RACIAL AND AGE-RELATED DISPARITIES IN INFANT AND MATERNAL MORTALITY IN THE UNITED STATES FROM 2000-2019

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ABSTRACT

Objectives: Infant and maternal mortality rates serve as important markers of a country's health. While infant mortality rates have declined, still more than 21,000 infants died in 2018 in the United States (US) and sudden infant death syndrome (SIDS) remains the leading cause of infant death. Also, the US is the only developed nation where maternal mortality rates are rising, with over 700 pregnant women dying annually. Most studies have excluded non-obstetrical causes of death due to the World Health Organization's (WHO) definition of maternal death, which is limited to obstetrical causes. This thesis will be addressing four objectives: 1) to report on estimates of SIDS and examine SIDS risk across sex and racial groups in the US, 2) to report on maternal mortality from all causes across race and examine racial disparities in the US, 3) to report on maternal mortality from all causes across age groups and examine age-related risk in the US, and 4) to report on non-obstetric causes of maternal mortality and examine associated racial disparities.

Methods: Four retrospective population-based cross-sectional studies were conducted. All studies utilized data from the Centers for Disease Control and Prevention's "Birth Data" and "Mortality Multiple Cause" data files, containing official birth and death certificate information in the US, from 2000-2019. In the first study, incidence rates of SIDS per 10,000 live births were calculated across sex and racial groups over the 20-year period and logistic regression models estimated the effects of sex and race on the risk of SIDS. The second study reported maternal mortality rates due to both obstetrical and non-obstetrical causes per 100,000 live births across racial groups and used logistic regression models to estimate effects of race on the risk of maternal mortality. The third paper estimated annual incidence and period trends in maternal

deaths by 5-year age groups and used multivariate logistic regression models to estimate associations between maternal age and risk of maternal mortality. The fourth paper reported annual incidence of non-obstetric maternal mortality and used logistic regression models to examine the effects of race on mortality.

Results: In the first study, a total of 39,591 SIDS cases were reported between 2000 and 2019. Male infants were at greater risk of SIDS (OR 1.36,95% CI 1.33-1.39), as were Black (2.25, 2.20-2.30) and American Indian infants (2.21, 2.06-2.37), compared with White infants. In the second and third studies, a total 21,241 maternal deaths were reported in women during pregnancy and childbirth during the study period, with 65.5% being caused by obstetrical and 34.5% by other non-obstetrical causes. The second study found that Black women, compared with White women, were at a greater risk of maternal mortality (OR 2.13,95% CI 2.06-2.20), as were American Indian women (2.02, 1.83-2.24). The third study found that 6,870 (32.3%) maternal deaths were in women ≥35 years, while only 15.1% of livebirths were attributed to women ≥35 years, with a significantly greater risk of maternal mortality among older women. The last study found 7,334 women died during pregnancy from non-obstetric causes over the past two decades, with transport accidents and accidental poisoning being the most common reasons. In terms of race, American Indian women were found to be at the highest risk of experiencing maternal death from a non-obstetric cause (OR 2.20,95% CI 1.90-2.56).

Conclusions: The incidence of SIDS in the US declined between 2000-2019; however, male, Black, and American Indian infants remain at a higher risk. We also found increases in maternal mortality rate from obstetrical and non-obstetrical causes over the past two decades,

with greater risk among American Indian, Black, and women ≥35 years, pointing to the need to prioritize targeted public health interventions to improve maternal health outcomes.

Keywords: Sudden Infant Death Syndrome, Maternal Mortality, Mortality, Pregnancy, Race, Sex, Age, Obstetric, Non-Obstetric

RÉSUMÉ

Objectifs: Les taux de mortalité infantile et maternelle servent de marqueurs importants de la santé d'un pays. Bien que les taux de mortalité infantile aient diminué, encore plus de 21 000 nourrissons sont morts en 2018 aux États-Unis et le syndrome de mort subite du nourrisson (SMSN) reste la principale cause de décès des nourrissons. Les États-Unis sont également la seule nation développée, où les taux de mortalité maternelle sont en hausse. La plupart des études ont exclu les causes de décès non obstétricales en raison de la définition de la mort maternelle de l'Organisation mondiale de la santé (OMS), qui se limite aux causes obstétricales. Cette thèse répondra à quatre objectifs : 1) rendre compte des estimations du SMSN et examiner le risque de SMSN à travers le sexe et les groupes raciaux aux États-Unis, 2) rendre compte de la mortalité maternelle toutes causes confondues à travers la race et examiner les disparités raciales aux États-Unis, 3) rendre compte de la mortalité maternelle toutes causes confondues à travers les groupes d'âge et examiner le risque lié à l'âge, et 4) rendre compte des causes non obstétricales de la mortalité maternelle.

Méthodes: Quatre études basées sur la population en utilisant des modèles de régression logistique ont été menées. Toutes les études utilise les données des fichiers de données <<données de naissance >> et << mortalité cause multiple >> des Centres pour le contrôle et la prévention des maladies, contenant les informations officielles des certificats de naissance et de décès aux ÉU de 2000 à 2019. Dans la première étude, les taux d'incidence du SMSN pour 10 000 naissances vivantes ont été calculés pour les groupes de sexe et de race sur la période de 20 ans et ont estimé les effets du sexe et de la race sur le risque de SMSN. La deuxième étude rapporte, les taux de mortalité maternelle dus à des causes obstétricales et non obstétricales pour

100 000 naissances à travers les groupes raciaux estime les effets de la race sur le risque de mortalité maternelle. Le troisième article estime l'incidence annuelle, les tendances périodiques des décès maternels par groupes d'âge de 5 ans et les associations entre l'âge maternel et le risque de mortalité maternelle. Le quatrième article rapporte l'incidence annuelle de la mortalité maternelle non obstétricale et examine les effets de la race.

Résultats: Dans la première étude, 39 591 cas de SMSN ont été signalés entre 2000 et 2019. Les bébés de sexe masculin étaient plus exposés au risque de SMSN (OR 1,36, IC 95% 1,33-1,39), comme les bébés noirs (2,25, 2,20-2,30) et amérindiens (2,21, 2,06-2,37), par rapport aux bébés blancs. 21 241 décès maternels ont été signalés chez les femmes pendant la grossesse et l'accouchement au cours de la période d'étude, 65,5% étant causés par des causes obstétriques et 34,5 % par d'autres causes non obstétriques. La deuxième étude a révélé que les femmes noires, contre les femmes blanches, avaient un risque élevé de mortalité maternelle (OR 2,13, IC 95% 2,06-2,20), tout comme les femmes amérindiennes (2,02, 1,83-2,24). La troisième étude a révélé que 6 870 (32,3%) décès maternels concernaient des femmes ≥35 ans, seulement 15,1% des naissances vivantes étaient attribuées à des femmes ≥35 ans, avec un risque de mortalité maternelle significativement plus élevé chez les femmes plus âgées. La dernière étude a révélé que 7 334 femmes sont décédées pendant la grossesse de causes non obstétricales et que les femmes amérindiennes présentaient le risque le plus élevé (OR 2,20, IC 95 % 1,90-2,56).

Conclusion: L'incidence du SMSN aux ÉU a diminué entre 2000 et 2019. Les bébés de sexe masculin, noirs et amérindiens restent à un risque plus élevé, soulignant la nécessité de cibler les interventions vers les mères noires et amérindiennes. Il ya aussi une hausse du taux de

mortalité maternelle due à des causes obstétricales et non obstétricales plus élevés chez les Amérindiens, les Noirs et les femmes ≥35 ans.

Mots-clés : Syndrome de la mort subite du nourrisson, Mortalité maternelle, Mortalité, Grossesse, Race, Sexe, Âge, Obstétrique, Non-obstétrique

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Contribution of Authors

Ryan Huang is the primary author of this thesis under the supervision of Dr. Haim A. Abenhaim.

Ryan Huang and Dr. Haim A. Abenhaim contributed to the study concept and design.

Ryan Huang, Dr. Andrea Spence, and Dr. Haim A. Abenhaim contributed to the analysis and interpretation of the data

Ryan Huang drafted the manuscript and all non-manuscript chapters of this thesis

Ryan Huang, Dr. Andrea Spence, and Dr. Haim A. Abenhaim contributed to the critical revision of the manuscript for important intellectual content

The thesis supervisor, Dr. Haim A. Abenhaim, contributed to the initial review and edits of the thesis.

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List of Abbreviations

AIM: Alliance for Innovation in Maternal Health

ART: Assisted Reproductive Technology

CDC: Centers for Disease Control and Prevention

CI: Confidence Interval

ICD: International Classification of Diseases

IPV: Intimate Partner Violence

NCHS: National Center for Health Statistics

NVSS: National Vital Statistics System

OR: Odds Ratio

SIDS: Sudden Infant Death Syndrome

US: United States

WHO: World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Rationale

Infant and maternal mortality serve as important indicators for the overall health of a country[1, 2]. Infant mortality remains a pressing medical concern as over 23,000 infants who are born alive in the United States (US) die before their first birthday[3]. Specifically, sudden infant death syndrome (SIDS) is a major contributor as the leading cause of death among infants between 1 week and 1 year of age in the US[4]. Although SIDS rates have decreased following public health recommendations through the Back to Sleep Campaign in 1994[5], few studies have presented a comprehensive picture of time trends of differentials in SIDS risk across sex and race over the last two decades. Further, the US is the only developed nation, where maternal mortality rates appear to be rising[6], with more than 700 American women dying during pregnancy and childbirth annually[7]. Most studies examining maternal mortality have been limited to obstetrical causes of death as per the World Health Organization's (WHO) definition[8], however non-obstetrical causes of death such as homicide and motor accidents remain high[9, 10] and should be examined to understand how to improve public health interventions to induce further declines in mortality.

1.2 Objectives

The thesis will address the following objectives:

1. To provide population-based estimates of SIDS rates in the US between 2000 and 2019 and examine SIDS risk across sex and racial groups.

2. To provide population-based estimates of maternal mortality rates from all causes of death in the US by race between 2000 and 2019 and to examine racial disparities in maternal mortality.
3. To provide population-based estimates of maternal mortality rates from all causes of death in the US by age groups between 2000 and 2019 and to examine age-related disparities in maternal mortality.
4. To provide population-based estimates of non-obstetric maternal mortality rates between 2000 and 2019 in the US and to examine racial disparities in non-obstetric causes of maternal mortality.

These objectives were addressed through four separate population-based cross-sectional studies. In this thesis, the findings from these analyses are presented as four manuscripts with linking chapters.

CHAPTER 2: LITERATURE REVIEW

2.1 Infant Mortality

Infant mortality is the death of an infant before reaching one year of age, with the mortality rate calculated for every 1,000 live births[11]. Examining infant mortality provides critical information on infant health as well as the overall health of a society[12]. SIDS remains as the leading cause of death in infants between one week and one year of age and is the target for many public health initiatives aiming to improve infant mortality[4].

2.1.1 Sudden Infant Death Syndrome

2.1.1.1 Definition

SIDS was first proposed in 1969 to describe infants whose deaths occurred unexpectedly in the postnatal period[13]. The definition of SIDS has evolved to refer to the sudden and unexpected death of an infant, who is less than 1 year of age, with the onset of the lethal episode occurring during sleep, but remaining unexplained after a thorough case investigation including a complete autopsy, review of medical and clinical history as well as death scene investigation[14]. While the definition includes infants of up to 1 year in age, 95% of SIDS deaths occur in the first six months of life, with the greater incidence observed in infants aged between two to four months[15]. The application of the term relies on a process of elimination. When no known cause of death can be determined, the term SIDS is applied, and therefore it remains a diagnosis of exclusion[14].

2.1.1.2 Diagnosis

SIDS is diagnosed when no known causes of death or contributing factors can be determined after a death scene investigation, autopsy, and review of medical history[16]. The initial investigation of the death scene involves both law enforcement and medical personnel to document the sleep environment, sleep position and factors that may have contributed to the death such as bedding[17]. Subsequently, a comprehensive autopsy is completed that includes full external and internal examinations, as well as a full assessment of the infant's medical history[18]. The history should provide insight into parental illnesses and maternal risk factors such as smoking. If after the rigorous and in-depth investigation no cause of death can be determined, then the term SIDS is used. Unfortunately, this creates ambiguity in how the term can be used and hence, limitations arise from improper usage of the term[19].

2.1.1.3 Incidence

About 3,500 babies in the US die suddenly and unexpectedly each year[20]. Since the introduction of safe sleep campaigns, SIDS rates have decreased in the US and around the world by over 50%[21]. Over the past two decades, SIDS rates declined from 130.3 deaths per 100,000 live births in 1990 to 33.3 deaths per 100,000 live births in 2019 in the US[22]. However, it remains as the leading cause of death for infants between 1 week and 1 year of age in the US[4], pointing to the need for better targeted public health interventions.

2.1.1.4 Risk Factors

SIDS has been proposed to involve the interactions between a variety of factors [23]. One of the most accepted models to explain SIDS is the "Triple Risk Model" proposed in 1994[24]. This

model proposes that SIDS results from an interplay between the presence of an underlying vulnerability, an exogenous stressor such as prone sleeping, and also having these events occurring during a critical development period. The interplay of these factors is associated with an increase in mortality, but each factor alone is not a sufficient cause of SIDS. Over the years there have been several proposed risk factors of SIDS that have been broadly grouped into intrinsic and extrinsic risk factors. Intrinsic risk factors affect the vulnerability of the infant that could make them susceptible to the influence of extrinsic risks. Major intrinsic risk factors include genetic polymorphisms, prematurity, low birth weight and prenatal exposure to drugs and alcohol[25]. Extrinsic risk factors take the form of physical stressors from the environment such as sleep positioning, soft bedding, unsafe sleep surfaces and overheating[26].

2.1.1.4.1 Prematurity and Low Birth Weight

Studies have reported that prematurity and low birth weight increase the risk of SIDS by four-fold[27, 28], with the likely cause being the increased vulnerability of these infants due to immature autonomic systems. Specifically, a study noted that the baroreflex, which is a system that regulates blood pressure, does not mature quickly in premature babies and as a result they are unable to compensate for a drop in blood pressure required during sleep that ultimately places them at a greater risk of SIDS[29].

2.1.1.4.2 Infant Sex

It has been reported that SIDS is higher in males than females[30]. While the exact cause is unclear, there have been speculations that this could just be an effect of male infants being more

vulnerable to disease in general, showing a greater mortality rate overall[31]. Other studies have found that female infants sleep more soundly than male infants, and the resulting increased sleep disruption in males could place them at a greater risk of SIDS[32, 33]. It has also been documented that males show increased night awakenings and problematic crying compared to female infants that suggest a delayed development of sleeping rhythms in males that could place them at a greater risk of SIDS[34].

2.1.1.4.3 Ethnicity

Studies have found that the incidence of SIDS is higher in African American populations[35], and lower in individuals with an Asian heritage[36]. However, the potential effects of ethnicity may be impacted by geography. In particular, a study showed that infants with an Asian heritage in California have higher rates of SIDS compared to Asian infants living in their country of origin[37]. Additional research into socioeconomic factors and the presence of other risk factors may better explain the effects of ethnicity on SIDS.

2.1.1.4.4 Genetic Polymorphisms

Currently, there is no specific gene that has been identified to cause SIDS, however there is the possibility that some infants may carry unidentified genetic mutations that can interact with the environment and subsequently increase their susceptibility to SIDS. For example, a sequencing study identified potentially causative gene variants in 20% of their 161 SIDS infants, with the greatest number of genes being associated with ion channelopathies[38]. This led to the

hypothesis that mutations in cardiac ion channels could contribute to lethal arrhythmia and lead to SIDS. Additional studies have reported over 17 genes with differential expression in SIDS infants[39], with polymorphisms being reported in the serotonin transporters, sodium channels, and genes involved in the development of the autonomic nervous system[40, 41]. However, it remains difficult to interpret the significance of gene mutations in SIDS due to the rarity of multiple SIDS deaths in a single family.

2.1.1.4.5 Use of Cigarettes and Drugs

There is substantial evidence that prenatal maternal cigarette smoking increases the risk of SIDS five-fold[42, 43]. However, it seems that public health interventions to limit maternal smoking have been unsuccessful as more than 13% of all women still continue to smoke while pregnant[44], with even higher numbers observed in high-risk populations[45]. More alarming, the prevalence of prenatal maternal smoking among SIDS mothers has increased over the last two decades by 30%[46]. The mechanism by which prenatal maternal smoking contributes to an increased SIDS risk remains unclear, but it has been hypothesized that nicotine can cross the placenta and bind to acetylcholine receptors in the fetal brain, inappropriately stimulating the function of these receptors[47]. Other studies have also pointed to nicotine's ability to control cell survival and regulate transmitter release to impair arousal[48] and alter the parasympathetic control of heart rate[49].

Literature also suggests that drug use including alcohol and cocaine use is linked with a greater risk of SIDS[50, 51]. The mechanisms are not clear, but alcohol and cocaine use are also

associated with prematurity and low birth weight, which have been established to be associated with an increased risk of SIDS[52].

2.1.1.4.6 Sleep Position

A prone sleeping position is widely regarded as the most significant environmental risk factor for SIDS, with estimates that prone sleeping can increase the risk of SIDS by up to 14-fold[53]. Prone sleeping characterizes the sleep position where an infant is lying on their abdomen (stomach) and is therefore lying face down. It places additional physiological stress on cardiorespiratory systems. Often, the mechanism of death associated with prone sleeping is suffocation[54], but additional theories include claims that the face-down sleeping position results in oxygen deprivation leading to hypoxia, increased body temperature, airway obstruction and compromised cerebral blood flow[55].

2.1.1.4.7 Sharing a Sleep Surface

It has been proposed that sharing a sleep surface, including beds and couches, increases the risk for SIDS because of a greater chance of suffocation or overheating[56]. Data from the past two decades in the United Kingdom show more than 50% of unexpected infant deaths to be associated with a shared environment[57]. This risk increases when more adults are present on the sleeping surface. However, it has also been observed that sharing sleep surfaces remains a common practice worldwide without associated increases in infant mortality[58]. Further studies are needed to truly understand why these differences exist.

2.1.1.4.8 Soft Bedding, Sleep Surfaces, Overheating

Soft bedding surfaces are also associated with increased infant mortality. This has been attributed to depression of the surface under the weight of the infant.[59]. In addition, blankets and pillows can also increase the risk of face covering and subsequent overheating. A recent study showed that more than 70% of babies dying between 2000 and 2017 were sleeping in an unsafe environment including soft surfaces and hazards like pillows and blankets[60].

2.1.1.5 Public Health Interventions

In 1994, the Back to Sleep Campaign was introduced in the US providing recommendations to place all babies to sleep on their back. This led to the greatest decline in rate of SIDS in the US, with decreases of up to 70 percent[61]. Since then, additional recommendations have followed. In 2000, recommendations against additional extrinsic risk factors including soft sleep surfaces, overheating, and loose bedding were introduced[62]. The Back to Sleep Campaign was later replaced by the Safe to Sleep campaign in 2012, which continued emphasizing the importance of a supine sleep position, but also focused on safe sleep environments in general to continue addressing the risk of SIDS[63]. The Safe to Sleep campaign dispelled many myths that led to dangerous sleeping behaviours that increased the risk of SIDS. In particular, the campaign warned against co-sleeping. Specifically, the campaign dispelled the idea that sleeping in the same bed with a baby was beneficial as it was possible to hear any problems that could occur.

2.2 Maternal Mortality

2.2.1 Definition

The WHO defines a maternal death as the death of a woman from any cause related to or aggravated by pregnancy or its management during pregnancy and childbirth, within 42 days of childbirth, but excluding accidental and incidental causes of death[64]. By excluding accidental and incidental causes of death however, many deaths in pregnant women are not captured. Specifically, a large portion of deaths arise from non-obstetric causes of death such as homicide, drug overdoses and transport accidents[65, 66]. Since the WHO definition is the most commonly used definition for maternal death, many studies have failed to capture all deaths during pregnancy and childbirth and instead have focused on obstetrical complications causing death. In addition, very few studies have actually enumerated the number of maternal deaths across the US from non-obstetrical causes. Further studies investigating non-obstetric causes of death in more detail and looking at all causes of death together would be beneficial in understanding the entire scope of maternal mortality.

2.2.2 Reporting of Maternal Mortality

Each country has a different system in place to record mortality data. In the United States, reporting states send copies of official death certificates, validated by medical practitioners, of women who died during pregnancy to the Center for Disease Control and Prevention (CDC), where they are compiled into national statistics[67]. In 2003, a checkbox was introduced to the death certificate to indicate whether the death occurred during pregnancy and childbirth to help diagnose maternal deaths, in addition to the cause and date of death, which are also included in the death certificate[68].

2.2.3 Measures of Maternal Mortality

The most commonly used measure of maternal mortality is the maternal mortality ratio (MMR), which is defined as the number of maternal deaths in a given period of time divided by the number of live births (per 100,000) during the same period[69]. Low MMR is defined as 20-99 maternal deaths per 100,000 live births, while high MMR is defined as an MMR greater than or equal to 300 maternal deaths per 100,000 live births[70]. In the literature, other measures of maternal mortality have also been used, but are less common. One such measure is the proportion of maternal deaths among deaths of women of reproductive age, which is defined as the number of maternal deaths in a given time divided by the total deaths among women of 15-49 years of age[71]. MMR is generally regarded as the preferred measure of maternal mortality because it describes the frequency of maternal death relative to the risk pool (live births)[72].

2.2.4 Incidence

In 2015, it was estimated that worldwide, 303,000 women died while pregnant or within 42 days of the end of pregnancy, which corresponds to an MMR of 216 maternal deaths per 100,000 live births[73]. Although still high, maternal mortality rates have decreased worldwide by 43.9% compared with the 385 maternal deaths per 100,000 live births observed in 1990[74]. A large disparity in maternal mortality is observed between developed and developing countries. In 2015, the MMR was considerably lower in developed countries at 12 per 100,000 live births compared to low-income countries such as sub-Saharan Africa showing an MMR of 546 per 100,000 live births[75]. In most developed countries, maternal mortality has continued to decline over the past two decades due to the movement of most births to hospitals, improved hygiene, aseptic techniques, increase in prenatal care and an increase in screening for preeclampsia[76]. The

US, however, is the only developed country to show an increase in MMR over the last two decades, with an MMR of 23.8 per 100,000 live births in 2014[77]. There is some speculation that the rise in maternal mortality, at least in part, was due to improved ascertainment from the addition of the pregnancy checkbox to the standard US death certificate, as prior studies revealed that more than half of pregnancy-related deaths were not identified through routine surveillance methods[78]. A study evaluating the addition of the checkbox in Maryland showed that more than 98% of maternal deaths were captured after the addition of the checkbox, while only 62% were identified before, suggesting a large number of missed maternal deaths prior to the introduction of the checkbox[79]. However, there has also been an increase in population risk factors such as maternal age and obesity. When increased ascertainment is accounted for, the maternal mortality in the US remains substantially higher than other developed countries, pointing to an actual increase in mortality[80]. It is likely that the observed rise is caused by a combination of both changes in data collection methods and increased prevalence of maternal risk factors.

2.2.5 Risk Factors of Maternal Morbidity and Mortality

Maternal and obstetrical outcomes of pregnancy are influenced by patient factors, as well as the heath system, and practitioners. The normal physiologic changes of pregnancy place all women at risk for adverse events, but some women are at a higher risk of morbidity and mortality than others. In the US, more women are becoming pregnant despite chronic health conditions including hypertension, cardiac disease and diabetes[81]. These chronic conditions place these women at a greater risk of experiencing adverse obstetrical outcomes. Further, these chronic conditions may be exacerbated during pregnancy. For example, pregnancy has been associated with worsening diabetes-related complications such as diabetic ketoacidosis[82]. The

physiological changes during pregnancy can place additional strain on the body. An increase in cardiac output and heart rate, which are characteristic of normal physiologic pregnancy changes, would further complicate problems with an abnormal heart from pre-existing diseases[83]. Other risk factors for poor outcomes in pregnancy are age and obesity, which are increasing in frequency as greater numbers of older women and obese women are becoming pregnant [84, 85]. In the US, more than one-third of women of reproductive age have a body mass index over 30 kg/m^2 [86]. Obese women are at an increased risk of cardiac disease, sleep apnea, gestational diabetes and pre-eclampsia leading to an increased risk of maternal mortality and morbidity[87]. In terms of age, older women are likely at a greater risk of maternal mortality due to increasing comorbidities such as hypertension and cardiac disease, as well as the increasing use of assisted reproduction technology (ART), which increases the risk of multiple gestations[88]. There have also been racial disparities observed in maternal mortality with a greater risk observed in Black women. From 2011-2013, data from the Pregnancy Mortality Surveillance System showed an MMR of 40.4 per 100,000 live births for Black women compared to 12.1 per 100,000 live births for White women in the US[89]. The exact causes of these disparities are still not completely understood, but current theories suggest multiple factors including younger age, less prenatal care, less education, lower insurance coverage and higher rates of pre-existing medical conditions[90]. Obstetrical risk factors also play a role in maternal morbidity and mortality. The rate of maternal death has been shown to be causally related to the mode of delivery. Compared with vaginal deliveries, caesarean delivers are associated with hemorrhage and infection, which subsequently increase the risk for maternal death[91]. In addition, health system and health provider factors also contribute to maternal mortality. The point of entry into health care, documentation, lack of equipment and delayed referrals to specialists all play a role in maternal

health. Studies have found that obstetric complications are increased in both rural hospitals and in hospitals with low delivery volumes, possibly due to the lack of resources and expertise at these facilities[92].

2.2.6 Public Health Interventions to Reduce Maternal Morbidity and Mortality

Approximately 30-40% of pregnancy-related deaths have been identified as potentially preventable, with 93% of deaths due to hemorrhage and 89% of deaths due to chronic conditions being deemed as preventable[93]. Although provider and system factors are more preventable than patient factors, there is room for intervention. Collaboration between multiple national organizations led to the creation of The National Partnership for Maternal Safety and the Council on Patient Safety in Women's Healthcare, which has publicly available educational tools aimed at improving maternal health and reducing caesarean births[94]. This organization has also created national guidelines on contributors to maternal mortality and developed a tool to allow for institutional review of severe maternal morbidity. The US government has also made great strides in promoting family planning and the use of contraceptives, which have prevented millions of maternal deaths[95]. However, the overall lack of contraceptive access rate is still 50% globally, with a low of 4% in Europe and a high of 57% in Africa[96]. Given the high rates of maternal deaths attributed to unwanted pregnancies, several countries have begun recognizing the importance of developing wider access to safe abortions, which remain nonexistent in some countries.

CHAPTER 3: REFERENCES I

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CHAPTER 4: NATIONAL SIDS TRENDS IN THE US FROM 2000-2019: A POPULATION-BASED STUDY ON 80 MILLION LIVE BIRTHS

The following chapter presents the methods and results of the first thesis objective: To provide population-based estimates of SIDS rates in the US between 2000 and 2019 and examine SIDS risk across sex and racial groups.

The topic presented in this manuscript will be introduced with some background information, followed by a comprehensive methods section that will cover the details of the study population and statistical methods used. The results are described in detail and the discussion provides insightful information as well as study limitations.

National SIDS Trends in the US from 2000-2019: A Population-Based Study on 80 Million Live Births

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Abstract

Objective

In the United States (US), sudden infant death syndrome (SIDS) is the most common cause of death for infants between 1 week and 1 year of age. The study objective was to examine recent trends in SIDS in the US, both over time and by sex and race.

Methods

A population-based cross-sectional study was conducted on 80,710,348 live births using data from the Centers for Disease Control and Prevention's "Birth Data" and "Mortality Multiple Cause" files from 2000-2019. Incidence rates of SIDS per 10,000 live births were calculated across sex and racial groups over the 20-year period. Logistic regression models estimated the effects of sex and race on the risk of SIDS and examined the temporal changes in risk across sex and race over the study period.

Results

A total of 39,591 SIDS cases occurred between 2000 and 2019, for an overall incidence of 4.9/10,000 births (95% CI 4.4-5.3). The incidence decreased from 6.3 to 3.4/10,000 births over the study period. Male infants were at greater risk of SIDS (OR 1.36,95% CI 1.33-1.39) as were Black (2.25, 2.20-2.30) and American Indian infants (2.21, 2.06-2.37), compared with White infants. Although SIDS incidence decreased by sex and race during the 20-year period, the decline was smaller among Hispanic and American Indian infants.

Conclusions

Between 2000-2019, the incidence of SIDS in the US declined, overall and by sex and race, but male, Black, and American Indian infants remain at a higher risk. Novel campaigns to reduce SIDS risk should especially target Black and American Indian mothers.

Keywords: Sudden Infant Death Syndrome, SIDS, Infant, Mortality, Sex, Race, Trends,

Introduction

Sudden infant death syndrome (SIDS) is the sudden and unexpected death of an infant who is less than 1 year of age, with the onset of the lethal episode occurring during sleep, while remaining unexplained after a thorough investigation, including autopsy, examination of death scene, and review of clinical history[1]. In 1994, the introduction of the Back to Sleep campaign with recommendations to put babies to sleep on their back led to a steep decline in SIDS mortality[2]. However, SIDS remains a pressing medical concern as it is still the most common cause of death for infants between 1 week and 1 year of age in the United States (US)[3]. Furthermore, there have been reports that the risk of SIDS is higher in male and Black infants[4, 5], but few studies have been sufficiently powered to provide accurate estimates of SIDS incidence across the nation by sex and race. The present large population-based study utilizes birth certificate information for all 80 million live births and medically certified death certificate information for all SIDS deaths to 1) describe the incidence of SIDS in the US and measure the trends over the last 20 years, 2) examine the associations between sex and race with the risk of SIDS, and 3) to examine the temporal changes in risk of SIDS across sex and race over the study period.

Methods

Study Design

We conducted a retrospective population-based cross-sectional study based on 20 years of infant birth and mortality records compiled by the National Center for Health Statistics (NCHS) at the Center for Disease Control and Prevention (CDC). In the US, state laws require

birth certificates to be completed for all births. The NCHS collects data from birth certificates of all births to residents and non-residents occurring in the US. The data are then merged to create the "Birth Data" files. For mortality data, the CDC's National Vital Statistics System (NVSS) captures all deaths from all causes across every state in the nation and then amalgamates the data to form the "Mortality Multiple Cause Data" files. These files contain extensive death certificate details including the cause of death.

Data Extraction

The study cohort was created by first extracting from the "Birth Data" files all live births that occurred in the US between 2000-2019. Then, the International Classification of Diseases (ICD)-10 code "R95" was used to identify SIDS deaths within the "Mortality Multiple Cause Data" files. All records for which the code R95 was included as one of the medically certified contributing causes of death as recorded in the "Record-Axis" conditions were included in the study. For the final data set, we combined the SIDS mortality data with the live births data. The data was further stratified by sex and race. For race, the "Race Recode" variable in the "Birth Data" files and "Mortality Multiple Cause" files did not contain a Hispanic category. In order the identify Hispanic infants, the "Hispanic Origin" variable was combined with the "Race Recode" variable. Infants were classified as White, Black, Hispanic, American Indian, Asian/Pacific Islander or other in this study. American Indian was defined as a person having origins in any of the original peoples of North, Central and South America, who maintain tribal affiliation or community attachment.

Statistical Analyses

Three sets of analyses were performed: First, the overall and annual SIDS rates per 10,000 live births were calculated for 2000-2019. The strata-specific rates were then calculated by sex and by race. Second, logistic regression models were used to describe associations between sex and risk of SIDS through the estimation of odd ratios (OR) and 95% confidence intervals (CI). This analysis was also repeated to determine the risk of SIDS by race. The subsequent analyses focused on the temporal trends of SIDS during the study period. The annual change in SIDS rates was estimated by calculating the slope and then logistic regression models, with year of SIDS death entered as a continuous independent variable, were used to examine the temporal trends in SIDS incidence across each sex and race stratum over the study period.

Analyses were conducted using SAS 9.4 statistical software and graphs were created with Excel 2019. P values < 0.05 were considered statistically significant.

Ethics Approval

According to the Tri-Council Policy of 2018, institutional ethics approval was not required for this study as it was solely based on data from a database freely available to the public [6].

Results

A total of 80,710,348 live births were extracted between 2000 and 2019, with the number of records ranging from 3.7-4.3 million annually. We identified 39,591 SIDS cases with either SIDS as the primary cause of death or 1 of 20 contributing causes as indicated on the death certificate. Overall, there was a downward trend in annual SIDS rates over the study period

(Figure 1). The SIDS rates for male infants remained higher than the females' rates throughout the study period but declined at a faster rate (Figure 2).

Table 1 summarizes the top 10 primary causes of death in all death certificates with a SIDS diagnosis over the study period. Of the 39,591 SIDS cases, 38,836(98.09%) had SIDS recorded as the primary cause of death using ICD-10 code "R95". Another 68(0.17%) SIDS cases were attributed to accidental suffocation and strangulation in bed, "W75", while 58(0.15%) SIDS cases were recorded as hanging, strangulation, and suffocation using "Y20".

Table 2 shows the distribution of SIDS cases, total number of live births, and SIDS rates by sex and race, as well as the association between sex and race with SIDS. Of the 39,591 SIDS cases, a greater proportion of them were male (58.7%), while 41.3% were female. Male infants averaged more SIDS cases per 10,000 births and were found to be at a significantly greater risk of SIDS compared to females. In addition, the SIDS rate was significantly higher for Black and American Indian infants relative to White infants. Black infants made up 31.1% of the SIDS cases, but only 14.8% of total births. Compared to White infants, both Black and American Indian infants were found to be more than twice as likely to die from SIDS. On the other hand, Hispanic and Asian or Pacific Islander infants were less likely to die from SIDS.

The temporal trend in the rate of SIDS stratified by sex and race is shown in Table 3. Over the 20-year period, males averaged a greater annual decline in SIDS cases compared to females. With regards to race, Black infants averaged a greater decline in SIDS, while Hispanic and American Indian infants showed a slower decline in SIDS deaths.

Discussion

SIDS remains a pressing medical problem in the US as the leading cause of death for infants between 1 week and 1 year of age[3]. Although interventions have led to an overall reduction in SIDS incidence, it remains high. The present population-based study found that SIDS risks have not been uniform among sex and racial groups, and emphasized the increased risk of SIDS among Black, American Indian, and male infants.

Our results highlighted a temporal decline in SIDS incidence between 2000 and 2019. However, recent studies have proposed the decline in SIDS in the US to be a result of changes in reporting practices and diagnoses[7, 8]. These studies suggest a "diagnostic shift", whereby the incidence of SIDS was observed to be decreasing in conjunction with the rise of other sleep related deaths, such as suffocations and strangulations in bed[8]. Since SIDS is diagnosed by excluding other identifiable causes of death using autopsy reports and death scene investigation, it is possible that there has been an increase in the ability to diagnose deaths from suffocation and strangulation. However, we found suffocation "W75" and strangulation "Y20" to only make up 0.17% and 0.15% of all SIDS cases, respectively, and therefore the diagnostic shift is not likely to be the only explanation for the decline in SIDS incidence over the study period.

Since the launch of the Back to Sleep campaign in 1994, which recommended that infants be placed in a supine sleeping position, SIDS rates have declined in Canada and the US by over 50%[9, 10]. In 2000, new recommendations that included additional risk factors, such as soft sleep surfaces, loose bedding, overheating, and maternal smoking, were introduced to further address SIDS[11, 12]. Our study observed that from 2000 to 2001, SIDS incidence rates in the US dropped from 6.3 to 5.6 cases per 10,000 births following the introduction of these recommendations. Since safe sleeping recommendations have been continuously addressed, it is reasonable to

hypothesize that this decrease in SIDS rates may in part be attributed to recommendations against maternal smoking. In a study by Hakeem et al, they found that maternal tobacco use increased the risk of SIDS by more than two-fold[13], which is similar to a meta-analysis by Zhang et al, reporting a significantly increased risk of SIDS associated with maternal smoking (OR 2.25; 95% CI 2.03-2.50)[14]. Following the 2000-2001 decrease in SIDS, our study showed that SIDS incidence rates remained relatively stagnant over the subsequent years until 2010, when incidence rates dropped from 5.3 to 4.3 cases per 10,000 births in 2012. This drop in SIDS incidence occurred during the same time the Back to Sleep campaign was replaced by the new Safe to Sleep campaign in 2011, which emphasized a safe sleep environment and advocated against bed-sharing[15]. This new initiative helped to dispel myths and misconceptions about SIDS, such as the idea that parents could hear problems occurring with their babies by sleeping in the same bed. However, since 2012, the study showed that SIDS rates have only slightly decreased and still remains as the leading cause of post-neonatal mortality in the US, pointing to the need for additional interventions[16].

In our study, a greater proportion of SIDS cases were male. In fact, male infants had a 1.36-fold greater risk of SIDS relative to females, which confirm previous reports[17]. These results are similar to a study by Mitchell and Stewart that found males had a 1.42-fold increased risk of SIDS[18]. Further, they found the distribution of SIDS risk factors, such as maternal smoking, to be similar among male and female infants[18]. Some studies have attributed the increased SIDS risk in males to reports of an immature sleep-wake cycle and increased sleep disruption compared to females[19], while others have disputed the findings showing similar sleep arousal processes in males and females[4]. Additional findings have reported an increased likelihood of male infants being placed in the prone sleeping position due to excessive crying,

which may consequently explain the sex-associated disparity in SIDS[20, 21]. From 2000-2019, the gap in the SIDS rates of male and female infants slowly declined, pointing to the need for the continual implementation of safe-sleeping educational programs.

Our study observed that infant race was also associated with likelihood of SIDS. Consistent with earlier epidemiologic research, we observed a more than two-fold greater risk of SIDS among Black infants than White infants[22]. This increased risk is likely due to the higher incidence of risk factors for SIDS in the Black infant group[23]. Specifically, findings from the 2004 National Vital Statistics Report from the CDC noted that a higher percentage of Black than White live births in the US had the following SIDS risk factors: births less than 2500 g, preterm births, births to mothers under 20 years, fourth and higher order births, and births to unmarried mothers[24]. Social factors have also been shown to play a role. For instance, Black women in the US have been shown to be more likely to have both a lower level of education and less prenatal care compared to White women, which are both associated with SIDS risk[25-27]. In addition, a study by Smith et al. found that 60.2% and 38.8% of White and Black infants, were placed to sleep in a supine position, respectively[28]. Further, Colson et al observed that mothers of Black infants were 3 times more likely to practice infant bed-sharing [29]. Our findings show that SIDS rates in Black infants decreased following the recommendations of the Back to Sleep campaign showing recommendations on safe sleep practices have proven to be effective. However, additional culturally appropriate interventions need to be implemented as SIDS rates, bed-sharing, and prone sleeping remain high among Black infants[22]. In Chicago, a multi-agency intervention to reduce SIDS was implemented among Black families using brochures, posters, videotapes and direct parental education[30]. These efforts resulted in a greater drop in SIDS rates

among Black infants in Chicago than previous years and points toward the need for additional interventions targeting Black mothers[30].

Similar to Black infants, we found American Indian infants were at a 2-fold greater risk of SIDS than White infants, which is consistent with prior studies[31]. For instance, Irwin et al found that Native American infants were three times more likely to develop SIDS in Washington State[32]. The greater risk of SIDS in American Indians in the US is likely due to the high prevalence of SIDS risk factors among Native American mothers[33]. A study by Bulterys et al found that maternal smoking was higher in American Indian populations in the US[34], while Castor et al found American Indians to be approximately twice as likely than the general population to be low-income earners, unemployed, without a college degree, to receive late or no prenatal care, and to bed-share with their infants, which are all factors associated with SIDS[35]. In addition, greater alcohol consumption has been observed in American Indians[36, 37] and a large population-based cohort study found that the use of alcohol during pregnancy increased SIDS risk by 3-fold[37]. Since many of these maternal factors are related to socioeconomic status, it is likely that programs to improve the overall socioeconomic status of the American Indian population might lessen the impact of SIDS, and counselling should be made more accessible for prenatal patients who drink alcohol or smoke. However, efforts to modify alcohol use and smoking during pregnancy, as well as teaching safe-sleep practices, in American Indian parents have largely been unsuccessful[38]. The National Center for the Review and Prevention of Infant Deaths collaborated with the International Association of Indigenous Aging to work with American Indian elders on the premise that they are trusted sources of information[38, 39]. Elders learn safe sleep practices through these interventions and share these strategies with young parents. Although there has been some success, American Indian infants remain at a high risk of

SIDS, which points to the need for additional public health programs that are geared specifically to American Indian mothers.

In contrast to the trends observed for Black and American Indian Infants, Hispanic and Asian/Pacific Islander infants showed lower rates of SIDS compared to White infants. The lower risk of SIDS observed in these populations is likely associated with the lifestyle choices made by parents. A study by Ball et al found Asian infants to be less likely to sleep in a room alone, sleep with a soft toy, use an infant sleeping bag, sofa-share, receive solid foods or be exposed to maternal smoking[40]. Also, it has been shown that Hispanic infants are less likely to share the bed with a parent, be exposed to smoke or placed in a prone sleeping position compared to Black infants[41]. These studies found that Asian/Pacific Islander and Hispanic mothers follow safer sleeping habits for their infants that are consistent with recommendations from the Back to Sleep and Safe to Sleep campaigns.

Finally, between 2000 and 2019, race-specific SIDS rates decreased significantly slower among Hispanic and American Indian infants compared to White infants. Although overall SIDS rates are still very high among Black infants, there was a high annual decline in SIDS rates among this group, which indicates that some progress has been made in conveying the importance of infant sleeping position and arrangement. Since practices such as prone sleeping and bed-sharing are still more prevalent among American Indian infants[42, 43], educational programs need to be better targeted to these groups. Studies have shown Hispanic and American Indian mothers to be associated with lower socioeconomic status and access to healthcare[27], and therefore programs to reduce disparities in income, education and healthcare access across Hispanic, and American Indian mothers should further lessen the impact of SIDS. Since SIDS rates in American Indian infants, who already have a two-fold greater risk of SIDS, were shown

to have the slowest decline, this research highlights the need for novel campaigns to reduce the risk of SIDS that especially target American Indian mothers.

We acknowledge some limitations in our study. Previous studies analyzing deaths assigned to the ICD-10 code "R95" denoting SIDS have shown a range of terminology being used by certifiers to code SIDS deaths[44]. Variations in reporting practices of SIDS coding could have introduced bias, but we found no significant increase in the reporting of other related causes of death and these deaths remain low each year. We used the same SIDS code throughout the study period of 2000-2019 to decrease the likelihood of misclassification and specifically chose this period to provide the longest contiguous period for which the same ICD-10 codes were utilized, as the CDC migrated from ICD-9 to ICD-10 in 1999[45]. Another limitation involved the limited list of demographic variables available in the "Mortality Multiple Case" data.

In spite of the limitations, our study has several strengths. To our knowledge, this is the first and largest population-based study that used the CDC's "Mortality Multiple Cause" data files to enumerate the annual rate and risk of SIDS, overall and stratified by sex and race. The population-based study allows for generalization of the study findings to the greater American population and the large sample size of the study provided sufficient power to examine the associations of sex and race with SIDS.

Conclusions

Although the incidence of SIDS in the US declined between 2000 and 2019, overall and by sex and race, it is still significantly higher among male, Black and American Indian infants. Novel educational and public health campaigns especially targeting mothers of Black and American Indian infants should be implemented to further reduce SIDS rates. Reducing maternal

smoking, discouraging infant bed-sharing, and encouraging supine sleep positioning, while also ensuring access to and use of adequate prenatal care services could help further lower SIDS incidence in the US.

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Figure Legends

Figure 1. Annual Incidence of SIDS per 10,000 Births from 2000-2019 in the US

Figure 2. Annual Incidence of SIDS per 10,000 Births from 2000-2019 in the US by Sex

Table 1. Top 10 Primary Causes of Death in all Death Certificates with a SIDS Diagnosis from 2000-2019

Record Axis Code	Condition	Frequency (%)
R95	Sudden Infant Death Syndrome	38,836 (98.09)
W75	Accidental Suffocation and Strangulation in Bed (ASSB)	68 (0.17)
Y20	Hanging, Strangulation and Suffocation, Undetermined Intent	58 (0.15)
I678	Other Specified Cerebrovascular Diseases	33 (0.08)
J81	Pulmonary Oedema	28 (0.07)
B348	Other Viral Infections of Unspecified Site	17 (0.04)
Q249	Congenital Malformation of Heart	17 (0.04)
G931	Anoxic Brain Damage	15 (0.04)
J849	Interstitial Pulmonary Disease	14 (0.04)
W84	Unspecified Threat to Breathing	14 (0.04)

Table 2. SIDS rates and risk of SIDS in the US population from 2000-2019, stratified by sex and race

Cohort	Died of SIDS N (%)	Livebirths from the General US Population N (%)	SIDS Rate per 10,000 Births (95% CI)	Odds Ratio (95% CI)	P-value
All	39,591 (100.0)	80,710,348 (100.0)	4.9 (4.4-5.3)		
Sex					
Female	16,334 (41.3)	39,410,111 (48.8)	4.1 (3.8-4.5)	Reference	
Male	23,257 (58.7)	41,300,237 (51.2)	5.6 (5.1-6.1)	1.36 (1.33-1.39)	<0.0001
Race					
White	20,392 (51.5)	44,384,643 (55.0)	4.6 (4.1-5.0)	Reference	
Black	12,320 (31.1)	11,930,146 (14.8)	10.3 (9.4-11.2)	2.25 (2.20-2.30)	<0.0001
Hispanic	5381 (13.6)	18,748,899 (23.2)	2.9 (2.6-3.1)	0.63 (0.61-0.64)	<0.0001
American Indian	795 (2.0)	782,950 (1.0)	10.2 (9.2-11.0)	2.21 (2.06-2.37)	<0.0001
Asian/Pacific Islander	606 (1.5)	4,362,792 (5.4)	1.4 (1.2-1.5)	0.30 (0.28-0.33)	<0.0001
Other	97 (0.3)	500,918 (0.6)	1.9 (1.4-2.5)	0.42 (0.35-0.52)	<0.0001

Table 3. Annual change in the SIDS rate from 2000-2019 in the US population, stratified by sex and race

Cohort	Annual Decline in SIDS/10,000 Births	Odds Ratio (95% CI)	P-Value
All	-0.15	0.97 (0.97-0.97)	<0.0001
Sex			
Female	-0.11	0.97 (0.97-0.98)	<0.0001
Male	-0.18	0.97(0.97-0.97)	<0.0001
Race			
White	-0.15	0.97 (0.97-0.97)	<0.0001
Black	-0.30	0.97 (0.97-0.97)	<0.0001
Hispanic	-0.07	0.98 (0.97-0.98)	<0.0001
American Indian	-0.14	0.99 (0.97-1.00)	<0.0001
Asian/Pacific Islander	-0.02	0.97 (0.96-0.99)	<0.0001
Other	-0.04	1.0 (0.98-1.3)	<0.0001

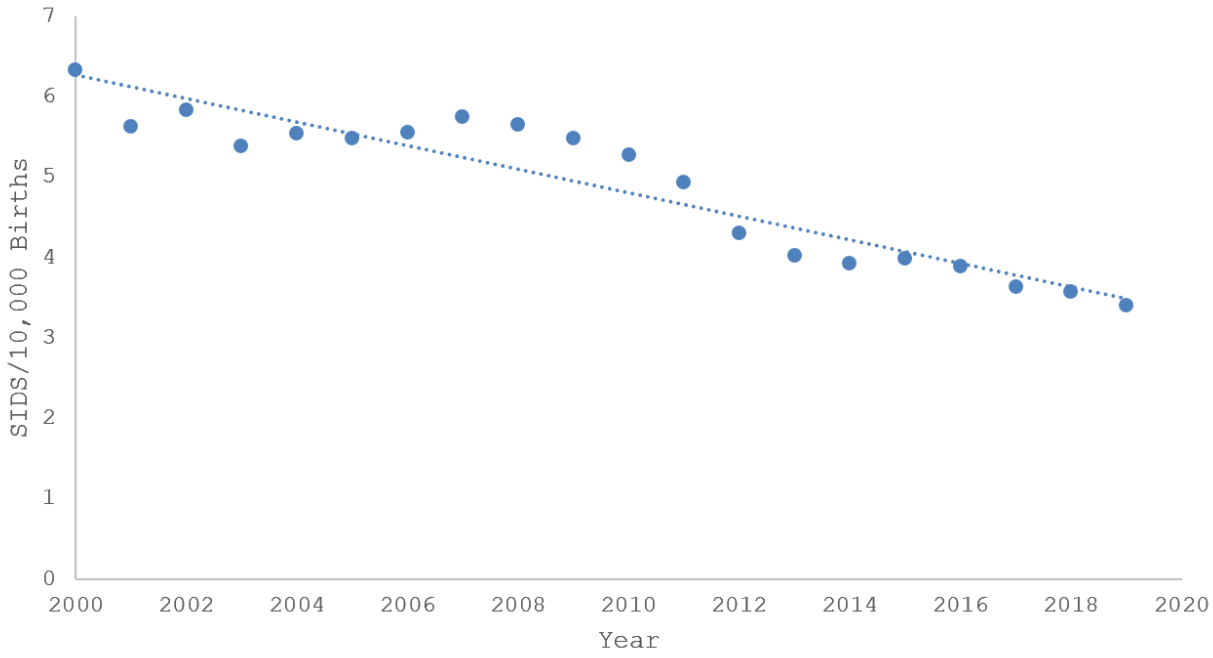

Figure 1. Annual Incidence of SIDS per 10,000 Births from 2000-2019 in the US

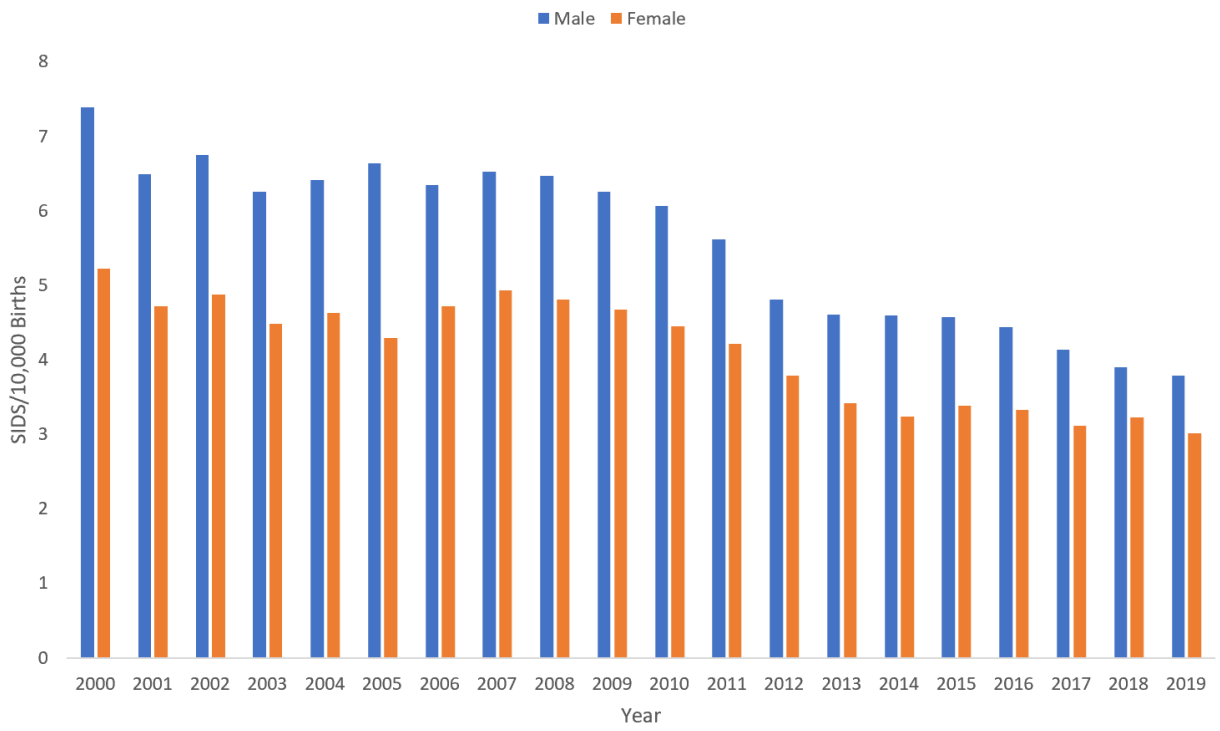

Figure 2. Annual Incidence of SIDS per 10,000 Births from 2000-2019 in the US by Sex

CHAPTER 5: PREFACE TO MANUSCRIPT II

Both infant and maternal mortality serve as important indicators for the overall health of a country. The previous chapter aimed to investigate the leading cause of infant mortality in the United States: SIDS, where public health interventions have made positive advances in reducing infant mortality. The overall findings showed that SIDS incidence has decreased in the US over the past two decades, but the risk of SIDS remains higher in male, Black and American Indian infants. To further address SIDS, novel educational campaigns to reduce SIDS risk should especially target Black and American Indian mothers to reduce risky behaviours including maternal cigarette smoking and prone sleeping.

The next chapter investigates the second key indicator of the health of a nation: maternal mortality. Specifically, the study builds on previous studies by expanding beyond the WHO's definition of maternal death that is exclusive to obstetric causes of death to include all pregnant women that have died within 42 days of the termination of pregnancy, regardless of whether the cause of death is obstetrical or non-obstetrical in nature. The study will examine maternal mortality trends over the past two decades and investigate racial disparities in the US.

CHAPTER 6: RACIAL DISPARITIES IN NATIONAL MATERNAL MORTALITY TRENDS IN THE UNITED STATES FROM 2000-2019

The following chapter presents the methods and results of the second thesis objective, which is to provide population-based estimates of maternal mortality rates from all causes of death in the US by race between 2000 and 2019 and examine racial disparities in maternal mortality.

The topic presented in this manuscript will be introduced through some background information, followed by a comprehensive description of the methods including details of the study population and statistical methods used. The results are described in detail and the discussion provides insightful information as well as study limitations.

Racial Disparities in National Maternal Mortality Trends in the United States from 2000-2019:
A Population-Based Study on 80 million Live Births

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Abstract

Objective

In the United States (US), deaths during pregnancy and childbirth have increased over the past 2 decades compared to other high-income countries, and there have been reports that racial disparities in maternal mortality have widened. The study objective was to examine recent trends in maternal mortality in the US by race.

Methods

A population-based cross-sectional study was conducted using data from the Centers for Disease Control and Prevention's "Birth Data" and "Mortality Multiple Cause" data files from 2000-2019. Maternal mortality rates due to obstetrical and non-obstetrical causes during pregnancy, childbirth, and puerperium per 100,000 live births were calculated across racial groups. Logistic regression models estimated the effects of race on the risk of maternal mortality and examined the temporal changes in risk across race over the study period.

Results

A total of 21,241 deaths occurred in women during pregnancy and childbirth during the study period, with 65.5% being caused by direct/indirect obstetrical complications and 34.5% by other non-obstetrical causes. Black women, compared to White women, were at a greater risk of maternal mortality (OR 2.13,95% CI 2.06-2.20), as were American Indian women (2.02, 1.83-2.24). The risk of maternal mortality increased overall during the 20-year study period, with an annual increase of 2.4 and 4.7 per 100,000 among Black and American Indian women, respectively.

Conclusions

Between 2000-2019, maternal mortality in the US increased, overall and especially in American Indian and Black women. Targeted public health interventions to improve maternal health outcomes should become a priority.

Keywords: Maternal Mortality, Pregnancy, Race, Trends,

Introduction

In the United States (US), annually more than 700 women die from pregnancy and childbirth-related complications and more than 50,000 women experience life-threatening complications each year[1]. Throughout the past two decades, maternal mortality has declined around the world, but in the US, rates have been reported to have increased by 26.6% between 2000 and 2014[2], marking the only developed country to show these trends[3]. Furthermore, it has been reported that maternal mortality rates vary significantly by race, with a greater number of maternal deaths observed in Black women[4, 5].

Most studies on maternal mortality have only examined deaths from direct and indirect obstetrical causes, and have ignored accidental and incidental causes of death[6], since the World Health Organization's (WHO) definition of maternal mortality excludes those deaths[7]. However, homicides, transport accidents and other non-obstetrical causes of death represent a large portion of deaths in pregnant women each year[8, 9]. Hence, there is a need to examine racial disparities pertaining to all causes of death contributing to maternal mortality, including non-obstetrical causes, in order to better focus the scope of public health prevention programs[10] and protect the 4 million US women giving birth each year.

The present large population-based study aims to report on population-based estimates of maternal mortality in the US from all causes of death, including accidental and incidental causes, and examine temporal changes in risk of maternal morality across race over the last 20 years.

Methods

Study Design and Data Sources

We conducted a retrospective population-based cross-sectional study based on 20 years of birth and mortality records compiled by the National Center for Health Statistics (NCHS) for the Center for Disease Control and Prevention (CDC). State laws in the US require birth certificates to be completed for all births. The data from birth certificates of all births to residents and non-residents occurring in the US are collected by the NCHS and merged to create the "Birth Data" files.

The CDC's NCHS is also the source of official US maternal mortality statistics used for both sub-national and international comparisons, based on information reported on death certificates[11]. This information is filed in vital statistics offices in each state and is subsequently compiled into national data through the National Vital Statistics System (NVSS). The NVSS captures all deaths from all causes across every state in the nation from death certificate information and then merges the data to form the "Mortality Multiple Cause Data" files. The medical portion of the death certificates are completed by physicians or medical examiners and indicate the primary cause of death as well as additional contributing causes of death, therefore providing extensive information on causes of death in the mortality data files.

The WHO defines a maternal death as "the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes"[7]. This definition does not provide a comprehensive picture of all deaths occurring in women during pregnancy or childbirth. In our study, maternal death refers to the death of a woman during pregnancy, childbirth, or the puerperium within 42 days of pregnancy

termination from all causes of death including those aggravated by pregnancy, as well as accidental and incidental causes.

Data Extraction

The study cohort was created by first extracting from the "Birth Data" files all live births that occurred in the US between 2000-2019. Next, we identified all deaths occurring in women while pregnant or within 42 days of termination of pregnancy from all causes including both causes aggravated by pregnancy, as well as accidental and incidental causes, from the "Mortality Multiple Cause Data" files. Since 1999, cause-of-death data in the US have been coded according to the International Classification of Diseases (ICD)-10 codes[12]. In order to identify deaths during pregnancy, childbirth, or the puerperium within 42 days of termination of pregnancy, we used the ICD-10 codes A34, O00-O95, and O98-O99, which is consistent with the WHO's classification of ICD-10 codes[12]. The "Record-Axis" conditions in the "Mortality Multiple Cause Data" files outline all contributing causes of death, with the first cause as the primary cause of death and additional codes providing information on contributing causes. All records where these codes were identified as one of twenty medically certified contributing causes of death as recorded in the "Record-Axis" conditions were included in the study. Using this method, we were able to also capture accidental and incidental causes of death, where the codes A34, O00-O95, and O98-O99 appeared as a contributing cause of death, but not the final primary cause of death. For the final data set, we combined the maternal mortality data with the live births data.

Statistical Analyses

Statistical analyses took place as follows: First, the overall and annual maternal mortality rates per 100,000 live births were calculated for 2000-2019. The strata-specific rates were then calculated by race. In the "Birth Data" files and "Mortality Multiple Cause" files, the "Race Recode" variable categorized race as White, Black, American Indian, Asian/Pacific Islander, or other. Since there was no Hispanic Category, the "Race Recode" variable was combined with the "Hispanic Origin" variable to identify Hispanic women. In our study, women were classified as White, Black, Hispanic, American Indian, Asian/Pacific Islander, or other. Second, logistic regression models were used to estimate associations between race and risk of maternal mortality through the estimation of odd ratios (OR) and 95% confidence intervals (CI). The last set of analyses focused on examining the temporal trends of maternal mortality over the study period. The annual change in maternal mortality rates was estimated by calculating the slope of the maternal mortality rate and year graph and then logistic regression models, with year of maternal death entered as a continuous independent variable, were used to examine the temporal trends in maternal mortality incidence across each race stratum over the study period.

Analyses were conducted using SAS 9.4 statistical software and graphs were created with Excel 2019. P values < 0.05 were considered statistically significant. The data used in this study was solely from obtained from a publicly available database and therefore institutional ethics approval was not required according to the Tri-Council Policy of 2018[13].

Results

In total, 80,710,348 live births were included in the study, with records ranging from 3.7-4.3 million annually. A total of 21,241 maternal deaths were identified with a pregnancy

outcome as either the primary underlying cause of death or 1 of 20 contributing causes as indicated on the death certificate. This translates into an overall period maternal mortality rate of 26.3 per 100,000 live births (95% CI 21.8-31.2). Obstetrical causes of death made up 65.5% of all deaths, while non-obstetrical causes represented 34.5%, with transport accidents, accidental poisoning, and assault as the most frequent causes of death (Table 1).

Figure 1 shows the annual incidence of maternal deaths per 100,000 deliveries from 2000-2019. Overall, there was an upward trend in annual maternal mortality rates over the study period, while the distribution of births by racial groups remained fairly constant, with the exception of an increase in Asian or Pacific Islander birth rates in 2003 (Figure 1).

Table 2 shows the distribution of maternal deaths, total number of live births and maternal mortality rate by race, as well as the association between race and maternal mortality. Of the 21,241 total cases of maternal deaths, 50.4% were recorded in White women, while 28.9% were in Black women. However, more than half of all live births (55.0%) were to White women, while only 14.8% were to Black women. Black women averaged the highest maternal death rate (51.4 deaths per 100,000 births) and were more than twice as likely to die during pregnancy, childbirth, or 42 days postpartum from obstetrical and non-obstetrical causes compared to White women. Similarly, American Indian women were also found to have a higher maternal mortality rate (48.8 deaths per 100,000 births) and a 2-fold greater risk of maternal mortality compared to White women. On the other hand, Hispanic and Asian or Pacific Islander women were at a lower risk death during pregnancy and childbirth and were found to have lower maternal mortality rates than White women.

Table 3 shows the temporal trend in maternal mortality rate overall and by race. During the 20-year study period, the greatest annual increase in maternal mortality rate was observed in

American Indian women, with the increase in maternal death rate being almost twice the magnitude of the annual rise in maternal death rate among Black women. Both American Indian women and Black women showed a greater increase in maternal death rate than White women, while Hispanic and Asian/Pacific Islander women showed a smaller increase in maternal mortality.

Discussion

Recent Trends

The present large population-based study examined all causes of death among women during pregnancy, childbirth and the puerperium and found that 34.5% of all deaths were attributed to non-obstetrical causes, highlighting the importance of considering these deaths in overall maternal mortality. An increase in maternal mortality was observed from 2000-2019, with the risk of death being greatest among Black and American Indian women.

In 2003, revisions to the US standard death certificate introduced a pregnancy question with several checkboxes to ascertain whether female decedents were pregnant at the time of death. However, the use of these checkboxes was adopted by each state at varying times, which is believed to have resulted in a steady increase in detected maternal mortality[14-16]. Our study showed a rise in maternal mortality attributed to all causes of death after 2003, but also observed differential temporal increase in race-specific mortality rates. Specifically, our study found a significantly greater increase in maternal mortality among Black and American Indian women compared to White women and exceedingly low increases in rates among Hispanic and Asian or Pacific islander women. Further, the increasing maternal mortality rates are likely to have also been the result of increases in drug use during pregnancy[17], increased homicides/violence[18] and

contributions from rising caesarean delivery rates[19], reduced and inequal access to abortion services[20], lack of funding for planned parenthood[21], and the effects of social determinants of health arising from racism[22].

Racial Disparities

Our study observed that race was significantly associated with maternal mortality. Consistent with earlier epidemiologic research[23], the greatest risk was observed in Black women, with a more than two-fold greater risk of maternal mortality and greater annual increase in mortality rates compared to White women throughout the study period. Both societal and health system factors are likely to have contributed to the high and increasing rates of maternal mortality in Black women, who often face racial discrimination and are more likely to experience barriers in obtaining quality care[24]. Compared to White women, Black women are more likely to face greater financial barriers to care, be uninsured, and are less likely to have access to prenatal care[25]. Furthermore, they also lack quality access to contraceptive care and counseling, and as a result experience higher rates of unintended pregnancies than other racial groups, which consequently leads to greater maternal mortality when combined with poor access to quality abortion services[26]. Recent studies have also highlighted an increasing disparity in the quality of maternal care in hospitals predominately serving black patietns[27, 28], finding the maternal in-hospital mortality to be double among Black patients during delivery hospitalization[29]. Additionally, Black women also experience higher rates of preventable diseases and chronic health conditions including diabetes, hypertension, and cardiovascular disease, which negatively influence maternal outcomes and appear to be growing in frequency[30,

[31]. Reports of an increased risk of homicide and inter-personal violence in pregnant Black women are also likely to have contributed to elevated risk of maternal mortality[32].

Similar to Black women, American Indian women were twice as likely to die while pregnant, during childbirth or within 42 days postpartum relative to White women, and the rate of maternal mortality increased more rapidly than any other racial group at a rate of 4.7 deaths per 100,000 births annually over the study period. Literature on American Indian maternal health is notably limited, although the high incidence of maternal mortality was also noted in a review by Heck et al[33]. Little is known about the root causes of increased maternal mortality in American Indian women. However, historical trauma produced by colonization is likely to have played a role in increased maternal mortality, manifesting in subsequent generations as substance abuse, discrimination, suicide[34], poor living conditions and chronic health issues[35]. Specifically, a study by Campbell et al highlighted a higher rate of homicide, suicide, and drug overdose among pregnant American Indian women[36]. Another contributing factor is living in rural communities, where often access to prenatal care is severely limited and often pregnant women have to leave their communities in order to give birth[37]. Findings show 40% of all American Indian people live in rural areas, and rural residents have been shown to face an elevated risk of maternal death[38]. Inequities in healthcare availability, access, and utilization have also been shown to contribute to unequal rates of chronic diseases and subsequently the increasing trend in maternal mortality in American Indian women[39].

On the other hand, although a previous study showed a higher pregnancy-related mortality ratio in Hispanic women compared to White women[40], our study found that Hispanic and Asian/Pacific Islander women had lower maternal mortality rates and little change in mortality over the study period. Lower rates of maternal mortality in these populations are likely

a result of a socio-cultural orientation that places a high value on family and children. Studies have concluded that the culturally based appreciation for children has led to increased efforts to reduce maternal mortality in these cultures including avoiding risky behaviours such as smoking and alcohol use during pregnancy[41, 42].

Moving Forward and Taking Action

The alarming incidence and increase in maternal mortality rates for American Indian and Black women point to the need for a multi-faceted approach to reducing maternal mortality. For instance, Black and American Indian women need to be supported through comprehensive and sustained public health programs that expand health coverage, address chronic health conditions, and improve the quality of care in hospitals that pre-dominantly serve these populations. Further educational campaigns directed at clinicians regarding racial disparities and historical outcomes may help mitigate systemic racism and implicit racial bias among healthcare professionals[43]. For American Indian maternal health outcomes, ensuring decision-making includes American Indian representation, expanding rural care, and addressing social determinants of health through addressing financial barriers and creating culturally safe communities will help decrease the increasing maternal mortality rates in the US.

Recently, The Council on Patient Safety in Women's Health Care and the Alliance for Innovation in Maternal Health (AIM) Program published the "Reduction of Peripartum Racial/Ethnic Disparities Patient Safety Bundle" that provides steps institutions and clinicians can take to reduce disparities in maternal mortality[44]. A study by Arrington et al examined the implementation of these steps in community hospitals and found an increasing number of staff who reported engaging in activities to address the healthcare needs of racial minority patients,

showing that interventions at the healthcare organization level can be effective in influencing health providers to address racial disparities[45]. A more widespread implementation of these recommendations that specifically target Black and American Indian health providers should further improve maternal health outcomes in the US.

Strengths and Limitations

One limitation of the study pertains to surveillance concerns in the misclassifications of pregnancy-related deaths. The high rates of maternal deaths attributed to less informative causes of death such as "Other specified pregnancy-related conditions" raise concerns of misclassification. This can be addressed in the future by requiring less informative ICD-10 codes to be accompanied by more informative codes with specific conditions. Nevertheless, we used the same ICD-10 codes throughout the study period of 2000-2019 to decrease the likelihood of misclassification and specifically chose this period to provide the longest contiguous period for which the same ICD-10 codes were utilized, as the CDC migrated from the ICD-9 to the ICD-10 classification in 1999[46]. Another study limitation involved the limited list of demographic variables available in the "Mortality Multiple Case" data. Variables including socioeconomic status, education, and access to prenatal care were not included in the dataset therefore could not be controlled for. Lastly, there is a possibility that the maternal mortality rate was over-estimated. Since the denominator used in the study was all live births, if a woman passed during pregnancy or after an abortion, with the baby also dying, then that was counted as a maternal death in the study, but without an accompanying record of a live birth, since the baby also passed.

The study also has several strengths. The use of vital statistics data in the population-based study provided information on all 80 million live births and medically certified death certificate details for all deaths in the US over the study period. To our knowledge, this is the largest population-based study that used the CDC's "Mortality Multiple Cause" data files to enumerate the annual rate and risk of maternal mortality, overall and stratified by race. The population-based study allows for generalization of the study findings to the greater American population and the large sample size provided sufficient power to examine the associations of race and maternal mortality.

Conclusions

Significant racial disparities in maternal mortality exist in the US and there is an urgent need to address the increasing rate of maternal mortality in Black and American Indian women. The complex nature of racial disparities requires a comprehensive approach to improve health outcomes from preconception to postpartum and to address systemic racism, as well as social determinants of health. In addition, there is a need to address non-obstetrical causes of death, which contribute over one-third of all maternal deaths. Improvements to the quality of care in hospitals serving Black and American Indian women and public health programs that provide greater socioeconomic security could help further reduce the risk of maternal mortality rates in the US.

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Figure Legends

Figure 1: Annual Incidence of Maternal Deaths per 100,000 Deliveries from 2000-2019 in the US

Table 1. Cause of Death Outlined in Death Certificates of all Pregnant Women Dying within 42 Days of Pregnancy Termination from 2000-2019

Death Cause	Condition	Frequency (%)
Direct/Indirect Obstetric		**13,907 (65.5)**
O20-O23, O25-O29	Maternal Disorders Related to Pregnancy	3,321 (15.6)
O85-O92	Puerperium Complications	1,957 (9.2)
	Other Specified Diseases Complicating Pregnancy, Childbirth, Puerperium	8,629 (40.7)
Non-Obstetric		**7,334 (34.5)**
V09-V99	Transport Accidents	2,295 (10.8)
X40-X49	Accidental Poisoning	2,002 (9.4)
X85-Y09, Y87	Assault	1,380 (6.5)
	Other	1,657 (7.8)
Total		**21,241 (100)**

Table 2. Race of Maternal Death Cases and Live Births in the US from 2000-2019

Cohort	Maternal Deaths N (%)	Livebirths from the General US Population N (%)	Maternal Deaths per 100,000 Births (95% CI)	Odds Ratio (95% CI)	P-value
All	21,241	80,710,348	26.3 (21.8-31.2)		
Race					
White	10,710 (50.4)	44,384,643 (55.0)	24.1 (19.3-30.0)	1.0 (Reference)	
Black	6130 (28.9)	11,930,146 (14.8)	51.4 (44.4-58.5)	2.13 (2.06-2.20)	<0.0001
Hispanic	3272 (15.4)	18,748,899 (23.2)	17.5 (15.2-19.6)	0.72 (0.70-0.75)	<0.0001
American Indian	382 (1.8)	782,950 (1.0)	48.8 (36.6-63.6)	2.02 (1.83-2.24)	<0.0001
Asian/Pacific Islander	708 (3.3)	4,362,792 (5.4)	16.2 (14.1-17.0)	0.67 (0.62-0.73)	<0.0001
Other	39 (0.2)	500,918 (0.6)	7.8 (3.1-12.4)	0.32 (0.24-0.44)	<0.0001

Table 3. Annual change in the Maternal Death rate from 2000-2019 in the US population, stratified by race

Cohort	Annual Increase per 100,000 Births	Odds Ratio (95% CI)	P-Value
All	1.6	1.07 (1.06-1.07)	<0.0001
Race			
White	1.9	1.08 (1.07-1.08)	<0.0001
Black	2.4	1.09 (1.09-1.10)	<0.0001
Hispanic	0.7	1.05 (1.05-1.06)	<0.0001
American Indian	4.7	1.11 (1.08-1.12)	<0.0001
Asian/Pacific Islander	0.3	1.02 (1.00-1.03)	<0.0001

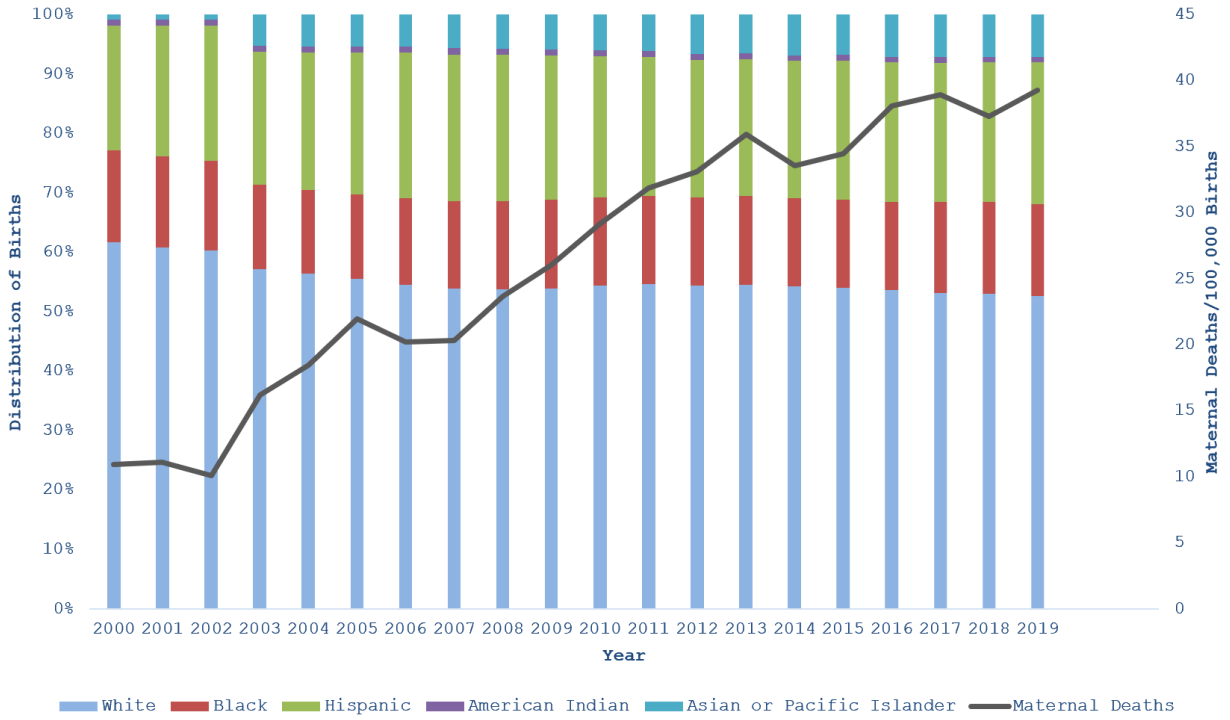

Figure 1: Annual Incidence of Maternal Deaths per 100,000 Deliveries from 2000-2019 in the US

CHAPTER 7: PREFACE TO MANUSCRIPT III

The previous chapter investigated maternal mortality from both obstetrical and non-obstetrical causes of death and provided population-based estimates of the maternal mortality rate over the past two decades in the US. The chapter focused on racial disparities and provided estimates of maternal mortality rate by race. The findings highlighted the importance of also examining non-obstetrical causes of death, which made up over one third of all deaths during pregnancy and childbirth within 42 days of delivery. The study also showed a greater risk of maternal mortality in American Indian and Black women, as well as a greater increase in risk among these groups over the past two decades, pointing to the need to prioritize especially targeted public health interventions to improve maternal health outcomes.

The next chapter expands on the findings of the previous chapter by examining another key risk factor of maternal mortality: maternal age. The study examines maternal mortality trends by age groups over the past two decades and examines the associated risk of maternal mortality across five-year maternal age bins. When combined with findings from the last chapter, these results identify populations that have the greatest risk of maternal mortality. Hence, public health interventions geared towards these women would potentially have the most significant impact on maternal mortality rates in the US.

CHAPTER 8: AGE-RELATED DISPARITIES IN NATIONAL MATERNAL MORTALITY TRENDS IN THE UNITED STATES FROM 2000-2019

The following chapter presents the methods and results of the third thesis objective: To provide population-based estimates of maternal mortality rates from all causes of death in the US by age groups between 2000 and 2019 and examine age-related disparities in maternal mortality.

The topic presented in this manuscript will be introduced with some background information, followed by a comprehensive methods section that will cover the details of the study population and statistical methods used. The results are described in detail and the discussion provides insightful information as well as study limitations.

Age-Related Disparities in National Maternal Mortality Trends in the United States from 2000-2019

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Abstract

Objective

Over the past 2 decades, there has been a trend toward increasing maternal age in the United States (US). The study objective was to examine the association of maternal age with maternal mortality in the US and examine temporal trends in mortality by maternal age.

Methods

A nationwide population-based cross-sectional study in the US between 2000-2019 was conducted using data from the Centers for Disease Control and Prevention's "Birth Data" and "Mortality Multiple Cause" data files. Annual incidence and period trends in maternal deaths were calculated using the annual maternal deaths over annual livebirths across age groups. Multivariate logistic regression models were used to estimate the association between maternal age and risk of maternal mortality and calculate temporal changes in risk of mortality over the study period.

Results

Between 2000-2019, 21,241 deaths were observed in women during pregnancy and childbirth for an average incidence of 26.3 maternal deaths/100,000 births (95% CI 21.8-31.2). Of all deaths, 6,870 (32.3%) were in women ≥35 years, while only 15.1% of livebirths were attributed to women ≥35 years. Compared with women 25-29 years of age, there was a significantly greater risk of maternal mortality among women 35-39 (OR 1.60, 1.53-1.67), 40-44 (3.78, 3.60-3.99), 45-49 (28.49, 26.49-30.65) and 50-54 (343.50, 319.44-369.37). Risk of mortality increased over time, with the greatest rise in women ≥35 years.

Conclusions

In the US, maternal mortality increased during the past two decades, especially in women ≥35 years. Given these findings, targeted strategies to reduce the increasing maternal mortality should become a priority.

Keywords: Maternal Mortality, Maternal Age, Pregnancy, Trends

Introduction

Maternal mortality remains high, with estimates by the World Health Organization (WHO) that over 300,000 women die each year from pregnancy or childbirth-related complications[1]. While maternal mortality has decreased in most developed countries over the past two decades, recent reports show maternal mortality has increased in the United States (US)[2, 3]. Maternal mortality is an important indicator of national healthcare quality and has devastating effects for both the family members involved, as well as the rest of society[4].

In several high-income countries, adolescent (10-19 years) birth rates are declining, while an upward trend toward increasing maternal age has been observed[5]. As a result, this has led to growing concerns regarding adverse outcomes in older mothers (≥35 years). Older maternal age has been associated with increased childbirth-related complications including stillbirth and preterm birth[6, 7], but little population-based information is available on associations of increasing maternal age and mortality[8].

Additionally, the few studies that have examined maternal mortality rates have only focused on deaths from obstetrical complications, while ignoring accidental and incidental causes of death[9]. This omission of non-obstetrical causes of death may be due to the WHO's definition of maternal death, which is limited to obstetrical causes[10]. However, drug-use and homicides as well as other non-obstetric causes represent a great portion of deaths in women during pregnancy and childbirth[11, 12] and therefore, there is a need to examine all causes of death in order to obtain a comprehensive summary of maternal deaths across age groups and more effectively direct public health interventions.

The purpose of our study was to carry out a nationwide population-based study to report on population-based estimates of maternal mortality and trends over the past two decades.

Methods

Study Design and Data

We conducted a 20-year retrospective population-based cross-sectional study using birth and mortality records compiled by the National Center for Health Statistics (NCHS) at the Center for Disease Control and Prevention (CDC). In the US, birth certificates are required to be completed for all births to residents and non-residents occurring in the US. This data is collected by the NCHS and merged to create the "Birth Data" files. The CDC's NCHS is also the source of all official US maternal mortality statistics[13]. Mortality data is based on information reported on official death certificates, where the medical portion is completed by physicians and medical examiners indicating the primary cause of death and additional contributing causes. This information is filed in vital statistics offices in each state and is subsequently compiled into national data through the National Vital Statistics System (NVSS) to create the "Mortality Multiple Cause" data files. In this way, the NVSS captures all deaths across every state in the US from medically certified death certificate information.

In this study, maternal death was defined as the death of a woman during pregnancy, childbirth, or the puerperium within 42 days of pregnancy termination from all causes of death including obstetric complications aggravated by pregnancy and accidental or incidental causes. This expands on the WHO definition that excludes accidental and incidental deaths, and therefore captures all deaths in women during pregnancy or childbirth[10].

Data Extraction

To create the study cohort, all live births that occurred in the US between 2000-2019 were extracted from the "Birth Data" files. Then, using the "Mortality Multiple Cause Data" files

which contains all death certificates, we applied the International Classification of Diseases (ICD)-10 codes A34, O00-O95, and O98-O99, according to the WHO classification of ICD-10 codes[14], to identify deaths during pregnancy, childbirth, or the puerperium within 42 days of the termination of pregnancy. Within these files, the "Record-Axis' column contains ICD-10 codes on both the primary and contributing causes of death. All records where the specified ICD-10 codes were identified as either the primary or one of the contributing causes of death in the "Record-Axis" column were included in the study. The final data set was created by combining the extracted maternal mortality data with the live births data. The data was furthered categorized by age into distinct 5-year age-bins: under 15, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, and 50-54. Age was used as a categorical variable in the analyses.

Statistical Analyses

Analysis was performed in three steps: First, we calculated the overall and annual maternal mortality per 100,000 live births from 2000-2019. The strata-specific mortality rates were then calculated for each age group and compared to the distribution of live births over the study period. Maternal mortality rates/100,000 births were plotted on a log scale with a base of 10 in response to the skewedness of large values[15] arising from the heightened risk of mortality among older age groups. Second, logistic regression models were used to estimate associations between maternal age and risk of maternal mortality through the estimation of odd ratios (OR) and 95% confidence intervals (CI). The models were adjusted for the potential confounding effects of calendar year and maternal race. The last set of analyses focused on examining the temporal trends of age-associated maternal mortality over the study period. We estimated the annual change in maternal mortality rates by calculating the slope of maternal mortality per

100,000 live births over year and then used race-adjusted logistic regression models that used year of maternal death as a continuous independent variable, to examine the temporal trends in maternal mortality incidence across age groups over the study period.

All analyses were conducted using SAS 9.4 statistical software and figures were developed using Excel 2019. P values < 0.05 were considered statistically significant.

Ethics Approval

Based on the Tri-Council Policy of 2018, institutional ethics approval was not required for this study as it was only based on data from a publicly available database[16].

Results

Between 2000 and 2019, 80,710,348 live births occurred in the US with a range of 3.7-4.3 million births each year. In total, 21,241 maternal deaths were identified with 34.5% of deaths occurring from non-obstetrical causes and 65.6% from obstetrical complications. As shown in Figure 1, an upward trend in maternal deaths per 100,000 deliveries was observed over the study period.

Figure 2 displays the distribution of maternal age and the maternal deaths per 100,000 births across age groups. The greatest proportion of births occurred in mothers aged 25-29 years and the number of births decreased with increased age. For maternal ages spanning 15-34, the number of maternal deaths per 100,000 births were fairly constant, however the maternal mortality rate increased exponentially with increased age reaching the highest point in women aged 50-54.

Table 1 shows the distribution of maternal deaths, total number of live births and maternal mortality rate by age group, as well as the association between age and maternal mortality. Although only 15.1% of all live births were attributed to a maternal age of 35 years or older, 32.3% of all maternal deaths occurred in women ≥35 years. Compared to women aged 25-29, women aged 35 years or older were found to be at a significantly greater risk of maternal mortality with the risk increasing in each older age group and reaching the highest risk in women aged 50-54. Similarly, the risk of maternal mortality was found to be 3-times greater in women under 15 compared to women aged 25-29, but these deaths only made up 0.2% of all maternal deaths.

Table 2 shows the temporal trend in maternal mortality rate by age. Over the 20-year period, a greater annual increase in maternal mortality was observed in women aged 40 years or older, with the greatest increase in women aged 50-54 and 45-49, respectively. An increase in maternal mortality for women under 15 years of age was also observed, while the increase was similar among women aged 20-39.

Discussion

Our study sought to report population-based maternal mortality incidence and trends in the United States. From 2000-2019, the incidence of maternal mortality rose, and this trend coincided with increases in the proportion of pregnancies to older mothers. Increasing maternal age was found to be associated with a higher risk of maternal mortality with the greatest risk in the oldest age group of 50-54, while mothers under the age of 15 were also found to be at a greater risk.

Trends in Maternal Mortality in the US

Similar to our study, other recent population-based studies have also demonstrated a rise in maternal mortality in the US[17, 18]. The maternal mortality ratio was reported to have increased from 7.2 deaths per 100,000 births in 1987 to 17.8 deaths per 100,000 births in 2009[19]. However only deaths from obstetrical complications were considered in these studies leading to a significant underreporting of total deaths in pregnant women. Our study found 26.1 deaths per 100,000 births in 2009, as opposed to 17.8 deaths per 100,000 births, when including non-obstetrical causes of death and draws attention to the importance of considering accidental and incidental causes of death. From 2000-2019, we found the number of deaths during pregnancy from both obstetrical and non-obstetrical causes to have increased from 10.9 to 39.3 deaths/100,000 births, however the reason behind the growth in the maternal mortality rate in the US remains unclear[20]. Some studies have pointed to the combination of the wide-spread use of computerized data by states[21], changes in the coding for causes-of-death data following the implementation of the ICD-10 codes in 1999[22], and the addition of the pregnancy checkbox on the standard US death certificates in 2003[23] to have improved identification of deaths during pregnancy over time leading to an increase in reported maternal mortality, while others have shown an increasing number of pregnant women in the US to have chronic health conditions that have led to greater mortality rates[24, 25]. Nonetheless, there is a need to shift attention from only considering obstetrical causes to including non-obstetrical causes of death, which have consistently made up a significant portion of all deaths during pregnancy.

Age Disparities in Maternal Mortality

Our study observed a greater risk of maternal mortality in women younger than 15, and in women 35 years or older, as well as an increase in maternal deaths in these groups over the last 2 decades. These results are similar to a study by Callaghan and Berg, who found a higher pregnancy-related mortality ratio for older women aged 40 years or older regardless of parity, the extent of prenatal care, and level of education[26]. The trend of older maternal age in pregnancy observed in the US is likely to have direct effects on the increase in maternal mortality[27]. Older women are becoming increasingly represented in the pregnant population with a 74% increase in pregnancy rates in women aged 35-39 years and a 38% increase in women aged 40 years and older from 1976-1997 in the US[28]. Studies have shown older women are more likely to have chronic morbidities prior to conception, such as hypertension, diabetes, and various autoimmune diseases. These pre-existing conditions also render them at greater likelihood of developing peripartum adverse conditions[29, 30]. For instance, cardiomyopathy, thromboembolic disease, and postpartum hemorrhage are especially prevalent in older women[31, 32]. Moreover, pregnant women in their mid-30s and older have a higher risk of experiencing obstetric acute renal failure[33], providing evidence that baseline variables associated with aging such as lower cardiac output and hypertension, could make older mothers less able to adapt to the normal physiological changes occurring during pregnancy and therefore, increasing their risk of death. Increasing oxidative stress with aging has also been shown to be a key factor of placental insufficiency and maternal mortality[34].

Over the past 2 decades, the growth in availability of assisted reproductive technology (ART) has allowed more women 35 years or older, when fertility is on the decline, to become pregnant[35]. In the US, ART has been associated with an elevated risk of maternal mortality[36, 37],

and hence, its use may have contributed to the elevated maternal mortality observed in our study among older women. However, the database used for this study did not include data regarding mode of conception. Recognition of the heightened risk of death among older pregnant women is needed to properly counsel women planning to become pregnant after their mid 30's and to better inform their care before, during and after pregnancy.

Previous studies have also shown adolescent pregnancy to increase the risk of perinatal outcomes such as preterm delivery, stillbirth, and neonatal death[38-40], which are consistent with the increased risk of maternal mortality in adolescents shown in our study. This problem is exacerbated in the US, which show increasing and higher adolescent birth rates compared to other developed countries[41]. Current evidence highlights a large role of social determinants of health such as socioeconomic status on the high rate of adolescent births in the US[42]. These findings should divert focus to efforts that address underlying socioeconomic factors to reduce adolescent pregnancy, which not only increases the risk of maternal mortality, but is central to the promotion of women's educational, social, and economic development. Increasing the availability of contraceptives and increasing accessibility to therapeutic abortions should also further decrease the number of adolescent pregnancies[43].

Strengths and Limitations

This study has some limitations. First, the "Mortality Multiple Cause" data files included a limited list of demographic variables and did not include some variables that could influence maternal mortality such as, body mass index, access to prenatal care, socioeconomic status, education level, and validated measures of ART among others. However, race was included in the dataset and controlled for in our regression models. Second, the use of vital statistics data and

changes to data collection processes throughout the study period, such as the introduction of the pregnancy check box to death certificates in 2003, could have caused some misclassifications of pregnancy-related deaths, especially where deaths were coded to less informative causes such as "Other specified pregnancy-related conditions". This can be addressed in the future by requiring less informative ICD-10 codes to be accompanied by more informative codes with specific conditions. However, to minimize misclassifications, we used the same ICD-10 codes throughout the study period of 2000-2019 and specifically chose this period to provide the longest contiguous period for which the same ICD-10 codes were utilized, as the CDC migrated from the ICD-9 to the ICD-10 classification in 1999.

Our study also has several strengths. First, to our knowledge, this is the most contemporary and largest nationwide population-based study examining maternal outcomes in the context of increasing maternal age in the US. Second, our study captures birth data on all 80 million live births in the US over the past two decades, and all maternal deaths verified by medical practitioners through official death certificates. The large sample size allowed for the interpretation of significant associations between maternal age and mortality and the population-based design allowed for the generalization of study findings to the American population.

Conclusions

Maternal mortality rose in the US over the past two decades, with the highest rates and most significant increases in mortality observed in adolescents younger than 15 years and women 35 years or older. These results highlight the need for medical providers to recognize the risk of death borne by women who become pregnant at either extreme of the reproductive age span in order to provide appropriate care. Further, the increased use of ART in older women, as

well as underlying socioeconomic factors to reduce adolescent pregnancy need to be addressed. Our results highlight rising maternal mortality in the United States as becoming an increasingly important concern that should be addressed as a public health priority.

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Figure Legends

Figure 1: Annual Incidence of Maternal Deaths per 100,000 Deliveries from 2000-2019 in the US

Figure 2: Distribution of Maternal Age and Mortality in the US from 2000-2019

Table 1. Maternal Deaths and Live Births in the US from 2000-2019

Cohort	Maternal Deaths N (%)	Live Births from the General US Population N (%)	Maternal Deaths per 100,000 Births (95% CI)	Adjusted Odds Ratio* (95% CI)	P-value
All	21,241	80,710,348	26.3 (21.8-31.2)		
Age					
< 15	52 (0.2)	95,470 (0.1)	54.5 (44.9-97.9)	3.12 (2.38-4.10)	<0.0001
15-19	1,409 (6.6)	6,830,109 (8.5)	20.6 (18.5-28.7)	1.10 (1.04-1.17)	<0.0001
20-24	3,908 (18.4)	18,840,439 (23.3)	20.7 (17.5-25.9)	1.04 (1.01-1.09)	<0.0001
25-29	4,673 (22.0)	22,582,967 (28.0)	20.7 (17.0-24.3)	Reference	
30-34	4,215 (19.8)	20,143,045 (25.0)	20.9 (17.6-23.6)	1.05 (1.03-1.10)	<0.0001
35-39	3,361 (15.8)	9,930,420 (12.3)	33.8 (28.8-37.8)	1.60 (1.53-1.67)	<0.0001
40-44	1,705 (8.0)	2,137,394 (2.6)	79.8 (65.1-91.3)	3.78 (3.60-3.99)	<0.0001
45-49	863 (4.1)	138,733 (0.2)	622.1 (413.8-755.6)	28.49 (26.49-30.65)	<0.0001
50-54	941 (4.4)	11,771 (0.0)	7,994.2 (4,410.4-10,036.5)	343.50 (319.44-369.37)	<0.0001

*Regression model adjusted for year and race

Table 2. Annual change in the Maternal Death rate from 2000-2019 in the US population, stratified by age

Cohort	Annual Increase per 100,000 Births	Adjusted Odds Ratio* (95% CI)	P-Value
All	1.6	1.07 (1.06-1.07)	<0.0001
Age			
Under 15	6.3	1.11 (1.06-1.17)	<0.0001
15-19	1.8	1.07 (1.07-1.08)	<0.0001
20-24	1.5	1.05 (1.05-1.06)	<0.0001
25-29	1.3	1.05 (1.05-1.06)	<0.0001
30-34	1.1	1.05 (1.04-1.06)	<0.0001
35-39	1.5	1.05 (1.04-1.05)	<0.0001
40-44	4.1	1.09 (1.08-1.10)	<0.0001
45-49	34.9	1.33 (1.31-1.36)	<0.0001
50-54	486.0	1.56 (1.32-1.80)	<0.0001

*Regression model adjusted for race

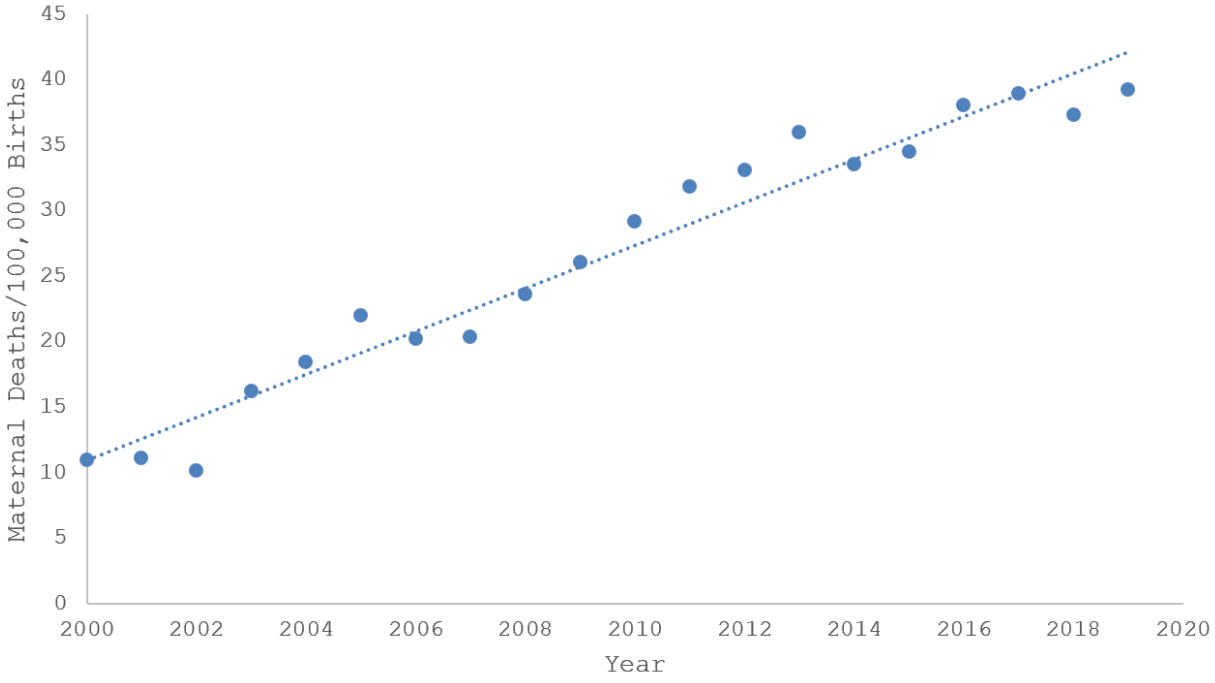

Figure 1: Annual Incidence of Maternal Deaths per 100,000 Deliveries from 2000-2019 in the US

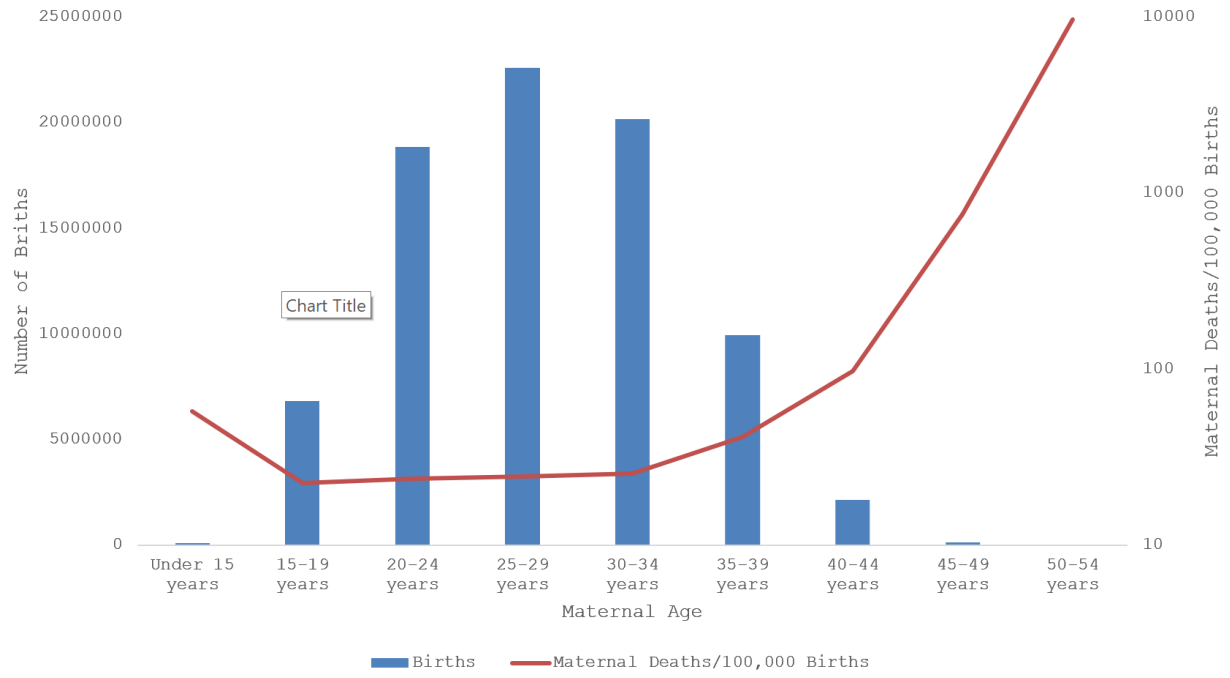

Figure 2: Distribution of Maternal Age and Mortality in the US from 2000-2019*

*Maternal Deaths/100,000 Births were plotted on a log scale with a base of 10.

CHAPTER 9: PREFACE TO MANUSCRIPT IV

The previous chapter aimed to provide population-based estimates of the maternal mortality rate over the past two decades in the US by maternal age groups and examine the risk of maternal mortality in each age group. The findings showed that women under 15 years and those greater than 35 years of age were at greater risks of maternal mortality and a greater increase in risk over the past two decades was observed in women greater than 35 years. Given these findings, providing a greater access to contraception and safe abortion services combined with a wider access to prenatal care and counselling to older women regarding the increased risk of maternal morbidity should become a priority.

The next chapter expands on the findings from the previous two chapters by focusing specifically on non-obstetric causes of death in maternal mortality. The past chapters highlighted the importance of including non-obstetric causes of death when examining maternal mortality as more than one-third of deaths during pregnancy can be attributed to theses causes. This study focuses on maternal deaths caused by non-obstetrical causes. Specifically, the particular causes of death, incidence, risk across race, and trends over the past two decades will be examined in this study.

CHAPTER 10: NON-OBSTETRIC MATERNAL MORTALITY TRENDS BY RACE IN THE UNITED STATES FROM 2000-2019

This chapter presents the methods and results of the fourth thesis objective, which is to provide population-based estimates of non-obstetric maternal mortality rates between 2000 and 2019 in the US and examine racial disparities in non-obstetric causes of maternal mortality.

The topic presented in this manuscript will be introduced with some background information and will have a comprehensive methods section that outlines the study population and statistical methods used in the analysis. The results are described in detail and a thorough discussion provides critical information as well as study limitations and future implications.

Non-Obstetric Maternal Mortality Trends by Race in the United States from 2000-2019: A Population-Based Study on 80 million Live Births

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Abstract

Objective

Public health interventions to reduce maternal mortality have largely focused on direct and indirect obstetric causes, while neglecting non-obstetric causes of death. The study objective was to examine recent trends in maternal deaths from non-obstetric complications by race in the United States (US).

Methods

A population-based cross-sectional study was conducted in the US using data from the "Birth Data" and "Mortality Multiple Cause" files compiled by the Centers for Disease Control and Prevention from 2000-2019. The annual incidence of maternal deaths attributed to non-obstetric causes per 100,00 live births were calculated across racial groups, while the effects of race on the risk of non-obstetric maternal mortality and temporal changes in risk across race over the study period were examined using logistic regression models.

Results

From 2000-2019, a total of 7,334 women died during pregnancy and childbirth from non-obstetric causes, where 31.3% of these deaths were caused by transport accidents and 27.3% by accidental poisoning. American Indian women were found to be at the highest risk of non-obstetric maternal mortality (OR 2.20,95% CI 1.90-2.56), and 46.1% of all deaths among pregnant American Indian women were caused by non-obstetric complications. The risk of non-obstetric maternal mortality increased overall during the 20-year study period, with a greater increase among Black (1.15, 1.13-1.17) and American Indian women (1.17, 1.13-1.21).

Conclusions

Non-obstetric causes of death have become increasingly prevalent in the US, overall and especially in American Indian women. Novel interventions to address these non-obstetric factors should especially target American Indian women to improve maternal outcomes.

Keywords: Maternal Mortality, Pregnancy, Obstetric, Non-obstetric, Race, Trends

Introduction

Maternal mortality is an important indicator of nationwide maternal and infant health[1], and remains a serious medical concern with more than an estimated 300,000 women dying from complications during pregnancy or childbirth each year[2]. Over the past two decades, maternal mortality has decreased in most developed countries, but this pattern has not been observed in the United States (US), which has shown an upward trend in maternal mortality[3, 4].

Globally, direct and indirect obstetric causes of maternal mortality have continued to receive attention from healthcare providers and policy makers, whereas non-obstetric causes have not received the same level of attention[5]. Maternal mortality, whether due to homicide, suicide, or obstetrical complications are equally tragic and deserves national attention[6]. The World Health Organization's (WHO) definition of maternal death, which is the one most commonly referenced in the literature, does not include accidental and incidental causes of death[2]; hence, it is not surprising that studies examining non-obstetric causes of death during pregnancy and childbirth are limited. Therefore, there is a need for a greater understanding of non-obstetric causes of death and racial disparities in maternal mortality in the US over the past two decades to better target public health interventions.

The purpose of our study was to carry out a nationwide population-based study to report on population-based estimates of maternal mortality arising from non-obstetrical causes in the US and examine associations between race and risk of non-obstetric maternal mortality.

Methods

Study Design and Data Sources

We conducted a 20-year retrospective population-based cross-sectional study using birth and mortality records compiled by the National Center for Health Statistics (NCHS) at the Center for Disease Control and Prevention (CDC). The birth data was extracted from the "Birth Data" files, which are developed by the NCHS annually by taking information from all birth certificates for all births to residents and non-residents occurring in the US. Birth certificates are required by state laws and the data is collected and merged by the NCHS to create the "Birth Data" files. The mortality data used in the study is collected from the "Mortality Multiple Cause" files from the CDC. These mortality data files contain information collected directly from official death certificates for every recorded death in the US[7]. The medical portion of each death certificate is completed by physicians and medical examiners indicating the primary cause of death and additional contributing causes. Subsequently, this information is filed in vital statistics offices in each state and compiled into national data through the National Vital Statistics System (NVSS) creating the "Mortality Multiple Cause" data files. In this way, the NVSS captures all deaths across every state in the US with medically certified death certificate information.

Although the WHO definition of maternal mortality does not include accidental and incidental deaths[2], we defined maternal mortality as the death in a woman during pregnancy or childbirth within 42 days of termination of pregnancy, from any cause including direct obstetric, indirect obstetric, and non-obstetric causes. Specifically, the non-obstetric complications that have contributed to these deaths were examined in this study.

Data Extraction

The study cohort was created by extracting all 80 million live births occurring in the US between 2000-2019 from the "Birth Data" files. Then, the International Classification of Diseases (ICD)-10 codes A34, O00-O95, and O98-O99 were used to identify all deaths during pregnancy, childbirth, or the puerperium within 42 days of pregnancy termination from the "Mortality Multiple Cause" data files according to the WHO application of ICD-10 to pregnancy-related deaths[8]. The same ICD-10 codes have been used to code cause-of-death data in the US since 1999[9], and therefore we used the same codes for the entire study period. The "Mortality Multiple Cause" files contain a "Record-Axis" conditions column highlighting the ICD-10 code for the primary cause of death and up to 20 contributing causes. Within the column, all records where the maternal death ICD-10 codes were identified as either the medically certified primary or 1-20 contributing causes of death were extracted from the data files. After extraction, the data was segmented by primary cause-of-death into deaths occurring from direct obstetric causes, indirect obstetric causes, or non-obstetric causes of death using the appropriate ICD-10 codes. All records where A34, O00-O95, and O98-O99 were not the primary cause of death but listed as a contributing condition were sorted into the non-obstetric cohort to identify women dying from non-obstetric conditions such as suicide, accidental poisoning, or assault occurring within 42 days of the termination of pregnancy. The final data set was created by combining the extracted non-obstetric maternal mortality data with the live births data. Further stratification by race was achieved using a combination of the "Race Recode" and "Hispanic Origin "variables to identify women as either White, Black, Hispanic, American Indian, or Asian/Pacific Islander in the study.

Statistical Analyses

First, we calculated the overall and annual maternal mortality rates attributed to non-obstetric causes per 100,000 live births from 2000-2019. Second, we enumerated the individual non-obstetrical cause of death. Third, race-specific mortality rates attributed to non-obstetric causes were calculated and logistic regression models were used to estimate associations between race and risk of maternal mortality from non-obstetric causes through the estimation of odd ratios (OR) and 95% confidence intervals (CI). Lastly, we examined the temporal trends of non-obstetric maternal mortality across each race stratum by calculating the annual change in maternal mortality rates from 2000-2019 using the slope and using logistic regression models, with year of maternal death entered as a continuous independent variable.

The analyses were conducted using SAS 9.4 statistical software and graphs were developed with Excel 2019. P values < 0.05 were considered statistically significant. According to the Tri-Council Policy of 2018, institutional ethics approval was not required for this study as it was only based on data from a publicly available database[10].

Results

Over the study period of 2000-2019, 80,710,348 live births were extracted, with births ranging from 3.7-4.3 million annually. In total, 7,334 maternal deaths had a primary cause of death labeled as a non-obstetric cause, comprising 34.5% of all 21,241 deaths occurring during pregnancy, childbirth, or the puerperium throughout the study period. Table 1 shows the most common causes-of-death for all deaths in pregnant women from non-obstetric causes. Transport accidents were the most common cause of death, making up 31.3% of all non-obstetric deaths, while the second was accidental poisoning (27.3%), and third was assault (18.8%).

Table 2 shows the distribution of non-obstetric maternal deaths, total number of live births, and non-obstetric maternal mortality rate by race, as well as the association between race and non-obstetric maternal mortality. The overall maternal mortality rate from non-obstetric causes over the study period was 17.4 deaths per 100,000 live births. The mortality rate due to non-obstetric causes was highest among American Indian women at a rate of 22.5 maternal deaths per 100,000 live births. Out of all maternal deaths in American Indian women, 46.1% had a primary cause of death labeled as a non-obstetric complication compared to the 34.5% observed for the entire cohort. Compared to White women, American Indian women were found to be at a more than 2-fold greater risk of maternal mortality from non-obstetric causes (2.20, 1.90-2.56), while Black women were also found to be at a greater risk (1.13, 1.07-1.20). On the other hand, Hispanic and Asian/Pacific Islander women showed a lower risk of maternal death from non-obstetric causes compared to White women.

Over the study period, there was an upward trend in annual maternal mortality rates from non-obstetric causes (Figure 1). The annual increase in maternal mortality rate from non-obstetric causes was the greatest in American Indian women, while Hispanic and Asian/Pacific Islander women showed little annual increase (Table 3).

Discussion

Research on accidental and incidental causes of maternal death is notably limited. To our knowledge, this is the first nation-wide study on the trend and characteristics of non-obstetric causes of maternal deaths in the United States. This analysis revealed that non-obstetric complications were the primary cause of death in 34.5% of women passing away within 42 days of pregnancy termination over the past 2 decades in the US, with transport accidents, accidental

poisoning, and assault representing the first, second and third most prevalent causes of death, respectively. An upward trend was observed in non-obstetric maternal mortality from 2000-2019 in the US, with the greatest annual increase and greatest risk observed in American Indian women.

Causes of Maternal Mortality

The study reported that transport accidents were the leading non-obstetric cause of maternal mortality making up 31.3% of all non-obstetric deaths, which is consistent with previous studies indicating motor vehicle accidents to be the leading cause of maternal mortality related to injury[11, 12]. A multi-state study by Sirin et al found that about 92,500 pregnant women were hurt annually by motor vehicle accidents in the United States[13], which emphasizes the importance of acknowledging and addressing the role of transport accidents in maternal mortality. It has been shown that physiologic changes of pregnancy increase fatigue and sleep deprivation in pregnant women[14], and drivers who experience sleep deprivation or fatigue have increased risks of car accidents[15]. Therefore, it is feasible that characteristics of pregnancy such as fatigue and maternal stress facilitate an association between pregnancy and increased risk of motor accidents[16]. Despite the proven efficacy of seatbelt use at reducing injuries and deaths due to motor vehicle accidents, a decreased compliance with seatbelt use during pregnancy has also been observed, placing these women at a greater risk of injury[17]. Additionally, the use of illicit drugs and alcohol have shown to significantly increase the risk of fatal crash involvement[18], making drug and alcohol use during pregnancy an even greater concern. Therefore, additional counseling to pregnant women regarding the effects of alcohol and drug use, as well as the

importance of seatbelts is necessary to address the increasingly large number of maternal deaths caused by transport accidents.

Accidental poisoning through drug overdoses, assault, and self-harm (suicide) are also important contributors to maternal mortality, as the second to fourth most prevalent causes of non-obstetric maternal mortality representing 27.3%, 18.8%, and 12.2% of deaths, respectively. A case series study in Colorado[19], found that 30% of 211 maternal deaths over a 9-year period were related to self-harm through suicide or drug overdose, while another study in Philadelphia found 40% of nonmedical causes of maternal death to be attributed to suicide, overdose and homicide[20]. A recent population-based study based on data from 2018-2019, found that homicide during pregnancy exceeded all obstetrical causes of maternal mortality by more than two-fold[21]. Narrowing the focus of maternal mortality to only obstetric causes would mean not considering these deaths, which evidently are important contributors to overall maternal mortality.

Previous studies have established intimate partner violence (IPV) as a significant risk factor of maternal mortality and severe maternal morbidity, often resulting in physical trauma[22, 23]. Similarly, young age, single relationship status, and poverty have also been linked to physical abuse and subsequently increasing the risk of maternal mortality[24, 25]. In addition to abuse, women with significant psychosocial stressors, such as the experience of IPV, are also more likely to engage in risk behaviours such as smoking, substance use, and alcohol use[26, 27], which are all associated with poor maternal outcomes including preterm births and stillbirths. A commitment to routine screening of IPV in pregnant women presenting for care and the provision of readily accessible prenatal care are essential steps in addressing the high number of maternal deaths attributed to self-harm and assault. Targeted interventions including home visitation programs such as the “nurse-family partnership” have also been proven to help

intervene with women experiencing abuse[28] and should continually be implemented to address risk factors contributing to the high number of non-obstetric maternal deaths in the US.

Racial Disparities

The study found that American Indian women were at a 2-fold greater risk of maternal death from non-obstetric causes compared with White women, with the mortality rates increasing the most over time among the former group. Maternal mortality and severe maternal morbidity have previously been reported to be higher in American Indian women than in White women[29, 30], but there is little literature on the contribution of accidental and incidental causes of mortality. This current study found that 46.1% of all maternal deaths in American Indian women were caused by non-obstetric complications, which is the highest out of all racial groups, pointing to a critical need to address these causes of death in addition to obstetric causes. American Indian women have been found to have a higher lifetime prevalence rate of IPV (47.5%) compared with White women (37.3%) placing them at a higher risk of abuse and poor maternal outcomes[31]. Suicide rates among American Indian women have also been found to be higher than all other racial groups[32]. A previous study found American Indian and Black women to report the highest number of stressful life events in the year preceding childbirth[33], and subsequently reported higher levels of alcohol use and smoking[34]. The use of alcohol becomes an even greater concern when examined in the context of transport accidents. Rates of driver alcohol impairment assessed by the police are much higher among American Indian drivers and highest among rural American Indian drivers, placing them at a greater risk of motor vehicle accidents[35, 36]. Additionally, this racial group has lower reported rates of seatbelt usage[37]. To address the disparity in transport accidents leading to deaths among American Indian women,

motor vehicle injury prevention programs should continue to be implemented targeting American Indian communities[38]. In particular, the CDC funded road safety interventions among four American Indian tribes from 2004-2009 that led to an increase in seat belt usage, as well as a decrease in alcohol-impaired driving[39], providing support for the continued implementation of these programs in the future. Additionally, unequal access to prenatal care, socioeconomic status and structural racism are complex factors that need to be addressed at a public health, economic, educational, and societal level in order to improve the health of childbearing American Indian women. Further investments into participatory research approaches and community-driven programs to improve access to health care in both rural and urban American Indian communities should also continue to decrease the maternal mortality rate[40].

The study also found that Hispanic and Asian/Pacific Islander women were at a lower risk of non-obstetric causes of maternal death. There is no literature examining accidental and incidental causes of death among Hispanic and Asian/Pacific Islander communities; however, the lower rates of maternal mortality due to non-obstetric causes are likely be a result of a socio-cultural orientation placing high values on children and families. Studies have shown the cultural appreciation for children have led to women exercising more caution when pregnant, and better efforts in avoiding risky behaviours such as alcohol use and smoking, which has resulted in lower maternal mortality rates[41, 42].

Strengths and Limitations

Death records are an important source of pregnancy mortality data as they are routinely collected by each state and comparable across the nation. However, limitations arise with this data as the cause of death information has been reported to be inaccurate through failing to report

women as pregnant in some cases, resulting in the misclassification of the underlying cause of death[43]. In our study, we addressed this possibility by examining all ICD-10 codes listed under the contributing causes of death in addition to the primary cause. Therefore, even if the primary cause of death failed to report the woman was pregnant, this information was retrieved from contributing causes of death. Another limitation in the data was the lack of additional demographic variables in the "Mortality Multiple Cause" files such as gestational age that could have allowed for additional analysis.

Our study has several strengths. This study represents the largest population-based evaluation of the contribution of non-obstetric causes of death to maternal mortality in the United States. Non-obstetric causes of death have received much less attention compared to obstetric complications, and the findings from this study provide strong evidence supporting the need to address these causes of death. All 80 million births in the US over the past two decades were captured in the study and all maternal deaths were verified by medical practitioners through official death certificates, allowing the study findings to be generalized to the American population and attesting to the validity of the data.

Conclusions

Most studies have focused their attention on obstetric causes of maternal mortality, while ignoring accidental and incidental causes. Non-obstetric causes of maternal mortality including transport accidents and assault have become more prevalent in the US, representing more than one-third of all maternal mortality. Risk is particularly high in American Indian women and therefore, public health interventions should especially target American Indian women to improve maternal outcomes.

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Figure Legends

Figure 1: Annual Incidence of Non-Obstetric Maternal Mortality per 100,000 Deliveries from 2000-2019 in the US

Table 1. Primary Causes of Death in all Death Certificates with a Non-Obstetric Maternal Death Diagnosis from 2000-2019 in the US

Record Axis Code	Condition	Frequency (% subset)	% of Total
All Maternal Deaths		21,241	100
Obstetric Deaths		13,907	65.5
Non-Obstetric Deaths		7,334 (100)	34.5
V01-V99	Transport Accidents	2,295 (31.3)	10.8
X40-X49	Accidental Poisoning	2,002 (27.3)	9.4
X85-Y09	Assault	1,380 (18.8)	6.5
X60-X84	Intentional Self-Harm	897 (12.2)	5.1
Y10-Y34	Events of Undetermined Intent	203 (2.8)	1.0
W00-X59	Accidental Exposure to Physical Forces	201 (2.7)	0.9
Y40-Y84	Complications of Medical Care	56 (0.8)	0.3
Y35-Y36	Legal Intervention	8 (0.1)	0.0
Y84-Y98	Other Non-Obstetric Unspecified Cause	292 (4.0)	1.4

Table 2. Non-Obstetric Maternal Death Incidence in the US Stratified by Race

Cohort	Non-Obstetric Deaths N (%)	Livebirths from the General US Population N (%)	Non-Obstetric Maternal Deaths per 100,000 Births (95% CI)	% of Maternal Deaths Non-Obstetric	Odds Ratio (95% CI)	P-value
All	7,334	80,710,348	17.4 (15.4-19.6)	34.5		
Race						
White	4,528 (61.7)	44,384,643 (55.0)	10.2 (7.3-13.8)	42.3	Reference	
Black	1,377 (18.8)	11,930,146 (14.8)	11.5 (7.7-15.5)	22.5	1.13 (1.07-1.20)	<0.0001
Hispanic	1,079 (14.7)	18,748,899 (23.2)	5.6 (4.3-7.2)	33.0	0.56 (0.53-0.60)	<0.0001
American Indian	176 (2.4)	782,950 (1.0)	22.5 (14.5-32.3)	46.1	2.20 (1.90-2.56)	<0.0001
Asian/Pacific Islander	172 (2.3)	4,362,792 (5.4)	3.9 (2.5-4.3)	24.3	0.39 (0.33-0.45)	<0.0001
Other	2 (0.0)	500,918 (0.6)	0.4 (-0.5-1.3)	5.2	0.04 (0.01-0.16)	<0.0001

Table 3. Annual change in the Non-Obstetric Maternal Mortality Rate from 2000-2019 in the US Population Stratified by Race

Cohort	Annual Increase per 100,000 Births	Odds Ratio (95% CI)	P-Value
All	1.0	1.12 (1.12-1.13)	<0.0001
Race			
White	1.2	1.13 (1.12-1.14)	<0.0001
Black	1.3	1.15 (1.13-1.17)	<0.0001
Hispanic	0.5	1.09 (1.08-1.10)	<0.0001
American Indian	2.7	1.17 (1.13-1.21)	<0.0001
Asian/Pacific Islander	0.2	1.03 (1.01-1.07)	<0.0001

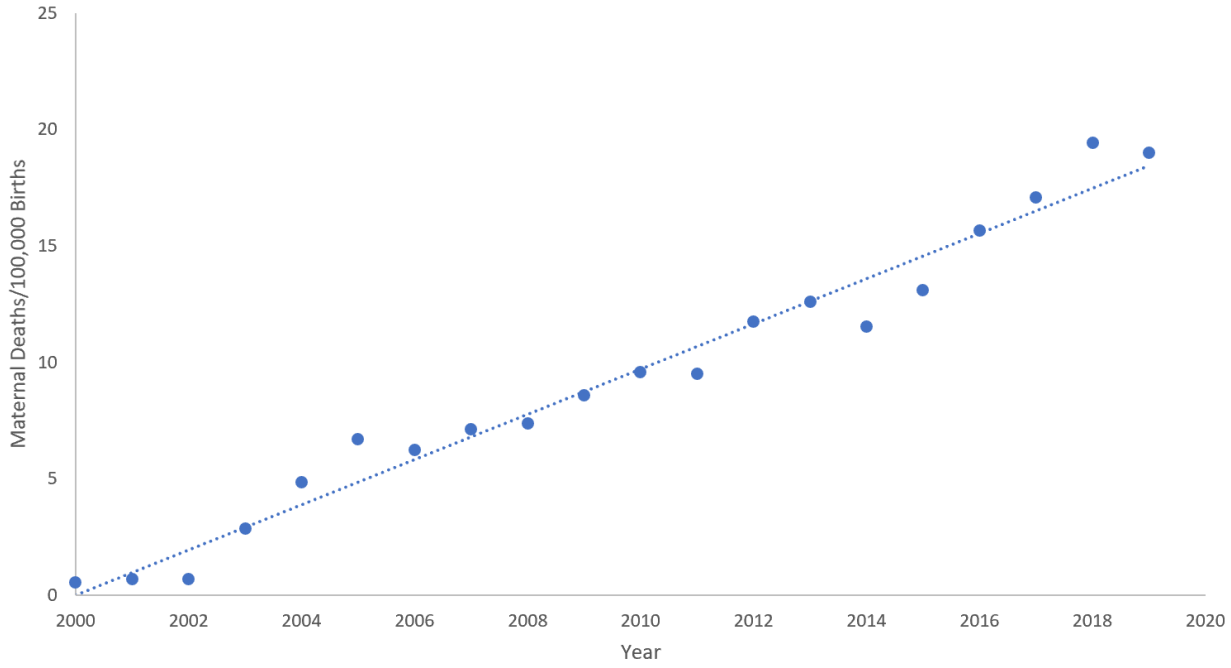

Figure 1: Annual Incidence of Non-Obstetric Maternal Mortality per 100,000 Deliveries from 2000-2019 in the US

CHAPTER 11: GENERAL DISCUSSION

The results provided in the manuscripts included in the thesis revealed population-based findings for infant and maternal mortality in the US. Over the past two decades, SIDS incidence has decreased, but male, American Indian and Black infants remain at a greater risk than females and other racial groups, respectively. On the other hand, maternal mortality has increased in the US over the past two decades, with the greatest increases observed in Black and American Indian women, and in women greater than 35 years of age. Black, American Indian, and women ≥35 years were found to be at the greatest risk of maternal mortality. Further, these manuscripts highlighted the importance of addressing non-obstetrical causes of maternal death, which made up more than one-third of all deaths during pregnancy over the past two decades.

11.1 Findings and summary of SIDS trends from 2000-2019

As the leading cause of infant mortality, the first objective of this thesis was to examine SIDS trends in the US from 2000-2019. The objective was addressed by conducting a retrospective population-based cross-sectional study on all SIDS deaths and live births in the US. The objective was accomplished using the CDC's "Birth Data" and "Mortality Multiple Cause" Data files that contain official birth and death certificate information for all live births and deaths in the US. A cohort of 80,710,348 live births and 39,591 SIDS cases were included in the study. Logistic regression models were used to estimate the effects of sex and race on the risk of SIDS and the temporal changes in risk across sex and race over the study period. SIDS rates varied by race, with the highest rates observed among Black and American Indian infants. A difference in SIDS rates was also found in terms of infant sex, with SIDS being more common among male infants. Further, although SIDS incidence rates decreased over the last two decades, this

temporal diminution of SIDS rates was not uniform across racial groups. Instead, Hispanic and American Indian infants had the smallest improvement in SIDS rates, although the SIDS rates are still higher among Black, American Indian and male infants.

Although the study found that SIDS incidence has declined from 2000-2019, it is important to note that the use of the term SIDS has become more controversial with arguments of a diagnostic shift in reporting over recent years[1]. The shift describes a decrease in the application of the term SIDS, with more deaths being attributed to other causes of death such as accidental suffocation and strangulation in bed[2], as well as using terms such as "undetermined" or "unknown" despite fulfilling SIDS criteria[3]. As a result, it is possible the observed reduction in SIDS rate over time was caused to some degree by changes in terminology, as opposed to an actual reduction in the number of deaths. However, our study found strangulation and suffocation to be included as causes of death in < 1% of the death certificates in all SIDS cases, and therefore it is unlikely for the diagnostic shift to be the sole explanation for decreases in SIDS incidence. Rather, our study identified that Black, American Indian and male infants were at a greater risk of SIDS, which is similar to previous studies[4-7]. An increase in public health interventions targeted towards these populations are likely to have contributed to decreases in SIDS incidence. Following the success of the Back to Sleep, Safe to Sleep and newer educational campaigns, the continued implementation of targeted campaigns to reduce SIDS risk in at-risk populations will further improve infant mortality rates in the US.

11.2 Findings and summary of maternal death trends from 2000-2019

The second, third, and fourth objectives of the thesis focused on examining temporal trends in maternal mortality rates and also obstetrical and non-obstetrical causes of maternal

death in the US over the past two decades. In addition, we examined the risk of maternal mortality across racial groups and maternal age. These objectives were addressed through three population-based cross-sectional studies using the CDC's "Birth Data" and "Mortality Multiple Cause" data files that includes information from the official birth certificates of all live births and death certificate information of all deaths in the US. This allowed for the identification of 21,241 maternal deaths from obstetrical and non-obstetrical causes of death and 80,710,348 live births. The timespan of this database allowed for trends in maternal mortality to be examined over a wide time interval. Logistic regression models estimated the effects of race and age on the risk of maternal mortality and examined the temporal changes in risk across race and age over the study period. The observed results of these studies showed the importance of expanding on the WHO definition of maternal deaths that is limited to obstetrical causes of death, to also include non-obstetrical causes of death, which were the leading cause of death in 34.5% of all maternal deaths. In fact, the percentage of maternal deaths attributed to non-obstetrical causes increased over the past two decades. The results also highlighted racial and age-related disparities in maternal mortality pointing towards the need for better targeted public health interventions addressing maternal mortality to become a priority.

Consistent with existing literature, our study showed a higher incidence of maternal mortality and greater increase in maternal mortality rate among Black and American Indian women compared to White women[8-10]. Black and American Indian women are more likely to face greater financial barriers to care, to be uninsured, and are less likely to have access to prenatal care, which are factors that may contribute to this discrepancy in mortality[11]. Furthermore, Black and American Indian women are more likely to lack access to contraceptive

care, and as a result experience higher rates of unintended pregnancies, which consequently leads to greater maternal mortality when combined with poor access to abortion services[12]. Another factor affecting American Indian women include historical trauma from colonization that have manifested as substance abuse, suicide and chronic health issues, in addition to living in rural communities, where care is limited[13]. On the other hand, although a past study showed higher mortality amongst Hispanic women[14], our study found lower maternal mortality rates among Hispanic and Asian women over the study period that is likely attributable to a greater culturally-based appreciation for families and children. This has resulted in mothers refraining from dangerous behaviours such as smoking and alcohol use that could place themselves or their children in danger.

We also found an association between increasing maternal age and higher risk of maternal mortality, with the greatest risk in the oldest age group of 50-54, while mothers under the age of 15 were also found to be at a greater risk. Therefore, the trend of older maternal age in pregnancy, due to the wider availability of ART and women delaying childbirth until later in life, is likely to have direct effects on the increase in maternal mortality[15]. Similarly, studies attribute the elevated risk of death in older women to the greater likelihood of having chronic morbidities prior to conception, such as hypertension, diabetes, and various autoimmune diseases. Further, age-related factors such as lower cardiac output and hypertension, could make older mothers less able to adapt to the normal physiological changes occurring during pregnancy and therefore, increasing their risk of death[16, 17].

It is important to note that research on accidental and incidental causes of maternal death is limited. Our analysis revealed an upward trend in non-obstetric related maternal mortality from 2000-2019, with non-obstetric complications labeled as the primary cause of death in 34.5% of women passing away within 42 days of childbirth in the US. Transport accidents, accidental poisoning, and assault represented the first, second and third most prevalent causes of death, respectively. These results are consistent with previous multi-state studies that found motor vehicle accidents to be the leading cause of maternal mortality related. They postulated that the normal physiologic changes of pregnancy lead to fatigue and sleep deprivation that result in an increased risk of motor accidents[18, 19]. Additional state-level studies have found that homicides during pregnancy have led to more maternal deaths than all obstetrical causes of maternal mortality by more than two-fold[20]. Narrowing the focus of maternal mortality to only obstetric causes would mean excluding these non-obstetric deaths, which evidently are important contributors to overall maternal mortality. The study also found an especially high risk of non-obstetric maternal mortality amongst American Indian women. Although, as far as we know, there is no literature that has examined non-obstetric maternal mortality among American Indian women, addressing the unequal access to prenatal care, socioeconomic status and structural racism should improve the health of childbearing American Indian women.

11.3 Strengths and limitations

There are several strengths and limitation of the studies included in this thesis. These studies were limited by the dataset used, which lacked some variables of interest that could have enhanced the analysis performed including maternal smoking, drug use, infant birth weight, delivery method, and access to prenatal care. Another limitation involves the changes to data

collection processes throughout the study period in obtaining the vital statics data such as the introduction of the pregnancy check box to death certificates in 2003 that could have caused some misclassifications and underestimations in maternal deaths prior to that time period. In spite of these limitations, the studies had several strengths. The first manuscript is the largest population-based study examining SIDS incidence in the US and uses medically certified death certificate information to classify causes of death. The second and third manuscripts are the largest population-based studies examining maternal death, and also expands on previous studies by examining all causes of death, using medically certified death certificate information to classify obstetrical and non-obstetrical causes. The fourth manuscript is the first nation-wide population study to examine non-obstetrical causes of maternal mortality by race. The large sample size provided the studies with the power to detect associations that existed. Further, the population-based nature of the dataset allows for the generalizability of the study findings to the lager American population. Moreover, the large time interval of the data, spanning 20 years, allowed for examination of temporal trends and the largest possible time interval in which the same ICD-10 coding system was used to identify causes of death.

CHAPTER 12: CONCLUSION

Infant and maternal mortality are important indicators for the overall health of a country[21, 22]. SIDS remains a pressing public health concern as the leading cause of infant mortality in the US. Although the incidence of SIDS in the US declined between 2000 and 2019, our findings showed that it is significantly higher among male, Black and American Indian infants. Therefore, there is a need for novel educational and public health campaigns that especially target these groups in order to further reduce infant mortality. Another concern is the rise in maternal mortality rates in the US over the past two decades compared to other developing countries. Our findings highlighted a greater risk and increasing incidence over the past two decades of maternal mortality from obstetrical and non-obstetrical causes among Black and American Indian women along with greater risks in adolescents younger than 15 years and women 35 years or older. These findings emphasize the need for maternal mortality to be addressed as a public health and social priority.

CHAPTER 13: REFERENCES II

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