0.96-1.53
O_3(ppb)					
	1,079	**2**	19.2	1.01	0.86-1.18
	1,094	**2,3**	19.2	1.07	0.89-1.28
	1,098	**2,3,4**	19.2	1.07	0.87-1.31
	1,103	**2,3,4,5**	19.2	1.03	0.83-1.29
	1,106	**2,3,4,5,6**	19.2	1.02	0.81-1.29

*Same as Table 5 but with ORs with constant IQR

Table 6: ORs with 95% CI for Risk of Stillbirth with One and Two pollutants' Models on Lag day 2

Pollutants	IQR	Stillbirth N	One Pollutant* RR (95% CI)	Two Pollutants RR (95% CI)
$PM_{2.5}$	9.7µg/m^3	595	1.03(0.90-1.17)	0.97(0.82-1.15)
NO_2	16.4 ppb		1.12(0.92-1.36)	1.14(0.91-1.43)
$PM_{2.5}$	9.7µg/m^3	586	1.09(0.96-1.24)	1.01(0.87-1.17)
SO_2	5.1 ppb		1.18(1.02-1.35)	1.17(1.00-1.33)
$PM_{2.5}$	9.7µg/m^3	426	1.09(0.94-1.26)	1.08(0.91-1.27)
CO	0.57 ppm		1.10(0.88-1.36)	1.05(0.82-1.33)
$PM_{2.5}$	9.7µg/m^3	498	1.05(0.90-1.21)	1.05(0.90-1.21)
O_3	19.2 ppm		0.97(0.77-1.21)	0.96(0.77-1.21)
SO_2	5.1 ppb	836	1.20(1.07-1.33)	1.17(1.01-1.34)
NO_2	16.4 ppb		1.20(1.05-1.36)	1.05(0.87-1.27)
SO_2	5.1 ppb	831	1.12(1.00-1.25)	1.06(0.93-1.20)
CO	0.57 ppm		1.22(1.05-1.41)	1.18(1.00-1.39)
SO_2	5.1 ppb	767	1.17(1.04-1.32)	1.18(1.03-1.34)
O_3	19.2 ppm		1.01(0.83-1.22)	1.06(0.88-1.28)
NO_2	16.4 ppb	529	1.24(1.02-1.50)	1.09(0.84-1.40)
CO	0.57 ppm		1.26(1.05-1.51)	1.19(0.94-1.51)
NO_2	16.4 ppb	849	1.15(0.98-1.34)	1.16(0.99-1.36)
O_3	19.2 ppm		0.94(0.78-1.14)	1.01(0.84-1.22)
CO	0.57 ppm	527	1.31(1.08-1.59)	1.36(1.11-1.67)
O_3	19.2 ppm		0.98(0.78-1.23)	1.12(0.86-1.46)

* N different from Table 5 because only subjects with data from both pollutants were tabulated

Table 7: Effect Modification of CO with the Risk Factors of Stillbirth on Lag day 2

Risk Factors	**OR (95% CI)**	**p-value**
Maternal Age*		
< 25 Years	0.95(0.69-1.31)	0.34
25-34 Years	1.16(0.95-1.41)	
≥ 35Years	1.30(0.90-1.87)	0.16
Maternal Race**		
White non-Hispanics	1.31(1.00-1.72)	
Black non-Hispanics	0.98(0.68-1.43)	0.93
Other non-Hispanics	0.85(0.50-1.43)	0.54
Hispanics	0.82(0.58-1.18)	0.28
Maternal Education		
≤ High School	0.88(0.67-1.17)	0.39
> High School	1.43(0.94-2.17)	
Prenatal Care		
None	0.96(0.72-1.28)	0.77
Ever	1.20(0.84-1.70)	
Smoking		
Yes	0.96(0.62-1.50)	0.88
No	1.18(1.01-1.38)	
Placental Abruption		
with	0.69(0.50-0.95)	0.02
without	1.33(1.13-1.56)	
Season		
Winter	1.07(0.68-1.66)	0.78
Summer	1.08(0.74-1.57)	

*OR for the IQR increase in pollutant concentration

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CONCLUSION

We found persistent racial disparities in the rates of stillbirth with the highest rates of stillbirth in black non-Hispanic women. Also the stillbirth rate was higher for foreign born women compared to US born women. Although there was a decrease in the rate of stillbirth in New Jersey from 1997 to 2005, the decline was only for white non-Hispanics and the rates have not changed for other race/ethnicity groups. The risk of stillbirth was higher in women 35 years or older and in women with no prenatal care. Pregnancy complications associated with increased risk of stillbirth were placental abruption, eclampsia, diabetes mellitus and preeclampsia. Over time the proportion of stillbirths associated with the following risk factors increased: no post-High school education, no prenatal care and diabetes mellitus. However, there was a decrease in the apparent role of placental abruption.

There was an association of stillbirth both with trimester specific and with short term increase in ambient air pollution. The effect of trimester specific exposure was assessed by evaluating the risk of stillbirth associated with incremental increase in ambient air pollution in each of the three trimesters of pregnancy. There was an increased risk of stillbirth with increase in mean concentrations of NO_2 in the first trimester, $PM_{2.5}$ in the first and second trimesters and with SO_2 in all three trimesters. The acute effect of short term increase in ambient air pollution was assessed by evaluating the risk of stillbirth associated with transient increase in mean concentration of ambient air pollution in 2 days prior to stillbirth by using a case crossover design. There was an increased risk of stillbirth with short term increase in mean concentration of SO_2 and CO in lag day 2.

Overall, these results add to the evidence that ambient air pollution is associated with the risk of stillbirth, but the susceptible period of gestation when exposure is harmful for the fetus varies by specific pollutant. Based on statistically significant findings an extended exposure to NO_2 and $PM_{2.5}$ was harmful in early gestation while SO_2 was harmful in all three trimesters. However, the OR for stillbirth exceeded 1.0 for all four pollutants in each trimester of pregnancy. There was also an association of stillbirth with short term increase in SO_2 and CO and although OR exceeded 1.0 for other pollutants, the associations were not statistically significant.

These findings suggest that extended exposure to $PM_{2.5}$ was associated with stillbirth but both extended and short term increase in the gaseous pollutants (NO_2, SO_2, CO) was harmful for the fetal survival. As the sources of these pollutants are both traffic related and industrial, it may be possible that exposure to ambient air pollution of any kind is harmful for fetal survival and both extended and short term exposure to ambient air pollution during pregnancy may be associated with stillbirth.

The biologic mechanism by which ambient air pollution effects fetal survival may be different between extended exposure in the different trimesters and short term exposure. It may be possible that trimester specific increase in the mean concentration of ambient air pollutants causes hypoxic and immune mediated injury to rapidly proliferating cells of fetus or to growing placenta leading to fetal death later in pregnancy. Short term increase in ambient air pollutants may cause fatal damage to the fetus by direct transfer of pollutants across placental barrier leading to stillbirth.

Although we found an association of ambient air pollution with stillbirth, further studies are needed to confirm these findings and to specify the effects of extended and short term exposure of specific pollutants.

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