# INVESTIGATING THE RELATIONSHIP BETWEEN UV-B RADIATION EXPOSURE AND RACIAL DISPARITIES IN PREECLAMPSIA: A MEDICAL GEOGRAPHY STUDY

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## ABSTRACT

INVESTIGATING THE RELATIONSHIP BETWEEN UV-B RADIATION EXPOSURE AND RACIAL DISPARITIES IN PREECLAMPSIA: A MEDICAL GEOGRAPHY STUDY

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Preeclampsia is the leading cause of morbidity and mortality in the United States. Research had demonstrated that adequate levels of vitamin D can help to circumvent the risk of preeclampsia. Vitamin D plays a role in cardiovascular health and in maternal health, and cutaneous exposure to ultra-violet (UV)-B radiation is critical to maintaining healthy vitamin D levels. The majority of vitamin D in humans is produced when the skin is exposed to ultraviolet radiation. UV-B varies geographically; therefore geography influences the availability of vitamin D and the potential risk for preeclampsia. However, research on the geographic relationship between UV-B and pregnancy induced hypertensive disorders, including preeclampsia has been relatively neglected. This research investigates the relationship between maternal UV-B exposure and preeclampsia for mothers giving birth in Michigan from 2008 to 2015 during 3 time periods, 1-pre-conception, 2-early pregnancy, and 3-late pregnancy. A medical geographic and human ecological framework conceptualizes the environmental, biological and behavioral factors influencing the UV-B and preeclampsia relationship. UV-B is estimated using the Erythemal Daily Dose calculated form OMI remote sensing data. Preeclampsia is measured using Michigan's Vital Statistics Birth Data 2008-2015. Multilevel models were estimated to study these relationships. This study found that slight increases in UV-B exposure prior to conception and later in pregnancy could reduce the odds of preeclampsia for white but not black mothers. Other important risk factors for preeclampsia were increasing BMI, chronic and gestational diabetes and living in urban areas. Receiving Medicaid was protective for preeclampsia for white

mothers but not black mothers. Enrollment in WIC was highly protective for all mothers. This medical geography research demonstrates the importance of utilizing remote sensing to begin to understand UV-B exposure on an important pregnancy outcome from a population perspective. Future research should also focus on reevaluating the measurement of the Erythemal Daily Dose to reflect people with high melanin concentrations. Future research could also branch out to other highly prevalent conditions with low vitamin D susceptibility such as cancers and dementia and Alzheimer's.

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## KEY TO ABBREVIATIONS

| | |
|---|---|
| ACOG | American College of Obstetrician and Gynecologists |
| ACS | American Community Survey |
| BMI | Body Mass Index |
| BUV | backscattered Ultraviolet Radiation |
| CDC | Center of Disease Control and Prevention |
| CI | Confidence Interval |
| CVD | Cardiovascular Disease |
| DHC | Dehyrocholesterol |
| HR | Hazard Ratio |
| GIS | Geographic Information System |
| IOM | Institute of Medicine |
| IU | International Unit |
| KJ | Kilojoules |
| NASA | National Aeronautics and Space Administration |
| OMI | Ozone Monitoring Instrument |
| OR | Odds Ratio |
| SES | Socio-economic Status |
| SPF | Sun Protection Factor |
| SZA | Solar Zenith Angle |
| UV-A | Ultraviolet-A Radiation |
| UV-B | Ultraviolet-B Radiation |

| | |
|---|---|
| UV-C | Ultraviolet-C Radiation |
| UVR | Ultraviolet Radiation |
| VDR | Vitamin D Receptors |
| WIC | Women, Infants, and Children |
| WHO | World Health Organization |

# CHAPTER 1: INTRODUCTION

## 1.1 Introduction

Hypertensive disorders are the most common medical disorders that occur during pregnancy (London, 2016). The most common pregnancy-related hypertensive disorder is preeclampsia, which affects an estimated 8% to 10% of pregnancies and is the leading cause of maternal morbidity and mortality in the United States and worldwide (American College of Obstetrics and Gynecology (ACOG), 2013; Venes, 2013). Preeclampsia is a pregnancy-specific multisystem disorder that is clinically defined as an increase in blood pressure (140 mm Hg systolic or higher, or 90 mm Hg diastolic or higher) after 20 weeks of gestation accompanied by proteinuria (300mg of protein or higher in a 24-hour period) in a previously normotensive woman (ACOG, 2013). The incidence of preeclampsia and gestational hypertension continues to increase (ACOG, 2013; Lo et al 2013). Although the exact mechanism(s) behind the pathogenesis remains unclear, maternal serum vitamin D at low levels has been shown to be associated with preeclampsia (Bodnar, 2007; Mulligan et al., 2010; Robison et al., 2010, Aghajafari et al., 2013). Furthermore, research (Evans et al., 2004; Bodnar et al., 2007) has reported that adequate levels of vitamin D could help to circumvent pregnancy-related diseases, specifically in the development of preeclampsia; and at normal levels may protect against the development of preeclampsia due to its influences on cardiovascular and immune functions (Hyppönen et al., 2014).

Vitamin D is an essential fat-soluble prohormone crucial for the development and health of the human musculoskeletal system and other important physiological processes. For example, vitamin D plays a critical role in cell proliferation, bone health, immune modulation, and

cardiovascular function, including the regulation of blood pressure (Holick, 2004a; Holick, 2004b; Giovannucci, 2005; Norman, 2008; Lappe, 2011) as will be further discussed below. An estimated 90% of vitamin D in humans is produced cutaneously (Holick, 2005) when the skin is exposed to ultraviolet (UV) radiation (UVR) from the sun. UVR is divided into three sub-types: UV-C, UV-B and UV-A. However, it is UV-B radiation that activates the photosynthetic processes that produce vitamin D cutaneously. The amount of vitamin D in the body is, therefore, dependent on the quantity of UV-B photons that penetrate the skin. Geography and skin pigmentation are two of the main factors that influence the amount of UV-B radiation available to humans. UV-B varies geographically with latitude; exposure to sunlight is reduced at higher latitudes, especially during the winter. Skin pigmentation is determined by the amount of melanin in the skin. Melanin is an evolutionary trait that protects against damage to the body from UVR, particularly in high solar equatorial latitudes. The loss of melanin to promote UV-B absorption is an evolutionary response to the lack of solar radiation at higher latitudes. Therefore, people with darker skin pigmentation living at higher latitudes may be at an increased risk of vitamin D deficiency due to (a) less physical availability of UV-B and (b) reduced bio-availability from dermal absorption. The degree to which low vitamin D exposure contributes to a higher prevalence of disease in organs that are dependent on vitamin D among darker skinned individuals in the United States is an important question in health disparity research. Racial disparities are present in preeclampsia incidence, severity, and risk as well (ACOG, 2002; Lee et al., 2007; Haney et al., 2008; Lisonkova and Joseph, 2013); however, these racial disparities are difficult to assess due to confounding by socioeconomic and cultural factors (ACOG, 2013).

## 1.2 Purpose of Study

Vitamin D plays a role in cardiovascular health and in maternal health, and exposure to UV-B is critical to maintaining healthy vitamin D levels. The geographic relationship between UV-B and pregnancy induced hypertensive disorders, including preeclampsia have been neglected. Therefore, the purpose of this study is to estimate the effect of maternal UV-B exposure on preeclampsia for mothers giving birth in Michigan from 2008 to 2015. Michigan is a higher latitude state, spanning from approximately 41°43'N to 47°29'N and has four distinct climate seasons. In addition, Michigan has a high incidence of preeclampsia with large racial disparities in adverse birth outcomes that could be precipitated by preeclampsia. The geography and population of Michigan make it an ideal location to study the relationship between UV-B exposure, which subsequently produces vitamin D cutaneously, and the incidence of preeclampsia.

An in-depth discussion of how cutaneous UV-B radiation exposure activates and produces vitamin D in the body and its impacts on various organs in general, and the cardiovascular system in particular is further provided in the Background Section. The gaps in this literature following followed by this dissertation's goal, objectives and hypotheses to be tested.

# CHAPTER 2: BACKGROUND

## 2.1 Molecular Structure of Vitamin D

Vitamin D—a term used to refer to nutritional forms of the prohormone, $D_2$ (ergocalciferol) and $D_3$ (cholecalciferol)—is comprised of three fused carbon rings with one broken ring, making it a secosteroid; steroids have four fused carbon rings. The molecular difference between the two forms of vitamin D is in their side chain structures; vitamin $D_2$ contains a double bond between carbons 22 and 23, and a methyl group on carbon 24. The molecular formula for vitamin $D_2$ is $C_{28}H_{44}O$ and for vitamin $D_3$ is $C_{27}H_{44}O$; whereas, vitamin $D_3$ does not have the double bond between carbons 22 and 23, nor does it have a methyl group on carbon 24. Although $D_2$ and $D_3$ isoforms act as prohormones, there is debate about their biological equivalency (Mulligan et al., 2010). Bikle (2009) suggested that because the side chains differ between $D_2$ and $D_3$, they must differ in the manner in which they are metabolized and in the manner in which they bind to vitamin D binding proteins (VDBP), which transport the prohormone through blood circulation. The potency of vitamin $D_2$ has been scrutinized and many studies have shown that it should not be regarded as equivalent to vitamin $D_3$ (Armas, Hollis, and Heaney, 2004; Houghton and Veith, 2006; Norman, 2008) because of their differences in the side chains.

There are three means by which a person gets vitamin D: diet, supplementation, and most importantly, it is synthesized in the skin. Vitamin $D_2$ and vitamin $D_3$ are prevalent in small quantities from dietary sources. Vitamin $D_2$, a plant-derived form, is available in some plants including fungi and is predominantly produced exogenously by irradiation of yeast and plant sterol ergosterol. Vitamin $D_3$ is found in animal-based foods -e.g. fatty fish, egg yolk, and liver. Although $D_2$ and $D_3$ are available from limited dietary sources, it does not naturally occur in

adequate quantities in day-to-day diets. As a result, both vitamin $D_2$ and $D_3$ are produced commercially for dietary supplementation and can be found in multivitamins, fortified cereals, fortified milk, and other fortified foods (Holick, 2006; Institute of Medicine, 2011). However, many fortified foods and multivitamins also contain vitamin A, which has been shown to interfere with the action of vitamin D (Rohde, 1999; Johansson and Melhus, 2001). While this is an important topic for future research, the relationship between vitamin A and D in the diet on human health will not be examine in this current research.

Because neither vitamin $D_2$ nor vitamin $D_3$ can be obtained in sufficient amounts through dietary means, the cutaneous production of vitamin D is the predominate source of vitamin $D_3$ for physiological needs (Webb, 1989). Historically, vitamin D was not naturally present in most of the foods that our hominid ancestors would have consumed. Thus, over millions of years, humans, along with many other vertebrate animal species, evolved a photosynthetic mechanism in their skin to produce large amount of this essential nutrient in order to survive. The majority (90%) of vitamin D in humans is obtained through cutaneous synthesis of UVR produced from sun exposure, making vitamin $D_3$ the major source of this essential nutrient (Holick, 2005). Therefore, this research focuses on the cutaneous synthesis of vitamin D, specifically vitamin $D_3$ from UV-B exposure from the sun.

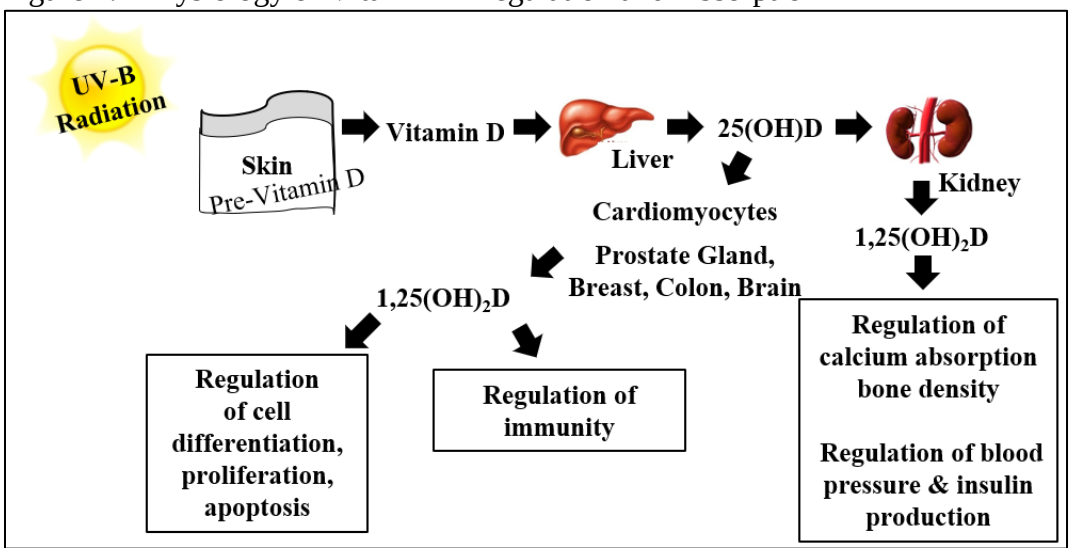
### 2.2 The Synthesis of Vitamin D

When UV-B is absorbed by the skin, it activates a chain reaction that produces vitamin D. Specifically, UV-B photons penetrate into the epidermis (stratum spinosum and basale) where they are absorbed by 7-Dehyrocholesterol. 7-Dehyrocholesterol is present in the plasma membrane of the cells in the stratum spinosum and basale. UV-B causes a bond cleavage

between the carbon 9 and carbon 10, opening the 7-Dehyrocholesterol molecule's B ring, forming pre-cholecalciferol, or pre-vitamin-D. Pre-vitamin D is an unstable molecule that rapidly undergoes thermal isomerization to vitamin $D_3$, or cholecalciferol, in the plasma membrane of the cells; this is the last phase of $D_3$ production that occurs in the skin. Importantly, Vitamin $D_3$ is a biologically inactive prohormone until it is metabolized to its hormonal active-form by two enzymatic hydroxylation reactions, one is the liver and the other is in the kidneys.

After vitamin $D_3$ is formed, it is drawn into the dermal capillary bed beneath the dermoepidermal junction by the vitamin D-binding protein (DBP); however, little is known about the mechanisms involved in this translocation process from the epidermis into circulation (Holick, 2006; Chen, Lu, and Holick, 2010). Vitamin $D_3$ does not circulate for long in the bloodstream. Immediately after entering circulation, vitamin $D_3$ is taken up by adipose tissue for storage or transported to the liver for further metabolism. Once deposited in the liver vitamin D-25-hydroxylase (25-OHase) converts vitamin $D_3$ to 25(OH)D, an inactive form of vitamin D. The exact enzyme involved in this enzymatic hydroxylation is unknown at this time; however, it known that it is a cytochrome P450 (CYP-450) gene (Chen, Lu, and Holick, 2010), which are enzymes that are involved in the synthesis and metabolism of various molecules and chemicals within cells (National Library of Medicine, 2008). 25(OH)D, enters the bloodstream where DBP aids in the transportation of 25(OH)D to the kidneys. In the kidneys, mediated by 1α-hydroxylase (1α-OHase) in the renal glands, 25(OH)D is converted to the active form of vitamin D, $1,25(OH)_2D$. CYP27B1 gene is the enzyme involved in the enzymatic hydroxylation of $1,25(OH)_2D$; it provides instructions for making 1α-OHase.

Figure 2.1 Physiology of Vitamin D Regulation and Absorption




In the kidneys, $1,25(OH)_2D$ binds to DBP to be transported to target cells in the intestines; only target cells for a given hormone, in this case $1,25(OH)_2D$, can respond to that hormone. Located in the nuclei of $1,25(OH)_2D$ target cells are vitamin D receptors (VDR). When the $1,25(OH)_2D$ ligand binds with the VDR in the intestines, it triggers an increase in intestinal absorption of both calcium and phosphorus, which then re-enters the blood. This mechanism helps to maintain the homeostasis of calcium and phosphate in the blood for use in the skeletal and neurological systems. Specifically, it is involved in the formation of bone, bone restoration, bone mineralization, and maintaining neuromuscular function. Importantly, recent research has concluded that VDRs can be found in most cellular tissues throughout the body, even those that are not associated with calcium and/or phosphorus production. Important for this study, VDRs are present in cardiomyocytes and in the vascular smooth muscle of the cardiovascular system, thus further influencing cardiovascular health. This suggests that that $1,25(OH)_2D$ could have a more general role or that non-$1,25(OH)_2D$ ligands could activate VDR.

The synthesis of $1,25(OH)_2D$ in the kidneys is tightly regulated by the parathyroid hormone (PTH). When vitamin D [25(OH)D] levels are low, calcium absorption is also low leading to an

insufficiency in calcium requirements for bone health, metabolic functions, and neuromuscular activity. In response to low levels of vitamin D [25(OH)D] levels PTH production increases, which enhances the production of $1,25(OH)_2D$. While $1,25(OH)_2D$ is the active form of vitamin D in the body, when measuring blood levels of vitamin D, 25(OH)D is used because it has been shown to be a better predictor of actual vitamin D levels in the body than serum concentrations of dihydroxylated vitamin D, or $1,25(OH)_2D$ (IOM, 1997; Holick, 2004). Herein 25(OH)D and "vitamin D" may be used interchangeably to refer to the blood concentration of vitamin D in the body.

### 2.3 Factors affecting the Availability and Bioavailability of Vitamin D

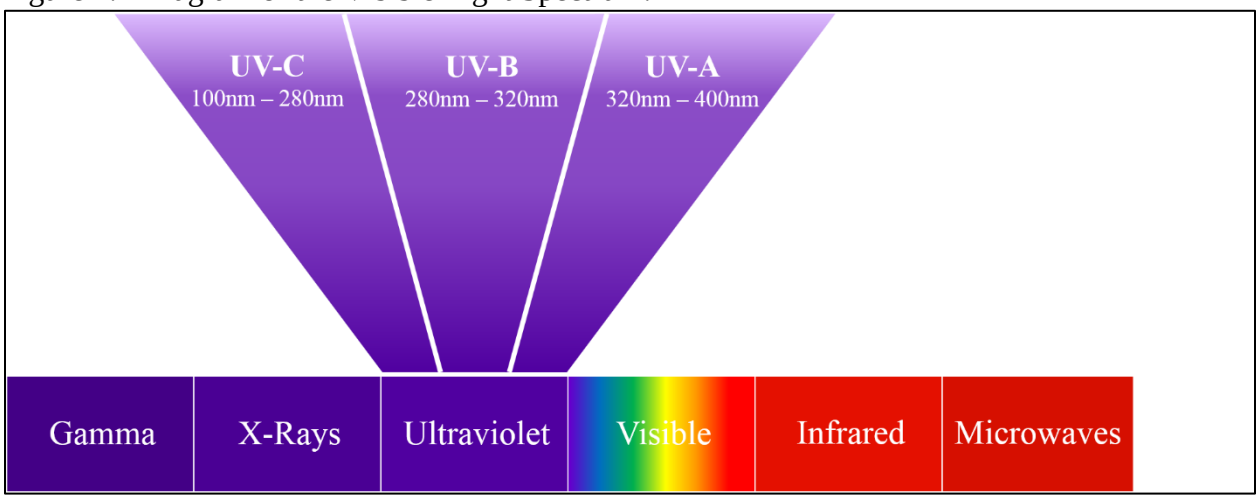
The major source of vitamin D for humans is through cutaneous production, and is dependent on the ability of UV-B radiation to stimulate the production of vitamin D. The interactions between UV-B and three sets of factors—environmental, biological, and behavioral—that influence vitamin D status are rooted in geography; therefore, medical geography's model of Human Ecology is the quintessential framework for studying the relationship between UV-B exposure, vitamin D, and preeclampsia. These three sets of factors, and the impact they have on vitamin D are further described below. The human ecology model is described more in depth in chapter 3.

#### 2.3.1 Human Ecology: The Environment

Solar ultraviolet radiation (UVR) is a type of electromagnetic energy with shorter wavelengths compared to visible radiation (light) and, because of these shorter wavelengths, UVR is a considerably higher energy source than visible light in the electromagnetic spectrum (Figure 2.2). UVR is the energy source responsible for creating and perpetuating the ozone layer that

protects life on earth from deadly UVR levels. UVR splits a free oxygen molecule ($O_2$) into two ions (O and O); each ion then combines with a free oxygen molecule ($O_2$) to form ozone ($O_3$). UVR splits ozone ($O_3$) into a free oxygen molecule ($O_2$) and an ion (O) that combines with another ion (O) to form a free oxygen molecule ($O_2$); which in turn, is split by UVR into two ions. This cyclical process absorbs most of the UVR. UVR wavelengths, which range from 100nm to 400nm, are subdivided into three sub-types: UV-C (100nm-280nm), UV-B (280nm-320nm), and UV-A (320nm-400nm). 2UV-C radiation is the most intense and harmful to humans; however, due its short wavelengths, UV-C is completely absorbed by the ozone layer and does not reach the earth's surface. UV-B radiation is partially absorbed by the ozone and, therefore, only comprises about 10% of the total UV radiation able to reach the earth's surface. The other 90% of the UVR able to reach the earth's surface is UV-A radiation, which has the longest wavelengths of the three and is less energetic than UV-C and UV-B. Due to its longer wavelength, UV-A is able to penetrate deeper into the skin than UV-B; however, the lower energy wavelengths of UV-A do not have the same biological effects as UV-B radiation on vitamin D production as UV-B radiation on vitamin D production and human health overall.

Figure 2.2 Diagram of the Visible Light Spectrum.




Solar UV-B radiation affects biological and chemical processes that produce vitamin D and is highly variable in its intensity and distribution over the earth's surface (Jablonski and Chaplin, 2010). Therefore, the environmental factors that influence the amount of solar UV-B able to reach the surface of the earth and make contact with human skin to catalyze the production of vitamin D are of interest; these factors include: latitude, season, altitude, ozone, cloud cover, air pollution, and urban settings.

Solar UV-B radiation is highly variable in its intensity and distribution across latitude and season (Jablonski and Chaplin, 2010); this dramatic variation is due to the solar zenith angle (SZA)—SZA is the angle measured at the earth's surface between the sun and the zenith, the point that lies directly above the observer (American Mereological Society, 2019). As the SZA increases, the distance solar rays, and thus UV-B radiation, must travel to the surface of the earth increases. Therefore, the potential for cutaneous production of vitamin D is dramatically influenced by latitude due to the lack of potential exposure to UV-B caused by the angle of the sun. UV-B is most intense when the sun is directly overhead; this only occurs in the lower latitudes of the tropics (the region between the Tropic of Cancer and the Tropic of Capricorn), because sun rays

strikes the equatorial regions of the earth nearly perpendicularly. As latitude increases out of the tropical latitudes, a beam of solar energy strikes the earth at a more oblique angle spreading it over a wider surface area of the earth, so that less falls on a given area and providing less energy per unit area. Therefore, as latitude increases, the amount of UV-B radiation decreases. The further the distance UV-B travels to the surface of the earth, the more UV-B is scattered and absorbed by ozone, aerosols, air pollution, and clouds. The distance solar rays must travel to the surface of the earth increases during the winter months as well.

The angle of the sun varies dramatically with season. During the winter months, the SZA increases causing the distance UV-B travels to increase and the amount of UV-B reaching the surface of the earth to decrease. Consequently, the strength or intensity of UV-B declines during the winter months, resulting in less available UV-B at the earth's surface to produce vitamin D. It is estimated that at latitude greater than 37°, during the winter months, the number of UV-B photons reaching the earth is decreased by 80% to 100%; consequently, substantially less vitamin D is cutaneously produced (Holick, 2004; Misra et al., 2008). Furthermore, during the winter months at higher latitudes, the duration of sunlight is significantly shorter than compared to other times of the year; due to the decreased hours of sunlight, there is less potential for UV-B exposure and the production of vitamin D. For example, at about 39 degrees north latitude it would take a relatively light skinned person more than two hours of sun exposure to obtain the recommended daily dose of vitamin D (1,000 IU) in January; however, in July the exposure time to produce the same amount is 7 minutes and in October 31 minutes (Serrano et al., 2017). Therefore, women living in higher latitudes are not getting enough vitamin D from the sun to satisfy their physiological needs, especially during the winter months.

UV-B radiation enters the earth's atmosphere and comes into contact with the ozone layer. Due its short wavelength, all of the UV-C radiation is absorbed and scattered by the ozone layer preventing it from reaching earth's surface. Ozone absorbs very little UV-A and about 90% of the UV-B radiation, substantially reducing available UV-B radiation at the earth's surface; however, the total column amount of ozone does not vary greatly spatially (Lee et al., 2013). As the remaining UV-B radiation makes its way to the earth's surface, it is scattered and absorbed by clouds and air pollution before reaching the surface of the earth; reducing the amount of surface UV-B further. Therefore, the spatial distribution and intensity of UV-B radiation is more variable. For example, at higher altitudes, there is a greater influx of UV-B radiation compared to lower altitudes; it has been estimated that UV intensity increases 10% for each 1,000 feet increase in elevation (Rigel et al., 1999). This increased influx is due to the thinner atmosphere and lower stratospheric ozone associated with these higher altitude regions (Mirsa et al., 2008).

In urban areas, due to the increased amount of air pollution and the buildings, the amount of surface UV-B available for the photosynthesis of vitamin D is further decreased. Urbanization has drastically increased worldwide; people are moving out of rural areas into more urban areas. In the United States, less than 46% of the population lived in urban areas in 1910; today, more than 80% of the US population lives in urban areas (United Sates Census Bureau 2016).

Because of the scattering and absorption of UV-B radiation and the angle of the sun, surface UV-B radiation is highly variable in its intensity and spatial distribution. (Jablonski and Chaplin, 2010). Therefore, a person's ability to produces vitamin D in the skin is highly dependent on their geographic location and the environmental factors that comprise the geographic area. Differences in vitamin D synthesis potential related to geography have been a driving force in

human evolution and, specifically, in the evolution of human skin pigmentation; this will be further discussed in the biological section of the human ecology model section.

### 2.3.2 Human Ecology: Biological

UV-B is the most important UV radiation in terms of health as it can damage the skin, cause sunburn, breakdown folic acid, and can contribute to other adverse health outcomes with over-exposure; however, the skin pigmentation melanin, and the ability to regulate its concentration, protects against the harmful effects of UV-B radiation. UV also has positive influence of humans. In infants with Jaundice, the liver is too immature to remove large amounts of bile pigment causing these yellowish pigments to stain the skin tissue; UV radiation obtained under lamps is able to destroy bile pigments, facilitating a faster recovery (Raven and Johnson, 2002). Most importantly, UV-B is responsible for the biological and chemical production of vitamin D in humans, which is responsible for the maintenance of human health.

Hypertensive disorders are the most common medical disorders that occur during pregnancy (London, 2016). Vitamin D plays a crucial role in the cardiovascular system, including the regulation of blood pressure. $1,25(OH)_2D$ regulates renin, one of the most important hormones for regulating blood pressure, gene expression and is a potent suppressor of renin biosynthesis (Li, 2003). Vitamin D may influence preeclampsia through the regulation of the rein-angiotensin system (Shin et al., 2010). Vitamin D receptors (VDR) are present in cardiomyocytes and in the vascular smooth muscle of the cardiovascular system, thus further influencing cardiovascular health. When Chen et al (2011) deleted the VDR gene in the cardiomyocytes (muscle cells in the heart) of mice, it caused the heart to increase in size and weight due to hypertrophy of the cardiomyocytes. By identifying a direct role of the VDR in myocytes, this study facilitated the

identification of another potential mechanism to account for reported beneficial effects of vitamin D in the cardiovascular system. These pathways show the biological and epidemiological importance of vitamin D facilitation of blood pressure regulation (Wimalawansa, 2018).

The most common pregnancy-related hypertensive disorder is preeclampsia, which affects an estimated 8% to 10% of pregnancies and is the leading cause of fetal and maternal morbidity and mortality in the United States and worldwide (American College of Obstetrics and Gynecology (ACOG), 2013; Venes, 2013). Preeclampsia is a pregnancy-specific multisystem disorder that is clinically defined as an increase in blood pressure (140 mm Hg systolic or higher, or 90 mm Hg diastolic or higher) after 20 weeks of gestation accompanied by proteinuria (300mg of protein or higher in a 24-hour period) in a previously normotensive woman (ACOG, 2013). The placenta, which is thought to be the origin of the development of preeclampsia, expresses the VDR and the enzyme that catalyzes the synthesis of $1,25(OH)_2D$, 1α-hydroxylase, and has been shown to actively synthesize and utilize $1,25(OH)_2D$locally in the tissue. In preeclamptic pregnancies, there is an abnormal expression of 1α-hydroxylase; therefore, $1,25(OH)_2D$ plays a potential role in the regulation of the placenta (Evans, 2004). The incidence of preeclampsia inversely correlates with the serum 25(OH)D levels. One study found a five-fold increase in preeclampsia in pregnant women with a vitamin D level below 15 ng/mL as compared with pregnant women with normal levels of vitamin D (Mulligan et al 2010). A recent meta-analysis of 15 prospective studies investigating the associations between vitamin D and preeclampsia found mothers with higher serum 25(OH)D levels had reduced odds of preeclampsia (pooled OR 0.52, 95% CI, 0.30, 0.89, $p = 0.02$) (Hyppönen et al., 2014).

Preeclampsia is characterized by maternal vasospasm and hemoconcentration, resulting in decreased blood flow to the mother's kidneys, liver, and brain, and the placenta (Haney et al 2008; Fannin et al 2015; London et al 2016). Since preeclampsia restricts blood flow to the placenta, it also causes fetal distress and intrauterine growth restriction (IUGR) and is the primary cause of placental insufficiency and premature birth (Haney et al 2008). Although the exact mechanism(s) behind the pathogenesis of preeclampsia remains unclear, maternal serum vitamin D at low levels has been shown to be highly associated with this condition (Bodnar 2007; Mulligan et al 2010; Robison et al 2010, Aghajafari et al 2013), and at normal levels may protect against the development of preeclampsia due to its influences on cardiovascular and immune functions (Hyppönen et al 2014).

Although the etiologic mechanism(s) underlying preeclampsia is/are unknown, the leading hypotheses on the etiology of preeclampsia are disturbed placental functions and compromised immunologic origin (Blackburn, 2003; Haney et al., 2008; Steegers et al., 2010; London et al., 2016). These authors concluded that the development of preeclampsia likely involves abnormal placental implantation, endothelial dysfunction, immune dysfunction, excessive inflammation, and defects in angiogenesis. Because $1,25(OH)_2D$ has been shown to have anti-proliferative and pro-differentiation activity in vascular endothelial and immune cells, it is hypothesized that vitamin D may protect against preeclampsia through influences on these biological processes (Liu et al., 2012; Shin et al., 2010). Furthermore, Vitamin D deficiency is associated with inflammation-link vascular endothelial dysfunction; this dysfunction appears to be a basic pathophysiological event on the maternal vascular system in women with preeclampsia (Wei, 2013).

Due to the indistinguishable true mechanisms that facilitate the pathogenesis of preeclampsia, preeclampsia has been referred to as the "disease of theories"; however, there are known risk factors for this condition. First pregnancy, advanced maternal age (>35), African American race, prior preeclamptic pregnancy, chronic or vascular disease, and obesity are common risk factors for preeclampsia (ACOG, 2002; Haney et al., 2008). In a prospective cohort study of 2,637 women examining clinical risk factors for preeclampsia in Boston and Philadelphia, researchers identified eight significant risk factors for preeclampsia, chronic hypertension, presentational diabetes, multiple gestation, African American race, prior preeclampsia, nulliparity, assisted reproduction techniques, and higher than normal BMI (>25); a summary of the significant risk factors recognized in this study are summarized in table 2.1 (Pare et al., 2014). Although advanced maternal age (> 35) is typically associated with an increased risk of preeclampsia (ACOG, 2013; Haney et al., 2008; Lisonkova and Joseph, 2013; English et al. 2015), age was not found to be statistically significant in this study. Also, in this study, smoking, which has been found to be protective against preeclampsia (North et al., 2001; Lisonkova and Joseph, 2013), was not associated with preeclampsia.

Table 2.1 Clinical Risk Factors[1] for Preeclampsia[2].

| Risk Factor | No. | Adjusted[1] Odds Ratio | 95% LCI UCI |
|---|---|---|---|
| Chronic Hypertension | 165 | 2.72 | (1.78-4.13) |
| Pre-gestational Diabetes | 57 | 3.88 | (2.08-7.26) |
| Multiple Gestation | 148 | 2.96 | (1.74-5.03) |
| African American Race | 598 | 1.91 | (1.35-2.71) |
| Prior Preeclampsia | 176 | 3.63 | (2.29-5.73) |
| Nulliparity | 1,157 | 1.73 | (1.26-2.38) |
| Assisted Reproductive Techniques | 312 | 1.72 | (1.10-2.68) |
| BMI > 25-30 overweight | 652 | 1.65 | (1.13-2.41) |
| BMI > 30-35 obesity | 323 | 2.34 | (1.51-3.61) |
| BMI > 35-40 obesity | 146 | 3.59 | (2.13-6.03) |
| BMI > 40 obesity | 107 | 6.04 | (3.56-10.24) |

[1]Source: Pare et al. 2014.
[2]Controlling for variables listed in this table as well as study site.

The risk factors for preeclampsia are also associated with vitamin D. Hypertension and diabetes are associated with vitamin D deficiency. As mentioned above, Vitamin D regulates the renin gene, which is responsible for regulating blood pressure, expression and helps to explain the relationship between hypertension and vitamin D. The risk factors hypertension, diabetes, age over 35, and higher than normal BMI that are associated with preeclampsia, are also classic risk factors for cardiovascular disease (CVD). These important CVD risk factors are also inversely associated with 25(OH)D levels (Martins, 2007). 25(OH)D has been shown to have an inverse association with CVD mortality (Dobnig, 2008; Ginde, 2009). Preeclampsia is associated with CVD later in life (ACOG, 2013); CVD is the number one cause of death among women (CDC, 2015). However, it is not clear if preeclampsia is in the causal pathway of CVD. Preeclampsia and CVD have the same risk factors; the American Heart Association recommends that pregnancy health should be included in the assessment of a women's risk of CVD (ACOG, 2013).

*2.3.2.1 Biological Factors that Influence UV-B Absorption*

In addition to known risk factors for preeclampsia, there are three biological factors that influence the amount of serum 25(OH)D: skin pigment, age, and body mass index (BMI). However, each of these influences the availability of vitamin in a different way. Skin pigment blocks UV-B from reaching 7-DHC to start the photosynthetic production, age decreases the amount of 7-DHC in the skin, and BMI reduces the bioavailability of vitamin D for utilization in the body. Skin pigmentation is an evolutionary response to sun exposure, and acts as a natural sunscreen. Melanin, the dark pigment produced by melanocytes responsible for skin color, absorbs and scatters UV-B photons; thus, reducing the cutaneous production of vitamin D by 90% or more (Clemens, 1982; Nielsen et al., 2004). Melanin evolved to prevent UV-B radiation from damaging DNA molecules and breaking down biologically important molecules, like folic acid ($B_9$), for example (Jablonski, 2010). However, due to these protective properties, melanin blocks the photochemical ring opening of 7-DHC, the steroidal precursor to vitamin D. Lighter skin pigmentation is a direct evolutionary response to this phenomenon. Due to the intensity of the sun at the equator, prehistoric humans evolved a dark skin pigmentation to protect against the harmful effects of UV radiation. Early humans began to evolve and migrate out of the tropics into higher latitudes with lower levels of sunlight that highly vary seasonally, initiating the evolution of light skin pigmentation. Through the mutations of melanin and other genes, the amount of melanin in the skin began to decrease resulting in the development lighter skin pigmentation (Jablonski, 2010). The reduction in skin pigmentation was a necessary adaptation for humans to support the cutaneous production of vitamin D and ensure a plentiful supply of this essential nutrient. Humans with darker skin pigmentation require longer sun exposure to make the same amount of vitamin D compared with people with lighter skin pigmentation

(Holick, 2005). Modern humans with darker pigmentation who do not live in equatorial geographical regions with high amounts of UV radiation are at a higher risk of being vitamin D deficient than their lighter skinned counterparts. Rapid human migrations and increasing urbanization has created mismatches between skin pigmentation and the environmental conditions leading to vitamin D deficiency (Jablonski and Chaplin, 2018).

Another cutaneous factor influencing the production of vitamin D is the natural biological process of aging. Aging has an immense effect on the skin and, thus, the cutaneous production of vitamin D. As one continues past early adulthood, the skin begins to degenerate and loses the ability to efficiently maintain itself, like it did during the early years of development (Patton and Thibodean, 2010). As people age, the skin thickens and the amount of oils in the skin are reduced; furthermore, aging significantly reduces the capacity of the skin to produce 7-DHC (MacLaughlin and Holick, 1985). In an evaluation of surgically obtained skin samples from healthy volunteers ages 8 to 92 years, researchers discovered an inverse relationship between age and the amount of 7-DHC in human skin revealing an age-dependent decrease in the epidermal concentrations of 7-DHC (MacLaughlin and Holick, 1985).

Body Mass Index (BMI) also affects a person's vitamin D status; however, not the ability to produce vitamin D like the other biological factors. People with a higher BMI tend to also have lower concentrations of 25(OH)D (Giovannucci, 2005). This is thought to be a result of the fat soluble nature of vitamin D. Vitamin D is fat soluble and is stored in the adipose tissue. Because people with a higher BMI have more adipose tissue, more vitamin D is sequestered and stored (Wortsman et al., 2000). This process decreases the bioavailability of 25(OH)D. Because it is

biologically unavailable, it cannot be converted into an active form of vitamin D and used by the body.

In summary, low vitamin D is shown to have a significant impact on the cardiovascular and immunologic functions, both of which are important in the study of preeclampsia. The role it plays in the regulation of blood pressure and in the formation of new blood vessels makes vitamin D essential to vascular and heart health; the role vitamin D plays in the placenta, and the biological processes associated with preeclampsia, makes it essential to maternal health. Vitamin D is emerging as a likely protective agent for hypertension and for pregnancy related hypertension disorders, like preeclampsia, prevention (Hypponen et al., 2005; Hypponen et al., 2014). The major source of vitamin D for humans is through cutaneous production. Therefore, because of the influence of UV-B on maternal hypertensive disorders through the production of vitamin D, geography could influence a women's risk of hypertensive disorders during pregnancy. Other individual-level risk factors for preeclampsia such as aging and elevated BMI requires further investigation.

### 2.3.3 Human Ecology: Behaviors

Behaviors are the observable aspects of culture that may protect or enhance the disease process. Behaviors, such as sunscreen use, clothing, and time spent outdoors, also influence the availability and production of vitamin D. Because cutaneous exposure to UV-B can stimulate numerous adverse photochemical reactions like erythema, premature aging, and skin cancer, sunscreen is used to protect the skin from harmful UV-B radiation. However, by blocking UV-B from stimulating photochemical processes, sunscreen blocks the cutaneous production of vitamin D. A sunscreen with a sun protection factor (SPF) as low as 8 is able to decrease the ability of

the skin to synthesize vitamin D by 95%; furtherer more, a sunscreen with a SPF of 15 decreases the ability by 98% (Matsuoka et al., 1988).

Clothing also impedes the cutaneous production of vitamin D because it covers the body and prevents UV-B from reaching the skin. During the winter season, especially in higher latitudes, more clothing is worn due to the colder temperatures; this is yet another factor affecting vitamin D during the winter in higher latitudes. Extensive covering of the skin due to ethnic practices also significantly effects the production of vitamin D. One study examined veiled Arab women living in Denmark, a higher latitude; researchers found that veiled Arab woman had significantly lower serum vitamin D (7.1 nmol/L) compared to non-veiled Arab women (17.5 nmol/L) and Danish controls (47.1 nmol/L) (Glerup et al., 2000). Another study of 316 Lebanese women in Beirut found that 25(OH)D levels were significantly lower in veiled women compared with their non-veiled women (5.12 ng/mL and 9.8 ng/mL, respectively; $p < 0.001$) (Gannage-Yared et al., 2000) again demonstrating the importance of UV-B cutaneous exposure in maintaining healthy vitamin D levels in the body.

As our environment increasingly becomes urbanized, the amount of time people spend outdoors increases. The time indoors limits the amount of solar UV-B exposure and, therefore, decreases the amount of vitamin D cutaneous produced. The shift from farming communities to urban communities has a significant impact on vitamin D, in the present and in the past. Recent archeological evidence examining vitamin D in the remains of early Middle Eastern and European populations suggest that vitamin D deficiency was present in populations that adopted urban and primarily indoor lifestyles and moved away from farming (Brickley et al., 2017;

Jablonski and Chaplin, 2018). In 1910 more than half of the United States' population lived in rural areas. Today, less than 20 percent live in rural areas (United Sates Census Bureau, 2016).

### 2.4 Vitamin D, Cardiovascular Health, and Gestational Hypertension/Preeclampsia

The role it plays in the regulation of blood pressure and in the formation of new blood vessels makes vitamin D essential to vascular and heart health and essential to the overall health of humans.

A substantial number of studies have found a significant inverse relationship between vitamin D and blood pressure. The inverse relationship between vitamin D and hypertensive disorders has been well established by decades if research. The potential explanation for this inverse relation came when Li (2003) examined the physiological role of vitamin D in the regulation of renin, one of the most important hormones for regulating blood pressure. They found that $1,25(OH)_2D$ regulates renin gene expression which explains the inverse relationship between vitamin D and blood pressure. The authors concluded that the renin–angiotensin system plays an essential role in regulating blood pressure, and $1,25(OH)_2D$ is a potent suppressor of renin biosynthesis (Li 2003). Blood Pressure has been shown to vary inversely with UV-B radiation availability (Rostand, 1997; Krause et al., 1998, Wang et al., 2008). Rostand examined the spatial relationship between Blood Pressure and latitude; he demonstrated that for each 10° of latitude north or south of the equator Blood Pressure increases by 22 mm/Hg and hypertension prevalence by 2.5% (Rostand, 1997). Krause et al. (1998) took a different approach; this team examined the relationship between UV-B exposure, plasma concentrations of vitamin D, and blood pressure. They found that UV-B exposure caused a 162% rise in plasma concentrations of

25(OH)D ($p<0.001$), and significantly decreased both systolic and diastolic blood pressure ($p<0.001$) in adult patients with untreated mild essential hypertension (Krause et al., 1998).

Research has reported that adequate levels of vitamin D could help to circumvent pregnancy related diseases, specifically the development of gestational hypertension and preeclampsia due to the nutrients effect on the cardiovascular system. The primary source of vitamin D is solar UV-B radiation, and both UV-B and gestational hypertension/ preeclampsia vary spatially.

**2.5 Vitamin D and Susceptible Populations**

Racial disparities in pregnancy outcomes is one of the most striking and poorly understood inequalities in American health due to the unexplained and complex etiology of these disparities (Swamy et al., 2011). Adequate maternal serum vitamin D levels are necessary during pregnancy for optimal fetal and maternal outcomes (Specker, 2004; Mulligan et al., 2010). Although inadequate vitamin D levels are common in pregnant women (Brunst, 2013; Mulligan et al., 2010), serum vitamin D levels seem to be extremely inadequate in racial/ethnic minorities. In a study of 200 white and 200 black pregnant women (90% were prenatal vitamin users) in Pittsburgh, at the time of delivery 54.1% of the black women and 42.1% of the white women were considered to be vitamin D insufficient [25(OH)D between 15 ng/mL and 32 ng/mL]; 42.1% of black women were vitamin D deficient [25(OH)D < 15 ng/mL] compared to only 5% of white women (Bodnar et al., 2007b). Because an estimated 90% of vitamin D in humans is obtained through sun exposure due to the UVR produced by the sun (Holick, 2005), and the skin pigmentation melanin absorbs UV-B photons and reduces the synthesis of vitamin $D_3$ by more than 90% (Clemens, 1982), it has been hypothesized that the lack of vitamin D could be one of many variables driving racial disparities in pregnancy outcomes, especially at higher latitudes

(Taylor, Wagner, Hollis, 2010). Rostand (2010) and Jablonski (2010) [and others] speculate that, as a consequence of their displacement from the equator, attenuated cutaneous vitamin D photosynthesis is further diminished, leading to a high prevalence of vitamin D deficiency.

However, latitude is not the only geographical factor that influences the cutaneous production of vitamin D; seasonality influences vitamin D levels in maternal populations and influences disparities in maternal 25(OH)D levels as well. In one study, Luque-Fernandez et al (2013) examined the season variation of 25(OH)D among 2,583 pregnant non-Hispanic black and non-Hispanic white women from three US pregnant cohorts from Washington, North Carolina, and Michigan. They found a definite seasonal pattern of mean 25(OH)D serum concentrations, regardless of maternal age and study site, with a peak at the end of summer and a nadir in winter. Black women had the lowest 25(OH)D concentrations during all four seasons; however, non-Hispanic white women had the most variability of 25(OH)D between seasons. The adjusted mean 25(OH)D levels were significantly different between non-Hispanic white and non-Hispanic black women ($P < 0.001$); non-Hispanic black women had an adjust mean 25(OH)D of 19.8ng/mL (95% CI, 18.9, 20.5) while non-Hispanic white women had an adjust mean 25(OH)D of 33.0ng/mL (95% CI, 32.6, 33.4) (Luque-Fernandez et al., 2013).

Hypertensive disorders, like preeclampsia, are the most common medical disorders in pregnancy, and, as discussed in the previous section, research indicates that vitamin D plays a key role in cardiovascular health and blood pressure. Blood Pressure has been shown to vary inversely with UV-B radiation availability (Rostand, 1997; Wang et al .,2008); Rostand demonstrated that for each 10° of latitude north or south of the equator blood pressure increases by 22 mm/Hg and hypertension prevalence by 2.5% (Rostand, 1997). Because the geographic variation of UV-B

radiation progressively decreases the cutaneous production of vitamin D and because people with darker skin pigmentation have a higher prevalence of low 25(OH)D, Rostand (2010) hypothesizes that vitamin D deficiency may contribute to an increased prevalence of hypertension blacks because vitamin D has an important role in the pathogenesis and maintenance of hypertension, thus, contributing to the health disparities issue. Therefore, it is crucial to examine the racial disparities in hypertensive disorders in the maternal population; this research specifically focuses on preeclampsia.

Furthermore, not only are black women at an increased risk for preeclampsia (ACOG, 2002), preeclampsia is also more common and severe in black women (Goodwin and Mercer, 2005; Fingar et al., 2017). In a recent study of 4,644 black women and 12,131 white women, from 1979 to 2006, there was an increasing trend in the prevalence of preeclampsia in both black and white women [0.76 (95% CI; 0.49, 1.03) and 0.29 (95% CI; 0.17, 0.41)] respectively. However, the mean prevalence over all 27 years was higher in black women at 40.1 per 1,000 deliveries than in white women at 28.1 per 1,000 deliveries; preeclampsia rates also remained higher in black women compared to white women, from a prevalence odds ratio POR of 1.75 (95% CI 1.73, 1.78) to (POR) of 0.98 (95% CI 0.96, 1.0). In the most recent time period in the study (1998-2006), the mean prevalence of preeclampsia was about two-thirds higher in black compared to white women (51.2 per 1,000 deliveries and 31.2 per 1,000 deliveries, respectively) (Breathett et al., 2014). This study indicates that not only is the prevalence of preeclampsia higher among black women than in their white counterparts, it is increasing at a significant rate in black women.

Due to the inability and inhabitation of the body's natural ability to produce this essential nutrient at higher latitudes, defined as latitudes above 35° (Webb et al., 1988; Holick, 2006; Holick, 2008) or latitudes above 37° (Holick, 2004; Chen, 2007; Holick, 2007c; Jablonski, 2010), may increase the risk of preeclampsia in pregnant women in general, and black pregnant women in particular (Lee et al., 2007; Haney, 2008; Lisonkova and Joseph, 2013). Rostand (2010) reviewed the circumstances leading to vitamin D deficiency in the African American population; he found that the body of evidence, accumulated over the last several decades, suggests an important role for vitamin D deficiency in the pathogenesis and maintenance of hypertension in African Americans.

Rostand (2010) hypothesizes the suggests that reduced photosynthesis of vitamin $D_3$ at increasing distances from the equator increased parathyroid hormone secretion and, in some circumstances, increased $1,25(OH)_2D_3$ concentrations may in turn affect vascular structure and function, thus influencing blood pressure in blacks and in others living at distances from the equator. The hypothesis attempts to integrate numerous clinical and experimental observations regarding vitamin D, calcium, and parathyroid hormone gathered from many disciplines in order to gain further understanding of the geographical differences in blood pressure and of the susceptibility of African Americans to developing hypertension. Racial disparities are present in preeclampsia incidence, severity, and risk as well (ACOG, 2002; Lee et al., 2007; Haney et al., 2008; Lisonkova and Joseph, 2013); however, these racial disparities are difficult to assess due to confounding by socioeconomic and cultural factors (ACOG, 2013) and historical racism. Racial disparities in preeclampsia and the contribution of maternal UV-B exposure will therefore, be a focus of this research.

Finally, some of the factors that influence the cutaneous production of vitamin D following UV-B radiation exposure are also risk factors/ markers for preeclampsia. Although both UV-B radiation and preeclampsia vary spatially, the relationship between maternal UV-B exposure and preeclampsia has been neglected in previous research.

### 2.6 Study Goal and Objectives

The goal of this dissertation research is to estimate the effect of maternal UV-B exposure on preeclampsia for mothers giving birth in Michigan from 2008 to 2015. To achieve this goal, this study has three main objectives and hypotheses to be tested.

**Objective 1**: To apply the theoretical framework of human ecology in medical geography to conceptualize environmental, biological and behavioral factors important in the understanding of maternal UV-B exposure on the risk of preeclampsia.

**Objective 2:** To estimate the effects of maternal UV-B exposure during three time periods: 20-weeks pre-conception to conception [T1], conception to 20 weeks gestation [T2] and 20 weeks gestation to birth [T3] on preeclampsia, controlling for potential confounding factors at the individual and contextual-levels. Multilevel models will be utilized to investigate mothers exposed to varying levels of UV-B nested within census tracts using remote sensing and a cohort of vital statistics birth data between 2008 to 2015.

$H_{o2.1}$: It is hypothesized that maternal UV-B exposure will increase the odds of preeclampsia and these odds will vary by time period of exposure (T1, T2 or T3).

**Objective 3**: To examine the racial (black-white) disparities in preeclampsia and the contribution of low maternal exposure to UV-B radiation during three time periods: 20-weeks pre-conception to conception [T1], conception to 20 weeks gestation [T2] and 20 weeks gestation to birth [T3] on preeclampsia, controlling for potential confounding factors at the individual and contextual-levels.

$H_{o3.1}$: It is hypothesized that the odds of preeclampsia for white mothers will be lower than the odds for black mothers experiencing similar levels of maternal UV-B exposure due to differences in cutaneous absorption at T1, T2 or T3.

# CHAPTER 3: THEORETICAL FRAMEWORK

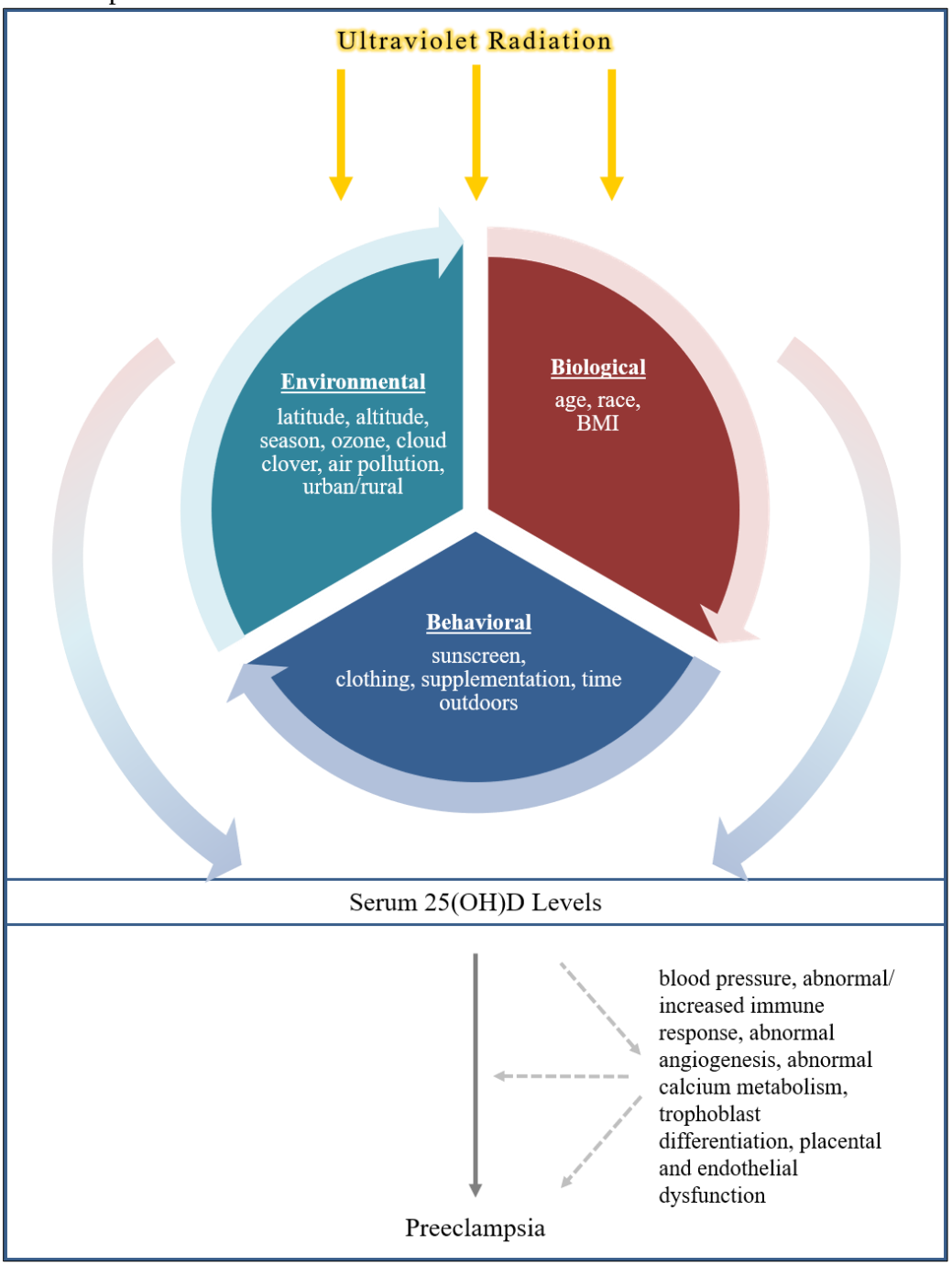
Medical geography investigates spatial and spatio-temporal patterns of health and disease, and the processes by which people interact with their environment to explain these spatial variations. To do this, medical geographers utilize a human ecology conceptual framework. This framework supports the notion that health and disease are attributable to three factors—environment, biology and behavior. It shows the complex relationships and interactions between people (or populations) as biological organisms, their behaviors and culture, and the physical, social, economic, and built environment(s) in which they operate that influence health. The environment—which is comprised of the physical, the built, and the social and structural/political environments—refers to the context in which people live and operate that further puts them at risk of disease or provides protection from disease. People (populations) refer to the biological and phenotypical characteristics of humans and the varying levels of susceptibility to disease, including genetics, nutrition and immunology and demographic factors, such as sex, age and race/ethnicity. Finally, behavior is the observable aspects of culture that may protect or enhance the disease process.

For this dissertation research, the human ecology framework conceptualizes interactions between UV-B, the biological, and behavioral factors that influence the cutaneous production and bioavailability of vitamin D; furthermore, it posits, due to its role in cardiovascular and immunological functions, low vitamin D could be responsible for the development of preeclampsia. Therefore, the framework also conceptualizes the relationship between UV-B radiation, vitamin D, and preeclampsia.

In this framework (Figure 1), a women's serum 25(OH)D level, which is used to reflect a person's Vitamin D blood concentration by biological, environmental, and behavioral factors because they influence the cutaneous production and bioavailability of vitamin D from UV-B radiation; the serum 25(OH)D level, due to its role in cardiovascular function, is responsible for the development of preeclampsia. Although the exact mechanism(s) behind the pathogenesis remains unclear, low maternal serum vitamin D levels have been shown to be associated with preeclampsia; and at normal levels may protect against the development of preeclampsia due to its influences on cardiovascular and immune functions (Hyppönen et al., 2014). A solid gray arrow in the framework depicts this possible association between vitamin D and preeclampsia; and the light gray dashed arrows lead to conditions and physiological processes that may act as mediators in the vitamin D and preeclampsia relationship.

The interactions between UV-B and three sets of factors (environmental, biological, and behavioral) that influence vitamin D status are rooted in geography; therefore, medical geography's model of Human Ecology is the quintessential framework for studying the relationship between UV-B exposure, vitamin D, and preeclampsia. These three sets of factors, and the impact they have on vitamin D are further described below. This framework posits that environmental, biological, and behavioral factors coalesce to influence the amount of vitamin D in a women's blood and those blood levels of vitamin D [25(OH)D] could be responsible for the development of preeclampsia due to factors, such as blood pressure regulation, that vitamin D has been shown to affect. All three sets of influential factors vary geographically; therefore, this framework also provides an explanation as to the spatial variation of preeclampsia. As seen in figure 3.1, this framework argues that person's vitamin D status is dependent on three sets of factors—environmental, biological, and behavioral.

Figure 3.1 Human Ecology Model of the Relationship between Ultraviolet Radiation and Preeclampsia.



These three sets of factors are represented as the three sections of the center circle in the framework; biological in red, behavioral in blue, and environmental in teal. The biological section refers to the characteristics of humans as biological organisms with age, race, and BMI status important individual-level characteristics; the behavioral factors are observable aspects of culture—i.e. people's choices and activities— such as the use of sunscreen, clothing, supplementation, and time spent outdoors; and the environmental section is comprised of physical and built environmental factors. Each of the three parts is comprised of factors that influence the amount of biologically available vitamin D, as discussed in the previous section. The relationships between these three sets of factors within this theoretical framework of human ecology will help to inform the statistical models of this study as outlined in chapter 4 of this dissertation.

# CHAPTER 4: DATA AND METHODS

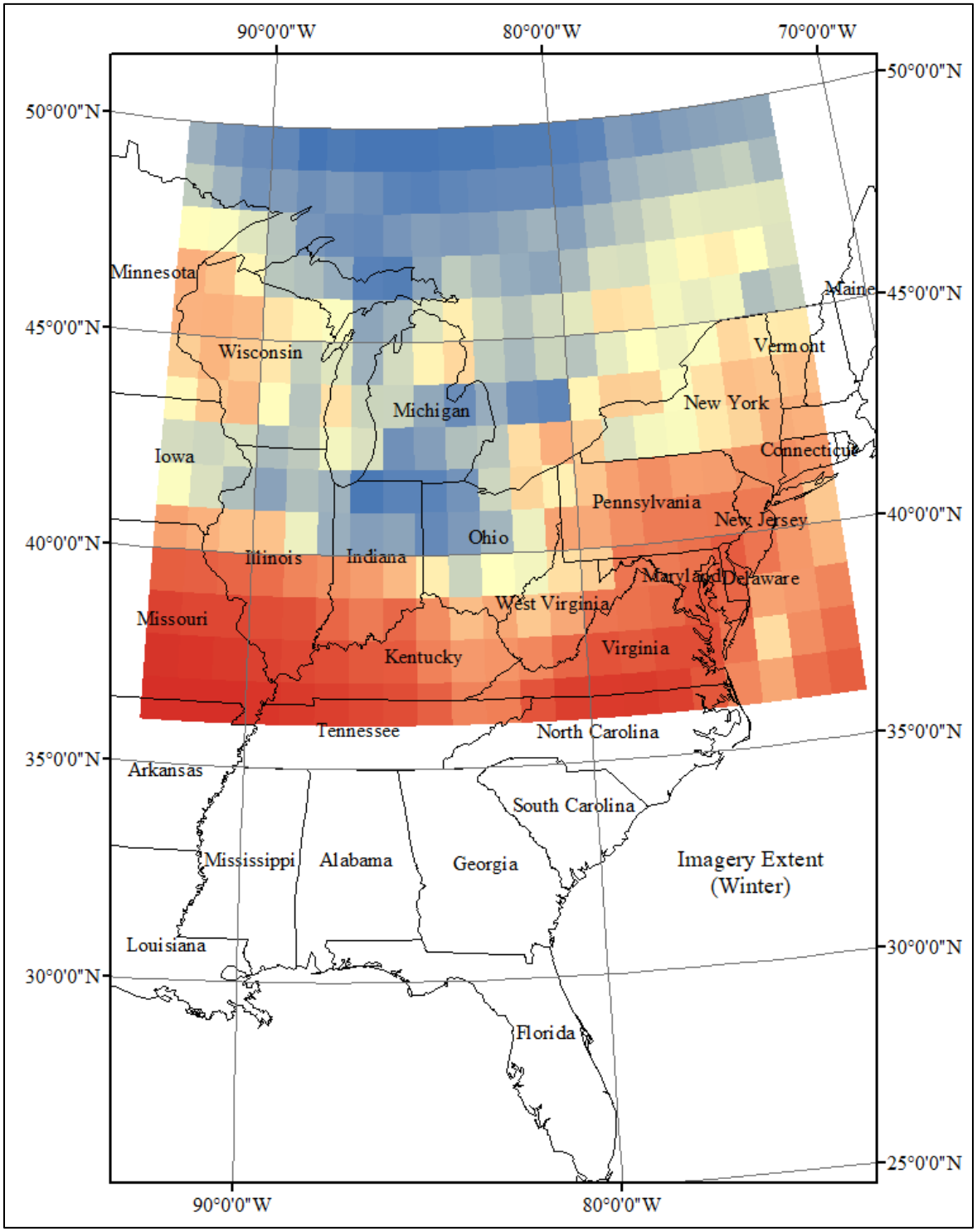
## 4.1 Study Area

The geographical study area for this study is the state of Michigan, USA. Michigan is a higher latitude (44.3148° N, 85.6024° W) state with four distinct climate seasons: spring (March, April, May), summer (June, July, August), fall (September, October, November) and winter (December, January, February) both features that provide substantial spatial and temporal variation in potential UV-B exposure.

## 4.2 UV-B Satellite Data

To estimate UV-B radiation at the Earth's surface, Ozone Monitoring Instrument (OMI) data was obtained from the National Aeronautics and Space Administration (NASA) Earth Observing System's (EOS) Aura satellite for the time period, January 01, 2008 to December 31, 2015 (2,921 days). The OMI spectrometer measures the UV solar irradiance and backscattered UV (BUV) radiation in the spectral region between 264nm and 383nm (Kalakoski 2012; NASA 2012). Using these measurements, OMI is able to provide data on erythemal UV exposure, which is used to estimate UV-B exposure at the Earth's surface based on the irradiance and backscattered radiation (Gao, Gao, and Chang 2010). OMI data was obtained for the geographical extent from -93 to -78 degrees longitude and 50 to 39 degrees latitude. The UV-B data utilized in this study was at a 1.00 degree by 1.00 degree spatial resolution; resulting in 15 by 12 grid of the area.

Figure 4.1 Reference Map of Erythemal-UV-B in Michigan.



The Erythemal Daily Dose data from OMI provides estimates of the surface UV irradiance at the surface of the earth for the local noon solar angles, when the maximum daily irradiance occurs. The Erythemal Daily Dose data is a measure of the potential for biological damage due to solar UV radiation. This data product is calculated using UV irradiance reaching the earth's surface and is weighted using the biological action spectrum model for the susceptibility potential of Caucasian skin to sunburn (erythema) corrected for cloud cover, ozone, and other absorbing aerosols (Bhartia 2005). This "biological action spectrum model" was developed from the McKinlay and Diffey (1987) model adopted as a standard by the International Commission on Illumination (Mckinlay and Diffey 1987). The weighting function of the "biological action spectrum model" estimates UV irradiance at the surface using UV-A and UV-B measurements with the importance of the UV-B component emphasized in the model; the estimated erythemal UV irradiance at the surface is 17% UV-A and 83% UV-B. The noontime product estimates surface UV irradiances at solar noon each day making these daily data outputs comparable over time (Torres et al 2007).

### 4.3 Maternal Data

Individual-level vital statistics birth data for Michigan for the years 2008 to 2015 were used in this study. This data, both maternal and infant, were obtained from the Vital Statistics birth registry from the Michigan Department of Health and Human Services (MDHHS) (http://www.michigan.gov/mdhhs/). The measurement of preeclampsia is defined using the outcome gestational hypertension as defined in the vital statistics birth records (high blood pressure (BP $\geq$ 140/90) occurring after 20 weeks of gestation). Importantly, gestational hypertension encompasses pregnancy induced hypertension (PIH), preeclampsia, and eclampsia,

a severe form of preeclampsia. Preeclampsia is the outcome of interest and is modeled as the dependent variable in statistical analyses as dichotomous (yes-present and no-absent). Race of the mother (non-Hispanic black or non-Hispanic white) will also be an important variable in this study. This individual-level vital statistics birth data used to identify the mothers diagnosed with preeclampsia and race also provides numerous individual-level variables used to further explain preeclampsia in this study. Table 3.2 provides a complete list of the variables that are included in the study and how the variables are utilized in this study.

Only pregnancies resulting in singleton live births weighing greater than 1,000 grams occurring on or after October 14, 2008 were included in the analysis. The infant variables were used to identify those mothers who met these criteria and, therefore, exclude those who did not meet these criteria. Maternal socio-economic status (SES) and maternal health variables allowed for the controlling of different individual characteristics that could influence the outcome, gestational hypertension. The individual-level variables age, race, and BMI are of particular interest because these characteristics influence vitamin D production as discussed in previously. The mothers' mailing addresses at the time of the infant's birth were geocoded in order to examine the spatial variability of gestational hypertension in Michigan. Geocoding is a process in which an address is converted into spatial data and is given a physical location (latitude and longitude) in a Geographic Information System (GIS). Because these addresses were used to approximate the location of the mother's residence, mothers with a non-Michigan mailing address were also excluded from this study.

Table 4.1 Infant and Maternal Variables from Vital Statistics Reports Utilized in the Study.

| Variable | Coding Structure | Purpose |
|---|---|---|
| **Infant** | | |
| Certificate Number | Certificate Number | Identification |
| Birth Year | Self-explanatory | Birth date |
| Birth Month | Self-explanatory | Birth date |
| Birth Day | Self-explanatory | Birth date |
| Plurality | Singleton = 1, all else delete | Exclusion (Singletons only) |
| Birth Weight (Grams) | Computer generated from pounds and ounces | Exclusion (> 1,000g) |
| Weeks of Gestation | Self-explanatory | Exclusion (≥ 20wks) |
| Mother Hispanic | 1=Yes 0=No | Exclusion Hispanic= 1 |
| Mother's Race | 2=Black 1=White | Only white and black were included |
| **Mother's Socioeconomic Status** | | |
| Mother received WIC | 1=Yes 0=No | Independent variable |
| Source of payment | Medicaid=1 Private, Self, Other = 0 | Independent variable |
| **Mother's Health** | | |
| Age of Mother[1] | Centered on 35 years | Independent variable |
| Mother's BMI | Body mass index centered on 21.75 | Independent variable |
| Pre-pregnancy Diabetes | 1=Yes 0=No | Independent variable |
| Gestational Diabetes | 1=Yes 0=No | Independent variable |
| **Outcome** | | |
| Gestational hypertension (PIH, PE, eclampsia) | 1=Yes 0=No | Outcome of Interest |
| **Mother's Residential Information** | | |
| Mother's mailing address, city, state, zip code | Mother's mailing address, city, state, zip code | Geocode |
| Residence County | County of residence | Geocode |
| Residence State | State of residence | County paired with state of residence |

[1]Age and BMI were also categorized as a dichotomous variable to investigate the risk associated with younger (< 25 years) and older (>=35 years) mothers compared to middle age (base = 25-35 years) and under-weight (18.5) and overweight and obese (≥25.0) mothers compared to mothers of normal weight (base=21.75).

The maternal data for this study were geocoded to the street shapefiles that corresponded to the year of the infant's birth. The maternal street addresses were first standardized (i.e. rd= Road; st=Street) to ensure the optimal geocoding outcome. After standardization, the geocoding was

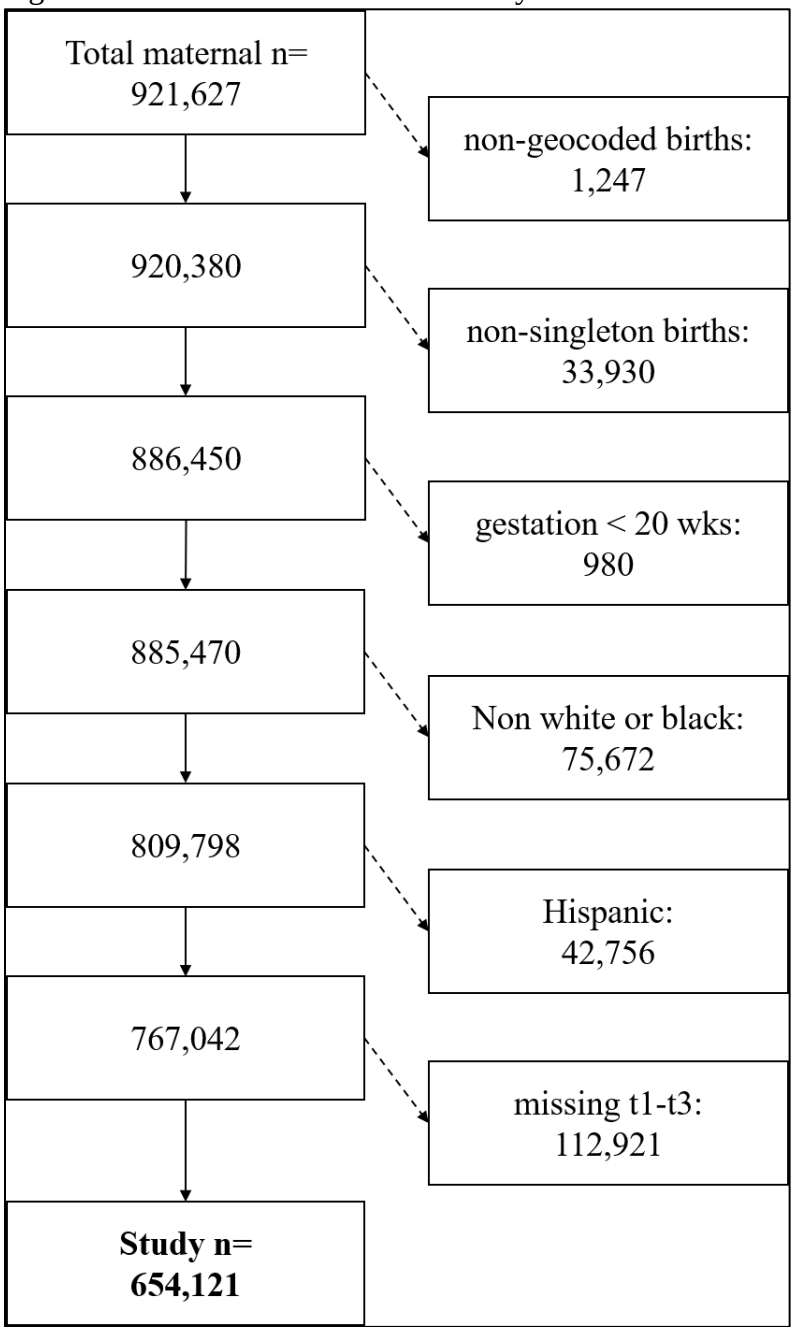
facilitated by ArcGIS (ESRI 2010) using a composite address locator and were offset from the street 15m and 30m at the corners; the purpose of the offset was to ensure that the geocoded points did not fall on the street itself. Streets are often used for defining the boundaries for geographic units, such as census tracts; if the geocoded points fall on the street, they could potentially be excluded when joining points to geographic units, such as census tracts. The automatic batch geocoding was preformed; this process assigned geographic locations to the table of addresses. The batch geocoding matched at least 96% of the maternal addresses to a location across the study years. Following the geocoding a random sample of points were selected to validate their locational accuracy. The findings from this evaluation demonstrated a high level of spatial accuracy in the geocoded maternal data. Using the latitude and longitude locations of the mother's residences (geocoded records) at the time of their infant's birth, the records were spatially joined to the 1.00 x 1.00 grid cells in order to determine the UV-B exposure during gestation.

### 4.3.1 Study Population

Between January 1, 2008 to December 31, 2015, there were 921,627 total live births in individual-level vital statistics birth data for the state of Michigan. Because this study only looked at live singleton births weighing greater than 1,000 grams born after 20 weeks gestation to non-Hispanic Black or non-Hispanic White mothers who are residents of the state of Michigan, 654,121 births were included in this study (Figure 4.2). Birth cases that did not fit the study criteria were excluded from the study population for this study. Births were excluded if the maternal residential address was not able to be geocoded (1,247); non-singleton (33,930); born before 20 weeks gestation (980); maternal race/ethnicity was indicated to be Hispanic, non-

white, or non-black; or if the case was missing a value for any of the UV-exposure time-periods. These time periods are further discussed in the next section.

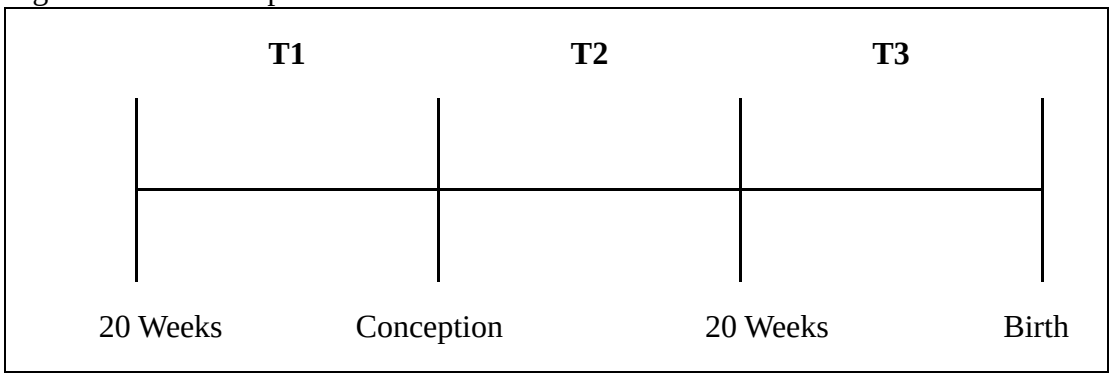
Figure 4.2 Flow-chart of Births for Study Area and Time Period (2008 to 2016).



### 4.4 Maternal Erythemal UV-B Exposure

In addition to the spatial location, this study assigned an Erythemal-UV-B (herein, also referred to as UV-B exposure) exposure dosage to the mother at three time periods (T1, T2, T3) (Figure 4.3). The three time periods were calculated as follows: (T1) estimated date of conception back 20 weeks, (T2) the estimated date of conception to 20 weeks of gestation, and (T3) 20 weeks of gestation to the date of birth. Because this study evaluates UV-B exposure prior to pregnancy and the study time period is January 1, 2008 and December 31, 2015, mothers who gave birth prior to October 14, 2008 were excluded from this study due to lack of UV-B exposure data for all three time periods.

Figure 4.3 UV-B Exposure Time Periods.




These time periods were selected because gestational hypertension is diagnosed after 20 weeks gestation so it will be important to understand the effect of UV-B on gestational hypertension prior to conception (e.g., the health of the mother going into pregnancy), conception to 20 weeks to assess early pregnancy impacts and after 20 weeks, when symptoms of gestational hypertension are likely to occur. Furthermore, because the average gestational period is about 40 weeks, the duration of these three time periods are relatively equal. The UV-B levels during these three study time periods will be averaged over each of the 20 week intervals (Figures 4.5,

4.6 and 4.7). Integrating averages over periods of time help to alleviate inaccuracies (e.g., missing data) in the data (Herman et al 1999). Figure 4.4 shows a histogram of the mean UV-B dose across all three time periods. Figures 4.5, 4.6 and 4.7 show the histograms the individual time periods.

Figure 4.4 Histogram of Mean Erythemal-UV-B Values in kilojoules (KJ) Across T1, T2, and T3 for Mothers (N=654,121) who gave Birth in Michigan 2008-2015.

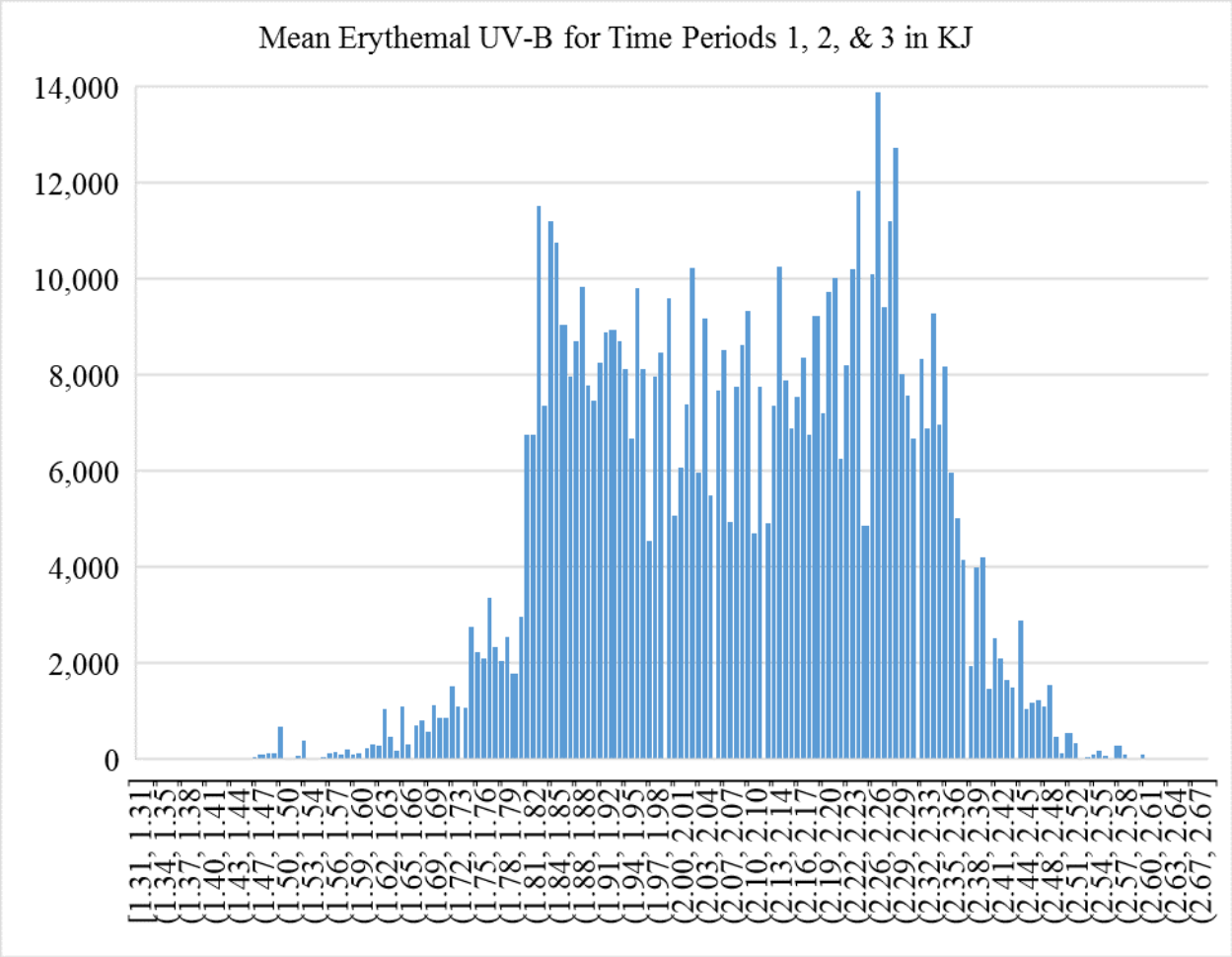


Figure 4.5 Histogram of T1 Erythemal-UV-B Values in kilojoules (KJ) for Mothers (N=654,121) who gave Birth in Michigan 2008-2015.

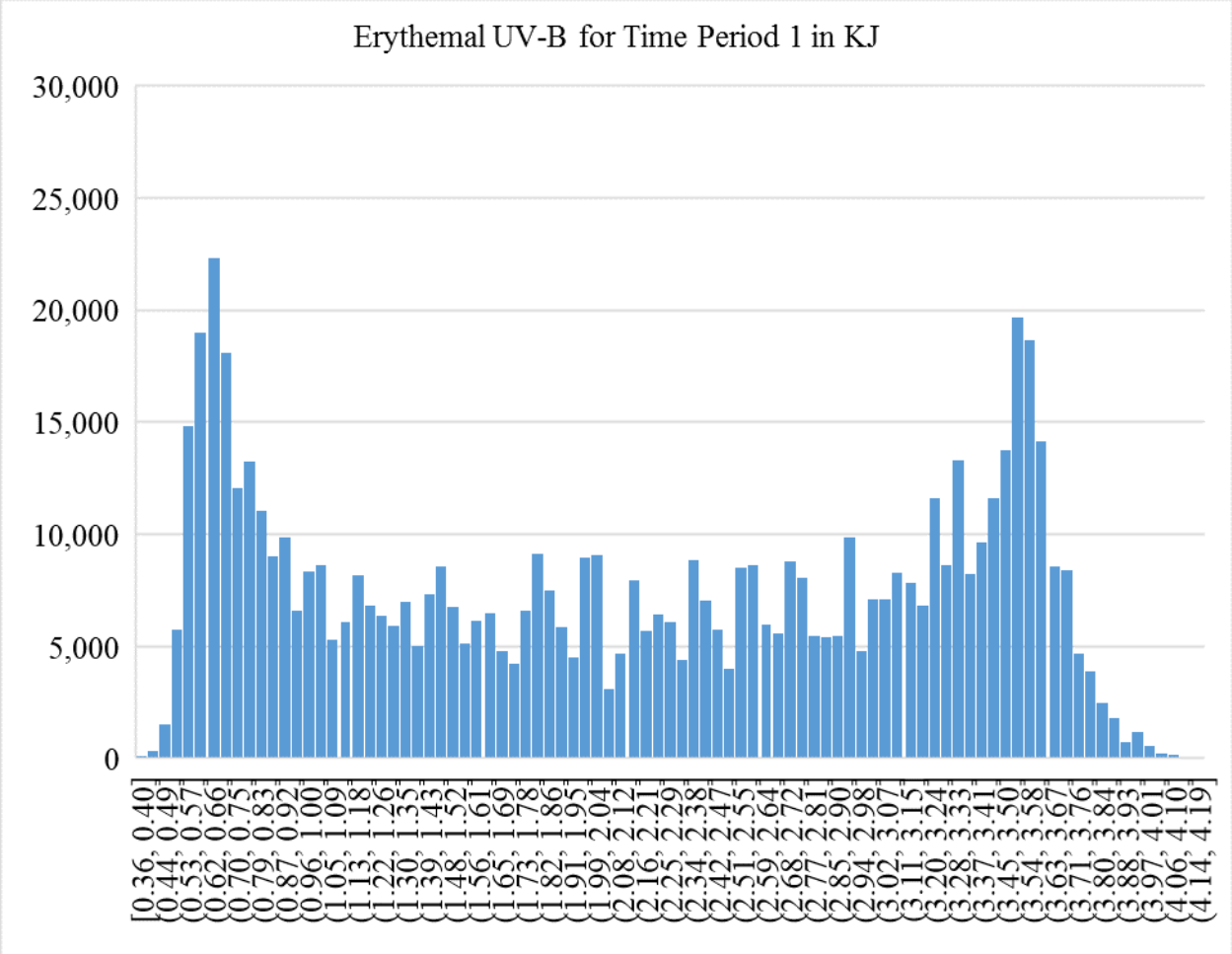


Figure 4.6 Histogram of T2 Erythemal-UV-B Values in kilojoules (KJ) for Mothers (N=654,121) who gave Birth in Michigan 2008-2015.

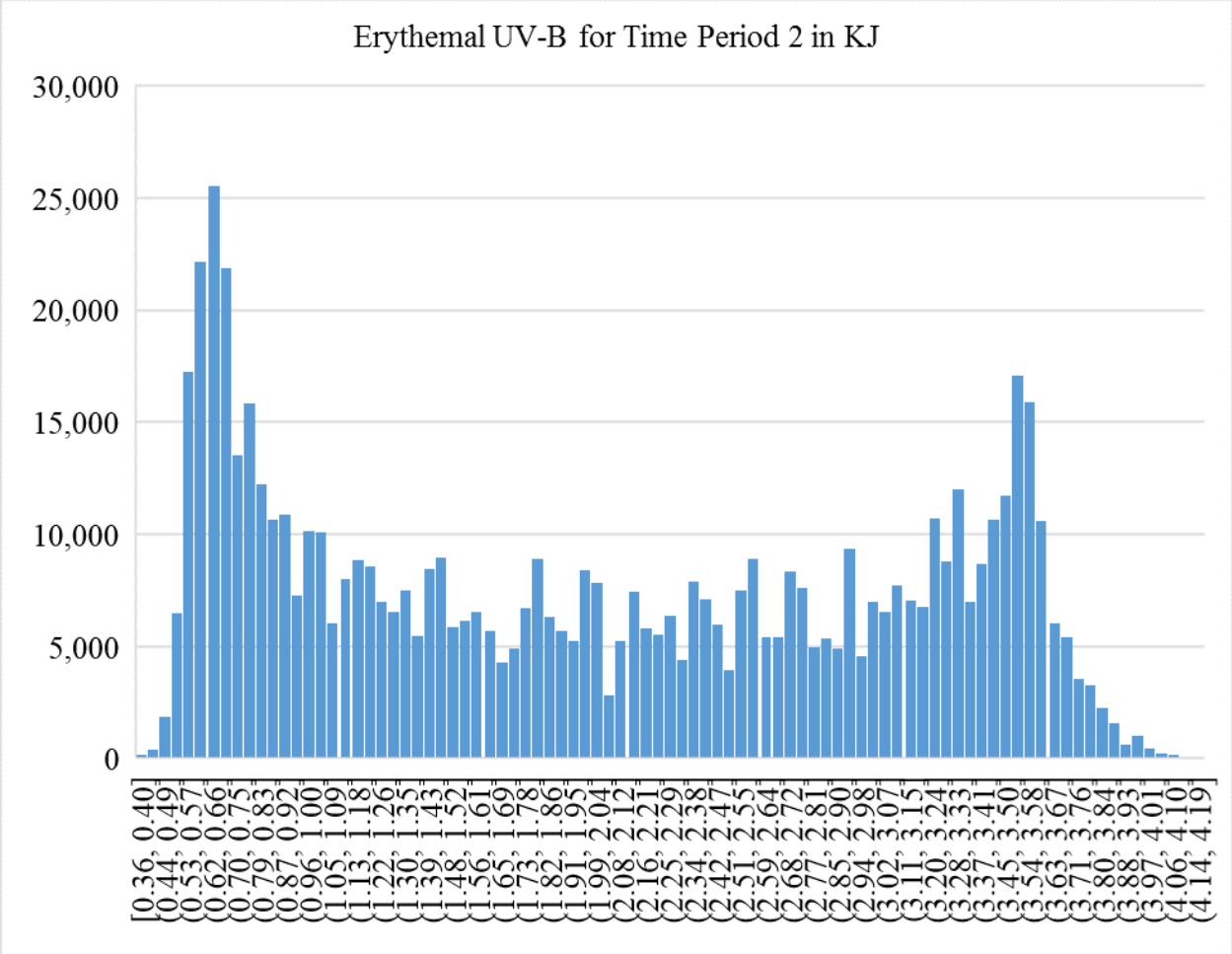
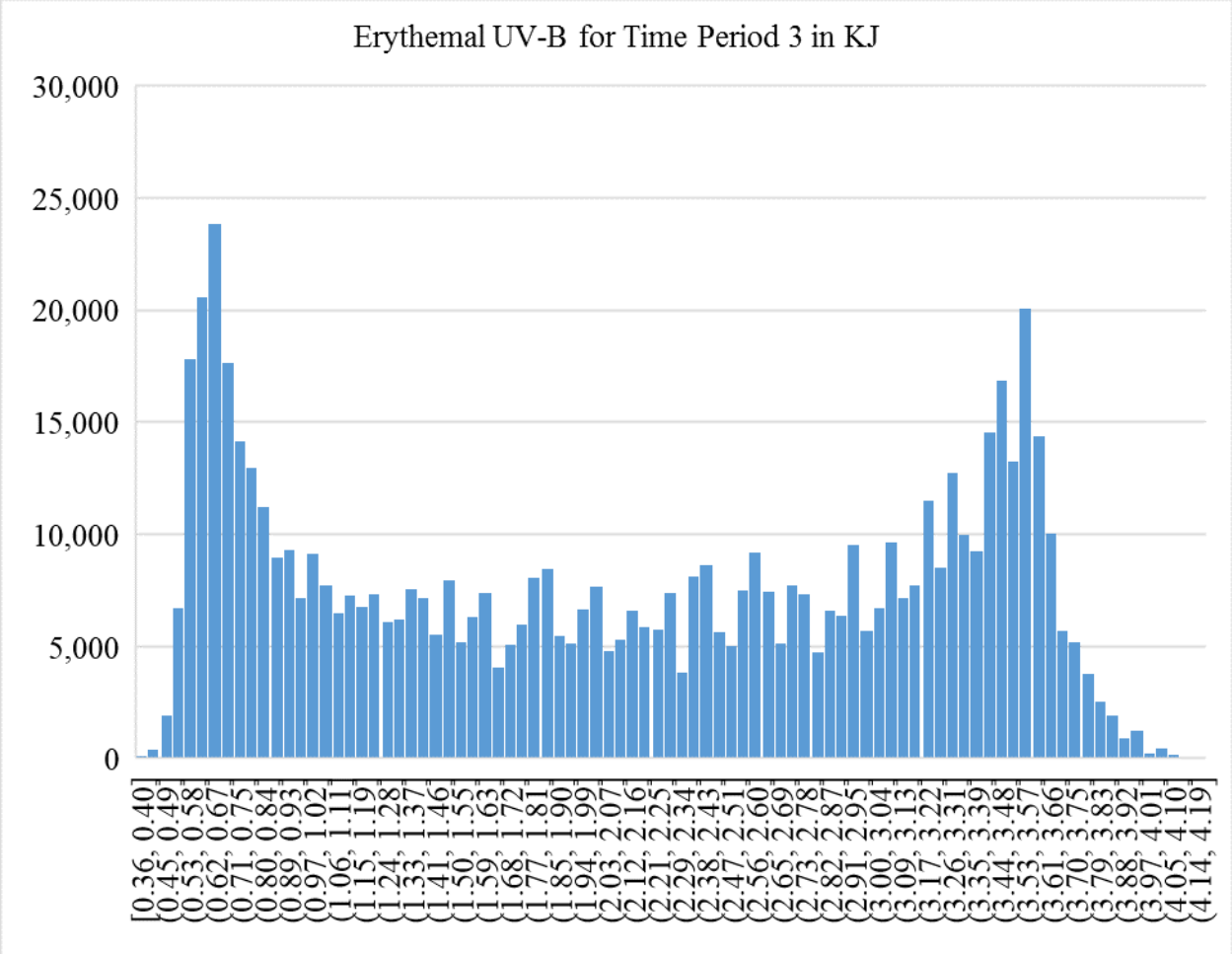


Figure 4.7 Histogram of T3 Erythemal-UV-B Values in kilojoules (KJ) for Mothers (N=654,121) who gave Birth in Michigan 2008-2015.




Figures 4.4 to 4.6 are histograms displaying the Erythemal-UV-B data in KJ; figure 4.3 is the mean for all three of the time periods. In figures 4.4, 4.5 and 4.6 there is a bi-modal distribution; these are the winter and summer months. Fall and spring have similar values and are not on the extreme in terms of values. Winter months are the low values and summer is the higher Erythemal-UV-B values.

Table 4.2 shows the summary statistics of UV-B across the three time periods all of which are relatively similar. The median dose at T2 is slightly lower than T1 and T3 demonstrating the higher number of lower values at the low-end of the distribution. These means were used as reference points from which to center the Erythemal-UV-B dose (T1_KJ, T2_KJ, and T3_KJ) as a continuous variable in subsequent reference models.

Table 4.2 Summary Statistics on Erythemal-UV-B Across Time Periods, Michigan 2008-2015

| | **Erythemal Daily Dose** ($KJ/m^2$) | | | |
|---|---|---|---|---|
| **Statistics** | T1 | T2 | T3 | Mean |
| Mean | 2.13108 | 2.00532 | 2.10986 | 2.08209 |
| Median | 2.14864 | 1.93108 | 2.12944 | 2.08723 |
| Std. Deviation | 1.07664 | 1.07262 | 1.08078 | 0.19536 |
| Range | 3.79461 | 3.79461 | 3.79461 | 1.37287 |
| Minimum | 0.35858 | 0.35858 | 0.35858 | 1.30704 |
| Maximum | 4.15319 | 4.15319 | 4.15319 | 2.67991 |

### 4.5 Area-Level (Contextual Data)

This study utilizes census tract data from the 2010 census and data from the American Community Survey (ACS) to examine area-level characteristics in which the mother is exposed and its potential influence on gestational hypertension. These area-level characteristics will also be used as control variables to improve the estimation of Erythemal-UV-B exposure effects on preeclampsia. In this study, contextual areas will be defined by census tracts; the TIGER (Topologically Integrated Geographic Encoding and Referencing) 2010 census tract boundaries available from United States Census Bureau will be used to geographically define these areas.

To describe area-level characteristics urban/rural and poverty will be used. Mother's exposure to UV-B may be lower in urban areas due to the higher likelihood of scattering and absorbing rays from pollution the built environment, therefore, urbanization will be accounted for. The Urban

variable comes from the 2010 United States Census and will be modeled as dichotomous (Urban =1; Rural = 0). The other variable area-level variable is Poverty and comes from American Community Survey (ACS). Poverty is modeled as a continuous variable that the ACS computes as the number of families below the federal poverty line in a census tract divided by the total number of families in that census tract. The ACS data used in this assessment was from the 2010-2014 ACS 5-year estimates (US Census Bureau 2019). Unlike the 10-year Census Data which is based on the population of the United States, ACS data are only based on a small sample of the population which introduces error and uncertainty; the margin of error for this data, due to sampling variability, can be relativity high. However, because the 2010 census data is included in the 5-year estimate, the potential bias associated with this error is reduced.

### 4.6 Descriptive Analyses

The descriptive analyses for this study will include univariate analyses (i.e., frequency tables and descriptive statistics) of preeclampsia. Statistical analyses will proceed from univariate to bivariate analyses, to investigate crude associations between preeclampsia and other maternal variables of interest. Histograms, descriptive statistics, odds ratios, and other analyses will provide a rough picture of the data and that will be useful in the subsequent multivariate multilevel analyses. For the variables, correlation coefficients will be calculated and displayed in a matrix. For the categorical independent variables odds ratios will be calculated. Crude univariate analyses of the dependent variables will be evaluated.

These descriptive analyses will be used to identify potential confounders for the multilevel models; these models will be discussed in the next section. Variables will be added and/or removed in the multilevel models to compare the change in magnitude of the Erythmal-UV-B

and gestational hypertension relationship with and without these adjustments. Continuous variables will also be centered on a reference value (obtained from Table 3.2) in the multilevel models; centering continuous variables on a reference value is necessary so that a value of zero can be interpreted meaningfully. A table of all the continuous variables used and the reference value they were centered on are in Table 4.3.

Table 4.3 Reference Values for Model Continuous Variables

| Variable | Value | Variable | Value |
|---|---|---|---|
| T1_KJ | 2.1311 | Mean UV-B | 2.0821 |
| T2_KJ | 2.0053 | Age | 35 years |
| T3_KJ | 2.1099 | BMI | 21.75 |

### 4.7 Multilevel Analysis

To investigate the relationship between erythmal-UV-B exposure and preeclampsia while controlling for individual-level and area-level variables, a two-stage multilevel model was used for this analysis with mothers (level-1) nested within area-level contextual environments (level-2). Because preeclampsia is modeled as a dichotomous variable (preeclampsia = 1 if yes; 0 if no)—a generalized linear model and logit link function was used. These hierarchical models were constructed and estimated in SAS software v.9.3 (SAS 2017). A brief description of the models constructed follows.

#### 4.7.1 Variance Components Model

First, to assess the magnitude of variation in preeclampsia within and across census tracts $\beta_{0j}$ a model with no predictors at either level will be estimated. Given a Bernoulli sampling model and logit link function, the level-1 model is:

$$\eta_{ij} = \beta_{0j}$$

Where $\eta_{ij}$ is the intercept or the mean level of preeclampsia in each census tract, $\beta_{0j}$.

The Level-2 model is:

$$\beta_{0j} = \gamma_{00} + u_{0j}, \qquad u_{0j} \sim \mathrm{N}(0,\tau_{00})$$

Where the mean level of preeclampsia in each census tract, $\beta_{oj}$, is represented as a function of the grand mean, or level of preeclampsia across all census tracts, $\gamma_{00}$, plus a random error, $u_{0j}$. The random error is assumed to be normally distributed with mean zero and variance $\tau_{00}$. $\tau_{00}$ is the variance between census tracts, in tract-average log-odds of preeclampsia.

### 4.7.2 Random Coefficients Model

The Random Coefficients Model adds Level-1 (individual-level) predictors to the previous model. Here the level-1 predictors are each of the Erythemal-UV-B exposure dosages at T1_KJ, T2_KJ and T3_KJ. In the example below, these predictors are assumed to modeled on their means.

$$\eta_{ij} = \beta_{0ij} + \beta_{1j}T1\_KJ_{iJ} + \beta_{2j}T2\_KJ_{ij} + \beta_{3j}T3\_KJ_{ij} + Black_{4ij} + r_{ij}$$

The intercepts or mean level of preeclampsia in each census tract and the slopes or mean level of each Erythemal-UV-B exposure dosage for each census tract will be output as Level-2 variables $\beta_{0j}$ and $\beta_{1j}$, $\beta_{2j}$, $\beta_{3j}$, $\beta_{4j}$ and $r_{ij}$ is the Level-1 residual. In the Level-2 structural model the Level-1 intercept coefficient will be allowed to vary and the slope coefficients are fixed.

$$\beta_{0j} = \gamma_{00} + \mu_{0j}$$

$$\beta_{1j} = \gamma_{10}$$

$$\beta_{2j} = \gamma_{20}$$

$$\beta_{3j} = \gamma_{30}$$

Where $\gamma_{00}$ is the grand mean, $\gamma_{10}, \gamma_{20}, \gamma_{30}$ are the grand slopes, and $\mu_{0j}$ is the intercept variation in preeclampsia across census tracts in Michigan.

In this model, additional Level-1 predictors will be added to control for the differences in characteristics between mothers.

### 4.7.3 Level-2 Predictor for Intercepts-as-Outcomes Model

In this model, the Level-1 equation is the same as in the previous model but the URBAN (and poverty- not shown) variables are added as Level-2 predictors of census tract (preeclampsia) intercepts, after controlling for Erythemal-UV-B and other individual-level characteristics. The Level-1 slope coefficients remain fixed.

$$\beta_{0j} = \gamma_{00} + \gamma_{01}(URBAN)_j + \mu_{0j}$$

$$\beta_{1j} = \gamma_{10}$$

$$\beta_{2j} = \gamma_{20}$$

$$\beta_{3j} = \gamma_{30}$$

where $\gamma_{00}$ is the grand mean, $\gamma_{01}$ is the effect of URBAN on $\beta_{0j}$, $\gamma_{10}$, $\gamma_{20}$, $\gamma_{30}$ are the grand slopes adjusting for URBAN on the preeclampsia intercepts, and $\mu_{0j}$ again is a random variation in tract intercepts assuming to be ~ independently N(0, $\pi_{00}$).

### 4.7.4 Level-2 Predictor for Intercepts- and Slopes-as-Outcomes Model

In this model the Level-1 equation is the same as in the previous two models but URBAN is added as a Level-2 predictor of census tract intercepts and slopes.

$$\beta_{0j} = \gamma_{00} + \gamma_{01}(URBAN)_j + \mu_{0j}$$

$$\beta_{1j} = \gamma_{10} + \gamma_{01}\,(URBAN)_j$$

$$\beta_{2j} = \gamma_{20} + \gamma_{02}\,(URBAN)_j$$

$$\beta_{3j} = \gamma_{30} + \gamma_{03}\,(URBAN)_j$$

Combining the Level-1 and Level-2 structural models yields a combined model:

$$\eta_{ij} = \gamma_{00} + \gamma_{01}(URBAN)_j + \gamma_{10}(\mathrm{T1})_j + \gamma_{11}(T1 * URBAN)_J + \gamma_{20}(T2)_j + \gamma_{22}(T2 * URBAN)_J + \gamma_{30}(T2)_j + \gamma_{33}(T3 * URBAN)_J + ..\gamma_{x0}x_j + \mu_{0j}$$

where $\eta_{ij}$ is the probability of preeclampsia, is viewed as a function of $\gamma_{00}$ the grand mean, $\gamma_{01}$ is the effect of URBAN on $\eta_{ij}$, $\gamma_{11}$, $\gamma_{22}$, $\gamma_{33}$ are the effects of the T1, T2, T3 * URBAN interaction terms on $\eta_{ij}$, controlling for potential confounders and a random error $\mu_{0j}$ assuming to be ~ independently N(0, $\pi_{00}$).

This study will estimate the effect of UV-B and race as an interaction, or an effect modifier on preeclampsia. An interaction occurs when two or more risk factors (in this case, UV-B and race) modify the effect of each other with regard to the occurrence of preeclampsia.

$$\eta_{ij} = \gamma_{00} + \gamma_{01}(BLACK)_j + \gamma_{10}(\mathrm{T1})_j + \gamma_{11}(T1 * BLACK)_J + \gamma_{20}(T2)_j + \gamma_{22}(T2 * BLACK)_J + \gamma_{30}(T2)_j + \gamma_{33}(T3 * BLACK)_J + .. \gamma_{x0}x_j + \mu_{0j}$$

where $\eta_{ij}$ is the probability of preeclampsia, is viewed as a function of $\gamma_{00}$ the grand mean, $\gamma_{01}$ is the effect of BLACK on $\eta_{ij}$, $\gamma_{11}$, $\gamma_{22}$, $\gamma_{33}$, are the effects of the T1, T2, T3 * BLACK interaction terms on $\eta_{ij}$, controlling for potential confounders and a random error $\mu_{0j}$ assuming to be ~ independently N(0, $\pi_{00}$).

To assess the contribution of UV-B exposure on racial disparities in preeclampsia, race-stratified models will also be estimated. The stratum specific effect measures will be compared with one another in order to assess the differences in the direction and magnitude of the preeclampsia intercepts and T1, T2 and T3 slope coefficients controlling for potential confounders at the individual and contextual levels.

# CHAPTER 5: RESULTS

## 5.1 Descriptive Analyses

The overall incidence of preeclampsia in Michigan is 5.0 per 100 live births (Table 5.1) which is above the national rate of 3.4 (Ananth et al., 2013). Excluding 2008 because of incomplete data from the cohort of mothers, the incidence of preeclampsia increased over time from 4.5 in 2009 to 5.8 in 2015 (Table 5.1). In Michigan, between 2008 and 2015, 79.1% of mothers were non-Hispanic white (herein, referred to as white) and accounted for 81.9% of preeclampsia diagnoses; 20.9% were non-Hispanic black (herein, referred to as black) and accounted for 18.0% of preeclampsia diagnoses (Table 5.1). Black mothers had a 17.6% reduction in preeclampsia compared to white mothers (OR = 0.824, 95% CI, 0.801-0.849). The incidence rate of preeclampsia for white mothers was 5.2 per 100 live births compared to 4.3 for black mothers (difference = + 0.9 for white mothers)

Table 5.1. Preeclampsia Incidence[1] Rate by Year in Michigan 2008-2015

| **Race-Ethnicity** | **Preeclampsia** | | | | | |
|---|---|---|---|---|---|---|
| | None | | Yes | | Total | |
| | No. | (%) | No. | (%) | No. | (%) |
| Non-Hispanic White | 486644 | 94.8 | 26786 | 5.2 | 513430 | 100.0 |
| | | 78.9 | | 81.9 | | 79.1 |
| Non-Hispanic Black | 129882 | 95.7 | 5894 | 4.3 | 135776 | 100.0 |
| | | 21.1 | | 18.0 | | 20.9 |
| Total | 616526 | 95.0 | 32680 | 5.0 | 649206 | 100.0 |
| | | 100.0 | | 100.0 | | 100.0 |

[1]Rate per 100 live births.
Odds Ratio = 0.824 (95% CI 0.801-0.849).

Table 5.2 shows birth rates to be highest in the summer (26.9%) followed by spring (25.6%), fall (25.1%) and lowest in the winter (22.3%). The incidence of preeclampsia however, is highest in

the winter (5.5) and lowest in the summer (4.7) supporting the hypothesis that low Erythemal-UV-B dosages during the winter may play a role in the etiology of preeclampsia.

Table 5.2 Preeclampsia Incidence[1] by Seasons[2] in Michigan 2008-2015

| | **Preeclampsia** | | | | | |
|---|---|---|---|---|---|---|
| | None | | Yes | | Total | |
| **Season** | No. | (%) | No. | (%) | No. | (%) |
| Winter | 136752 | 94.5 | 7885 | 5.5 | 144637 | 22.3 |
| Spring | 157878 | 94.9 | 8495 | 5.1 | 166373 | 25.6 |
| Summer | 166783 | 95.3 | 8212 | 4.7 | 174995 | 26.9 |
| Fall | 155113 | 95.0 | 8088 | 5.0 | 163201 | 25.1 |
| Total | 616526 | 94.9 | 32680 | 5.0 | 649206 | 100.0 |

[1]Rate per 100 live births.
[2]Winter = December, January, February; Spring = March, April, May; Summer = June, July, August; Fall=September, October, November.

These disparities in preeclampsia rates for white and black mothers (Tables 5.3 and 5.4) is also present across seasons with black mothers having a consistently lower rate of preeclampsia compared to white mothers. For both groups, preeclampsia incidence is highest in winter months (black, 4.7 and whites, 5.7) and lowest in summer months (blacks, 4.0 and whites, 4.9). The black/white rate ratio (RR) is highest in fall (RR=0.843) followed by spring (RR=0.830), winter (RR=0.824) and lowest in the summer (RR=0.816).

Table 5.3 Preeclampsia Incidence[1] by Season for Non-Hispanic Black Mothers in Michigan 2008-2015

| | | **Non-Hispanic Black Mothers** | | | |
|---|---|---|---|---|---|
| | **Births** | **Preeclampsia** | | | |
| | Total | None | | Yes | |
| **Season** | No. | No. | (%) | No. | (%) |
| Winter | 32548 | 31029 | 95.3 | 1519 | 4.7 |
| Spring | 33909 | 32417 | 95.6 | 1492 | 4.4 |
| Summer | 35230 | 33823 | 96.0 | 1407 | 4.0 |
| Fall | 34089 | 32613 | 95.7 | 1476 | 4.3 |
| Total | 135776 | 129882 | 95.7 | 5894 | 4.3 |

[1]Rate per 100 live births.

Table 5.4 Preeclampsia Incidence[1] by Season for Non-Hispanic White Mothers in Michigan 2008-2015

| Season | | Non-Hispanic White Mothers | | | |
|---|---|---|---|---|---|
| | **Births** | **Preeclampsia** | | | |
| | Total | None | | Yes | |
| | No. | No. | (%) | No. | (%) |
| Winter | 112089 | 105723 | 94.3 | 6366 | 5.7 |
| Spring | 132464 | 125461 | 94.7 | 7003 | 5.3 |
| Summer | 139765 | 132960 | 95.1 | 6805 | 4.9 |
| Fall | 129112 | 122500 | 94.9 | 6112 | 5.1 |
| Total | 513430 | 486644 | 94.8 | 26786 | 5.2 |

Young mothers (< 25 years) accounted for 46.3% of births. Table 5.5 shows the differences in preeclampsia for younger mothers compared to middle-aged mothers (25-35 years). Younger mothers were significantly less likely to be diagnosed with preeclampsia compared to middle-aged mothers (OR=0.883, 95% CI 0.861-0.905). Younger black mothers were at lower odds of preeclampsia (OR=0.765, 95% CI 0.724-0,809) compared to younger white mothers (OR=0.960, 95% CI 0.933-0.988).

Table 5.5 Preeclampsia Incidence[1] by Race for Mothers Age < 25 Years in Michigan 2008-2015

| Race-Ethnicity and Ages | | Preeclampsia | | | | | |
|---|---|---|---|---|---|---|---|
| | | None | | Yes | | Total | |
| | | No. | (%) | No. | (%) | No. | (%) |
| **White** | 25 to 35 | 296819 | 59.3 | 17053 | 3.4 | 313872 | 62.7 |
| | < 25 | 177890 | 35.5 | 9142 | 1.8 | 187032 | 37.3 |
| | Total | 474709 | 94.8 | 26195 | 5.2 | 500904 | 100.0 |
| **Black** | 25 to 35 | 37133 | 28.5 | 2019 | 1.6 | 39152 | 30.1 |
| | < 25 | 87345 | 67.1 | 3633 | 2.8 | 90978 | 69.9 |
| | Total | 124478 | 95.7 | 5652 | 4.3 | 130130 | 100.0 |

[1]Rate per 100 live births.
Odds of Preeclampsia White Mothers Age 25 to 35 vs <25 Years = 0.960 (95% CI, 0.933-0.988).
Odds of Preeclampsia Black Mothers Age 25 to 35 vs <25 Years = 0.765 (95% CI, 0.724-0.809).
Odds of Preeclampsia All Mothers Age 25 to 35 vs <25 Years =0.883 (95% CI, 0.861-0.905).

Older mothers (< 35 years) accounted for 7.7% of births. Table 5.6 shows the differences in preeclampsia for older mothers compared to middle-aged mothers (25-35 years). Older mothers were significantly more likely to be diagnosed with preeclampsia compared to middle-aged mothers (OR=1.262, 95% CI 1.218-1.307). Older black mothers were at higher odds of preeclampsia (OR=1.548, 95% CI 1.421-1.687) compared to older white mothers (OR=1.213, 95% CI 1.167-1.262).

Table 5.6 Preeclampsia Incidence[1] by Race for Mothers Age >35 Years in Michigan 2008-2015

| Race-Ethnicity and Ages | | Preeclampsia | | | | | |
|---|---|---|---|---|---|---|---|
| | | None | | Yes | | Total | |
| | | No. | (%) | No. | (%) | No. | (%) |
| White | 25 to 35 | 306464 | 81.9 | 16700 | 4.5 | 323164 | 86.3 |
| | >35 | 47953 | 12.8 | 3170 | 0.8 | 51123 | 13.7 |
| | Total | 354417 | 94.7 | 19870 | 5.3 | 374287 | 100.0 |
| Black | 25 to 35 | 53467 | 80.8 | 2642 | 4.0 | 56109 | 84.8 |
| | >35 | 9319 | 14.1 | 713 | 1.1 | 10032 | 15.2 |
| | Total | 62786 | 94.9 | 3355 | 5.1 | 66141 | 100.0 |

[1] Rate per 100 live births.
Odds of Preeclampsia White Mothers Age 25 to 35 vs >35 Years = 1.213 (95% CI, 1.167-1.262).
Odds of Preeclampsia Black Mothers Age 25 to 35 vs >35 Years = 1.548 (95% CI, 1.421-1.687).
Odds of Preeclampsia All Mothers Age 25 to 35 vs >35 Years = 1.262 (95% CI, 1.218-1.307).

In summary, white mothers had a higher incidence of preeclampsia (5.2) compared to black mothers (4.3) but this difference can be explained by age. Young white mothers had a higher incidence of preeclampsia (3.4) compared to young black mothers (2.8) with young mothers of both races protective compared to middle-aged mothers. In contrast, older black mothers had a higher incidence of preeclampsia (1.1) compared to older white mothers (0.8) with older mothers of both races at increased odds of preeclampsia compared to middle-aged mothers. Black mothers > 35 years had the highest odds of preeclampsia (OR=1.548, 95% CI 1.421-1.687).

Overall, 46.2% of mother's had a pre-pregnancy weight that was normal with 26.0% of mothers overweight and 24.3% of mothers obese. Table 5.7 shows the differences in preeclampsia by age group with 47.6% of young mothers of normal pre-pregnancy weight compared to 46.0% of middle-aged mothers and 42.3% of older mothers. Young white and black mothers had the highest rates of 'underweight' with decreasing 'underweight' status with age. For both white and black mother's being overweight or obese increased with age. Middle-aged black mothers compared to middle-aged white mothers had substantially higher rates of overweight (29.3 vs. 26.1) and obesity (37.9 vs. 22.6) RR =1.67. The disparities were similar for older black mothers compared to older white mothers (41.6 vs. 25.2) RR=1.65.

Table 5.7 Preeclampsia Incidence[1] by Race and Mother's Pre-Pregnancy Body Mass Index (BMI) in Michigan 2008-2015

| **Race-Ethnicity by Age and BMI Status** | | **Preeclampsia** | | | | | |
|---|---|---|---|---|---|---|---|
| | | <24 Years | | 25-35 Years | | >35 Years | |
| | | No. | Rate | No. | Rate | No. | Rate |
| **White** | Under | 7772 | 5.8 | 8559 | 2.8 | 908 | 1.9 |
| | Normal | 65087 | 48.9 | 147953 | 48.5 | 21512 | 45.4 |
| | Over | 31738 | 23.9 | 79655 | 26.1 | 13022 | 27.5 |
| | Obese | 28455 | 21.4 | 68846 | 22.6 | 11917 | 25.2 |
| | Sub-Total | 133052 | 100.0 | 305013 | 100.0 | 100 | 100.0 |
| **Black** | Under | 3162 | 5.0 | 1133 | 2.3 | 110 | 1.3 |
| | Normal | 28386 | 44.8 | 15033 | 30.5 | 2187 | 25.2 |
| | Over | 16167 | 25.5 | 14474 | 29.3 | 2775 | 31.9 |
| | Obese | 15591 | 24.6 | 18723 | 37.9 | 3620 | 41.6 |
| | Sub-Total | 63306 | 100.0 | 49363 | 100.0 | 8692 | 100.0 |
| **Total** | Under | 10934 | 5.6 | 9692 | 2.7 | 1018 | 1.8 |
| | Normal | 93473 | 47.6 | 162986 | 46.0 | 23699 | 42.3 |
| | Over | 47905 | 24.4 | 94129 | 26.6 | 15797 | 28.2 |
| | Obese | 44046 | 22.4 | 87569 | 24.7 | 15537 | 27.7 |
| | Sub-Total | 196358 | 100.0 | 35476 | 100.0 | 56051 | 100.0 |

Table 5.8 shows the overall prevalence of chronic diabetes is lower (0.7) compared to gestational diabetes (4.6) but the odds of preeclampsia are substantially elevated for mothers with either reported condition (chronic diabetes, OR=2.652) and (gestational diabetes, OR=2.514).

Table 5.8 Preeclampsia Incidence[1] by Pre-Pregnancy and Gestational Diabetes of Mothers in Michigan 2008-2015

| | | | **Preeclampsia** | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | No | | Yes | | Total | |
| | | | No. | Rate | No. | Rate | No. | Rate |
| **Gestational Diabetes** | White | No | 464103 | 90.4 | 23991 | 4.7 | 488094 | 95.1 |
| | | Yes | 22541 | 4.4 | 2795 | 0.5 | 25336 | 4.9 |
| | | Total | 486644 | 94.8 | 26786 | 5.2 | 513430 | 100.0 |
| | Black | No | 125619 | 92.5 | 5338 | 3.9 | 130957 | 96.5 |
| | | Yes | 4263 | 3.1 | 556 | 0.4 | 4819 | 3.5 |
| | | Total | 129882 | 95.7 | 5894 | 4.3 | 135776 | 100.0 |
| | Total | No | 589722 | 90.8 | 29329 | 4.5 | 619051 | 95.4 |
| | | Yes | 26804 | 4.1 | 3351 | 0.5 | 30155 | 4.6 |
| | | Total | 616526 | 95.0 | 32680 | 5.0 | 649206 | 100.0 |
| **Chronic Diabetes** | White | No | 483823 | 94.2 | 26371 | 5.1 | 510194 | 99.4 |
| | | Yes | 2821 | 0.5 | 415 | 0.1 | 3236 | 0.6 |
| | | Total | 486644 | 94.8 | 26786 | 5.2 | 513430 | 100.0 |
| | Black | No | 128665 | 94.8 | 5753 | 4.2 | 134418 | 99.0 |
| | | Yes | 1217 | 0.9 | 141 | 0.1 | 1358 | 1.0 |
| | | Total | 129882 | 95.7 | 5894 | 4.3 | 135776 | 100.0 |
| | Total | No | 612488 | 94.3 | 32124 | 4.9 | 644612 | 99.3 |
| | | Yes | 4038 | 0.6 | 556 | 0.1 | 4594 | 0.7 |
| | | Total | 616526 | 95.0 | 32680 | 5.0 | 649206 | 100.0 |

[1] Rate per 100 live births.

Odds of Preeclampsia for White Mothers Gestational Diabetes = 2.399 (95% CI, 2.301-2.500).
Odds of Preeclampsia for Black Mothers Gestational Diabetes =3 .069 (95% CI, 2.798-3.367).
Odds of Preeclampsia for All Mothers Gestational Diabetes = 2.514 (95% CI, 2.421-2.611).
Odds of Preeclampsia for White Mothers Chronic Diabetes = 2.699 (95% CI, 2.433-2.994).
Odds of Preeclampsia for Black Mothers Chronic Diabetes = 2.591 (95% CI, 2.172-3.091).
Odds of Preeclampsia for All Mothers Chronic Diabetes = 2.625 (95% CI, 2.401-2.871).

The odds of preeclampsia for mothers with chronic diabetes is slightly higher for white mothers (OR=2.699, 95% CI 2.433-2.994) compared to black mothers (OR=2.591, 95% CI 2.172-3.091); however, black mothers with gestational diabetes are at considerably higher odds of preeclampsia (OR=3.069, 95% CI 2.798-3.367) compared to white mothers with gestational diabetes (OR=2.399, 95% CI 2.301-2.500).

Furthermore, fewer mothers received Medicaid (Table 5.9) compared to other payment types and the percentage of mothers not on Medicaid diagnosed with preeclampsia was slightly higher compared to those on Medicaid (3.0 vs. 2.0). When not stratified by race, Medicaid was protective of preeclampsia (OR=0.873, 95% CI 0.853-0.893). However, when stratified, Medicaid increases the odds of preeclampsia by 1.154; Medicaid remains protective for whites.

Table 5.9 Preeclampsia Incidence[1] by Race and Mother's Payment Method in Michigan 2008-2015

| | | | **Preeclampsia** | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | No | | Yes | | Total | |
| | | | No. | Rate | No. | Rate | No. | Rate |
| **Medicaid** | **White[1]** | All Others | 297208 | 58.2 | 17455 | 3.4 | 314663 | 61.6 |
| | | Medicaid | 186661 | 36.6 | 9227 | 1.8 | 195888 | 38.4 |
| | | Total | 483869 | 94.8 | 26682 | 5.2 | 510551 | 100.0 |
| | **Black[2]** | All Others | 52537 | 38.8 | 2182 | 1.6 | 54719 | 40.4 |
| | | Medicaid | 76948 | 56.8 | 3689 | 2.7 | 80637 | 59.6 |
| | | Total | 129485 | 95.7 | 5871 | 4.3 | 135356 | 100.0 |
| | **Total[3]** | All Others | 349745 | 54.1 | 19637 | 3.0 | 369382 | 57.2 |
| | | Medicaid | 263609 | 40.8 | 12916 | 2.0 | 276525 | 42.8 |
| | | Total | 613354 | 95.0 | 32553 | 5.0 | 645907 | 100.0 |

[1] Rate per 100 live births.
Odds of Preeclampsia for White Mothers Medicaid = 0.842 (95% CI, 0.820-0.864).
Odds of Preeclampsia for Black Mothers Medicaid = 1.154 (95% CI, 1.094-1.218).
Odds of Preeclampsia for All Mothers Medicaid v= 0.873 (95% CI, 0.853-0.893).

The percentages of mothers receiving WIC were lower for mothers diagnosed with preeclampsia compared to mothers who did not receive WIC (Table 5.10). Receiving WIC services was protective of preeclampsia for both races (OR=0.843, 95% CI 0.824-0.863).

Table 5.10 Preeclampsia Incidence[1] by Mother's Participation in WIC[2] in Michigan 2005-2015

| | | | **Preeclampsia** | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | No | | Yes | | Total | |
| | | | No. | Rate | No. | Rate | No. | Rate |
| **WIC** | **White** | No | 296819 | 59.3 | 17053 | 3.4 | 313872 | 62.7 |
| | | Yes | 177890 | 35.5 | 9142 | 1.8 | 187032 | 37.3 |
| | | Total | 474709 | 94.8 | 26195 | 5.2 | 500904 | 100.0 |
| | **Black** | No | 37133 | 28.5 | 2019 | 1.6 | 39152 | 30.1 |
| | | Yes | 87345 | 67.1 | 3633 | 2.8 | 90978 | 69.9 |
| | | Total | 124478 | 95.7 | 5652 | 4.3 | 130130 | 100.0 |
| | **Total** | No | 333952 | 52.9 | 19072 | 3.0 | 353024 | 55.9 |
| | | Yes | 265235 | 42.0 | 12775 | 2.0 | 278010 | 44.1 |
| | | Total | 599187 | 95.0 | 31847 | 5.0 | 631034 | 100.0 |

[1] Rate per 100 live births.
[2]WIC = Women, Infants and Children.
Odds of Preeclampsia for WIC (No/Yes) = 0.843 (95% CI, 0.824-0.863).

In summary, the descriptive findings from this study support the previous literature on risk factors for preeclampsia—specifically older age, being overweight or obese and having chronic or gestational diabetes. These risk factors also vary by race with black mothers on Medicaid at increased odds of preeclampsia (OR=1.154, 95% CI 1.094-1.218) compared to white mothers also on Medicaid who were protective of preeclampsia (OR=0.842, 95% CI 0.820-0.864). These maternal characteristics are thereby, further investigated for their correlation with preeclampsia and the three UV-B exposure time periods using the Pearson' correlation coefficient (r) for continuous and point-biserial correlation ($r_{pb}$) for dichotomous variables (Table 5.11).

Table 5.11 Correlation Matrix of Dependent and Independent Variables.

| Correlations | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Preeclampsia | T1_KJ | T2_KJ | T3_KJ | Black | Age | BMI | Medicaid | WIC | Chronic Diabetes | Gestational Diabetes | Urban | Poverty |
| Preeclampsia | Pearson | 1 | .021** | .010** | .020** | .004** | -.018** | -.015** | .010** | .014** | 0.002 | 0.001 | .003** | .007** |
| | N | 654121 | 654121 | 654121 | 654121 | 654121 | 654063 | 606841 | 650725 | 635801 | 649423 | 649423 | 654121 | 653960 |
| T1_KJ | Pearson | .021** | 1 | -.717** | .085** | -.017** | .008** | -.006** | -.019** | -.026** | -.002* | -.004** | .008** | -.014** |
| | N | 654121 | 654121 | 654121 | 654121 | 654121 | 654063 | 606841 | 650725 | 635801 | 649423 | 649423 | 654121 | 653960 |
| T2_KJ | Pearson | .010** | -.717** | 1 | -.723** | .026** | -.011** | 0.000 | .014** | .013** | 0.001 | 0.000 | .017** | .020** |
| | N | 654121 | 654121 | 654121 | 654121 | 654121 | 654063 | 606841 | 650725 | 635801 | 649423 | 649423 | 654121 | 653960 |
| T3_KJ | Pearson | .020** | .085** | -.723** | 1 | -.006** | .009** | .005** | -.008** | 0.001 | 0.000 | .005** | .009** | -.005** |
| | N | 654121 | 654121 | 654121 | 654121 | 654121 | 654063 | 606841 | 650725 | 635801 | 649423 | 649423 | 654121 | 653960 |
| Black | Pearson | .004** | -.017** | .026** | -.006** | 1 | -.193** | .092** | .174** | .265** | .018** | -.027** | .255** | .528** |
| | N | 654121 | 654121 | 654121 | 654121 | 654121 | 654063 | 606841 | 650725 | 635801 | 649423 | 649423 | 654121 | 653960 |
| Age | Pearson | -.018** | .008** | -.011** | .009** | -.193** | 1 | .076** | -.335** | -.376** | .037** | .093** | .008** | -.229** |
| | N | 654063 | 654063 | 654063 | 654063 | 654063 | 654063 | 606785 | 650668 | 635744 | 649366 | 649366 | 654063 | 653902 |
| BMI | Pearson | -.015** | -.006** | 0.000 | .005** | .092** | .076** | 1 | .049** | .086** | .055** | .116** | -.009** | .078** |
| | N | 606841 | 606841 | 606841 | 606841 | 606841 | 606785 | 606841 | 605321 | 597296 | 602498 | 602498 | 606841 | 606707 |
| Medicaid | Pearson | .010** | -.019** | .014** | -.008** | .174** | -.335** | .049** | 1 | .577** | .007** | -.005** | .006** | .246** |
| | N | 650725 | 650725 | 650725 | 650725 | 650725 | 650668 | 605321 | 650725 | 634253 | 646096 | 646096 | 650725 | 650564 |
| WIC | Pearson | .014** | -.026** | .013** | 0.001 | .265** | -.376** | .086** | .577** | 1 | .012** | -.007** | .006** | .309** |
| | N | 635801 | 635801 | 635801 | 635801 | 635801 | 635744 | 597296 | 634253 | 635801 | 631242 | 631242 | 635801 | 635652 |
| Chronic Diabetes | Pearson | 0.002 | -.002* | 0.001 | 0.000 | .018** | .037** | .055** | .007** | .012** | 1 | -.019** | .004** | .015** |
| | N | 649423 | 649423 | 649423 | 649423 | 649423 | 649366 | 602498 | 646096 | 631242 | 649423 | 649423 | 649423 | 649262 |
| Gestational Diabetes | Pearson | 0.001 | -.004** | 0.000 | .005** | -.027** | .093** | .116** | -.005** | -.007** | -.019** | 1 | -.004** | -.016** |
| | N | 649423 | 649423 | 649423 | 649423 | 649423 | 649366 | 602498 | 646096 | 631242 | 649423 | 649423 | 649423 | 649262 |
| Urban | Pearson | .003** | .008** | .017** | .009** | .255** | .008** | -.009** | .006** | .006** | .004** | -.004** | 1 | .365** |
| | N | 654121 | 654121 | 654121 | 654121 | 654121 | 654063 | 606841 | 650725 | 635801 | 649423 | 649423 | 654121 | 653960 |
| Poverty | Pearson | .007** | -.014** | .020** | -.005** | .528** | -.229** | .078** | .246** | .309** | .015** | -.016** | .365** | 1 |
| | N | 653960 | 653960 | 653960 | 653960 | 653960 | 653902 | 606707 | 650564 | 635652 | 649262 | 649262 | 653960 | 653960 |
| **. Correlation is significant at the 0.01 level (2-tailed). | | | | | | | | | | | | | | |
| *. Correlation is significant at the 0.05 level (2-tailed). | | | | | | | | | | | | | | |

The correlation matrix shows positive and significant correlation between preeclampsia and the three UV-B time period exposures, black race, Medicaid and WIC recipients, chronic and gestational diabetes and urban residence and poverty. A negative and significant correlation was found for preeclampsia and mother's age and BMI. The most highly positive correlations were between the variables Medicaid and WIC ($r_{pb}$ =0.577, p-value < 0.01) and being black and poverty ($r$ =0.528, p-value < 0.01). Therefore, mothers receiving Medicaid were also likely to receive WIC and black mothers were more likely than white mothers to reside in poverty. The most highly negative correlations were between the variables age and WIC ($r$ =-0.376, p-value < 0.01) and age and Medicaid ($r$ =-0.335, p-value < 0.01). Therefore, with increasing age mothers appeared to be less likely to receive Medicaid or WIC.

## 5.2 Multilevel Analysis

### 5.2.1 Variance Components Model

The results of the Variance Components model (Table 5.12) showed significant variation in the incidence of preeclampsia across census tracts in Michigan; the random intercept was 0.1266, with a corresponding standard error of 0.006087, indicating there was significant variation in preeclampsia across census tracts.

Table 5.12 Variance Components Model

| **Fixed Effects** | | | | | | |
|---|---|---|---|---|---|---|
| | Estimate | Standard | t Value | P > \|t\| | Lower | Upper |
| Intercept | 2.97 | 0.009142 | 324.85 | <.0001 | 2.952 | 2.9879 |
| **Random Effects** | | | | | | |
| | Variance | | se | Z Value | P> Z | |
| Intercept | 0.1266 | | 0.006087 | 20.8 | <.0001 | |
| Residual | 0.9578 | | 0.001684 | 568.58 | <.0001 | |

### 5.2.2 Random Coefficients Model

Table 5.13 shows the results from the Random Coefficients Model. In this model, maternal exposure during T3_KJ (OR=0.937, 95% CI 0.903-0.973) and T1_KJ (OR=0.946, 95% CI 0.912-0.982) were protective of preeclampsia, controlling for black race and the variation in preeclampsia across census tracts. Interestingly, maternal exposure during T2_KJ was not significant for preeclampsia. Black mothers were at lower odds of preeclampsia (OR=0.897, 95% CI 0.866-0.928) comapred to white mothers, controlling for maternal UV-B exposure and variation in preeclampsia across census tracts. Black race explained a small portion of the unexplained variation in preeclampsia (random intercept decreased drom 0.1266 to 0.1239).

Table 5.13 Random Coefficients Model

| **Fixed Effects** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Effect | Estimate | se | t Value | p-value | OR | Lower | Upper |
| Intercept | -2.6231 | 0.1330 | -19.72 | <.0001 | 0.073 | 0.056 | 0.094 |
| T1_KJ | -0.0551 | 0.0188 | -2.92 | 0.0035 | 0.946 | 0.912 | 0.982 |
| T2_KJ | -0.0342 | 0.0274 | -1.25 | 0.2124 | 0.966 | 0.916 | 1.020 |
| T3_KJ | -0.0649 | 0.0190 | -3.42 | 0.0006 | 0.937 | 0.903 | 0.973 |
| MBlack | -0.1091 | 0.0177 | -6.16 | <.0001 | 0.897 | 0.866 | 0.928 |
| **Random Effects** | | | | | | | |
| Random Effects | Variance | | se | | Z Value | | P > Z |
| Intercept | 0.1239 | | 0.006136 | | 20.19 | | <.0001 |
| Residual | 0.9575 | | 0.00171 | | 559.84 | | <.0001 |

Other individual-level predictors of preeclampsia were added to the model as control variables to further assess the effect(s) of maternal UV-B exposure on preeclampsia (Table 5.14). Controlling for BMI, Medicaid, WIC and chronic and gestational diabetes, T3_KJ provided slightly more protection (OR=0.933 [decreased from 0.937]) and T1_KJ also remained significantly protective of preeclampsia. Furthermore, the protection acquired for black mothers increased (OR=.850 [decreased from 0.897]). Those risk factors that increased the odds of

preeclampsia were increasing BMI and chronic and gestational diabetes. Medicaid and WIC operated similarly as protective of preeclampsia. This model containing the important individual-level variables also reduced the unexplained variation in preeclampsia intercepts across census tracts (from 0.1239 to 0.1195) and Level-1 residuals (0.9757 to 0.9531) (Table 5.14).

Table 5.14 Random Coefficients Model Adding Individual Level Predictors

| **Fixed Effects** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Effect | Estimate | se | t Value | p-value | OR | Lower | Upper |
| Intercept | -4.5805 | 0.1425 | -32.15 | <.0001 | 0.010 | 0.008 | 0.014 |
| T1_KJ | -0.0487 | 0.0198 | -2.46 | 0.0139 | 0.952 | 0.916 | 0.990 |
| T2_KJ | -0.0317 | 0.0288 | -1.1 | 0.2706 | 0.969 | 0.916 | 1.025 |
| T3_KJ | -0.0689 | 0.0199 | -3.45 | 0.0006 | 0.933 | 0.898 | 0.971 |
| MBlack | -0.1625 | 0.0192 | -8.45 | <.0001 | 0.850 | 0.819 | 0.883 |
| BMI | 0.0716 | 0.0009 | 74.12 | <.0001 | 1.074 | 1.072 | 1.076 |
| Medicaid | -0.0795 | 0.0155 | -5.13 | <.0001 | 0.924 | 0.896 | 0.952 |
| WIC | -0.1644 | 0.0158 | -10.41 | <.0001 | 0.848 | 0.823 | 0.875 |
| Chr_Diab | 0.8202 | 0.0524 | 15.64 | <.0001 | 2.271 | 2.049 | 2.517 |
| Gest_Diab | 0.6092 | 0.0215 | 28.31 | <.0001 | 1.839 | 1.763 | 1.918 |
| **Random Effects** | | | | | | | |
| | Variance | | se | | Z Value | | P > Z |
| Intercept | 0.1195 | | 0.006303 | | 18.95 | | <.0001 |
| Residual | 0.9531 | | 0.001757 | | 542.6 | | <.0001 |

Importantly, when the interaction of Black*BMI was controlled for tin the model (Table 5.15), the odds of preeclampsia for black mothers changed from being protective to a substantial increase in odds of preeclampsia (OR=2.045, 95% CI 1.765-2.369) while the effect of BMI remained relatively the same (for every unit increase in BMI preeclampisa increased by +0.0768 units). These findings suggests that BMI explained a substantial portion of black protection and black race independent of BMI was a highly significant risk factor for preeclampsia. This interaction term also reduced the unexplained Level-1 residuals in preeclampsia (from 0.9531 to 0.9495).

Table 5.15 Random Coefficients Model (Adding Individual Predictors and Interaction Term)

| **Fixed Effects** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Effect | Estimate | se | t Value | p-value | OR | Lower | Upper |
| Intercept | -4.7344 | 0.1429 | -33.12 | <.0001 | 0.009 | 0.007 | 0.012 |
| T1_KJ | -0.0478 | 0.0198 | -2.41 | 0.0158 | 0.953 | 0.917 | 0.991 |
| T2_KJ | -0.0308 | 0.0288 | -1.07 | 0.2843 | 0.970 | 0.917 | 1.026 |
| T3_KJ | -0.0683 | 0.0199 | -3.43 | 0.0006 | 0.934 | 0.898 | 0.971 |
| MBlack | 0.7152 | 0.0751 | 9.53 | <.0001 | 2.045 | 1.765 | 2.369 |
| BMI | 0.0769 | 0.0011 | 72.65 | <.0001 | 1.080 | 1.078 | 1.082 |
| Medicaid | -0.0816 | 0.0155 | -5.27 | <.0001 | 0.922 | 0.894 | 0.950 |
| WIC | -0.1678 | 0.0158 | -10.66 | <.0001 | 0.846 | 0.820 | 0.872 |
| Chro_Diab | 0.8262 | 0.0524 | 15.77 | <.0001 | 2.285 | 2.062 | 2.532 |
| Gest_Diab | 0.6028 | 0.0215 | 28.02 | <.0001 | 1.827 | 1.752 | 1.906 |
| MBlack*BMI | -0.0298 | 0.0025 | -11.94 | <.0001 | 0.971 | 0.966 | 0.975 |
| **Random Effects** | | | | | | | |
| | Variance | | se | | Z Value | | P > Z |
| Intercept | 0.1203 | | 0.006326 | | 19.02 | | <.0001 |
| Residual | 0.9495 | | 0.00175 | | 542.59 | | <.0001 |

### 5.2.3 Predictor for Intercepts- and Slopes-as-Outcomes Models

In Table 5.16, the census tract predictors are added to a model. The odds of T1_KJ decreased slightly (OR=0.953 to 0.945) followed by T3_KJ (OR=0.934 to 0.925) and T2_KJ remained non-significant for preeclampsia. Living in urban areas had a slightly higher odds (OR=1.125) of preeclampisa compared to some protection gained from living in poverty (OR=0.987) an anomaly finding that is further discussed below. Black mothers continued to have a high odds of preeclampsia (OR=2.302, 95% CI 1.984-2.670) compared to white mothers, controlling for potential confounders at the individual and contextual-levels.

Table 5.16 Intercepts- and Slopes-as-Outcomes Model (Combined Model)

| **Fixed Effects** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Effect | Estimate | se | t Value | p-value | OR | Lower | Upper |
| Intercept | -4.6345 | 0.1426 | -32.51 | <.0001 | 0.010 | 0.007 | 0.013 |
| T1_KJ | -0.0567 | 0.0198 | -2.87 | 0.0041 | 0.945 | 0.909 | 0.982 |
| T2_KJ | -0.0439 | 0.0287 | -1.53 | 0.1269 | 0.957 | 0.904 | 1.013 |
| T3_KJ | -0.0775 | 0.0199 | -3.88 | 0.0001 | 0.925 | 0.890 | 0.962 |
| Urban | 0.1176 | 0.0223 | 5.26 | <.0001 | 1.125 | 1.077 | 1.175 |
| Poverty | -0.0128 | 0.0008 | -16.15 | <.0001 | 0.987 | 0.986 | 0.989 |
| MBlack | 0.8336 | 0.0756 | 11.02 | <.0001 | 2.302 | 1.984 | 2.670 |
| BMI | 0.0775 | 0.0010 | 73.16 | <.0001 | 1.081 | 1.078 | 1.083 |
| Medicaid | -0.0645 | 0.0155 | -4.15 | <.0001 | 0.938 | 0.909 | 0.967 |
| WIC | -0.1367 | 0.0159 | -8.59 | <.0001 | 0.872 | 0.845 | 0.900 |
| Chr_Diab | 0.8302 | 0.0524 | 15.83 | <.0001 | 2.294 | 2.070 | 2.542 |
| Gest_Diab | 0.6001 | 0.0215 | 27.87 | <.0001 | 1.822 | 1.747 | 1.901 |
| MBlack*BMI | -0.0304 | 0.0025 | -12.16 | <.0001 | 0.970 | 0.965 | 0.975 |

| **Random Effects** | | | | |
|---|---|---|---|---|
| | Variation | se | Z Value | P > Z |
| Intercept | 0.1077 | 0.005808 | 18.54 | <.0001 |
| Residual | 0.9514 | 0.001753 | 542.6 | <.0001 |

When the T1, T2, T3*URBAN interaction terms were added to the model the protective effects of T1 and T3 became slightly stronger suggesting that living in urban areas has an influence on the maginitude of UV-B received during these two time periods. Importantly, the odds of preeclampisa for black mothers becomes non-signficiant. UV-B exposure in urban areas and its attenuation of the race effect on preeclampsia requires futher investigation and may in part be explained using the race-stratified models below.

Table 5.17 Intercepts- and Slopes-as-Outcomes Model (Adding Cross-Level Interaction Term)

| **Fixed Effects** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Effect | Estimate | se | t Value | p-value | OR | Lower | Upper |
| Intercept | -4.5962 | 0.1527 | -30.1 | <.0001 | 0.010 | 0.007 | 0.014 |
| T1_KJ | -0.0627 | 0.0213 | -2.94 | 0.0033 | 0.939 | 0.901 | 0.979 |
| T2_KJ | -0.0516 | 0.0310 | -1.67 | 0.0959 | 0.950 | 0.894 | 1.009 |
| T3_KJ | -0.0827 | 0.0215 | -3.85 | 0.0001 | 0.921 | 0.883 | 0.960 |
| Urban | 0.1182 | 0.0224 | 5.29 | <.0001 | 1.125 | 1.077 | 1.176 |
| Poverty | -0.0129 | 0.0008 | -16.15 | <.0001 | 0.987 | 0.986 | 0.989 |
| MBlack | 0.5576 | 0.4040 | 1.38 | 0.1675 | 1.746 | 0.791 | 3.855 |
| BMI | 0.0775 | 0.0011 | 73.16 | <.0001 | 1.081 | 1.078 | 1.083 |
| WIC | -0.0645 | 0.0156 | -4.14 | <.0001 | 0.938 | 0.909 | 0.967 |
| Medicaid | -0.1369 | 0.0159 | -8.59 | <.0001 | 0.872 | 0.845 | 0.900 |
| Diab-Chronic | 0.8300 | 0.0525 | 15.82 | <.0001 | 2.293 | 2.069 | 2.542 |
| Diab-Gestation | 0.6001 | 0.0215 | 27.87 | <.0001 | 1.822 | 1.747 | 1.901 |
| BMI*MBlack | -0.0304 | 0.0025 | -12.16 | <.0001 | 0.970 | 0.965 | 0.975 |
| T1_KJ*Urban | 0.0410 | 0.0559 | 0.73 | 0.4633 | 1.042 | 0.934 | 1.163 |
| T2_KJ*Urban | 0.0548 | 0.0814 | 0.67 | 0.5009 | 1.056 | 0.901 | 1.239 |
| T3_KJ*Urban | 0.0369 | 0.0564 | 0.65 | 0.5125 | 1.038 | 0.929 | 1.159 |

| **Random Effects** | | | | |
|---|---|---|---|---|
| | Estimate | se | Z Value | P > Z |
| Intercept | 0.1077 | 0.005809 | 18.54 | <.0001 |
| Residual | 0.9514 | 0.001753 | 542.6 | <.0001 |

Table 5.18 Stratified Variables to Predict the Odds of Preeclampsia

| **Odds Ratio Estimates** | | | |
|---|---|---|---|
| Comparison | OR | 95% Confidence Limits | |
| unit change of T1_KJ from mean | 0.945 | 0.909 | 0.982 |
| unit change of T2_KJ from mean | 0.957 | 0.905 | 1.013 |
| unit change of T3_KJ from mean | 0.925 | 0.890 | 0.962 |
| unit change of Poverty from mean | 0.987 | 0.986 | 0.989 |
| Urban vs Rural at mean | 1.125 | 1.077 | 1.175 |
| Black vs White at mean | 1.187 | 1.125 | 1.253 |
| unit change of BMI from mean for Black | 1.048 | 1.044 | 1.053 |
| unit change of BMI from mean for White | 1.081 | 1.078 | 1.083 |
| Medicaid vs non-Medicaid at mean | 0.938 | 0.909 | 0.967 |
| WIC yes vs no at mean | 0.872 | 0.845 | 0.900 |
| Chr_Diab yes vs no at mean | 2.294 | 2.070 | 2.542 |
| Diab_Gest yes vs no at mean | 1.822 | 1.747 | 1.901 |

Finally, when race-stratified models are estimated maternal UV-B exposure for black mothers at the three time periods is not significant (Table 5.18). There is also a substantial decrease in the unexplained Level-1 variation in preeclampsia. However, for white mothers maternal UV-B exposure is significantly protective (Table 5.19). Importantly for black mothers on Medicaid the odds or preeclampsia increases (OR=1.256) and for white mothers on Medicaid the odds of preeclampsia decreases (OR=0.845) a finding in the random coefficients model that is also shown here. Both black and white mothers receive protection from being a recipient of WIC with black mothers benefiting more than white mothers (OR=0.760 vs. 0.936). With increasing BMI the odds of preeclampsia slightly increases for both black and white mothers. Black mothers have a higher odds of gestational diabetes compared to white mothers (OR=2.510 vs. 1.725) and white mothers have a higher odds of chronic diabetes compared to black mothers (OR=2.309 vs. 2.284). These findings demonstrate that maternal UV-B exposure during T3 and T1 is protective for white mothers; however, black mothers do not receive that same protection controlling for known risk factors for preeclampsia.

Table 5.19 Race-Stratified by Black Mothers

| Fixed Effects | | | | | | | |
|---|---|---|---|---|---|---|---|
| Effect | Estimate | se | t Value | p-value | OR | Lower | Upper |
| Intercept | -4.2387 | 0.3993 | -10.62 | <.0001 | 0.014 | 0.007 | 0.032 |
| T1_KJ | -0.02428 | 0.05142 | -0.47 | 0.6368 | 0.976 | 0.882 | 1.080 |
| T2_KJ | -0.00096 | 0.0749 | -0.01 | 0.9898 | 0.999 | 0.863 | 1.157 |
| T3_KJ | -0.04661 | 0.05189 | -0.9 | 0.369 | 0.954 | 0.862 | 1.057 |
| Urban | 0.2809 | 0.1422 | 1.98 | 0.0482 | 1.324 | 1.002 | 1.750 |
| Poverty | -0.01411 | 0.0012 | -11.77 | <.0001 | 0.986 | 0.984 | 0.988 |
| BMI | 0.046 | 0.00227 | 20.27 | <.0001 | 1.047 | 1.042 | 1.052 |
| Medicaid | 0.2279 | 0.03239 | 7.04 | <.0001 | 1.256 | 1.179 | 1.338 |
| WIC | -0.2741 | 0.03212 | -8.53 | <.0001 | 0.760 | 0.714 | 0.810 |
| Chr_Diab | 0.8258 | 0.1122 | 7.36 | <.0001 | 2.284 | 1.833 | 2.845 |
| Gest_Diab | 0.9201 | 0.05286 | 17.41 | <.0001 | 2.510 | 2.263 | 2.783 |

| Random Effects | | | | |
|---|---|---|---|---|
| | Variation | se | Z Value | P > Z |
| Intercept | 0.1452 | 0.01702 | 8.53 | <.0001 |
| Residual | 0.9212 | 0.003833 | 240.32 | <.0001 |

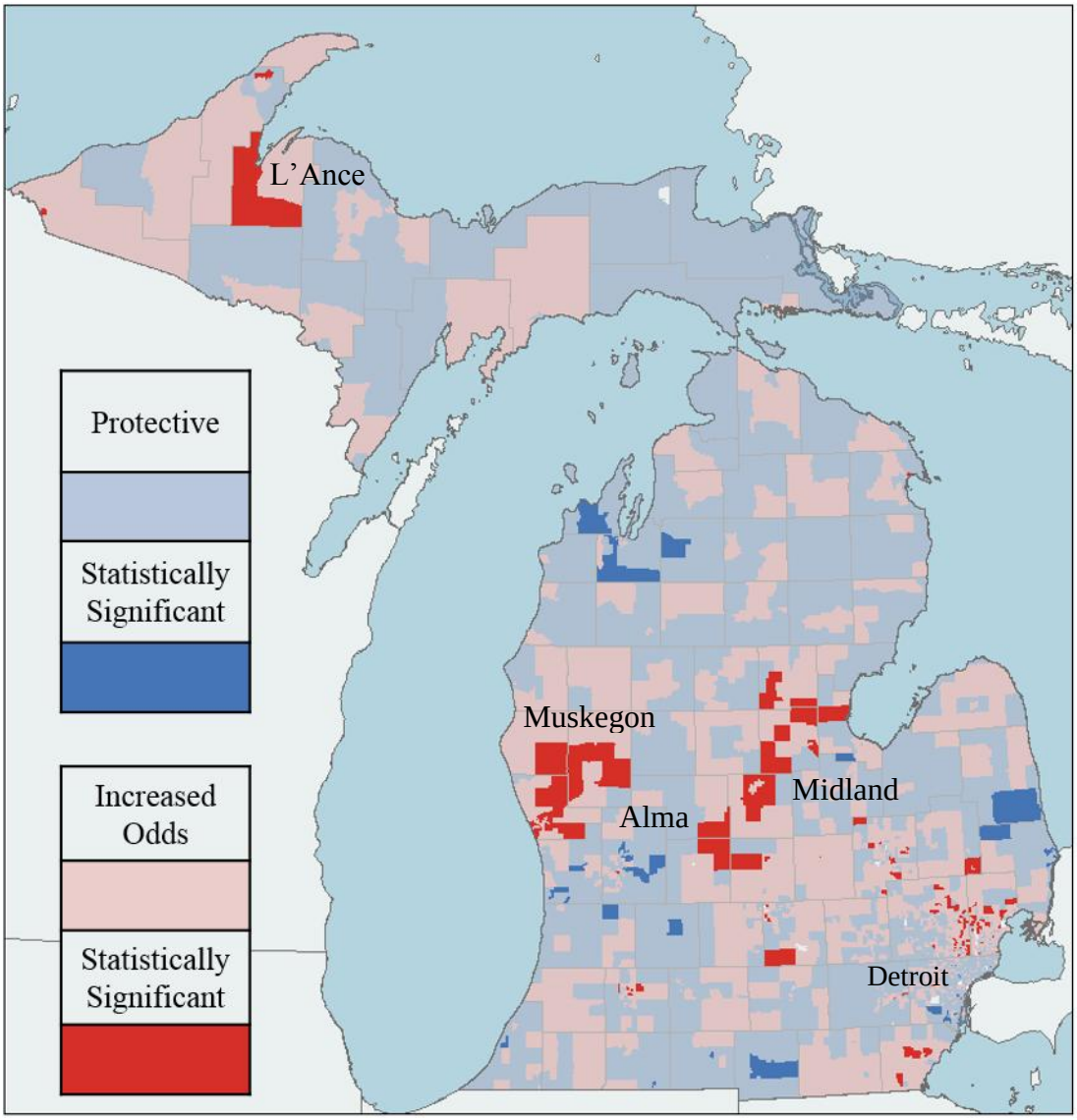
Table 5.20 Race-Stratified by White Mothers

| Fixed Effects | | | | | | | |
|---|---|---|---|---|---|---|---|
| Effect | Estimate | se | t Value | p-value | OR | Lower | Upper |
| Intercept | -4.6370 | 0.1533 | -30.26 | <.0001 | 0.010 | 0.007 | 0.013 |
| T1_KJ | -0.0587 | 0.0214 | -2.75 | 0.006 | 0.943 | 0.904 | 0.983 |
| T2_KJ | -0.0454 | 0.0310 | -1.46 | 0.1434 | 0.956 | 0.899 | 1.016 |
| T3_KJ | -0.0785 | 0.0215 | -3.64 | 0.0003 | 0.924 | 0.886 | 0.964 |
| Urban | 0.1225 | 0.0227 | 5.38 | <.0001 | 1.130 | 1.081 | 1.182 |
| Poverty | -0.0101 | 0.0010 | -10 | <.0001 | 0.990 | 0.988 | 0.992 |
| BMI | 0.0776 | 0.0010 | 73.12 | <.0001 | 1.081 | 1.079 | 1.083 |
| Medicaid | -0.1684 | 0.0181 | -9.26 | <.0001 | 0.845 | 0.815 | 0.876 |
| WIC | -0.0660 | 0.0184 | -3.59 | 0.0003 | 0.936 | 0.903 | 0.971 |
| Chro_Diab | 0.8368 | 0.0591 | 14.15 | <.0001 | 2.309 | 2.056 | 2.593 |
| Gest_Diab | 0.5455 | 0.0234 | 23.26 | <.0001 | 1.725 | 1.648 | 1.807 |

| Random Effects | | | | |
|---|---|---|---|---|
| | Estimate | se | Z Value | P > Z |
| Intercept | 0.1124 | 0.006458 | 17.4 | <.0001 |
| Residual | 0.9494 | 0.001953 | 486.07 | <.0001 |

## 5.3 Spatial Variation

Figure 5.1 Spatial Distribution of the Odds Ratios for Preeclampsia by Census Tract in Michigan




(Dark Blue Significantly Protective and Dark Red Significantly Increased Odds).

In Figure 5.1, the spatial distribution of the odds ratios for the final model (Table 5.16) are displayed. The darker census tracts denote statistically significant tracts (p-value >= 0.05) for elevated preeclampsia (red) and reduced odds of preeclampsia (blue) controlling for the most well-known risk factors. There are statistically significant clusters of increased odds of preeclampsia north east of Muskegon, around Alma, and Midland. There are also clusters

located in the northern Detroit suburbs: Rochester/Rochester Hills, Mt. Clemens, Royal Oak, Sterling Heights, and Troy and the Upper Peninsula of Michigan in the area of L'Ance (Figure 5.1). These areas of high preeclampsia cannot be unexplained by the modeled risk factors and should therefore, be further investigated.

# CHAPTER 6: DISCUSSION

In this research, T1 (20 weeks to conception) and T3 (20 weeks gestation to birth) were found to be consistently protective of preeclampsia. Other studies focusing on vitamin D in maternal populations, found a similar pattern. Maternal vitamin D deficiency defined by a blood serum level of <20 nmol/L at late-mid-trimester (24 to 36 weeks) gestation is associated with an increased risk of preeclampsia (aOR 3.2); and this study found no significant associated between vitamin D at early gestation 12 to 18 weeks of gestation (Wei et al., 2012) a finding similar to this study. However, another study found that maternal vitamin D deficiency early pregnancy could be an independent risk factor for preeclampsia; this study revealed an association between low vitamin D status at less than 20 weeks gestation and preeclampsia diagnosis (Achkar, 2012). These studies also suggest that the levels of vitamin D pre-conception could have been a factor in the prognosis; furthermore, these studies concluded that there was no significant difference between preeclamptic and non- preeclamptic women in maternal age. Another study looking at dose response to vitamin D during pregnancy found that vitamin D levels at 10 to 18 weeks gestation and 32 to 38 weeks gestation were associated with a lower risk of preeclampsia (rr=0.20). A meta-analysis investigating the associations between vitamin D and preeclampsia found mothers receiving vitamin D supplementation earlier in pregnancy had lower odds of preeclampsia (Hyppönen et al., 2014).

When examining UV-B and race, this research found that being white is protective of preeclampsia, specifically in urban areas. Although being black was not found to increase the odds of preeclampsia, being white was found to be protective. Moreover, Medicaid was found to increase the odds of preeclampsia among black mothers but Medicaid was protective among

white mothers. This finding could be due to a lack of health care access in black communities and institutionalized racism. It can be concluded that racial disparities do exist between these populations. Racial disparities are present in preeclampsia incidence, severity, and risk as well (ACOG, 2002; Lee et al., 2007; Haney et al., 2008; Lisonkova and Joseph, 2013). The increased odds of preeclampsia could be because of lower vitamin D levels (Reeves et al., 2014). Not only are black women at an increased risk for preeclampsia (ACOG, 2002), preeclampsia is also more common and severe in black women (Goodwin and Mercer, 2005; Fingar et al., 2017). In one study, the mean prevalence of preeclampsia was about two-thirds higher in black compared to white women (51.2 per 1,000 deliveries and 31.2 per 1,000 deliveries, respectively) (Breathett et al., 2014). Racial disparities exist in vitamin D levels as well. Although, inadequate vitamin D levels are common in pregnant women (Brunst, 2013; Mulligan et al., 2010), it disproportionately effects blacks when compared to their white counter parts. The majority of mothers from a high-risk populations (mostly black, northern latitude, winter season) were vitamin D deficient in the immediate postpartum period (Lee et al., 2007). In a study of white and black pregnant women in Pittsburgh, at the time of delivery, 54.1% of the black women and 42.1% of the white women were considered to be vitamin D insufficient [25(OH)D between 15 ng/mL and 32 ng/mL]. Furthermore, 42.1% of black women were vitamin D deficient [25(OH)D < 15 ng/mL] compared to only 5.0% of white women (Bodnar et al., 2007b). Bodnar (2007b) concluded that both black and white pregnant women residing in the northern U.S. latitudes were at increased risk of vitamin D insufficiency, even when mothers were compliant with prenatal vitamins; however, blacks were at a substantially increased risk. Racial disparities in pregnancy outcomes is one of the most striking and poorly understood inequalities in American health due to the unexplained and complex etiology of these disparities (Swamy et al.,

2011). It has been suggested that the long-term psychological toll racism experienced by African American women increases their risk for preeclampsia, eclampsia, and embolisms (Taylor et al., 2019). These, coupled with lower vitamin D levels, may be important drivers behind the racial disparities in preeclampsia.

This research also notes that BMI is a critical factor in the racial disparities in preeclampsia, although BMI does increase the risk or preeclampsia for both blacks and whites. In a cohort study on supplemented women, maternal prepregnancy obesity was associated with lower serum 25(OH)D concentrations and higher odds of vitamin D deficiency among mothers in mid-gestation (OR=2.0, 95% CI, 1.2-3.6) and neonates at birth (OR=2.1, 95% CI, 1.2-3.8) (Bodnar, 2007d). Importantly, vitamin D insufficiency is an independent risk factor for preeclampsia, an outcome that is also more common in obese women. These finding suggest that reduced 25(OH)D levels in pregravid obese women may partially mediate the obesity-preeclampsia association. BMI affects the bioavailability of vitamin D. People with a higher BMI tend to also have lower concentrations of 25(OH)D (Giovannucci, 2005). This is thought to be a result of the fat soluble nature of vitamin D. Vitamin D is fat soluble and is stored in the adipose tissue. Because people with a higher BMI have more adipose tissue, more vitamin D is sequestered and stored (Wortsman et al., 2000). This process decreases the bioavailability of 25(OH)D. Because it is biologically unavailable, it cannot be converted into an active form of vitamin D and used by the body. This study found that black women with increasing BMI operated differently than black women independent of BMI on the risk of preeclampsia, suggesting the need for future research to disentagle the role of vitamin D in BMI and preeclampsia pathways.

This dissertation examined the complex relationships between preeclampsia, solar UV-B, and vitamin D by investigating the association of maternal UV-B exposure and preeclampsia in Michigan using a medical geographic perspective. The interactions between UV-B, the biological, environmental, and behavior factors that influence the bioavailability of vitamin D are important when studying hypertensive disorders due to the impact of vitamin D on their etiologic mechanisms. The behavioral aspects were not explored due to the lack of data about mother's behavior. It would be beneficial to provide a more complete picture if these behavioral factors could have been accounted for in the models.

### 6.1 Limitations

There are specific limitations to this study relating to potential measurement error. For example, the grid size of the remote sensing imagery was quite large (~69 square miles) and assumed an even distribution of solar rays across the area. Furthermore, the Erythemal daily dose, which was used to estimate Erythemal-UV-B, is weighted using the biological action spectrum model for the susceptibility potential of Caucasian skin to sunburn (erythema). Although Erythmal daily dose can be used to estimate UV-B exposure at the Earth's surface (Gao, Gao, and Chang., 2010) it does not take into account skin tone variation. Furthermore, UV-B for T1, T2 and T3 are averaged across these time periods and does not account for significant variation within these time periods. However, Martin et al. (2000) reported that averaging over time helps to alleviate the associated uncertainty in the data. Measurements of the OMI Erythemal daily dose product have been estimated to be about 20.0%; however, using monthly averages reduced the uncertainty to 5.0% (Martin et al., 2008). Our study averages over 20 weeks in T1 and T2 and may vary beyond 20 weeks to time of birth T3. This study therefore, recognizes the potential for

uncertainty in the exposure assessment. Related to the mother's exposure assessment are the lack of information on her movement during T1, T2 and T3 which may result in varying UV-B exposures, especially if she traveled to higher or lower latitude regions of Michigan. Time outdoors, clothing and sunscreen behavior were also missing information in this study, that may affect mother's exposure to UV-B and its effect on preeclampsia incidence.

# CHAPTER 7: CONCLUSIONS AND RECOMMENDATIONS

Vitamin D is an important factor in maternal health. Vitamin D insufficiency and deficiency are highly prevalent in women of reproductive age and in maternal populations (Mulligan et al., 2010; Brunst, 2013). The majority of pregnant women have vitamin D serum levels below what the IOM (Institute of Medicine, 2011) defines as sufficient, 50nmol/L (20ng/mL) and this problem persists even with vitamin D supplementation (Bodnar, 2007b; Lee et al., 2007; Holmes et al., 2009; Merewood et al., 2010; Hypponen et al., 2014). Vitamin D has emerged as a promising agent for lowering the risk preeclampsia. Because the majority of vitamin D is obtained from exposure to solar radiation, casual sun exposure is important. As discussed in this dissertation, Vitamin D regulates the renin gene, which is responsible for regulating blood pressure, expression and helps to explain the relationship between hypertension and vitamin D. Furthermore, vitamin D plays a role in vascular smooth muscle cell functions and modulation of vascular tone and endothelium maintenance. Vitamin D is an essential nutrient that plays a critical role in cell proliferation, bone health, immune modulation, and cardiovascular function, and, therefore, may influence women's health, pregnancy health, and fetal development.

Cardiovascular disease (CVD) is the number one cause of death among women (CDC, 2015). Preeclampsia is associated with CVD later in life (ACOG, 2013); however, it is not clear if preeclampsia is in the causal pathway of CVD. Preeclampsia and CVD have the same risk factors; the American Heart Association recommends that pregnancy health should be included in the assessment of a women's risk of CVD (ACOG, 2013). The risk factors hypertension, diabetes, age over 35, and higher than normal BMI that are associated with preeclampsia, are also classic risk factors for CVD. These important CVD risk factors are also inversely associated

with 25(OH)D levels (Martins, 2007). 25(OH)D has been shown to have an inverse association with CVD mortality (Dobnig, 2008; Ginde, 2009). The African American population is at an increased risk of CVD compared to whites. Furthermore, there are racial disparities in preeclampsia; this puts the black mothers at a disadvantage compared to their white counterparts.

UV-B varies geographically with latitude; exposure to sunlight is reduced at higher latitudes above 35° (Webb et al., 1988; Holick, 2006; Holick, 2008) or latitudes above 37° (Holick, 2004; Chen, 2007; Holick, 2007c; Jablonski, 2010), especially during the winter. Therefore, at these latitudes, the potential for cutaneous production of vitamin D is minimal. Skin pigmentation is determined by the amount of melanin in the skin. Latitude and season play a role in potential UV exposure; for example, at about 39 degrees north latitude it would take a relatively light skinned person more than two hours of sun exposure to obtain the recommended daily dose of vitamin D (1,000 IU) in January; however, in July the exposure time to produce the same amount is 7 minutes and in October 31 minutes (Serrano et al., 2017). Geography and skin pigmentation are two of the main factors that influence the amount of UV-B radiation available to humans. It is important for the maternal population to be aware of the time they spend indoors; specifically, in northern latitudes and in urban areas.

Because geography plays a critical role in the spatial distribution of health and diseases, it is crucial to look at health and disease through the lens of medical geography. Medical geography studies the spatial and spatio-temporal distribution of health and disease and the environmental and social factor that influence that distribution; where, when, and how people interact with their environment are important when studying health and disease. The biological characteristics and behavior play a role in a person's health. However, where people as biological organisms interact

with the environment also plays a role. The physical, built, and social environments in which one lives impacts their health. Geography must be considered when studying health and disease.

# APPENDIX

## APPENDIX

## Appendix I

Table I. Running 20 Week Calendar.

| Week | Date Beginning | Date Ending | Total Days |
|---|---|---|---|
| 1 | 12/30/2007 | 1/5/2008 | 138 |
| 2 | 1/6/2008 | 1/12/2008 | 140 |
| 3 | 1/13/2008 | 1/19/2008 | 140 |
| 4 | 1/20/2008 | 1/26/2008 | 140 |
| 5 | 1/27/2008 | 2/2/2008 | 140 |
| 6 | 2/3/2008 | 2/9/2008 | 140 |
| 7 | 2/10/2008 | 2/16/2008 | 140 |
| 8 | 2/17/2008 | 2/23/2008 | 140 |
| 9 | 2/24/2008 | 3/1/2008 | 140 |
| 10 | 3/2/2008 | 3/8/2008 | 140 |
| 11 | 3/9/2008 | 3/15/2008 | 140 |
| 12 | 3/16/2008 | 3/22/2008 | 140 |
| 13 | 3/23/2008 | 3/29/2008 | 140 |
| 14 | 3/30/2008 | 4/5/2008 | 140 |
| 15 | 4/6/2008 | 4/12/2008 | 140 |
| 16 | 4/13/2008 | 4/19/2008 | 140 |
| 17 | 4/20/2008 | 4/26/2008 | 140 |
| 18 | 4/27/2008 | 5/3/2008 | 140 |
| 19 | 5/4/2008 | 5/10/2008 | 140 |
| 20 | 5/11/2008 | 5/17/2008 | 139 |
| 21 | 5/18/2008 | 5/24/2008 | 136 |
| 22 | 5/25/2008 | 5/31/2008 | 136 |
| 23 | 6/1/2008 | 6/7/2008 | 136 |
| 24 | 6/8/2008 | 6/14/2008 | 136 |
| 25 | 6/15/2008 | 6/21/2008 | 136 |
| 26 | 6/22/2008 | 6/28/2008 | 140 |
| 27 | 6/29/2008 | 7/5/2008 | 136 |
| 28 | 7/6/2008 | 7/12/2008 | 136 |
| 29 | 7/13/2008 | 7/19/2008 | 136 |
| 30 | 7/20/2008 | 7/26/2008 | 136 |
| 31 | 7/27/2008 | 8/2/2008 | 136 |
| 32 | 8/3/2008 | 8/9/2008 | 136 |
| 33 | 8/10/2008 | 8/16/2008 | 136 |
| 34 | 8/17/2008 | 8/23/2008 | 136 |

| | | | |
|---|---|---|---|
| 35 | 8/24/2008 | 8/30/2008 | 136 |
| 36 | 8/31/2008 | 9/6/2008 | 136 |
| 37 | 9/7/2008 | 9/13/2008 | 136 |
| 38 | 9/14/2008 | 9/20/2008 | 136 |
| 39 | 9/21/2008 | 9/27/2008 | 136 |
| 40 | 9/28/2008 | 10/4/2008 | 137 |
| 41 | 10/5/2008 | 10/11/2008 | 140 |
| 42 | 10/12/2008 | 10/18/2008 | 140 |
| 43 | 10/19/2008 | 10/25/2008 | 140 |
| 44 | 10/26/2008 | 11/1/2008 | 140 |
| 45 | 11/2/2008 | 11/8/2008 | 140 |
| 46 | 11/9/2008 | 11/15/2008 | 140 |
| 47 | 11/16/2008 | 11/22/2008 | 140 |
| 48 | 11/23/2008 | 11/29/2008 | 140 |
| 49 | 11/30/2008 | 12/6/2008 | 140 |
| 50 | 12/7/2008 | 12/13/2008 | 140 |
| 51 | 12/14/2008 | 12/20/2008 | 140 |
| 52 | 12/21/2008 | 12/27/2008 | 140 |
| 53 | 12/28/2008 | 1/3/2009 | 140 |
| 54 | 1/4/2009 | 1/10/2009 | 140 |
| 55 | 1/11/2009 | 1/17/2009 | 140 |
| 56 | 1/18/2009 | 1/24/2009 | 140 |
| 57 | 1/25/2009 | 1/31/2009 | 140 |
| 58 | 2/1/2009 | 2/7/2009 | 140 |
| 59 | 2/8/2009 | 2/14/2009 | 140 |
| 60 | 2/15/2009 | 2/21/2009 | 140 |
| 61 | 2/22/2009 | 2/28/2009 | 140 |
| 62 | 3/1/2009 | 3/7/2009 | 140 |
| 63 | 3/8/2009 | 3/14/2009 | 140 |
| 64 | 3/15/2009 | 3/21/2009 | 140 |
| 65 | 3/22/2009 | 3/28/2009 | 140 |
| 66 | 3/29/2009 | 4/4/2009 | 140 |
| 67 | 4/5/2009 | 4/11/2009 | 140 |
| 68 | 4/12/2009 | 4/18/2009 | 140 |
| 69 | 4/19/2009 | 4/25/2009 | 140 |
| 70 | 4/26/2009 | 5/2/2009 | 140 |
| 71 | 5/3/2009 | 5/9/2009 | 140 |
| 72 | 5/10/2009 | 5/16/2009 | 140 |
| 73 | 5/17/2009 | 5/23/2009 | 140 |
| 74 | 5/24/2009 | 5/30/2009 | 140 |
| 75 | 5/31/2009 | 6/6/2009 | 140 |
| 76 | 6/7/2009 | 6/13/2009 | 140 |
| 77 | 6/14/2009 | 6/20/2009 | 140 |

| | | | |
|---|---|---|---|
| 78 | 6/21/2009 | 6/27/2009 | 140 |
| 79 | 6/28/2009 | 7/4/2009 | 140 |
| 80 | 7/5/2009 | 7/11/2009 | 140 |
| 81 | 7/12/2009 | 7/18/2009 | 140 |
| 82 | 7/19/2009 | 7/25/2009 | 140 |
| 83 | 7/26/2009 | 8/1/2009 | 140 |
| 84 | 8/2/2009 | 8/8/2009 | 140 |
| 85 | 8/9/2009 | 8/15/2009 | 140 |
| 86 | 8/16/2009 | 8/22/2009 | 140 |
| 87 | 8/23/2009 | 8/29/2009 | 140 |
| 88 | 8/30/2009 | 9/5/2009 | 140 |
| 89 | 9/6/2009 | 9/12/2009 | 140 |
| 90 | 9/13/2009 | 9/19/2009 | 140 |
| 91 | 9/20/2009 | 9/26/2009 | 140 |
| 92 | 9/27/2009 | 10/3/2009 | 140 |
| 93 | 10/4/2009 | 10/10/2009 | 140 |
| 94 | 10/11/2009 | 10/17/2009 | 140 |
| 95 | 10/18/2009 | 10/24/2009 | 140 |
| 96 | 10/25/2009 | 10/31/2009 | 140 |
| 97 | 11/1/2009 | 11/7/2009 | 140 |
| 98 | 11/8/2009 | 11/14/2009 | 140 |
| 99 | 11/15/2009 | 11/21/2009 | 140 |
| 100 | 11/22/2009 | 11/28/2009 | 140 |
| 101 | 11/29/2009 | 12/5/2009 | 140 |
| 102 | 12/6/2009 | 12/12/2009 | 140 |
| 103 | 12/13/2009 | 12/19/2009 | 140 |
| 104 | 12/20/2009 | 12/26/2009 | 140 |
| 105 | 12/27/2009 | 1/2/2010 | 140 |
| 106 | 1/3/2010 | 1/9/2010 | 140 |
| 107 | 1/10/2010 | 1/16/2010 | 140 |
| 108 | 1/17/2010 | 1/23/2010 | 140 |
| 109 | 1/24/2010 | 1/30/2010 | 140 |
| 110 | 1/31/2010 | 2/6/2010 | 140 |
| 111 | 2/7/2010 | 2/13/2010 | 140 |
| 112 | 2/14/2010 | 2/20/2010 | 140 |
| 113 | 2/21/2010 | 2/27/2010 | 140 |
| 114 | 2/28/2010 | 3/6/2010 | 140 |
| 115 | 3/7/2010 | 3/13/2010 | 140 |
| 116 | 3/14/2010 | 3/20/2010 | 140 |
| 117 | 3/21/2010 | 3/27/2010 | 140 |
| 118 | 3/28/2010 | 4/3/2010 | 140 |
| 119 | 4/4/2010 | 4/10/2010 | 140 |
| 120 | 4/11/2010 | 4/17/2010 | 140 |

| | | | |
|---|---|---|---|
| 121 | 4/18/2010 | 4/24/2010 | 140 |
| 122 | 4/25/2010 | 5/1/2010 | 140 |
| 123 | 5/2/2010 | 5/8/2010 | 140 |
| 124 | 5/9/2010 | 5/15/2010 | 140 |
| 125 | 5/16/2010 | 5/22/2010 | 140 |
| 126 | 5/23/2010 | 5/29/2010 | 140 |
| 127 | 5/30/2010 | 6/5/2010 | 140 |
| 128 | 6/6/2010 | 6/12/2010 | 140 |
| 129 | 6/13/2010 | 6/19/2010 | 140 |
| 130 | 6/20/2010 | 6/26/2010 | 140 |
| 131 | 6/27/2010 | 7/3/2010 | 140 |
| 132 | 7/4/2010 | 7/10/2010 | 140 |
| 133 | 7/11/2010 | 7/17/2010 | 140 |
| 134 | 7/18/2010 | 7/24/2010 | 140 |
| 135 | 7/25/2010 | 7/31/2010 | 140 |
| 136 | 8/1/2010 | 8/7/2010 | 140 |
| 137 | 8/8/2010 | 8/14/2010 | 140 |
| 138 | 8/15/2010 | 8/21/2010 | 140 |
| 139 | 8/22/2010 | 8/28/2010 | 140 |
| 140 | 8/29/2010 | 9/4/2010 | 140 |
| 141 | 9/5/2010 | 9/11/2010 | 140 |
| 142 | 9/12/2010 | 9/18/2010 | 140 |
| 143 | 9/19/2010 | 9/25/2010 | 140 |
| 144 | 9/26/2010 | 10/2/2010 | 140 |
| 145 | 10/3/2010 | 10/9/2010 | 140 |
| 146 | 10/10/2010 | 10/16/2010 | 140 |
| 147 | 10/17/2010 | 10/23/2010 | 140 |
| 148 | 10/24/2010 | 10/30/2010 | 140 |
| 149 | 10/31/2010 | 11/6/2010 | 140 |
| 150 | 11/7/2010 | 11/13/2010 | 140 |
| 151 | 11/14/2010 | 11/20/2010 | 140 |
| 152 | 11/21/2010 | 11/27/2010 | 140 |
| 153 | 11/28/2010 | 12/4/2010 | 140 |
| 154 | 12/5/2010 | 12/11/2010 | 140 |
| 155 | 12/12/2010 | 12/18/2010 | 140 |
| 156 | 12/19/2010 | 12/25/2010 | 140 |
| 157 | 12/26/2010 | 1/1/2011 | 140 |
| 158 | 1/2/2011 | 1/8/2011 | 140 |
| 159 | 1/9/2011 | 1/15/2011 | 140 |
| 160 | 1/16/2011 | 1/22/2011 | 140 |
| 161 | 1/23/2011 | 1/29/2011 | 140 |
| 162 | 1/30/2011 | 2/5/2011 | 140 |
| 163 | 2/6/2011 | 2/12/2011 | 140 |

| | | | |
|---|---|---|---|
| 164 | 2/13/2011 | 2/19/2011 | 140 |
| 165 | 2/20/2011 | 2/26/2011 | 140 |
| 166 | 2/27/2011 | 3/5/2011 | 140 |
| 167 | 3/6/2011 | 3/12/2011 | 140 |
| 168 | 3/13/2011 | 3/19/2011 | 140 |
| 169 | 3/20/2011 | 3/26/2011 | 140 |
| 170 | 3/27/2011 | 4/2/2011 | 140 |
| 171 | 4/3/2011 | 4/9/2011 | 140 |
| 172 | 4/10/2011 | 4/16/2011 | 140 |
| 173 | 4/17/2011 | 4/23/2011 | 140 |
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