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The association between diabetes mellitus among American Indian/Alaska Native populations with preterm birth in eight U.S. states from 2004-2011

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2011

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Abstract

The association between diabetes mellitus among American Indian/Alaska Native populations with preterm birth in eight U.S. states from 2004-2011
By Haley Dorfman

American Indians and Alaska Natives (AI/AN) have the highest prevalence of diabetes mellitus (DM) in the United States. Previous research has indicated that women with prepregnancy DM or gestational DM are at increased risk for poor perinatal outcomes, such as preterm birth (PTB). Disparities in preterm birth between racial/ethnic groups are well documented; however, data on the association of maternal risk factors and poor perinatal outcomes within AI/AN women is limited. We utilized surveillance data from the Centers for Disease Control and Prevention's Pregnancy Risk Assessment Monitoring System (PRAMS) to assess whether DM is associated with PTB among AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah and Washington from 2004-2011. We further examined whether this association differed between states. Using a population-based retrospective cohort of 12,420 live singleton births to AI/AN women we conducted backwards elimination and forward selection to construct a multivariable logistic regression model that estimates the odds of preterm birth among women with DM compared to women without DM. Women with DM had 1.83 (95% CI: 1.21-2.78, $p = 0.004$) times the odds of having a preterm birth than women without DM after controlling for maternal age and prepregnancy BMI. After stratifying on state, women with DM in Nebraska had the greatest odds of preterm birth (aOR = 6.63, $p = 0.00$) while AI/AN women in Alaska had a protective effect of DM (aOR = 0.17, $p = 0.00$). This finding suggests a misreporting or lack of adequate diagnosis of DM and GDM in Alaska. Our results indicate a significant association of DM with preterm birth in AI/AN women. Differences across states call for increased surveillance, assessment of health data quality, and public health efforts in high-risk areas. Further research is needed to compare these results to other minority populations and to assess whether differences across states can be attributed to tribal, healthcare or lifestyle factors.

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Introduction

Preterm delivery is defined as a pregnancy resulting in a live birth at gestational age less than 37 weeks.[1] Preterm delivery affects nearly 1 in 8 infants and accounts for 35% of all infant deaths.[1] Infants born preterm have an increased risk of breathing problems, feeding difficulties, cerebral palsy, developmental delay, vision problems, and hearing impairment.[1] Preterm birth not only results in long-term disability, but also costs approximately $26 billion to the US healthcare system annually.[1] Many chronic and acute conditions increase the risk of delivering a preterm baby. Polyhydramnios, infection, and fetal stress are proximate causes of preterm birth that are often associated with maternal diabetes mellitus.[2,3]

Diabetes mellitus (DM) is a chronic disease that encompasses a group of metabolic disorders, which are characterized by defects in insulin action, insulin secretion, or both, resulting in hyperglycemia.[4] Serious complications can result from diabetes mellitus, and women require additional attention during pregnancy to prevent adverse outcomes to the mother and offspring.[4-6] DM can be diagnosed in childhood (usually type 1), during adulthood (usually type 2) or during pregnancy (gestational). Currently, there is an increasing prevalence of early-onset type 2 DM in adolescents.

A DM epidemic is occurring among the AI/AN population.[7-12] AI/ANs have the highest rate of DM among all races in the United States.[5,13] Simultaneously, disparities in the occurrence of preterm birth among AI/AN women compared to all other races in the United States contribute to a dangerous cycle.[14] Offspring of women with DM are at greater risk of being born preterm and at greater risk of developing diabetes later in life.[15-19] This is due to the effects of being born preterm and from exposure to the altered intrauterine environment of a diabetic mother.[15,20] Female children who develop diabetes and become

pregnant later in life then predispose their children to the same risks of preterm birth and DM.[15,18] This cycle among the AI/AN population contributes to their increase odds of DM and preterm birth (Figure 1).

This study aims to examine this cycle within a population with increased prevalence of both DM and preterm birth. The specific research questions are:

1) Is DM (prepregnancy and gestational) associated with preterm birth among AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington across states from 2004-2011?
2) Does the association of DM with preterm birth among AI/AN women differ between states?

The results of this study will provide a framework for the public health community to determine the distribution of resources and interventions. Our data will also contribute to literature on the association of DM with preterm birth in a unique population and could beget future research that addresses whether this association manifests differently in AI/AN populations compared to other racial/ethnic groups. If differences in states are observed future research could examine whether these differences are due to healthcare surveillance or quality/distribution, environmental differences between states, or cultural/behavioral/genetic differences between tribes.

Background

American Indian/Alaska Native Demographics and Culture

As of 2012 the American Indian/Alaska Native (AI/AN) population, including those of more than one race, has grown to 5.2 million and comprises 2% of the US population.[21] Approximately 51% of the AI/AN population is of more than one race.[21] With 566 federally recognized Indian tribes across the U.S., American Indians and Alaska Natives are a culturally heterogeneous population.[21] AI/ANs live on reservations, in rural and urban settings with various levels of involvement in traditional AI/AN cultural beliefs and practices. Among AI/ANs living a more traditional lifestyle, diets vary by geographic region depending on availability of food and government subsidies.[22-36] Of the 381 distinct non-English languages identified by the American Community Survey, 169 were Native North American languages spoken by AI/ANs.[37]

Eskimo

The proportion of Alaska's population of AI/AN descent (19.6%) is the highest of any state.[21] Alaska is the home to 231 federally recognized tribes.[38] Eskimos are the largest Alaska Native group with 54,761 Alaska Natives identifying as Eskimo in 2000.[23] When Eskimos first arrived in Alaska, at least 6,000 years ago, they created villages along the Western coast and divided into separate 'bands', which developed different cultural identities.[39] Today, the largest band of Eskimos is the Yup'ik. In 2010, 34,000 Alaska Natives identified as Yup'ik alone or in combination with another race. Of the 34,000, 29,000 Alaska Natives identified as only Yup'ik.[40] Many Eskimos continue to depend upon subsistence fishing, hunting and gathering food. Sea mammals traditionally comprise the majority of their dietary intake.[41] As the Alaska Natives experience increased contact with other cultures, they continue to lose their land where they hunt for food and are introduced to more fatty

and sugary diets. Alaska Natives' inability to cultivate plants in the Arctic environment along with other cultures' influence on their diets, has resulted in a diminished food supply and adoption of less traditional diets, which now contain almost 75% of average daily energy intake from fat.[24] Traditional birthing practices of Alaska Natives were surrounded by many cultural taboos and traditions.[25] Women gave birth in aanigutyaks or birthing houses and delivered the infant in a squatting position.[25]

Cherokee

Cherokee Tribal members comprise the largest proportion of both Oklahoma and Oregon AI/AN residents.[42,43] Oklahoma has the second largest proportion of residents who are AI/ANs (13.4%) and 31 federally recognized tribes.[21,38] Oregon has 10 federally recognized tribes[38], and 1.2% of the Oregon population identifies as single race AI/AN.[44] In the 2000 Census, Oklahoma and Oregon had 97,317 and 4,221 American Indians identified as single race Cherokee Tribal, respectively.[42,43] This equated to approximately 8% of all Oklahoma residents identified as Cherokee in 2013.[45]

Cherokee diets traditionally consisted primarily of wild meat along with corn, bean bread, pumpkins, dried fruit and nuts.[27] Western medicine, which has become more prevalent in Cherokee society, is in stark contrast to their historical medical practices such as herbal treatments, sweat baths, bleeding, scratching and rubbing of affected areas.[27] Medicine Men and Women practiced with medicinal herbs for both curing ailments and prevention.[26] The Cherokee tribes in Oklahoma suffer significantly more from health ailments such as diabetes, hypertension, cardiovascular disease, and substance abuse compared to other races in Oklahoma, which is largely due to their lower income levels.[27]

Traditional Cherokee cultures, like many other tribes, are matrilineal. Women are in complete control of the children, and men move to the woman's village and take her family

name upon marriage.[27] Husbands are permitted to have more than one wife if they are able to hunt enough food to feed multiple families. A second wife is traditionally chosen by the first and is a sister or widowed member of the village.[27] Pregnant Cherokee women believe they should avoid certain foods such as squirrel, trout, rabbit and salt.[27] The Cherokee traditionally had rituals to induce labor, such as scaring the child out of the womb by repeating specific words, or drinking an infusion of wild cherry bark.[46] A woman who has just given birth should avoid sexual intercourse for three months and ideally should not touch her husband at all.[27]

Six main festivals are celebrated in traditional Cherokee culture throughout the year: the First New Moon of Spring, the Green Corn Ceremony, the Mature Green Corn Ceremony, the Great New Moon Festival, the Propitiation and Cementation Festival and the sixth festival in which people danced while gathering tobacco in the winter.[26] Their land is important to the Cherokee in their festivals and in everyday life. American Indians generally have a strong cultural identity and close family ties.[27] These values are currently challenged when parents must look outside of reservations for work and children leave home for school.[27] The separation of families amplifies emotional stress that result further disadvantage among the Cherokee population.[27]

Navajo

New Mexico follows Oklahoma with the third largest proportion of residents who are AI/ANs (10.4%).[21] Of the 23 federally recognized tribes in New Mexico[38], the Navajo Nation represents the largest with 102,286 identifying as Navajo Tribal in 2000.[47] Utah's AI/AN population makes up 1.1% of the state's population.[44] Eight tribes are federally recognized in Utah; of these the Navajo comprise the largest proportion with 14,634 AI/ANs identifying as single race Navajo.[38,48]

A standard traditional diet for Navajos consist of mutton, fried bread, coffee with sugar and goat milk, goat meat, and wild plants.[28] Traditional Navajo recipes are passed down orally from mother to daughter and often contain wild plants and vegetables.[29] Throughout the early 1900s sheep were the Utah Navajo's primary food source and a cornerstone of their economy. During the Great Depression the land in Utah could not support the growing number of sheep, and the government forced the Navajo to reduce the size of their herds, causing emotional and economic distress.[49] Recently many Navajos have migrated to urban settings, which has contributed to an evolving culture especially among Navajo youth.[30] Christian missionaries have played a significant role in altering traditional Navajo society by introducing the concept of a male-dominated society.[30]

Compared to other tribes the Navajo have a substantial number of publications discussing their birthing practices. Navajo culture considers pregnancy as a blessing and as such Navajo women take many precautions during pregnancy to ensure the health of the child.[50] Taboos such as tying knots, thinking bad thoughts, and consuming of salty and fatty foods must be avoided.[50] Pregnant women are expected to participate in ceremonies that incorporate corn pollen as well as daily dawn prayers.[50,51] During pregnancy women are advised to avoid contact with dead or ill people and animals, arguments, conflict, and negative thoughts.[50,51]

Women hold onto sash belts during labor and give birth in a squatting position. Immediately after birth mothers bury the placenta, drink juniper/ash tea, wrap the sash belt around their waist for four days, smear their baby's first stool on their faces, and shake the infant's hand.[51] Like the Cherokee, Navajo women avoid intercourse for three months after delivery.[51]

The Navajo Nation is a strong spiritual community who believe the Great Spirit will ensure the survival of the Navajo for eternity.[29] When Navajo people are ill, traditionally, medicinemen (who are bestowed with supernatural power) use herbs, prayers, songs and ceremonies to heal.[29] However, in modern times many Navajo people use hospitals on the reservation for Western medicine or use both traditional and modern treatments.[29]

Puget Sound Salish

American Indians and Alaska Natives comprise 1.4% of Washington's population.[44] Of 30 federally recognized tribes in Washington[38], the Puget Sound Salish is the largest with 9,624 American Indians.[52] Traditionally the Puget Sound Salish hunt elk, deer, seals, bear, ducks, and gather huckleberries and root foods.[31] Shellfish are harvested on beaches and mud flats and every year many Salish go to the ocean to help collect salmon for the tribe to store for winter.[31] In 2012, the Tulalip Hibulb Cultural Center in Marysville, Washington hosted an exhibit named 'Salish Bounty: Traditional Native American Foods of Puget Sound'.[32] The exhibit chronicles the evolution of the Puget Sound Salish diet.[32] Traditional food was based on hunting and gathering; but when American Indians were confined to reservations in the 20th century their diets became more assimilated as they relied on commodity foods.[32] Today cheap and fast food has become the norm for many American Indians in Washington.[32]

Chippewa

The United States Census Bureau reported that 1.0% of Minnesota's population is single race AI/AN.[44] The Chippewa tribe is the largest of the nine federally recognized tribes in Minnesota with approximately 32,184 AI/ANs identifying as single race Chippewa.[38,53] Like many other American Indian tribes the Chippewa value spirituality and strive to maintain a good relationship with spirits, plants and animals.[54] Traditional Chippewa clans

operated on a 'totemic' system.[55] A totem animal represented each individual and clan identity was passed from the father to his children.[55] These clans were considered to tie individuals together more than blood indicated by the fact that individuals within a clan were forbidden to marry.[55]

In traditional Chippewa culture, only women were allowed to be present at the birth of a child.[56] The women allowed were typically the mother or sister of the woman delivering.[56] Once the infant was born the umbilical cord was sewed into a bag and hung on the cradleboard (a board used to ensure the child would have an upright posture).[56] The decline of breastfeeding among Chippewa women began at a later time than most of the United States.[54] The Women, Infants and Children (WIC) program provided formula to women in the U.S. in the 1970's and the program was not extended to the Chippewa until the 1980's.[54] Despite their lag in the uptake of formula feeding, the Chippewa have significantly lower rates of breastfeeding compared to the general population in Minnesota (20%-55% vs. 72.8% breastfed). [54]

Sioux

In 2012, 0.9% of Nebraska's population identified as single race AI/AN.[44] Of the six federally recognized tribes[38], the Sioux are the largest tribal group in Nebraska with 3,993 AI/AN who identify as single race Sioux.[57] Sioux Indian culture is largely based around spirituality.[34] While some practice Christianity, those that believe in the all-powerful god Wakan Tanka, participate in seven ceremonies throughout the year.[34] Family and the maintenance of traditional gender roles (the men provide food and the women have control of the house) are important to the Sioux people.[34] Polygamy, in which the husband may have multiple wives, is common.[34] Traditional food sources in Sioux culture were predominantly buffalo, as well as other wild meats including bear, deer, antelope, turkey and hens.[34] Fry

bread is the most commonly eaten traditional food today, as the Sioux diet has evolved to include more American foods.[34]

AI/AN health disparities/social determinants of health

The health disparities of AI/ANs compared with the U.S. population as a whole and specifically Non-Hispanic Whites can be largely attributed to social determinants of health. The World Health Organization defines social determinants of health as, "…the conditions in which people are born, grow, live work and age…These [conditions] are shaped by the distribution of money, power and resources at global, national and local levels, which are themselves influenced by policy choices."[35] David Jones chronicles the plight of AI/AN populations since their first interactions with Europeans.[58] Colonization dramatically increased mortality among American Indians by introducing new pathogens and abuse from Europeans.[58] The reservation system was introduced in the mid 1800's and shifted the burden of disease from acute to chronic infections due to the poor living conditions on the reservations. Europeans had various explanations for the health disparities including biological variation, God's will for the American Indian race to become extinct, and God granting them land as a gift. When government officials did become involved in AI/AN health, their approach has historically been paternalistic and based in the belief of White superiority, which has often led to a wider gap in health status.

Today, the health status of AI/ANs has improved; however, disparities between AI/ANs and Non-Hispanic Whites have persisted.[7,59-63] Most American Indians have lost their land and consequently their source of commerce and traditional food.[36] During the American Indian/Alaska Native heritage month, the U.S. Census Bureau released a fact sheet documenting AI/AN social position in America.[21] The economic adversity and poor social conditions have resulted in widespread poverty for single race AI/ANs compared to

the nation as a whole (29.1% compared to 15.9%, in 2011).[21] The median annual income of AI/AN single race households is $35,310 compared to the national median of $51,371 in 2012.[21] Further, educational disparities are obvious as well with only 78.8% of AI/ANs older than 25 completing high school or equivalent and 13.5% obtaining a bachelor's degree or higher in 2012 compared to 86.4% and 29.1%, respectively, in the general population.[21]

Prior to colonization, AI/ANs practiced a subsistence lifestyle and lived off the land. European settlement in the Americas forced AI/ANs from their traditional lands and onto reservations that did not offer the same opportunity to grow, hunt and gather their traditional foods.[64] When the Coolidge dam was created in 1930 American Indians whose lives and diets were based on that water source were without food security.[36] Government-sponsored commodity food programs were a consolation offered by Europeans; however, these foods, which were higher in fat and calories and lower in fiber served to deteriorate AI/AN health rather than provide a beneficial alternative.[64] The loss of land and persistent poverty has resulted in AI/ANs having to rely on the federal government for food subsidies. These subsidies consist primarily of processed foods high in fat and sugar leading to poor health outcomes such as obesity, diabetes, and cardiovascular diseases. The National Center for Health Statistics estimates that from 2004-2008, 29.7% of AI/AN women were obese; that is six times as likely as Asian women and more likely than Non-Hispanic White women (23.0%).[65] Compared to all other races, AI/ANs have dramatically higher proportions of people who have ever been told they had diabetes (17.5%) compared to 11.8% of Blacks, 10.6% of Hispanics, 8.0% of Asians and 6.6% of Non-Hispanic Whites.[65] Functional limitation caused by at least one chronic disease is highest among AI/ANs at 41.1% compared to only 31.6% of Non-Hispanic Whites.[65]

Explanations for the high incidence of chronic disease among AI/AN populations are varied. In essence there is not a single explanation but a combination of institutional, cultural, behavioral and genetic variables that play a role. In 1962, geneticist James V. Neel proposed the thrifty gene hypothesis, which addressed populations whose traditional food source was based on fluctuations in food abundance. The thrifty gene hypothesis is rooted in evolutionary theory and proposes that populations, such as AI/ANs, are biologically predisposed for greater storage of fat, a genetic advantage that would be beneficial in times of food scarcity but now results in increased risk for diabetes mellitus and obesity.[66,67] However, genetics cannot be exclusively responsible for the obesity epidemic. Only one case of diabetes was recorded among American Indians prior to 1930, and now AIs have the highest rates in the world.[64] In order to explain this dramatic transition of disease prevalence, one must employ the theory of social determinants of health, which posits, "inequalities in health are avoidable occurrences that are influenced by political, social, environmental, economic conditions".[64] Historical trauma allows AI/ANs' genetic susceptibility to manifest due to risk conditions rather than individual behaviors. The postcolonial environment does not support healthy lifestyle choices. If the DM epidemic is to be curtailed, there must be a drastic overhaul of the current social order and health services on a population level instead of individual behavior changes.[64]

American Indians' and Alaska Natives' decreased quality of life not only affects their physical health status but also their mental health. Facing constant adversity can often lead to drug and alcohol abuse, depression and suicide. Compared to all other races, AI/ANs have a life expectancy that is 4.1 years less (73.6 years compared to 77.7 years) and die at significantly higher rates from alcoholism, diabetes, unintentional injuries, and suicide. [68] In a Morbidity and Mortality Weekly Report (MMWR) the Centers for Disease Control and

Prevention on cigarette smoking in the U.S. from 2009-2010, AI/ANs had the highest prevalence of current smokers aged 12-17 years (13.6% compared to 10.2% Non-Hispanic Whites) and among adults (34.4% compared to 15.8% Non-Hispanic Whites).[69] In other MMWRs, the CDC reported, AI/ANs die at disproportionately higher rates from alcoholism (552% higher) than other races in the U.S. from 2005-2009.[68] In 2009, although similar to Non-Hispanic Whites, AI/ANs had the highest rates of suicide among all races (15.6 per 100,000 AI/AN population vs. 15.2 per 100,000 White population).[70] More AI/ANs are smokers (32.7%) than all other races.[59] The poor health status of many AI/ANs can be partly attributed to lack of health services and access to healthy foods. A significantly greater proportion of the AI/AN population lacked health insurance (27.4%) compared 14.8% of the nation as a whole.[21] Even when AI/ANs do have health insurance, lack of access to service can still mean AI/ANs are not receiving appropriate medical care. About 10.3% of AI/ANs, more than any other race, did not receive needed medical care due to cost of care compared to only 7.3% of Non-Hispanic Whites and 3.4% of Asians.[65] While the Indian Health Service (IHS) provides healthcare on or near reservations, many AI/ANs are not served in urban areas or other places not served by IHS.[71] The IHS reported that from 1998-1999 only 60% of AI/ANs in the United States lived in IHS service areas.[72] Only 56% of AIs qualify to receive care through IHS in Minnesota.[71] Transportation to medical centers can be problematic for AI/ANs living in rural settings.[71] Impetus to seek medical care can also be complicated by communication difficulties with health care professionals as well as past experiences of cultural intolerance and discrimination with health services.[71,73,74] This is particularly an issue in prenatal care and birthing practices, because each AI/AN tribe has unique beliefs and practices regarding pregnancy and delivery.[73,74]

Preterm birth

Normal pregnancies are approximately 9 months, or 40 weeks, from a woman's last menstrual period (NIH and CDC). When an infant is born prior to 37 completed weeks of gestation the birth is classified as preterm.[1,75] During the last few weeks of pregnancy the fetus is still developing organ systems such as the brain, lungs and liver.[1] When labor begins prior to 40 completed weeks of gestation, the infant is at an increased risk for poor perinatal outcomes because it is not fully developed. Preterm births result in an increased rate of perinatal mortality, long-term neurological disabilities, breathing and feeding difficulties, cerebral palsy, vision and hearing impairment, and developmental delays.[1] As a result of disabilities stemming from preterm birth, the US healthcare system spent more than 26 billion dollars in 2005.[1]

The CDC reports that annually in the U.S. nearly 500,000 babies, or 1 in every 8 infants, are born preterm.[1] Preterm infants accounted for 35% of all infant deaths in 2009;[1] and while poor perinatal outcomes decrease the later an infant is born, the National Institutes of Health reports that infants born between 34 and 37 weeks gestation still have 3 times the risk of a full term infant of dying within the first year of life.[75] A 2006 report by MacDorman that investigated US birth certificates found that from 1990-2008 the infant mortality rate for early preterm births (<32 weeks gestation) was 74 times the infant mortality rate for term births. Similarly, the infant mortality rate for late preterm births (34-36 weeks gestation) was 7.08 times the infant mortality rate for term births.[62] Among all births, 2/3 of all infant deaths in the U.S. occurred among the 13% of infants born preterm and more than half occurred in the 2% of infants born very preterm.[62] Among American Indian women, 12% of infant deaths occur in preterm infants.[62]

The etiology of preterm birth is complex and can be caused by various pathways. A preterm birth can occur spontaneously or be induced due to medical complications that pose a risk to the health of either the mother or fetus. There are four principal mechanisms proposed for preterm labor. First, inflammation can activate a cytokine response and lead to increased matrix metalloproteinases (MMPs, a degradative enzyme that breaks down collagen and leads to cervical ripening) and uterotonics.[2] Inflammation can be decidual, chorioamniotic, or systemic and result from infections (bacterial vaginosis, chorioamnionitis, periodontal disease etc.), uteroplacental ischemia, allergic response, excessive uterine expansion, and cervical incompetence.[2,76] Second, maternal and fetal stress can increase corticotropin-releasing hormone leading to increased estriol production and prostaglandins resulting in the activation of labor.[2] Third, decidual hemorrhage caused by placental abruption can activate phosphatidylinositol-signaling pathways that initiate uterine contractions and release MMPs.[2] If an intrauterine infection exists, either secretions of uterotonics agents result in preterm labor or MMPs are produced resulting in premature rupture of membranes (PROM).[2] Finally, pathologic uterine distention, which results from either uterine overdistension or the reduction in expansive capacity, activates cytokines that initiate labor.[2] Uterine overdistension is a result of polyhydramnios or multifetal gestations.[2] A reduction in expansive capacity is due to uterine anomalies.[2] The incidence of preterm birth is appreciably higher in homo sapiens compared to other mammals.[77] This is due to the combination of narrower pelvises for bipedal movement and development of larger brains resulting in a benefit of early birth to avoid obstructed labor.[77]

The National Vital Statistics Births: Final Data Report estimates that approximately 1.2% (46,419) of births in the U.S. were to American Indian and Alaska Native women in 2011.[65] The general fertility rate declined for both the U.S. and AI/AN women from 2010 to

2011 (1% vs. 2% respectively).[65] AI/AN women were younger compared to US women at age of first birth (22.4 vs. 25.6) and less likely to be unmarried (66.2% vs. 40.7%, respectively).[65]

Extensive evidence exists on the increased risk of preterm birth among AI/AN women compared to Non-Hispanic White women. Preterm birth (<37 weeks gestation) rates were higher among AI/AN women (13.5%) compared to all races (11.7%) and Non-Hispanic Whites (10.5%).[14] This pattern persisted when stratifying by early preterm, prior to 34 weeks gestation, (AI/AN: 3.9%; all races: 3.4%; Non-Hispanic White: 3.0%) and late preterm, 34-36 weeks gestation, (AI/AN: 9.6%; all races: 8.3%; Non-Hispanic White: 7.8%).[65] In a population based retrospective study comparing AI/AN births to Non-Hispanic Whites in Washington and Montana, AI/AN mothers had significantly higher odds of preterm birth in both states and in total had 1.34 times the odds of preterm birth compared to whites (1.25-1.44, $p<0.001$).[60] The increased incidence is not a new phenomenon as we see in a retrospective cohort study by Alexander et al. from 1995-2001, which showed a significant increased risk of very preterm birth (RR= 1.27, 95% CI = 1.25-1.34, $p<0.0001$) among American Indians compared to Hispanics and Non-Hispanic Whites as well as significant increased risk of preterm births (RR = 1.32, 95% CI = 1.30-1.34, $p<0.0001$).[63] Among American Indians, the incidence of preterm birth was significantly different between different geographic regions, with the highest incidence of preterm birth in the South/Northeast (11.2%) and the lowest incidence in the Mid-west (10.4%) ($p<0.05$).[63]

The perinatal health disparities seen between AI/ANs and Non-Hispanic Whites is confirmed and extended to populations outside the US in which Aboriginal populations are shown to have consistently higher rates of preterm birth than majority populations. A meta-

analysis by Shah et al. of 37 studies on Aboriginal populations in Canada, New Zealand, Australia and the U.S. concluded that Aboriginal women are at a significant increased risk for preterm birth (chi-square = 74.03, $p<0.00001$).[67] Within the meta-analysis subgroup analysis maintained that American Indians in the US had 1.29 (95%CI 1.28-1.31) times the odds of preterm birth compared to non-native populations.[67]

Poor perinatal outcomes among AI/AN women are a result of multiple barriers unique to AI/AN populations as well as some barriers that are common in other minorities. Principally for AI/AN women who often come from traditional backgrounds in which Western medicine is not the norm, trust of health care professionals is often lacking due to generations of discrimination and cultural intolerance. Various communication barriers exist due to language and cultural differences.[73] Further compounding the issue of poor communication is the lack of cultural appropriateness regarding birthing practices. An unpublished survey by the March of Dimes revealed that only 49 pamphlets on prenatal care of more than 500 were relevant to AI/AN women.[74] Many women may also be uncomfortable with a male physician.[73] Institutional barriers such as long wait times and lack of continuity of provider result in further distrust of the medical system.[73] Other issues such as poor transportation to health care facilities, embarrassment of unplanned pregnancy, and lack of partner support all result in late or no prenatal care visits.[73] In 2011, only 76.7% of AI/AN women had adequate prenatal care utilization upon initiation as measured by 2003 revised birth certificates in 36 states, the lowest of all other races.[78] From 1994-1997 13.5% of pregnant AI/ANs women in Idaho, Oregon and Washington received no prenatal care, a drastic decrease from 1991-1993 in which 39.3% received no prenatal care.[61]

Diabetes Mellitus

Several etiologies exist that lead to the group of metabolic diseases classified as diabetes mellitus. This chronic disease is characterized by defects in either insulin action, insulin secretion, or both, resulting in hyperglycemia.[4] Insulin is produced in the pancreas by β-cells and when secreted is used to move glucose in the blood into cells so it can be used for energy.[4] Normally, this process occurs with the ingestion of carbohydrates in order to promote glucose uptake and suppress glucose production by the liver and lipolysis by adipocytes.[79] When the receptor sites are not able to use insulin properly it is called insulin resistance.[79] DM results when the pancreas cannot produce enough insulin to make up for insulin resistance.[79] When there is either not enough insulin produced or the sites in which insulin binds to are defective, an increased amount of glucose builds up in the bloodstream leading to long term damage of various organs.[4] The high levels of blood glucose is a condition called hyperglycemia, which is a precursor to DM.[4] There are three predominant classifications of DM: type 1- and type 2 diabetes and gestational diabetes. Other forms of DM include: genetic defects of the β-cell, genetic defects in insulin action, diseases of the exocrine pancreas, endocrinopathies, drug-or chemical-induced diabetes, infections, uncommon forms of immune-mediated diabetes, and other genetic syndromes associated with chromosomal defects.[4]

The American Diabetes Association defines DM through assessment of its symptoms. These include plasma glucose concentrations ≥ 200mg/dl, fasting plasma glucose ≥126 mg/dl, or 2-hour postload glucose during an oral glucose tolerance test of ≥200 mg/dl.[4]

There are many serious complications associated with DM.[4-6] Most chronic complications are related to vascular difficulties.[4] DM is one of the most common causes of

nephropathy leading to renal failure.[4,6] Retinopathy leading to vision loss, peripheral neuropathy resulting in foot ulcers and amputations, and cardiovascular symptoms leading to heart disease, stroke and hypertension are just some of most common complications.[4-6]

Type 1 DM develops due to an absolute insulin deficiency caused by β-cell destruction, an autoimmune process.[4] This type of DM usually has its onset in early adolescence. Another type of type 1 DM not related to autoimmunity or HLA is termed idiopathic DM. This classification is strongly inherited but has no known etiology.[4]

Individuals who develop DM in adulthood usually have type 2 DM characterized by insulin resistance and relative insulin deficiency rather than absolute deficiency.[4] This is the most common classification of DM, accounting for 90-95% of all diagnoses. The destruction of β-cells through autoimmune antibodies is not present in these individuals.[4] Many patients appear to have normal or elevated insulin levels due to the initial increased production of insulin to keep up with the increased amount of glucose in the bloodstream; however, eventually insulin production cannot keep up with the amount of glucose in the blood, resulting in DM.[4] The most common cause of type 2 DM mellitus is a combination of obesity (especially central adiposity) and genetic predisposition.[80,81]

Gestational DM is glucose intolerance first recognized after the onset of pregnancy.[79] Risk factors include obesity, race, age over 25 years old, previous pregnancy with gestational DM, and family history of diabetes. By the third trimester of a normal pregnancy, insulin sensitivity has decreased by approximately 50%.[79] This process is necessary to divert nutrients to the fetus and allow for accumulation of calorie storage in the mother.[79] In a normal pregnancy this process is compensated by increased production of insulin. When this mechanism fails, gestational DM ensues.[79] DM during pregnancy can have harmful effects on the infant. Gestational DM can increase the risk of stillbirth, miscarriage,

macrosomia, birth defects and preeclampsia.[82] Risk of obesity and early onset of type 2 DDM are increased for these infants.[82]

Diabetes mellitus in the AI/AN population

Diabetes mellitus has long been a critical issue for the AI/ANs and is so prevalent that it is referred to as an epidemic among the AI/AN population.[7-12] A cross-sectional analysis by Roberts et al. using the Behavioral Risk Factor Surveillance System between 1994 and 2000 found that AI/ANs were 1.7 times as likely as Whites to be diagnosed with DM.[83] This disparity continues to increase; in 2001 and 2007 AI/ANs had 2.5 (1.93-3.32) times the odds of being diagnosed with DM compared to Non-Hispanic Whites.[83] The prevalence of DM from 2004-2008 among AI/ANs was significantly higher compared to Non-Hispanic whites (AI/AN 4.8%, Non-Hispanic Whites 2.6%, $p<0.05$).[59] From 2007-2009, AI/AN adults 20 and over had the highest prevalence of diagnosed DM (16.1% AI/ANs compared to 7.1% of Non-Hispanic Whites).[5] In 2012 AI/AN adults were 2.3 times as likely as Non-Hispanic Whites to have been diagnosed with DM.[8] According to the Indian Health Service (IHS) in January 2013, among all races in the United States, AI/ANs continue to have the highest rates of type 2 DM.[13] Not only do AI/ANs have a higher prevalence of DM compared to other Americans, but the IHS also reports that they die at higher rates (152% higher) from DM.[68]

This increased risk could be partly attributed to increased diagnosis and screening; however, it has been shown that for every 1 individual diagnosed with DM three cases remain undiagnosed.[59] According to the Behavioral Risk Factor and Surveillance Survey, diagnosis of DM differs by state as well as race. Among the 8 states of interest in our analyses, Alaska had the lowest prevalence of ever being diagnosed with DM (5.3%), followed by Utah (6.5%), Minnesota (6.7%), Oregon (7.2%), Nebraska (7.7%) and New

Mexico (8.5%), Washington (7.6%), and Oklahoma (10.4%).[84] These differences are most likely attributed to actual differences in the prevalence of DM by state and to the varying rates of diagnosis of DM across states. Many variables factor into the high prevalence of DM among AI/AN populations. Cultural perceptions of DM and chronic disease management contribute to the increasing incidence and lack of control among culturally traditional AI/AN populations. Henderson et al. conducted a qualitative study of 30 elder AI adults in the Southeastern region of the United States to better understand opposing models of conceptualizing DM among the AI population.[85] His interviews revealed that those who live in culturally traditional areas value cultural networks in which non-adherence to medical advice is perceived as acceptable and even desirable because it creates solidarity with others in the community.[85] Many perceive development of type 2 DM as inevitable and normal, which does not encourage behavior change.[85]

Resistance to change behaviors increases severity of the disease. This is evident when examining the rate of DM complications in AI/ANs compared to the general U.S. population. Hypertension affects approximately 2/3 off AI/ANs with DM in IHS according to a cross-sectional analysis of over 30,000 AI adults in central Arizona.[86] A fact-sheet released by the Department of Health and Human Services states that in 2008, AI/ANs with DM had a 1.6 times higher death rate and 1.9 times higher incidence of kidney failure compared to the general U.S. population with DM.[8] AI/ANs with DM have 2-4 times the rates of heart disease death and stroke as well as 3-8 times the risk for cardiovascular disease.[8] Adults with DM in the Indian Health Service in central Arizona had treatment costs that accounted for more than 1/3 of all costs to adults in the system.[86] The costs of treatment accrued for AI/ANs with diabetes in the IHS was $7682 annually per individual for treatment from 2004-2005.[86]

A cycle that perpetuates the epidemic is created in this population when DM women become pregnant thereby predisposing their offspring to early onset of impaired glucose tolerance[87] and DM leading to DM during pregnancy again.[59] This trend has consistently increased over the last 20 years. Acton et al. used an IHS outpatient database from 500 tribal health facilities to find that from 1990-1998 the number of children, adolescents and young adults diagnosed with DM in the IHS system had increased by 71% over that period.[7] The prevalence of DM among youth aged 15-19 has increased 110% from 1990 to 2009.[8] In 2012 the Department of Health and Human Services reported that AI/AN youth aged 10-19 were 9 times as likely to have been diagnosed with Type 2 DM compared to Non-Hispanic Whites.[8] Evidence of this trend is seen especially among Pima Indians who have the highest prevalence of DM in the world.[7] Using the National Health Interview Surveys, Barnes et al. revealed that Pima Indians aged 15-19 who were exposed to DM in utero were 9 times as likely as those not exposed to develop DM by age 20-24 (24.72% vs. 2.75%).[59]

Gestational DM is also a concern among the AI/AN with 11.1% of women affected compared to 6.0% of white women in 5,440 mothers in Oregon in a cross-sectional study conducted in 2004 and 2005.[88] However, after controlling for maternal age, BMI, income, maternal education, and nativity (native born/foreign born) Hunsberger et al. finds no difference between AI/AN and non-Hispanic whites (OR = 1.17, CI 0.71-1.95).[88]

Diabetes mellitus and Preterm birth

Gestational, maternal type 1, and maternal type 2 DM have been shown to be risk factors for preterm birth, both spontaneous and induced. A study spanning from 1988-2006 by Kock et al. analyzed whether spontaneous preterm birth as well as total preterm birth was more likely in mothers with DM from Vienna.[89] Results indicated that women with DM had a significant increase in incidence of preterm birth (17.4% vs. 7.3%, p=0.002) and a

significant increase in spontaneous preterm birth (10.7% vs. 5.2%, p=0.0479).[89] While it has previously been customary for physicians to induce labor in the late preterm period among women with DM, more recently, Thung et al. comment that with improvement of disease management and fetal testing, all aspects of disease and pregnancy need to be taken into consideration when deciding whether to induce labor.[90] It has become more common to wait until spontaneous delivery.

A retrospective cohort study of 11,153 pregnancies in Alberta from 1991-1997 found a significant association between gestational DM and preterm birth (membrane rupture and spontaneous delivery ≤37 weeks gestation).[91] From 1996-1998 a large retrospective cohort was conducted in Northern California in the Kaiser Permanente program, Hedderson found that pregnant women in all different degrees of glucose intolerance (categorized by 1-h plasma glucose at least 140 mg/dL, Carpenter-Coustan, and gestational DM) have an increased risk of spontaneous preterm birth compared to women with a normal glucose intolerance test.[92] Ten years later, a prospective cohort study from 2008-2010 conducted by Niromanesh et al., 440 normal pregnant women between 20 and 35 years of age were analyzed. Preterm birth was found to be 10.9 (95% CI: 1.6-74.4, p<0.0001) times as likely among the women with hypertriglyceridaemia (17.8%) compared to controls (5.9%) after adjusting for age.[93] This finding was replicated when glucose challenge test results were analyzed among 192 pregnant women recruited from an urban obstetrical hospital in Pittsburgh, PA; adjusted models suggest that there is a significant increased odds for preterm birth among those with increasing GCT levels.[94] This study reaffirmed findings that mothers with GDM or other conditions such as gestational hyperglycemia have a higher incidence of preterm birth.[94]

In a Danish prospective cohort study from 1993-1999, women with Type 1 DM were 7 times as likely as the total population to have a preterm delivery (95% CI: 6.3-7.6).[95] Following this study, from 1999-2000, Evers et al. showed a similar outcome among women with type 1 DM in the Netherlands when he found a risk ratio of 4.5 (95% CI: 3.8-5.3) for preterm birth compared to national data.[96] Trend analyses have revealed risks of poor perinatal outcomes are increased when DM is not well controlled. Danish women with type 1 DM in a prospective cohort study by Damm et al. had an increased risk of preterm birth as their HbA_{1c} levels increased, indicating decreased control of disease (adjusted OR = 1.75, 95% CI: 1.08-2.82; p=0.023).[97]

Another Danish retrospective single center exploratory analysis over a 12 year period (1992-2006) revealed that preterm delivery occurred in 21.4% of women with type 2 DM, significantly higher than the normal population ($p<0.02$).[98] Of these preterm deliveries, 25% were spontaneous and the remaining 75% were induced for medical reasons. During the same time period, Type 2 DM was also associated with preterm birth in a single center study conducted by Ezimokhai et al.[99] In Saudi Arabia, diabetic mothers were found to be more likely than nondiabetic mothers to have a pregnancy result in preterm birth (17.5% vs. 7.0%, respectively).[99]

Within the U.S., Rosenberg et al. conducted a population based retrospective cohort study from 1999-2001 of all singleton births in New York City.[100] They found that women with chronic DM had 2.54 times the risk of preterm birth compared to those without DM after adjusting for maternal age, marital status, mother's education and birthplace, prenatal care payer, social risk, parity, and trimester in which prenatal care began (95% CI: 2.18-2.95, $p<0.001$).[100] Over the past 15 years studies with large sample sizes in the U.S. (Sibai et al.) and Saudi Arabia (Wahabi et al.) have replicated those studies previously mentioned and

compared the odds of preterm birth among pregnant women with prepregnancy DM to non-diabetic pregnant women with similar statistically significant results (OR = 2.70 and 2.23, respectively).[101,102] This same U.S. study further investigated the association of multiple classifications of preterm birth and demonstrated vast differences between women with pregestational DM and controls. When Sibai et al. looked at spontaneous preterm birth prior to 35 weeks gestation they saw an increased risk for women with pregestational DM compared to non-diabetic women (OR=2.1, 1.4-3.0).[101] Indicated delivery prior to 37 weeks was 8.1 (6.0-10.9) times as likely among women with pregestational DM compared to controls.[101] Disparities for the risk of indicated preterm birth prior to 35 weeks narrowed but were still significantly increased in women with pregestational DM (OR= 4.8; 95%CI = 3.0-7.5).[101] These findings represent an enormous difference with major clinical implications. As discussed above, preterm birth increases infant's risk for a host of serious health problems that can last a lifetime.[103,104] Preterm birth increases infant's risk for infections and can cause problems in the baby's brain, lungs, intestines, vision, and hearing.[103,104] In addition, being born preterm predisposes an infant to obesity and DM later in life.[15-20] This creates a cycle that increases the prevalence of DM and therefore puts future infants at greater risk of premature birth and consequently developing DM.[15-20]

Clausen et al. conducted a large retrospective cohort study that compared type 1 and type 2 DM pregnancy outcomes from 1996-2002. They found that women with type 2 DM had significantly longer gestational periods (38.0 vs. 37.3, p=0.03).[105] The prevalence of delivery prior to 34 weeks gestation was greater in type 2 DM compared to type 1 (14%vs. 7%, respectively), and women with type 2 DM were less likely to deliver prior to 37 weeks gestation compared to women with Type 1 DM (31% vs. 38%, respectively); however neither of these differences were significant.[105] In the same study, preterm delivery was

found to significantly increase in women with type 2 DM, from the time period 1996-2001 compared to the time period from 1980-1992 (15% vs. 31%, respectively, p=0.04).[105] A similar prospective cohort study of 682 pregnancies from 2006-2009 by Murphy et al. compared perinatal outcomes among pregnant women with Type 1 versus Type 2 DM and found that women with Type 1 DM delivered infants at significantly shorter gestational weeks (37.4 weeks versus 38.1 weeks, p<0.0001) and had significantly more premature deliveries (<37 weeks) (37.1% for Type 1 and 17.5% Type 2).[106] When the researchers looked at differences in early premature delivery, no significant difference was observed.[106] A U.S. study by Sibai et al. revealed that increasing severity of pregestational DM resulted in increased incidence of preterm delivery (both prior to 37 weeks gestation and 35 weeks gestation) using a trend test.[107]

Gaps in Literature

The diabetes mellitus epidemic among American Indians/Alaska Natives has been well documented over the past 40 years. Extensive literature exists on health disparities in poor birth outcomes, particularly preterm birth, between AI/ANs and Non-Hispanic Whites. The biological plausibility connecting DM to preterm birth has also been well established. Therefore, we understand that AI/AN women are at greater risk for poor health outcomes in maternal and infant health separately; however, linking these aspects has yet to be accomplished. This study will assess the association of prepregnancy DM and gestational DM with preterm birth among participating AI/AN women. We have also yet to examine whether there is a difference in the association of DM and preterm birth between AI/AN tribes. In order to examine this possibility, state of residence will be used as a proxy for tribe. State of residence will be assumed to represent the largest tribe in that state. This study could be a catalyst for further research on how DM might differently affect AI/AN women of

various tribes or states during pregnancy. This understanding could enable better interventions and contribute to the decision making process of distribution of attention and resources from the public health community. By comparing the association of DM and preterm birth, among AI/ANs and between states, we can hypothesize whether an amplification of risk is associated with specific behavioral or cultural variables or genetic composition of specific tribes. This knowledge can lead to action improving the health of AI/AN women and children.

Methods

Women who delivered a live singleton birth between the years 2004 and 2011 and participated in the Pregnancy Risk Assessment Monitoring System (PRAMS) were included in this retrospective cohort study.

PRAMS is a surveillance project in the United States that collects data in 40 states on women who recently had a live birth.[108] The project spans from 1987 to the present and is run by the Centers for Disease Control and state health departments.[109] The questionnaire is updated periodically and each update is identified as a phase.[109] A stratified systematic sample is drawn each month from current eligible birth certificates within each participating state.[108] Each state samples approximately 1300 to 3400 women annually, which comprise approximately 3-6 strata.[108] Low birth weight infants as well as women from minority race/ethnicities are oversampled in order to achieve large enough statewide samples to estimate stratum-specific proportions of risk factors within 3.5% at 95% confidence and 5% at 95% confidence.[109]

Data collected include a self-report questionnaire and demographic information from vital records.[109] One of PRAMS' strengths is that the data collection process is standardized across and within states enabling analysis of different geographical populations.[109] All women selected receive their first mailing, a preletter, 2-4 months after delivery that introduces the study and informs the women that they will be receiving a survey in the mail.[108] The initial mail questionnaire packet is sent approximately 3-7 days after the preletter and contains five components.[108] The first is a cover letter that describes the purpose of the study, how and why they were chosen, description of the process, explanation of a reward or incentive and a phone number to contact for questions.[109] Second, the packet contains the questionnaire booklet. A 3-year calendar is provided in order

to aid with answering questions in the survey.[108] A brochure that answers frequently asked questions and provides additional information about the surveillance system is included as well as a participation incentive, which varies by state.[109] PRAMS selects 100-200 birth certificates each month using a stratified systematic sample from women who delivered a live-born infant within the last 2-4 months and are state residents.[110] A 'tickler' is sent to selected women 7-10 days after the initial mailing to thank the women for participating and remind them to return the survey.[109] If women do not respond after 7-14 days after the tickler, a second mailed questionnaire packet is sent.[108] The third mailed questionnaire is sent 7-14 days after the 2nd if there is still no response.[108] If 7-14 days pass with no response after the third mailing, the state health departments resort to telephone calls.[109] The calling period lasts 2-3 weeks in which up to 15 attempts can be made at various times and days of the week.[109] This entire process lasts approximately 60-95 days.[108]

Due to PRAMS' complex sample design, analysis weights that correspond to the number of women that each respondent represents are applied in analysis.[108] These weights are calculated by multiplying the sampling weight, nonresponse weight and noncoverage weight.[108]

Sampling weights equal the reciprocal of the sampling fraction that is applied to stratum for each respondent and can range from 1 to 211 depending on the size of state and stratum to which the respondent belongs.[108]

When multivariable analysis shows that nonresponse in a stratum is associated with specific characteristics, nonresponse adjustment factors (the ratio of the sample size in the category to the number of respondents in the category) are applied to each category to compensate.[108] Otherwise, when there is no pattern of nonresponse based on characteristics, the adjustment factor is applied to the entire stratum and is calculated as the ratio of the

sample size in the stratum to respondents in the stratum.[108] Nonresponse rates are calculated by assuming that nonrespondents have similar answers to questionnaires as other women in their stratum and adjustment category.[108]

Noncoverage weights are determined by conducting frame omission studies to identify problems that occur during frame construction.[108] Omitted records can be evenly distributed across the state due to late processing or can be clustered in specific hospitals, counties or time of year.[108] States provide a calendar year birth tape to the CDC, which is compared to frame files for the year of births.[108] The noncoverage weights are essential to have total estimates from sample data in accordance with the known totals from the birth tape.[108] A more detailed explanation of the PRAMS methodology can be found elsewhere.[109]

This analysis was conducted among states that had at least five percent of all live births to AI/AN women[110], participated in PRAMS Phase 5 (2004-2008) and Phase 6 (2009-2011), and had a ≥70% response rate from 2004-2006 and a ≥60% response rate from 2007-2011. States that met the inclusion criteria included: Alaska (2004-2010), Minnesota (2004-2011), Nebraska (2004-2011), New Mexico (2004-2005, 2011), Oklahoma (2004-2011), Oregon (2004-2011), Utah (2004-2011), and Washington (2004-2011).[110] Arizona, Montana, North Dakota, and South Dakota also have a high prevalence of AI/AN births; however, these states either do not participate in PRAMS or did not participate in Phase 5 or Phase 6 and therefore were not included in the analysis.

The main analysis included only singleton births (n = 92,123) and was further refined to include only AI/AN women (n = 12,420).

To account for the complex sample design, SAS 9.3 and SAS callable SUDAAN were used to analyze data (Cary, NC, USA). This software employs first-order Taylor series to calculate accurate standard errors for estimates. Women without information on diabetes

mellitus (n = 7) and women with missing data on preterm birth (n = 188) were excluded from the model that compared any DM with no DM (n=12,225). Separate models were run for gestational DM and prepregnancy DM. In the gestational DM model (n = 11,976), women with prepregnancy DM (n = 210) were excluded and women with missing information on gestational DM were excluded (n = 39). In the prepregnancy DM model (n = 11700), women with gestational DM were excluded (n = 493) and women with missing information on prepregnancy DM were excluded (n = 32).

American Indians/Alaska Natives were identified from birth certificate variables. Single race American Indian, single race Alaska Native, and mixed race American Indian/Alaska Native were included in the American Indian/Alaska Native study population.

Preterm birth was defined as live births that occurred prior to 37 weeks gestational age. The 2003 version of the birth certificate updated the diabetes variable used on the 1989 version to gestational diabetes only. In this analysis, gestational diabetes was defined with the birth certificate variable for observations collected after their state adopted the 2003 birth certificate (2009 or all states except New Mexico which adopted the 2003 birth certificate in 2011). Observations were also considered to have gestational diabetes if observations were collected before the 2003 birth certificate was adopted, the birth certificate diabetes variable is 'yes', and the gestational diabetes variable in the PRAMS questionnaire indicated gestational diabetes. Births in states before the birth certificate change that indicated diabetes on the birth certificate were considered to have prepregnancy diabetes if the PRAMS questionnaire confirms diagnosis of diabetes prior to pregnancy. The PRAMS questionnaire was used alone to indicate prepregnancy diabetes when the birth occurred after the adoption of the 2003 birth certificate in the mother's respective state. In

the multivariable analyses diabetes was defined as having either gestational or prepregnancy diabetes, irrespective of the data source.

Maternal age was obtained from the birth certificate variable and was grouped into age categories: 20 and younger, 21-24, 25-29, 30-34, and 35 and older, with 21-24 years old used as the reference age group. Prepregnancy hypertension was defined first with the birth certificate variable and, if missing, with the prepregnancy hypertension PRAMS variable. The World Health Organization (WHO) Body Mass Index (BMI) classification guidelines were used to categorize pregestational BMI into underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥30.0 kg/m^2).[111] Observations with BMI's less than 13 kg/m^2 or greater than 70 kg/m^2 were considered implausible and set to missing. Weight gain during pregnancy was categorized as inadequate, appropriate, or excess based on the 2009 Institute Of Medicine's guidelines.[112]

Alcohol use during pregnancy was defined as drinking any alcoholic beverage in the last three months of pregnancy. We used the PRAMS question 'During the last 3 months of your pregnancy, how many alcoholic drinks did you have in an average week?' and identified any alcohol use in the last three months of pregnancy as any answer other than 'I didn't drink then'. Cigarette smoking was defined as smoking any cigarettes during the entire pregnancy and was examined with both birth certificate and PRAMS variables. We considered smoking during pregnancy as any answer to the PRAMS question 'In the last 3 months of your pregnancy, how many cigarettes did you smoke on an average day' other than I didn't smoke then or any answer greater than 0 for the three birth certificate variables that report number of cigarettes in each trimester. Pregnancy intention was assessed with the PRAMS question 'When you got pregnant with your new baby, were you trying to get pregnant?'. If this question was blank, pregnancy intention was determined with the

question 'Thinking back to just before you got pregnant with your new baby, how did you feel about becoming pregnant?'. If the answer was 'I didn't want to be pregnant then or at any time in the future' or 'I wanted to be pregnant later' the pregnancy was considered unintended. If the answer to the previous question was 'I wanted to be pregnant sooner' or 'I wanted to be pregnant then' the pregnancy was intended. Maternal education was categorized as greater than 12 years, 12 years, and less than 12 years. Federal Poverty Level was categorized as >138% and ≤138% FPL. The midpoint of a PRAMS variable corresponding to a range of total income 12 months before the birth was used in conjunction with the number of dependence and state and year specific poverty cutoffs to calculate the percent of FPL.[113] Insurance type was categorized into Indian Health Services, private, Medicaid and other.

Macrosomia was defined with a birth certificate variable as greater than or equal to 4500 grams at birth. The large for gestational age variable was defined based on the 90th percentile. Premature rupture of membranes was defined with a birth certificate variable when available and the PRAMS variable when the birth certificate variable was missing.

Descriptive statistics of maternal demographics, pregnancy characteristics and birth outcomes were conducted to determine prevalence estimates, 95% confidence intervals (CIs), and chi squares tests for the outcome (preterm birth) and exposure (diabetes mellitus). Preterm birth was categorized as a binary variable (preterm/term birth) as well as categorized as >37 weeks gestation, 34-36 weeks gestation, 28-33 weeks gestation, and ≤27 weeks gestation. Diabetes mellitus was categorized as a binary variable (ever diabetes/never diabetes) as well as sub categorized into prepregnancy diabetes, gestational diabetes and never diabetes.

Crude odds ratios for prepregnancy DM and preterm birth as well as gestational DM and preterm birth were calculated with 95% confidence intervals. Possible confounders were assessed from previous research and biological plausibility with a Directed Acyclic Graph (Figure 1). Variables determined plausible were then assessed with a bivariate logistic regression model to determine crude odds ratios with the main exposure and main outcome. Three separate models were used to assess the association of potential confounders with preterm birth. The first excluded women with prepregnancy DM, the second excluded women with gestational DM, and the third included all women despite their DM type. Variables with significant association with the exposure and outcome were added to the multivariable logistic regression model. Two models were built, one including prepregnancy BMI as a confounder and the other without prepregnancy BMI, to ensure comparability with previous studies.

Confounders that were added by the method mentioned above were then combined with all other confounders as well as the exposure to assess the joint effect of the variables by creating interaction terms. Likelihood ratio tests were used to perform backwards elimination of interaction terms. Interaction terms were also assessed using forward selection. Following interaction assessment, backwards elimination was used to identify confounding variables that did not change the adjusted odds ratio more than 10% from the fully adjusted odds ratio and again identifying confounders that did not change the beta estimate by more than 10%. After consideration of the differences in DM prevalence between states, especially Alaska's low prevalence, we conducted separate analyses, one omitting Alaskan women and a second with a new definition of DM. Women who reported being diagnosed with DM either in the PRAMS questionnaire or on the birth certificate were considered to have DM. The new DM variable was used in another multivariable analysis.

A secondary analysis was conducted to assess the association of DM and preterm birth among AI/AN women separately for each of the eight states. The final model from the multivariable analysis was used to assess this association in each state. Separate models for each state were also constructed with our new definition of DM.

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Abstract

Background: Diabetes mellitus (DM) is associated with preterm birth, but data on this association in American Indian and Alaska Natives (AI/AN), a population with increased risk of DM and preterm birth, is limited.
Methods: We used surveillance data from the Centers for Disease Control and Prevention's Pregnancy Risk Assessment Monitoring System to assess the association of DM with preterm birth among AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington from 2004-2011. Our second aim was to examine whether this association differed between states. Using a population-based retrospective cohort 12,420 live singleton births to AI/AN women we conducted multivariable logistic regression models to estimate the odds ratio adjusted for maternal age and prepregnancy BMI with all observations and then stratified by state.
Results: Women with DM had 1.83 times the odds of having a preterm birth than women without DM [95% confidence interval (CI) 1.21, 2.78]. After stratifying on state, women with DM in Nebraska had the greatest odds of preterm birth (aOR = 6.63, [95%CI 3.80, 11.6]) while women in Alaska had a protective effect of DM (aOR = 0.17, [95% CI 0.07, 0.42]) compared to women without DM.
Conclusion: AI/AN women with DM had significantly greater odds of preterm birth compared to AI/AN women without DM across states. Differences between states calls for increased public health efforts in high-risk areas as well as further research to assess whether differences are attributable to diagnosis, reporting, tribal, healthcare or lifestyle factors.

Background

Preterm delivery is defined as a pregnancy resulting in a live birth at gestational age less than 37 weeks.[1] Preterm delivery affects nearly 1 in 8 infants and accounts for 35% of all infant deaths.[1] Many chronic and acute conditions increase the risk of delivering a preterm baby, such as maternal diabetes mellitus.[2,3]

Diabetes mellitus (DM) is a chronic disease that encompasses a group of metabolic disorders, which are characterized by defects in insulin action, insulin secretion, or both, resulting in hyperglycemia.[4] Serious complications can result from DM and women require additional attention during pregnancy to prevent adverse outcomes to the mother and offspring.[4-6]

A DM epidemic is occurring among the AI/AN population.[7-12] AI/ANs have the highest rate of DM among all races in the United States.[5,13] AI/ANs represent a unique population in the United States that has suffered from displacement and discrimination for centuries.[58] Prior to colonization, AI/ANs practiced a subsistence lifestyle and lived off the land. European settlement in the Americas forced AI/ANs from their traditional lands and onto reservations that did not offer the same opportunity to grow, hunt and gather their traditional foods.[64] Their loss of land has resulted in a history of poverty that is persistent today.[36] Government-sponsored commodity food programs were a consolation offered by Europeans; however, these foods, which were higher in fat and calories and lower in fiber served to deteriorate AI/AN health rather than provide a beneficial alternative.[64] These conditions have resulted in poor health outcomes, such as higher incidence of diabetes and obesity in AI/AN populations. Simultaneously, AI/AN women have a higher incidence of preterm birth compared to other populations in the United States.[60]

Currently, no data exist on the association of DM with preterm birth in an AI/AN population and if this association differs by geographical region. This information would be beneficial in clinical and public health settings to assess the need for pregnancy interventions in this population and to determine geographic distribution of resources. In a population-based retrospective cohort of 12,420 live singleton births to AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington from 2004-2011, we investigated the association of DM and preterm birth across and between states.

Methods

Women who delivered a live singleton birth between the years 2004 and 2011 and participated in the Pregnancy Risk Assessment Monitoring System (PRAMS) were included in this population-based retrospective cohort study. PRAMS is a surveillance project in the

United States that collects data in 40 states on women who recently had a live birth. Data collected include a self-report questionnaire and demographic information from vital records. Due to PRAMS' complex sample design, analysis weights that correspond to the number of women that each respondent represents are applied in analysis. These weights are calculated by multiplying the sampling weight, nonresponse weight and noncoverage weight.

This analysis was conducted among states that had at least five percent of all live births to AI/AN women, participated in PRAMS Phase 5 (2004-2008) and Phase 6 (2009-2011), and had a ≥70% response rate from 2004-2006 and a ≥60% response rate from 2007-2011.[110] States that met the inclusion criteria included: Alaska (2004-2010), Minnesota (2004-2011), Nebraska (2004-2011), New Mexico (2004-2005, 2011), Oklahoma (2004-2011), Oregon (2004-2011), Utah (2004-2011), and Washington (2004-2011).[110]

The main analysis included only singleton births (n = 92,123) and was further refined to include only AI/AN women (n = 12,420). To account for the complex sample design, SAS 9.3 and SAS callable SUDAAN was used to analyze data (Cary, NC, USA). Women without information on DM (n = 7) and women with missing data on preterm birth (n = 188) were excluded from the model that compared any DM with no DM (n=12,225).

American Indians/Alaska Natives were identified from birth certificate variables. Single race American Indian, single race Alaska Native, and mixed race American Indian/Alaska Native were included in the American Indian/Alaska Native study population.

Preterm birth was defined as live births that occurred prior to 37 completed weeks gestational age. The 2003 version of the birth certificate updated the diabetes variable used on the 1989 version to gestational diabetes only. In this analysis, gestational diabetes was

defined with the birth certificate variable for observations collected after their state adopted the 2003 birth certificate (2009 or all states except New Mexico which adopted the 2003 birth certificate in 2011). Observations were also considered to have gestational diabetes if observations were collected before the 2003 birth certificate was adopted, the birth certificate diabetes variable is 'yes', and the gestational diabetes variable in the PRAMS questionnaire indicated gestational diabetes. Births in states before the birth certificate change that indicated diabetes on the birth certificate were considered to have prepregnancy diabetes if the PRAMS questionnaire confirms diagnosis of diabetes prior to pregnancy. The PRAMS questionnaire was used alone to indicate prepregnancy diabetes when the birth occurred after the adoption of the 2003 birth certificate in the mother's respective state. In the multivariable analyses diabetes was defined as having either gestational or prepregnancy diabetes, irrespective of the data source.

Potential confounders were considered a priori using a Directed Acyclic Graph (DAG), biological plausibility and consulting previous literature. The following variables were identified as potential confounders: weight gain during pregnancy, prepregnancy BMI, poverty, prepregnancy hypertension, education and maternal age.

Descriptive statistics of maternal demographics, pregnancy characteristics and birth outcomes were conducted to determine prevalence estimates, 95% confidence intervals (CIs), and chi squares tests for the outcome (preterm birth) and exposure (diabetes mellitus). Preterm birth was categorized as a binary variable (preterm/term birth). DM was categorized as a binary variable (ever DM/never DM) as well as sub categorized into prepregnancy DM, gestational DM and never DM.

Crude odds ratios for DM and preterm birth were calculated with 95% confidence intervals. Variables determined as plausible confounders were then assessed with a bivariate

logistic regression model to determine crude odds ratios with the main exposure and main outcome. Variables with significant association with the exposure and outcome were added to the multivariable logistic regression model. Two models were built, one including prepregnancy BMI as a confounder and the other without prepregnancy BMI, to ensure comparability with previous studies.

Confounders that were added by the method mentioned above were then combined with all other confounders as well as the exposure to assess the joint effect of the variables by creating interaction terms. Likelihood ratio tests were used to perform backwards elimination of interaction terms. Interaction terms were also assessed using forward selection. Following interaction assessment, backwards elimination was used to identify confounding variables that did not change the adjusted odds ratio more than 10% from the fully adjusted odds ratio and again identifying confounders that did not change the beta estimate by more than 10%. After consideration of the differences in DM prevalence between states, especially Alaska's low prevalence, we conducted separate analyses; one omitting Alaskan women and a second with a new definition of DM. Women who reported being diagnosed with DM either in the PRAMS questionnaire or on the birth certificate were considered to have DM. The new DM variable was used in another multivariable analysis.

A secondary analysis was conducted to assess the association of DM and preterm birth among AI/AN women separately for each of the eight states. The final model from the multivariable analysis was used to assess this association in each state. Separate models for each state were also constructed with our new definition of DM.

Results

The study population consisted of 12,420 live singleton births to AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington

between 2004-2011. DM was reported in 5.92% of the study population (Table 1). Preterm birth occurred in 8.95% (1,861 of 12,420) of births in the study population (Table 1). Older age, greater than 12 years completed education, marriage, obesity, hypertension, or preeclampsia were all significantly more common in women with DM (Table 1). Women 35 years and older, with 12 years or less completed education, who smoked during pregnancy, entered prenatal care after the first trimester or not at all, with prepregnancy or gestational DM, women with inadequate weight gain during pregnancy, or women with preeclampsia were significantly more likely to have a preterm birth (Table 1). Women 35 years and older had 3.71 (95% CI: 2.25-6.11) times the odds of having DM and 2.09 (95% CI: 1.45-3.00) times the odds of preterm birth compared to women 21-24 (Table 2). Variables found to be significantly associated with DM were women who were obese (OR = 5.28, 95% CI = 3.40-8.20) compared to normal weight, overweight (OR = 1.91, 95% CI: 1.16-3.16) compared to normal weight, and hypertensive (OR = 3.61, 95% CI: 2.48-5.27) compared to non-hypertensive women (Table 2). Women with prepregnancy hypertension had significantly higher odds of preterm birth compared to women without hypertension (OR 1.89, 95% CI: 1.49-2.40) (Table 2).

The covariates evaluated were our main exposure (diabetes mellitus), maternal age, education, and prepregnancy hypertension. A second model was run including prepregnancy BMI to enable comparison to previous literature, even though it was not found to be associated with exposure and outcome in the preliminary analysis. After interaction assessment in both models, all interaction terms dropped out.

The full multivariable logistic regression model including all confounders except prepregnancy BMI found that diabetes mellitus was significantly associated with preterm birth (aOR = 1.65, 95% CI: 1.11-2.47) (Table 3). After confounding assessment, the reduced

model contained maternal age in addition to DM. Women with DM had significantly greater times the odds of preterm birth compared to women without DM (aOR = 1.76, 95% CI: 1.20-2.58, p = 0.004). A woman with DM had 1.92 (95% CI: 1.30, 2.85, p = 0.0011) times the odds of preterm birth as a woman without DM when we controlled for maternal age and prepregnancy BMI (Table 3).

Our second analysis indicated a difference in the association of DM with preterm birth by state. In Alaska, DM demonstrated a significant protective effect against preterm birth with the crude and adjusted ORs in the models with and without prepregnancy BMI (Table 4). Women in Nebraska with diabetes had 5.92 (95% CI = 3.45-10.16, p = 0.000) times the odds of preterm birth compared to women without DM, the largest association among all states (Table 4).

Discussion

This study examined the association of diabetes mellitus with preterm birth among AI/AN women in eight states between 2004-2011. Our results indicated a significant increase in the odds of preterm birth among women with any type of DM compared to women without DM after controlling for maternal age, prepregnancy hypertension and prepregnancy BMI. Women with diabetes had 1.76 times the odds of preterm birth compared to women without when controlling for maternal age and had 1.92 times the odds of preterm birth after controlling for maternal age and prepregnancy BMI. Our results are consistent with previous literature that show a significant association of DM with preterm birth (both spontaneous and induced) in other populations.[33,89,91-100,102] This association has major implications for AI/AN women and could contribute to a "vicious cycle" described by Lacroix et al. [19] Infants born preterm have an increased risk of developing DM later in life compared to term infants; when these offspring begin having children they place their

infants at an increased risk of preterm birth.[19] In a population that currently has the highest incidence of DM in the United States this cycle may be a contributing factor and, without intervention, could continue to increase the incidence of DM in the AI/AN population.[5,13]

The second aim of our study assessed the association of DM and preterm birth stratified on state. Our results supported Johnson et al.'s findings that the quality of prenatal care is heterogeneous across states for AI/AN women and therefore studies should avoid national aggregation and perform analyses on as geographically specific areas as possible.[114] . Our results indicate that differences do exist between states. AI/AN women with DM in Nebraska had 6.63 times the odds of preterm birth compared to women without DM. Nebraska had the greatest OR of any state in this study and was most consistent with ORs in previous studies. In contrast, women in Alaska demonstrated a significant protective effect of DM on preterm birth. Preliminary analyses revealed Alaska's low prevalence of DM (0.92%) compared with all other states, which had at least 5.92% of their populations diagnosed with DM (Table 1a). Alaska also had the highest prevalence of preterm birth (10.2%) (Table 1b). If women in Alaska are under-diagnosed with DM, due to healthcare utilization or quality, their resulting odds ratio will be biased towards the null. However, PRAMS data do not indicate a significant difference in frequency of testing for DM during pregnancy between states, and only 4 AI/AN women in Alaska had missing birth certificate data on DM, which was not significantly different compared to other states. We did not find a difference in the frequency of reporting DM before and after the adoption of the 2003 birth certificate in Alaska or in any other state. In our analysis we first identified women with DM according to the birth certificate and only included data from PRAMS when the DM variable was missing on the birth certificate. Further analyses revealed a significant difference in the prevalence of DM when we included women who reported diagnosis with DM in

PRAMS but the birth certificate indicated no DM. In Alaska, 9.36% of women reported having been diagnosed with DM when we used this alternative coding compared to 0.86% in original analyses. Using this definition of DM also produced a different adjusted odds ratio in multivariable analyses for Alaska (aOR = 1.15, 95% CI: [0.85-1.55] versus aOR = 0.14, 95% CI: [0.06-0.35]). However, this definition of DM was not significantly different from the result of our aggregated multivariable analyses.

Previous research suggests that Alaska Natives have a low prevalence of DM compared to other American Indians and the U.S. population as a whole.[115-118] In 2007, the age-adjusted prevalence of DM among Alaska Natives was 38 per 1,000 compared to 51 per 1,000 among all races in the United States.[116] The Behavioral Risk Factor Surveillance System (BRFSS) annually reports data on the prevalence of DM in Native and non-Native populations.[119-125] Their data suggest that the Alaska Native population does not have a significantly greater prevalence of DM compared to the Non-Native population in Alaska.[119-125] Their estimates of the prevalence of DM among Alaska Natives (3-7% from 2000-2009) was greater than data discussed above but lower than our estimate based on either birth certificate or PRAMS report of DM. This may reflect an over-reporting of DM in PRAMS because of the respondent's misunderstanding of the test for DM as a diagnosis of DM. However it is also possible that the prevalence estimate using this definition is more accurate than the BRFSS estimate, which may be an underestimate owing to under-diagnosis of DM in the general population. In any event, the BRFSS data does confirm Alaskans have a lower reported prevalence of DM than other states in the United States.[84,119-124] This indicates that, using our initial definition of DM, prevalence estimates of DM among Alaska Natives may underestimate the true prevalence, but when we compare Alaska Natives to other American Indian populations, our results are consistent with previous research. Future research is

needed to determine whether differences between states are significant, and if so, whether they are representative of differences in tribe, healthcare quality/utilization, or cultural behaviors.

Despite the significant implications of our study, limitations exist which affect our estimates and representativeness. First, our study excluded multiple births and therefore is not representative of these pregnancies, which are at greater risk for preterm birth. Second, AI/AN women who identified as both single and mixed race were included in our study. Third, we lacked data on women's tribal memberships and therefore could not make conclusions on differences between tribes. Fourth, we could not separately model women with gestational DM and women with prepregnancy DM due to strata sample size restrictions. Finally, some states had smaller sample sizes resulting in wider confidence intervals and less precise estimates.

The present study had many strengths. Our data consisted of a large population based study with an adequate number of AI/AN women to produce stable estimates. DM and preterm birth were both assessed and confirmed with multiple data sources (birth certificate and self reported PRAMS questionnaire). Our ability to stratify on state revealed important differences in the association of DM with preterm birth between states that may have implications for the distribution of public health efforts for quality of disease surveillance and treatment.

Prevention and management of DM among the AI/AN community, especially during pregnancy, is a public health priority considering the high and increasing prevalence in this population.[8] The large differences in the odds of preterm birth among women with DM between states calls for action to address the underlying issues in these populations. Further research and attention on state differences in both cultural and behavioral practices

as well as in prenatal care management in high-risk pregnancies among AI/AN women should be a priority in the public health community.

Conclusion

In a population-based retrospective cohort of 12,420 live singleton births to AI/AN women, DM was significantly associated with higher odds of preterm birth. Our results establish that this association, which has been demonstrated in other populations, is consistent in AI/AN women. However, stratification on state confirmed this association in some states, demonstrated a protective effect, or was not significant. Future investigation is needed to compare these findings to other races and identify underlying differences between states. Public health efforts should focus on intervening during pregnancies complicated by DM and distributing resources to high-risk areas.

Table 1. Demographic and Pregnancy characteristics of live singleton births to AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington[a] by diabetes mellitus status and preterm birth[b]

	Diabetes Mellitus			Preterm Birth[b]		
	Weighted[€] %	95% CI LCL	UCL	Weighted[€] %	95% CI LCL	UCL
Total	5.92	5.13	6.83	8.95	8.16	9.80
Maternal Age						
≤20	1.38	0.84	2.23	8.5	6.96	10.3
21-24	4.38	3.14	6.08	7.68	6.52	9.02
25-29	5.70	4.39	7.36	9.42	7.74	11.4
30-34	11.4	8.72	14.7	8.95	7.08	11.2
≥35	14.5	10.6	19.6	14.8	11.2	19.2
Birthplace						
Alaska	0.92	0.65	1.31	10.2	9.33	11.0
Minnesota	10.6	8.22	13.7	7.46	5.8	9.54
Nebraska	7.27	5.86	8.89	9.37	7.86	11.1
New Mexico	7.45	5.42	10.2	9.53	7.22	12.5
Oklahoma	6.07	4.50	8.15	8.84	7.23	10.8
Oregon	5.92	5.02	6.96	8.23	7.17	9.42
Utah	9.62	5.86	15.4	7.77	5.04	11.8
Washington	6.19	4.47	8.53	9.00	7.23	11.2
Education						
>12	7.02	5.64	8.71	7.05	5.95	8.33
12	6.27	4.95	7.92	9.45	8.14	10.9
<12	4.16	3.07	5.61	10.7	9.03	12.6
Federal Poverty Level						
>138%	6.36	4.87	8.27	8.39	6.79	10.3
≤138%	6.03	5.03	7.20	8.85	7.90	9.90
Medical Insurance						
Tribal	12.2	5.58	24.6	8.10	4.09	15.4
Private	6.90	4.54	10.4	8.23	5.90	11.4
Medicaid	6.99	5.37	9.06	8.47	6.23	9.91
Other	4.73	2.88	7.69	13.5	7.76	22.5
Marital Status						
Married	7.17	5.82	8.80	9.32	7.93	10.9
Other	5.15	4.22	6.27	8.70	7.79	9.70
Prepregnancy BMI[c]						
Underweight	3.07	1.20	7.61	14.3	8.46	23.2
Normal	2.67	1.83	3.88	8.62	7.47	9.94
Overweight	5.00	3.69	6.74	8.90	7.23	10.9
Obese	12.7	10.5	15.2	8.67	7.33	10.2

Table 1 continued

Weight Gain During Pregnancy[d]						
Inadequate	6.92	5.01	9.48	13.1	11.2	15.2
Appropriate	6.38	5.67	8.66	10.9	8.86	13.3
Excess	5.47	4.45	6.71	5.16	4.34	6.12
Pregnancy Intention						
Intended	5.35	4.46	6.41	9.36	8.35	10.5
Unintended	7.03	5.58	8.83	8.28	7.07	9.67
Alcohol Consumption During Pregnancy[e]						
Yes	4.62	2.28	9.14	14.2	9.31	20.9
No	6.04	5.21	6.99	8.73	7.93	9.59
Prenatal Smoking[f]						
Yes	5.06	3.63	7.01	10.5	8.76	12.5
No	6.28	5.36	7.36	8.41	7.54	9.38
Early Entry into Prenatal Care[g]						
Yes	6.19	5.24	7.29	8.23	7.37	9.18
No	5.60	4.16	7.49	10.9	9.10	12.9
Prepregnancy DM						
Yes				16.9	11.4	24.4
No				8.81	8.02	9.68
Gestational DM						
Yes				14.9	9.86	21.8
No				8.65	7.87	9.50
Any DM						
Yes				15.0	10.9	20.3
No				8.56	7.78	9.42
Prepregnancy Hypertension						
Yes	15.8	11.8	20.8	14.7	12.3	17.6
No	4.93	4.18	5.81	8.36	7.53	9.26
Preeclampsia						
Yes	15.9	12.0	20.8	14.9	12.5	17.7
No	5.02	4.26	5.92	8.41	7.58	9.32
Preterm Birth[b]						
Yes	10.0	7.30	13.5			
No	5.54	4.72	6.50			
PROM[h]						
Yes	10.2	5.16	19.0	37.3	29.3	46.1
No	5.77	4.98	6.67	7.88	7.14	8.70

Table 1 Continued

Macrosomia Baby[i]							
	Yes	15.1	11.5	19.5	3.18	1.77	5.66
	No	5.74	4.94	6.67	9.05	8.24	9.92
Large for Gestational Age Baby[j]							
	Yes	11.4	9.34	13.8	8.17	6.34	10.5
	No	5.16	4.31	6.17	8.49	7.63	9.43

[a]Based on PRAMS data, 2004-2011.

[h]Live birth 24-37 weeks gestation

[c]Underweight = <18.5 kg/m^2, normal = 18.5-24.9 kg/m^2, overweight = 25-29.9 kg/m^2, obese = 30+ kg/m^2

[d]Underweight: inadequate = less than 28 lbs, appropriate = 28-40 lbs, excess = greater than 40 lbs; Normal: inadequate = less than 25 lbs, appropriate = 25-35 lbs, excess = greater than 35 lbs; Overweight: inadequate = less than 15 lbs, appropriate = 15-25 lbs, excess = greater than 25 lbs; Obese: inadequate = less than 11 lbs, appropriate = 11-20 lbs, excess = greater than 20 lbs

[e]Any alcohol consumption during last three months of pregnancy

[f]Any cigarette smoking during entire pregnancy

[g]Attended prenatal care visit within first trimester of pregnancy

[h]Premature rupture of membranes

[i]4500+ gram birth weight

[j]Based on 90th percentile

*$p<0.05$

[€]Percepts based on data weighted for sample design, non-response, and non-coverage
Totals may not add up to total population due to missing observations

Table 2. Unadjusted Odds Ratios (OR), and 95 percent Confidence Intervals (CI) for preterm birth[a] and diabetes mellitus in a cohort of live singleton births to AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington[b€]

	Preterm Birth[a]			Any Diabetes Mellitus[c]		
	crude OR	95% CI[€]		crude OR	95% CI[€]	
Maternal Age						
≤20	1.12	0.85	1.48	0.30	0.17	0.56
21-24[d]	1.00	1.00	1.00	1.00	1.00	1.00
25-29	1.25	0.95	1.65	1.32	0.85	2.05
30-34	1.18	0.87	1.61	2.81	1.78	4.42
≥35	2.09	1.45	3.00	3.71	2.25	6.11
Birthplace						
Alaska	1.26	1.06	1.50	0.15	0.10	0.22
Minnesota	0.90	0.66	1.22	1.89	1.36	2.64
Nebraska	1.15	0.90	1.47	1.25	0.93	1.66
New Mexico	1.17	0.84	1.65	1.28	0.87	1.88
Oklahoma	1.08	0.83	1.41	1.03	0.72	1.48
Oregon[d]	1.00	1.00	1.00	1.00	1.00	1.00
Utah	0.94	0.58	1.52	1.69	0.96	2.98
Washington	1.10	0.83	1.46	1.05	0.71	1.55
Education						
>12[d]	1.00	1.00	1.00	1.00	1.00	1.00
12	1.38	1.08	1.76	0.89	0.63	1.25
<12	1.58	1.22	2.05	0.57	0.39	0.85
Federal Poverty Level						
≥138%[d]	1.00	1.00	1.00	1.00	1.00	1.00
<138%	1.06	0.82	1.37	0.94	0.67	1.33
Prepregnancy BMI[e]						
Underweight	1.77	0.96	3.27	1.15	0.41	3.23
Normal[d]	1.00	1.00	1.00	1.00	1.00	1.00
Overweight	1.03	0.79	1.36	1.91	1.16	3.16
Obese	1.01	0.79	1.28	5.28	3.40	8.20

Table 2 continued

Weight Gain During Pregnancy[f]						
Inadequate	1.24	0.93	1.64	1.09	0.68	1.76
Appropriate[d]	1.00	1.00	1.00	1.00	1.00	1.00
Excess	0.45	0.33	0.60	0.85	0.57	1.26
Prepregnancy Diabetes						
Yes	2.10	1.31	3.37			
No[d]	1.00	1.00	1.00			
Gestational Diabetes						
Yes	1.84	1.14	2.97			
No[d]	1.00	1.00	1.00			
Any Diabetes						
Yes	1.89	1.29	2.76			
No[d]	1.00	1.00	1.00			
Prepregnancy Hypertension						
Yes	1.89	1.49	2.40	3.61	2.48	5.27
No[d]	1.00	1.00	1.00	1.00	1.00	1.00
Preterm birth[a]						
Yes				1.89	1.29	2.76
No[d]				1.00	1.00	1.00

weeks inclusive.

[b]Based on PRAMS data, 2004-2011.

[c]Includes all diabetes categories

[d]Reference

[e]Underweight = <18.5 kg/m2, normal = 18.5-24.9 kg/m2, overweight = 25-29.9 kg/m2, obese = 30+ kg/m2

[f]Underweight: inadequate = less than 28 lbs, appropriate = 28-40 lbs, excess = greater than 40 lbs; Normal: inadequate = less than 25 lbs, appropriate = 25-35 lbs, excess = greater than 35 lbs; Overweight: inadequate = less than 15 lbs, appropriate = 15-25 lbs, excess = greater than 25 lbs; Obese: inadequate = less than 11 lbs, appropriate = 11-20 lbs, excess = greater than 20 lbs

[€]Analysis of data weighted for sample design, non-response, and non-coverage

Table 3: Odds ratios for the association of diabetes mellitus with preterm birth[a] among American Indian and Alaksa Natives[b€]

	Odds Ratio	95% Confidence Interval[€]		p-value	Width of CI
Model 1[c]	1.76	1.20	2.58	0.004*	2.15
Model 2[d]	1.68	1.12	2.50	0.011*	2.23
Model 3[e]	1.92	1.30	2.85	0.001*	2.19
Model 4[f]	1.83	1.21	2.78	0.004*	2.30

[a]Live birth 24-37 weeks gestation

[b]Based on PRAMS data, 2004-201

[c]Maternal Age

[d]Maternal Age and prepregnancy hypertension

[e]Maternal Age and prepregnancy BMI

[f]Maternal Age, prepregnancy BMI, prepregnancy hypertension

*$p<0.05$

[€]Analysis of data weighted for sample design, non-response, and non-coverage

Table 4: Odds ratios for the association of diabetes mellitus with preterm birth[a] by state among American Indian and Alaksa Natives[b€]

	cOR	95% CI[€]	p-value	aOR[c]	95% CI[€]	p-value	aOR[d]	95% CI[€]	p-value
State									
Alaska	0.15	(0.06-0.37)	0.000	0.14	(0.06-0.35)	0.000*	0.17	(0.07-0.42)	0.000*
Minnesota	2.07	(1.13-3.77)	0.018	1.91	(1.07-3.39)	0.028*	2.30	(1.30-4.08)	0.004*
Nebraska	5.85	(3.38-10.11)	0.000	5.92	(3.45-10.16)	0.000*	6.63	(3.80-11.56)	0.000*
New Mexico	2.67	(1.10-6.47)	0.029	2.42	(0.95-6.19)	0.065	2.78	(1.04-7.42)	0.042*
Oklahoma	1.51	(0.68-3.35)	0.312	1.39	(0.61-3.15)	0.437	1.51	(0.64-3.55)	0.343
Oregon	1.87	(1.16-3.02)	0.010	1.82	(1.11-2.98)	0.017*	1.73	(1.04-2.86)	0.034*
Utah	2.18	(0.48-9.99)	0.316	1.38	(0.31-6.23)	0.672	1.88	(0.46-7.61)	0.376
Washington	2.40	(0.87-6.60)	0.090	2.34	(0.94-5.84)	0.067	2.23	(0.89-5.61)	0.088

[a]Live birth 24-37 weeks gestation

[b]Based on PRAMS data, 2004-2011.

[c]Adjusted for maternal age

[d]Adjusted for maternal age and bmi

*$p<0.05$

[€]Analysis of data weighted for sample design, non-response, and non-coverage

Results

The study population consisted of 12,420 live singleton births to AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington between 2004-2011 (Figure 2). Three observations were missing data on diabetes status and 188 observations were missing data on weeks gestation. Diabetes mellitus was reported in 5.92% of the study population (Table 1a). Among women eligible births 1.78% were diagnosed with prepregnancy DM and 4.53% were diagnosed with gestational DM. Preterm birth occurred in 8.95% (1,861 of 12,420) of births in the study population (Table 1b). Women in the study population were most likely to reside in Oklahoma (39.1%) followed by Washington (16.2%), Alaska (15.5%), Minnesota (7.71%), New Mexico (7.20%), Oregon (6.95%), Utah (3.91%), and Nebraska (3.64%). Alaska had the highest prevalence of preterm births (10.2%) and Minnesota had the lowest prevalence of preterm birth (7.46%); however, the 95% CIs were overlapping and did not indicate a significant difference in prevalence of preterm birth (Table 2). DM was most prevalent in Minnesota (10.6%) and least prevalent in Alaska (0.92%) (Table 2). Oregon had the lowest prevalence other than Nebraska (5.92%) (Table 2). Prevalence of preterm birth was greater in women who identified as single-race AI/AN (9.28%) compared to women who identified as mixed-race AI/AN (7.23%) (Table 3). There was no significant difference in DM status between single-race and mixed-race AI/AN women (Table 3).

Women 30 years and older, women with greater than 12 years education, and married women were significantly more likely to have DM (Table 1a). Obesity, hypertension, and preeclampsia were significantly more common in women with DM (Table 1a). Maternal

diabetes was significantly associated with poor birth outcomes such as macrosomia and large for gestational age babies (Table 1a).

Preterm birth was significantly more prevalent among women 35 years and older and women with 12 years or less completed education (Table 1b). Women who smoked during pregnancy, entered prenatal care after the first trimester or not at all, women with prepregnancy or gestational diabetes, and women with preeclampsia were significantly more likely to have a preterm birth (Table 1b). Inadequate weight gain was significantly more common in preterm births (Table 1b). The percent of women with inadequate weight gain increases as gestational age at birth decreases, 21.07% of term infants, 28.50% late preterm infants, 47.87% of preterm, and 68.05% of very preterm infants (data not shown). Premature rupture of membranes was also significantly associated with preterm birth (Table 1b).

Variables found to be associated with either the exposure or outcome in the existing literature were considered in a DAG (Figure 1). Possible confounders identified by assessing the DAG included: maternal age, education, prepregnancy BMI, poverty, prepregnancy hypertension, and weight gain during pregnancy (Figure 1).

Women 30-34 had 2.81 (95% CI: 1.78-4.42) times the odds and women 35 and older had 3.71 (95% CI: 2.25-6.11) times the odds of having DM than women aged 21-24 (Table 4a). Less than 12 years education appeared to have a protective effect of DM compared to women with greater than 12 years of education (OR = 0.94, 95% CI: 0.67-0.85) (Table 4a). Other variables found to be significantly associated with DM were women who were obese (OR = 5.28, 95% CI = 3.40-8.20) compared to normal weight, overweight (OR = 1.91, 95% CI: 1.16-3.16) compared to normal weight, and hypertensive (OR = 3.61, 95% CI: 2.48-5.27) compared to non-hypertensive women (Table 4a). Federal poverty level and weight gain during pregnancy were not significantly associated with DM (Table 4a). When prepregnancy

DM and gestational DM were considered separately, excess weight gain was significantly associated with gestational DM (OR = 0.61, 95% CI: 0.38-0.97) compared to appropriate weight gain, while prepregnancy DM showed no significant association (Table 4b). Preliminary analysis found women with prepregnancy DM had 2.10 (95% CI: 1.31-3.37) times the odds of preterm birth and women with gestational DM had 1.84 (95% CI: 1.14-2.97) times the odds of preterm birth compared to women without DM (Table 4b).

Women 35 and older had 2.09 (95% CI: 1.45-3.00) times the odds of preterm birth compared to women 21-24. Women with less than 12 years completed education had 1.58 (95% CI: 1.22-2.05) times the odds of having preterm birth compared to women with greater than 12 years completed education (Table 4a). Compared to appropriate weight gain, inadequate weight gain during pregnancy was associated with non-significant increased odds (OR = 1.24, 95%CI: 0.93-1.64) of preterm birth while excess weight gain had a significant protective effect (OR 0.45, 95% CI 0.33-0.60) (Table 4a). Women with prepregnancy hypertension had significantly higher odds of preterm birth compared to women without hypertension (OR 1.89, 95% CI: 1.49-2.40) (Table 4a). Despite findings based on the DAG, preliminary analysis did not show significant associations of preterm birth with federal poverty level and prepregnancy BMI (Figure 1 and Table 4a).

We identified covariates that met our criteria for modeling inclusion (biologically plausible and significantly associated with both exposure and outcome) as well as all possible interaction terms that included either the exposure and covariate or two covariates. Interaction terms were evaluated first using backwards elimination at 5% significance level and second with forward selection at 5% significance level. The covariates evaluated were our main exposure (diabetes mellitus), maternal age, education, and prepregnancy hypertension. A second model was run including prepregnancy BMI to enable comparison

to previous literature, even though it was not found to be associated with exposure and outcome in the preliminary analysis. After interaction assessment in both models, all interaction terms dropped out. Two methods for confounder assessment were used: dropping terms that changed the OR by 10% from the full model and terms that changed the diabetes beta by more than 10% from the full model.

Tables 5 and 6 show the adjusted odds ratios (ORs) and their percent change from the full model. The full multivariable logistic regression model including all confounders except prepregnancy BMI found that DM was significantly associated with preterm birth (aOR = 1.65, 95% CI: 1.11-2.47) (Table 5). After confounding assessment, the reduced model contained maternal age in addition to DM. Women with DM had significantly greater odds of preterm birth compared to women without DM (aOR = 1.76, 95% CI: 1.20-2.58, p = 0.004) (Table 5 and Table 7). When DM was defined as indicating diagnosis of DM on either the PRAMS questionnaire or the birth certificate the results were similar (aOR = 1.68, 95% CI = 1.30-2.19, p = 0.000) (results not shown). If Alaskan women were removed from the analyses, the association was somewhat stronger (aOR = 1.89, 95% CI = 1.28-2.79, p = 0.001) (results not shown).

Prepregnancy hypertension was added to the model with DM (defined with the birth certificate variable first and with the PRAMS variable if missing on the birth certificate) when we assessed confounding using the change in beta estimate. The aOR was not changed, but the confidence interval was broader with this addition (aOR = 1.68, 95% CI: 1.12-2.50, p = 0.011) (Table 5 and Table 7). DM was significantly associated with preterm birth in the full model including DM, education, maternal age, prepregnancy hypertension, and prepregnancy BMI (aOR = 1.83, 95% CI: 1.20-2.78) (Table 6 and Table 7). After confounding assessment, prepregnancy BMI did not change the aOR more than 10%;

however, it remained in the model for comparison purposes along with maternal age (Table 6 and Table 7). A woman with DM had 1.92 (95% CI: 1.30, 2.85, p = 0.0011) times the odds of preterm birth as a woman without DM when we controlled for maternal age and prepregnancy BMI (Table 6 and Table 7). When confounders were assessed with the change in beta estimate, and prepregnancy BMI remained in the model regardless of its affect on the estimate, the resulting model included maternal age, prepregnancy hypertension, and prepregnancy BMI. This model produced an estimated odds ratio similar to the models mentioned above (aOR = 1.83, 95% CI: 1.21-2.78, p = 0.0041) (Table 6 and Table 7).

Our second analysis indicated a difference in the association of DM with preterm birth by state. In Alaska, DM demonstrated a significant protective effect against preterm birth with the crude and adjusted ORs in the models with and without prepregnancy BMI (Table 8). The model without prepregnancy BMI found a non-significant increased aOR for the association of preterm birth in women with DM compared to women without in New Mexico, Oklahoma, Utah, and Washington (Table 8). Women in Nebraska with diabetes had 5.92 (95% CI = 3.45-10.16, p = 0.000) times the odds of preterm birth compared to women without DM, the largest association among all states (Table 8). Women with diabetes in Minnesota (aOR = 1.92, 95% CI: 1.07-3.39, p = 0.028) and Oregon (aOR = 1.82, 95% CI: 1.11-2.98, p = 0.017) had significantly greater odds of preterm birth compared to women without DM (Table 8).

After removing Alaskan women, the overall OR after adjusting for maternal age was 1.89 (95% CI: 1.28-2.79, p = 0.001) (data not shown). When DM was defined as indicating diagnosis of DM on either the PRAMS questionnaire or the birth certificate the odds ratios for each state were altered after adjusting for maternal age. Results for Nebraska, New Mexico, Oklahoma, Oregon and Utah all remained similar in direction and significance;

however, the association found in Minnesota (aOR = 1.63, 95% CI = 0.95-2.78, p = 0.073) was no longer significant and the association in Washington (aOR = 2.28, 95% CI = 1.23-4.20, p = 0.009) became significant (Table 9). The results for Alaska also became non-significant (aOR = 1.15, 95% CI = 0.85-1.55, p = 0.375) (Table 9).

In models that controlled for BMI, women who had DM and resided in Minnesota, New Mexico, or Oregon, had significantly increased odds of preterm birth which were 2.30 times (95% CI: 1.30-4.08), 2.78 times (95% CI: 1.04-7.42), and 1.73 times (95% CI: 1.04-2.86) that of women without DM, respectively (Table 8) (Figure 4). Women in Oklahoma, Utah and Washington had non-significant increased aORs of preterm birth among women with DM compared to women without DM (Table 8) (Figure 4). The adjusted odds of preterm birth in Nebraskan women with DM was 6.63 (95% 3.80-11.56) times the odds of preterm birth in non-diabetic women (Table 8) (Figure 4).

Discussion

This study examined the association of diabetes mellitus with preterm birth among AI/AN women in eight states between 2004-2011. Our results indicated a significant increase in the odds of preterm birth among women with any type of DM compared to women without DM after controlling for maternal age, prepregnancy hypertension and prepregnancy BMI. Women with diabetes had 1.76 times the odds of preterm birth compared to women without when controlling for maternal age and had 1.92 times the odds of preterm birth after controlling for maternal age and prepregnancy BMI. This association has major implications for AI/AN women and could contribute to the "vicious cycle" described by Lacroix et al (Figure 3).[19] Pregnancies complicated by DM have an increased risk of preterm birth.[19] Their preterm offspring not only have an increased risk of DM due to genetic and cultural factors passed down by their mothers, but also have an increased risk of DM because of its association with preterm birth.[19] Female offspring that become pregnant in the future are then at greater risk of having a preterm baby and therefore continue the cycle.[19] In a population that currently has the highest incidence of DM in the United States this cycle could be detrimental.[5,13] Our study points to the need for clinical interventions to better control diabetes during pregnancy in this population in order to curb the effects of this cycle.

Our results are consistent with previous literature that show a significant association of type 1 and type 2 DM with preterm birth (both spontaneous and induced) in other populations.[33,89,91-100,102] Our study resulted in a smaller OR compared to previous literature. Jensen et al. and Evers et al. found that women with type 1 DM had 7 (95% CI: 6.3-7.6) times and 4.5 (95% CI: 3.8-5.3) times the odds of preterm birth compared to women without DM, respectively.[95,96] Rosenberg et al. found a 2.54 (95% CI: 2.18-2.95) increased

risk of preterm birth to women with prepregnancy DM compared to women without DM.[100] One possible explanation is that Jensen and Evers only include women with type 1 DM and our analysis did not have information to distinguish between type 1 and type 2 and did not have a large enough sample size to create separate models for prepregnancy and gestational diabetes. Another possibility is that DM may be misclassified. Jensen et al. and Evers et al. collect data from national databases in Denmark and the Netherlands where cases are reported by medical professionals. In contrast, our data and Rosenberg et al. rely mainly on self-reported data. The use of self-reported diagnosis of diabetes instead of either performing tests or reports by a medical professional may underestimate the true prevalence of the disease. It has been shown for every one individual diagnosed with DM, three others go undiagnosed.[59] This can result in non-differential misclassification, which will lead to a conservative estimate of our odds ratio. Currently, the results from this study have not been statistically compared to other studies or populations and therefore are not indicative of a protective effect of race. We must consider previous literature that warns against assessing aggregated data on AI/AN women across states and the possibility that these analyses lead to inaccurate or misleading results.[114] If future research concluded a significant difference in the association of DM and preterm birth in AI/AN women compared to other populations, this finding could indicate a genetic, cultural or behavioral advantage that AI/AN women with DM possess. If specific behaviors that AI/AN women practice decrease the association of preterm birth among women with DM, future research should attempt to identify these behaviors to both increase them among AI/AN women and promote them in other populations.

The second aim of our study assessed the association of DM and preterm birth stratified on state. Johnson et al. concluded the quality of prenatal care is heterogeneous

across states for AI/AN women and therefore studies should avoid national aggregation and perform analyses on as geographically specific areas as possible.[114] While our data did not show an association of early entry into prenatal care with preterm birth, we did not assess the quality or number of prenatal care visits. If birth outcomes differ by healthcare system, data on the quality and quantity of care would be imperative. Information available on birth certificates includes the number of prenatal visits, which some have used as a proxy for quality. However, this information may be inaccurate and its use may introduce misclassification bias. With the advent of electronic medical records, reliance on these for entering information on vital records increases accuracy of information on both maternal health conditions and prenatal care.

Our results indicate that differences in preterm birth risk associated with DM exist between states. AI/AN women with DM in Nebraska had 6.63 times the odds of preterm birth compared to women without DM. Nebraska had the greatest OR of any state in this study and was most consistent with ORs in previous studies. In contrast, women in Alaska demonstrated a significant protective effect of DM on preterm birth. Preliminary analyses revealed Alaska's low prevalence of DM (0.92%) compared with all other states, which had at least 5.92% of their populations diagnosed with DM (Table 1a). Alaska also had the highest prevalence of preterm birth (10.2%) (Table 1b). If women in Alaska are underdiagnosed with DM, due to healthcare utilization or quality, their resulting odds ratio will be biased towards the null. However, PRAMS data do not indicate a significant difference in frequency of testing for DM during pregnancy between states, and only 4 AI/AN women in Alaska had missing birth certificate data on DM, which was not significantly different compared to other states. We did not find a difference in the frequency of reporting DM before and after the adoption of the 2003 birth certificate in Alaska or in

any other state. In our analysis we first identified women with DM according to the birth certificate and only included data from PRAMS when the DM variable was missing on the birth certificate. Further analyses revealed a significant difference in the prevalence of DM when we included women who reported diagnosis with DM in PRAMS but the birth certificate indicated no DM. In Alaska, 9.36% of women reported having been diagnosed with DM when we used this alternative coding compared to 0.86% in original analyses. Using this definition of DM also produced a different adjusted odds ratio in multivariable analyses for Alaska (aOR = 1.15, 95% CI: [0.85-1.55] versus aOR = 0.14, 95% CI: [0.06-0.35]). When we used this definition of DM (i.e., reporting diagnosis with DM on either the birth certificate or in the PRAMS questionnaire) for all states, we did not find a significant difference in our adjusted ORs [the new definition (aOR = 1.68, 95% CI = 1.30-2.19, p = 0.000) compared to the original definition (aOR = 1.76, 95% CI = 1.20-2.58, p = 0.004)]. When we excluded Alaskan women from our analyses, women with DM had 1.89 (95% CI: 1.28-2.79) times the odds of preterm birth compared to women without DM after adjusting for maternal age. This result was not significantly different from our result when we included Alaska (aOR = 1.76, 95% CI: 1.20-2.58).

Previous research suggests that Alaska Natives have a low prevalence of DM compared to other American Indians and the U.S. population as a whole.[115-118] In 2007, the age-adjusted prevalence of DM among Alaska Natives was 38 per 1,000 compared to 51 per 1,000 among all races in the United States.[116] The Behavioral Risk Factor Surveillance System (BRFSS) annually reports data on the prevalence of DM in Native and non-Native populations (Table 10).[119-125] Their data suggest that the Alaska Native population does not have a significantly greater prevalence of DM compared to the Non-Native population in Alaska.[119-125] Their estimates of the prevalence of DM among Alaska Natives (3-7% from

2000-2009) was greater than data discussed above but lower than our estimate based on either birth certificate or PRAMS report of DM. This may reflect an over-reporting of DM in PRAMS because of the respondent's misunderstanding of the test for DM as a diagnosis of DM. However it is also possible that the prevalence estimate using this definition is more accurate than the BRFSS estimate, which may be an underestimate owing to under-diagnosis of DM in the general population. In any event, the BRFSS data confirm that Alaskans have lower prevalence of DM than other states in the United States.[84,119-124] This indicates that, using our initial definition of DM, prevalence estimates of DM among Alaska Natives may underestimate the true prevalence, but when we compare Alaska Natives to other American Indian populations, our results are consistent with previous research. Differences in diabetes prevalence and our ORs relating DM to preterm birth may reflect variation in genetics, healthcare quality/utilization, diet, or other cultural practices between tribes. Aspects from Alaska Native culture could be helpful to other American Indians in decreasing the prevalence of DM. In order to utilize this information further research is needed to better understand what causes these differences between states.

Despite the significant implications of our study, limitations exist which affect our estimates and representativeness. First, our study excluded multiple births and therefore is not representative of these pregnancies, which are at greater risk for preterm birth. Second, AI/AN women who identified as both single and mixed race were included in our study. This decision was made to attain an adequate sample size but results in conclusions that may not be specific to single race AI/AN women. Third, we lacked data on women's tribal memberships and therefore could not make conclusions on differences between tribes. Fourth, we could not separately model women with gestational DM and women with

prepregnancy DM due to strata sample size restrictions. Finally, some states had smaller sample sizes resulting in wider confidence intervals and less precise estimates.

The present study has many strengths. Our data consisted of a large population based study with an adequate number of AI/AN women to produce stable estimates. DM and preterm birth were both assessed and confirmed with multiple data sources (birth certificate and self reported PRAMS questionnaire). Our ability to stratify on state revealed important differences in the association of diabetes with preterm birth between states that may have implications for the distribution of public health efforts for quality of disease surveillance and treatment.

Prevention and management of DM among the AI/AN community is a public health priority considering the high and increasing prevalence in this population.[8] Evidence of the disparity in poor birth outcomes among AI/AN women compared to other populations in the U.S. and previous findings of increased risk of preterm birth in women with DM indicated the need for this study.[65,89,101,102] Our findings support the need for more research and public health attention in this area in order to better manage DM during pregnancy in a population with a greater prevalence. The large differences in the odds of preterm birth among women with DM between states calls for further action to address the underlying issues in these populations. Our results also support Johnson et al.'s suggestion that future research on AI/AN women should be geographically specific.[114] Further research and attention on state differences in both cultural and behavioral practices as well as in prenatal care management in high-risk pregnancies among AI/AN women should be a priority in the public health community.

Conclusion

In a population-based retrospective cohort of 12,420 live singleton births to AI/AN women, DM was significantly associated with higher odds of preterm birth. Our results established that this association, which has been demonstrated in other populations, is consistent in AI/AN women. However, stratifying on state revealed that this association varies by geographic region. All states had increased odds of preterm birth in women with DM, except for Alaska, which showed a protective effect. Future research should focus on comparing these results to other racial and ethnic groups and identifying possible underlying factors that affect differences in this association between states. These findings will be beneficial to understand the public health impact on the distribution of resources and interventions during pregnancy.

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Tables

Table 1a: Demographic and Pregnancy characteristics of live singleton births to AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington[a] by diabetes mellitus status

	Any DM				
	Unweighted N	Weighted[€] %	95% CI LCL	UCL	p-value[b]
Total	678	5.92	5.13	6.83	
Maternal Age					0.00*
≤20	2055	1.38	0.84	2.23	
21-24	4277	4.38	3.14	6.08	
25-29	3213	5.70	4.39	7.36	
30-34	1874	11.4	8.72	14.7	
≥35	1049	14.5	10.6	19.6	
Birthplace					0.00*
Alaska	3364	0.92	0.65	1.31	
Minnesota	1277	10.6	8.22	13.7	
Nebraska	1333	7.27	5.86	8.89	
New Mexico	481	7.45	5.42	10.2	
Oklahoma	1705	6.07	4.50	8.15	
Oregon	2337	5.92	5.02	6.96	
Utah	178	9.62	5.86	15.4	
Washington	1745	6.19	4.47	8.53	
Education					0.01*
>12	4050	7.02	5.64	8.71	
12	4935	6.27	4.95	7.92	
<12	3081	4.16	3.07	5.61	
Federal Poverty Level					0.74
>138%	3238	6.36	4.87	8.27	
≤138%	7897	6.03	5.03	7.20	
Medical Insurance					0.30
Tribal	205	12.2	5.58	24.6	
Private	1406	6.90	4.54	10.4	
Medicaid	3152	6.99	5.37	9.06	
Other	377	4.73	2.88	7.69	
Marital Status					0.03
Married	4656	7.17	5.82	8.80	
Other	7754	5.15	4.22	6.27	
Prepregnancy BMI[c]					0.00*
Underweight	375	3.07	1.20	7.61	
Normal	4914	2.67	1.83	3.88	
Overweight	3063	5.00	3.69	6.74	
Obese	3348	12.7	10.5	15.2	

Table 1a continued

Macrosomia Baby[j]					0.00*
Yes	344	15.1	11.5	19.5	
No	12039	5.74	4.94	6.67	
Large for Gestational Age Baby[k]					0.00*
Yes	1885	11.4	9.34	13.8	
No	10101	5.16	4.31	6.17	

[a]Based on PRAMS data, 2004-2011.

[b]P-value for chi-square test comparing proportions of covariates among participants with any diabetes mellitus to proportions among women without any diabetes mellitus.

[c]Underweight = <18.5 kg/m^2, normal = 18.5-24.9 kg/m^2, overweight = 25-29.9 kg/m^2, obese = 30+ kg/m^2

[d]Underweight: inadequate = less than 28 lbs, appropriate = 28-40 lbs, excess = greater than 40 lbs; Normal: inadequate = less than 25 lbs, appropriate = 25-35 lbs, excess = greater than 35 lbs; Overweight: inadequate = less than 15 lbs, appropriate = 15-25 lbs, excess = greater than 25 lbs; Obese: inadequate = less than 11 lbs, appropriate = 11-20 lbs, excess = greater than 20 lbs

[e]Any alcohol consumption during last three months of pregnancy

[f]Any cigarette smoking during entire pregnancy

[g]Attended prenatal care visit within first trimester of pregnancy

[h]Live birth 24-37 weeks gestation

[i]Premature rupture of membranes

[j]4500+ gram birth weight

[k]Based on 90th percentile

*p<0.05

[t]Percepts based on data weighted for sample design, non-response, and non-coverage

Totals may not add up to total population due to missing observations

Table 1b: Demographic and Pregnancy characteristics of live singleton births to AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington[a] by preterm birth[b]

	Preterm[b]				
	Unweighted N	Weighted[€] %	95% CI LCL	UCL	p-value[c]
Ttoal	12232	8.95	8.16	9.80	
Maternal Age					0.02
≤20	2055	8.5	6.96	10.3	
21-24	4277	7.68	6.52	9.02	
25-29	3213	9.42	7.74	11.4	
30-34	1874	8.95	7.08	11.2	
≥35	1049	14.8	11.2	19.2	
Birthplace					0.10
Alaska	3364	10.2	9.33	11.0	
Minnesota	1277	7.46	5.8	9.54	
Nebraska	1333	9.37	7.86	11.1	
New Mexico	481	9.53	7.22	12.5	
Oklahoma	1705	8.84	7.23	10.8	
Oregon	2337	8.23	7.17	9.42	
Utah	178	7.77	5.04	11.8	
Washington	1745	9.00	7.23	11.2	
Education					0.00
>12	4050	7.05	5.95	8.33	
12	4935	9.45	8.14	10.9	
<12	3081	10.7	9.03	12.6	
Federal Poverty Level					0.65
>138%	3238	8.39	6.79	10.3	
≤138%	7897	8.85	7.90	9.90	
Medical Insurance					0.61
Tribal	205	8.10	4.09	15.4	
Private	1406	8.23	5.90	11.4	
Medicaid	3152	8.47	6.23	9.91	
Other	377	13.5	7.76	22.5	
Marital Status					0.49
Married	4656	9.32	7.93	10.9	
Other	7754	8.70	7.79	9.70	
Prepregnancy BMI[d]					0.51
Underweight	375	14.3	8.46	23.2	
Normal	4914	8.62	7.47	9.94	
Overweight	3063	8.90	7.23	10.9	
Obese	3348	8.67	7.33	10.2	

Table 1b continued

Weight Gain During Pregnancy[e]					0.00*
Inadequate	2594	13.1	11.2	15.2	
Appropriate	3029	10.9	8.86	13.3	
Excess	5277	5.16	4.34	6.12	
Pregnancy Intention					0.21
Intended	7840	9.36	8.35	10.5	
Unintended	4529	8.28	7.07	9.67	
Alcohol Consumption During Pregnancy[f]					0.07
Yes	610	14.2	9.31	20.9	
No	11535	8.73	7.93	9.59	
Prenatal Smoking[g]					0.05*
Yes	3341	10.5	8.76	12.5	
No	8876	8.41	7.54	9.38	
Early Entry into Prenatal Care[h]					0.01*
Yes	8588	8.23	7.37	9.18	
No	3313	10.9	9.10	12.9	
Prepregnancy Diabetes					0.00*
Yes	215	16.9	11.4	24.4	
No	12173	8.81	8.02	9.68	
Gestational Diabetes					0.04*
Yes	495	14.9	9.86	21.8	
No	11886	8.65	7.87	9.50	
Any Diabetes					0.01*
Yes	678	15.0	10.9	20.3	
No	11739	8.56	7.78	9.42	
Prepregnancy Hypertension					0.00*
Yes	1077	14.7	12.3	17.6	
No	11194	8.36	7.53	9.26	
Preeclampsia					0.00*
Yes	1095	14.9	12.5	17.7	
No	11323	8.41	7.58	9.32	
PROM[i]					0.00*
Yes	574	37.3	29.3	46.1	
No	11844	7.88	7.14	8.70	

Table 1b continued

Macrosomia Baby[j]						0.00*
	Yes	344	3.18	1.77	5.66	
	No	12039	9.05	8.24	9.92	
Large for Gestational Age Baby[k]						0.78
	Yes	1885	8.17	6.34	10.5	
	No	10101	8.49	7.63	9.43	

[a]Based on PRAMS data, 2004-2011.

[b]Live birth 24-37 weeks gestation

[c]P-value for chi-square test comparing proportions of covariates among participants with preterm birth to proportions among women without preterm birth.

[d]Underweight = <18.5 kg/m^2, normal = 18.5-24.9 kg/m^2, overweight = 25-29.9 kg/m^2, obese = 30+ kg/m^2

[e]Underweight: inadequate = less than 28 lbs, appropriate = 28-40 lbs, excess = greater than 40 lbs; Normal: inadequate = less than 25 lbs, appropriate = 25-35 lbs, excess = greater than 35 lbs; Overweight: inadequate = less than 15 lbs, appropriate = 15-25 lbs, excess = greater than 25 lbs; Obese: inadequate = less than 11 lbs, appropriate = 11-20 lbs, excess = greater than 20 lbs

[f]Any alcohol consumption during last three months of pregnancy

[g]Any cigarette smoking during entire pregnancy

[h]Attended prenatal care visit within first trimester of pregnancy

[i]Premature rupture of membranes

[j]4500+ gram birth weight

[k]Based on 90th percentile

*p<0.05

[€]Percepts based on data weighted for sample design, non-response, and non-coverage

Totals may not add up to total population due to missing observations

Table 1c: Demographic and Pregnancy characteristics of live singleton births to AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington[a] by gestational/prepregnancy diabetes mellitus status

	Prepregnancy DM					Gestational DM				
	Unweighted N	Weighted[€] %	95% CI LCL	95% CI UCL	p-value[b]	Unweighted N	Weighted[€] %	95% CI LCL	95% CI UCL	p-value[c]
Total	153	1.39	0.99	1.95		433	3.97	3.34	4.73	
Maternal Age					0.00*					0.00*
≤20	2032	0.19	0.10	0.37		2041	0.98	0.51	1.85	
21-24	4111	1.52	0.74	3.10		4168	2.58	1.73	3.84	
25-29	3065	0.88	0.58	1.34		3154	4.35	3.16	5.95	
30-34	1738	3.13	1.76	5.49		1804	8.08	5.77	11.2	
≥35	947	2.25	1.36	3.69		1003	8.90	6.09	12.8	
Birthplace					0.00*					0.00*
Alaska	3346	0.46	0.28	0.77		3342	0.22	0.11	0.44	
Minnesota	1171	1.64	1.06	2.54		1234	7.85	5.58	10.9	
Nebraska	1266	1.53	0.99	2.35		1303	5.25	3.98	6.90	
New Mexico	455	2.22	1.21	4.07		466	4.49	2.94	6.78	
Oklahoma	1615	1.78	0.95	3.30		1641	3.68	2.52	5.34	
Oregon	2222	1.60	1.02	2.49		2295	3.95	3.32	4.69	
Utah	161	0.00				177	9.53	5.77	15.3	
Washington	1659	1.07	0.47	2.43		1713	4.60	3.07	6.83	
Education					0.18					0.15
>12	3857	1.83	1.17	2.85		3982	4.47	3.42	5.83	
12	4819	1.39	0.74	2.62		4923	4.28	3.22	5.68	
<12	3048	0.88	0.44	1.76		3095	2.99	2.06	4.33	
Federal Poverty Level					0.92					0.73
>138%	3088	1.43	0.89	2.30		3164	3.89	2.79	5.40	
≤138%	7558	1.48	0.94	2.32		7740	4.17	3.35	5.17	
Medical Insurance					0.34					0.70
Tribal	194	4.73	1.08	18.5		198	7.89	2.92	19.6	
Private	1325	1.28	0.73	2.24		1373	4.69	2.91	7.46	
Medicaid	2981	2.43	1.37	4.28		3065	4.30	3.14	5.86	
Other	357	1.14	0.52	2.48		368	3.54	1.92	6.44	

Table 1c continued

Marital Status					0.60*				0.01*
Married	4411	1.24	0.77	1.99		4552	5.33	4.15	6.84
Other	7476	1.48	0.94	2.33		7610	3.12	2.45	3.97
Prepregnancy BMI[d]					0.00*				0.00*
Underweight	366	0.14	0.02	0.86		373	2.76	0.99	7.51
Normal	4815	0.79	0.30	2.05		4870	1.73	1.16	2.56
Overweight	2949	1.25	0.68	2.27		3017	3.57	2.44	5.20
Obese	3073	2.93	1.93	4.43		2304	8.46	6.66	10.7
Weight Gain During Pregnancy[e]					0.15				0.06
Inadequate	2569	1.75	0.70	4.31		2537	4.78	3.34	6.78
Appropriate	2916	0.88	0.48	1.61		2981	4.96	3.43	7.13
Excess	5060	1.73	1.13	2.64		5157	3.08	2.37	4.00
Pregnancy Intention					0.46				0.17
Intended	7549	1.24	0.86	1.78		7689	3.62	2.87	4.56
Unintended	4309	1.68	0.88	3.15		4431	4.67	3.58	6.07
Alcohol Consumption During Pregnancy[f]					0.36				0.63
Yes	588	0.96	0.39	2.34		595	3.25	1.22	8.37
No	11048	1.43	1.00	2.03		11309	4.05	3.38	4.84
Prenatal Smoking[g]					0.444				0.07
Yes	3221	1.83	0.86	3.87		3283	3.04	2.15	4.29
No	8477	1.26	0.89	1.79		8669	4.33	3.54	5.28
Early Entry into Prenatal Care[h]					0.88				0.80
Yes	8201	1.44	1.01	2.06		8407	4.08	3.32	5.02
No	3192	1.35	0.58	3.09		3253	3.89	2.79	5.40
Prepregnancy Hypertension					0.012				0.00*
Yes	985	4.54	2.54	7.99		1013	8.80	6.00	12.7
No	10775	1.13	0.75	1.72		11013	3.45	2.84	4.19

Table 1c continued

Preeclampsia					0.01*					0.00*
	Yes	998	4.50	2.52	7.92		1031	9.00	6.22	12.9	
	No	10897	1.13	0.75	1.70		11139	3.54	2.91	4.31	
Preterm Birth[i]					0.01*					0.07
	Yes	1770	2.74	1.86	4.02		1792	6.64	4.17	10.4	
	No	9943	1.27	0.85	1.90		10195	3.73	3.09	4.50	
PROM[j]					0.34					0.17
	Yes	549	0.91	0.35	2.36		561	8.69	3.91	18.2	
	No	11345	1.41	0.99	1.99		11610	3.80	3.18	4.53	
Macrosomia Baby[k]					0.03*					0.00*
	Yes	304	3.89	2.16	6.89		325	9.99	6.96	14.1	
	No	11555	1.34	0.94	1.92		11809	3.86	3.22	4.63	
Large for Gestational Age Baby[l]					0.04*					0.00*
	Yes	1732	2.67	1.67	4.25		1814	7.96	6.19	10.2	
	No	9740	1.21	0.79	1.86		9941	3.46	2.79	4.29	

[a]Based on PRAMS data, 2004-2011.

[b]P-value for chi-square test comparing proportions of covariates among participants with prepregnancy diabetes mellitus to proportions among women without any diabetes mellitus.

[c]P-value for chi-square test comparing proportions of covariates among participants with gestational diabetes mellitus to proportions among women without gestational diabetes mellitus.

[d]Underweight = <18.5 kg/m^2, normal = 18.5-24.9 kg/m^2, overweight = 25-29.9 kg/m^2, obese = 30+ kg/m^2

[e]Underweight: inadequate = less than 28 lbs, appropriate = 28-40 lbs, excess = greater than 40 lbs; Normal: inadequate = less than 25 lbs, appropriate = 25-35 lbs, excess = greater than 35 lbs; Overweight: inadequate = less than 15 lbs, appropriate = 15-25 lbs, excess = greater than 25 lbs; Obese: inadequate = less than 11 lbs, appropriate = 11-20 lbs, excess = greater than 20 lbs

[f]Any alcohol consumption during last three months of pregnancy

[g]Any cigarette smoking during entire pregnancy

[h]Attended prenatal care visit within first trimester of pregnancy

[i]Live birth 24-37 weeks gestation

[j]Premature rupture of membranes

[k]4500+ gram birth weight

[l]Based on 90th percentile

*p<0.05

[6]Percepts based on data weighted for sample design, non-response, and non-coverage

Totals may not add up to total population due to missing observations

Table 2: Preterm birth[a] and DM frequency in live singleton births to AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington[b] by state

	Alaska	Minnesota	Nebraska	New Mexico	Oklahoma	Oregon	Utah	Washington
	% (95% CI)[€]	% (95% CI)[€]	% (95% CI)[€]	% (95% CI)[€]	% (95% CI)[€]	% (95% CI)[€]	% (95% CI)[€]	% (95% CI)[€]
Preterm[a]								
Yes	10.2 (9.33-11.0)	7.46 (5.80-9.54)	9.37 (7.86-11.4)	9.53 (7.22-12.5)	8.84 (7.23-10.8)	8.23 (7.17-9.42)	7.77 (5.04-11.8)	9.00 (7.23-11.2)
No	89.9 (89.0-90.7)	92.5 (90.5-94.2)	90.6 (88.9-92.1)	90.5 (87.5-92.8)	91.2 (89.2-92.8)	91.8 (09.6-02.8)	92.2 (88.22-95.0)	91.0 (88.9-92.8)
Diabetes								
Yes	0.92 (0.65-1.31)	10.6 (8.22-13.7)	7.27 (5.86-8.98)	7.45 (5.43-10.2)	6.07 (4.50-8.15)	5.92 (5.02-6.96)	9.62 (5.86-15.4)	6.19 (4.47-8.53)
No	99.1 (98.7-99.4)	89.4 (86.3-91.8)	92.7 (91.0-94.1)	92.6 (89.8-94.6)	93.9 (91.9-95.5)	94.1 (93.0-95.0)	90.4 (84.6-94.1)	93.8 (91.5-95.5)
Prepregnancy diabetes								
Yes	0.46 (0.28-0.77)	1.64 (1.06-2.54)	1.53 (0.99-2.35)	2.22 (1.21-4.07)	1.78 (0.95-3.30)	1.60 (1.02-2.49)	0.00 (0.00-0.00)	1.07 (0.47-2.43)
No	99.5 (99.2-99.7)	98.4 (97.5-98.9)	98.5 (97.7-99.0)	97.8 (95.9-98.8)	98.2 (96.7-99.1)	98.4 (97.5-99.0)	100 (100-100)	98.9 (97.6-99.5)
Gestational diabetes								
Yes	0.22 (0.11-0.44)	7.85 (5.58-10.9)	5.25 (3.98-6.90)	4.49 (2.94-6.78)	3.68 (2.52-5.34)	3.95 (3.32-4.69)	9.53 (5.77-15.3)	4.60 (3.07-6.83)
No	99.8 (99.6-99.9)	92.2 (89.1-94.4)	94.8 (93.1-96.0)	95.5 (93.2-97.1)	96.3 (94.7-97.5)	96.1 (95.3-96.7)	90.5 (84.7-94.2)	95.4 (93.2-96.9)

[a]Live birth 24-37 weeks gestation

[b]Based on PRAMS data, 2004-2011

[€]Percepts based on data weighted for sample design, non-response, and non-coverage

Table 3: Preterm birth[a] and maternal DM frequency in live singleton births to AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington[b] by AI/AN classification

	Single Race[d]	**Mixed Race[e]**
	% (95% CI)[€]	% (95% CI)[€]
Preterm[a]		
Yes	9.28 (8.41-10.2)	7.23 (5.58-9.33)
No	90.7 (89.8-91.6)	92.8 (90.7-94.4)
Any diabetes		
Yes	6.04 (5.19-7.03)	5.32 (3.49-8.03)
No	94.0 (93.0-94.8)	94.7 (92.0-96.5)
Gestational diabetes		
Yes	4.12 (3.43-4.95)	3.20 (1.88-5.42)
No	95.9 (95.1-96.7)	96.8 (94.6-98.1)
Prepregnancy diabetes		
Yes	1.36 (0.92-2.01)	1.52 (0.77-3.00)
No	98.6 (98.0-99.1)	94.5 (97.0-99.2)

[a]Live birth 24-37 weeks gestation

[b]Based on PRAMS data, 2004-2011

[c]Women who identify as single race AI or single race AN

[e]Women who identify as mixed race AI/AN

[€]Percepts based on data weighted for sample design, non-response, and non-coverage

Table 4a. Unadjusted Odds Ratios (OR), and 95 percent Confidence Intervals (CI) for preterm birth[a] and diabetes mellitus in a cohort of live singleton births to AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington[b€]

	Preterm Birth[a]				Any Diabetes Mellitus[c]			
	crude OR	95% CI[€]		p-value	crude OR	95% CI[€]		p-value
Maternal Age				0.00				0.00
≤20	1.12	0.85	1.48		0.30	0.17	0.56	
21-24[d]	1.00	1.00	1.00		1.00	1.00	1.00	
25-29	1.25	0.95	1.65		1.32	0.85	2.05	
30-34	1.18	0.87	1.61		2.81	1.78	4.42	
≥35	2.09	1.45	3.00		3.71	2.25	6.11	
Birthplace				0.12				0.00
Alaska	1.26	1.06	1.50		0.15	0.10	0.22	
Minnesota	0.90	0.66	1.22		1.89	1.36	2.64	
Nebraska	1.15	0.90	1.47		1.25	0.93	1.66	
New Mexico	1.17	0.84	1.65		1.28	0.87	1.88	
Oklahoma	1.08	0.83	1.41		1.03	0.72	1.48	
Oregon[d]	1.00	1.00	1.00		1.00	1.00	1.00	
Utah	0.94	0.58	1.52		1.69	0.96	2.98	
Washington	1.10	0.83	1.46		1.05	0.71	1.55	
Education				0.00				0.02
>12[d]	1.00	1.00	1.00		1.00	1.00	1.00	
12	1.38	1.08	1.76		0.89	0.63	1.25	
<12	1.58	1.22	2.05		0.57	0.39	0.85	
Federal Poverty Level				0.65				0.74
≥138%[d]	1.00	1.00	1.00		1.00	1.00	1.00	
<138%	1.06	0.82	1.37		0.94	0.67	1.33	
Prepregnancy BMI[e]				0.33				0.00
Underweight	1.77	0.96	3.27		1.15	0.41	3.23	
Normal[d]	1.00	1.00	1.00		1.00	1.00	1.00	
Overweight	1.03	0.79	1.36		1.91	1.16	3.16	
Obese	1.01	0.79	1.28		5.28	3.40	8.20	

Table 4a continued

Weight Gain During Pregnancy[f]				0.00				0.43
Inadequate	1.24	0.93	1.64		1.09	0.68	1.76	
Appropriate[d]	1.00	1.00	1.00		1.00	1.00	1.00	
Excess	0.45	0.33	0.60		0.85	0.57	1.26	
Prepregnancy Diabetes				0.00				
Yes	2.10	1.31	3.37					
No[d]	1.00	1.00	1.00					
Gestational Diabetes				0.01				
Yes	1.84	1.14	2.97					
No[d]	1.00	1.00	1.00					
Any Diabetes				0.00				
Yes	1.89	1.29	2.76					
No[d]	1.00	1.00	1.00					
Prepregnancy Hypertension				0.00				0.00
Yes	1.89	1.49	2.40		3.61	2.48	5.27	
No[d]	1.00	1.00	1.00		1.00	1.00	1.00	
Preterm birth[a]								0.00
Yes					1.89	1.29	2.76	
No[d]					1.00	1.00	1.00	

[a]Preterm birth includes live births that occurred at gestational ages 24-37 weeks inclusive.

[b]Based on PRAMS data, 2004-2011.

[c]Includes all diabetes categories

[d]Reference

[e]Underweight = <18.5 kg/m2, normal = 18.5-24.9 kg/m2, overweight = 25-29.9 kg/m2, obese = 30+ kg/m2

[f]Underweight: inadequate = less than 28 lbs, appropriate = 28-40 lbs, excess = greater than 40 lbs; Normal: inadequate = less than 25 lbs, appropriate = 25-35 lbs, excess = greater than 35 lbs; Overweight: inadequate = less than 15 lbs, appropriate = 15-25 lbs, excess = greater than 25 lbs; Obese: inadequate = less than 11 lbs, appropriate = 11-20 lbs, excess = greater than 20 lbs

[€]Analysis of data weighted for sample design, non-response, and non-coverage

Table 4b. Unadjusted Odds Ratios (OR), and 95 percent Confidence Intervals (CI) for gestational diabetes mellitus and prepregnancy diabetes mellitu live singleton births to AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington[a€]

	Gestational Diabetes				Prepregnancy Diabetes		
	crude OR	95% CI[€]		p-value	crude OR	95% CI[€]	
Maternal Age				0.00			
≤20	0.37	0.17	0.80		0.13	0.05	0.33
21-24[b]	1.00	1.00	1.00		1.00	1.00	1.00
25-29	1.71	1.01	2.90		0.57	0.25	1.34
30-34	3.31	1.92	5.71		2.09	0.82	5.34
≥35	3.68	2.07	6.56		1.49	0.61	3.63
Birthplace				0.00			
Alaska	0.05	0.03	0.11		0.29	0.14	0.57
Minnesota	2.07	1.38	3.11		1.03	0.55	1.94
Nebraska	1.35	0.96	1.90		0.96	0.51	1.79
New Mexico	1.14	0.71	1.83		1.40	0.65	3.03
Oklahoma	0.93	0.60	1.43		1.12	0.51	2.43
Oregon[b]	1.00	1.00	1.00		1.00	1.00	1.00
Utah	2.56	1.45	4.53		.	.	.
Washington	1.17	0.74	1.85		0.67	0.26	1.72
Education				0.20			
>12[b]	1.00	1.00	1.00		1.00	1.00	1.00
12	0.96	0.64	1.44		0.76	0.34	1.67
<12	0.66	0.41	1.06		0.47	0.21	1.09
Federal Poverty Level				0.74			

Table 4b continued

Prepregnancy BMI[c]				0.00			0.00
Underweight	1.61	0.53	4.96		0.18	0.02	1.38
Normal[b]	1.00	1.00	1.00		1.00	1.00	1.00
Overweight	2.10	1.20	3.69		1.59	0.51	4.99
Obese	5.25	3.26	8.47		3.80	1.32	10.99
Weight Gain During Pregnancy[d]				0.05			0.18
Inadequate	0.96	0.56	1.64		2.00	0.66	6.08
Appropriate[b]	1.00	1.00	1.00		1.00	1.00	1.00
Excess	0.61	0.38	0.97		1.98	0.94	4.18
Prepregnancy Hypertension				0.00			0.00
Yes	2.70	1.71	4.27		4.16	1.99	8.66
No[b]	1.00	1.00	1.00		1.00	1.00	1.00
Preterm birth[e]				0.03			0.01
Yes	1.83	1.08	3.11		2.18	1.23	3.86
No[b]	1.00	1.00	1.00		1.00	1.00	1.00

[a]Based on PRAMS data, 2004-2011.

[b]Reference

[c]Underweight = <18.5 kg/m2, normal = 18.5-24.9 kg/m2, overweight = 25-29.9 kg/m2, obese = 30+ kg/m2

[d]Underweight: inadequate = less than 28 lbs, appropriate = 28-40 lbs, excess = greater than 40 lbs; Normal: inadequate = less than 25 lbs, appropriate = 25-35 lbs, excess = greater than 35 lbs; Overweight: inadequate = less than 15 lbs, appropriate = 15-25 lbs, excess = greater than 25 lbs; Obese: inadequate = less than 11 lbs, appropriate = 11-20 lbs, excess = greater than 20 lbs

[e]Preterm birth includes live births that occurred at gestational ages 24-37 weeks inclusive.

[€]Analysis of data weighted for sample design, non-response, and non-coverage

Table 5: Evaluation of confounders of the relationship between any diabetes and preterm birth[a] among live singleton births to AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington[b€]

Change in OR

Main Models	Unweighted N	Odds Ratio	95% Confidence Interval[€]		Change from full model OR (%)	Width of CI
Full Model*	12060	1.65	1.11	2.47		2.23
Crude Model	12229	1.89	1.29	2.76	0.15	2.14
One Variable Dropped						
education, prepregnancy hypertension	12062	1.84	1.23	2.75	0.12	2.24
maternal age, prepregnancy hypertension	12226	1.68	1.12	2.50	0.02	2.23
maternal age, education	12061	1.75	1.19	2.56	0.06	2.15
Two Variables Dropped						
prepregnancy hypertension	12228	1.78	1.19	2.66	0.08	2.24
education	12063	1.95	1.33	2.86	0.18	2.15
maternal age	**12227**	**1.76**	**1.20**	**2.58**	**0.07**	2.15

Change in beta estimate

Main Models	Unweighted N	Beta Coeff.	95% Confidence Interval[€]		Change from full model beta (%)	Width of CI
Full Model*	12060	0.50	0.10	0.90		9.00
Crude Model	12229	0.64	0.25	1.02	0.28	4.08
One Variable Dropped						
education, prepregnancy hypertension	12062	0.61	0.21	1.01	0.22	4.81
maternal age, prepregnancy hypertension	**12226**	**0.52**	**0.12**	**0.92**	**0.04**	7.67
maternal age, education	12061	0.56	0.17	0.94	0.12	5.53
Two Variables Dropped						
prepregnancy hypertension	12228	0.58	0.18	0.98	0.16	5.44
education	12063	0.67	0.29	1.05	0.34	3.62
maternal age	12227	0.57	0.19	0.95	0.14	5.00

[a]Live birth 24-37 weeks gestation

[b]Based on PRAMS data, 2004-2011.

*Adjusted for maternal age, education, and prepregnancy hypertension

[€]Analysis of data weighted for sample design, non-response, and non-coverage

Table 6: Evaluation for confounding of the relationship between any diabetes and preterm birth[a] including prepregnancy BMI as a potential confounder among live singleton births to AI/AN women in Alaska, Minnesota, Nebraska, New Mexico, Oklahoma, Oregon, Utah, and Washington[b€]

					Change in OR	
Main Models	Unweighted N	Odds Ratio	95% Confidence Interval[€]		Change from full model OR (%)	Width of CI
Full Model, GS*	11363	1.83	1.20	2.78		2.32
Crude Model	12229	1.89	1.29	2.76	0.033	2.14
One variable dropped						
education, prepregnancy hypertension, prepregnancy BMI	11365	2.01	1.32	3.07	0.098	2.33
maternal age, prepregnancy hypertension, prepregnancy BMI	11513	1.83	1.21	2.78	0.00	2.30
maternal age, education, prepregnancy BMI	11364	1.92	1.29	2.86	0.049	2.22
maternal age, education, prepregnnacy hypertension	12060	1.65	1.11	2.47	-0.098	2.23
Two variables dropped						
maternal age, education	12061	1.75	1.19	2.56	-0.044	2.15
maternal age, prepregnancy hypertension	12226	1.68	1.12	2.50	-0.082	2.23
maternal age, prepregnancy BMI	11514	1.92	1.30	2.85	0.049	2.19
education, prepregnancy hypertension	12062	1.84	1.23	2.75	0.005	2.24
education, prepregnancy BMI	11366	2.13	1.42	3.17	0.164	2.23
prepregnancy hypertension, prepregnancy BMI	11515	1.96	1.29	2.98	0.071	2.31
Three Variables Dropped						
maternal age	12227	1.76	1.20	2.58	-0.038	2.15
education	12063	1.95	1.33	2.86	0.066	2.15
prepregnancy hypertension	12228	1.78	1.19	2.66	-0.027	2.24
prepregnancy BMI	11516	2.07	1.39	3.07	0.131	2.21

Table 6 continued

Change in beta estimate						
Main Models	Unweighted N	Beta estimate	95% Confidence Interval[€]		Change from full model beta (%)	Width of CI
Full Model, GS*	11363	0.60	0.19	1.02		5.37
Crude Model	12229	0.64	0.25	1.02	0.07	4.08
One variable dropped						
education, prepregnancy hypertension, prepregnancy BMI	11365	0.7	0.28	1.12	0.17	4.00
maternal age, prepregnancy hypertension, prepregnancy BMI	11513	0.61	0.19	1.02	0.02	5.37
maternal age, education, prepregnancy BMI	11364	0.65	0.26	1.05	0.08	4.04
maternal age, education, prepregnancy hypertension	12060	0.50	0.10	0.90	-0.17	9.00
Two variables dropped						
maternal age, education	12061	0.56	0.17	0.94	-0.07	5.53
maternal age, prepregnancy hypertension	12226	0.52	0.12	0.92	-0.13	7.67
maternal age, prepregnancy BMI	11514	0.65	0.26	1.05	0.08	4.04
education, prepregnancy hypertension	12062	0.61	0.21	1.01	0.02	4.81
education, prepregnancy BMI	11366	0.75	0.35	1.15	0.12	3.29
prepregnancy hypertension, prepregnancy BMI	11515	0.67	0.25	1.09	0.12	4.36
Three Variables Dropped						
maternal age	12227	**0.57**	**0.19**	**0.95**	**-0.05**	5.00
education	12063	0.67	0.29	1.05	0.12	3.62
prepregnancy hypertension	12228	0.58	0.18	0.98	-0.03	5.44
prepregnancy BMI	11516	0.73	0.33	1.12	0.22	3.39

[a]Live birth 24-37 weeks gestation

[b]Based on PRAMS data, 2004-2011.

*Adjusted for maternal age, education, prepregnancy hypertension, and prepregnancy BMI

[€]Analysis of data weighted for sample design, non-response, and non-coverage

Table 7: Odds ratios for the association of diabetes mellitus with preterm birth[a] among American Indian and Alaska Natives[b€]

	Odds Ratio	95% Confidence Interval[€]		p-value	Width of CI
Model 1[c]	1.76	1.20	2.58	0.004*	2.15
Model 2[d]	1.68	1.12	2.50	0.011*	2.23
Model 3[e]	1.92	1.30	2.85	0.001*	2.19
Model 4[f]	1.83	1.21	2.78	0.004*	2.30

[a]Live birth 24-37 weeks gestation

[b]Based on PRAMS data, 2004-2011.

[c]Maternal Age

[d]Maternal Age and prepregnancy hypertension

[e]Maternal Age and prepregnancy BMI

[f]Maternal Age, prepregnancy BMI, prepregnancy hypertension

*$p<0.05$

[€]Analysis of data weighted for sample design, non-response, and non-coverage

Table 8: Odds ratios for the association of diabetes mellitus with preterm birth[a] by state among American Indian and Alaska Natives[b€]

State	Unweighted N	cOR	95% CI[€]	p-value	aOR[c]	95% CI[€]	p-value	aOR[d]	95% CI[€]	p-value
Alaska	3364	0.15	(0.06-0.37)	0.000	0.14	(0.06-0.35)	0.000*	0.17	(0.07-0.42)	0.000*
Minnesota	1277	2.07	(1.13-3.77)	0.018	1.91	(1.07-3.39)	0.028*	2.30	(1.30-4.08)	0.004*
Nebraska	1333	5.85	(3.38-10.11)	0.000	5.92	(3.45-10.16)	0.000*	6.63	(3.80-11.56)	0.000*
New Mexico	481	2.67	(1.10-6.47)	0.029	2.42	(0.95-6.19)	0.065	2.78	(1.04-7.42)	0.042*
Oklahoma	1705	1.51	(0.68-3.35)	0.312	1.39	(0.61-3.15)	0.437	1.51	(0.64-3.55)	0.343
Oregon	2337	1.87	(1.16-3.02)	0.010	1.82	(1.11-2.98)	0.017*	1.73	(1.04-2.86)	0.034*
Utah	178	2.18	(0.48-9.99)	0.316	1.38	(0.31-6.23)	0.672	1.88	(0.46-7.61)	0.376
Washington	1745	2.40	(0.87-6.60)	0.090	2.34	(0.94-5.84)	0.067	2.23	(0.89-5.61)	0.088

[a]Live birth 24-37 weeks gestation

[b]Based on PRAMS data, 2004-2011.

[c]Adjusted for maternal age

[d]Adjusted for maternal age and bmi

*$p<0.05$

[€]Analysis of data weighted for sample design, non-response, and non-coverage

Table 9: Odds ratios for the association of diabetes mellitus with preterm birth[a] by state among American Indian and Alaksa Natives using all diabetes variables[b€]

	aOR[c]	95% CI[€]	p-value
State			
Alaska	1.15	(0.85-1.55)	0.375
Minnesota	1.63	(0.95-2.78)	0.073
Nebraska	4.58	(2.97-7.06)	0.00*
New Mexico	1.10	(0.47-2.58)	0.819
Oklahoma	1.51	(0.89-2.55)	0.129
Oregon	1.86	(1.16-2.99)	0.011*
Utah	2.63	(0.93-7.41)	0.068
Washington	2.28	(1.23-4.20)	0.009*

[a]Live birth 24-37 weeks gestation

[b]Based on PRAMS data, 2004-2011.

[c]Adjusted for maternal age

*$p<0.05$

[€]Analysis of data weighted for sample design, non-response, and non-coverage

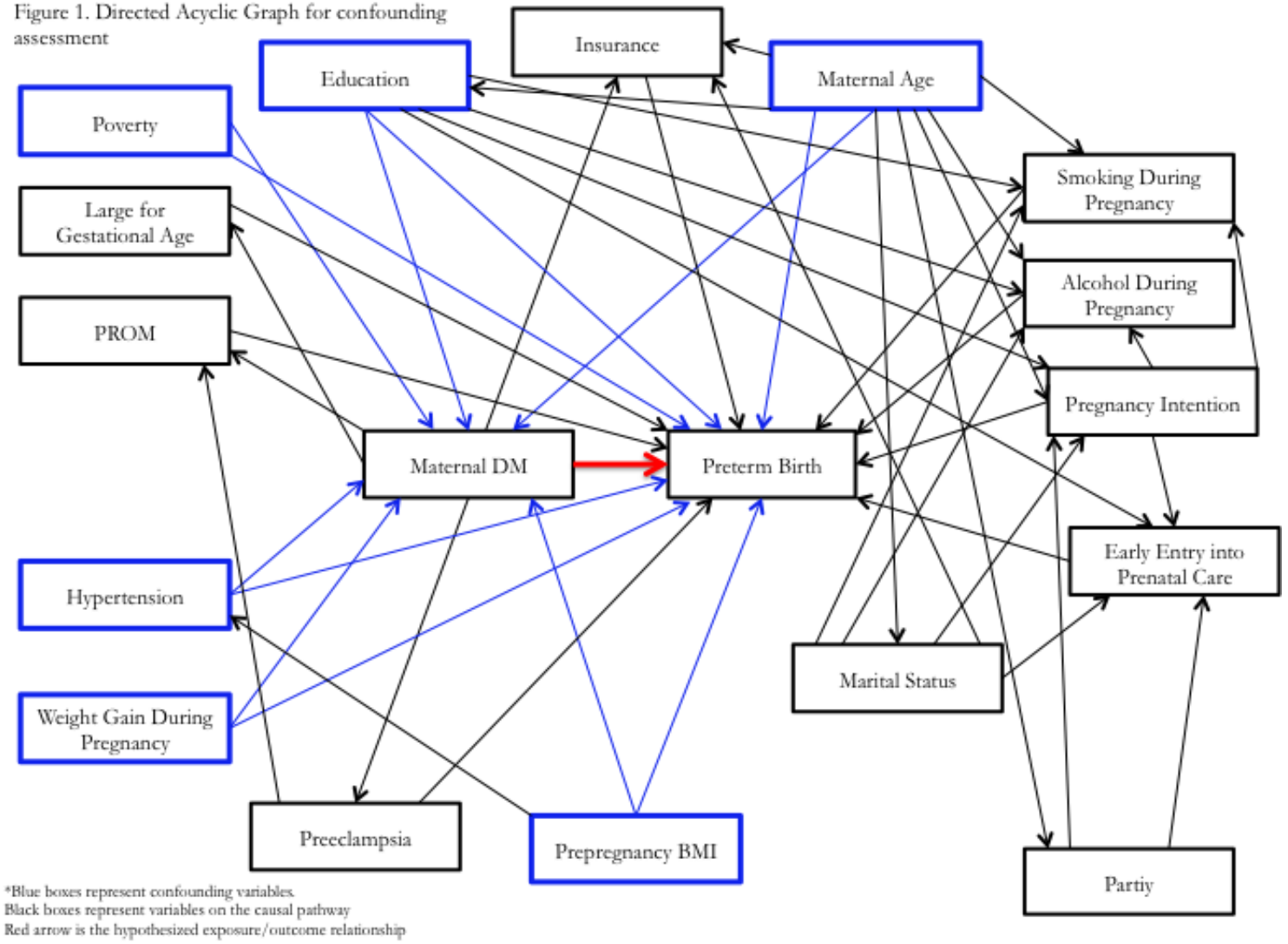
Table 10: Diabetes Prevalence among AI/AN in Alaska from 2000-2009

	% Diagnosed with diabetes mellitus	95% CI		% Diagnosd with diabetes mellitus	95% CI	
	Natives	Lower Limit	Upper Limit	Non-Native	Lower Limit	Upper Limit
Year						
2000	7	1	12.3	3.4	2.2	4.6
2001	3.6	2	5.2	4.1	3	5.2
2003	6	3.2	11.9	5	3.7	6.1
2004	4	2.5	5.5	4	3.2	5.7
2005	3	3	4.8	5	3.6	5.9
2006	7	3.7	11.3	6	4.5	7.3
2007	6	3.6	10.3	6	4.7	7.9
2008	6.8	4.6	10	5.9	5	7
2009	5.1	3.7	7	6	5.2	7

Source: Behavioral Risk Factor Surveillance System Annual Reports 2000-2009

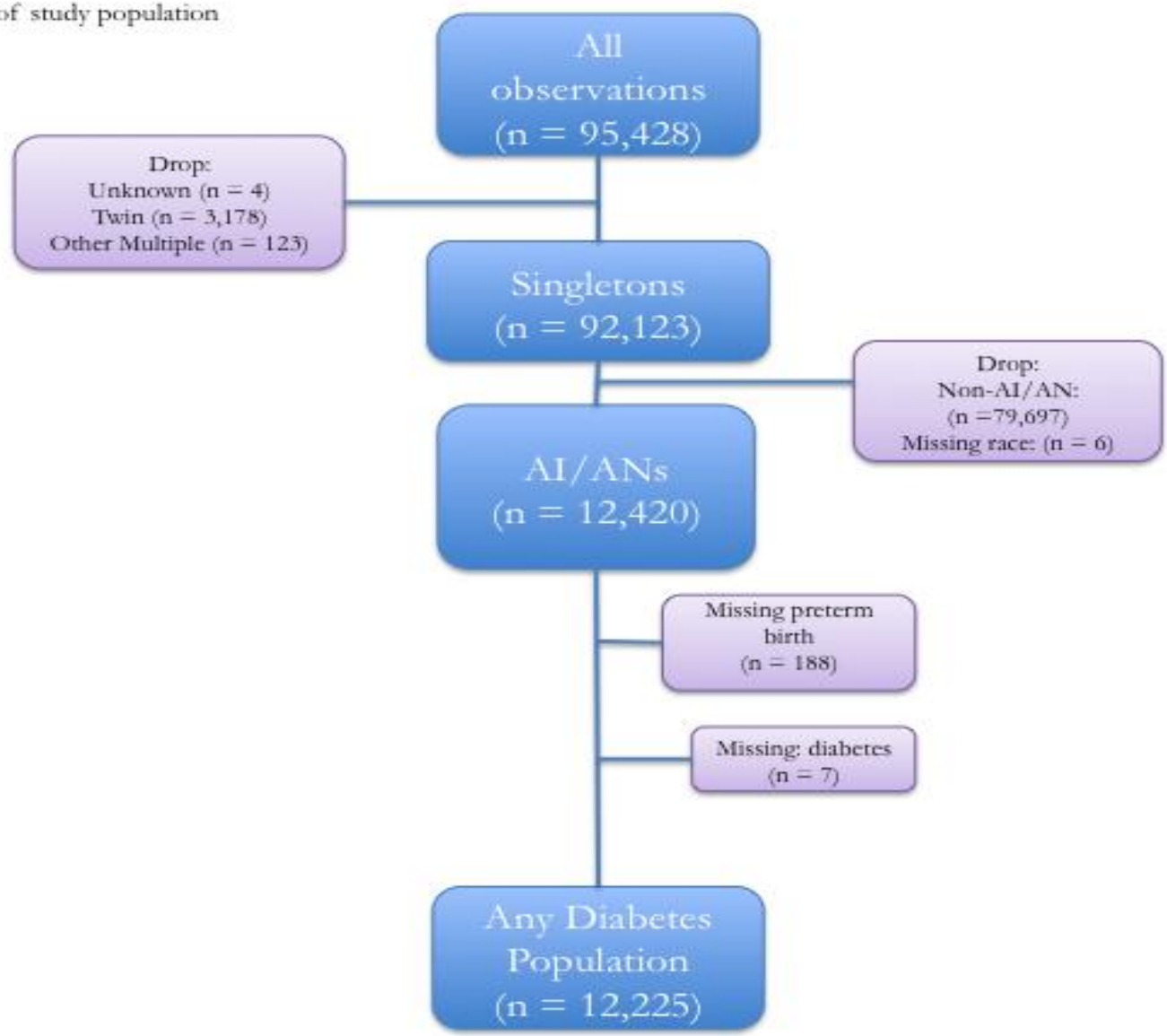
Figures

Figure 1. Directed Acyclic Graph for confounding assessment



*Blue boxes represent confounding variables.
Black boxes represent variables on the causal pathway
Red arrow is the hypothesized exposure/outcome relationship

Figure 2. Flowchart of study population



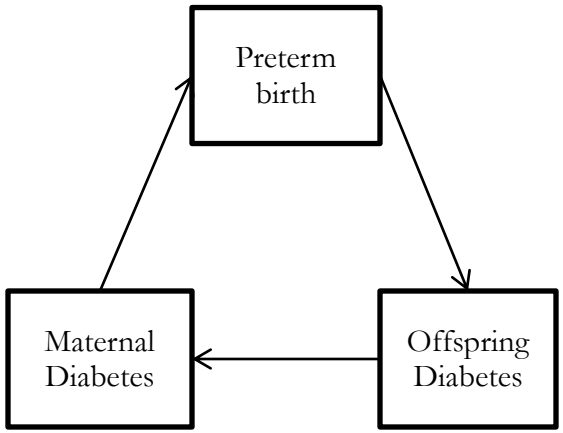
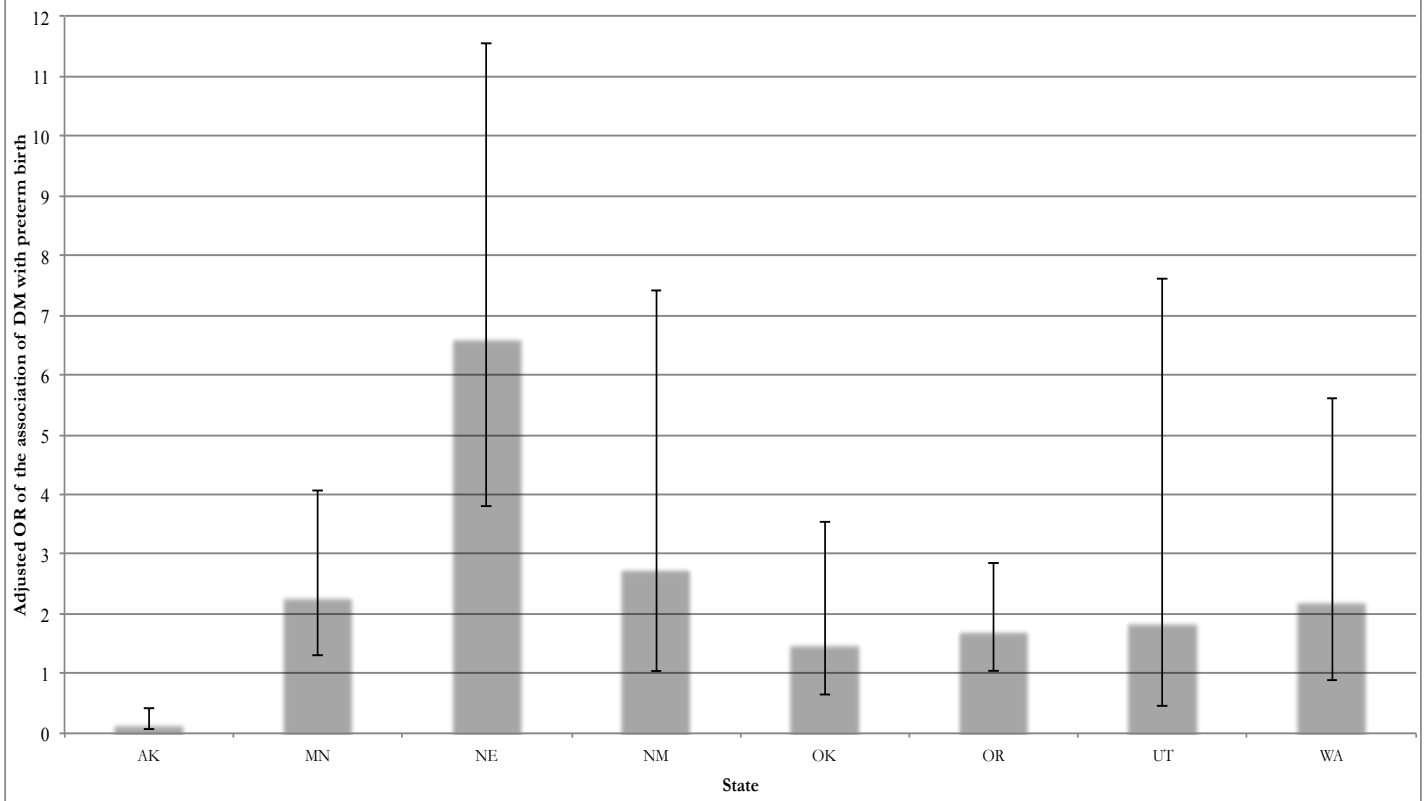


Figure 3. Conceptual diagram of the relationship between diabetes mellitus and preterm birth

Figure 4 Adjusted Odds Ratios* of the association of DM with preterm birth by state€



*OR adjusted for maternal age and prepregnancy BMI
[a]Live birth 24-37 weeks gestation
€Analysis of data weighted for sample design, non-response, and non-coverage
Error bars represent 95%CI
AK = Alaska, MN = Minnesota, NE = Nebraska, NM = New Mexico, OK = Oklahoma, UT = Utah, WA = Washington