Maternal Risk Factors Associated with Fetal and Infant Mortality

Background:

Maternal chronic medical conditions, infectious diseases, psychiatric conditions, parental and environmental exposures, and psychosocial stressors have an established impact on fetal and neonatal health. Although countless studies have shown relationships between maternal risk factors and low-birth weight, pre-term birth, and fetal and infant morbidity (e.g. reduced apgar scores), fewer have demonstrated direct associations with fetal and infant death.

This literature review focuses on maternal risk factors directly associated with fetal and infant mortality including the following: pre-term birth, low birth weight, obesity, diabetes, hypertension, alcohol, tobacco, HIV, rural residence, race, and psychosocial stressors.

Research Study Results:

Pre-term birth

(Matthews 2010) According to the 2006 infant mortality statistics from the nationally linked birth/infant death data set, infant mortality rates were highest for very preterm (less than 32 weeks) infants, and the risk decreased sharply with increasing gestational age. In 2006, the infant mortality rate for very preterm infants (175.94/ 1,000 live births) was 74 times the rate of 2.39 for term infants. The mortality rate for infants born at 32–33 weeks of gestation was 16.19, nearly seven times the rate for term infants. Although mortality falls with increasing gestational age, even infants born only a few weeks early have a substantially increased risk of death when compared with term infants. In 2006, the infant mortality rate for late preterm infants (34–36 weeks of gestation) was 7.08, 2.9 times the rate for term infants. Even within the term period, infants born at 37–39 weeks of gestation had mortality rates that were 28 percent higher than those for infants born at 40–41 weeks of gestation.

(Khashu 2009) To compare the mortality and morbidity of late-preterm infants to those born at term, data from the British Columbia Perinatal Database Registry were analyzed including all singleton births between 33 and 40 weeks' gestation from April 1999 to March 2002 in the province of British Columbia, Canada. This birth cohort was divided into late preterm (33–36 weeks, n=6,381) and term (37–40 weeks, n= 88,867) groups. The stillbirth rate and perinatal, neonatal, and infant mortality rates were significantly higher in the late-preterm group compared to the term group.

(McIntire 2008) To analyze neonatal mortality and morbidity rates at 34, 35, and 36 weeks of gestation compared with births at term over the past 18 years and to estimate the magnitude of increased risk associated with late preterm births compared with births later in gestation, a retrospective cohort study was conducted on all live-born singleton infants between 34 and 40 weeks of gestation and without anomalies that were delivered to women who received prenatal care in The University of Texas Southwestern Medical Center hospital system. Late preterm

neonatal mortality rates per 1,000 live births were 1.1, 1.5, and 0.5 at 34, 35, and 36 weeks, respectively, compared with 0.2 at 39 weeks (P<.001).

(Tomashek 2007) To assess differences in mortality between late-preterm (34-36 weeks) and term (37-41 weeks) infants, researchers used U.S. period-linked birth/infant death files for 1995 to 2002 to compare overall and cause-specific early-neonatal, late-neonatal, post-neonatal, and infant mortality rates between singleton late-preterm infants and term infants. Infant mortality rates in 2002 were three times higher in late-preterm infants than term infants (7.9 versus 2.4 deaths per 1,000 live births); early and post-neonatal rates were six and two times higher, respectively.

(Larroque 2004) A prospective observational population-based study was conducted to evaluate the outcome for all infants born before 33 weeks gestation until discharge from hospital, including all births or late terminations of pregnancy for fetal or maternal reasons between 22 and 32 weeks gestation in nine regions of France in 1997. Survival increased with gestational age: 31% of all infants born alive at 24 weeks survived to discharge, 78% at 28 weeks, and 97% at 32 weeks.

Low birth weight

(Zeitlin 2010) To assess the impact of being small for gestational age on very preterm mortality and morbidity rates by using different birth-weight percentile thresholds, a study was conducted which included singletons and twins alive at onset of labor between 24 and 31 weeks of gestation without congenital anomalies for very preterm births in 10 European regions in 2003 (n = 4,525). The mortality rate was significantly higher for infants with birth-weights <25th percentile when compared with the 50th to 74th percentile.

(Matthews 2010) According to the 2006 period infant mortality statistics from the linked birth/infant death data set, infant mortality rates were much higher for low birth weight (less than 2,500 grams) infants (55.38 per 1,000) than for infants with birth weights of 2,500 grams or more (2.24). The infant mortality rate for very low birth weight (less than 1,500 grams) infants was 240.44, more than 100 times the rate for infants with birth weights of 2,500 grams or more.

(Kaushik 1998) A study conducted in the department of pediatrics and its neonatology unit at Indira Gandhi Medical College, Shimla examined all live born babies between July 1994 to June 1995, and found that although low birth weight babies accounted for 27.8% of the live births, they accounted for 79.5% of neonatal deaths.

(Wilcox 1992) Data from 400,000 singleton births in the Norwegian Medical Birth Registry were used to distinguish the contributions to perinatal mortality made by gestational age and by relative birth weight at each gestational age. Results showed that relative mortality rates across gestational age groups were highest at the lowest birth weights and fell rapidly as weights increased. Perinatal mortality ranged from 4.3/1,000 births at 40 weeks gestational age to 364.9/ 1,000 births at 28-31 weeks (RR=85 comparing 28-31 weeks to 40 weeks).

Obesity

(Mantakas 2010) This study examined the influence of body mass index (BMI) in pregnancy on rates of adverse pregnancy outcome in overweight women who had never given birth (nulliparous). A retrospective review was conducted of all nulliparous women whose BMI was recorded at booking between January 2001 and November 2008 at the Jessop Wing of the Royal Hallamshire Hospital in Sheffield, UK. The women all delivered singleton babies and information was obtained from the hospital's database. All the women were stratified into five groups (underweight, normal, overweight, obese, and morbidly obese) and different BMI range groups were compared with the group of women with a normal BMI (20– 25). The stillbirth rate was associated with increasing obesity with RR 16.7 (CI 4.9–56) for the morbidly obese women compared to women with a normal BMI.

(Owens 2010) To examine the impact of obesity on pregnancy outcome in glucose-tolerant women, women with normo-glycemia were examined from the Irish Atlantic Diabetes in Pregnancy network. Reported miscarriages were significantly increased in obese women compared to women with normal pre-pregnancy body mass index (BMI). Fourteen (0.6%) stillbirths and two (0.1%) neonatal deaths occurred; however, BMI was not a positive predictor for these outcomes.

(Chen 2009) To study the association between maternal obesity and the risk of infant death a case-control study was conducted using 4,265 infant deaths as cases and 7,293 randomly selected live births. Compared with normal weight women who gained 0.66 to 0.97 pounds/week during pregnancy, obese women had significantly increased risk of neonatal death and overall infant death.

(Nohr 2007) To examine the association between pre-pregnancy body mass index (BMI) and neonatal mortality, 85,375 live-born singletons of mothers in the Danish National Birth Cohort (1996–2002) interviewed during the second trimester were assessed. Compared with infants of mothers who were at a normal weight before pregnancy, neonatal mortality was increased in infants of mothers who were overweight or obese.

(Salihu 2007) To estimate the risk for stillbirth among three generally accepted obesity subtypes based on severity, the Missouri maternally linked cohort data containing births from 1978 to 1997 was used to examine pre-pregnancy weight and height. The study showed that obese mothers were about 40% more likely to experience stillbirth compared with non-obese gravidas. Furthermore, the risk for stillbirth increased in a dose-dependent fashion with increase in body mass index (BMI).

(Nohr 2006) Pre-pregnancy body mass index (BMI) and fetal death were examined in the Danish National Birth Cohort among 54,505 pregnant women who participated in a comprehensive interview during the second trimester to examine the association between high pre-pregnancy BMI and fetal death, allowing for the effects of gestational age, weight gain, and maternal diseases in pregnancy. Results showed that pre-pregnancy obesity was associated with an increasing excess risk of fetal death with advancing gestation.

(Kristensen 2005) A large prospective cohort study based in Denmark evaluated the association between maternal pre-pregnancy weight and the risk of stillbirth and neonatal death in a large cohort study, taking into account a number of potential confounding factors. A total of 24,505 singleton pregnancies were included in the analyses. Pre-pregnancy body mass index (BMI) was used to classify the population as underweight, normal weight, overweight, and obese. Compared with women of normal weight, the relative risk of stillbirth and neonatal death in children of obese women more than doubled in the analyses.

(Cedergren 2004) In a prospective population-based cohort study, 3,480 women with morbid obesity and 12,698 women with a body mass index (BMI) between 35.1 and 40 were compared with normal-weight women to evaluate whether morbidly obese women have an increased risk of pregnancy complications and adverse perinatal outcomes. Compared to normal weight mothers, overweight and obese mothers were associated with a significantly increased risk of antepartum stillbirth and early neonatal death. The association was stronger in morbidly obese women.

(Baeten 2001) A population-based cohort study on the effect of maternal pre-pregnancy obesity or overweight on pregnancy complications and adverse pregnancy outcomes was conducted on 96,801 singleton births to nulliparous women from Washington State birth certificate data between 1992 and 1996. The risk of infant death within one year of birth was significantly higher for obese women (BMI $\geq$ 30.0) than for lean women (BMI < 20.0).

(Sebire 2001) A retrospective analysis of data from a validated maternity database system was analyzed to examine the maternal and fetal risks of adverse pregnancy outcome in relation to maternal obesity. Compared to women with normal BMI, intrauterine death was significantly more common in obese pregnant women.

(Stephansson 2001) To investigate whether the risk of antepartum stillbirth increases with body mass index during early pregnancy, a population-based case-control study was conducted on 649 women with antepartum stillbirths and 690 control subjects among Swedish nulliparous women. Compared with infants of lean mothers (body mass index $\leq$19.9 kg/m2), infants born to overweight and obese mothers showed significantly increased risks for antepartum death.

(Cnattingius 1998) In a population-based cohort of 167,750 women in Sweden, pre-pregnancy body mass index (BMI) was used to categorize women lean, normal, overweight, and obese. The BMI categories were compared to examine the effect of pre-pregnancy BMI to the risk of late fetal death and early neonatal death. Among nulliparous women, the odds ratios for late fetal death were increased among women with higher body-mass indexes as compared with lean women (BMI < 20.0), as follows: normal women, 2.2 (CI 1.2 to 4.1); overweight women, 3.2 (CI 1.6 to 6.2); and obese women, 4.3 (CI 2.0 to 9.3). Among parous women, only obese women had a significant increase in the risk of late fetal death (odds ratio, 2.0; CI 1.2 to 3.3).

(Naeye 1990) A large prospective cohort study examined the relationship of relative maternal pre-gravid body weight to pregnancy outcome including perinatal mortality and pre-term birth. Data for the analyses came from the Collaborative Perinatal Study (CPS) of the National Institute of Neurological and Communicative Disorders and Stroke. The CPS was set up to identify

antepartum and subsequent events that affect children's morbidity, mortality, and development. CPS prospectively followed the course of 58,957 children from before birth to age 7 years in 12 medical school-affiliated hospitals in different regions of the United States between 1959 and 1966. The study found a significant progressive increase in perinatal mortality rates with increasing maternal relative body weight. Pre-term birth was responsible for most of the increases in perinatal mortality.

(Lucas 1988) In a study of 284 pre-term infants, researchers examined the effect of maternal obesity on mortality to 18 months of age (corrected for prematurity). Complete data from one of the five centers participating in a study examining the effect of diet on early growth of low birth weight infants were examined. The study analyzed birth weight, gestation, mother's weight and height, and whether the infant died for all infants born in the centre. The relative risk of death by 18 months post-term was nearly four times greater in infants born to obese mothers than in those born to normal weight mothers.

(Garbaciak 1985) To determine the effect of obesity when no prenatal complications are present, on perinatal mortality, maternal and infant data were abstracted from deliveries occurring at 18 institutions within the University of Illinois perinatal network. The study includes 16,858 records of women who delivered in 1982. Among 2,597 women with antenatal complications, there was a significant increase in perinatal mortality in the obese and morbidly obese women; however, there was not a significant association between obesity and perinatal mortality in the absence of antenatal complications.

Diabetes

(Reddy 2010) A retrospective cohort study of pre-pregnancy risk factors compared 712 singleton antepartum stillbirths with 174,097 singleton live births at or after 23 weeks of gestation to identify possible pre-pregnancy risk factors for antepartum stillbirth and to determine whether these factors identify women at higher risk for term stillbirth. In adjusted multivariable analyses, pre-existing diabetes was independently associated with increased risk of stillbirth; (2.7, CI 1.8–3.9).

(Persson 2009) To perform comparative analyses of obstetric and perinatal outcomes between type 1 diabetic pregnancies and the general obstetric population, a population-based study was conducted using records from the Medical Birth Registry between 1991 and 2003, covering 98% of all pregnancies in Sweden. A total of 5,089 type 1 diabetic pregnancies and 1,260,207 control pregnancies were included. Stillbirth and perinatal mortality were significantly more common in type 1 diabetic than in control pregnancies.

(Dunne 2009) Irish investigators prospectively followed 104 singleton pregnancies from women diagnosed with pre-gestational diabetes to evaluate pregnancy outcome along the Irish Atlantic seaboard from 2006-2007. Significant associations were found with stillbirth and perinatal mortality, whose rates were 5 and 3.5 times that of the background population, respectively.

(Macintosh 2006) To provide perinatal mortality and congenital anomaly rates for babies born to women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland, investigators conducted a national population based pregnancy study on a cohort of 2,359 pregnancies to women with type 1 or type 2 diabetes. Perinatal mortality was comparable in babies of women with type 1 and type 2 diabetes and was nearly four times higher than that of the general maternity population.

(Clausen 2005) Investigators retrospectively studied all women with pre-gestational type 2 diabetes referred to the Department of Obstetrics, Copenhagen University Hospital, Rigshospitalet, Denmark, from January 1996 to December 2001 for antenatal care and delivery to evaluate the frequency of maternal complications and serious adverse fetal outcome. A total of 80 singleton pregnancies in women with pre-gestational type 2 diabetes referred from either general practitioners (44%) or hospital unit (56%) were registered. Women with type II diabetes were compared to women with type I diabetes and to the general population for the same time period. The perinatal mortality in pregnancies complicated by type 2 diabetes was four times that of pregnancies complicated by type I diabetes, and nine times that of the general population.

(Jensen 2004) In a nationwide population-based study in Denmark, all pregnancies in women with type I diabetes were prospectively followed to compare pregnancy outcomes in women with type I diabetes to the general population. Results showed that type I diabetes was significantly associated with increased rates perinatal mortality and stillbirth.

(Evers 2004) To investigate maternal, perinatal, and neonatal outcomes of pregnancies in women with type 1 diabetes in the Netherlands, a nationwide prospective cohort study of 323 women with type 1 diabetes was conducted. The perinatal mortality rate among women with type 1 diabetes was 3.5 times higher than that of the general population.

(Boulot 2003) A cross-sectional study was conducted in 12 perinatal centers in France in 2000–2001 to investigate perinatal mortality outcomes, major congenital malformations, and preterm delivery among women with type 1 and type 2 diabetes. Women with increased blood glucose in the first trimester had higher rates of perinatal mortality (9.2 vs. 2.5; odds ratio 3.9; CI 1.5–9.7; $P<0.005$) than women with normal blood glucose in the first trimester.

(Penney 2003) To determine the outcomes of pregnancies in women with pre-existing, type 1 diabetes, investigators conducted a prospective, population-based study with a cohort of 273 women with type 1 diabetes with a pregnancy ending in miscarriage, abortion or delivery. Compared to the Scottish birth rate in 1999, Scottish babies born to mothers with type 1 diabetes showed substantially higher rates of stillbirth, perinatal death, and infant death.

(Schmidt 2001) The Brazilian Gestational Diabetes Study evaluated the new World Health Organization (WHO) and American Diabetes Association (ADA) criteria for gestational diabetes mellitus (GDM) by following 4,977 women who attended general prenatal clinics to examine macrosomic birth, preeclampsia, and perinatal death. All women were requested to undertake a standardized two-hour 75-gram oral glucose tolerance test (OGTT) between their estimated 24^{th} and 28^{th} gestational weeks and were then followed to delivery. There was a significant association between perinatal death and gestational diabetes mellitus using American Diabetes

Association criteria (relative risk: 3.10, 1.42– 6.47). Though not statistically significant, World Health Organization criteria also showed an increased risk (1.59, 0.86 –2.90).

(Cundy 2000) To report observational data on perinatal mortality in Type 2 diabetes mellitus (DM) from a population with a high background rate of this disorder, a study of pregnant women with Type 1, Type 2, and gestational diabetes mellitus (GDM) were compared to pregnant women without diabetes visiting the same hospital over a 12 year period. The study showed that late fetal death among women with Type 2 DM is significantly increased compared to women without established diabetes or GDM. Intermediate fetal death and early neonatal death were also increased but not significantly so.

(Casson 1997) A cohort of insulin dependent diabetic women identified in a geographically discrete area in the north west of England was followed to monitor pregnancy loss, congenital malformations, and fetal growth. Pregnancy outcome recording included termination for social and medical reasons, spontaneous abortions, stillbirths, and neonatal (0-28 days) and post-neonatal (29 days to 1 year) deaths. The perinatal mortality rate was over four times and the stillbirth rate five times that in the general population of England and Wales and the population of Merseyside and Cheshire over the same period.

(Hawthorne 1997) To determine whether the St Vincent declaration (1989) target of diabetic pregnancy outcome approximating non-diabetic pregnancy outcome is near to being achieved (In 1989 the St Vincent declaration stated as a five year goal that the "outcome of diabetic pregnancy should approximate that of the non-diabetic pregnancy."), researchers prospectively followed 111 diabetic women who attended an antenatal clinic in 1994 to examine pregnancy outcome. Significant associations were found between diabetic pregnancies and increased risks of perinatal mortality (OR=5.83, CI=2.27 to 12.70) and the neonatal mortality (OR=15.0; CI=6.77 to 33.10).

Hypertension

(Reddy 2010) A retrospective cohort study of pre-pregnancy risk factors compared 712 singleton antepartum stillbirths with 174,097 singleton live births at or after 23 weeks of gestation to identify possible pre-pregnancy risk factors for antepartum stillbirth and to determine whether these factors identify women at higher risk for term stillbirth. In adjusted multivariable analyses, chronic hypertension was independently associated with increased risk of stillbirth; 2.0 (CI 1.5–2.8).

(Ananth 2010) To examine trends in stillbirth and neonatal mortality related to pregnancy-induced hypertension (PIH), researchers carried out a population-based study of 57 million singleton live births and stillbirths (24-46 weeks gestation) in the United States between 1990 and 2004 and estimated rates and adjusted odds ratios of stillbirth and neonatal death in relation to PIH. For the two time periods studied (1990-1991 and 2003-2004), risk of stillbirth (1.37; CI 1.24-1.50 for 1990-1991 & 1.52; CI 1.40-1.64 for 2003-2004) and neonatal death (1.32; CI 1.20-1.44 for 1990-1991 & 1.30; CI 1.18-1.43 for 2003-2004) were significantly higher for first births

among women with PIH. Risks were even greater with second or higher births, showing a statistically significant linear trend with increasing order of birth.

(Vanek 2004) A retrospective comparison of all singleton, term (>36 weeks) deliveries between 1988 and 1999 in Israel, complicated with chronic hypertension, was undertaken to determine the risk factors and pregnancy outcome of patients with chronic hypertension during pregnancy after controlling for superimposed preeclampsia. After adjustment for superimposed preeclampsia, pregnancies complicated with chronic hypertension had a significantly higher rate of perinatal mortality.

(Ferrer 2000) The San-Antonio Evidence-based Practice Center reviewed 215 articles that met multiple pre-specified patient selection, study population, and design criteria to conduct a systematic review of evidence relating to management of mild chronic hypertension during pregnancy, including associated risks, benefits, and harms of treatment with antihypertensive agents, non-pharmacologic measures, and aspirin and benefits of various monitoring strategies. Forty-six studies consistently showed that chronic hypertension triples the risk for perinatal mortality (odds ratio [OR] 3.4; 95% confidence interval [CI] 3.0, 3.7)

(Ananth 1995) To assess the effect of hypertensive disorders of pregnancy on the risk of stillbirth a retrospective cohort of approximately 400,000 pregnancies identified through the birth and fetal death certificates in North Carolina between 1988 and 1991 were examined. Pregnancies among chronic hypertensive patients were more than twice as likely to result in early stillbirth compared to pregnancies among non-hypertensive patients.

(Walles 1994) To identify markers for late fetal death based on routinely obtained data from maternal health care units, prospectively recorded data were obtained from maternal health care units belonging to five delivery units. In all, 233 consecutive cases of singleton pregnancy involving late fetal death were identified between 1983 and 1989. As a control for each case, the next consecutive mother giving birth to a live infant at the same delivery unit was selected. A significantly increased risk was seen in women with medical treatment for essential hypertension.

(Rey 1994) A longitudinal cohort study was performed between 1987 and 1991 in Montreal, Quebec, Canada, including 337 pregnancies in 298 women with chronic hypertension to assess pregnancy outcomes in women with chronic hypertension from a population with a maternal mortality rate of 12 deaths per 1,000 live births. Perinatal mortality was significantly more frequent in chronic hypertensive women compared to the general population.

Alcohol

(Henriksen 2004) Danish investigators studied the association between female and male alcohol intake and the risk of spontaneous abortion. Alcohol intake was tracked by monthly questionnaire and spontaneous abortions were detected only by pregnancy test (urinary human chorionic gonadotropin). Female alcohol intake was associated with 2–3 times the adjusted risk of spontaneous abortion compared with no intake, and male alcohol intake was associated with

2–5 times the adjusted risk, although only the adjusted relative risks for 10 or more drinks/week compared with no intake were statistically significant.

(Rasch 2003) To study the association between cigarette, alcohol, and caffeine consumption and the occurrence of spontaneous abortion, Danish investigators conducted a case-control study with 330 women with history of spontaneous abortion and 1,168 pregnant women receiving antenatal care as controls. There was a significant association between alcohol consumption (5 or more units of alcohol per week) during pregnancy and spontaneous abortion.

(Kesmodel 2002) Danish researchers examined the association between maternal alcohol consumption during pregnancy and the risk of spontaneous abortion in a cohort of pregnant women through questionnaires received from women representing 24,679 singleton pregnancies. There was a significant association between women consuming >=5 drinks/week and an increase in spontaneous abortion in the first trimester (7-11 completed weeks of gestation). No association was found between alcohol consumption in the second trimester and spontaneous abortion.

(Alm 1999) Researchers found a significant association between heavy postnatal intake of alcohol and an increased risk for sudden infant death syndrome (SIDS), based on analyses from the Nordic epidemiological SIDS case control study. There was not a significant association between prenatal intake of alcohol and SIDS after adjusting for social variables.

(Windham 1997) In a prospective cohort study of over 5,000 pregnant women an interview in the first trimester asked about alcohol consumption during and before pregnancy to investigate the pattern and timing of alcohol consumption before and during pregnancy in relation to risk of spontaneous abortion. They found an increased risk of spontaneous abortion in women who drank more than three drinks per week during the first trimester, with an adjusted OR of 2.3 (CI= 1.1-4.5). Consumption of alcohol before pregnancy was not strongly associated with spontaneous abortion.

(Blair 1996) A two-year population based case-control study of 195 babies who died and 780 matched controls investigated the effects of exposure to tobacco smoke and of parental consumption of alcohol and illegal drugs as risk factors for SIDS. Alcohol use was higher among index than control mothers but was strongly correlated with smoking and on multivariate analysis was not found to have any additional independent effect.

(Long 1994) A case-control study of 95 cases who presented with confirmed spontaneous first trimester miscarriage and 3,348 controls that went on to deliver a live child after 28 weeks were examined to describe patterns of drinking and smoking related to first trimester miscarriage. There was a significant association between drinking alcohol in the early stages of pregnancy and an increased relative risk of first trimester miscarriage. Compared to non-drinkers, the relative risks for light drinkers (1-10 units/week), moderate drinkers (11-14 units/week), and heavy drinkers (>15 units/week) were 3.79 (CI 1.18-12.17), 8.36 (CI 2.52-27.69), and 5.08 (CI 1.18-21.84) respectively.

(Scragg 1993) Researchers in New Zealand investigated alcohol consumption in relation to bed-sharing as risk factors for SIDS. Results showed no association between maternal alcohol consumption and SIDS, and no association between bed-sharing, maternal alcohol consumption and SIDS.

(Armstrong 1992) Surveys of 56,000 women examining occupational factors and pregnancy outcomes were analyzed to study the relationship of smoking, alcohol, and coffee on spontaneous abortion. There was a significant association between alcohol consumption and spontaneous abortion with increasing odds with increasing drinking volume. There was a significant association between alcohol consumption and spontaneous abortion with increasing odds with increasing drinking volume. Compared to non-drinkers, odds ratios of those who drank 1-2, 3-6, 7-20, and >20 drinks/week were 1.11 (CI 1.05-1.18), 1.23 (CI 1.13-1.34), 1.47 (CI 1.31-1.65), and 1.82 (CI 1.21-2.34) respectively.

(Southall 1987) A case-control study of siblings of SIDS cases showed that mothers of siblings consumed alcohol more often during pregnancy than did mothers of controls.

Tobacco

(Wikström 2010) To examine the effect of Swedish snuff on pregnancy complications, researchers conducted a population-based cohort study to estimate the risk of stillbirth in snuff users, light smokers (1-9 cigarettes/day), and heavy smokers (≥10 cigarettes/day), using nontobacco users as reference. Compared with nontobacco users, snuff users had a significantly increased risk of stillbirth with higher odds associated with preterm birth. Increased risks were also seen for light and heavy smokers.

(Khoury 2004) A secondary analysis of data on pregnant women with type I diabetes from an interdisciplinary program of Diabetes in Pregnancy showed that early pregnancy smoking was associated with a significant increased risk of spontaneous abortion after controlling for confounders.

(Wisborg 2000) To study the association between smoking during pregnancy and SIDS, Danish researchers conducted a study using prospectively collected data, making it possible to account for a number of potential confounders. Three questionnaires were received from 24,986 women booking for delivery at the Department of Obstetrics and Gynaecology, Aarhus University Hospital, from September 1989 to August 1996. There was a significant association between maternal smoking and an increased risk of SIDS. Children of smokers had more than three times the risk of SIDS compared with children of non-smokers and the risk of SIDS increased with the number of cigarettes smoked per day. (Wisborg 2001) The same cohort was used to evaluate the association between exposure to tobacco smoke in utero and the risk of stillbirth and increased mortality in the first year of life. Results showed significant associations between exposure to tobacco smoke in utero and both increased stillbirth and increased infant mortality.

(Pollack 2000) Researchers assessed the effects of maternal smoking on birth outcomes among singletons and twins by linking twins with their siblings in a 1995 Perinatal Mortality Data Set.

Among singleton births there were significant associations between maternal smoking and infant mortality in both the 1-10 cigarettes/day group (adjusted relative risk: 1.60; CI 1.38-1.85) and the >10 cigarettes/day group (1.73; CI 1.45-2.01) when compared to non-smokers. No significant associations were observed when evaluating twins.

(Cooke 1998) A case control study among 104 SIDS cases and 206 controls matched for place and date of birth, examined maternal smoking and SIDS risk. Logistic regression analysis showed SIDS to be significantly related to maternal smoking (OR=4.8; CI=2.76-8.53).

(Blair 1996) A two-year population based case-control study of 195 babies who died and 780 matched controls investigated the effects of exposure to tobacco smoke and of parental consumption of alcohol and illegal drugs as risk factors for sudden infant death syndrome. Significantly more index than control mothers smoked during pregnancy. Paternal smoking had an additional independent effect when other factors were controlled for. The risk of death rose with increasing postnatal exposure to tobacco smoke, which had an additive effect among those also exposed to maternal smoking during pregnancy. The population attributable risk was over 61%, which implies that the number of deaths from the syndrome could be reduced by almost two thirds if parents did not smoke.

(Scragg 1993) Researchers in New Zealand investigated maternal smoking in relation to bed-sharing as risk factors for SIDS. Compared to infants not exposed to bed-sharing and smoking, those exposed to both had a significantly increased risk for SIDS.

(Wilcox 1993) To test the hypothesis that the lower birth weight of infants born to smokers is unrelated to their higher perinatal mortality, a Missouri vital statistics file from 1980-1984 linking birth, fetal death, and neonatal death records compared rates of perinatal mortality and maternal smoking. Perinatal mortality was 14.5/1,000 infants born to non-smokers, compared with 10.4 for unexposed infants. Infants exposed to maternal smoking were shown to have a higher risk of mortality across all relative birth weights.

(Schoendorf 1992) Data from the 1988 National Maternal and Infant Health Survey was used to conduct a case-control study of normal birth weight infants to examine the relationships between prenatal and postnatal exposure to tobacco smoke and SIDS risk. After adjustment for demographic risk factors, the odds ratio for SIDS among normal birth weight infants showed a significant increase at approximately 2 for passive exposure and 3 for combined exposure.

(Haglund 1990) A large prospective Swedish study investigating the influence of maternal smoking and other risk factors on SIDS in an unselected, homogeneous low-risk population (N=279,938), found that smoking doubled the risk for SIDS and observed a clear dose-response relation by amount smoked. Maternal smoking also seemed to influence the time of death, as infants of smokers died at an earlier age.

HIV

(Venkatesh 2010) Researchers conducted a prospective cohort study of 848 HIV-exposed infants receiving antiretroviral post-exposure prophylaxis from three hospitals in South Africa to

examine maternal and infant correlates of infant morbidity and mortality within the first three months of life. Mortality was significantly higher with infant HIV infection.

(Brocklehurst 1998) To investigate the association between maternal HIV infection and perinatal outcome, a systematic review of the literature and meta-analysis was conducted on 31 eligible studies from 1983-1996. The summary odds ratios showed strong associations between HIV exposure and spontaneous abortion, stillbirth, and infant mortality. A significant association was also seen with perinatal mortality. Sensitivity analyses also showed that the association between infant mortality and maternal HIV infection was stronger in studies conducted in developing countries when compared with developed countries, and much stronger associations were seen with studies of higher methodological quality than those of poorer quality.

(Bloland 1995) To examine the relationship between maternal HIV infection and infant mortality as a first step in investigating the possibility of increased vertical transmission to HIV due to placental malaria infection, researchers conducted a retrospective analysis of data from a cohort of mothers and infants in rural Malawi conducted from 1987 to 1990. Infant mortality rates were significantly higher among children born to HIV sero-positive women compared to those born to HIV sero-negative women.

Rural Residence

(Larson 1997) The association between non-metropolitan residence and the risk of poor birth outcome in the United States was examined using the records of 11.06 million singleton births in the United States between 1985 and 1987 to examine and compare non-metropolitan and metropolitan rates of poor birth outcome in order to assess the importance of non-metropolitan residence as a risk factor for poor birth outcome and inadequate prenatal care. Results showed that non-metropolitan residence was associated with greater risk of post-neonatal mortality at the national level (relative risk: 1.11; $P < 0.01$). In particular the south was shown to be considerably disadvantaged with respect to post-neonatal mortality. No association was observed between non-metropolitan residence and increased risk of neonatal mortality.

(Rock 1994) A study among Illinois residents examined differences in access to prenatal care and birth outcomes comparing rural and urban residents. Using records from 1983, rural fetal and post-neonatal death rates were higher ($R<0.05$ and $P<0.01$, respectively) than for urban areas. Records from 1988 were also analyzed and although rural fetal and post-neonatal death rates were higher than for urban areas the results were not statistically significant.

(Larson 1992) To examine rural and urban differences in rates, neonatal linked birth and death certificates of all infants born in Washington state to state residents in 1984 through 1988 were used. Although no significant differences were seen when comparing rural and urban residence neonatal death rates, the neonatal death rate for rural residents delivering at urban hospitals was significantly higher than for urban residents delivering at urban centers and rural residents delivering at rural centers.

(Clarke 1991) Using Florida state vital statistics data, researchers linked birth and death records of all persons born in 1987 to identify the effects of maternal residence (urbanicity along a five category rural-urban continuum) on infant mortality. Outcome data showed that residence did not have an independent direct effect on infant mortality when the influence of the other risk factors was controlled, although the study authors conclude it does influence mortality indirectly through its association with key risk factors.

(Allen 1991) To determine if there is a correlation between the availability of obstetrical services and the infant mortality rate in nonmetropolitan counties, physician (those who accept obstetrical patients) to birth ratios were analyzed in conjunction with infant mortality rates for nonmetropolitan counties in Indiana from 1986-1988. There was a significant negative correlation (-.38; $P > 0.02$) between physician availability and infant mortality in Indiana's nonmetropolitan counties. An R^2 of 14.44 was calculated, implying that 14.44% of Indiana's infant mortality in nonmetropolitan counties is explained by a lack of physician availability.

Race

(Wingate 2010) Deliveries to U.S. white, black, and Hispanic mothers were selected from the NCHS linked live birth-infant death cohort and fetal deaths files (1990-1991 and 2001-2002) to compare changes in overall and gestational age-specific proportions and rates of fetal death, first-day death (<24 hour), and combined fetal/first-day death from 1990-1991 to 2001-2002. Changes were considered by race/ethnicity. While the fetal mortality rate among whites and Hispanics declined 4.32 and 12.82 percent, for blacks, the fetal mortality rate increased 4.06 percent between 1990–1991 and 2001–2002. Despite overall reductions in perinatal and 24-hour mortality, black rates in all outcomes maintained a twofold disparity.

(Kitsantas 2010) To examine predictors of neonatal and post-neonatal mortality among infants born to black, white, and Hispanic women linked birth/infant death records from North Carolina for the period 1999–2007 were analyzed. Analyses revealed an increased risk among black infants for post-neonatal death compared to white infants (adjusted odds ratio: 1.26; CI 1.14-1.39). Results also showed that Hispanic infants have a decreased risk to post-neonatal mortality compared to white infants (0.67; CI 0.57, 0.79).

(Alexander 2008) To examine trends in birth weight-gestational age distributions and related infant mortality for black and white women, live births to U.S.-resident mothers with a maternal race of white or black were selected from the National Center for Health Statistics' linked live birth-infant death cohort files and time periods were compared (1985-1988 and 1995-2000). The racial disparity in infant mortality widened despite an increasing rate of white low-birth weight infants. It is estimated that 3,303 excess Black infant deaths occurred annually during the 1995-2000 period. Slightly more than 20% of the excess deaths occurred to infants who were 2,500 grams or greater or at term or beyond.

(Besculides 2005) To determine the feto-infant mortality rate for New York City, assess racial/ethnic variations and identify areas for intervention using the Perinatal Periods of Risk (PPOR) approach, the PPOR model was applied to fetal and infant deaths occurring in New York City using vital records data from 1996-2000. The feto-infant mortality rate for black non-

Hispanics was higher than for other racial/ethnic groups. Observed rates among blacks were 8.2/1,000 live births compared to 10.0 among Hispanics, 7.3 among white non-Hispanics, and 7.2 among Asians/Pacific Islanders.

(Hessol 2005) To identify ethnic differences in neonatal and post-neonatal mortality as well as the causes and risk factors among infants born in California, researchers performed analyses on California linked birth-infant death certificate data related to 1,277,393 singleton infants live-born to black, Hispanic, and white women from 1995 to 1997. Black women had a higher risk of post-neonatal mortality and Hispanic women had a lower risk compared with white women after adjusting for maternal and infant factors.

(Vintzileos 2002) A retrospective population-based study using the national perinatal mortality data for 1995–1997, examined the impact of prenatal care in the United States on the fetal death rate in the presence and absence of obstetric and medical high-risk conditions, and explored the role of these high risk conditions in contributing to the black–white disparity. Results showed that fetal death rates were higher for blacks than whites in the presence (4.2 versus 2.4 per 1,000) and absence (17.2 versus 2.5 per 1,000) of prenatal care.

(Demissie 2001) Researchers used live birth and infant death records from the National Center for Health Statistics to examine the reasons for the black-white disparity in preterm birth trends and their implications for neonatal and infant mortality. Evidence showed that neonatal mortality among preterm whites dropped 34% during the 8 years of the study, while the decrease was only 24% among blacks.

(Lane 2001) To examine the racial disparities in mortality across the life-span, Onondaga County (New York) vital records data for three years (1994-1996) were studied. After controlling for the difference in size between the two populations by examining the timing of death by age group, investigators found a much larger proportion of Black children die in infancy than white residents.

(Zuvekas 2000) To determine whether results from previous studies showing Mexican Americans' low infant mortality rates (IMRs) are real or the result of anomalous data, linked 1983-1987 birth/infant death data from the National Center for Health Statistics were examined. The study found that the low Mexican American IMRs are real and not simply a data anomaly. Mexican Americans' low-birth-weight total was 5.7 percent, comparable to that of non-Hispanic white infants and significantly lower than that of non-Hispanic black infants (13.0 percent).

(Alexander, Kogan 1999) 1990-1991 U.S. linked live birth-infant death data were used to determine to what extent differences in fetal growth and infant mortality persist between extremely low risk (ELR) white and black women. Compared with ELR white mothers, the risk of infant mortality was significantly greater for ELR black mothers.

(Alexander, Tompkins 1999) Data from the 1975-1994 South Carolina public access linked live birth-infant death data files were used to compare weight specific neonatal mortality rates between whites and blacks. Birth weight specific neonatal mortality decreased for both races, although greater reductions accrued to white low birth weight infants.

(Poma 1999) To compare infant mortality rates among the largest ethnic groups in Chicago-Blacks, Hispanics, and whites, researchers examined City of Chicago infant data from 1989-1996. Of the six most common causes of infant mortality in this study, short gestational age-low birth weight, SIDS, congenital anomalies, respiratory distress syndrome, other respiratory conditions, and other perinatal conditions, Blacks suffered two to three times more infant deaths from each of these conditions than the other two groups ($P<.0001$), except in deaths from congenital anomalies.

(Din-Dzietham 1998) Investigators from North Carolina used state linked birth and death records to examine the joint effect of maternal race and education on infant mortality in North Carolina from 1988-1993. After adjusting for covariates, results showed that black infants had a significantly higher risk of infant death than their white counterparts at every level of maternal education. Data further showed that although education beyond high school resulted in reduced risk of infant mortality in whites, it had little effect among blacks.

(Din-Dzietham 1997) Data from North Carolina's linked birth and infant file for 1988 through 1993 were used to examine the impact of education on race differences in neonatal and post-neonatal mortality. Significant associations were observed between increased neonatal and post-neonatal deaths among African Americans compared to European Americans. Education had no impact on neonatal mortality in either race.

(Hsieh 1997) To examine the impact of changes in birth weight distribution in individual groups and in birth weight-specific fetal death rates on the decline in the crude fetal death rate in the United States, data on live births and fetal deaths in the U.S. for the period 1979-1990 were examined. Although both black and white populations showed decreases in the crude death rate, the reduction was greater in whites and others (~22%) than in blacks (10%). The disparity can be explained almost entirely by differences in birth weight distribution.

(Herschel 1995) To discover the most likely clinical causes or medical pathology associated with fetal mortality in a black population a record review of the primary causes of fetal deaths occurring over an 11-year period in a population of 26,852 black Chicago women. The fetal death rate per 10,000 births attributed to hypertension was nine times greater in this population than in a historical comparison population of Canadian white women, although the prevalence of hypertension was only 1.2 times greater in the population of black women.

(Laveist 1993) To examine the relationship between racial segregation and infant mortality, infant mortality rates from 176 cities were compared. Black infant mortality is significantly higher in highly segregated cities (unadjusted correlation co-efficient: 0.247, $P < 0.01$), whereas white rates were essentially unaffected by a city's level of segregation.

(Druschel 1987) To identify reasons for the racial differential in post-neonatal deaths Alabama's linked birth-death file was used to evaluate causes of post-neonatal mortality for the 1980 to 1983 cohorts of normal birth weight infants. The relative risk of SIDS comparing blacks to whites was 2.4 (CI 1.9-3.1).

Psychosocial stressors

(Singh 2007) To examine the changing patterns of inequalities in U.S. infant, neonatal, and postneonatal mortality rates between 1969 and 2001 by area deprivation and maternal education, a deprivation index was linked to county vital records data to derive annual infant mortality rates by deprivation quintiles from 1969 to 2000. In 1985-1989, infants in the most deprived group had, respectively, 36% and 57% higher risks of neonatal and post-neonatal mortality than infants in the least deprived group. The corresponding relative risks increased to 43% and 96% in 1995-2000.

(Luo 2004) Canadian researchers conducted a birth cohort-based study of all 720,586 births registered in Quebec for the years 1990 to 1997 to assess the risks and trends of adverse pregnancy outcomes among mothers in common-law unions versus traditional marriage relationships. Analyses showed that the rate of post-neonatal mortality among infants born to common-law mothers was significantly higher than for infants born to married mothers.

(Tan 2004) To assess whether, and to what extent, outcomes in pregnant women who did not have partner information differ from those who had, a population-based retrospective cohort study was conducted on twins born from 1995-1997 based on the registry data in the United States. Study subjects were divided into three groups according to the availability of partner information: available, partly missing, and totally missing. The rates of fetal mortality, neonatal mortality, and post-neonatal mortality were significantly increased in mothers whose partner's information was partly or totally missing compared to mothers whose partner's information was listed.

(Phipps 2002) To evaluate risk disparities and risk factors for infant mortality among adolescent childbearing age groups, researchers analyzed 777,762 singleton, first births to women aged 12–19 years linked to 4,631 infant deaths. Not reporting the father on the child's birth certificate was associated with a 24% increased risk for infant mortality among infants born to mothers less than or equal to 15 years old.

(Stephansson 2001) According to a population-based case-control study of Swedish women, compared with women who were high level white-collar workers, those who were unskilled-blue collar workers (adjusted relative risks: 2.2; CI 1.3-3.7), skilled blue-collar workers (2.4; CI 1.3-4.1), and low level white-collar workers (1.9; CI 1.2-3.2) had significantly increased risk of stillbirth. Low social class was most associated with risks of term and antepartum and intrapartum stillbirths.

(Scholer 1999) A historical cohort study using The National Center for Health Statistics linked U.S. infants birth/death records studied socio-demographic predictors of infant injury mortality. Highest risk infants were born to mothers who were younger than 20 years compared with older than 30 years, had less than a high school education compared with a college education, had more than 2 other children compared with no other children, were unmarried, or had birth weights under 1,500 grams compared with over 2,500 grams. Infants in the highest risk group

(21.0% of the population) had a greater than 10-fold increased risk of injury mortality compared with the lowest risk group (18.1% of the population).

(Gaudino 1999) To test whether the lack of father's names on birth certificates would be independently associated with infant survival, birth and death certificates of singleton Georgia infants from 1989-1990 were examined. Compared with the rate for married women listing names, the death rates were significantly higher for unmarried mothers not listing fathers, unmarried mothers listing fathers, and married women not listing fathers.

(Kawachi 1997) In a cross-sectional ecologic study based on data from 39 states, social capital was measured by weighted responses to two items from the General Social Survey: per capita density of membership in voluntary groups in each state and the level of social trust, as gauged by the proportion of residents in each state who believed that people could be trusted. Income inequality was strongly correlated with both per capita group membership and lack of social trust. In turn, both social trust and group membership were significantly associated with infant mortality.

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