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Jennifer Lynn Williams

Shortened Sleep Duration in Pregnancy and Adverse Maternal and Infant Outcomes

By

Jennifer Lynn Williams

Doctor of Philosophy

Nursing

Ann E. Rogers, PhD, RN, FAAN, FAASM

Advisor

Elizabeth Corwin, PhD, RN, FAAN

Committee Member

Michele Marcus, PhD, MPH

Committee Member

Mark Thompson, PhD

Committee Member

Accepted:

Lisa A. Tedesco, Ph.D.

Dean of the James T. Laney School of Graduate Studies

Date

Shortened Sleep Duration in Pregnancy and Adverse Maternal and Infant Outcomes

By

Jennifer L. Williams

BSN, Nell Hodgson Woodruff School of Nursing, Emory University, 1996

MSN, Nell Hodgson Woodruff School of Nursing, Emory University, 2001

MPH, Rollins School of Public Health, Emory University, 2001

Advisor: Ann E. Rogers, PhD, RN, FAAN

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Abstract

Shortened Sleep Duration in Pregnancy and Adverse Maternal and Infant Outcomes

By Jennifer Lynn Williams

Background: Women's sleep needs increase during pregnancy. Most pregnant women need more sleep than the 7-8 hours needed by non-pregnant individuals. One-quarter to one-third of pregnant women experience short sleep duration (<7 hours) as early as the first trimester; with the proportion experiencing shortened sleep duration increasing as pregnancy progresses. Limited evidence suggests that self-reported shortened sleep duration (SRSSD) in pregnancy adversely affects maternal cardiometabolic and infant birth outcomes. The purpose of this study is to determine if SRSSD is independently associated with clinically diagnosed gestational diabetes mellitus (GDM), incident hypertension in pregnancy, preeclampsia, preterm birth (PTB) or small for gestational age (SGA).

Sample and Design: Data was derived from the Pregnancy and Influenza Study (PIP), a prospective, observational cohort of pregnant women receiving prenatal care through two managed health care systems. Data from a subset of PIP enrollees (n=1271) were obtained from enrollment interviews, and electronic medical records. Univariate associations between SRSSD and dependent clinical outcomes, between SRSSD and covariates, and between clinical outcomes and covariates was conducted using Pearson chi-squared (χ 2) tests. Multinomial logistic regression models were conducted for each outcome. Analyses were conducted with SPSS version 21(SPSS Inc., Chicago, IL).

Results: The majority of women reported sleeping seven to nine hours a night (69%). SRSSD was reported by 11% of respondents. Factors associated with SRSSD at a p value <0.05 included maternal age at conception, race/ethnicity, education, cohabiting with a spouse or partner, and smoke exposure. Percentages of women with selected outcomes were: GDM (9%); incident hypertension in pregnancy (7%); preeclampsia (3%), preterm (3%) and SGA (6%). In logistic regression models, SRSSD was not associated with clinically diagnosed GDM (Adjusted Odds Ratio (aOR) 1.18, 95% confidence interval (CI) 0.55-1.98), incident hypertension in pregnancy (aOR 0.69, CI 0.29-1.66), preeclampsia, (aOR 1.54 CI 0.56-4.25), PTB (aOR 0.87, 95% CI 0.25-2.98) or SGA (aOR 1.39, 95% CI 0.86-2.70).

Conclusion: Results from this analysis did not find associations between SRSSD and clinically diagnosed GDM, incident hypertension in pregnancy, preeclampsia, PTB or SGA. Further research is needed on the effects of sleep duration and adverse pregnancy and infant outcomes.

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Chapter 1: Introduction and Specific Aims:

According to the National Institute of Neurological Disorders and Stroke, most adults need 7-8 hours a night. Women during their first three months of pregnancy might need several more hours (NIH, 2014). However recent studies have reported that a quarter to one third of pregnant women experience shortened sleep duration in the first trimester with the proportion of women experiencing shortened sleep duration increasing as pregnancy progresses with 40-50% of pregnant women report shortened sleep duration by the third trimester. (Facco, Kramer, Ho, Zee & Grobman, 2010; Mindell, Cook & Nikolovski, 2015; Signal et al. 2014; Sivertsen, Hysing, Dørheim & Eberhard-Gran, 2015.).

Epidemiological data from non-pregnant adult populations have linked self-reported shortened sleep duration, (typically reported as 6 hours or less a night), to metabolic and cardiovascular diseases such as hypertension (Altman et al. 2012; Faraut et al. 2012; Gangwisch, Feskanich, Malaspina, Shen & Forman, 2013; Gottlieb et al. 2006; Kim et al. 2012), myocardial infarction (Altman et al. 2012), stroke (Altman et al. 2012; von Sarnowski et al. 2013), diabetes and insulin resistance (Altman et al. 2012; Chao et al. 2011; Chaput, Deprés, Bouchard & Tremblay, 2007; Hancox & Landhuis, 2012; Liu, Kushida & Reaven, 2013; Rafalson et al. 2010; Zizi et al. 2012;) metabolic syndrome (Choi et al. 2008), diabetic nephropathy (Afsar, 2013), hyperlipidemia (Altman et al. 2012; Bjorvatn et al. 2007; Charumathi & Shankar, 2012), atherosclerosis (Wolff et al. 2008), and obesity (Bjorvatn et al. 2007). Although this body of research has focused on non-pregnant adults, researchers have argued that disease states associated with shortened sleep duration seen in the general

population might also have cardiometabolic correlates in pregnancy (Chang, Pien, Duntley & Macones, 2010; Izci-Balserak & Pien, 2014; Okun, Roberts, Marsland & Hall, 2009).

There is an emerging (but limited) body of evidence suggesting that self-reported shortened sleep duration in pregnancy is associated with adverse pregnancy outcomes. Some of the outcomes that have be examined and show associations include hypertensive disorders (Williams et al. 2010), preterm birth (Micheli et al. 2011; Reutrakul et al. 2011), gestational diabetes and impaired glucose tolerance (Facco et al., 2010; Qiu, et al., 2010; Rawal et al. 2016; Reutrakul et al. 2011), longer labor (Lee & Gay, 2004), cesarean delivery (Lee & Gay, 2004), and placental abruption (Qiu et al. 2014). The association between shortened sleep duration and adverse pregnancy outcomes also appears to be mediated by some risk factors; for example obesity (Qiu et al. 2010; Qiu, Gelaye, Fida & Williams, 2012) or depression (Okun et al. 2013; Okun, Luther, Wisniewski & Wisner, 2013; Qiu, Gelaye, Fida & Williams, 2012).

While these studies support the biologic plausibility of shortened sleep duration as a contributing factor to adverse pregnancy outcomes, other studies have shown no association between shortened sleep duration and pregnancy outcomes. Specifically, some studies examining self-reported shortened sleep duration have failed to show an association with hypertensive disorders (Hayney et al. , 2014; Reutrakul et al. 2011), diabetes (Izci-Balserak et al. , 2013) preterm birth (Blair, Porter, Leblebicioglu & Christian, 2015; Guendelman et al. 2013; Strange et al. 2009), small for gestational age (Micheli et al. 2011), low birth weight (Kennelly et al. 2011; Micheli et al. 2011; Reutrakul et al. 2011), cesarean delivery (Kennelly et al.2011; Tsai et al. , 2013), or labor duration (Tsai, et al. 2013). Much of the prior research in pregnant women is limited by small or non-representative samples, varying definitions of shortened sleep duration, retrospective reports of sleep, or cross-sectional designs, which

make it difficult to determine if shortened sleep durations have adverse effects on pregnancy outcomes.

Whether shortened sleep duration contributes to poor pregnancy outcomes is still undetermined. Measuring sleep objectively in clinical settings among pregnant women is logistically difficult and cost prohibitive, therefore, the use of self-reported sleep duration to identify women at risk for adverse pregnancy outcomes is clinically important. Given that sleep is altered as pregnancy progresses, reliance on the cross-sectional, or retrospective data most likely results in misclassification of women with shortened sleep duration, and potentially biases associations with adverse pregnancy outcomes. Prospective studies of adequate sample size are needed. Specifically, research is needed to determine the maternal characteristics or combinations of risk factors that identify women at risk for shortened sleep duration and the impact shortened sleep duration might have on perinatal outcomes. Therefore, the purpose of this study is to determine if shortened sleep duration is independently associated with adverse infant and maternal outcomes (i.e. has a direct effect). To answer these questions, a secondary data analysis of a large cohort study is proposed. The Pregnancy and Influenza Study (PIP) is a large prospective cohort study among pregnant women recruited from a large integrated health care delivery system and will be used to address the following specific aims and hypotheses (H):

Specific Aim 1: To identify risk factors for shortened sleep duration among pregnant women.

Specific Aim 2:_ To evaluate the association between shortened sleep duration during pregnancy and subsequent adverse maternal outcomes.

H1: Pregnant women with shorter sleep durations will be more likely to experience adverse maternal outcomes than pregnant women with longer sleep durations.

Adverse maternal outcomes include an ICD-9 coded clinical diagnosis in the medical record of: gestational hypertension, preeclampsia, or gestational diabetes.

H2: Associations between sleep duration and adverse maternal outcomes will be statistically independent of potential confounders associated with both sleep duration and adverse outcomes.

Specific Aim 3: To evaluate the association between shortened sleep duration during pregnancy and subsequent adverse infant outcomes.

H1: Pregnant women with shorter sleep durations will be more likely to experience adverse infant outcomes than pregnant women with longer sleep durations. Adverse infant outcomes include a preterm delivery (defined as >32 weeks and < 37 weeks), and small for gestational age (defined as <10% of weight for given week of gestation).

H2: Associations between sleep duration and adverse infant outcomes will be statistically independent of potential confounders (associated with both sleep duration and adverse outcomes)

Chapter 2: Background and Significance

Sleep Duration in U.S. Adults

Chronic sleep restriction, generally defined as average sleep durations of less than 7 hours a night but greater than 4 hours a night (Banks and Dinges, 2011), is an under-recognized public health concern that affects over a third of all U.S. adults (McKnight-Eily et al. 2011; Wheaton, Liu, Perry & Croft, 2011). Epidemiologic data on the prevalence of shortened sleep duration from the National Health and Nutrition Examination Survey (NHANES) found that 37.1% of U.S. adults reported getting less than 7 hours of sleep on average (Wheaton, Liu, Perry & Croft, 2011); similar

results have been found in the Behavioral Risk Factor Surveillance System (BRFSS) with 35.3% of respondents reporting averaging less than 7 hours of sleep (McKnight-Eily et al. 2011).

Effects of Shortened Sleep Duration

The effects of chronic sleep insufficiency can negatively alter cognition, mood and motor performance (Banks & Dinges, 2007; Pilcher & Huffcutt, 1996), metabolic and endocrine function (Knutson, 2012; Spiegel et al. 2008; Spiegel, Leproult & Van Cauter, 1999), and inflammatory and immune processes (Irwin et al. 1999; Irwin 2002; Majde & Krueger, 2005). These alterations are thought to increase the risk for several disease states of cardiometabolic, inflammatory or endocrine origin, such as hypertensive disorders and disorders of metabolism. The following sections will identify what is known about the influence of sleep duration on the development of cardiovascular disease, diabetes, dyslipidemias, obesity, and metabolic syndrome.

Cardiovascular Disease

Several studies lend support that shortened sleep duration increases the risk of cardiovascular disease in non-pregnant populations. In 2007, Cappuccio et al. examined sleep duration and incident hypertension among 10,308 British civil servants and found that women who report sleeping less ≤5 hours a night were over two times more likely to be hypertensive compared to those sleeping at least 7 hours (Odds Ratio [OR] 2.01; 95% confidence interval [CI] 1.13to 3.58). In another European study, examining short sleep duration and prevalent hypertension among French adults accessing primary care services, Farault et al (2012) found that individuals sleeping ≤5 hours a night were 1.8 times more likely to have hypertension than those individuals sleeping 7 hours (OR=1.80, 95% CI 1.06-3.05). These results have been corroborated domestically. Data recently published from The Nurses' Health Study revealed an odds ratio of 1.19 (CI 1.14-1.25) for prevalent hypertension among women sleeping ≤5 hours compared to those women sleeping 7

hours (Gangwisch et al. , 2013). In the Sleep Heart Health Study, men and women sleeping ≤6 hours a night were 1.66 times more likely to have hypertension, compared to subjects sleeping 7-8 hours a night (CI 1.35-2.04) (Gottlieb et al. 2006.) Lastly, in a 2009 BRFSS survey comprised of data for more than 30,000 individuals, respondents with a sleep duration of ≤5 hours a night were over 2 and a half times more likely to have hypertension than those respondents sleeping 7 hours (OR 2.72, 95% CI 1.61-3.82) (Altman et al. 2012).

Ischemic cerebrovascular events and myocardial infarction are also suggested to be linked to shortened sleep duration in the general population. In an examination of prevalent risk factors among younger (under 55 years of age) female ischemic stroke patients, almost 14% reported sleeping less than 6 hours a night (von Sarnowski et al. 2013). When looking at stroke or myocardial infarction as the outcome, BRFSS data reported that short sleepers (≤5 hours a night) compared to individuals sleeping 7 hours were 4.5 times more likely to suffer a stroke (OR 4.56, 95% CI 2.29-6.83) and 4.7 times more likely to suffer a heart attack (OR 4.70 95% CI 2.29-6.83)(Altman et al. 2012).

While the preponderance of evidence suggests an association between shortened sleep duration and cardiovascular disease, it is important to note that some studies have reported partial to complete attenuation of this association with adjustment of certain covariates. For example, Olafiranye and colleagues analyzed the 2005 National Health Interview Survey (n=29,818) and found that in univariate analysis, an association was found with short sleep (≤5 hours) or long sleep (≥9 hours) and coronary heart disease (OR 1.65, 95% CI 1.38-1.97) but this association was abolished in multivariate regression analysis after adjustment for sociodemographic and health characteristics (Olafiranye et al. 2012). In a prospective cohort study among Australian adults over 45 years of age, sleeping less than 6 hours each night was associated with incident cardiovascular

disease (Cox proportional hazard ratio [HR] 1.38, 95% CI 1.12-1.70) but not after the exclusion of individuals with baseline illness and after adjustment for baseline health (HR 1.03, 95% CI 0.88-1.21) (Holliday et al. 2013).

Diabetes

In recent years, data from several epidemiologic studies have provided conclusive evidence that supports an association between shortened sleep duration and risk of developing diabetes. Among several cross sectional studies from the United States and Canada, short sleep durations (typically measured as sleep duration of 6 hours or less) reveal an association with diabetes mellitus after controlling for BMI (Altman et al 2012; Zizi et al. 2012; Chaput, Després, Bouchard & Tremblay, 2007). Altman et al reported an odds ratio of 1.25 (95% CI 1.03-1.48) for persons sleeping 5-6 hours; and this risk increased with increasingly shorter sleep durations. Those sleeping less than 5 hours were over three times more likely to have diabetes (OR 3.16, 95% CI 2.14 - 4.18) than those sleeping 7 hours (Altman et al 2012). Data from the National Health Interview Survey also reported increased risk among short sleepers that differed by race. In model adjusted for several sociodemographic and medical factors including obesity, Black and White participants who reported sleeping less than 5 hours were more likely to have diabetes than those participants who averaged 6 to 8 hours of sleep a night (OR 1.66 95% CI 1.19-2.30 and 1.87 95% CI 1.57-2.24 respectively) (Zizi et al. 2011). In the Quebec Family Study, the adjusted OR for type 2 diabetes was 2.09 (95% CI 1.34-2.98) for short sleepers (5-6 hours) versus referent sleepers (7-8 hours) (Chaput, Després, Bouchard & Tremblay, 2007). These results are not limited to North American studies. In a large sample of Taiwanese adults, short sleepers (<6 hours) had a higher risk of incident diabetes (newly diagnosed diabetes) that was over 1.5 times greater than subjects with a more normal sleep duration (6-8.49 hours) (OR 1.55, 95% CI 1.07-2.24)(Chao et al. 2011). In a large, cross-sectional study

among younger Iranians (under 60 years of age), sleep durations of 5 hours or less revealed an increase odds ratio for diabetes compared to individuals sleeping 7-8 hours a night (OR 1.37, 95% CI 1.13-1.67), (Najafian et al. 2013).

A few prospective studies are available that support the theory that shortened sleep has a causal role in development of Type II diabetes. Among a study prospective occupational study of Japanese workers without a family history of diabetes, short sleepers (≤5 hours) were 5.37 times more likely (95% CI 1.38-20.91) to develop diabetes when compared to workers sleeping more than 7 hours a night (Kita et al. 2012). In a prospective examination of the U.S. based NHANES I data, participants sleeping less 5 hours or less were significantly more likely to develop diabetes over an 8-10 year follow up period than those participants sleeping 7 hours (OR 1.47, 95% CI 1.03-2.09) (Gangwisch et al. 2007). Among a multiethnic cohort of 900-diabetes free individuals, Whites and Hispanics who slept less ≤7 hours were 2.36 times more likely to develop diabetes within the 5 years than those sleeping 8 hours (95% CI 1.21-3.79) (Beihl, Liese & Haffner, 2009).

Markers of altered glucose metabolism have also been associated with short sleep duration. In the cross sectional Western New York Health Study, impaired fasting glucose among short sleepers (defined as less than 6 hours) was three times higher than among mid-range sleepers (OR 3.0, 95% CI 1.05-8.59) (Rafalson et al. 2010). In another U.S. study comparing the sleep habits of insulin resistant versus non-insulin resistant obese individuals, a statistically significant difference in prevalence was found with short sleep of less than 7 hours. More insulin resistant participants than non-insulin resistant participants were short sleepers (60% vs. 24%, p-value <0.05) (Liu, Kushida & Reaven, 2013). Hemoglobin A_{1C}, a marker of longer term glycemic control, has also been shown to be associated with shortened sleep duration. In a cohort study of approximately 1,000 New Zealanders, linear regression models showed that time in bed was inversely associated elevated

Hemoglobin A_{1C} (p=0.002) as was higher a prevalence of pre-diabetes (p=0.015)(Hancox & Landhuis, 2012). Diabetic neuropathy has also been associated with shortened sleep duration. In a linear regression analysis of newly diagnosed type 2 diabetes patients, both urinary albumin excretion and urinary protein excretion were independently associated with sleep duration (Beta (β)-0.152 95% CI -0.254- -0.050 p=0.004; and β= -0.179, 95% CI -0.271- -0.086 p <0.001 (Afsar, 2013).

Dyslipidemias

Independent associations with shortened sleep duration have been found with cholesterol, triglycerides or lipid metabolism. In a large population based cross-sectional study of Norwegian adults, hierarchical linear regression analyses found that both cholesterol and triglycerides were statistically significantly higher in respondents that self-reported shortened sleep duration (Bjorvatn et al. 2007). Results from the 2008 National Health Interview Survey reveal that those individuals sleeping ≤ 5 hours were more likely to have hypercholesterolemia than those sleeping 7 hours (OR 1.27 95% CI=1.04-1.54);additionally, there appear to be gender differences in shortened sleep duration's effects on hypercholesterolemia. In a sub analysis stratified by gender, the most pronounced effects were seen in women sleeping on average less than 5 hours (OR 1.47 95% CI 1.22-1.78) (Charumathi & Shankar, 2012). Lastly, recent BRFSS data reported short sleepers were almost twice as likely as mid-range sleepers to have hypercholesterolemia (OR 1.92 95% CI 1.36-2.49 sleep duration <5 hours compared to 7 hours) (Altman et al 2012).

Longer-term complications of dyslipidemias have also been reportedly associated with shortened sleep duration. Atherosclerotic changes in relation to self-reported sleep duration were measured among approximately 2400 German subjects. In this study, short sleep duration was associated with an increased risk of atherosclerosis. In analyses adjusted for sex and age, in participants who slept 5 hours or less, there were differences in carotid intima-media thickness of

0.042 mm when compared to individuals sleeping 8 hours (95% CI 0.008-0.076)(Wolff et al. 2008).There is evidence to support that the relationship between sleep duration and atherosclerosis might be causative and not just associative. In the prospective CARDIA study, five year incident coronary artery calcifications were measured among participants with no detectable calcifications at baseline. In this analysis adjusted for several sociodemographic factors, longer measured sleep duration decreased the odds of calcification incidence (0.67 per hour, 95% CI 0.49-0.91 per hour) (King et al. 2008).

Obesity

Obesity defined as a body mass index (BMI) of 30 or higher, affects well over a third of all adults in the United States (CDC, 2010; Flegal, Carrol, Ogden & Curtin 2010). Interestingly, it has been postulated that one of the contributing factors to the obesity epidemic in the United States is self-imposed sleep restriction; that the rise in obesity is directly related to the lack of sleep in American society (Bass & Turek 2005). Several studies in in both US and non- US non-pregnant adults have reported relationships between shortened sleep duration and obesity. In a prospective study of approximately 1,000 primary care patients, Vorona et al. found that in both men and women, total sleep time decreased as BMI increased. Normal weight men reported an average of 473 minutes (± 104 minutes) whereas obese men reported an average of 469 minutes (± 95 minutes). This difference was much more pronounced in women, with normal weight women reporting an average of 483 minutes (± 96 minutes) and obese women reporting an average of 434 minutes (± 89 minutes)(Verona et al. 2005). In the Hordaland Health Study, researchers found that among Norwegian adults aged 40-45 years pf age; BMI was statistically different at the 0.05 level in the short sleepers (less than 6 hours a night) when compared to those respondents sleeping 7-7.99 hours a night. The mean values for those sleeping less than 5 hours were 26.34 (standard deviation

[SD] 4.30), and the mean value for those sleeping 5-5.99 hours was 25.87 (SD 4.04) compared to mean values of those sleeping 7-7.99 hours (mean 25.05, SD 3.74) (Bjorvatn et al. 2007). Likewise, obesity (BMI >30) in this study was related to sleep duration. Individuals sleeping less than 5 hours were had almost twice the risk of obesity and those individuals sleeping 7 to 7.99 hours a night (aOR 1.97, 95% CI=1.29-3.02); and those with 5-5.99 hours of sleep had almost 1 and a half times the risk for obesity (aOR 1.42, 95% CI 1.10-1.84) (Bjorvatn et al. 2007). Authors using 2009 BRFSS data also reported an association between incremental increases in BMI, obesity (classified at BMI ≥30), and sleep duration. In linear regression modeling reported as unstandardized beta coefficients, sleep duration of less than 5 hours compared to 7 hours was related to both increasing BMI (ß=2.72, p=<0.01) and obesity (ß=2.08, p=<0.000001)(Altman et al. 2012).

Metabolic Syndrome

Given the accumulating evidence on sleep duration's association with hypertensive disorders, hyperlipidemias, and obesity, a literature search was conducted on sleep duration and metabolic syndrome (a condition typified by centralized adiposity, hypertriglyceridemia, hypertension, and hyperglycemia). In the 2001 Korean National Health and Nutrition Survey, a nationally representative survey among Korean adults, Choi et al. (2008) reported that respondents who slept ≤ 5 hours a night were at greatest risk for metabolic syndrome when compared with respondents who reported sleeping 7 hours (OR 1.74, 95% CI 1.33-2.26). In a more recent cross-sectional study among Japanese patients with type 2 diabetes, patients sleeping less than 5.5 hours a night were 1.71 times more likely to have metabolic syndrome compared to their diabetic counterparts sleeping 6.5-7.4 hours a night (95% CI 1.39-2.11); when examining the component risks for metabolic syndrome individually, elevated waist circumference (aOR 1.92, 95% CI 1.54-2.39), elevated blood pressure (aOR 1.29 95% CI 1.02-1.62), and elevated triglycerides (aOR 1.25 95% CI 1.01-1.55) were all

statistically different in the short sleepers compared to the referent (Ohkuma et al. 2014). In a recent analysis of the longitudinal Quebec Family Study (1995-2001), the relative risk of developing metabolic syndrome over the 6 year follow up period was 1.74 (95% CI 1.30-3.05), for those sleeping ≤ 6 hours a night when compared to adults sleeping 7-8 hours a night (Chaput et al. 2013). However, the data on the association between shortened sleep duration and metabolic syndrome is inconsistent. Three recent studies published have shown no association with short sleep and metabolic syndrome. In the Korea National Health and Nutrition Examination Survey comprised of 24,511 adults aged 20-79 years, short sleep (defined as ≤5 hours) was not associated with metabolic syndrome, in any age group examined or by sex (Stefani, Kim, Kim, Oh & Suh, 2013). Using a subsample of participants from the 2003-2006 U.S. National Health and Nutrition Examination Survey, among those participants who did not have any chronic disease but with all component markers of metabolic syndrome (n=1371), sleep duration was divided into quartiles, e.g. Q1=3.0-7.2 hours, Q2=7.2-8.6 hours, Q3=8.6-9.7 hours, Q4=9.7-11.8hours). The lowest quartile was not associated with metabolic syndrome or any of its sub components (Salah & Janssen, 2014). In another cross-sectional study from Japan, participants with total PSQI scores of 6 or greater had greater odds of metabolic syndrome compared to participants with total PSQI scores less than 5 (OR 2.37, 95% CI 1.23-4.58 males; OR 2.71 95% CI 1.45-5.07 females) but no consistent associations with incremental decreases in sleep duration were found. The odds ratio for men sleeping 6-≤7 hours a night compared to men sleeping 7 hours or more was 1.89 (95% CI 1.14-3.13) but no similar association among men sleeping 5 hours to < 6 hours. Among women no associations were found in any duration category when compared to the referent 7 hours or more (Okubo et al. 2014).

Summary

Short sleep duration is endemic in the U.S. general population of adults. The preponderance of current evidence suggest associations of shortened sleep duration and several disease states of cardiometabolic or endocrine origin such as hypertensive disorders, diabetes, obesity, and dyslipidemias. While studies of shortened sleep duration in men and non-pregnant women might directly correlate to pregnant women, it is unclear if shortened sleep duration's effects in pregnancy are consistent with the findings from non-pregnant populations.

Sociodemographic Factors of Shortened Sleep Duration

Several sociodemographic factors have been associated with shortened sleep duration in non-pregnant and pregnant adults. Among BRFSS data of non-pregnant adults, higher proportions of non-Hispanic Blacks (48.3%) and other non-Hispanic races (38.7%) report sleeping less than 7 hours a night than either non-Hispanic Whites (34.9%) or Hispanics (33.0%) McKnight-Eily et al. 2011). Adequate amounts of sleep also vary by educational and marital status. Adults with a high school diploma or GED (37%) and adults with at least some college (35.8%) report sleeping <7 hours a night or less more frequently than adults without a high school diploma (32.0%) (McKnight-Eily et al. 2011). Likewise, adults who are divorced, widowed or separated (39.1%) or never married (37.9%) are more likely to report insufficient sleep than married or coupled adults (35.1% and 34.2% respectively) (McKnight-Eily et al. 2011). While the proportion of men versus women who report shortened sleep duration is essentially the same (35.3%- 38.9% men vs. 35.2% -35.3 %women, BDRFS and NHANES respectively) (McKnight-Eily et al. 2011; Wheaton, Liu, Perry & Croft, 2011), women report greater cognitive difficulties with insufficient sleep (Wheaton, Liu, Perry & Croft, 2011). Among pregnant women, self-rated health, a popular standardized item used to assess one's general perceptions of personal health status, has been associated with poor sleep and

tiredness in pregnant and postpartum women. Haas et al. reported pregnant women who had trouble sleeping were 1.52 times more likely to report poor or fair self-rated health than women who didn't report such problems (OR 1.52; 95% CI 0.93-2.47)(2004). Among post-partum women, tiredness was a risk factor for poor self-rated health both at 2 months (OR 5.8; 95% CI 2.2-15.5) and 1 year (OR 3.4; 95% CI 1.9-6.2) (Schytt & Waldenstrom, 2007).

Shortened Sleep Duration in Pregnant Women

Several studies have shown that pregnant women's total sleep time is inadequate. Whether defining shortened sleep duration as <7 hours a night (Facco et al. 2010; Sivertsen, Hysing, Dørheim & Eberhard-Gran, 2015) or <6hrs a night (Mindell, Cook & Nikolovski, 2015; Signal et al. 2014) a quarter to a third of pregnant women experience shortened sleep duration, as early as the first trimester (26% to 33%) and the proportion of women experiencing shortened sleep duration increases as pregnancy progresses (Facco et al. 2010; Mindell, Cook & Nikolovski, 2015). Depending in the study examined, 30% to up to half of pregnant women report shortened sleep duration by the third trimester (Facco et al. 2010; Mindell, Cook & Nikolovski, 2015; Signal et al. 2014; Sivertsen, Hysing, Dørheim & Eberhard-Gran, 2015). Many of the normal changes in pregnancy predispose a woman to sleep problems. Physiologic, anatomic, and hormonal changes such as (but not limited to) gestational weight gain, estrogenic effects, displacement from the gravid uterus, nasopharyngeal edema, and decreased functional reserve capacity contribute to the frequent arousals and disruptions in the quality, quantity, and makeup of a pregnant woman's sleep (Micheli et al. 2011; Pien & Schwab, 2004; Sahota, Jain & Dhand, 2004). Like sleep in the general population, several physiologic functions, such inflammation and oxidative stress, and altered metabolism, are affected by shortened sleep duration. These functions share common pathways through which sleep

disturbances might negatively influence pregnancy (Izci-Balserak & Pien 2014; O'Keeffe & St-Onge, 2013; Okun, Roberts, Marsland & Hall, 2009).

Shortened sleep duration, one of the more common disturbances of sleep in pregnancy has been implicated in several adverse maternal and infant outcomes. To gain an understanding of the full range of possible adverse maternal and infant outcomes, a review of the literature from 1995 to current on shortened sleep duration in pregnancy was conducted. In all, 22 articles were found that examined the association of shortened sleep duration with adverse maternal or infant outcomes (Appendix A). The outcomes examined included preterm birth (6 studies), labor duration/type of delivery (5 studies), hyperglycemia/gestational diabetes (6 studies), depression/mood disorders (2 studies), hypertensive disorders (3 studies), placental abruption (1 study), birth weight or fetal growth restriction (2 studies) and APGAR (1 study). In Appendix A, listed by year of publication and organized alphabetically by first author, are the summaries of the articles identified, including type of study, primary instrumentation, and major findings. While the data is emerging and sometimes conflicting, Appendix A provides a snapshot of the available evidence accumulated to date.

Preterm Birth

Six studies were found that have looked at shortened sleep duration in relation to preterm birth. In 2009, Strange, Parker, Moore, Strickland & Bliwise were the first to assess shortened sleep duration and the risk of preterm birth. Using a convenience sample of 220 pregnant women assessed by the Pittsburgh Sleep Quality Index Scale (PSQI) in the second trimester, the authors found a general lack of association between the PSQI global score or any of its subscale scores with the exception of sleep latency which only just reached significance (OR 1.04 95% CI 1.01-1.07). In 2011 Micheli et al. re-examined the issue among a large prospective cohort study of Greek pregnant

women, the authors found that sleeping 5 hours or less each night increased the risk for preterm birth (RR 1.7 95% CI 1.1-2.8). Reutrakul and colleagues corroborated these findings later the same year when they reported on second trimester sleep disturbances and pregnancy outcomes in a smaller cohort of pregnant women. These researchers found that shortened sleep (defined as less than 7 hours a night) was associated with an increased risk of preterm birth (OR 4.3, 95% CI 1.1-16.7) (Reutrakul et al. 2011). Okun and colleagues (2012) conducted a secondary analysis of data from the Antidepressant use in Pregnancy Study. This particular study was underpowered to assess preterm birth; all measures of subjective sleep resulted in null findings. In a more recent study to examine the effects of sleep duration on preterm birth, a nested case (n=344) control (n=698) study was conducted among postpartum women in Southern California. In this study, shortened sleep duration (<7 hours vs. 7-8 hours) was not associated with preterm birth (OR 1.09, 95% CI 0.80-1.48) (Guendelman et al. 2013). Several limitations, however, might be responsible for the null findings. In this retrospective study, sleep variables were gathered months after the time period of interest, many sociodemographic factors and health characteristics that are risk factors for preterm birth and for shortened sleep duration were used as exclusion criteria versus controlling for these variables in analysis, and the cut points for defining short sleep duration all could have biased findings towards the null. The latest study examining this relationship is by Blair, Porter, Leblebicioglu & Christian (2015) who assessed sleep quality, proinflammatory cytokines, and preterm birth among African American and white pregnant women in Ohio (n=138). Sleep was assessed using the PSQI; pro-inflammatory markers (IL 6, IL 8, IL-1β, and TNF-α were drawn simultaneously drawn. Shorter gestation was associated with poorer overall sleep quality (r_s = -0.35 p=0.002) and the subscales of subjective sleep quality (r_s =-0.34 p=0.002) Sleep latency (r_s= -0.27 p=0.02) and sleep efficiency (r_s= -0.27 p=0.02) but not total sleep time. Of the proinflammatory markers drawn, IL 8 was found to mediate the relationship between sleep quality and length of

gestation, but only among African American women (indirect effect estimate -0.027, 95% CI -0.06 to -0.002).

Labor Length and Delivery Type

Shortened sleep duration's effect on length and type of delivery has been examined by several authors. Evans, Dick & Clark (1995) conducted a correlational study examined the quality of sleep during the week before onset of labor and the outcomes of labor and delivery. Using the Verran and Snyder-Halpern Scale (VSH), the authors concluded that sleep supplementation (the scale measurement within the VSH that assesses sleep duration) played no significant part in length of labor or perceptions of labor. The study however had several fundamental flaws, including high attrition rates, a small sample size, the use of a scale that was invalidated in pregnant women, and the inability to parse out sleep duration from other sleep characteristics. In 2004, Lee and Gay revisited the inquiry into sleep duration and its relationship with labor length and delivery type. They found that while self-reported time in bed was not associated with labor duration or cesarean birth (Pearson correlation coefficients -0.15 and 0.06 respectively) objective total sleep time was. Women sleeping < 6 hours had significantly longer labors (Pearson 29.0 ±12.5 compared to 17.7 ±15.6) and higher C-section rates (OR 4.54 95% CI 1.36-15.21) than women sleeping 7 hours or more. While this study was well done, conclusions that can be drawn are limited due to its small sample size (n=131). No additional studies on shortened sleep duration and labor length and delivery type were found in the literature until 2011, when Kennelly, Fallon, Farah, Stuart & Turner conducted a retrospective, hospital based observational study among 200 postpartum women. The authors concluded that even though sleep duration declined as pregnancy progressed; there was no effect on mode of delivery. The study was subject to several limitations that might call in question the authors' conclusions, namely the retrospective nature of the study, the small sample size, and the

inability to determine how the sleep variables were collected. The following year, Zafarghandi et al. conducted a cross-sectional study of primigravid women to assess the effects of sleep duration on length of delivery stages, type of delivery, and infant APGAR; however it is difficult to interpret the results. Sleep duration was dichotomized to less than 8 hours and more than 8 hours, and among the stratified table variables, only p-values and frequency counts are given, making it difficult to determine where the differences among the comparisons exist. Findings from this study have limited usefulness. The last study found examined the effects of third trimester nighttime, daytime, and 24 hour sleeping patterns on labor duration and type of delivery among Taiwanese nulliparous women (Tsai et al. 2013). The authors concluded that none of the self-reported sleep variables that were examined were associated with labor duration in women who had C-sections or with women's mode of delivery. Many of the outcomes of interest had extremely small numbers however. There appears to be a paucity of available data on sleep duration in relation to labor length and delivery type, and this line of inquiry is under-assessed. Further exploratory research with adequate sample size is needed to determine if a relationship exists between sleep duration and length of labor or mode of delivery.

Gestational Diabetes and Impaired Glucose Tolerance

Six studies were found examining a relationship between shortened sleep duration and impaired glucose tolerance or gestational diabetes. The most recent study is from the Growing Up Singapore Towards healthy Outcomes (GUSTO) Study. This cohort study among Asian pregnant women (n=1247) examined sleep duration and OGTT among a subset of GUSTO enrollees (n=686) at 24-28 weeks gestation. In this study, 19% of women had a diagnosis of gestational diabetes, and 11% were short sleepers. In univariate analysis, sleeping < 6 hrs. a night was marginally associated with development of GDM chi sq. 3.75, p-value 0.053. Unadjusted Odds Ratios (OR) was

1.70 with a confidence interval that overlapped zero (95% CI 0.99-2.93). Adjusted OR was significant for development of GDM. Short sleepers had an aOR of 1.96 (95% CI 1.05-3.66) compared to normal sleepers (Cai et al. 2017). This study, while reaching significance, raises questions about selection bias. The rates of GDM in the sample were much higher than GDM rates in similar populations. No comparison was made based on outcomes between cohort enrollees not included and those included for the analysis. It is possible that the subset had more disease and were thus not comparable. Rawal et al. (2016) prospectively examined associations in self-reported sleep duration in the 1st and 2nd trimesters and clinically diagnosed gestational diabetes among 2581 pregnant women. These researchers found that among non-obese but not obese women, both short sleep durations and long sleep durations were associated with a risk of gestational diabetes, suggesting a curvilinear relationship. Relative risks for sleeping 5-6 hours, 7 hours, and ≥10 hours a night were aRR 2.52, 95% CI 1.27-4.99; aRR 2.01, 95% CI 1.09-3.68; and aRR 2.17, 95% CI 1.01-4.67 respectively. Facco et al. (2010) conducted a secondary analysis on a prospective cohort of 189 nulliparous women, and found that shortened sleep duration of < 7 hours a night was associated with increased oral glucose tolerance (OGT) values (116mg/dl, standard deviation [SD] ±31 vs. 105mg/dl, SD ±23, p=.008). In multivariable logistic regression analyses, women with shortened sleep duration had a greater frequency of overt gestational diabetes (GDM) incidence (Adjusted odds ration [aOR] 10.6, 95% confidence interval [95% CI] 1.3-85.5). The increases in OGT values are of interest, however, the clinical significance of the findings are debatable. While the GDM incidence findings were statistically significant, the confidence intervals are wide and limit interpretation. Also in 2010, Qiu et al. conducted a large, retrospective cohort study of US pregnant women (n=1290) to examine whether habitual short sleep duration in early pregnancy was associated with post load glucose concentrations or with an increased risk of clinically diagnosed gestational diabetes. In this study, mean glucose values were highest in women sleeping ≤ 4 hours a

night. Additionally, mean glucose concentrations were 16.3 mg/dl higher than in the referent group of women sleeping 9 hours (95% CI 1.1-31.6). For women with gestational diabetes, sleeping ≤ 4 hours a night had an increased risk compared to the referent (9 hrs.) (RR 5.56, 95% CI 1.31-23.69); this relationship was attenuated by adjustment for BMI (RR 4.18, 95% CI 0.94-18.60) (Qiu et al. 2010). In this study, the referent values, cut off values, and timing of collected sleep variables did not seem based in the current literature; confidence intervals were also extremely wide, so findings from this study are suspect. Additionally the overlapping standard errors reported in the mean plasma glucose levels of women in various sleep categories mean that the associations as reported might not exist. Another recent study by Reutrakul et al. (2011) found that sleep duration inversely correlated with glucose values ($r=0.21$, $p<.01$); additionally, an increased risk for GDM was found for shortened sleep (Odds Ratio [OR] =2.4, 95% CI=1.0-5.9). The Reutrakul article represents some of the best evidence to date, but sleep and OGT variables were collected only at one point in time, so causality cannot be established. Additionally sleep in pregnancy represents a dynamic state, so a lack of sufficient sleep at one point in time does not mean an absence of insufficient sleep in a woman, which could bias findings towards the null. Another recent study examining potential associations was conducted by Iczi-Balserak et al. (2013). This case control study was a secondary analysis of a cohort study of sleep-disordered breathing among pregnant women. The authors examined whether there was an association between high glucose challenge test values and nocturnal sleep duration. They found that mean self-reported sleep duration was not significantly different between women with hyperglycemia (7.45 hours ±2.7 hours) and women with normoglycemia (7.71 hours ±2.10 hours, $p=0.7$); in bivariate analysis, self-reported sleep duration was not significantly associated with hyperglycemia (OR 0.95, 95% CI 0.70-1.27). While this study was methodologically sound, only 20 individuals in the entire sample reported sleeping less than 6 hours, only 11 subjects had hyperglycemia, of which only 6 of these were ultimately diagnosed with gestational diabetes.

Therefore this study is likely underpowered to assess associations between shortened sleep duration and impaired glucose tolerance and gestational diabetes. From the review of the literature available, unlike the literature in the general population, there appears to be no consensus on the contribution of shortened sleep duration to impaired glucose functioning in pregnancy.

Hypertensive disorders

Outside the literature found in non-pregnant populations, only two additional studies were found to examine the relationship between hypertensive disorders and shortened sleep duration in pregnant women. Williams et al. (2010) conducted a prospective cohort study among 1272 healthy pregnant women and examined short and long sleep duration and its association with increased mean blood pressures, incident pregnancy induced hypertension, and preeclampsia. The authors found that in adjusted multivariate modeling, short sleepers (defined as ≤6 hours) when compared to those sleeping 9 hours had higher systolic blood pressures in the third trimester (3.72 mm Hg higher, 95% CI 2.1-5.8) as did those individuals sleeping ≥10 hours (3.88 mm Hg higher, 95% CI 2.6-5.2). No differences were found in the first and second trimesters. For diastolic blood pressures, a similar pattern was found. Both short sleepers and long sleepers had higher mean diastolic blood pressures than did the referent (3.04 mm Hg, 95% CI 1.9-4.2; 3.43, 95% CI 2.3-4.6 respectively); no additional differences were found in the first or second trimesters.

When the authors examined clinically diagnosed incident pregnancy induced hypertension and preeclampsia, they reported that no sleep duration category was statistically significant for pregnancy induced hypertension, and that only women sleeping < 5 hours had an increased risk for preeclampsia (aOR 9.52, 95% CI 1.83-49.40). When stratifying by weight, overweight women who were very short or long sleepers were statistically significant for preeclampsia (aOR 12.7, 95% CI 1.04-154.4 and aOR 5.14 95% CI 1.20-22.10 respectively) (Williams et al. 2010).

A more recent secondary analysis study from the University of Pittsburg examined self-reported sleep (via diary) and objectively reported sleep (via actigraphy) and two cardiometabolic risk factors (blood pressure and body mass index) among women in early pregnancy (n=161) (Haney, Buysse, Rosario, Chen &Okun, 2014). In contrast to the Williams study, total sleep time assessed either by objective measures or by subjective self-report was not associated with either cardiometabolic outcome of interest.

While these studies are the only ones found to quantify the sleep duration and hypertensive disorders in pregnancy, it is difficult to draw any conclusions, and comparisons between the studies is problematic. In the Haney study, the sleep and cardiometabolic measurements were assessed in the early months of pregnancy (at 10-12 weeks gestation, 14-16 weeks gestation, and 18-20 weeks gestation) which is often before more pronounced sleep and cardiometabolic changes are evident. In Williams et al. for many of the comparisons, an atypical referent category and extreme definitions of shortened sleep duration resulted in small cell sizes and extremely wide confidence intervals. It is also unclear whether the third trimester changes in systolic and diastolic pressures are purely of statistical significance or whether these findings bear some clinical relevance. Additional studies of adequate sample size are needed to determine if sleep duration contribute to clinically significant hypertensive disorders.

Depression and Mood Disorders

Depressive symptoms, most typically thought of as arising during the postpartum period, have been associated with sleep duration in pregnancy. The first of two studies found examining this relationship, a cross sectional retrospective cohort study among ~1300 pregnant women < 20 weeks' gestation, women with physician-diagnosed clinical mood or anxiety disorders were found to be almost twice as likely than women without this history to report shorter sleep durations (OR 1.95

95% CI 1.03-3.69). This effect was more pronounced in overweight and obese women (aOR 2.88, 95% CI 1.14-7.32) (Qiu, Gelaye, Fida and Williams, 2012). In the second study, Okun et al. conducted a longitudinal cohort study of healthy pregnant women (n=160) with no underlying sleep or psychological disorders. The authors found that women who were sleep deficient had more perceived stress as measured by the Perceived Stress Scale ($p<0.01$) and more depressive symptoms as measured by the Inventory for Depressive Symptoms ($p<0.02$) than women who were not sleep deficient (Okun et al. 2013). While the Okun study was very well done, sleep duration was just one component of the authors' definition of sleep deficiency, therefore sleep duration and its contributions to stress and depression cannot be parsed out from other components of the authors' definition, namely insomnia and sleep quality. In summary, sleep duration is suggested to have a negative effect on mood and affect in pregnancy.

Birth weight, Fetal Growth Restriction, and Infant APGAR

There is a paucity of data available assessing the role of sleep duration on infant birth weight, fetal growth restriction, or infant APGAR. Only two studies have examined the potential association between sleep duration and fetal growth restriction or birth weight, and, in both studies, no associations were reported (Kennelly et al. 2011; Micheli et al. 2011). The only study found to examine infant APGAR and sleep duration reported a statistical difference between women sleeping less than 8 hours a night and women sleeping more than 8 hours a night and their infant's APGAR scores, but only one child had an abnormal score with an APGAR less than 7 (Zafarghandi et al. 2012). Further, the majority of infants in this study were scored with a perfect APGAR (10) which should be a relatively uncommon score because of the commonness of transient cyanosis. Further, no correlation coefficients were given, just frequency counts and a p-value making the results

extremely difficult to interpret. This poorly done study contributes essentially nothing to the current literature on sleep duration and pregnancy outcomes.

Conceptual Framework

The conceptual framework guiding this research is an adaptation from Katherine Lee's Theory of Impaired Sleep. In its most simplistic definition, Lee's theory postulates that the main concept of impaired sleep (or sleep loss) is a result of two distinct pathways, sleep deprivation (inadequate amounts of sleep) or sleep disruption (fragmentation of sleep), indicating that a directional relationship exists (Lee, 2003). These two distinct pathways can affect impaired sleep individually (e.g. independent of each other) or concomitantly. Impaired sleep in turn can affect a myriad of adverse health outcomes that have consequences affecting physiologic, cognitive, behavioral, emotional or social functioning domains (again representing a directional relationship). Risk factors for sleep deprivation and sleep disruption can be environmental, personal or developmental, with some risk factors being multifactorial. According to Lee, sleep deprivation is a direct result of 'self-imposed sleep restriction, lifestyle or work demands, or disruptions in circadian rhythms' (Lee, et al 2004). Given this definition, sleep deprivation can be viewed cumulatively as sleep deficit. For this line of inquiry, the specific question to be answered whether shortened sleep duration (or sleep deficit) is independently associated with adverse pregnancy outcomes, while controlling for risk factors for sleep disruption. In the proposed model (Appendix G), shortened sleep duration (represented by the darkened black arrow) can contribute directly to the pathogenesis several adverse infant outcomes (preterm birth, low birth weight, small for gestational age, and low APGAR) and several maternal outcomes (gestational hypertension, preeclampsia, gestational diabetes, postpartum depression, prolonged labor and cesarean section.) This model also represents the certain risk factors for sleep disruption (fragmentation) that might confound the relationship

between shortened sleep duration and adverse infant and maternal outcomes. On the right side of the model are the preexisting conditions and behaviors that will be controlled for as moderating risk factors for our outcomes of interest.

This framework is considered appropriate for several reasons. One, it is adaptable to pregnancy, and can account for physiologic changes specific to the pregnant state that might affect sleep. Two, because the pathways by which impaired sleep affects adverse infant and pregnancy outcomes are poorly defined at this time, the ability of the model to identify whether sleep primarily exerts its influence on adverse infant and pregnancy outcomes through sleep restriction alone or whether risk factors (e.g. co-morbid conditions) for disrupted sleep moderate these relationships is of great scientific benefit. Lastly, because shortened sleep duration and adverse infant and maternal outcomes is an emerging area of study, minimal research has been conducted in this area. For comparability purposes, it is beneficial to use similar a framework to pioneering researchers in the field.

Chapter 3: Research Design and Methods

Study Design

This dissertation work will be derived from a secondary analysis of the Pregnancy and Influenza Project (PIP), a prospective, observational cohort study assessing vaccine efficacy for prevention of lab-confirmed influenza illness among pregnant women receiving care through large, managed care health systems. Because of the relatively limited documented evidence on shortened sleep duration and infant and maternal outcomes (refer to Chapter 2), an exploratory study using existing data is deemed appropriate, despite the inability to determine definitively a cause and effect relationship. The major advantage for using the PIP as secondary data source in this exploratory design is the ability to cost-effectively examine our outcomes of interest in a large, prospectively collected dataset that is comprised of detailed clinical and maternal self-report.

Description of Parent Study

The PIP was a prospective cohort design. The primary objective of PIP was to estimate the effectiveness of influenza vaccine for the prevention of laboratory confirmed influenza illness among pregnant women, and therefore, the original sampling design was based on this primary research objective. A main consideration in determining vaccine effectiveness (VE) is dependent on observed person-time at-risk for influenza infection in vaccinated and unvaccinated groups; therefore, a prospective design was considered the most appropriate methodological approach. Prospective cohort studies are useful in assessing temporal sequences between exposure and the incidence of outcomes of interest by following an identified group without disease through time. Additional benefits for selection of a prospective cohort design are the ability to accurately track rates of infection in the cohort against the "background" rates of infection in the community, and to

accurately determine the onset of any outcome of interest. The main disadvantages in prospective designs (namely time and loss to follow up) were addressed by utilizing large managed care organizations that possessed strong research capabilities.

Nonprobability convenience sampling using a consecutive sampling design was selected based on the need to have availability and accessibility to sufficient numbers of pregnant women for a VE study. Two west coast large managed care health care systems were used to recruit subjects. The annual birth cohort in Site A is approximately 7,000, and in Site B approximately 25,000. Identification of the pregnancy cohort was based on an expected delivery date after the onset of influenza season (determined through local influenza activity surveillance) and a pregnancy at any given point through the end of the influenza season (determined through surveillance.) The cohort was dynamic, meaning that women were enrolled over time as they became pregnant, and exited the cohort over time due to completion or termination of the pregnancy and subsequent follow up.

Inclusion criteria for the pregnancy cohort consisted of the following: (a) Pregnant during the local influenza season (b) At least 16 years of age (Site A) and at least 18 years of age (Site B) (c) Accessed primary prenatal care through Site A or Site B and had attended at least one prenatal visit and (d) Able and willing to provide informed consent for study activities from point of enrollment through 6 months post-delivery. Exclusion criteria consisted of the following; (a) The woman was not pregnant (b) Informed consent was not obtained from the individual (c) The woman was unable to speak in either English or Spanish or (d) The woman had an anticipated delivery date outside established onset of influenza season.

In addition to cohort enrollment, women not already enrolled were identified through a health care visit for medically attended acute respiratory infection (MAARI) and asked to join the study. Despite complicating the study design, nesting a case-control sampling frame within the cohort was determined appropriate in order to maximize the numbers of influenza positive women

available for inclusion. Participant retention was addressed by the following: (a) Call to the participant if web-based surveillance was not completed (b) Staggering of the incentives to women for completing various phases of study and (c) Retention training and protocol for procedures on participants who decline further participation. The sites had the final responsibility for ensuring retention, and reserved the right to employ additional site-specific strategies.

Determining the adequate sample size for VE is dependent on the projected background incidence rates of influenza and on projected vaccine coverage. The original power calculations were developed under the following assumptions: (a) 17,000 women available to contribute 5 months of person-time to the study (total person-years = 7083) (b) Vaccination coverages in the study population of 25% to 40% (c) Background incidence rates of 5% (5/100 p-yrs.) and 10% (10/100 p-yrs.) and (d) A hypothesized vaccine effectiveness of 40% and 50%. The expected N was approximately 1,000 infected women with influenza with an equal number of women uninfected with influenza (~2000 total). Because background incidence rates of influenza were less than originally expected, the PIP study enrollment period was extended. Final sample size for the PIP study was 1,872 women. Determination of power calculations for the secondary study aims are discussed in a later section.

Procedures of the Parent Study

Patient recruitment:

Recruitment for PIP and consent differed at the two sites. At Site A, on-site study staff mailed study information to all eligible pregnant women identified through medical record rosters. Women not actively declining were contacted to attend an orientation session. Women choosing to join the study were provided written informed consent and received information on the weekly surveillance. Women not signing informed consent immediately were provided the consent and a

return envelope. On-site study staff contacted these potential participants 4-5 days later to go over consent and answer questions. At Site B, study brochures were given to all eligible pregnant women attending a Site B laboratory for pregnancy testing and at Site B prenatal clinics. Women were asked to call back to indicate interest. Women not actively declining were contacted by telephone and, if interested, were mailed a consent form. Women were re-contacted in 5-7 days to review consent information and were asked that the signed consent be returned. For women recruited through medically attended acute respiratory infection (MAARI visits), site study staff contacted presumed cases and asked for verbal informed consent for a screening interview (by phone). Women who met the acute respiratory infection (ARI) screening definition of self-reported fever, feverishness, or cough in the last 7 days were asked for written l informed consent to enroll in the study, provide a nasal aspirate specimen, and complete data collection. Depending on the development of ARI symptoms, participants potentially had 6 different data collection points including 4 interview (either in-person, or by phone) opportunities in the PIP study (see Table 1).

All phone interviews were conducted by call center study staff and in-person interviews were conducted by on-site study staff. **Enrollment interviews** were given to all cohort women with informed consent. The questionnaire was 15 minutes in length, covered ARI and symptom severity (for women with ARI symptoms at time of enrollment) pregnancy history, vaccination history, general health and medical history, sleep experience, health habits and general questions about household and demographics. **Weekly surveillance interview for ARI illness** asked enrolled women to log via the web or call in and complete an ARI screening questionnaire. If a participant failed to call or log in, call center study staff contacted the participant. If a woman screened positive for ARI, a visit was scheduled to ask a 5 minute **ARI illness episode interview** (to confirm reported symptoms and ask about symptom and illness severity) and to collect a nasal pharyngeal swab. The goal was to collect specimens and questionnaires within 4 – 7 days of symptom onset.

Approximately 1 week after collection of NP swabs, regardless of positivity, women were called back to assess the duration and severity of illness. If still experiencing symptoms, the interview was repeated weekly until the illness subsided. To identify MAARI participants, on-site study staff conducted daily surveillance of medical visits or call-ins for ARIs and contacted women seeking ARI care for screening. If screened positive, this triggered the ARI illness episode interview and nasal specimen collection outlined above. **Vaccination ascertainment** was triangulated through any self-report of vaccination and confirmed through EMR queries. If the participant received the vaccine outside of the Site A or Site B healthcare systems, participants were asked to provide a written record of the vaccination or (when possible) study staff queried the state vaccination registry. **Chart Abstraction/EMR Data Extraction** was used to provide medical record information on previously diagnosed medical conditions, influenza vaccination history, obstetrical and labor and delivery information, and information on ARI.

Problems encountered in the PIP Parent Study:

Several problems were encountered during the PIP Parent Study which might be pertinent to the secondary data analysis. First, the study had some participant losses because written consent was needed to initiate enrollment interviews. Second, PIP experienced a less than robust influenza season. The study period was extended for as long as any influenza activity was reported locally, yet despite the extension, fewer than expected women were flu positive. This resulted in a heavier reliance on MAARI participants than on cohort participants, and these two groups had differing enrollment interview timing. Lastly because of PIP's prospective nature, incomplete data and loss to follow-up was always a concern, however, completion of all study components was fairly robust >73%.

Secondary Analysis Study Methods

The planning, execution, analysis, and evaluation of this study will be based on the internationally accepted standards of epidemiological research, using the Good Epidemiologic Practice (GEP) Guidelines as a framework (HRSA, 2009).

Exclusion Criteria for Secondary Analysis

In order to reduce the influence of known confounders as much as possible at the onset of this exploratory research, women with certain risk factors will be excluded. Exclusion criteria ascertained via maternal self-report or medical record query will include the following:

- Multiple gestation in the current pregnancy
- Current pregnancy is less than < 6 months from last delivery (inadequate birth spacing)
- Women who have medical conditions in the year preceding the index pregnancy that are considered high risk indicators of the specific outcome of interest being examined (e.g. preexisting hypertension and preeclampsia, eclampsia, or preterm delivery; preexisting depression and depression in pregnancy, etc.)

Secondary analysis power calculations

Because the sample size in PIP is fixed, an analysis to determine the minimum detectible percent change in the prevalence for each outcome of interest (given the sample size, n=1872) was undertaken. Calculations are based on previously published rates from the literature, and preliminary estimates of statistical power, assuming $\alpha = .05$, and power at 80% with one independent variable. An on-line sample size calculator, available at http://clincalc.com/Stats/SampleSize.aspx , was used to input the known values of p_0 = proportion (prevalence) of population, the N = sample size for study group, α = probability of

type I error (set at 0.05), β = probability of type II error (set at 0.2), z = critical Z value for a given α or β in order to determine a hypothetical p_1 = proportion (prevalence) in the study group using following formula:

$$N = \frac{p_o q_0 \{ z_{1-\alpha/z} + z_{1-\beta} \sqrt{p_1 q_1 / p_o q_0} \}^2}{(p_1 - p_0)^2}$$

The hypothetical proportion prevalence was then subtracted from the population prevalence found in the literature to derive the minimum percent change detectable by our current study size.

When prevalence is known in the PIP study population, then more formal tests for statistical power can be determined if needed. With significance set at α = .05, and power at 80% and an expected effect size (ES) (small, medium, large), power can be calculated using a multiple and multiple partial correlation approach for correlation analyses or one way analysis of variance (ANOVA) approach for logistic regression in consultation with a previously published power primer (Cohen, 1992). Per Cohen, determination of the ES index formula for use in the multiple and multiple partial correlation approach and for a one-way ANOVA approach is as follows:

Correlation	One-way ANOVA
$f^2 = R^2 / 1 - R^2$	$f = \delta\mu / \delta$

Statistical Analysis

All data will be analyzed using IBM SPSS Statistics for Windows, Version 20 (Armonk, NY: IBM Corp.) or other appropriate statistical software with alphas set at <0.05, and 1-ß of 0.80. All raw data will be reviewed for accuracy, consistency, and completeness (Greenland & Rothman, 2008). Potential selection bias will be assessed by assessing demographic differences between

women included vs. excluded from the analysis (due to incomplete reporting/missing variables), using Chi-square tests for categorical variables and Student's t-test for continuous descriptive variables.

Variables and measures

All variables and measures in this secondary analysis will be gathered from maternal interview, medical records, or laboratory data. Katherine Lee's Theory of Impaired Sleep is the underlying conceptual framework (see Chapter 2), and all variables and concepts are mapped accordingly. Table 3 lists the variables and instruments, corresponding Aims, and the proposed collection times. Maternal self-reported questionnaire for the PIP study is found in Appendix B. Methodologies for all derived variables are found in Appendices C, D, E, and F.

Instruments and Measures

Pittsburgh Sleep Quality Index (PSQI)

The PSQI assesses sleep quality and disturbances using 19 self-rated items that are combined to form seven "component" scores. These score range from "0-3", with "3" indicating severe difficulty within each component (Buysse, Reynolds III, Monk, Berman & Kupfer, 1989). Component scores are then totaled for a composite global score (0-21) of "Sleep Quality". The PSQI has been used extensively in a variety of study populations. The original diagnostic psychometrics were determined in several psychiatric patients and revealed a sensitivity and specificity for global PSQI scores > 5 of 89.6% and 86.5% respectively,) with all component scores of interest correlating >0.80, indicating a high degree of internal homogeneity; stability across time, and can discriminate poor sleepers from non-impaired sleepers (Buysse, Reynolds III, Monk, Berman & Kupfer, 1989). Though not extensively evaluated in pregnancy, the PSQI has demonstrated acceptable psychometrics in pregnant populations. In a study examining the psychometrics of the PSQI in depressed and non-depressed pregnant women by Jomeen and Martin

(2007) internal consistency measured by Cronbach's alpha was .073 for all component subscale scores. In a more recent study examining psychometric aspects of the PSQI in pregnant women by Skouteris et al, internal consistency (measured by Cronbach's alpha) was .70 and .76 in two distinct time periods in pregnancy (2009). For the proposed analysis, the component scores subjective sleep quality, sleep duration, and habitual sleep efficiency will be used.

APGAR

APGAR scores will be used to assess condition and prognosis of the infant in the neonatal period. APGAR, a 10 point system, examines features of vital activity including heart rate, respiration and neuromuscular function. Poor APGAR outcome at birth have been shown to be significantly associated with neonatal death and is thought to be a better predictor of neonatal outcome than more objective measures such as arterial blood, even in the presence of acidemia (Casey, McIntire & Leveno, 2001).

Self-rated health

The single item standardized ordinal measure of perceived health status (self-rated health) will be used to assess pregnant women's overall perceptions of their general health. Self-rated health has been used extensively in population and epidemiologic research and is thought to be highly predictive of morbidity, mortality, and disability (Zajacova & Dowd, 2007). Several studies of self-rated health have been conducted recently among pregnant and postpartum women (Haas et al. 2004; Schytt & Waldenstrom, 2007; Teoli, Zullig & Hendryx, 2014), however, psychometrics of this variable specific to pregnant women were not found. A recent psychometric evaluation of self-rated health measured at two time points among the general population of U.S. adults showed a moderate correlation between the two measurements (0.75 correlation) but that the inter-rater agreement measured by Cohen's kappa coefficient was much lower at 0.43 and further, the reliability statistics of self-rated health varied by race and education (Zajacova & Dowd, 2011). Given the possibility of

bias in this item, consultation with a statistician on methods to correct for measurement error in regression analyses will be undertaken.

Subjective social status

The validated MacArthur Scale of Subjective Social Status, a scale that captures social status across several SES indicators, will be used to assess pregnant women's perceptions of where they stand in their social hierarchy (e.g. their place in their on their social ladder) (Adler & Stewart, 2007). The scale asks participants to "Picture a ladder with 9 steps on it. At the top of the ladder [Step 9], are the people in the United States who are the best off-those who have the most money, most education, and most respected jobs. At the bottom [Step 1] are the people who are the worst off - who have the least money, the least education, and the least respected jobs or no job. Pick a number from 1 to 9 to represent which step you would place yourself on the ladder with 1 being the worst off, 5 being in the middle, and 9 being the best off'. Subjective social status has been used to appraise SES in pregnant study populations (Dennis et al. 2012; Ostrove, Adler, Kuppermann & Washington, 2000; Stewart, Dean, Gregorich, Brawarsky & Haas, 2007). Psychometrics, while not assessed in pregnant populations, appear to be sound. In 2004, Operario et al. reported that among U.S. adults participating in a large random digit dial consumer survey, the test-retest reliability was p -0.62 (p-value <0.01).

Variables

Maternal Sleep Variables

Maternal self-report will be used to determine the following variables:

- Pre-pregnancy sleep duration
- Sleep changes since becoming pregnant
- Total sleep time
- Usual bed time and wake times

- Sleep latency

Pre-Pregnancy Physiologic and Psychologic Factors:

ICD-9 information from 1 year prior to pregnancy was electronically extracted from the medical record will be used to determine the following pre-existing medical conditions

- Pre-pregnancy depression, anxiety, hypertension, diabetes, epilepsy, cancer, chronic lung disease
- Heart, hepatic or renal disease
- Blood, neuromuscular, musculoskeletal, metabolic or immunological disorders
- Pre-pregnancy weight and obesity as determined by body mass index (BMI) will be measured two ways: via self-reported height and pre-pregnancy weight or by electronic medical records. Among childbearing age females, sensitivity and specificity for self-reported BMI is 82-85% and 99% respectively (Nieto-Garcia, Bush & Keyl, 1990). In the event of discordant findings between self-report and medical record BMI, the more objective measure of provider recorded weights will be used for the basis of analysis.

Conditions during pregnancy

ICD-9 information arising after date of conception will be used to derive the following variables:

- Threatened delivery
- Bleeding in pregnancy
- Hyperemesis gravidarum
- Epilepsy
- Infection in pregnancy

Current and past pregnancy history

Because women who have experienced pregnancy and childbirth are most likely different than women who have not, pregnancy history will also be considered as potential confounders in the current study. ICD-9 information will be used to determine the following variables:

- Best obstetric estimation for gestational age (~70% obtained from ultrasound dating; ~30% LMP)

Maternal report will be used to determine the additional variable s of:

- Current singleton or multiple gestation
- History of past multiple gestation
- Number of times the woman has been pregnant
- Number of resultant live births
- Number of resultant still births
- Number of miscarriages
- Number of ectopic pregnancies
- Number of terminations

Delivery information from electronic medical records will be used to derive the following:

- Cumulative weight gain by trimester

Infant outcomes

ICD-9 information will be used to derive/determine the following infant outcome variables:

- Preterm delivery
- Small for gestational age
- Infant birth weight/low birth weight

Delivery information from electronic medical records will be used to determine the following:

- 1 and 5 minute APGAR scores

Maternal outcomes

ICD-9 information will be used to generate the following derived maternal outcomes variables:

- Maternal gestational hypertension
- Preeclampsia and eclampsia
- Depression in pregnancy
- Prolonged labor
- Cesarean section

Laboratory values

Antenatal clinic records from electronic medical records will be used to determine the variables below. For mean values all available lab values in a given period of time are be averaged to derive mean variables.

- Mean systolic blood pressure (by time period)
- Mean diastolic blood pressure (by time period)
- Highest recorded systolic blood pressure (by time period)
- Highest recorded diastolic blood pressure (by time period)
- The highest recorded glucose tolerance test in a given time frame

Demographic variables

Maternal self-report will be used to determine the following variables:

- Race
- Hispanic ethnicity
- Age

- Marital status
- Household size
- Number of children in the household
- Maternal education
- Subjective social status will be used as a proxy for socioeconomic status since household income was not assessed in the PIP

Perceived health

Maternal self-report will be used to determine the following variables:

- Self-rated health

Health behaviors

Maternal self-report will be used to determine the following variables:

- Frequency of vitamin consumption
- Use, frequency, and history of maternal smoking
- Second hand smoke exposure
- Use, frequency, and history of maternal alcohol use

Data analysis by Specific Aim

Specific Aim 1: To identify risk factors for shortened sleep duration among pregnant women.

The analysis of Aim 1 seeks to determine the associated factors of shortened sleep duration in pregnant women. The following analytic steps are proposed:

Step 1: Describe the Data

Descriptive statistics, violations of assumptions, and assessments of normality will be conducted for the outcome of interest (sleep duration), participant characteristics, and covariates included in A1 analysis in accordance with the steps outlined by Greenland & Rothman (2008).

Step 2: Examine associations between covariates and outcome

Univariate associations between each potential covariate and the dependent variable total sleep time will be assessed. Because sleep duration will be examined as a continuous variable, Pearson correlation coefficients will be used. A minimum correlation coefficient (defined as $\varrho > \pm.25$) will be included in further linear regression modeling.

Step 3: Testing of collinearity

To ensure that any variability in the outcome of interest is not derived from highly correlated covariates, tests of collinearity will be performed. Pearson correlation coefficients will be used to assess continuous variables, t-tests will be used to assess dichotomous variables, and an analysis of variance (ANOVA) will be used to assess categorical variables with more than two categories. Correlation coefficients of $\varrho > \pm.25$ and AVOVA and t-test comparisons with p-values ≤ 0.1 will be considered in further regression modeling.

Step 4: Conduct linear regression modeling

Linear regression modeling will be conducted to examine the associations between sleep duration and the covariates meeting inclusion criteria. A significant association will be established if the Coefficient $\beta \neq 0$. To assess for moderation effects, interactions among variables included in the final model will be tested.

Specific Aim 2: To evaluate the association between shortened sleep duration during pregnancy and subsequent adverse maternal outcomes.

The analysis of Aim 2 seeks to establish if a relationship between sleep duration (independent variable) and adverse maternal outcomes (gestational diabetes and incident hypertensive disorders in pregnancy; the dependent variables) exists. Because of the multiple a-priori comparisons being proposed, a Bonferroni adjustment will be used to protect against Type 1 error (Portney & Watkins, 2009). For Specific Aim 2, the following analytic steps are proposed:

Step 1: Describe the data

Same procedure as outlined in Aim 1

Step 2: Examine the association between independent variable of sleep duration and each outcome of interest.

The univariate association will be assessed using the Pearson correlation coefficient. If the result has a minimum correlation coefficient (defined as $\varrho > \pm.25$) then further analysis is warranted.

Step 3: Assess for potential confounders

Univariate associations between the independent variable of sleep duration and each potential confounder and between the dependent infant outcomes variables and each potential confounder will be assessed. Pearson correlation coefficients will be used to assess the continuous variables, and ANOVA will be used to assess the categorical variables. Correlation coefficients greater than $\varrho > \pm.25$ will be included in further linear regression modeling. For ANOVA comparisons, F-ratio p-values ≤ 0.1 will be considered in further regression modeling.

Step 4. Conduct linear regression modeling

Linear regression modeling will be conducted to examine the associations between sleep duration and infant outcomes, controlling for the psychological, sociodemographic, behavioral, and physiological/medical variables which also meet criteria as potential confounders. A significant

association will be established if the Coefficient β and the 95% confidence interval do not overlap with zero.

Specific Aim 3: To evaluate the association between shortened sleep duration during pregnancy and subsequent adverse infant outcomes.

The analysis of Aim 3 seeks to establish if a relationship between sleep duration (independent variable) and adverse infant outcomes (preterm birth and small for gestational age; the dependent variables) exist. The same steps outlined in Aim 2 will be employed for the analysis of Aim 3. Again, because of the multiple a-priori comparisons that are proposed, a Bonferroni adjustment will be used.

Limitations

Several limitations to the proposed approach exist. First, not all variables associated with maternal sleep in pregnancy are available in this dataset. For example, only three subscales of the PSQI are available for analysis. There is a possibility that if associations are shown, the results are actually reflecting an unmeasured bias. Second, only subjective measures for sleep are available, which introduces the possibility of recall bias. Third, a commonly accepted condition known to affect sleep, anxiety, was not collected using a validated instrument. Therefore any interpretation of the findings of this variable can be called into question, and thus the decision was made to exclude it from the current analysis. Exclusion of a known risk factor can introduce differential measurement bias into the results. Lastly, in secondary analyses, there is a lack of control regarding data collection procedures; there is no ability to go back to respondents to clarify answers, add questions, or correct missing/incorrect data.

Summary

Some but limited evidence suggests that there is a possible relationship between maternal self-reported sleep duration and several pregnancy and infant outcomes. The current study proposes looking at several maternal and infant outcomes in the context of shortened sleep duration; and is one of the few datasets of adequate sample size available to date. The goal of this exploratory study is to first describe any associations and the potential magnitude of the problem. Without this critical first step, we can only guess at whether shortened sleep duration would be a potential causal factor in the development of poor maternal and infant outcomes in experimental designs. Even though this exploratory study cannot establish any causality, given the expense, subject risks, and time commitment that is inherent with experimental designs, and the paucity of data that currently exists on the topic, it makes sense to examine shortened sleep duration and maternal and infant outcomes first in existing data. If impaired sleep, a potentially intervenable condition, is determined to be a factor in the development of adverse outcomes, then addressing this clinical concern has great potential for positive impact through decreasing maternal and neonatal morbidity and mortality and associated health care costs.

TABLE 1. Data Collection Points PIP Parent Study

Study procedures	Participants	
	Cohort	MAARI
Enrollment to time of delivery		
Enrollment interview	¥	
Weekly follow up	¥	¥
Collect NP swab, temp, and illness episode interview*	Ŧ	¥
If tested for flu, Illness duration interview	Ŧ	¥
Chart abstraction	¥	¥
EMR data extraction	¥	¥
¥ = data collection Ŧ = potential data collection *illness episode interview for MAARI cases include enrollment interview questions from cohort instrument		

Table 2. Sample Size Calculations for Outcomes of Interest given N=1872

Variable/Definition	Prevalence from literature	Minimum detectable % change in prevalence given N	Source
Sleep duration <7 hours	25% to 40% dependent on trimester of pregnancy	2.85% and 3.2% respectively	Facco, Kramer, Ho, Zee & Grobman, 2010
Preterm birth < 37 weeks	11.6%	2.15%	Martin, Hamilton, Osterman, Curtin & Mathews, 2013
Small for gestational age Birth weight at or below 10% for a given gestational age	10% for Hispanics, non-Hispanic whites, Asian/Pacific Islander (14%) and 17% for non-Hispanic blacks	2%, 2.3% and 2.5% respectively	CDC, 2008
Gestational hypertension	3.06%	1.19%	Wallis, Saftlas, Hsia & Atrash, 2008
Preeclampsia	2.94%	1.16%	Wallis, Saftlas, Hsia & Atrash, 2008
Gestational diabetes	4.6% (birth certificates) 8.7% (maternal self-report)	1.4% and 1.9% respectively	DeSisto, Kim & Sharma, 2014

Table 3. Variables and Measures

Variables, Instruments, and Data Origin				
Variable	**Measured By:**	**Variable Type by Aim**	**Treated as**	**Data Origin**
Total sleep time	Self-reported Standardized item "During the past month, how many hours of actual sleep did you get at night? Please estimate as close as possible in 15 minute increments."	Dependent A1 Independent A2, A3	Continuous	Enrollment interview
Bedtime	Self-reported Standardized item "During the past month, what time have you usually gone to bed at night?"	Dependent A1 Independent A2, A3	Continuous	Enrollment interview
Awaken time	Self-reported Standardized item "During the past month, what time have you usually gotten up in the morning?"	Dependent A1 Independent A2, A3	Continuous	Enrollment interview
Sleep latency	Self-reported Standardized item "During the past month, how long (in minutes) has it usually taken you to fall asleep each night?"	Dependent A1 Independent A2, A3	Continuous	Enrollment interview
Gestational age at time of delivery	Best obstetric estimation derived from EMR (U.S. 70%, LMP 30%)	Dependent A2	Continuous	Electronic medical records/Delivery file
Preterm delivery	Gestational age between 32 and < 37 weeks	Dependent A2	Categorical	Derived variable; see Infant Variable Creation Plan (IVCP)
Very Preterm	Gestational age < 32 weeks	Dependent A2	Categorical	Derived variable; see IVCP

Infant birth weight	Birth weight grams	Dependent A2	Continuous	Electronic medical records/Delivery file
Low birth weight	<2500 grams	Dependent A2	Categorical	Electronic medical records/Delivery file
Small for Gest Age	Fetal birth weight below 10^{th} percentile for gest age	Dependent A2	Categorical	Derived variable; see IVCP
1 minute APGAR	Total APGAR score at 1 minute (range 1-10)	Dependent A2	Continuous	Electronic medical records/Delivery file
5 minute APGAR	Total APGAR score at 5 minutes (range 1-10)	Dependent A2	Continuous	Electronic medical records/Delivery file
Systolic blood pressures (average)	Maternal systolic blood pressure (average of all values in given time period)	Dependent A3	Continuous	Derived variable; See Vitals and Labs Variable Creation Plan (VLVCP)
Systolic blood pressures (highest)	Maternal systolic blood pressure (highest recorded value in given time period)	Dependent A3	Continuous	Derived variable; See VLVCP
Diastolic blood pressures (average)	Maternal diastolic blood pressure (average of all values in given time period)	Dependent A3	Continuous	Derived variable; See Vitals and Labs Variable Creation Plan (VLVCP)
Diastolic blood pressures (highest)	Maternal systolic blood pressure (highest recorded value in given time period)	Dependent A3	Continuous	Derived variable; See VLVCP
Glucose tolerance test (GTT)	Glucose tolerance test (highest recorded value in given time period recorded in EMR)	Dependent A3	Continuous	Derived variables; See VLVCP
Maternal gestational hypertension	Hypertension in pregnancy from ICD 9 codes	Dependent A3 Covariate A1*, A2	Categorical	Derived variable; See MVCP

Preeclampsia or eclampsia	Preeclampsia or eclampsia from ICD 9 codes	Dependent A3 Covariate A2	Categorical	Derived variable; See MVCP
Maternal gestational diabetes (GDM)	GDM in pregnancy from ICD 9 codes	Dependent A3 Covariate A1*, A2	Categorical	Derived variable; See MVCP
Depression in pregnancy	Depression in pregnancy from ICD 9 codes	Dependent A3 Covariate A1*, A2	Categorical	Derived variable; See MVCP
Prolonged labor	Prolonged labor from ICD 9 codes	Dependent A3 Covariate A2	Categorical	Derived variable; See MVCP
C-section	C-section from ICD 9 codes	Dependent A3	Categorical	Derived variable; See MVCP
Covariates				
Basic Demographics				
	Ethnicity	Covariate A1, A2, A3	Categorical	Enrollment interview
	Race	Covariate A1, A2, A3	Categorical	Enrollment interview
	Age	Covariate A1, A2, A3	Continuous	Enrollment interview
	Marital status	Covariate A1, A2, A3	Categorical	Enrollment interview
	Household size	Covariate A1, A2, A3	Categorical	Enrollment interview
	# of children in household	Covariate A1, A2, A3	Categorical	Enrollment interview
	Maternal education	Covariate A1, A2, A3	Categorical	Enrollment interview
Self-rated health				
Self-rated health	Standardized item; ordinal scale "How would you describe your overall health?"	Covariate A1, A2, A3	Categorical	Enrollment interview
Maternal depression prior to pregnancy	Pre-existing depression from ICD9 codes	Covariate A1, A2, A3	Categorical	Derived variable; see Maternal Outcomes Variable Creation Plan (MVCP)

Pregnancy history				
# of babies carrying	Self-reported "How many babies are you carrying?"	Covariate A1, A2, A3	Categorical	Enrollment interview
# of pregnancies	Self-reported "How many times have you been pregnant?"	Covariate A1, A2, A3	Continuous	Enrollment interview
Multiple births	Self-reported "Were any of your previous pregnancies multiple pregnancies, which is twins, triplets, or other multiple?	Covariate A1, A2, A3	Categorical	Enrollment interview
Cesarean section	Self-reported "Have you ever had a cesarean delivery?"	Covariate A3	Categorical	Enrollment interview
Live births	Self-reported "How many live born babies have you had?"	Covariate A1, A2, A3	Continuous	Enrollment interview
Miscarriages	Self-reported "Have you ever had a miscarriage?"	Covariate A1, A2, A3	Categorical	Enrollment interview
Miscarriage count	Self-reported "How many miscarriages have you had?"	Covariate A1, A2, A3	Continuous	Enrollment interview
Stillborn	Self-reported "Have you ever had a stillborn infant?"	Covariate A1, A2, A3	Categorical	Enrollment interview
Stillborn count	Self-reported "How many stillborn infants have you had?"	Covariate A1, A2, A3	Continuous	Enrollment interview
Abortion	Self-reported "Have you ever had an elective termination or abortion?"	Covariate A1, A2, A3	Categorical	Enrollment interview
Abortion count	Self-reported "How many elective terminations or abortions have you had?"	Covariate A1, A2, A3	Continuous	Enrollment interview

Ectopic pregnancy	Self-reported "Have you ever had an ectopic pregnancy?"	Covariate A1, A2, A3	Categorical	Enrollment interview
Other pregnancy outcome	Self-reported "Have you ever had any other outcome?" (text field results will be manually examined)	Covariate A1, A2, A3	Categorical	Enrollment interview
Maternal weight				
Maternal weight prior to pregnancy	Self-reported pre-pregnancy weight	Covariate A1, A2, A3	Continuous	Enrollment interview
Pre-pregnancy weight EMR	Most recent weight obtained in the year prior to date of conception available in EMR	Covariate A1, A2, A3	Continuous	Derived variable; see VLVCP
Cumulative weight gain EMR	Cumulative weight gain by trimester available in EMR	Covariate A1, A2, A3	Continuous	Derived variables; see VLVCP
Maternal BMI prior to pregnancy	BMI calculated from self-reported weight and height	Covariate A1, A2, A3	Continuous	Enrollment interview
BMI classification	BMI classification using: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html	Covariate A1, A2, A3	Categorical	Enrollment interview
Pre-existing conditions 1 year prior to DOC				
Pre-existing maternal hypertension	Hypertension prior to pregnancy from ICD 9 codes	Covariate A1, A2, A3	Categorical	Derived variable; See MVCP
Pre-existing maternal diabetes	Diabetes prior to pregnancy from ICD 9 codes	Covariate A1, A2, A3	Categorical	Derived variable; See MVCP
Pre-existing maternal depression	Depression prior to pregnancy from ICD 9 codes	Covariate A1, A2, A3	Categorical	Derived variable; See MVCP
Pre-existing maternal epilepsy	Epilepsy prior to pregnancy from ICD 9 codes	Covariate A1, A2, A3	Categorical	Derived variable; See MVCP
Chronic lung disease or asthma	Pre-pregnancy lung disease or asthma from ICD 9 codes	Covariate A1, A2, A3	Categorical	Derived variable; See High Risk Respiratory

				Variable Creation Plan (HRRVCP)
Chronic heart disease	Pre-pregnancy heart disease from ICD 9 codes	Covariate A1, A2, A3	Categorical	Derived variable; See High Risk Respiratory Variable Creation Plan (HRRVCP)
Chronic hepatic disease	Pre-pregnancy hepatic disease from ICD 9 codes	Covariate A1, A2, A3	Categorical	Derived variable; See High Risk Respiratory Variable Creation Plan (HRRVCP)
Chronic renal disease	Pre-pregnancy renal disease from ICD 9 codes	Covariate A1, A2, A3	Categorical	Derived variable; See High Risk Respiratory Variable Creation Plan (HRRVCP)
Blood disorders	Pre-pregnancy blood disorders from ICD 9 codes	Covariate A1, A2, A3	Categorical	Derived variable; See High Risk Respiratory Variable Creation Plan (HRRVCP)
Neurological or musculoskeletal disorders	Pre-pregnancy neurological or musculoskeletal disorders from ICD 9 codes	Covariate A1, A2, A3	Categorical	Derived variable; See High Risk Respiratory Variable Creation Plan (HRRVCP)
Immunological disorders	Pre-pregnancy immunological disorders from ICD 9 codes	Covariate A1, A2, A3	Categorical	Derived variable; See High Risk Respiratory Variable Creation Plan (HRRVCP)
Cancer	Pre-pregnancy cancer from ICD 9 codes	Covariate A1, A2, A3	Categorical	Derived variable; See High Risk Respiratory Variable Creation Plan (HRRVCP)
Metabolic disorders (excludes diabetes)	Pre-pregnancy metabolic disorders from ICD 9 codes	Covariate A1, A2, A3	Categorical	Derived variable; See High Risk Respiratory Variable Creation Plan (HRRVCP)
Conditions during pregnancy				
Threatened delivery	Threatened delivery from ICD 9 codes	Covariate A1*, A2, A3	Categorical	Derived variable; See MVCP

Bleeding in pregnancy	Bleeding in pregnancy from ICD 9 codes	Covariate A1*, A2, A3	Categorical	Derived variable; See MVCP
Hyperemesis gravidarum in pregnancy	Hyperemesis gravidarum from ICD 9 codes	Covariate A1*, A2, A3	Categorical	Derived variable; See MVCP
Epilepsy in pregnancy	Epilepsy in pregnancy from ICD 9 codes	Covariate A1*, A2, A3	Categorical	Derived variable; See MVCP
Infection in pregnancy	Infection in pregnancy from ICD 9 codes	Covariate A1*, A2, A3	Categorical	Derived variable; See MVCP
Behaviors				
Preconception vitamin use	Self-reported "Have you taken any multivitamins, prenatal vitamins or Vitamin D before becoming pregnant?"	Covariate A1, A2, A3	Categorical	Enrollment interview
Prenatal vitamin use	Self-reported "Have you taken any multivitamins, prenatal vitamins or Vitamin D since becoming pregnant?"	Covariate A1, A2, A3	Categorical	Enrollment interview
Preconception vitamin use frequency	Self-reported "How often did you take [insert vitamin] Ordinal scale	Covariate A1, A2, A3	Categorical	Enrollment interview
Prenatal vitamin use frequency	Self-reported "How often did you take [insert vitamin] Ordinal scale	Covariate A1, A2, A3	Categorical	Enrollment interview
Preconception folic acid use	Self-reported "Have you taken a folic acid supplement other than what was in a multivitamin or prenatal vitamin before becoming pregnant?"	Covariate A1, A2, A3	Categorical	Enrollment interview
Prenatal folic acid use	Self-reported "Have you taken a folic acid	Covariate A1, A2, A3	Categorical	Enrollment interview

	supplement other than what was in a multivitamin or prenatal vitamin since becoming pregnant?"			
Preconception folic acid use frequency	Self-reported "How often did you take folic acid?" Ordinal scale	Covariate A1, A2, A3	Categorical	Enrollment interview
Prenatal folic acid use frequency	Self-reported "How often did you take folic acid?" Ordinal scale	Covariate A1, A2, A3	Categorical	Enrollment interview
Current smoker	Self-reported "Do you currently smoke?"	Covariate A1, A2, A3	Categorical	Enrollment interview
Smoking frequency	Self-reported "How many cigarettes do you smoke per week?"	Covariate A1, A2, A3	Continuous	Enrollment interview
Smoking Hx	Self-reported "Have you ever smoked?"	Covariate A1, A2, A3	Categorical	Enrollment interview
Smoke quit	Self-reported "Did you quit smoking before or after you became pregnant?"	Covariate A1, A2, A3	Categorical	Enrollment interview
Secondhand smoke	Self-reported "Does anyone in your household currently smoke cigarettes in your presence?"	Covariate A1, A2, A3	Categorical	Enrollment interview
Sleep quality	Self-reported Standardized question "During the past month, how would you rate your sleep quality overall?" Likert scale	Covariate A1, A2, A3	Categorical	Enrollment interview
Sleep change	Self-reported Standardized question	Covariate A1, A2, A3	Categorical	Enrollment interview

	"Overall, has the amount you sleep each night decreased, stayed the same or increased since you became pregnant?"			
Pre-pregnancy sleep duration	Self-reported Standardized question "During the month before you became pregnant, how many hours of actual sleep did you get at night? Please estimate as close as possible in 15-minute increments"	Covariate A1, A2, A3	Continuous	Enrollment interview
Prenatal ETOH consumption	Self-reported Standardized question "During the past month have you had a beverage containing ETOH?"	Covariate A1, A2, A3	Categorical	Enrollment interview
Prenatal ETOH consumption frequency	Self-reported Standardized question "During the past month how often did you drink beverages containing ETOH?" [days per week or days per month]	Covariate A1, A2, A3	Continuous	Enrollment interview
Prenatal ETOH consumption high risk	Self-reported Standardized question "During the past month did you have 4 or more beverages containing ETOH on one occasion?" [# of times]	Covariate A1, A2, A3	Continuous	Enrollment interview
Prenatal ETOH consumption ever	Self-reported Standardized question	Covariate A1, A2, A3	Categorical	Enrollment interview

	"Have you had a beverage containing ETOH since becoming pregnant?"			
Subjective SES				
Subjective SES	Standardized instrument; ordinal scale (1-9) [see q85 on enrollment interview]	Covariate A1, A2, A3	Categorical	Enrollment interview

***if diagnosis in pregnancy prior to date of reported sleep duration**

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Paper 1

Shortened sleep duration and risk of gestational diabetes mellitus and incident hypertensive disorders in pregnancy

Jennifer Lynn Williams MSN, MPH, FNP-BC

Nell Hodgson Woodruff School of Nursing

Emory University

Abstract

Objective: The contribution of self-reported sleep duration (SRSSD) in pregnancy to adverse maternal outcomes is poorly understood. The purpose of this study is t**o** determine if SRSSD defined as < 7 hours a night is associated with clinically diagnosed gestational diabetes mellitus (GDM), incident hypertension, or preeclampsia in the second or third trimesters of pregnancy.

Sample and Design: Data was derived from the Pregnancy and Influenza Study (PIP), a prospective, observational cohort of pregnant women receiving prenatal care through two managed health care systems.

Participants:This secondary analysis focused on a subset of women with singleton pregnancies who enrolled during gestation. Exclusions included preexisting diabetes or hypertension, or a diagnosis in the first trimester (final sample n=1165).

Methods: Univariate associations were conducted using Pearson chi-squared (χ 2) tests. Multinomial logistic regression models were conducted separately for each outcome. Analyses were conducted with SPSS version 21(SPSS Inc., Chicago, IL)

Results: The majority of women reported sleeping 7-9 hours a night (69%). SRSSD was reported by 11% of respondents. Nine percent of women had clinically diagnosed GDM; 7% incident hypertension in pregnancy, and 3% had preeclampsia. In logistic regression models, SRSSD was not associated with clinically diagnosed GDM (Adjusted Odds Ratio (aOR) 1.18, 95% confidence interval (CI) 0.55-1.98), incident hypertension in pregnancy (aOR 0.69, CI 0.29-1.66), or preeclampsia, (aOR 1.54 CI 0.56-4.25).

Conclusion: Results from this analysis did not find associations between SRSSD and clinically diagnosed GDM, incident hypertension in pregnancy, or preeclampsia. Further research is needed

on longitudinal effects of sleep duration and adverse pregnancy and infant outcomes.

Shortened sleep duration and risk of gestational diabetes mellitus and incident hypertensive disorders in pregnancy

Introduction

According to the National Institute of Neurological Disorders and Stroke, most adults need 7-8 hours of sleep a night (NIH 2014). The effects of shortened sleep duration in the general population can negatively alter metabolic and endocrine function (Knutson, 2012; Spiegel, Knutson, Leproult, Tasali & Van Cauter, 2008; Spiegel, Leproult & Van Cauter, 1999), and increase inflammatory and immune processes (Irwin, Thompson, Miller, Gillin & Ziegler, 1999; Irwin 2002; Majde & Krueger, 2005), and there is a growing body of evidence that shortened sleep duration is a risk factor for cardiometabolic disturbances. Epidemiological data from non-pregnant adult populations have linked shortened sleep duration (i.e., typically reported as 6 hours or less a night) to metabolic and cardiovascular diseases such as hypertension (Altman et al. 2012; Faraut et al. 2012; Gangwisch, Feskanich, Malaspina, Shen & Forman, 2013; Gottlieb et al. 2006; Kim et al. 2012), myocardial infarction (Altman et al. 2012), stroke (Altman et al. 2012; von Sarnowski et al. 2013), diabetes and insulin resistance (Altman et al. 2012; Chao et al. 2011; Chaput, Després, Bouchard & Tremblay, 2007; Hancox & Landhuis, 2012; Liu, Kushida & Reaven, 2013; Rafalson et al. 2010; Zizi et al. 2012), metabolic syndrome (Choi et al. 2008), and obesity (Bjorvatn et al. 2007). Although this body of research has focused on non-pregnant adults, researchers have argued that disease states associated with shortened sleep duration seen in the general population might also have cardiometabolic correlates in pregnancy (Chang, Pien, Duntley & Macones, 2010; Izci-Balserak & Pien, 2014; Okun, Roberts, Marsland & Hall, 2009).

There is an emerging but limited body of evidence suggesting that self-reported shortened sleep duration in pregnancy adversely affects maternal cardiometabolic control of hypertension and

impairs glucose intolerance or is associated with clinically diagnosed gestational diabetes or hypertensive disorders in pregnancy. (Facco et al., 2010; Qiu et al., 2010; Rawal et al. 2016; Reutrakul et al. 2011 Williams et al. 2010). While these studies support the hypothesis that shortened sleep duration is a contributing factor to adverse cardiometabolic outcomes, other studies have shown no associations. Specifically, some studies examining self-reported shortened sleep duration have failed to show an association with hypertensive disorders (Hayney, Buysse, Rosario, Chen & Okun, 2014; Reutrakul et al. 2011), or gestational diabetes (Izci-Balserak, Jackson, Ratcliffe, Pack & Pien, 2013). Table I summarizes the literature to date examining sleep duration in pregnancy and cardiometabolic outcomes and is organized by study type, methods for determining sleep duration, sample size, study outcomes (cardiometabolic markers or clinically diagnosed disease), and major findings. The majority of the studies reviewed focused on cardiometabolic markers versus clinically diagnosed disease. Regardless of which study outcomes were examined (markers vs. disease), from the review of the available studies, there appears to be no consensus on the contribution of shortened sleep duration to cardiometabolic disturbances in pregnancy. Several limitations might explain these conflicting data in the current body of evidence, including cross-sectional or retrospectively collected sleep data, small or non-representative samples, and different definitions of sleep. Prospective studies of sufficient size are needed to explicate any associations that shortened sleep duration in pregnancy might have on adverse cardiometabolic outcomes in pregnancy.

Women's sleep needs increase during pregnancy, especially during their first three months; most pregnant women may need more hours than the 7-8 hours needed by non-pregnant individuals (NIH, 2014). However, recent studies using either < 7 hours duration or < 6 hours duration to define short sleep have reported that a quarter to one-third of pregnant women experience shortened sleep duration in the first trimester, and the proportion of women experiencing shortened sleep duration increases as pregnancy progresses, with up to half of pregnant women reporting

shortened sleep duration in the third trimester (Facco et al. 2010; Mindell, Cook & Nikolovski, 2015; Signal et al. 2014; Sivertsen, Hysing, Dørheim & Eberhard-Gran, 2015). Compared to non-pregnant women, pregnant women are three times more likely to experience short sleep duration (≤ 6hours) (Signal et al. 2014). To summarize, during pregnancy when women's sleep needs tend to increase, many women suffer inadequate sleep, and more women will experience inadequate sleep as the pregnancy continues.

Many of the normal changes in pregnancy predispose a woman to sleep problems. Physiologic, anatomic, and hormonal changes such as (but not limited to) gestational weight gain, estrogenic effects, displacement from the gravid uterus, nasopharyngeal edema, and decreased functional reserve capacity contribute to the frequent arousals and disruptions in the quality, quantity, and makeup of a pregnant woman's sleep (Micheli et al. 2011; Pien & Schwab, 2004; Sahota, Jain & Dhand, 2004). Like sleep in the general population, several physiologic functions, such inflammation and oxidative stress, and altered metabolism, are thought to be affected by shortened sleep duration. These functions share common pathways through which sleep disturbances might negatively influence pregnancy (Izci-Balserak & Pien 2014; O'Keeffe & St-Onge, 2013; Okun, Roberts, Marsland & Hall, 2009).

Whether shortened self-reported sleep duration contributes to adverse cardiometabolic outcomes in pregnancy is still undetermined. Given the high prevalence of shortened sleep duration among pregnant women, the previously reported strong associations between sleep and cardiometabolic disturbances seen in the general population, and the paucity of available literature on sleep duration in pregnancy and clinically diagnosed cardiometabolic disease in pregnancy, this study aimed to examine whether self-reported shortened sleep duration is associated with clinical diagnoses of gestational diabetes or hypertensive disorders in pregnancy (preeclampsia and gestational hypertension). Given that objective measures of sleep duration such as the gold standard

polysomnography (PSG) are intrusive, difficult to administer, and are not considered a realistic method for assessing sleep outside a sleep research setting (Marino et al. 2013), the current study examined whether an easily collected measure such as self-reported sleep duration could be used to identify women at risk for adverse cardiometabolic conditions in pregnancy. Specifically, the hypothesis examined was that pregnant women who self-report shorter sleep durations will be more likely to be clinically diagnosed with gestational diabetes or have gestational hypertension or preeclampsia in the 2nd or 3rd trimester of pregnancy.

Study Design

Data for this study was obtained from the Pregnancy and Influenza Study (PIP study) a prospective, observational cohort study assessing vaccine efficacy for prevention of lab-confirmed influenza illness among pregnant women receiving care through large, managed care health systems. Recruitment began in 2011, and nonprobability convenience sampling using a consecutive sampling design was selected based on the need to have availability and accessibility to sufficient numbers of pregnant women for a VE study. Two west coast large managed care health care systems were used to recruit subjects. Detailed methods on the identification of the pregnancy cohort and protocol have been described elsewhere (Thompson et al. 2011).The cohort was dynamic, meaning that women were enrolled over time as they became pregnant, sought care, and consented to participate, and exited the cohort over time due to completion or termination of the pregnancy and subsequent follow-up. PIP data were obtained from interviews at enrollment, medical chart abstraction, and electronic medical records (EMR) extraction.

This study focuses on a subset of women in the PIP Study who completed enrollment interviews during gestation, had all values for determining self-reported sleep duration, and had a singleton pregnancy.

The enrollment interview questionnaire was given to all cohort women with informed consent. The questionnaire was 15 minutes in length, covered acute respiratory illness (ARI) and symptom severity (for women with ARI symptoms at the time of enrollment), pregnancy history, vaccination history, general health and medical history, sleep experience, health habits and questions about household and demographic characteristics. Chart Abstraction/EMR Data Extraction was used to provide medical record information on gestational age, previously diagnosed medical conditions, vaccination history, obstetrical and labor and delivery information, vital signs and laboratory data, and information on medical encounters from one year prior to pregnancy though six months post-partum.

Final Analytic Sample

A total of 1,271 women with singleton pregnancies completed enrollment interviews in pregnancy. Forty respondents were excluded due to missing values where total sleep time could not be calculated (n=35) or had implausible total sleep times (reported sleep durations of ≤3 hours or less, or > 20 hours a night) (n=5). An additional 66 respondents were ineligible because they had pre-existing diabetes or hypertension (n=49), or were diagnosed with hypertension, diabetes, or preeclampsia in the first trimester (n=17). The final analytic sample with singleton pregnancies and clinical information available from the 2nd and 3rd trimester of pregnancy was 1,165 women. (Figure 1).

Self-reported Sleep Duration

Information on sleep duration for this study was collected from women during their enrollment interviews. The independent variable of total sleep time was calculated by determining the usual bedtime, asked as "During the past month, what time have you usually gone to bed at night?" and subtracting from the usual awaken time asked as "During the past month, what time

have you usually gotten up in the morning?" to derive the in-bed total minutes. Sleep latency asked as "During the past month, how long (in minutes) has it usually taken you to fall asleep each night?" was then subtracted from the in-bed total minutes to derive the final asleep total minutes variable. Because of the curvilinear relationship between poor sleepers and adverse cardiometabolic outcomes reported in the literature (Williams 2010; Qiu, Frederick, Sorensen, Enquobahrie, Williams, 2014), sleep was examined categorically with 7-9 hours duration set as the referent. A variety of cut-points has been used to describe extreme sleep categories. Because of small numbers of very short sleepers (< 6 hours) and very long sleepers (>10 hours), short sleep was defined as < 7 hours and long sleep as > 9 hours.

Cardiometabolic Outcomes

The International Classification of Diseases, Ninth Edition (ICD-9) information documenting medical encounters from 1 year prior to pregnancy was electronically extracted from the medical record and was used to determine selected pre-existing medical conditions, any diagnoses during pregnancy, and the cardiometabolic outcomes diagnoses of interest.

Gestational Diabetes Mellitus

Gestational diabetes mellitus was defined as any ICD 9 diagnosis of gestational diabetes (648.8) identified from the electronic medical record in the second or third trimesters. Women with a previous ICD 9 diagnoses of preexisting diabetes (250. inclusive) or pancreatic disorders (251. inclusive) in the year prior to pregnancy were excluded. Women with a diagnosis of gestational diabetes mellitus in the 1st trimester were also excluded as these women most likely had undiagnosed preexisting diabetes mellitus.

Hypertension in Pregnancy

Incident hypertension in pregnancy was defined as any ICD 9 diagnosis of gestational hypertension (642.3, 642.9), preeclampsia or eclampsia (642.4 through 642.7) identified from the electronic medical record in the second or third trimesters. In order to examine the entire spectrum of hypertensive disorders in pregnancy, the ICD 9 diagnoses for gestational hypertension and preeclampsia were combined into one hypertension in pregnancy variable. Incident hypertension that first developed during the 2nd or 3rd trimester in pregnancy was the primary interest, therefore women with a previous ICD 9 diagnosis of essential hypertension (401. Inclusive), essential hypertension complicating pregnancy (642.0) hypertension secondary to renal disease (642.1) or other preexisting hypertension (642.2) in the year prior to pregnancy were excluded. Additionally, women with a diagnosis of gestational hypertension or preeclampsia in the 1st trimester were also excluded because these women most likely had an undiagnosed preexisting hypertensive disorder. Because of higher risks for adverse pregnancy outcomes seen in preeclampsia, preeclampsia in the 2nd and 3rd trimester of pregnancy was also examined separately as a subset of hypertension in pregnancy.

Covariates and Potential Confounders

Several covariates were included to describe this population of pregnant women but also to be considered as possible confounders of any associations between shortened sleep and the outcomes of interest. These variables are described in the following sections and include sociodemographic characteristics, health and health behaviors, and obstetric history characteristics.

Based on prior research, four *a priori* factors were identified as likely potential confounders due to their association with both sleep (the exposure of interest) and at least one of the cardiometabolic outcomes of interest. Specifically, factors recognized to have a known association

with gestational diabetes (Zhang & Ning, 2011, Taber 2010), hypertensive disorders (Zhou 2015; Gudnadottir et al 2016, Masho 2016; Umesawa, 2016) and sleep (McKnight-Eily et al 2011, Verona et al 2005) were considered *a priori* characteristics and included the sociodemographic factors of maternal age (≤ 25 years, 25 – 35 years, > 35 years), education (less than high school/high school diploma/GED diploma, some college, college bachelor degree or higher), race/ethnicity (Non-Hispanic White, versus non-white), and the health characteristic of excessive adiposity (normal BMI or lower <24.9, Overweight 25-29.9, Obese ≥30). To calculate BMI, pre-pregnancy weight and maternal height obtained via maternal self-report were used. In the event either self-reported variable was missing, the electronic medical records were queried to identify further documentation of heights or pre-pregnancy weights. BMI was calculated with following formula from the CDC Division of Nutrition, Physical Activity and Obesity: Weight (lb.) / [height (in)]^2 x 703 (available at https://www.cdc.gov/nccdphp/dnpao/growthcharts/training/bmiage/page5_2.html).

In addition to the a priori covariates, covariates that were significantly associated at a $p \leq 0.1$ with both self-reported sleep duration and either clinically diagnosed gestational diabetes, incident gestational hypertension in pregnancy, or preeclampsia were tested for inclusion in the model.

Sociodemographic Covariates

The descriptive results include study site (whether the woman received care in the San Francisco Bay Area or in Portland Oregon), trimester when the enrollment interview was collected (1st -2nd trimester or 3rd trimester), whether the woman was cohabitating with a spouse or partner (Yes/No), and whether there were young children under 5 years of age living in the household (Yes/No), and subjective social status. Because information on household income was not available, the validated MacArthur Scale of Subjective Social Status (SSS) was used as one indicator of socioeconomic status; this visual analogue scale uses a 9-step ladder to rate relative social position

on education, occupation, and income; it has previously been used to in studies of pregnant women (Adler & Stewart, 2007). Similar to previous studies, SSS ratings was examined by tertiles of 1-5 (low), 6-7 (moderate), 8-9 high) (Thompson et al. 2014).

Health and Health Behavior Covariates

Several maternal health and health behavior covariates were examined. The single item standardized ordinal measure of perceived health status or self-rated health (Poor/Fair/Good, Very Good, Excellent) and was used to assess pregnant women's overall perceptions of their general health (Ostrove, Adler, Kuppermann & Washington, 2000). Stress levels were assessed using a previously used adaptation of the Holmes and Rahe Stress Scale inventory that was modified for pregnant women (Li, Liu, Odouli, 2009). Women were asked a 17 item questionnaire about stressful life events, and a weight was assigned to each event. Sums of weights of the stressful events were calculated and were dichotomized into low stress (weight score of 0-99) or high stress (weight score ≥100). To determine the presence of selected pre-existing medical conditions (Yes/No), ICD-9 information from 1 year prior to pregnancy was electronically extracted from the medical record. Women were also asked about certain health behaviors: any alcohol use in the past month (Yes/No), current/previous smoking history and current second-hand smoke exposures. Because very few women reported a current smoking history, current smokers, women who quit smoking after conception, and women who reported ongoing second-hand cigarette smoke exposure were combined into one variable denoting fetal smoke exposure (Yes/No).

Obstetric History Covariates

To determine trimester of enrollment, information on gestational age was obtained from the medical record, and was based on best estimate. Approximately 70% of gestational age dating was from ultrasound estimation, the remaining 30% was based on last menstrual period (M. Thompson,

personal communication, March 22, 2017). From the enrollment interviews, women were asked their total number of pregnancies, including the index pregnancy (1 time, 2 times, 3 or more times), their history of a previous cesarean section surgery (Yes/No), history of an ectopic pregnancy (Yes/No), and any miscarriages or stillbirths. Because of the small numbers of stillborn infants, stillbirths and miscarriages were combined into a single variable called fetal loss (Yes/No).

Characteristics

Characteristics of the women included in this study are presented in Table II. The majority of women were between 25 and 35 years of age (66%), were white and non-Hispanic (64%), college educated (76%), and living with a spouse or partner (94%). Sixty-four percent (64%) considered themselves of moderate subjective social status. About 80% of women considered themselves to be in very good to excellent health. Only 14% of women reported a preexisting medical condition and even fewer women were categorized as being obese by BMI (12%). For about 1/3 of women, this was their first pregnancy.

Statistical Considerations

In preparing for this retrospective analysis, preliminary statistical power calculations were made using the following assumptions; an observed a base-rate of gestational diabetes of 9% (DeSisto, Kim, & Sharma, 2014) among second and third trimester pregnant women, and a conservative estimate that approximately 60% of the sample would sleep 7-9 hours, and 26% would sleep < 7 hours a night. With these assumptions, there was 80% power (alpha = .05) to detect 15% with gestational diabetes among those with short sleep duration a relative risk ratio of 1.71.

Power calculations for hypertension in pregnancy were based on an assumption of a base-rate of 7% (Roberts, et. al 2011) among second and third trimester pregnant women and the sleep groups remaining the same. There was 80% power to detect 13% with gestational hypertension

among those with short sleep duration or a relative risk ratio of 1.84. Power calculations for the hypertension in pregnancy subset of preeclampsia were based on an assumed rate of 3% (Ananth, Keyes, Wapner, 2013); there was 80% power to detect 7.4% with preeclampsia among those with short sleep duration or a relative risk ratio of 2.58.

Despite the relatively large effect sizes that were required to demonstrate significance, effects sizes of similar magnitude or greater were seen in previous studies (Facco et al. 2010; Qiu et al. 2010; Rawal et al. 2016; Reutrakul et al. 2011). It was a realistic assumption that similarly large effect sizes could be found in this study.

Analysis Plan

The primary outcome variables were clinically diagnosed gestational diabetes, hypertension in pregnancy, and the more clinically significant preeclampsia, which is a subset of hypertension in pregnancy. The primary independent variable of interest was self-reported sleep duration. Women with missing sleep variables and invalid sleep variables were excluded. A small number of covariate values that were missing were imputed using a multiple imputation program that averaged the best estimate of the missing value using associations with all available data. Specifically, this involved imputing in descending order of frequency: maternal prepregnancy weight (n=17), maternal height (n=6), fetal loss (n=4), subjective health (n=3), alcohol use (n=3), history of elective abortion (n=2), and total pregnancies (n=1). Crude associations were examined between the independent variable of self-reported sleep duration and each outcome of interest. The primary interest was to examine the association between low self-reported sleep duration and clinically diagnosed gestational diabetes or hypertensive disorders in pregnancy. Although the current study did not include specific hypotheses regarding the impact of relatively high self-reported sleep duration, for hypothesis generation

purposes, all three levels of sleep duration (low, normal, and high) were included as the independent variable.

Univariate associations between self-reported sleep duration and each potential covariate, and between the dependent clinical outcomes variables and each potential covariate were performed. As noted above, a factor associated with both sleep and clinical outcomes would be adjusted for in the final regression models. Pearson chi-squared (χ 2) test was used to assess significance.

Possible effect modification by subgroups of the *a priori* covariates (maternal age at conception, race/ethnicity, education, and BMI) were examined. Using standardized methods, an interaction term for sleep by the covariate was entered into the model after adjusting for the main effects of sleep and the covariate. A significant interaction term ($p < .05$) indicated that the associations between sleep and the clinical outcome were best represented by stratifying the effect by levels of the covariate.

Multinomial binary logistic regression models were conducted separately for each outcome in the 2nd or 3rd trimester: gestational diabetes, hypertension in pregnancy, and the more clinically significant subset of preeclampsia. The effect of low sleep (< 7 hours) was estimated using women sleeping 7-9 hours a night as the referent group. Each model was *a priori* adjusted for age, education, race/ethnicity, and BMI. Additional model-specific variables were to be considered if covariates were associated with outcomes and with self-reported sleep duration at a p-value of 0.1 or less. In logistic regression modeling, p-values of <0.05 were considered as significant. Analyses were conducted with SPSS version 21(SPSS Inc., Chicago, IL)

Results

Self-reported sleep duration among pregnant women is listed in Table III. The vast majority of women reported sleeping seven to nine hours a night (69%). Ten and 21% of respondents reported short (<7 hours) or long (>9 hours) self-reported sleep duration, respectively. When looking at the extreme ends, 8% of respondents reported less than 6 hours (4%) or greater than 10 hours (4%).

Table IV presents the percentage of women with clinically diagnosed gestational diabetes, hypertension in pregnancy, and preeclampsia in the 2nd or 3rd trimester of pregnancy. Nine percent of women had an ICD9 diagnosis of gestational diabetes (n=107), 7% had a diagnosis of hypertension in pregnancy (n=82). When looking specifically at the subset of preeclamptic women, 3% of all women were clinically diagnosed with preeclampsia (n=36).

No associations between self-reported sleep duration and clinically diagnosed gestational diabetes (Chi Square [Chi-sq.] 0.60, p-value [p] = 0.74), hypertension in pregnancy (Chi-sq. 1.36, p = 0.51), or preeclampsia in the 2nd or 3rd trimesters (Chi-sq. 3.10, p = 0.21) were found in univariate (unadjusted) analyses (Table V).

Self-reported sleep duration was associated with several covariates at a p-value of 0.1 or less (Table VI). Surprisingly, short sleepers did not appear to be different by maternal age; however, longer sleep durations were reported in younger women. More non-White women had short sleep durations. Having a college education and cohabitating with a spouse or partner were associated with normal sleep reports. Additionally, women with low subjective social status and who had fetal smoke exposure were more likely to be either short or long sleepers. In this dataset, BMI was not associated with self-reported sleep duration.

Several characteristics were significantly associated with clinically diagnosed cardiometabolic outcomes of interest (Table VII). Variables associated at a p-value of 0.1 or less with gestational

diabetes included older maternal age at conception, non-white race, being obese, and low subjective health. Lower rates of GDM were seen among women with a college degree. Gestational hypertension was associated with living in the San Francisco Bay Area, childless households, first pregnancies, and being classified as obese by BMI. Preeclampsia was associated with living in the San Francisco Bay area, childless households, and first pregnancies. Women with a history of fetal loss had less preeclampsia than women without a history of fetal loss.

Maternal age at conception, race/ethnicity, education, and BMI were planned to be examined as *a priori* potential confounders to the relationship between self-reported sleep and clinically diagnosed gestational diabetes, hypertension in pregnancy, and preeclampsia. In univariate analysis, however, BMI was not significantly associated with self-reported sleep duration. Maternal age at conception, race/ethnicity, and education likewise were not associated with either hypertension in pregnancy or preeclampsia. Nonetheless, each of these variables were included in subsequent modeling. In addition, no other covariates were observed as associated with both self-reported sleep duration and a clinical outcome of gestational diabetes, incident hypertension in pregnancy, or the incident hypertension in pregnancy subset of preeclampsia; therefore only the *a priori* variables are included in multivariate modeling.

Table VIII reports the crude and adjusted odd ratios for self-reported sleep duration and the cardiometabolic clinical outcomes of interest. No association was found between short self-reported sleep duration and clinically diagnosed gestational diabetes. The bivariate odds ratio (OR) for short self-reported sleep duration and gestational diabetes was 1.18, with 95% confidence intervals that included one; the adjusted odds ratio (aOR) was not appreciably different and was also not statistically significant. When examining long self-reported sleep duration and gestational diabetes, both crude and aORs were similar (crude OR 0.89, CI 0.53-1.49; aOR 0.92, CI 0.54-1.57).

For incident hypertension in pregnancy and both short and long self-reported sleep duration, there were no crude associations found (OR 0.70, CI 0.29-1.65 and OR 1.20, CI 0.71-2.04 respectively). Adjusted models yielded similar results.

For the hypertension in pregnancy subset of preeclampsia, interestingly (while not significant), the point estimates in both short and long sleepers suggest a higher risk. In crude analyses, the odds of preeclampsia among women sleeping less than 7 hours a night were 1.7-fold higher than those sleeping 7-9 hours a night (OR 1.69 CI 0.62-4.58). The odds of preeclampsia were even higher among women sleeping longer than 9 hours, though here too the CI included one; the crude OR for long sleepers was 1.86 (CI 0.88-3.94). The trends for both short and long sleepers remained largely the same in both adjusted models. When interaction terms were tested for self-reported sleep duration and maternal age at conception, race/ethnicity, education, and BMI, only the interaction term for self-reported sleep duration by race/ethnicity was marginally significant (after adjusting for main effects) for gestational diabetes at $p = 0.053$. Therefore, Table IX presents additional multivariate modeling stratified by race for clinically diagnosed gestational diabetes, controlling for maternal age at conception, education, and BMI (Table 9). Again, no significant estimates were found, but point estimates suggest a racial difference that appears to be driven by women with longer self-reported sleep durations, whereby non-white women who are longer sleepers had a lower odds ratio point estimate (aOR 0.48, CI 0.19-1.22) compared to white women (aOR = 1.39, CI 0.71-2.71); although, again, confidence intervals included one.

Sensitivity Analyses

To examine whether parameter values and assumptions in the original model were sound, sensitivity analyses based on the exposure and the covariates were conducted. For exposure, given the possible need for longer sleep times (NIH, 2014), the referent defining "normal sleep" was shifted one hour. A new referent of 8-10 hours was used to represent "optimal sleep" duration. All

outcomes remained non-significant and point estimates trended towards the null in post hoc analyses (data not shown). For covariate assumptions, more inclusive models where covariates associated with either sleep or the outcomes were compared to the parsimonious original models where covariates were associated with both sleep and outcomes; doing so did not appreciably alter any point estimates or confidence intervals (data not shown).

Discussion

In this dataset of relatively healthy, white, educated and insured women, no associations with self-reported total sleep time and clinically diagnosed gestational diabetes, incident hypertension in pregnancy or preeclampsia were found. This study provides evidence that sleeping less than 7 hours a night does not appreciably increase the risk of adverse maternal outcomes in healthy pregnant populations like PIP. The findings of this particular analysis do not support our hypothesis that self-reported sleep duration of less than 7 hours is associated with these clinically diagnosed cardiometabolic disorders in pregnancy.

Null results are difficult to interpret, nonetheless, there are at least six possible explanations of the null results. First, it is possible that self-reported sleep duration is in fact not associated with gestational diabetes, hypertension in pregnancy or preeclampsia. As noted in Table I, of the two previous studies that examined self-reported sleep and similar hypertensive disorders during pregnancy, one also failed to observe significant associations (Reutrakul et al. 2011).

Second, any true effect might have been at a smaller magnitude than this study was powered to detect. As noted earlier, this study had adequate statistical power to detect differences in risk of these clinical outcomes that were 1.7- to 2.5-fold higher in short sleepers (compared to normal sleepers) assuming that about a quarter of women would report sleeping < 7 hours a night. This was a reasonable assumption given that the prior studies that observed significant associations between

self-reported sleep duration and gestational diabetes or hypertension in pregnancy reported 2.0 to 10.6 fold differences (Facco et al. 2010; Rawal et al. 2016; Reutrakul et al. 2011; Williams et al. 2011). The effects of self-reported sleep on the outcomes of interest observed in this study were of a much lower magnitude.

Third, to demonstrate a significant association two criteria were required, an adequate number of women with the clinical outcomes of interest and an adequate number of women with shortened sleep duration. The number of women with short sleep duration in this sample (11%) was much lower than expected and projected in the original power analyses, where 26% were assumed to have short sleep duration. This further reduced the ability to make precise estimates. Other studies of adequate sample size had both adequate numbers of women with disease and adequate numbers of poor sleepers. A prime example is The Eunice Kennedy Shriver National Institute of Child Health and Human Development Fetal Growth Studies-Singleton Cohort, [n=2581]) in which 30.7% of respondents reported sleeping less than 7 hours a night and approximately 4% of the cohort had clinically diagnosed gestational diabetes (Rawal, et al. 2016) compared to the 11% sleeping <7 hrs. and the 3% with GDM in this analysis.

Fourth, poor measurement of the clinical outcomes, poor measurement of self-reported sleep duration, or of both could also explain the lack of findings. Clinical diagnoses are imperfect; any misclassification of women reduced the likelihood of observing any true effect. However, the prevalence estimates for clinically diagnosed gestational diabetes, incident hypertension in pregnancy, and preeclampsia in this analysis (Table IV) roughly mirrored the national estimates which reduces the likelihood that null findings in this study are due to misclassification of disease (Ananth, Keyes, Wapner, 2013; DeSisto, Kim, & Sharma, 2014; Roberts, et. al 2011).

Poor measurement of sleep is the more likely contributor to measurement error in the current study. Self-reported sleep, despite the ease of its collection, is imperfect for assessing a woman's total sleep time. Self-reported sleep has been shown to overestimate objective sleep, thereby biasing findings towards the null (Lauderdale et al. 2008). If associations had been found, the direction of the bias secondary to overestimation of self-reported sleep would support the conclusion that self-report could be used to identify increased risk. This study also did not assess the contribution of daytime napping to total sleep time. Additionally, sleep in pregnancy represents a dynamic state; lack of sufficient sleep at one point in time does not mean an absence of insufficient sleep in a woman at another point in time. All these considerations also could have biased our findings towards the null.

Other potential measurement error in self-reported sleep measure of this study could be related to the actual cut-points selected. A referent of 7-9 hours was chosen, based on available literature for adults in the general population (NIH 2014).It is not clear if this is the ideal recommended estimate for pregnant women. The unexpected finding that longer sleep was associated with lower odds point estimates of gestational diabetes (Table VIII) suggests that it may be important to examine the impact of longer sleep duration in this population. Nonetheless, identifying the appropriate threshold for normal vs. long sleep will likely be challenging. Among the long sleepers (>9 hours) in this study, approximately 80% of women fell into the 9 to 10-hour range. In the sensitivity analyses using 8-10 hours a night as the referent, sleeping an hour longer did not support the theory that women need more sleep than the general population, but, due to the small numbers of sleepers in this analysis sleeping at the extremes, this exercise warrants repeating in a dataset with a greater proportion of poor sleepers.

Fifth, although the main effect between sleep duration and clinical outcomes was null in this study, it's possible that effect modification exists and this association is true for some subgroups but not others. Indeed, race/ethnicity appeared to modify the association between sleep and gestational diabetes (Table IX). The unexpected results suggest that the protective effects of longer sleep may only be seen among non-white women. This suggests that there is a possibility the threshold selected was not entirely wrong, but rather that the thresholds for optimal sleep in pregnancy can differ by race/ethnicity. In other words, the amounts of sleep needed in pregnancy can vary by race/ethnicity. Certainly, future studies would require a larger and more diverse sample to examine the possibility of effect modification.

The sixth and final explanation of the null results could be selection bias. Recruiting pregnant women for cohort studies is extremely difficult (Frew 2014). There is a possibility that a much healthier cohort was enrolled, who, with their access to a large integrated healthcare delivery system, received more preventive care and earlier services than the general population, and thus might be generally healthier. In a previous case-control analyses where PIP cohort women (used as controls) were compared to women who were medically attended with acute respiratory infections (cases) and were recruited from the same two west coast large managed care health care systems as our cohort, it was found to be that the controls were more likely to be white non-Hispanic women and to describe their health as excellent (Thompson et al, 2013), lending credibility to the possibility that there was selection bias in the current study which may have reduced the variability in sleep and negative clinical outcomes or biased our results in other unknown ways.

There are, however, several strengths of this dataset worth mention. PIP is a large, prospectively collected cohort of pregnant women with detailed information available from medical and laboratory records, which allowed for the ability to describe accurately the characteristics of self-

reported sleep among pregnant women and to adjust for established risk factors for the outcomes of interest. An additional strength was the relative completeness of the data. Very few women were excluded, and even fewer variables required imputation. Further, associations were found between certain covariates and self-reported sleep duration consistent with previous studies, which supports the overall validity of the results.

Future Directions

The current study did not include cardiometabolic markers such as glucose challenge testing or averages of systolic and diastolic blood pressure readings over the course of pregnancy, but follow-up analyses are planned. These follow-up analyses might shed light on whether cardiometabolic markers might be a more useful metric than clinical diagnoses in women with shortened sleep duration. If self-reported sleep duration still does not prove a reliable measure for identifying women at risk for adverse cardiometabolic outcomes, other simple measures for quantifying sleep duration should be considered. The built-in actigraphy technology in many popular fitness devices might provide more reliable estimates of total sleep time than self-report. In a recent study by Marino et al. (2013), the overall accuracy of research actigraphy compared to polysomnography for individual-level estimates was approximately 89% for women. These findings are extremely promising for reducing the burden on research participants for collecting accurate sleep measures. However, further studies are needed to determine whether application of non-research actigraphy technology will prove to be a rigorous enough approach to population level assessments of sleep both in the general population and in specific populations like pregnant women.

Conclusion

In conclusion, the results from this analysis did not meet the yardstick for detecting associations between self-reported sleep duration and clinically diagnosed cardiometabolic diseases gestational diabetes and incident hypertension in pregnancy. These null findings may be limited by this particular sample and the relatively large effects the study was powered to investigate; it should not be interpreted to imply that shortened sleep duration does not have any effect on clinically diagnosed cardiometabolic disease. Sleep disturbances are common in pregnancy, and although we were not able to replicate findings from other studies, there is biologic plausibility that sleep adversely affects the health of pregnant women. Further research is needed to determine the most useful and valid measures for determining sleep duration, to study longitudinal effects of sleep duration in representative samples of adequate size, and to explore the possible cardiometabolic pathways affected by shortened sleep duration.

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Figure 1. Final Analytic Sample

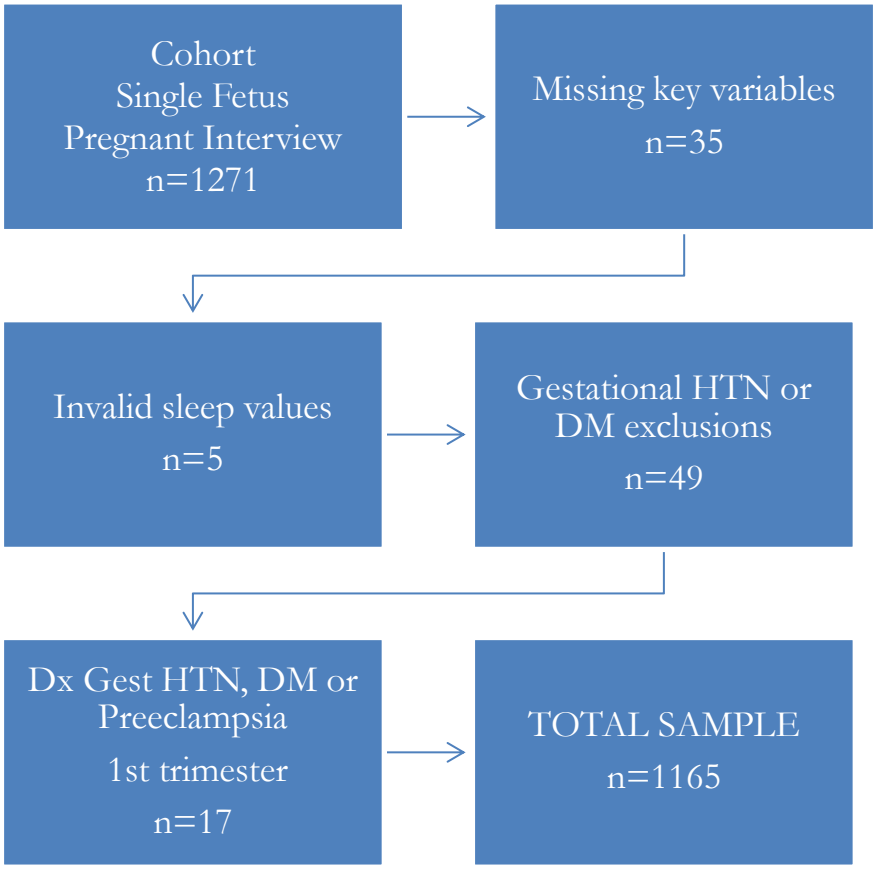

Table I. Summary of Studies Examining Self-Reported Sleep Duration and Cardiometabolic Outcomes					
Author/Year / Citation	**Study Design Study Group(s)**	**Sleep Measures**	**Pertinent Research Question**	**Clinical Outcomes & Cardio-metabolic Measures**	**Major Findings**
Cai et al. (2017) Sleep: 40 1-8.	Cohort study (n=1247) Subset (n=686) GCT[¶] and PSQI [α] at 26-28 weeks	"During the past month, how many hours of actual sleep did you get a night?" SSRSD[∞] < 6hrs	Exposure to short sleep duration will associate with increased risk of GDM*	GDM*	19% diagnosed with GDM* 11% slept < 6 hrs. HS GDM* and SSRSD[∞]: Unadjusted OR 1.7 (CI0.99-2.93) aOR 1.96 (1.05-3.66) NOTE: No comparisons on outcomes between included & excluded women available
Rawal et al. (2016) Am J Obstet Gynecol volume:x.ex-x.ex.	Prospective cohort Pregnant women in 1st - 2nd trimest (n=2581)	"What is your typical sleep duration?" ≤5 hrs. 6, 7, 8, 9, ≥10 hrs.	Examine trimester specific association between SRSD and GDM* risk	GDM*	In non-obese women, both short & long sleep associated with GDM; 5-6 hrs. (aRR[#] 2.52, 95% CI[®,] 1.27-4.99) 7 hrs. (aRR 2.01, 95% CI 1.09-3.68) ≥10 hrs. (2.17, 95% CI 1.01-4.67)
Haney et al. (2014) Sleep Medicine 15(4) 444-450.	Prospective cohort Pregnant women in 1st and 2nd trimester (n=161)	Sleep diaries and actigraphy SSRSD[∞] < 7hrs	Examine if short SD increases BPs and BMI.	Systolic and Diastolic BPs BMI	No association with total sleep time (either by actigraphy or diary) and blood pressure or BMI NOTE: Sleep measurements taken in early pregnancy; BP assessed in early pregnancy
Balserak et al. (2013) Sleep and Breathing 17: 1093-1102.	Case control Pregnant women with sleep disordered breathing (n=104)	Time in-bed subtracted from total wake time	Examine associations between high GCT[¶] and nocturnal sleep	1 hr. GCT[¶]	SRSD not associated with hyperglycemia. (OR[▪] 0.95, 95% CI 0.70-1.27) NOTE: Likely underpowered
Reutrakul et al. (2011) Diabetes Care 34: 2454-2457	Prospective cohort Pregnant women in 2nd trimest with GCT[¶] (n=169)	Derived from PSQI[α] SSRSD[∞] < 7 hrs.	Examine association between SRSD & glucose intolerance, GDM* and GHTN**	GDM* GHTN** 1 hr. GCT[¶]	SRSD associated with GDM* (OR[▪] 2.4, 95% CI 1.0–5.9) SRSD inversely correlated with glucose values from 50-g GCT[¶] (r^{o} =20.21, P [oo]=.01). SRSD not associated with GHTN** [data not shown]

Williams et al. 2011 Sleep 33; 1363-1371	Prospective cohort Pregnant women (U.S.) 18-22 wks. gestation (n=1272)	"Since becoming pregnant how many hrs. per night do you sleep?" ≤ 6, 7-8, 9 (ref.), ≥10 hrs. Clinical: <5, 5-6, 7-9, ≥10 hrs.	Short and long SRSD will be associated with elevated mean systolic and diastolic blood pressures (BP), mean arterial pressures (MAP) (all trimesters) and GHTN** or preeclampsia	GHTN** Preeclampsia Systolic and diastolic BPs MAPs	Short and long SRSD associated with 3rd trimester systolic and diastolic mean BPs. for ≤ 6 h SBP ↑3.72 mm Hg (95% CI 2.1-5.8), DBP ↑3.04 mm Hg (95% CI 1.9-4.2 7-8 h SBP ↑2.43 mm Hg (95% CI 1.3-3.6) DBP ↑2.13 mm Hg (95% CI 1.4-2.9) >10 h SBP ↑ 4.21 mm Hg (95% CI 2.6-5.8) DBP ↑ 3.43 mm Hg (95% CI 2.3-4.6) No differences in 1st or 2nd trimesters MAP same pattern: statistically significant <5 hrs. and preeclampsia (aOR 9.52, 95% CI 1.83-49.40); Stratified by overweight: < 5 hrs. (aOR 12.7, 95% CI 1.04-154.4) ≥10 hrs. (aOR 5.14, 95% CI 1.20-22.1) NOTE: Atypical referents, wide CIs
Facco, Grobman, Kramer, Ho & Zee (2010) Am J Obstet Gynecol 203; 142e1-142e5	Prospective cohort Nulliparous pregnant women in the NE U.S. (n=189)	"During the past month, how many hours of actual sleep did you get a night?" Short SRSD < 7hrs	Evaluate the impact of short SRSD on glucose metabolism	GDM* 1 hr. GCTǂ	Short SRSD associated with GCT value >130 (OR 2.6, 95% CI 1.3-5.7) and clinically diagnosed GDM (OR 10.6, 95% CI 1.3-85.5)
Qiu, Enquobahrie, Frederick, Abetew & Williams (2010) BMC Women's Health 10;17	Retrospective cohort Pregnant women < 20 wks. gestation in NW U.S. (N=1290)	"Since becoming pregnant, how many hours per night do you sleep?" ≤ 4, 5-8, 9, ≥10 hrs.	Evaluate associations with SRSD and post load glucose concentrations and clinically diagnosed GDM	GDM* 1 hr. GCTǂ	Mean glucose levels highest in ≤ 4hrs; but not statistically significant For GDM; ≤ 4hrs (RR 5.56, 95% CI 1.31-23.69) Attenuated by adjustment for BMI ≤ 4hrs (RR 4.18 95% CI 0.94-18.60) NOTE: Atypical definition if shortened SRSD. Wide CIs.

∞Self-reported shortened sleep duration

* Gestational diabetes mellitus; ǂ Glucose challenge test levels; **Gestational hypertension

Adjusted relative risk; ® 95% confidence interval; ▪ Odds ratio; ºCorrelation coefficient; °° P-value

¤Pittsburgh Sleep Quality Index

Sociodemographic Characteristics	N	%
Study Site		
San Francisco Bay Area	665	57
Portland, Oregon	500	43
Maternal Age at Conception		
Under 25 years	109	9
> 25 - 35 years	769	66
> 35 years	287	25
Trimester of Enrollment Interview		
1st or 2nd trimester	666	57
3rd trimester	499	43
Race/Ethnicity*		
White non-Hispanic	748	64
Non-white	417	36
Education		
High school diploma or less, or General Education Development diploma	98	8
Some college	183	16
College bachelor degree or higher	884	76
Cohabitating with spouse or partner		
Yes	1099	94
No	66	6
Children in household < 5 years old		
No children	649	56
One or more children	415	36
Subjective Social Status ◦		
Low (1-5)	301	26
Moderate (6-7)	743	64
High (8-9)	121	10

Health and Health Behavior Characteristics	N	%
Subjective Health‡		
Poor Fair or Good	243	21
Very Good	462	40
Excellent	460	40
High vs Low Stress €		
High score ≥100	276	24
Low score < 100	889	76
Body Mass Index (BMI)		
Normal BMI or lower <24.9	762	65
Overweight 25-29.9	268	23
Obese >30	135	12
Preexisting Condition		
Yes	165	14
No	1000	86
Any Alcohol Use in Past Month		

Yes	94	8
No	1071	92
Fetal Smoke Exposure ◊		
Yes	62	5
No	1103	95

Obstetric History Characteristics	**N**	**%**
Total Times Pregnant		
1 time	430	37
2 times	377	32
3 or more times	358	31
Prior History of Cesarean Section		
Yes	138	12
No	1027	88
Prior History of Ectopic Pregnancy		
Yes	22	2
No	1143	98
Prior History of Fetal Loss***		
Yes	260	22
No	905	78
Prior History of Elective Termination of Pregnancy		
Yes	174	15
No	991	85

Footnotes:
* Non-white is inclusive of Black non-Hispanic (38) Asian (179) Hispanic (129) and Other or Mixed Race (71)
◦MacArthur Scale of Subjective Social Status
ŧStandardized measure of perceived health status
€Adaptation for pregnant women of the Holmes and Rahe Stress Scale Inventory; women asked about 17 weighted stress events, sums of weights calculated and dichotomized into high stress (total score ≥100) and low stress (total score <100)
◊Current smoker, former smoker but quit during current pregnancy, or ongoing second-hand smoke exposure
***Miscarriages and stillbirths

Table III. Self-reported Sleep Duration*								
≤ 6 hours	>6 to 7 hours	> 7 to 9 hours	> 9 to 10 hours	> 10 hours		Normal Sleep ≥ 7 to 9 hours	Short Sleep < 7 hours	Long Sleep ≥ 9 hours
N (%)	N (%)	N (%)	N (%)	N (%)		N (%)	N (%)	N (%)
43 (4)	78 (7)	802 (69)	193 (17)	49 (4)		802 (69)	121 (10)	242 (21)

Footnote: * Self-reported sleep duration calculated from a woman's self-report of usual bed time in past 30 days, usual wake time in past 30 days, and usual time it takes to fall asleep in past 30 days.

	N	%
Gestational Diabetes**		
Yes	107	9
No	1058	91
Hypertension in Pregnancy◊		
Yes	82	7
No	1083	93
Preeclampsia (subset)ǂ		
Yes	36	3
No	1129	97

**ICD 9 diagnosis of gestational diabetes (648.8) in second or third trimester. Exclusions included previous diagnosis of preexisting diabetes (250. Inclusive) pancreatic disorders (251. inclusive) 1 year prior to pregnancy or diagnosis in 1st trimester

◊ICD 9 diagnosis of gestational hypertension (642.3, 642.9) or ICD 9 diagnosis of preeclampsia or eclampsia (642.4 – 642.7) in second or third trimester. Exclusions included previous diagnosis of essential hypertension (401. Inclusive) essential hypertension complicating pregnancy (642.0) hypertension secondary to renal disease ((642.1) or other preexisting hypertension (642.2) 1 year prior to pregnancy or diagnosis in 1st trimester

ǂICD 9 diagnosis of preeclampsia or eclampsia (642.4 – 642.7) in second or third trimester. Exclusions included previous diagnosis of preexisting diabetes (250. Inclusive) pancreatic disorders (251. inclusive) 1 year prior to pregnancy or diagnosis in 1st trimester

Table V. Univariate Associations between Self-Reported Sleep Duration and Cardiometabolic Outcomes Initially Diagnosed in the 2nd or 3rd Trimester of Pregnancy					
	Normal Sleep Duration ≥7 to 9 hours	**Short Sleep Duration <7 hours**	**Long Sleep Duration >9 hours**		
	N (%)	**N (%)**	**N (%)**	**Chi Square**	**P-value**
Gestational Diabetes Mellitus					
YES	74 (69)	13 (12)	20 (19)	0.60	0.74
NO	728 (69)	108 (10)	222(21)		
Hypertension in Pregnancy					
YES	56 (68)	6 (7)	20 (24)	1.36	0.51
NO	746 (69)	115 (11)	222 (21)		
Preeclampsia					
YES	20 (56)	5 (14)	11 (31)	3.10	0.21
NO	782 (69)	116 (10)	231 (21)		

Table VI. Univariate Associations between Self-Reported Sleep Duration and Characteristics					
	Self-Reported Sleep Duration				
	Normal Sleep duration ≥7 to 9 hours	Short Sleep Duration <7 hours	Long Sleep Duration >9 hours		
SOCIODEMOGRAPHICS					
	N (%)	**N (%)**	**N (%)**	**Chi Square**	**P-value***
Study Site				3.01	0.222
San Francisco Bay Area	462 (70)	75 (11)	128 (19)		
Portland, Oregon	340 (68)	46 (9)	114 (23)		
Maternal Age at Conception				27.96	0.000*
Under 25 years	55 (51)	12 (11)	42 (39)		
> 25 - 35 years	534 (69)	78 (10)	157 (20)		
> 35 years	213 (74)	31 (11)	43 (15)		
Trimester of Enrollment Interview				4.01	0.134
1st or 2nd trimester	464 (70)	59 (9)	143 (22)		
3rd trimester	338 (68)	62 (12)	99 (20)		
Race/Ethnicity▪				12.77	0.002*
White non-Hispanic	536 (72)	61 (8)	151 (20)		
Non-white	266 (64)	60 (14)	91 (22)		
Education				28.17	0.000*
High school diploma or less, or General Education Development diploma	53 (54)	15 (15)	30 (31)		
Some college	105 (57)	24 (13)	54 (30)		
College bachelor degree or higher	644 (73)	82 (9)	158 (18)		
Cohabitating with spouse or partner				9.89	0.007*
Yes	768 (70)	111 (10)	220 (20)		
No	34 (52)	10 (15)	22 (33)		
Children in household < 5 years old				2.52	0.283
No children	435 (67)	69 (11)	145 (22)		
One or more children	367 (71)	52 (10)	97 (19)		
Subjective Social Status ◦				10.24	0.037*
Low (1-5)	189 (63)	36 (12)	76 (25)		
Moderate (6-7)	534 (72)	68 (9)	141 (19)		
High (8-9)	79 (65)	17 (14)	25 (21)		
HEALTH AND HEALTH BEHAVIORS					
Subjective Health‡				1.05	0.902
Poor Fair or Good	171 (70)	24 (10)	48 (20)		
Very Good	311 (67)	52 (11)	99 (21)		
Excellent	320 (70)	45 (10)	95 (21)		
High vs Low Stress €				0.21	0.902
High score ≥100	187 (68)	30 (11)	59 (21)		
Low score < 100	615 (69)	91 (10)	183 (21)		

Body Mass Index (BMI)				5.84	0.211
Normal BMI or lower <24.9	537 (71)	68 (9)	157 (21)		
Overweight 25-29.9	174 (65)	37 (14)	57 (21)		
Obese >30	91 (67)	16 (12)	28 (21)		
Preexisting Condition				2.06	0.356
Yes	109 (66)	15 (9)	41 (25)		
No	693 (69)	106 (11)	201 (20)		
Any Alcohol Use in Past Month				4.18	0.123
Yes	70 (75)	12 (13)	21 (34)		
No	732 (68)	109 (10)	221 (20)		
Smoke Exposure ◊				9.31	0.01*
Yes	32 (52)	9 (15)	21 (34)		
No	770 (70)	112 (10)	221 (20)		
OBSTETRIC HISTORY					
Total Times Pregnant				5.26	0.262
1 time	290 (67)	43 (10)	97 (23)		
2 times	271 (72)	32 (9)	74 (20)		
3 or more times	241 (67)	46 (13)	71 (20)		
Prior History of Cesarean Section				377	0.152
Yes	103 (75)	15 (11)	20 (15)		
No	699 (68)	106 (10)	222 (22)		
Prior History of Ectopic Pregnancy				3.62	0.164
Yes	18 (82)	3 (14)	1 (5)		
No	784 (69)	118 (10)	241 (21)		
Prior History of Fetal Loss* **				0.41	0.813
Yes	180 (69)	29 (11)	51 (20)		
No	622 (69)	92 (10)	191 (21)		
Prior History of Elective Termination of Pregnancy				2.53	0.293
Yes	111 (64)	22 (13)	41 (24)		
No	591 (70)	99 (10)	201 (20)		

Footnotes:

* Statistically significant at a p-value of 0.05 or less

▪Non-white is inclusive of Black non-Hispanic (38) Asian (179) Hispanic (129) and Other or Mixed Race (71)

◦MacArthur Scale of Subjective Social Status

ŧStandardized measure of perceived health status

€Adaptation for pregnant women of the Holmes and Rahe Stress Scale Inventory; women asked about 17 weighted stress events, sums of weights calculated and dichotomized into high stress (total score ≥100) and low stress (total score <100)

◊Current smoker, former smoker but quit during current pregnancy, or ongoing second-hand smoke exposure

Table VII. Univariate Associations between Characteristics and Cardiometabolic Outcomes Initially Diagnosed in the 2nd or 3rd Trimester of Pregnancy *									
	Gestational Diabetes ** N (%)	**Chi Square (P-value)**		**Hypertension in Pregnancy◊ N (%)**	**Chi Square (P-value)**		**Preeclampsia (subset)ǂ N (%)**	**Chi Square (P-value)**	
SOCIODEMOGRAPHICS									
Study Site									
San Francisco Bay Area	52 (49)			56 (68)			27 (75)	4.87	0.039*
Portland, Oregon	55 (51)	3.46	0.066	26 (32)	4.53	0.04	9 (25)		
Maternal Age at Conception									
Under 25 years	8 (8)			12 (15)			5 (14)		
> 25 - 35 years	59 (55)	10.33	0.006*	48 (59)	3.55	0.170	20 (56)	1.96	0.375
> 35 years	40 (37)			22 (27)			11 (31)		
Trimester of Enrollment									
1st or 2nd	57 (53)			47 (57)			19 (53)		
3rd	50 (47)	0.73	0.413	35 (43)	0.001	1.000	17 (47)	0.29	0.611
Race/Ethnicity ▪									
White non-Hispanic	57 (53)	6.13	0.015*	54 (66)	0.10	0.812	20 (56)	1.21	0.292
Non-white	50 (47)			28 (34)			16 (44)		
Education									
High school diploma or less, or GED diploma	10 (9)	5.67	0.059	7 (9)	0.46	0.794	4 (11)	1.74	0.419
Some college	25 (23)			15 (18)			8 (22)		
College bachelor degree or higher	72 (67)			60 (73)			24 (67)		
Cohabitating with partner									
Yes	100 (94)			78 (95)			35 (97)		
No	7 (7)	0.17	0.660	4 (5)	0.10	1.000	1 (3)	0.58	0.717
Children in household < 5 years old									
No children	68 (64)			66 (81)			27 (75)		
At least 1 child	39 (36)	2.94	0.102	16 (20)	21.95	0.00*	9 (25)	5.60	0.025*
Subjective Social Status ◦									
Low (1-5)	27 (25)			22 (27)			12 (33)		
Moderate (6-7)	72 (67)	1.21	0.547	47 (57)	3.15	0.207	18 (50)	3.32	0.190
High (8-9)	8 (8)			13 (16)			6 (17)		

Table VII. Univariate Associations between Characteristics and Cardiometabolic Outcomes Initially Diagnosed in the 2nd or 3rd Trimester of Pregnancy * (Continued)

Subjective Health‡‡									
Poor Fair or Good	34 (32)	11.37	0.003*	23 (28)	3.16	.206	10 (28)	1.08	0.583
Very Good	44 (41)			32 (39)			13 (36)		
Excellent	29 (27)			27 (33)			13 (36)		
High vs Low Stress €									
High score ≥100	28 (26)	0.40	0.551	23 (28)	0.93	0.346	12 (33)	1.91	0.167
Low score < 100	79 (74)			59 (72)			24 (67)		
Body Mass Index (BMI)									
Normal BMI or lower <24.9	57 (53)	21.70	0.000*	46 (56)	6.02	0.049*	22 (61)	0.94	0.625
Overweight 25-29.9	23 (22)			20 (24)			8 (22)		
Obese >30	27 (25)			16 (20)			6 (17)		
Preexisting Condition									
Yes	21 (20)	2.89	0.108	16 (20)	2.08	0.187	8 (22)	1.99	0.151
No	86 (84)			66 (81)			28 (78)		
Any Alcohol Use in Past Month									
Yes	8 (8)	0.056	1.00	4 (5)	1.21	0.398	1 (3)	1.40	0.355
No	99 (93)			78 (95)			35 (97)		
Fetal Smoke Exposure ◊◊									
Yes	8 (8)	1.09	0.264	3 (4)	0.48	0.617	1 (3)	0.48	1.00
No	99 (93)			79 (96)			35 (97)		
OBSTETRIC HISTORY									
Total Times Pregnant									
1 time	50 (47)	4.88	0.087	48 (59)	17.74	0.000*	22 (61)	9.35	0.009*
2 times	29 (27)			18 (22)			7 (19)		
3 or more times	28 (26)			16 (20)			7 (19)		
Prior History of Cesarean									
Yes	91 (85)	1.09	0.276	73 (89)	0.06	1.000	31 (86)	0.15	0.606
No	16 (15)			9 (11)			5 (14)		

Prior History of Ectopic Pregnancy									
Yes	2 (2)	0.00	1.000	1 (1)	0.21	1.000	0	N/A	N/A
No	105 (98)			81 (99)			36 (3)		

Table VII. Univariate Associations between Characteristics and Cardiometabolic Outcomes Initially Diagnosed in the 2nd or 3rd Trimester of Pregnancy * (Continued)

Prior History of Fetal Loss* **									
Yes	20 (19)	0.89	0.395	13 (16)	2.13	0.169	3 (8)	4.19	0.041*
No	87 (81)			69 (84)			33 (92)		
Prior History of Elective Termination of Pregnancy									
Yes	14 (13)	0.32	0.670	14 (17)	0.32	0.524	5 (14)	0.03	1.000
No	93 (87)			68 (83)			31 (86)		

Footnotes:

* Statistically significant at a p-value of 0.05 or less

**ICD 9 diagnosis of gestational diabetes (648.8) in second or third trimester. Exclusions included previous diagnosis of preexisting diabetes (250. Inclusive) pancreatic disorders (251. inclusive) 1 year prior to pregnancy or diagnosis in 1st trimester

◊ICD 9 diagnosis of gestational hypertension (642.3, 642.9) or ICD 9 diagnosis of preeclampsia or eclampsia (642.4 – 642.7) in second or third trimester. Exclusions included previous diagnosis of essential hypertension (401. Inclusive) essential hypertension complicating pregnancy (642.0) hypertension secondary to renal disease ((642.1) or other preexisting hypertension (642.2) 1 year prior to pregnancy or diagnosis in 1st trimester

ǂICD 9 diagnosis of preeclampsia or eclampsia (642.4 – 642.7) in second or third trimester. Exclusions included previous diagnosis of preexisting diabetes (250. Inclusive) pancreatic disorders (251. inclusive) 1 year prior to pregnancy or diagnosis in 1st trimester

▪Non-white is inclusive of Black non-Hispanic (38) Asian (179) Hispanic (129) and Other or Mixed Race (71)

◦MacArthur Scale of Subjective Social Status

ǂǂStandardized measure of perceived health status

€Adaptation for pregnant women of the Holmes and Rahe Stress Scale Inventory; women asked about 17 weighted stress events, sums of weights calculated and dichotomized into high stress (total score ≥100) and low stress (total score <100)

◊◊Current smoker, former smoker but quit during current pregnancy, or ongoing second-hand smoke exposure

***Miscarriages and stillbirths

Table VIII. Crude and Adjusted Odds Ratio for Self-Reported Sleep Duration and Cardiometabolic Outcomes®		
Self-reported Sleep Duration*	**Crude Odds Ratio (95% CI)**	**Adjusted Odds Ratio (95% CI)**
Gestational Diabetes**		
<7 hours sleep	1.18 (0.64-2.21)	1.04 (0.55-1.98)
7-9 hours sleep	Reference	Reference
>9 hours sleep	0.89 (0.53-1.49)	0.92 (0.54-1.57)
Hypertension in Pregnancy◊		
<7 hours sleep	0.70 (0.29-1.65)	0.69 (0.29-1.66)
7-9 hours sleep	Reference	Reference
>9 hours sleep	1.20 (0.71-2.04)	1.16 (0.67-2.00)
Preeclampsiał		
<7 hours sleep	1.69 (0.62-4.58)	1.54 (0.56-4.25)
7-9 hours sleep	Reference	Reference
>9 hours sleep	1.86 (0.88-3.94)	1.80 (0.83-3.87

Footnote: * Self-reported sleep duration calculated from a woman's self-report of usual bed time in past 30 days, usual wake time in past 30 days, and usual time it takes to fall asleep in past 30 days. **ICD 9 diagnosis of gestational diabetes (648.8) in second or third trimester. Exclusions included previous diagnosis of preexisting diabetes (250. Inclusive) pancreatic disorders (251. inclusive) 1 year prior to pregnancy or diagnosis in 1st trimester

◊ICD 9 diagnosis of gestational hypertension (642.3, 642.9) or ICD 9 diagnosis of preeclampsia or eclampsia (642.4 – 642.7) in second or third trimester. Exclusions included previous diagnosis of essential hypertension (401. Inclusive) essential hypertension complicating pregnancy (642.0) hypertension secondary to renal disease ((642.1) or other preexisting hypertension (642.2) 1 year prior to pregnancy or diagnosis in 1st trimester

łICD 9 diagnosis of preeclampsia or eclampsia (642.4 – 642.7) in second or third trimester. Exclusions included previous diagnosis of preexisting diabetes (250. Inclusive) pancreatic disorders (251. inclusive) 1 year prior to pregnancy or diagnosis in 1st trimester

®All models adjusted for maternal age at conception, Non-Hispanic white versus Non-white, education, and BMI

Table IX. Adjusted Odds Ratio* for Self-Reported Sleep Duration and Gestational Diabetes Stratified by Non-Hispanic Whites and Non-white®		
Self-reported Sleep Duration*	**Non-Hispanic White Odds Ratio (CI)**	**Non-white Odds Ratio (CI)**
<7 hours sleep	1.08 (0.39-2.99)	0.87 (0.37-2.03)
7-9 hours sleep	Reference	Reference
>9 hours sleep	1.39 (0.71-2.71)	0.48 (0.19-1.22)

Footnote: * Self-reported sleep duration calculated from a woman's self-report of usual bed time in past 30 days, usual wake time in past 30 days, and usual time it takes to fall asleep in past 30 days. **ICD 9 diagnosis of gestational diabetes (648.8) in second or third trimester. Exclusions included previous diagnosis of preexisting diabetes (250. Inclusive) pancreatic disorders (251. inclusive) 1 year prior to pregnancy or diagnosis in 1st trimester

®Model adjusted for maternal age at conception, education, and BMI

Paper 2

Shortened sleep duration and risk of preterm birth and small for gestational age

Jennifer Lynn Williams, MSN, MPH, FNP-BC

Nell Hodgson Woodruff School of Nursing

Emory University

Abstract:

Background: Women's sleep needs increase during pregnancy. Most pregnant women need more sleep than the 7-8 hours needed by non-pregnant individuals. One-quarter to one-third of pregnant women experience short sleep duration (<7 hours) as early as the first trimester; with the proportion experiencing shortened sleep duration increasing as pregnancy progresses. Limited evidence suggests that self-reported shortened sleep duration (SRSSD) in pregnancy adversely affects infant birth outcomes. The contribution of SRSSD in pregnancy to adverse outcomes is undetermined. The purpose of this study is to determine if SRSSD is independently associated with preterm birth (PTB) between 32-37 weeks or small for gestational age (SGA) defined as birthweight < 10^{th} percentile of the recommended sex-specific birthweight for gestational age.

Sample and Design: Data was derived from the Pregnancy and Influenza Study (PIP), a prospective, observational cohort of pregnant women receiving prenatal care through two managed health care systems. PIP data were obtained from enrollment interviews, medical chart abstraction, and electronic medical records extraction. This secondary analysis focused on a subset of women with singleton pregnancies who completed enrollment during gestation. Exclusions included diagnosis of preeclampsia or delivering very preterm (<32 weeks gestation) (final sample n=1176).

Univariate associations between SRSSD and dependent clinical outcomes, between SRSSD and covariates, and between clinical outcomes and covariates was conducted using Pearson chi-squared (χ 2) tests. Multinomial logistic regression models were conducted separately for each outcome. Analyses were conducted with SPSS version 21(SPSS Inc., Chicago, IL).

Results: The majority of women reported sleeping 7-9 hours a night (69%). SRSSD was reported

by 11% of respondents. Factors associated with SRSSD at a p value <0.05 included maternal age at conception, race/ethnicity, education, cohabiting with a spouse or partner, and fetal smoke exposure. Percentages of women delivering preterm and SGA were 3 % and 6% respectively. In logistic regression models, SRSSD was not associated with PTB (aOR 0.87, 95% CI 0.25-2.98) or SGA (aOR 1.39, 95% CI 0.86-2.70).

Conclusion: Results from this analysis did not find associations between SRSSD and PTB or SGA. Further research is needed on longitudinal effects of sleep duration and adverse infant outcomes.

Self-reported sleep duration and risk of preterm birth and small for gestational age

Introduction

Preterm birth, defined as birth before the completion of the 37TH week of gestation, is the second leading cause of infant mortality in the United States, accounting for 17% of all infant deaths (Mathews & MacDorman, 2012). In 2015, approximately 9% of the 3.8 million U.S. singleton births were preterm (8%) or very preterm (1%); (Martin et al., 2017). Prematurity can affect critical stages in infant development and can adversely impact several body systems, including neurological, respiratory, gastrointestinal or immunologic systems (Institute of Medicine, 2007a). Long term, many of these children suffer from motor, cognitive, sensory, growth and social-emotional or behavioral deficits (Institute of Medicine, 2007b). The societal, economic burden due to premature birth is high; the latest available data places estimates for preterm birth costs in the US around 26.2 billion dollars annually or just over 50 thousand dollars for each infant born premature (Institute Of Medicine, 2007c). Behavioral, social, and emotional consequences are harder to quantify, but many children born premature have deficits in attention and executive function that negatively influences performance and behavior at home and school (Institute Of Medicine, 2007c). Given the potential for serious long-term deficits and the significant societal costs, understanding the causes of preterm birth is a public health priority.

Preterm birth is currently understood as a multifactorial constellation of problems that is best thought of as a condition arising from heterogeneous composites of interacting causative factors (Green et al. 2005; Williamson et al. 2008). The known risk factors for preterm birth include biological, genetic, behavioral, societal, environmental, psychosocial, and medical factors that exert influence primarily through pathophysiologic pathways, such as inflammation/infection, stress,

uterine distention, and bleeding/hemorrhage (Green et al. 2005; Institute of Medicine, 2007d; Romero et al. 2006). Unfortunately, for the majority of preterm deliveries, the exact mechanism which precipitated early labor is unknown (Goldenberg, Culhane, Iams & Romero, 2008).

Likewise, small for gestational age (SGA), defined as birthweight < 10^{th} percentile of the recommended sex-specific birthweight for gestational age, affects about 8%-10% of all US births (Morisake et al., 2013; MMWR, 2008). Like preterm birth, risk factors for SGA include biological (race/ethnicity, parental SGA), medical (hypertension, renal disease, and maternal weight), and behavioral factors (smoking) (McCowan & Horgan, 2009). Infants that are SGA are at increased risk of death (Baer et al. 2016; Bartels et al., 2004; Pulver et al., 2009) and metabolic disturbances (Soto et al 2003; Iñiguez et al. 2006; Bazeas et al. 2003; Mericq et al. 2017). SGA also and confers an independent risk for preterm birth associated morbidities (Baer et al. 2016).

Recently, self-reported shortened sleep duration has been examined as a contributing factor to preterm birth and SGA. Some preliminary evidence suggests an association between sleep duration and preterm birth (Micheli, et al. 2011; Reutrakul et al. 2011) but others studies fail to corroborate these findings (Blair, Porter, Leblebicioglu, & Christian, 2015; Guendelman et al. 2013; Okun et al. 2012; Strange et al. 2009). Only two studies examining self-reported shortened sleep duration and SGA were found in the literature; both failed to show an association with SGA using the standard definition of < 10^{th} percentile of the recommended sex-specific birthweight for gestational age (Micheli et al. 2011; Abeysena, Jayawardana, Seneviratne 2009). Table 1 summarizes the available studies for self-reported sleep duration and these two adverse infant outcomes and is organized by study type, group, sleep duration measurement, and major findings. There appears to be no consensus on the contribution, if any that self-reported shortened sleep duration in pregnancy might have to preterm birth or SGA. Several limitations might explain the inconsistent findings,

including retrospectively collected data, small analytic sample sizes, lack of variation among samples, and atypical definitions of sleep. Prospective studies of sufficient size are needed to clarify any associations that self-reported shortened sleep duration in pregnancy might have on preterm birth and SGA.

The average adult needs 7-8 hours of sleep each night, but pregnant women typically need several more hours (NIH, 2014). Despite the need for more sleep in pregnancy, between one-quarter to one-third of pregnant women report shortened sleep durations in their 1st trimester of pregnancy. This proportion with reduced sleep increases as pregnancy progresses with up to half of pregnant women experiencing shortened sleep duration in later pregnancy. (Facco et al., 2010; Mindell, Cook & Nikolovski, 2015; Signal et al. 2014; Sivertsen, Hysing, Dørheim & Eberhard-Gran, 2015.).

Additionally, shortened sleep duration in pregnancy might be a potential contributor to several adverse pregnancy outcomes (such as preeclampsia, diabetes and depression) that are themselves associated with preterm birth (Facco et al., 2010; IOM, 2007d; Qiu et al. 2010; Okun et al. 2013; Rawal et al. 2016; Reutrakul et al. 2011, Williams et al. 2010);and several socio-demographic factors (such as race, age, education) known to affect preterm birth and small for gestational age are also associated with shortened sleep duration (IOM, 2007d; McCowan & Horgan, 2009). Given that the prevalence of shortened sleep duration in pregnant populations is high, the potentially modifiable nature of sleep, and detrimental effects of preterm birth and SGA, determining whether and how sleep affects preterm birth and SGA is scientifically and clinically important. The hypothesis for this study was that pregnant women who self-report shorter sleep durations will be more likely to deliver an infant preterm or SGA than pregnant women who self-report normal (7-9 hour) sleep durations.

Study Design

The current study is a secondary analysis of the Pregnancy and Influenza Study (PIP study), a prospective, observational cohort study designed to assess vaccine efficacy for the prevention of lab-confirmed influenza illness among pregnant women. Detailed methods on the PIP study design have been previously published (Thompson et. al 2011). All women in the study received their care through two large US west coast, managed care health systems. Recruitment for PIP began in 2011, and a nonprobability convenience sampling approach using a consecutive sampling design was selected to ensure that the study would have a sufficient population of pregnant women to conduct a vaccine efficacy study. Women enrolled in the study as they became pregnant, and exited the cohort at the completion or termination of their pregnancy and follow-up period. PIP data were obtained from maternal interviews, medical chart abstraction, and electronic medical records (EMR) extraction. All women who consented to participate completed a 15-minute enrollment interview questionnaire. Topics covered in the enrollment questionnaire were the presence of acute respiratory illness in pregnancy, symptom severity, pregnancy and vaccination history, general health and medical history, current past behavioral health habits, sleep experience, and general sociodemographic characteristics.

For this secondary analysis, women were considered for inclusion if they had a singleton pregnancy with a delivery outcome, completed the enrollment interview during pregnancy, and had all key information for determining sleep duration.

A total of 1,271 women with singleton pregnancies had completed enrollment interviews in pregnancy. Forty respondents were excluded for missing (n=35) or invalid (n=5) key sleep variables. An additional 49 respondents were ineligible because they had very preterm infants (n=6)

or were diagnosed with preeclampsia (n=43). The final analytic sample of women with singleton pregnancies was 1,176 women. (Figure 1).

Calculation of Self-reported Sleep Duration

Information on total sleep time was calculated by using the following three self-reported items, usual bedtime, usual wake time, and usual sleep latency. Usual bedtime, asked as "During the past month, what time have you usually gone to bed at night?" was subtracted from usual awaken time asked as "During the past month, what time have you usually gotten up in the morning?" to calculate the total minutes a woman reported as being in bed. Sleep latency asked as "During the past month, how long (in minutes) has it usually taken you to fall asleep each night?" was subtracted from the total minutes a woman reported as being in bed. The difference was used to derive how long a woman reported as asleep (self-reported sleep duration). A U-shaped relationship of both short and long poor sleepers has been reported in the literature (Lee, 2009), therefore, instead of a continuous variable, sleep was examined categorically with 7-9 hours duration set as the referent. This cohort had small numbers of very short sleepers (< 6 hrs.) and very long sleepers (>10 hours), so self-reported sleep duration at the extremes were collapsed; shortened sleep duration was examined as < 7 hours and long sleep duration was examined as > 9 hours with 7-9 hours set as the referent.

Preterm birth and Small for Gestational Age

Information on the birth outcomes and the anthropometric measures of infants were obtained from the electronic medical record. Gestational age and birth weight were determined by delivering clinicians. Preterm birth was defined as less than 37 weeks gestation. Preterm birth was further divided into <32 weeks gestation and 32-37 weeks gestation. Preterm infants <32 weeks gestation were categorized as "very preterm." Mothers delivering very preterm infants often have

ongoing risk factors that predispose them to very early delivery. Therefore these outcomes were excluded and only the preterm infants reaching a gestational age of at least 32 weeks were analyzed. Neonates were determined to be small for gestational age if their birth weight fell below the 10th percentile for sex-specific birthweight for a given gestational age.

Covariates and Potential Confounders

Several covariates were included in this analysis to describe the study population but were also examined as possible confounders for associations between self-reported sleep duration and preterm birth or SGA. Similar to other analyses utilizing the PIP Study data, the variables were classified by characteristics; sociodemographic, health and health behaviors, and obstetric history characteristics. Covariates were considered as potential confounders if, in univariate analyses, the variable was significantly associated at a p-value ≤0.1

with both self-reported sleep duration and preterm birth or SGA.

***A priori* Confounders**

A few *a priori* confounders were considered based on known associations in the literature with sleep and either preterm birth or SGA. Recognized factors for sleep and preterm birth or SGA, were maternal age (≤ 25 years, 25 – 35 years, > 35 years), race (White-non Hispanic, Non-White), education (high school or general education development diploma or less, some college, college bachelor degree or higher), smoke exposure (Yes, No) and BMI (normal BMI<25, overweight BMI 25-<30, obese BMI ≥30) (Goldenberg, Culhane & Romero, 2008; McCowan & Horgan, 2009; McKnight-Eily et al 2011; IOM, 2007d; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004; Wetter & Young, 1994). Body mass index (BMI) was calculated from pre-pregnancy weight and maternal height obtained from maternal self-report using the following formula from the

CDC Division of Nutrition, Physical Activity and Obesity**:** weight (lb.) / [height (in)]^2 x 703 (available at https://www.cdc.gov/nccdphp/dnpao/growthcharts/training/bmiage/page5_2.html**).** In instances where either self-reported pre-pregnancy weight or maternal height was missing, EMRs were queried for the missing information.

Sociodemographic Covariates

Sociodemographic factors used to describe the analytic sample included study site (either the San Francisco Bay Area or in Portland, Oregon), trimester of enrollment (1st or 2nd trimester vs. 3rd trimester), living with a spouse or partner (Yes/No), the presence of children under 5 years of age in the house (Yes/No), and a woman's view of her position in the social hierarchy. To assess social position, The MacArthur Scale of Subjective Social Status was used. This visual analogue scale uses a 9-step ladder to capture perceived social position across several SES indicators, including education, occupation, and income (Adler & Stewart, 2007). Subjective social status was examined in tertiles, low (1-5), moderate (6-7), and high (8-9) as was done in in prior studies (Thompson et al. 2014).

Health and Health Behavior Covariates

Since maternal health is inextricably linked to the health outcomes of infants, several maternal health and health behavior covariates were considered. To assess a pregnant woman's view of her personal health, a common measure of health that has been used in pregnant populations (Haas et al. 2004; Schytt & Waldenstrom, 2007; Teoli, Zullig & Hendryx, 2014), was used. The standardized ordinal measure self-rated health asked women to describe their current overall health on a Likert-like scale (poor, fair, good, very good, excellent) and is thought to be highly predictive of morbidity, mortality, and disability (Zajacova & Dowd, 2007).

An adaptation of the Holmes and Rahe Stress Scale inventory that was previously modified for pregnant women was used to assess stressful events (Li, Liu, Odouli, 2009). Women answered a 17 item questionnaire about stressful life events; weights was assigned according to each event and summed across all events. Values were dichotomized into low stress (weight score of 0-99) or high stress (weight score ≥100).

A preexisting medical condition was predicated in the presence of a high-risk condition found in the EMR in the year prior to pregnancy. Medical conditions were identified through ICD-9 codes for specific medical diagnoses. Broadly, diagnoses fell into one of eleven categories: hematologic, endocrine, cardiovascular, malignancies, immunologic, renal, hepatic, respiratory, metabolic, neurologic, and pregnancy-related conditions. Specific ICD-9 codes for each broad category are available from the author upon request. For analytic purposes, the presence of any condition in the eleven categories was rolled up into a dichotomous variable preexisting condition (Yes/No).

Women were asked about specific health behaviors known to affect sleep, specifically drinking and smoking behaviors. Alcohol use was assessed by asking women about any alcohol consumption in the past 30 days (Yes/No). Women were asked a series of questions regarding tobacco smoke exposure. Because very few women reported current cigarette use, current smokers, women who quit smoking at some point after conception, and women who reported ongoing second-hand smoke exposure were rolled up into a composite variable called smoke exposure (Yes/No).

Recently an exploratory study among a general population of adults preliminarily noted that multivitamin users had shorter sleep duration compared to non-users (Lichstein et al., 2008). Folic acid containing supplements taken before and during pregnancy are proven to prevent certain birth

defects (CDC, 1992). Given the high use of vitamins in women desiring pregnancy and the even higher use of vitamins in pregnant women, the role of vitamins was considered during planning for this study. However, because of the almost unanimous vitamin use during pregnancy, (97%) prenatal vitamin use was not assessed. Rather preconception use of a folic-acid containing supplement (Yes/No) was included.

Obstetric History Covariates

Trimester of enrollment was derived from gestational age obtained from the medical record. Gestational age was based on best estimate. Approximately 70% of gestational age dating was from ultrasound estimation, the remaining 30% was based on last menstrual period (M. Thompson, personal communication, March 22, 2017). From the enrollment interview, women were asked about their prior obstetric history, including the total number of pregnancies, including the index pregnancy (1 time, 2 times, 3 or more times), prior history of cesarean section surgery (Yes/No), prior history of ectopic pregnancy (Yes/No), prior history of elective termination of pregnancy (Yes/No), and prior history of miscarriages and prior history of stillbirths. There were very few stillbirths, so stillbirths and miscarriages were combined into one single derived variable, fetal loss (Yes/No). Because of potential associations of fetal sex and preterm birth (Zeitlin et al. 2002) and of known differences in birth weights of infant boys and girls (Oken, Kleinman, Rich-Edwards, & Gillman, 2003) sex of the child (Male/Female) was also examined.

Statistical Considerations

In planning for this secondary analysis, some preliminary statistical power calculations were made under the following assumptions based on the literature; a base rate of 8% for preterm birth (Martin et al., 2017) and a conservative 26% estimation of women sleeping < 7 hours in the second and third trimester gave 80% power (alpha = 0.05) to detect 17% of preterm birth among those with

self-reported short sleep duration or a relative risk ratio of 1.85. For SGA, a base rate of 9% (Morisake et al., 2013; CDC, 2008) was assumed, giving 80% power to detect again 17% among those with short self-reported short sleep duration or a relative risk of 1.80.

Analysis Plan

The primary infant outcome variables were preterm births between 32 and 37 weeks gestation, and SGA. The primary independent variable was self-reported sleep duration. Women missing key sleep variables necessary for calculating total sleep duration were excluded. Women delivering very preterm infants under 32 weeks gestation and women with a diagnosis of preeclampsia in the first trimester were also excluded. Very few covariate values were missing, but, in these instances, a multiple imputation program was used to average the best estimate of the missing value using associations with all available data. Specifically, this involved imputing values for the following covariates in descending order of frequency: BMI (n=23), gender (n=8), fetal loss (n=4); subjective health (n=3), alcohol use (n=3), education (n=1) and total pregnancies (n=1).

Crude associations between the independent variable (self-reported sleep duration) and preterm birth (32-37 weeks gestation) and SGA were examined separately. The primary hypothesis was to examine associations of short self-reported sleep duration (> 7hours vs. 7-9 hours) and preterm birth and SGA. Although the study hypothesis centers on the role of short sleep duration (< 7 hours) versus normal sleep duration (7-9 hours), we maintain that those with longer sleep duration (> 9 hours) for data completeness and for hypothesis generation, since there is little information on the possible role of longer sleep and infant outcomes.

Using Pearson chi-squared (χ 2) to test for significance, uunivariate analyses between self-reported sleep duration and each covariate, and between each covariate and preterm birth and small for gestational age was performed. A factor determined to be associated with both self-reported

sleep duration, and preterm birth or SGA was considered to be a potential confounder and thus adjusted for in final regression models in addition to the *a priori variables* included in the models.

To establish if the effect of self-reported sleep duration on preterm birth or SGA was any different by *a priori* subgroups, (i.e. did associations vary by characteristics?) a test for interaction effects was created between self-reported sleep duration and the following subgroups: maternal age at conception, race/ethnicity, education, BMI, and smoke exposure. Two additional covariates were potentially associated with both sleep and either PTB or SGA; trimester of enrollment and history or prior cesarean section surgery. Using standard methods, the interaction term was entered into a model after adjustment for the main effects of self-reported sleep duration, the potential confounders, and the *a priori* covariates. A significant interaction term ($p < 0.05$) was indicative that the association between sleep and preterm birth or SGA would best be represented as a stratified variable.

Multinomial binary logistic regression models were conducted separately for preterm birth and SGA, using women sleeping 7-9 hours a night on average as the referent. Each model was adjusted for the *a priori* maternal age at conception, race/ethnicity, education, and smoke exposure. Additional model-specific variables were to be included if the covariate was associated with self-reported sleep duration and the outcomes at a p-value of 0.1 or less. In logistic regression modeling, significance was established at a p-value of 0.05 or less. All analyses were conducted with the statistical package SPSS version 23 (SPSS, Inc., Chicago IL).

Results

Table 2 reports the characteristics of women included in this analysis. The majority of women were 25-35 years of age (66%), white non-Hispanic (65%), college educated (76%), and living with a spouse or partner (94%). About one-fifth to one-quarter considered themselves in the

lowest tertile for subjective social status (26%), in poor/fair to good subjective health (21%) or be currently subject to high stress (24%). Just over 1/3 of respondents were overweight (24%) or obese (13%). Only 15% of women had a preexisting condition identified in the year preceding pregnancy. Substance use was very low in this population; only 8% and 6 % reported alcohol use or fetal smoke exposure respectively. For about one-third of respondents, this was their index (first) pregnancy.

Self-reported sleep duration of the pregnant women is reported in Table 3. Most women (69%) reported sleeping 7-9 hours a night. Eleven percent (11%) of women reported sleeping less than 7 hours a night. When looking at very short sleep duration, 4 % of women reported sleeping ≤ 6 hours a night.

The percentage of women with infants born prematurely between 32-37 weeks and SGA are found in Table 4. In this sample, 3% of infants were premature, and 6% were born SGA.

In univariate (unadjusted) analyses, no associations between self-reported sleep duration and preterm birth (Chi Square [Chi-sq.] 2.76, p-value [p] = 0.25) or SGA (Chi-sq. 2.80, p = 0.25) were found (Table 5).

Self-reported sleep duration was associated at a p-value or 0.05 or less with several covariates (Table 6). Younger women reported longer sleep durations while short sleep duration did not appear to be different by maternal age. More non-White women reported sleeping < 7 hours. Graduating college was associated with adequate amounts of sleep (7-9 hours). Women living without a partner and women reporting smoke exposure were more likely to report either short or long sleep durations. While marginally significant (Chi-sq. 9.26, p =0.055) heavier (overweight or obese) women had more shortened sleep duration than normal weight women.

Characteristics significantly associated at a p-value of 0.05 or less with preterm birth between 32-37 weeks and SGA are found in Table 7. Only one variable was associated with preterm birth; being born in the San Francisco Bay area cohort. Two variables were associated with SGA: more SGA babies had fetal smoke exposure or had mothers who had no other children in the household.

In this analysis, maternal age at gestation, race/ethnicity, BMI, smoke exposure, and education was examined as *a priori* covariates and potential confounders to the relationship between self-reported sleep and preterm birth. In univariate analysis, neither maternal age, race/ethnicity nor education was associated with preterm birth or SGA. Regardless, these variables were included in the subsequent statistical model. Two additional covariates were associated at a p-value of 0.1 or less with both sleep and at least one of the outcomes, namely trimester of enrollment and prior history of cesarean section and were included is subsequent modeling. The *a priori* variable smoke exposure was associated with both self-reported sleep duration and SGA; Tests for interaction was conducted for smoke exposure, trimester of enrollment and prior history of cesarean section surgery. Interaction terms for self-reported sleep duration by the covariates of smoke exposure, trimester of enrollment interview, and prior history of cesarean section surgery was not significant after adjusting for main effects.

Table 8 reports the crude and adjusted odds ratios for self-reported sleep duration and preterm birth and small for gestational age. There was no association with self-reported sleep duration and preterm birth (32-37 weeks gestation). In bivariate analysis, the odds ratio for short self-reported sleep duration and preterm birth was 0.93 with 95% confidence intervals that included one. The adjusted odds ratio (aOR) was not substantially different or significant (aOR 0.82, 95% CI 0.24-2.83). When examining long self-reported sleep duration and preterm birth, both crude and aORs imply a higher risk (crude OR 1.82; aOR 2.05), but both Cis included one. For SGA, although not significant, the point estimates in both short and long sleepers suggest an increased risk. In

crude analyses, the odds of SGA among women sleeping less than 7 hours a night were 1.5-fold higher than those sleeping 7-9 hours a night (OR 1.52 CI 0.74-3.10); odds for women sleeping more than 9 hours were essentially the same (OR 1.51 CI 0.86-2.64). Trends for short and long sleepers were not drastically different in the adjusted model.

Sensitivity Analyses

To examine whether parameter values and assumptions in the original model were sound, sensitivity analyses based on the exposure and the covariates were conducted. For exposure, given the possible need for longer sleep times (NIH, 2014), the referent defining "normal sleep" was shifted one hour. A new referent of 8-10 hours was used to represent "optimal sleep" duration. All outcomes remained non-significant and point estimates trended towards the null in post hoc analyses (data not shown). For covariate assumptions, more inclusive models where covariates associated with either sleep or the outcomes were compared to the parsimonious original models where covariates were associated with both sleep and outcomes; doing so did not appreciably alter any point estimates or confidence intervals (data not shown).

Discussion

In this dataset of relatively healthy women, no associations with shortened self-reported sleep duration and either preterm birth or small for gestational age were found. The findings of this analysis do not support the hypothesis that shortened self-reported sleep duration contributes significantly to preterm birth or small for gestational age.

There are several possibilities that might explain the null results found in this analysis. The simplest explanation is that self-reported sleep duration is not associated with either preterm birth or SGA. As was reported in Table 1, more studies reported null results (Blair, Porter, Leblebicioglu, & Christian, 2015; Guendelman et al 2013, Okun et al 2012; Strange et al. 2015) than associations

((Micheli, et al 2011; Reutrakul et al 2011) for preterm birth and neither study of SGA reported significant findings using standard definitions of SGA (Micheli et al 2011; Abeysena, Jayawardana, Seneviratne 2009).

Second, this study might have been underpowered to detect any true effect. This study had adequate statistical power to detect differences in the risk of preterm birth, and SGA was approximately 1.8-fold higher in short sleepers (compared to normal sleepers) using the assumed metric of about a quarter of women would report sleeping an average of < 7 hours a night, based on reports from previous studies (Facco et al., 2010; Mindell, Cook & Nikolovski, 2015; Signal et al. 2014; Sivertsen, Hysing, Dørheim & Eberhard-Gran, 2015). Despite the conflicting evidence in the available literature (Table 1), at least two studies of similar design observed significant associations between self-reported sleep duration and preterm birth; reporting 1.7to 4.3 fold differences (Micheli e al. 2011; Reutrakul et al. 2011). Therefore it was possible that a large effect size could have been detected. The effects of short sleep duration observed in this study were of a much lower magnitude for both preterm birth and SGA.

Third, poor measurement of the clinical outcomes, poor measurement of self-reported sleep duration, or of both might explain the null results. Clinical diagnoses are imperfect; any misclassification of study infants would have lowered the ability to observe any true effect. The prevalence estimates for preterm birth and SGA in this analysis (Table 4) were lower than national estimates of 8% for preterm birth between 32-37 weeks, and 8-10% for SGA. While this most likely reflects a healthier infant population, it is possible the null findings in this study might be due to misclassification of disease (Martin et al., 2017; Morisake et al., 2013; CDC, 2008).

Poor measurement of sleep is a more likely candidate for any measurement error of this study. Even though self-reported sleep is an easy metric to collect, it might not be an appropriate

measure for gauging a woman's total sleep time. Self-reported sleep tends to overestimate objective sleep, thus biasing findings towards the null (Lauderdale et al. 2008). Moreover, sleep is ever changing; therefore, lack of sufficient sleep at one point in time (as was used for this analysis) should not be interpreted as the nonexistence of deficiency at another unmeasured point in time. These factors could have biased findings towards the null as well.

Other potential measurement error in self-reported sleep measure of this study might be related to the actual cut-points selected for this analysis. In several studies, using the cut point of < 7 hours failed to show an association (Guendelman et al. 2013; Okun et al. 2012) with preterm birth. In a recent study, reporting less than 5 hours of sleep was associated with preterm birth; in that same study, no associations were found with sleep durations of 6-7 hours (Micheli et al. 2011). It might be that women can physiologically compensate for shortened sleep duration up to a point, but it is at the more extremes of shortened sleep duration that women start to experience physiologic consequences of shortened sleep that could lead to the outcomes examined. The lack of association in this analysis might be related to the selection of < 7 hours to define shortened sleep duration. Unfortunately, the relatively few women in the analytic sample at the extreme ends (Table 3) preclude examination of this potential explanation.

Fourth, the number of women with short sleep duration in the analytic sample (11%) (Table 3) was much lower than expected and projected in the original power analyses (assumption of 26% would have shortened sleep duration). Coupled with the above-mentioned factor of lower than expected outcomes (Table 4) this further reduced the capacity for determining precise estimates. The one study examined similar in design and size to PIP had both adequate numbers of infants born preterm and had adequate numbers of poor sleepers (Micheli et al. 2011). In the "Rhea" study in Crete, Greece 2007–2009, (n=1091) 35% of respondents reported sleeping less than 7 hours a night

compared to PIP's 11%, and, while percentages of SGA were comparable between studies (PIP, 6% vs. Rhea 7%), a full 12% of "Rhea "mothers delivered preterm infants compared to PIP's 3% (Micheli et al. 2011).

The fifth explanation centers on the possible role of selection bias. Recruiting pregnant women for cohort studies fraught with difficulties (Frew 2014). There is a possibility that the PIP cohort consists of a much healthier population than is seen in the general population of pregnant women. Additionally, PIP respondents were relatively homogenous and lacked sociodemographic diversity. In this cohort, women were mostly white, married, college-educated, and relatively healthy. An indication that the current analysis might be subject to selection bias comes from a previous case-control analyses where the PIP cohort of women was used as controls and compared to women who were medically attended with acute respiratory infections and who were recruited from the same two west coast large managed care health care systems. In that study, controls were more likely to be white non-Hispanic and to describe their health as excellent (Thompson et al. 2013). The potential selection bias might have reduced the variability in sleep and negative infant outcomes or biased results in other unidentified ways.

The current study has several strengths. First, this study draws from a large, prospectively collected cohort of pregnant women with detailed medical information, which allowed for accurate descriptions of the characteristics of self-reported sleep among pregnant women and also to adjust for established risk factors for preterm birth and SGA. Few studies of preterm birth and SGA to date have this advantage (Table 1). Second, the data was reasonably complete. Very few women were excluded, and even fewer variables required imputation. Further, associations were found between certain covariates and self-reported sleep duration that were consistent with previous studies, which defends the overall validity of the findings.

Future Directions

These null findings should not imply that shortened sleep duration is not associated with preterm birth or SGA, but the verdict is still out on whether self-reported sleep duration can be used as a measure for identifying women at risk of delivering a preterm or SGA baby consistently. Other measures for quantifying sleep duration should also be considered. In a recent study, the overall accuracy of actigraphy compared to the gold standard polysomnography for individual-level estimates was 89% for women (Marino et al. 2013). The built-in actigraphy technology found in many fitness devices, while not as accurate as actigraphy used in sleep research, might be able to provide more consistent estimates of sleep duration than self-report. Additional research is needed to see if personal actigraphy might have the potential for improving accuracy and reducing the burden for collecting accurate sleep measures.

Lastly, information is needed on the biologic plausibility of the effects of shortened sleep duration on preterm birth and SGA. Inflammation has been suggested by some researchers to be a pathway through which sleep deprivation contributes to negative infant outcomes like preterm birth (Chang, Pien, Duntley & Macones, 2010; Okun, Hall, Coussons-Read, 2007). In this dataset, we were unable to explore the role of sleep on inflammatory processes and the subsequent effects on pregnancy outcomes. Therefore further prospective studies among sociodemographically diverse women of adequate sample size which collect both self-reported and objective sleep data and inflammatory markers at several points during pregnancy are needed.

Conclusion

In conclusion, no associations between self-reported sleep duration and preterm birth or SGA were found. In this study, the null findings might be due to the homogeneity of the cohort and

relatively large effect sizes necessary to show an association. The lack of findings however should not be concluded that there is definitively no association between shortened sleep duration and preterm birth or SGA. Shortened sleep duration is common in pregnancy (Facco et al., 2010; Mindell, Cook & Nikolovski, 2015; Signal et al. 2014; Sivertsen, Hysing, Dørheim & Eberhard-Gran, 2015), and there a biologically plausible working theory on how sleep might adversely affect preterm birth and SGA (Chang, Pien, Duntley & Macones, 2010; Okun, Hall, Coussons-Read, 2007). Further research is needed to determine the most useful and valid measures for determining sleep duration, to study longitudinal effects of sleep duration in representative samples of adequate size, and to explore the possible effects on inflammation by shortened sleep duration.

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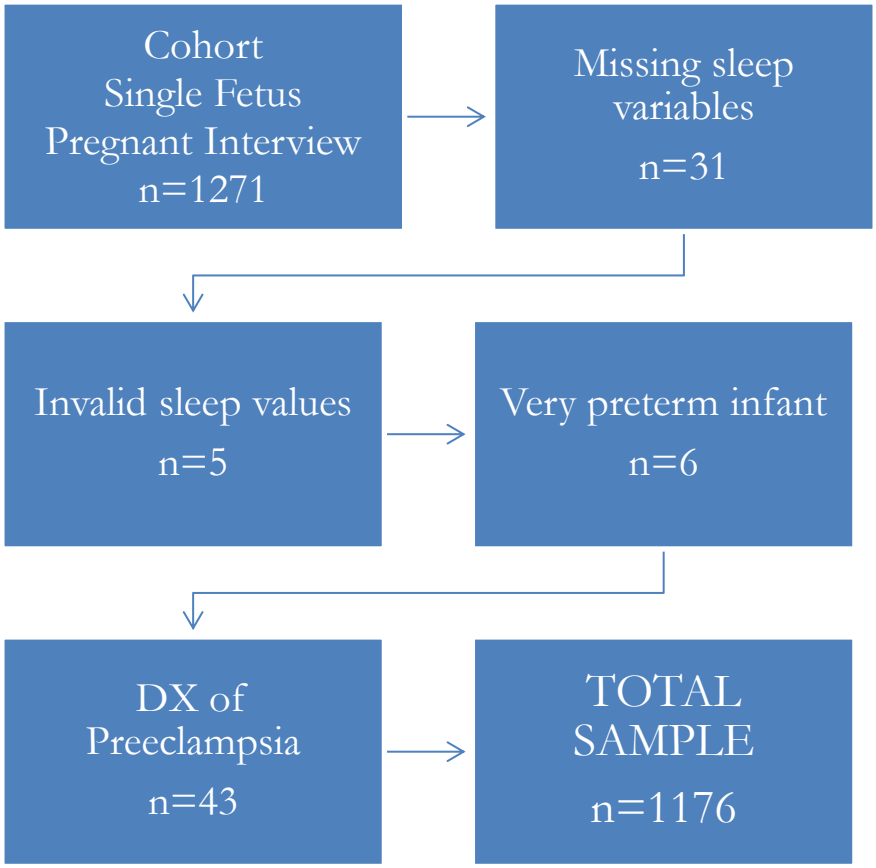
Table 1. Summary of Studies Examining Self-Reported Sleep Duration and Preterm Birth and Small for Gestational Age					
Author/Year / Citation	**Study Design Study Group(s)**	**Sleep Measures**	**Pertinent Research Question**	**Clinical Outcomes & Cardio-metabolic Measures**	**Major Findings**
Blair, Porter, Leblebicioglu, & Christian (2015) Sleep 38: 1259-1267.	Cross sectional study Pregnant women 2nd trimester (n=138)	Derived from PSQI[α]	Describe associations among sleep quality, serum proinflammatory cytokines, and length of gestation	PTB	PTB associated with poor sleep quality (global PSQI) ($rs = -0.35$, P = 0.002) and subscales of subjective quality, latency and efficiency (not duration) in black women. IL-8 mediates relationship Effect not seen in white women NOTE: PTB cases=12; 9 black women & 3 white women
Guendelman et al. (2013) Matern Child Health J 17: 723-731	Nested case-control study Postpartum women with PTB (n=344) controls (n=698)	"How many hours of sleep did you typically get each night during the second 3 months of your pregnancy?" < 7 h (short) 7–8 (normal) > 8 h (long)	Determine the individual and joint associations of modifiable factors (sleep, exercise, BMI) on PTB.	PTB	Sleep duration not associated with PTB <7 hours: OR = 1.09, 95 % CI = 0.80–1.48 >8 hours: OR = 0.88, 95 % CI = 0.57–1.48
Okun et al. (2012) J Women's Health 21: 54-60	Prospective cohort Pregnant women 20 or 30 weeks gestation (n=217)	total nocturnal sleep minus time to sleep onset and time spent awake <7 h (short) > 9 hours (long)	Is sleep disturbance associated with PTB and whether association is affected by other psychosocial risk factors	PTB	PTB is not associated with sleep duration of < 7 hours Crude 0.86 (0.33-2.27) Adjusted 0.86 (0.29-2.59) Or > 9 hours Crude 1.85 (0.68-5.03) Adjusted 1.19 (0.38-3.75) PTB (n=26) 7 early 19 late
Micheli et al. (2011) Epidemiology 22: 738-744.	Prospective cohort study Greek women in 3rd trimester of pregnancy (n=1091)	-Likert scale response "During the past month, how many hours do you sleep per day?" ≤5 hours 6–7 hours ≥8 hours	Assessed the prevalence of sleep deprivation and snoring in the 3rd trimester and determined the associations between sleep disturbances and PTB, low birth weight, or SGA infants	PTB SGA	Sleep duration of ≤5 hours a night associated is associated with PTB aRR 1.7 95% CI 1.1-2.8 But not with 6-7 hours RR 0.8 95% CI 0.4–1.3 Sleep duration was not associated with SGA (excludes preterm) ≤5 hours 0.6 (0.2–2.0) 6-7 hours 0.8 (0.4–1.3) PTB included very preterm infants
Reutrakul et al. (2011) Diabetes Care 34: 2454-2457	Prospective cohort Pregnant women in 2nd trimest with GCT[ł] (n=169)	Derived from PSQI[α] SSRSD[∞] < 7 hrs.	Examine association between SRSD & glucose intolerance, and pregnancy outcomes	PTB	-In women with normal GT, the risk of preterm delivery was associated with: -Higher ESS score OR 1.2 95% CI 1.0-1.3 p=.02 -Higher PSQI score OR 1.2, 95% CI 1.0-1.3 p=.02 -Shortened sleep OR 4.3 95% CI = 1.1-16.7 p=.003

					Sleep duration not assessed in women with gestational diabetes due to small numbers
Abeysena, Jayawardana, & Seneviratne (2009) ANZJOG 49; 382-387	Prospective cohort Sri Lankan women ≥16 weeks gestation (n=550)	Short sleep defined as ≤ 8 hours	Determine the trimester-specific effect of physical activity and psychological status of the mother on the delivery of SGA infants < 5th centile and < 10th centile.	SGA	Sleeping ≤ 8 hours a day was associated with SGA <10th centile in crude but not adjusted modeling Crude OR 1.66 95% CI 1.04–2.67 Adjusted OR 1.53 95% CI 0.92-2.54 For SGA <5th centile, both crude and adjusted were associated Crude OR 2.26 95% CI 1.16–4.39 NOTES: Unclear how sleep duration assessed. High study attrition.
Strange, Parker, Moore, Strickland & Bliwise (2009) Clin Exp Obstet & Gyn 36: 166-168	Cross sectional study Pregnant women 20-29 weeks gestation (n=220)	Derived from PSQI[α]	Is disturbed sleep a significant summary indicator of the risk of preterm birth?	PTB	PTB not associated with sleep quality (global PSQI) or with sleep duration subscale. Sleep latency subscale associated with PTB.

Figure 1. Analytic Sample



Sociodemographic Characteristics	N	%
Study Site		
San Francisco Bay Area	659	56
Portland, Oregon	517	44
Maternal Age at Conception		
Under 25 years	107	9
> 25 - 35 years	780	66
> 35 years	289	25
Trimester of Enrollment Interview		
1st or 2nd trimester	671	57
3rd trimester	505	43
Race/Ethnicity**		
White non-Hispanic	761	65
Non-white	415	35
Education		
High school diploma or less, or General Education Development diploma	102	9
Some college	182	16
College bachelor degree or higher	892	76
Cohabitating with spouse or partner		
Yes	1107	94
No	69	6
Children in household < 5 years old		
No children	645	55
One or more children	531	45
Subjective Social Status ◦		
Low (1-5)	308	26
Moderate (6-7)	746	63
High (8-9)	122	10

Health and Health Behavior Characteristics	N	%
Subjective Health‡		
Poor Fair or Good	250	21
Very Good	469	40
Excellent	457	39
High vs Low Stress €		
High score ≥100	281	24
Low score < 100	895	76
Body Mass Index (BMI)		
Normal BMI or lower <24.9	746	63
Overweight 25-29.9	280	24
Obese >30	150	13
Preexisting Condition		
Yes	173	15
No	1003	85
Any Alcohol Use in Past Month		

Yes	94	8
No	1082	92
Fetal Smoke Exposure ◊		
Yes	65	6
No	1111	96
Preconception Folic Acid Intake		
Yes	827	70
No	349	30

Obstetric History Characteristics	**N**	**%**
Total Times Pregnant		
1 time	416	35
2 times	386	33
3 or more times	374	32
Prior History of Cesarean Section		
Yes	143	12
No	1033	88
Prior History of Ectopic Pregnancy		
Yes	23	2
No	1153	98
Prior History of Fetal Loss* **		
Yes	271	23
No	905	77
Prior History of Elective Termination of Pregnancy		
Yes	177	15
No	999	85
Sex of Child		
Male	561	48
Female	615	52

Footnotes:
*Percentages might not equal 100% due to rounding
* *Non-white is inclusive of Black non-Hispanic (42) Asian (177) Hispanic (128) and Other or Mixed Race (68)
◦MacArthur Scale of Subjective Social Status
ŀStandardized measure of perceived health status
€Adaptation for pregnant women of the Holmes and Rahe Stress Scale Inventory; women asked about 17 weighted stress events, sums of weights calculated and dichotomized into high stress (total score ≥100) and low stress (total score <100)
◊Current smoker, former smoker but quit during current pregnancy, or ongoing second-hand smoke exposure
***Miscarriages and stillbirths

Table 3. Self-reported Sleep Duration*								
≤ 6 hours	>6 to 7 hours	> 7 to 9 hours	> 9 to 10 hours	> 10 hours		Normal Sleep ≥ 7 to 9 hours	Short Sleep < 7 hours	Long Sleep ≥ 9 hours
N (%)	N (%)	N (%)	N (%)	N (%)		N (%)	N (%)	N (%)
44 (4)	81 (7)	812 (69)	186 (16)	53 (5)		812 (69)	125 (11)	239 (20)

Footnote: * Self-reported sleep duration calculated from a woman's self-report of usual bed time in past 30 days, usual wake time in past 30 days, and usual time it takes to fall asleep in past 30 days.

	N	%
Preterm Birth*		
Yes	35	3
No	1141	97
Small for Gestational Age **		
Yes	73	6
No	1103	94

* Preterm birth defined as 32- < 37 weeks gestation. Excludes very preterm birth < 32 weeks gestation

** Small for gestational age if their birth weight fell below the 10th percentile for sex specific birthweight for a given gestational age

Table 5. Univariate Associations between Self-Reported Sleep Duration and Preterm Birth and Small for Gestational Age					
	Normal Sleep Duration ≥7 to 9 hours	**Short Sleep Duration <7 hours**	**Long Sleep Duration >9 hours**		
	N (%)	**N (%)**	**N (%)**	**Chi Square**	**P-value**
Preterm Birth *					
YES	21 (60)	3 (9)	11 (31)	2.76	0.252
NO	791 (69)	122 (11)	228 (20)		
Small for Gestational Age **					
YES	44 (60)	10 (14)	19 (26)	2.80	0.246
NO	768 (70)	115 (10)	220 (20)		

* Preterm birth defined as 32- < 37 weeks gestation. Excludes very preterm birth < 32 weeks gestation

** Small for gestational age if their birth weight fell below the 10th percentile for sex specific birthweight for a given gestational age

Table 6. Univariate Associations between Self-Reported Sleep Duration and Characteristics					
	Self-Reported Sleep Duration				
	Normal Sleep duration ≥7 to 9 hours	Short Sleep Duration <7 hours	Long Sleep Duration >9 hours		
SOCIODEMOGRAPHICS					
	N (%)	**N (%)**	**N (%)**	**Chi Square**	**P-value***
Study Site				2.90	0.234
San Francisco Bay Area	459 (70)	76 (12)	124 (19)		
Portland, Oregon	353 (68)	49 (10)	115 (22)		
Maternal Age at Conception				26.92	0.000*
Under 25 years	57 (53)	10 (10)	40 (37)		
> 25 - 35 years	540 (69)	81 (10)	159 (20)		
> 35 years	215 (74)	34 (12)	40 (14)		
Trimester of Enrollment Interview				4.78	0.092
1st or 2nd trimester	470 (70)	60 (9)	141 (21)		
3rd trimester	342 (68)	65 (13)	98 (20)		
Race/Ethnicity▪				11.94	0.003*
White non-Hispanic	547 (72)	65 (9)	149 (20)		
Non-white	265 (64)	60 (15)	90 (22)		
Education				33.67	0.000*
High school diploma or less, or General Education Development diploma	56 (55)	15 (15)	31 (30)		
Some college	101 (56)	26 (14)	55 (30)		
College bachelor degree or higher	655 (73)	84 (9)	153 (17)		
Cohabitating with spouse or partner				11.54	0.003*
Yes	777 (70)	113 (10)	217 (20)		
No	35 (51)	12 (17)	22 (32)		
Children in household < 5 years old				1.94	0.378
No children	435 (67)	70 (11)	140 (22)		
One or more children	377 (71)	55 (10)	99 (19)		
Subjective Social Status ◦				8.14	0.087
Low (1-5)	195 (63)	39 (13)	74 (24)		
Moderate (6-7)	535 (72)	70 (9)	141 (19)		
High (8-9)	82 (67)	16 (13)	24 (20)		
Subjective Health‡				1.25	0.871
Poor Fair or Good	176 (70)	26 (10)	48 (20)		
Very Good	316 (67)	54 (12)	99 (21)		
Excellent	320 (70)	45 (10)	92 (20)		
High vs Low Stress €				1.08	0.583
High score ≥100	188 (67)	34 (12)	59 (21)		
Low score < 100	624 (70)	91 (10)	180 (20)		

Body Mass Index (BMI)				9.26	0.055
Normal BMI or lower <24.9	535 (72)	66 (9)	145 (19)		
Overweight 25-29.9	179 (64)	40 (14)	61 (22)		
Obese >30	98 (65)	19 (13)	33 (22)		
Preexisting Condition				1.57	0.456
Yes	113 (65)	19 (11)	41 (24)		
No	699 (70)	106 (11)	198 (20)		
Any Alcohol Use in Past Month				5.16	0.076
Yes	70 (75)	13 (14)	11 (12)		
No	742 (69)	112 (10)	228 (21)		
Fetal Smoke Exposure ◊				10.99	0.004*
Yes	33 (51)	12 (19)	20 (31)		
No	779 (70)	113 (10)	219 (20)		
Preconception Folic Acid Use				3.30	0.193
Yes	582 (70)	80 (10)	165 (20)		
No	230 (66)	45 (13)	74 (21)		
Total Times Pregnant				5.94	0.204
1 time	286 (69)	40 (10)	90 (22)		
2 times	276 (72)	34 (9)	76 (20)		
3 or more times	250 (67)	76 (20)	73 (20)		
Prior History of Cesarean Section				5.15	0.076
Yes	103 (72)	20 (14)	20 (14)		
No	709 (69)	105 (10)	219 (21)		
Prior History of Ectopic Pregnancy				n/a	n/a
Yes	20 (87)	3 (13)	0		
No	792 (69)	122 (11)	239 (21)		
Prior History of Fetal Loss* **				0.17	0.918
Yes	188 (69)	30 (11)	53 (20)		
No	624 (69)	95 (11)	186 (21)		
Prior History of Elective Termination of Pregnancy				3.52	0.172
Yes	112 (63)	24 (14)	41 (23)		
No	700 (70)	101 (10)	198 (20)		
Sex of Child				0.72	0.696
Male	394 (70)	58 (10)	109 (20)		
Female	418 (68)	67 (11)	130 (21)		

Footnotes:

* Statistically significant at a p-value of 0.05 or less

▪Non-white is inclusive of Black non-Hispanic (42) Asian (177) Hispanic (128) and Other or Mixed Race (68)

◦MacArthur Scale of Subjective Social Status

ŧStandardized measure of perceived health status

€Adaptation for pregnant women of the Holmes and Rahe Stress Scale Inventory; women asked about 17 weighted stress events, sums of weights calculated and dichotomized into high stress (total score ≥100) and low stress (total score <100)

◊Current smoker, former smoker but quit during current pregnancy, or ongoing second-hand smoke exposure

***Miscarriages and stillbirths combined

Table 7. Univariate Associations between Characteristics, Preterm Birth, and Small for Gestational Age						
	Preterm Birth ** N (%)	**Chi Square (P-value)**		**Small for Gestational Age‡ N (%)**	**Chi Square (P-value)**	
Study Site						
San Francisco Bay Area	26 (74)	4.88	0.037*	44 (60)	0.57	0.468
Portland, Oregon	9 (26)			29 (40)		
Maternal Age at Conception						
Under 25 years	1 (3)	1.81	0.405	7 (10)	0.03	0.988
> 25 - 35 years	24 (69)			48 (66)		
> 35 years	10 (29)			18 (25)		
Trimester of Enrollment						
1st or 2nd	14 (40)	4.28	0.055	39 (54)	0.42	0.543
3rd	21 (60)			34 (47)		
Race/Ethnicity▪						
White non-Hispanic	19 (54)	1.72	0.210	41 (56)	2.49	0.129
Non-white	16 (46)			32 (44)		
Education						
High school diploma or less, or GED diploma	4 (11)	1.51	0.470	2 (3)	3.46	0.177
Some college	3 (9)			12 (16)		
College bachelor degree or higher	28 (80)			59 (81)		
Cohabitating with partner						
Yes	33 (94)	0.002	1.00	68 (93)	0.14	0.611
No	2 (6)			5 (7)		
Children in household < 5 years old						
No children	24 (69)	2.74	0.12	52 (71)	8.44	0.004*
At least 1 child	11 (31)			21 (29)		
Subjective Social Status ◦						
Low (1-5)	9 (26)	0.04	0.978	22 (30)	0.74	0.691
Moderate (6-7)	22 (63)			43 (59)		
High (8-9)	4 (11)			8 (11)		
Subjective Health‖						
Poor Fair or Good	8 (23)	0.86	0.649	17 (23)	0.33	0.848
Very Good	16 (46)			27 (37)		
Excellent	11 (31)			29 (40)		
High vs Low Stress €						
High score ≥100	7 (20)			18 (25)		

Low score < 100	28 (80)	0.30	0.690	55 (75)	0.03	0.887
Body Mass Index (BMI)						
Normal BMI or lower <24.9	20 (57)	1.72	0.422	48 (66)	0.27	0.873
Overweight 25-29.9	8 (23)			17 (23)		
Obese >30	7 (20)			8 (11)		
Preexisting Condition						
Yes	9 (26)	3.48	0.085	10 (14)	0.06	0.801
No	26 (74)			63 (86)		
Any Alcohol Use in Past Month						
Yes	2 (6)	0.26	1.00	6 (8)	0.01	0.826
No	33 (94)			67 (92)		
Fetal Smoke Exposure ◊◊						
Yes	1 (3)	0.49	0.717	10 (14)	9.95	0.005*
No	34 (97)			63 (86)		
Preconception Folic Acid Intake						
Yes	27 (77)	0.80	0.454	55 (75)	0.94	0.358
No	8 (23)			18 (25)		
Total Times Pregnant						
1 time	13 (37)	0.30	0.860	32 (44)	4.02	0.134
2 times	10 (29)			25 (34)		
3 or more times	12 (34)			16 (22)		
Prior History of Cesarean						
Yes	30 (86)	0.15	0.605	69 (95)	3.25	0.093
No	5 (14)			4 (6)		
Prior History of Ectopic Pregnancy						
Yes	0	N/A	N/A	1 (1)	0.14	1.000
No	35 (100)			72 (98)		
Prior History of Fetal Loss* **						
Yes	22 (63)	4.04	0.064	60 (82)	1.20	0.317
No	13 (37)			13 (18)		
Sex of Child						
Male	5 (14)	0.02	1.000	13 (18)	0.46	0.499
Female	30 (86)			60 (82)		

* Statistically significant at a p-value of 0.05 or less

**Preterm birth defined as 32 to < 37 weeks gestation. Excludes very preterm births <32 weeks gestation

ǂSmall for gestational age if the birth weight falls below the 10th percentile for sex specific birth weight for a given gestational age

▪Non-white is inclusive of Black non-Hispanic (38) Asian (179) Hispanic (129) and Other or Mixed Race (71)

◦MacArthur Scale of Subjective Social Status

ǂǂStandardized measure of perceived health status

€Adaptation for pregnant women of the Holmes and Rahe Stress Scale Inventory; women asked about 17 weighted stress events, sums of weights calculated and dichotomized into high stress (total score ≥100) and low stress (total score <100)
◊◊Current smoker, former smoker but quit during current pregnancy, or ongoing second-hand smoke exposure
***Miscarriages and stillbirths

Table 8. Crude and Adjusted Odds Ratio for Self-Reported Sleep Duration And Infant Outcomes®		
Self-reported Sleep Duration*	**Crude Odds Ratio (95% CI)**	**Adjusted Odds Ratio (95% CI)**
Preterm Birth		
<7 hours sleep	0.93 (0.27-3.15)	0.82 (0.24-2.83)
7-9 hours sleep	Reference	Reference
>9 hours sleep	1.82 (0.86-3.83)	2.05 (0.95-4.40)
Small for Gestational Age		
<7 hours sleep	1.52 (0.74-3.10)	1.38 (0.66-2.90)
7-9 hours sleep	Reference	Reference
>9 hours sleep	1.51 (0.86-2.64)	1.50 (0.84-2.67)

* Statistically significant at a p-value of 0.05 or less
**Preterm birth defined as 32 to < 37 weeks gestation. Excludes very preterm births <32 weeks gestation
ŧSmall for gestational age if the birth weight falls below the 10th percentile for sex specific birth weight for a given gestational age
®All models adjusted for maternal age at conception, trimester of enrollment, Non-Hispanic white versus Non-white, education, smoke exposure, prior Hx of cesarean section, and BMI

Integrative Summary and Synthesis

Shortened sleep duration in pregnancy is common, with up to 40% of all women sleeping less than < 7 hours a night (Facco et al. 2010), therefore, determining whether self-reported shortened sleep duration is a potential factor in the development of adverse maternal and infant outcomes is clinically significant. There is limited and conflicting evidence to date suggesting a relationship between maternal self-reported sleep duration and several pregnancy and infant outcomes (Appendix A).

The overriding purpose of this study was to describe any associations between self-reported sleep duration and certain adverse maternal and infant outcomes. To accomplish this, a secondary data analysis was conducted. The data source was the Pregnancy and Influenza Project (PIP), a prospective, observational cohort study assessing vaccine efficacy for prevention of lab-confirmed influenza illness among pregnant women receiving care through large, managed care health systems. A detailed description of the parent study is found in Chapter 3 and has been described elsewhere (Thompson et al. 2011). The PIP dataset was one of only a handful of U.S. based datasets available to date of an adequate size capable of assessing these potential relationships. To my knowledge, only two other U.S. based prospective cohort studies of comparable size have been used to examine these clinical outcomes of interest. This exploratory study contributes to the limited available data on self-reported sleep duration and specifically the cardiometabolic outcomes of clinically diagnosed gestational diabetes, incident hypertensive disorders in pregnancy, preterm birth and small for gestational age.

In this chapter, the main findings of the research hypotheses described in Chapter 1 will be discussed. The following chapter is divided into three sections. Section 1 is a brief synopsis of the

dissertation results, Section 2 is a discussion on the interpretation of my findings, and Section 3 presents my conclusions and next steps.

Section 5.1 Results

Summary of the examination of self-reported shortened sleep duration and clinically diagnosed gestational diabetes mellitus and incident hypertensive disorders in pregnancy

The purpose of the study presented in the paper entitled "Self-reported shortened sleep duration and clinically diagnosed gestational diabetes mellitus and incident hypertensive disorders in pregnancy" was to evaluate the association between self-reported shortened sleep duration during pregnancy and selected adverse cardiometabolic maternal outcomes. Specifically, it was hypothesized that pregnant women who reported shorter sleep durations would be more likely to be clinically diagnosed with gestational diabetes or have gestational hypertension or preeclampsia in the 2nd or 3rd trimester of pregnancy. The PIP dataset was used, and consisted of 1,165 participants (after exclusions) to test this hypothesis. (Paper 1, Figure 1).

Self-reported sleep duration calculated as a woman's usual bedtime subtracted from her usual wake time was examined. The result was a woman's in-bed total minutes. The time (in minutes) it took a woman to fall asleep once in bed was subtracted from the in-bed total minutes, and the difference was a woman's final sleep duration in minutes. Total minutes were converted to hours, and self-reported sleep durations were categorized as short < 7 hours, normal 7-9 hours, and long > 9 hours. Outcomes for this analysis were gestational diabetes, gestational hypertension, and preeclampsia which were extracted from the medical record using The International Classification of Diseases, Ninth Edition (ICD-9). Approximately 11% (n=121) of women were reportedly short sleepers. The percentage of participants with a diagnosis of gestational diabetes was 9% (n=107), gestational hypertension was 7% (n=82) or with preeclampsia was 3% (n=36). Associations between

self-reported sleep and the outcomes of interest, between self-reported sleep and the covariates, and between covariates and the outcomes of interest are described in Paper 1, Tables 5, 6, and 7. In both crude and adjusted models, self-reported sleep duration was not statistically significant for developing diabetes or incident hypertension in pregnancy; Paper 1, Tables 8 and 9. Thus, there was a failure to reject the null hypothesis.

These results were compared to the available body of literature. A synopsis of prior studies is found in Paper 1, Table 1. For gestational diabetes, the positive findings of the one study of comparable size and design that used similar sleep duration cut points could not be replicated (Rawal et al. 2016). For incident hypertensive disorders in pregnancy, again, associations seen in the one large prospective cohort study found (Williams et al., 2011) were not replicated. The Williams paper did find an association with preeclampsia among very short sleepers < 5hours (aOR 9.52, 95% CI 1.83-49.40). The authors again found significant findings when stratifying by weight; overweight women sleeping < 5 hours were more likely than lean women do develop preeclampsia (aOR 12.7, 95% CI 1.04-154.4) as were overweight long sleepers ≥ 10 hours (aOR 5.14, 95% CI 1.20-22.1). However, it is difficult to directly compare the PIP results to the results from the Williams et al. paper because the authors used an atypical referent (7-9 hours) and, among the significant point estimates, all had extremely wide confidence intervals. The general body of literature on self-reported sleep duration and clinically diagnosed gestational diabetes and incident hypertensive disorders in pregnancy remains incongruent.

Summary of the examination of self-reported sleep duration and risk of preterm birth and small for gestational age

The purpose of the study presented in the paper entitled "Examination of self-reported sleep duration and risk of preterm birth and small for gestational age" was to evaluate the association

between self-reported shortened sleep duration during pregnancy and the adverse infant outcomes of preterm birth and small for gestation age. The working hypothesis for the study was that pregnant women who self-report shorter sleep durations will be more likely to deliver a preterm infant or one that was small for gestational age than pregnant women who reported longer sleep durations. The PIP dataset was used and consisted of 1,176 participants after exclusions (Paper 2, Figure 1).

Self-reported sleep duration was calculated as outlined earlier. Preterm birth was defined as less than 37 weeks gestation. Preterm birth was further divided into <32 weeks gestation and 32-37 weeks gestation. Preterm infants <32 weeks gestation were categorized as "very preterm." Since mothers delivering very preterm infants often have ongoing risk factors that predispose them to very early delivery, only the preterm infants reaching a gestational age of at least 32 weeks were included in this analysis. Neonates were determined to be small for gestational age if their birth weight fell below the 10^{th} percentile for sex-specific birthweight for a given gestational age. Three percent of the infants (n=35) were considered preterm between 32-37 weeks gestation, and 6% (n=73) of infants were small for gestational age.

Associations between self-reported sleep duration and preterm birth, and small for gestational age; between self-reported sleep and the covariates; and between the covariates and preterm birth and small for gestational age are found in Paper 2, Tables 5, 6, and 7. In both crude and adjusted models, self-reported sleep duration was not statistically significant for delivering a preterm or small for gestational age infant Paper 2, Table 8. Again, there was a failure to reject the null hypothesis.

For small for gestational age defined as < 10^{th} percentile, the null findings were consistent with the two available studies (Abeysena, Jayawardana, Seneviratne, 2009; Micheli et al. 2011). My findings are also generally compatible with six other studies examining preterm birth (Blair, Porter,

Leblebicioglu, & Christian, 2015; Guendelman et al., 2013; Okun et al. 2012; Micheli, 2011; Reutrakul et al., 2011; Strange, Parker, Moore, Strickland & Bliwise, 2009).

Section 5.2 Discussion

In this dataset, there is little evidence that self-reported short sleep duration was associated with any of the adverse maternal or infant outcomes examined. This population was also healthy, well-educated, and relatively affluent. At face value, it would appear that self-reported sleep duration is not associated with gestational diabetes or incident hypertensive disease in pregnancy or increase the chance a woman will deliver a preterm or small for gestational age infant. The effects of shortened sleep duration might not be problematic in populations of healthy women like the PIP. Null results are, however, infamously complicated and challenging to interpret. There are at least six different explanations of these results, only one of which is that there is no true association. More extensive discussions on the explanations of these null findings are found in Papers 1 and 2, but generally speaking, any one of the following factors might be responsible these null results:

- Null hypothesis is correct
- True effects were of a smaller magnitude than the PIP was powered to detect
- Inadequate numbers of poor sleepers, of outcomes, or both
- Measurement error
- Effect modification present for some subgroups but not others
- Selection bias

Despite these limitations that preclude determining any definitive associations, there are several noteworthy strengths of this work. PIP is one of the largest, prospectively collected cohorts of U.S. pregnant women that has been used to date to examine the role of self-reported sleep duration in

pregnancy. PIP also has detailed information from medical and laboratory records, which allowed for accurate descriptions of the cohort characteristics. An additional strength was the completeness of the PIP data. This study further adds to the body of available literature on self-reported sleep duration in pregnancy.

Section 5.3 Conclusions and next steps

Conclusions

In conclusion, the results from this study did not detect any significant association between self-reported sleep duration and clinically diagnosed gestational diabetes, incident hypertension in pregnancy, preterm birth or small for gestational age infants. Sleep disturbances are common in pregnancy (Facco et al., 2010; Mindell, Cook & Nikolovski, 2015; Signal et al. 2014; Sivertsen, Hysing, Dørheim & Eberhard-Gran, 2015), and although the findings from other studies reporting associations was not replicated in this analyses, there is biologic plausibility that sleep adversely affects the health of pregnant women. Further research is needed using objective measures for determining sleep duration, to study longitudinal effects of sleep duration in representative samples of adequate size, and to explore the possible cardiometabolic pathways affected by shortened sleep duration.

Next steps and recommendations

The current study did not evaluate sleep durations from pre-pregnancy or postpartum periods, perceived sleep quality, nor does it evaluate associations between reported sleep duration effects on laboratory markers such as glucose challenge testing or averages of systolic and diastolic blood pressure readings over the course of pregnancy. Further analyses with the current dataset are planned. It might be that it's the magnitude of change or how well one feels about one's sleep that is

more important than actual hours slept, or that cardiometabolic markers might be a more useful metric than clinical diagnoses in women with shortened sleep duration.

Further as noted earlier, PIP is a large cohort, and it consisted of healthy, educated, and insured women. It might be that shortened sleep duration disproportionately affects women more socio-economically disadvantaged. Identifying other prospectively collected studies among sociodemographically varied women of adequate sample size to examine this question are needed. If self-reported sleep measures still do not prove reliable for identifying women at risk for adverse outcomes, other simple measures for quantifying sleep should be considered. Built-in actigraphy technology might be able to provide more reliable estimates of total sleep time than self-report. While actigraphy devices used for research purposes are acceptable measures of objective sleep (Marino et al. 2013), further studies are needed to determine whether actigraphy readings from personal devices will prove to be a rigorous enough approach to population level assessments of sleep both in the general population and in specific populations like pregnant women. Lastly, information is needed on the biologic plausibility of the effects of shortened sleep duration on adverse maternal and infant outcomes. In the PIP dataset, we were unable to explore biologic processes and the subsequent effects on pregnancy outcomes. Therefore ideal studies in the future are needed which would be prospective in nature, among sociodemographically diverse group of women of adequate sample size, and would collect both self-reported and objective sleep data and biomarkers at several points during pregnancy. This design is the type of study that is needed to explain any relationship between sleep duration and adverse maternal and infant outcomes and to elucidate potential causative factors.

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