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Association between maternal origin and severe maternal morbidity : exploring the obesity-mediated pathway

Ayesha Siddiqui

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**Association between maternal origin and severe maternal morbidity:
exploring the obesity-mediated pathway**

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List of abbreviations

ART	Assisted reproductive technologies
BMI	Body mass index
CDC	Centers for Disease Prevention and Controls
DAG	Directed acyclic graph
DOHMH	Department of Health and Mental Health (New York City)
EPIMOMS	Epidémiologie de la morbidité maternelle severe (longitudinal study)
MMR	Maternal mortality ratio
NYC	New York City
PPH	Postpartum hemorrhage
SMM	Severe maternal morbidity
SPARCS	Statewide Planning and Research Cooperative System (New York State)
VS	(Bureau of) Vital statistics (New York City)

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Summary

Severe maternal morbidity (SMM) occurs more frequently than mortality and is a sensitive tool to investigate disease mechanisms, particularly in high-income countries. Maternal origin, race-ethnicity or maternal place of birth (immigrant status), has emerged as an important social factor associated with SMM in high-income countries. The current challenge in maternal health research is to identify causal mechanisms, a first step towards reduction of social disparities. Obesity is a significant health concern among women of reproductive age in most high-income countries and is more prevalent among minority and immigrant women. There is some limited evidence of an association between obesity and SMM. Obesity is therefore a candidate of interest on the causal pathway between maternal origin and SMM.

We hypothesized that prepregnancy maternal obesity is associated with SMM and that it mediates the relationship between maternal origin and SMM in two high-income countries – France and the USA. We also postulated that the strength of the mediation effect does not vary by national context. The project was divided into two specific objectives:

1. To test and quantify the association between prepregnancy BMI and SMM.
2. To test the hypothesis through path analysis methods that maternal obesity is an intermediary in the association between maternal origin and SMM.

Secondary analyses of existing data were conducted using three data sets with complementary strengths, two in France and one in the USA. We reasoned that a cross-national approach would lead to more robust conclusions and provide insights regarding the importance of context.

In both countries we confirmed an association between maternal obesity and SMM. Additionally, in the French data we demonstrated that maternal obesity is specifically associated with SMM that occurs in the antepartum, mostly due to severe hypertensive disorders.

The mediation analysis conducted using French data found an 18% indirect effect of prepregnancy obesity in the association between Sub-Saharan African maternal place of birth and severe preeclampsia. In the American data, Black race was strongly associated with global SMM but the obesity-mediated effect represented only 3.2% of the total association. Latina ethnicity was also associated with severe maternal morbidity and the obesity-mediated effect was similarly small: 3.4% of the total association. In a sensitivity analysis we found a higher mediation effect of obesity in the association with Black race and Latina ethnicity (15.3% and 15.2% of the total association, respectively) and SMM cases excluding blood transfusion, consisting largely of SMM due to severe hypertensive disease.

Our analyses confirm that maternal prepregnancy obesity is associated with global SMM, and suggest that obesity is a relevant although partial mediator specifically of SMM due to severe hypertensive disease. Our congruent findings in both national settings have significant implications for clinical practice, public health policy, and health disparities research. Our results highlight the need to investigate other mediators of health disparities relating to maternal origin, such as social-structural factors and quality of care.

Résumé

La morbidité maternelle sévère (MMS) est plus fréquente que la mortalité et est un évènement plus pertinent pour étudier les mécanismes physiopathologiques, en particulier dans les pays à revenu élevé. L' « origine » maternelle, qu'elle soit caractérisée par la race-ethnicité ou le lieu de naissance de la mère (statut d'immigrant), est apparue comme un facteur de risque social important de MMS dans les pays à revenu élevé. Le défi actuel de la recherche en santé maternelle est d'identifier les mécanismes causaux de cette association, un premier pas vers la réduction de ces disparités sociales. L'obésité devient un problème de santé important chez les femmes en âge de procréer dans la plupart des pays à revenu élevé et est plus fréquente chez les femmes appartenant à des groupes minoritaires, les immigrantes notamment. Il existe quelques données étayant une association entre l'obésité et la MMS. L'obésité est donc un candidat d'intérêt sur la voie causale entre origine maternelle et MMS.

Nous avons émis l'hypothèse que l'obésité maternelle est associée à la MMS et qu'elle est un médiateur dans la relation entre l'origine maternelle et la MMS, dans deux pays à revenu élevé- la France et les États-Unis. Nous avons également postulé que la force de l'effet de médiation ne varie pas selon le contexte national.

Le projet était divisé en deux objectifs spécifiques :

1. Tester et quantifier l'association entre l'obésité maternelle et la morbidité maternelle sévère.
2. Tester par des méthodes d'analyse de cheminement l'hypothèse selon laquelle l'obésité maternelle est un médiateur dans l'association entre l'origine maternelle et la morbidité maternelle sévère.

Des analyses secondaires de données existantes ont été menées à partir de trois bases de données aux atouts complémentaires, deux en France et une aux États-Unis. Nous avons estimé qu'une approche transnationale conduirait à des conclusions plus solides et fournirait des informations sur le rôle du contexte.

Dans les deux pays, nous avons confirmé une association entre l'obésité maternelle et la MMS. De plus, les données françaises, nous ont permis de montrer que l'obésité maternelle est spécifiquement associée à la MMS qui survient dans la période prénatale, principalement en liée aux complications hypertensives sévères.

L'analyse de médiation menée à partir des données françaises a révélé un effet indirect de l'obésité maternelle estimé à 18% de l'association entre le lieu de naissance maternel en Afrique subsaharienne et la prééclampsie sévère. Dans les données américaines, la race Noire était fortement associée au MMS globale, mais l'effet médié par l'obésité ne

représentait que 3,2% de l'association totale. L'origine ethnique d'Amérique latine était également associée à une morbidité maternelle sévère et l'effet médié par l'obésité était tout aussi faible, représentant 3,4% de l'association totale. Dans une analyse de sensibilité excluant la transfusion sanguine de la définition de la MMS, nous avons trouvé un effet de médiation plus élevé de l'obésité dans l'association entre la race Noire d'une part et celle d'Amérique latine d'autre part et la MMS (15,3% et 15,2% de l'association totale, respectivement), dont on peut penser qu'elle est en grande partie constituée des complications hypertensives sévères.

Nos analyses confirment que l'obésité maternelle est associée à la MMS globale, et suggèrent que l'obésité est un médiateur pertinent mais spécifique de la MMS due aux complications hypertensives sévères. Nos résultats concordants dans les deux contextes nationaux ont des implications pour la pratique clinique, les politiques de santé publique et la recherche sur les disparités en santé. Nos résultats soulignent la nécessité d'étudier d'autres médiateurs des disparités de santé liées à l'origine maternelle, tels que les facteurs socio-structurels et la qualité des soins.

Chapter 1: Introduction

Since achieving significant gains in maternal mortality by the middle part of the last century, the emphasis of perinatal care and research in high-income countries has historically centered on improving fetal and neonatal outcomes. There has been a renewed interest in maternal health outcomes more recently however ⁷⁸. Maternal mortality in high income countries is low, with an average maternal mortality ratio (MMR) of 12 deaths per 100,000 live births ², although the incidence and trends vary by country considerably. Due to the rarity of maternal mortality overall in high-income countries the study of severe maternal morbidity (SMM), which occurs more frequently than mortality, has emerged as a more sensitive tool to investigate disease mechanisms ^{105,130}.

Maternal mortality has remained stable in France between 1999 and 2015 at around 10 per 100,000 live births ^{102,103} while it increased drastically from 7.2 to 17.4 per 100,000 live births in the United States between 1987 and 2018 ^{22,52}. Similarly, SMM in the United States has been trending upwards, from 49.5 to 144 per 10,000 birth hospitalizations between 1993 and 2014 ⁹⁴, although this trend may be partly explained by improved surveillance and reporting of these events. SMM trends in France are less certain, due to a dearth of reliable surveillance data at the national level ¹¹. A systematic review of SMM studies found that rates of SMM in Europe overall are declining, however there were significant measurement issues in ascertaining the findings ¹¹⁶.

Various socioeconomic factors are associated with severe maternal outcomes ^{22,37,71,84,118}. Maternal origin has emerged as the most salient factor in high-income

countries. In Europe these disparities have been studied heterogeneously by race, ethnicity, or maternal place of birth – the latter being the primary exposure of interest in France. European data suggest that non-Western immigrant women experience a higher incidence of SMM^{1,122,134}. In particular mothers from Sub-Saharan Africa have a rate of SMM that is nearly double that of European-born women ^{84,118}, and a risk of maternal death that is over five times greater ⁹². In the United States, where race is the predominant focus of studies examining social disparities in SMM, Black women are 2-3 times as likely to experience SMM as compared to non-Hispanic White women ^{23,50} and have a 3-4 times higher risk of maternal death ^{9,81}. The current challenge in maternal health research is to identify causal mechanisms in order to identify relevant levers to reduce these disparities.

Maternal obesity is a candidate of interest on the causal pathway. Obesity is an increasingly significant health concern among women of reproductive age in most high-income countries ^{10,27,41}, and is more prevalent among minority and immigrant women ^{24,56,87,100}. The majority of studies examining the impact of maternal obesity on perinatal outcomes have primarily focused on antepartum conditions, cesarean and instrumental birth, and neonatal health outcomes, with little emphasis on the effects of maternal weight on maternal mortality or SMM. Associations between obesity and maternal mortality have nevertheless been reported ^{20,86}. The rarity of mortality cases however makes adjustment for confounders (e.g. age) difficult, limiting the ability to isolate an independent association. There is growing evidence suggesting a link between obesity and SMM ^{19,90,108,121,128}. However there are only a few previous investigations, and these are limited

by their sizes, SMM definitions, national contexts, and their statistical adjustment approaches.

Individual-level risk factors, as opposed to social-structural or healthcare factors, have classically been the focus of health disparities research. Individual risks include personal medical and social characteristics as well as behaviors (such as smoking, nutrition, physical activity, medical compliance, and contraceptive self-efficacy). Yet the current literature is heterogeneous, and beyond simple associations there is limited evidence in support of specific causal mechanisms for individual-level risk factors in maternal health disparities. In this doctoral work we attempted to better elucidate and quantify the role of one specific individual-level risk factor, prepregnancy obesity, as a potential mediator of the association between maternal origin and SMM in two high-income countries – France and the USA.

Chapter 2: State of the art

2.1 Severe maternal morbidity

As mentioned previously, maternal mortality in high-income countries constitutes a low proportion of the burden of disease and is likely just the “tip of the iceberg” when considering severe outcomes in maternal health. SMM is a precursor to and occurs at a rate that is one hundred times higher than maternal mortality¹⁴, thus making it a more useful indicator of maternal health both clinically and at the population level. It is imperative to examine SMM from a research perspective in order to better understand causal pathways leading to the occurrence of serious life-threatening maternal outcomes and death⁴⁶.

2.1.1 Definitions and incidence

SMM surveillance globally is hindered by inadequate routine data collection in some countries and also by a lack of a singular definition, which makes tracking trends in incidence and cross-context comparisons difficult. There are preliminary efforts to standardize and validate a uniform consensus definition of SMM in high-income countries¹⁰⁶, but at present a multitude of definitions persist. The majority of global SMM definitions have typically evolved from a combination of diagnoses, organ dysfunctions, management interventions, and in some instances, length of hospital stay^{14,16,57,105,120,127,130}. SMM case definitions are frequently constructed to allow for easy identification from the type of data source available to researchers and agencies. For example, Callaghan et al built upon an existing definition of SMM created by the Centers for Disease Control and Prevention (CDC)^{15,63} in the United States which facilitates identification of cases from

large administrative databases using readily available diagnosis and management billing codes¹⁴. In Europe, much of the incidence data on SMM is based on unique study-specific definitions, variably validated, constructed by researchers in consultation with maternal health experts. Widely used SMM expert consensus definitions include the WHO “near miss”, the Dutch LEMMoN study, and the French EPIMOMS definitions, which are based on case identification via clinical audit using pre-defined criteria ^{110,114,132}.

The advantages and limitations of SMM definitions vary by the data source type. Retrospective data from administrative databases offer a significant advantage by allowing for a large and potentially representative population, yet the definition of SMM is constrained by existing diagnoses and procedure codes. Data from prospective studies where SMM definition is chosen before data collection can be more comprehensive and specific, however it may be limited in its generalizability due to sample size constraints and is difficult to routinely update over time.

Direct comparisons of global SMM rates across studies and contexts are thus complicated due to large variations in case definitions, yet they do still provide best estimates of global trends. SMM incidence in the United States is rising, from 0.50% of birth hospitalizations in 1993 to 1.44% in 2014 ⁹⁴. SMM rate trends in Europe overall are estimated to be in decline however there are significant measurement issues in ascertaining this trend ^{114,116}. More reliable recent SMM estimates from France indicate that the overall incidence of SMM is similar to that in the USA, 1.4% in the 2012-2013 multiregional Epimoms study ¹¹⁴.

2.1.2 Causes and timing

In general, the data suggest that SMM in high-income countries is overwhelmingly due to the component causes of postpartum hemorrhage (PPH) and hypertensive disease^{11,14,15,23,63}. Of note, most global SMM definitions share similar clinical diagnoses and intervention criteria. These are typically based on uniform standard clinical definitions and do not vary significantly between contexts, and it may be possible to isolate individual SMM component rates to use for examining more precise comparisons between studies or countries. To illustrate: in 2014 the overall SMM rate in the USA was 1.44% of birth hospitalizations, receiving a blood transfusion for PPH was by far the most common diagnostic criteria (1.22% of birth hospitalizations), followed by emergency hysterectomy (0.11%), and ventilation or temporary tracheostomy (0.08%)⁹⁴. In France, overall rates and trends of SMM are uncertain due to a dearth of national-level data, however evidence suggests the rate of transfusion for PPH is 0.4% and emergency hysterectomy is 0.05%¹⁸. Isolating rates by specific SMM diagnostic or management criteria thus allows for a credible point of comparison between countries and facilitating improved comparability of data across studies. Furthermore, examining SMM by component cause also has obvious clinical utility as well as research and policy implications. From this perspective, an additional valuable stratification of SMM is by timing of occurrence of the SMM event, that is, in the antepartum, intrapartum, or postpartum (both during the birth hospitalization and after discharge). Notably, the timing of SMM is usually not available from routine administrative databases. Identifying the precise timing of occurrence of the SMM event,

ideally along with the component SMM indicator, in a research study can provide valuable insights regarding prevention and management. To our knowledge no studies have investigated SMM from this perspective⁶⁸.

2.2 Severe maternal morbidity risk factors

Various factors and events intersect throughout the life course of a woman to influence the occurrence of SMM. In order to better conceptually understand the pathogenesis of SMM, risk factors can broadly be divided into individual-level medical, individual-level social, and healthcare-level factors.

2.2.1 Individual-level medical and obstetrical risk factors

Advanced maternal age is an established risk factor for SMM. Maternal age >35, has been shown to have a 1.5 to 2.5 higher risk of SMM^{34,66,79}, and age >45 is associated with nearly three times the risk^{5,22} as compared to age 20-24. Chronic medical conditions are also associated with a higher risk of SMM. Mothers with prepregnancy hypertension have twice the risk of experiencing SMM^{28,51} and those with chronic diabetes have over 1.5 times the risk^{36,51}. Obstetric factors such as parity extremes are associated with SMM: nulliparity is associated with a 1.3-2 fold higher risk^{28,34,36} whereas parity ≥ 3 is associated with twice the risk of SMM³⁴. A history of prior cesarean birth is associated with twice the risk of experiencing SMM in a subsequent birth^{28,34,36}. Multiple pregnancy is associated with a 4.0 times higher risk of SMM⁸⁰. There is also evidence that having undergone fertility treatment to conceive is associated with SMM^{64,124}. Section 2.4 below

details some limited data suggesting that maternal prepregnancy obesity is associated with SMM.

2.2.2 Individual-level social risk factors

Various social and economic factors have been shown to be associated with an increased risk of SMM ¹²³, including overall low socioeconomic status in various settings ^{22,74}. Employment status, whether unemployed or non-managerial status, has been found to be linked to twice the risk of SMM in one European study ⁵⁵. Being on public insurance or being uninsured is associated with a 1.2-1.5 higher risk of SMM in the USA ^{22,28,29,31,50,79,95}. Living in a low-income zip code has been shown to be variably associated with a marginally higher risk of SMM in the USA ^{23,30,52,55,96}. Maternal place of birth, immigrant status, and race-ethnicity have been shown to be strongly associated with SMM in many high-income countries (see section 2.3 below). Consequently, most studies examining social determinants of SMM have focused on these factors.

Notably the causal pathway for most social risks for SMM is complex, and there are often several possible pathways by which a specific risk may operate. Social risks are therefore challenging to study and an examination of intermediaries must routinely be employed ⁶. Additionally social and medical determinants of health are intertwined and several independent risks of SMM congregate in vulnerable groups of mothers, further complicating the ability to study mechanisms of effect.

2.2.3 Healthcare-related risk factors

There are known provider and system-level risk factors of SMM, particularly within the realm of quality of care. Substandard care was found among more than half of women experiencing SMM in a clinical audit of a subset of Dutch national study, mostly due to delays in appropriate care provision¹³⁶. Inadequate prenatal care visits have been shown to be independently associated with SMM in France⁷⁰. An increased risk of SMM was independently associated with an overnight or weekend birth in a large population-based cohort in South Korea⁸⁶. Data from the USA show that up to 60% of excess maternal deaths among women of color are preventable, a finding which suggests that quality issues are implicated in the occurrence of SMM^{9,82}. Similarly, in France 58% of maternal deaths are thought to be preventable and in 66% of cases the cause was sub-optimal care¹⁰². Furthermore, maternal deaths among socially vulnerable women were more likely to be preventable as compared to overall maternal deaths in France. This latter finding indicates a probable interaction between healthcare-related and individual-level risk factors.

2.3 Disparities in risk of severe maternal complications by maternal origin

Maternal place of birth and race-ethnicity are used to identify maternal origin depending on the differing paradigms which dictate how maternal origin has historically been studied in varying national contexts. Race-ethnicity is the predominant variable of interest in the USA whereas maternal place of birth is more often available and used in France.

In Europe, the rate of maternal mortality among immigrant mothers from Sub-Saharan Africa is between 1.5 to 6 times higher than that of non-immigrant women¹ . Specifically in France, immigrant women from Sub-Saharan Africa are over 3 times more likely to die as a result of childbirth as compared to non-immigrant women ^{1,93} Non-Western immigrant women in Europe also experience a higher incidence of SMM^{1,124,136}. In particular mothers from Sub-Saharan Africa have rates of SMM between 2-5 times higher than those of non-immigrant women ^{85,120}. Data show that immigrant women from Sub-Saharan Africa also have a higher risk of SMM specifically due to severe hypertensive disorders of pregnancy: they have approximately a 4 times higher risk of severe preeclampsia ³⁹ and 6 times higher risk of experiencing eclampsia ¹³⁶ as compared to non-immigrant mothers. Women from Sub-Saharan Africa are also 7 times more likely to experience maternal mortality due to a hypertensive disorder of pregnancy as compared to non-immigrant women ⁹³.

In the United States, Black women are 3-4 times more likely to die as a result of childbirth as compared to non-Hispanic White women ^{9,82}. . Black and Latina mothers also suffer from disproportionately higher rates of severe hypertensive disorders of pregnancy as compared to White mothers ^{114,133}, and are 2-3 times as likely to experience SMM^{24,51} Studies examining temporal trends in the incidence of SMM by race in the United States indicate rising rates among all racial groups, however it is uncertain if the disparities between the group with the lowest rates (non-Hispanic White) and others are stable or increasing^{68,83}.

Data examining the effect mechanisms of maternal origin disparities in severe maternal outcomes in Europe are lacking. Prior studies examining racial disparities and SMM in the USA suggest that racial disparities are not easily accounted for by medical, obstetric, social, or birth factors. One cohort analysis of over 8 million women conducted on an administrative database utilizing birth and hospital discharge records in California found that the risk of SMM among Black and Latina women remained significantly higher than that of White women despite adjustments for foreign born status, maternal education, insurance, maternal age, chronic medical conditions, pre-existing anemia, parity, prior cesarean birth, prenatal care, multiple gestation, abnormal placentation, and preterm birth ⁶⁸. A multistate cohort analysis of over 100,00 women in the USA found up to two times the risk of post partum hemorrhage (PPH) among Black and Latina women as compared to White women, after adjusting for age, insurance, smoking, BMI, chronic medical conditions, prior vaginal birth, multiple gestation, abnormal placentation, premature and preterm rupture of membranes, gestational age, birth weight, and birth hospital ³⁸. Notably, these prior findings are limited by the statistical approaches of employing the explanatory variables, which occur temporally after the “exposure” of race, as simply adjustment confounding covariables in regression models.

Multiple known risk factors for SMM often co-exist among minority and immigrant women in high-income countries. Compared with Whites, Black Americans are 50% more likely to suffer from hypertension and 60% more likely to be diagnosed with diabetes ¹²¹. They are also less likely to have health insurance or have private insurance ¹²¹. Immigrant

mothers and women of color are more likely to receive substandard prenatal and obstetric care^{50,71,105}. One study in the USA found that almost half of the disparity in SMM among Black and White mothers may be attributed to site of birth, with Black women more likely to give birth at hospitals with worse outcomes⁵⁰. In France, data suggest that immigrant women from Sub-Saharan Africa receive a lower quality of prenatal care³³, as further evidenced by delayed diagnoses of hypertensive disorders of pregnancy¹⁰⁵, which increases their likelihood of severe pregnancy complications. Sub-Saharan African-born women are also three times more likely than French-born women to have a cesarean birth, with its increased risks of poor outcomes, for non-medical reasons⁷¹.

It emerges that the etiologies of SMM are complex and reflect multiple layers of inequities that exist simultaneously and are likely specific by region or country⁴⁹. As described above, maternal origin disparities are clearly supported by the data. However the mechanisms by which they operate are not well understood and quantified.

2.4 Maternal obesity: a potentially modifiable risk factor for severe maternal complications

Rates of obesity have been trending up globally. Prepregnancy obesity rates increased from 6.0% to 11.8% between 1998 and 2016 in France and obesity rates among women of reproductive age increased from 17.6% to 31.6% in the United States between 2003 and 2019, with evidence of accelerating incidence^{8,10,28,42}. It is plausible that the increasing prevalence of maternal obesity will contribute to a higher burden of SMM in the future, since maternal obesity has been shown to be associated with SMM in some limited

studies^{37,66,72,78,91,109}. A population register-based study of 292,253 singleton births in Finland reported an increased risk of global SMM among obese women⁹¹. A Dutch case-control study of 4,561 low-risk pregnant women found a dose-response relationship between overweight, obesity, and morbid obesity and global SMM outcome¹³⁰. A population-based cohort of 743,630 women in the USA similarly found a dose-response relationship between elevated BMI and global SMM⁷⁷. A population-based case-control study of 50,597 births in the USA found only a modest association between obesity and SMM³⁴. Conversely, two smaller case-control studies of 1,443 and 3,400 women in the UK⁷³ and Australia⁷⁴ respectively found no association between maternal obesity and global SMM. The aforementioned investigations not only had mixed findings but were also limited by varying global SMM case definitions ascertained by administrative/billing data or incomplete clinical information. No prior study examined SMM by cause or timing. Notably, the UK⁷³, Australian⁷⁴, and one of the USA³⁴ analyses included intermediate variables on the causal pathway between obesity and SMM in the multivariable model.

Black and Latina women in the United States are more likely to be obese than White women^{46,89,101}. Notably, Black women have the highest incidence of obesity overall in the USA, at 57%¹⁸. Immigrant women from Sub-Saharan Africa have higher incidence of obesity as compared to all other groups in France⁵⁷. Although some immigrants arriving in high income countries typically have lower rates of obesity as compared to native-born populations, due to acculturation with increasing length of residence they are more likely to experience weight gain due to a variety of environmental and socio-economic factors

and as a consequence have higher rates of obesity than non-immigrants⁸⁴. Minority and immigrant women are more likely to experience poverty and lower educational attainment which are in turn also associated with obesity^{31,42,89}.

Given the existing evidence, we conceptualize a causal pathway between maternal origin, obesity, and SMM. Testing this proposed mechanism has specific implications since obesity, unlike maternal origin or other more proximal factors, is potentially modifiable.

Chapter 3: Research aims and approach

3.1 Hypotheses and objectives

We hypothesized that prepregnancy maternal obesity is associated with SMM and that it mediates the relationship between maternal origin and SMM. We also hypothesized that the mediation effect does not vary by national context.

Accordingly, the project was divided into two specific objectives:

1. To test and quantify the association between prepregnancy BMI and SMM. The primary SMM outcomes were examined from two perspectives, (i) timing and (ii) cause. This relationship was investigated by considering prepregnancy maternal BMI (kg/m^2) as a categorical variable as per routinely accepted clinical cutoffs (underweight = <18.5 , normal weight = $18.5\text{--}24.9$, overweight = $25\text{--}29.9$, obese = > 30). Thus, SMM was variably defined as: SMM occurring at any time and from any cause, SMM occurring at a specific time (i.e. before, during, or after birth), a single SMM component cause, and SMM as a global indicator of timing and cause.
2. To test the hypothesis through path analysis methods that maternal obesity is an intermediary in the association between maternal origin and SMM.

Maternal origin as an exposure was defined variably as race in the USA or maternal place of birth in France. We focused on the global SMM indicator as well as the component of severe preeclampsia, of which both obesity and maternal origin are known risk factors.

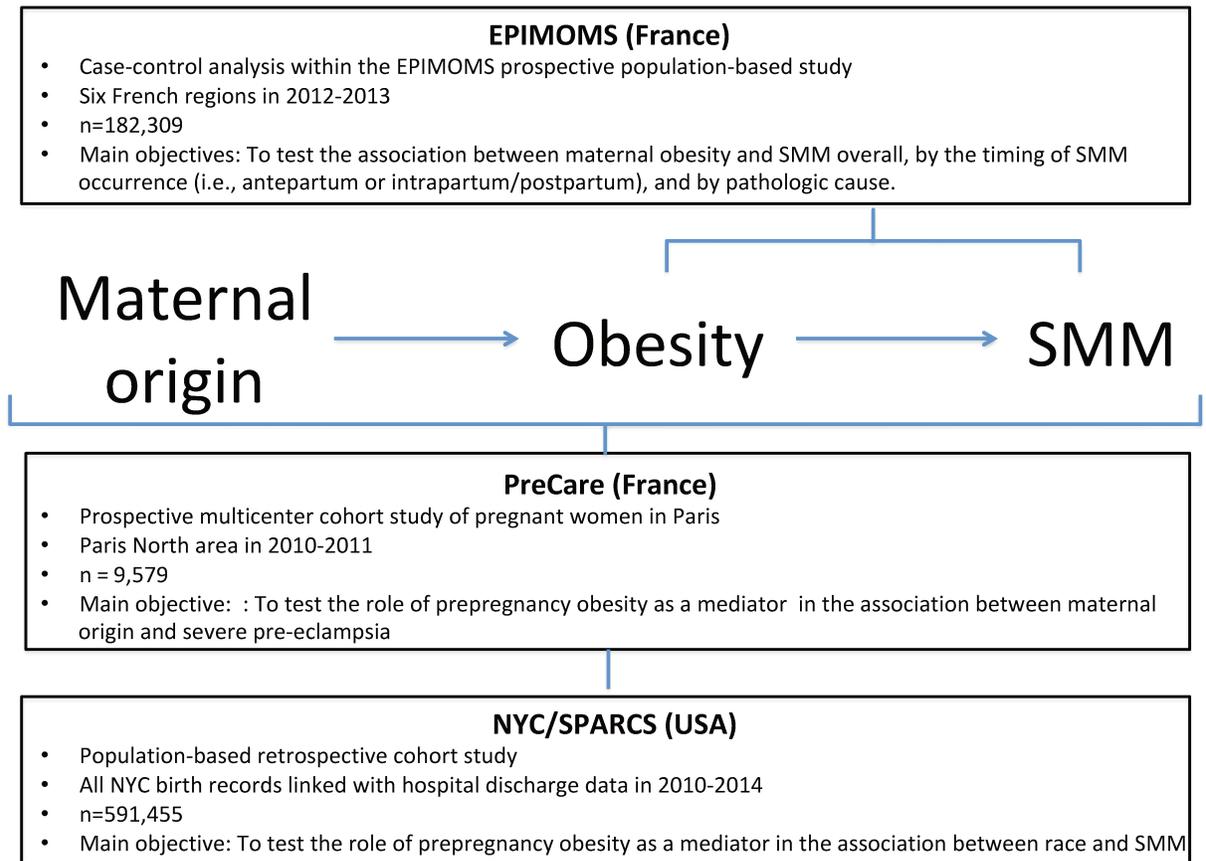
SMM risk disparity was examined from the perspective of identifying an intermediate factor on the pathway to SMM. This approach is necessitated by the fact that many social risks of health outcomes (e.g. race) are not modifiable. We investigated the disparities in SMM risk by maternal origin via testing for a hypothesized mediating effect of prepregnancy obesity, a potentially modifiable risk factor.

3.2 Workplan

Our work consisted of secondary analyses of existing data with a primary focus on a social risk factor, specifically maternal origin, and its relationship with SMM. Given the variability of effects of social factors on health outcomes by context, as well as the very different rates of obesity, we chose to conduct our analyses separately in France and the United States and did not pool data across countries. We selected three data sets with differing and complementary strengths. We postulated that similar or contrasting findings among the data sources, both by data set type and country, would lead to more robust conclusions and furthermore provide insights regarding the importance of context.

We conducted three separate investigations in succession, with each informing the analytic approach of the next. The approach is outlined in figure 1 below. Data sources by country and full methodologies are described in more detail in chapters 4 and 5.

Figure 1: Doctoral Study Workplan



Chapter 4: General methodology

The general methodology employed in the three analyses that constitute this doctoral dissertation is presented here. The specific details of each investigation are unique and differ in important ways and are further described in Chapter 5.

4.1 Data sources

We selected three databases with complementary strengths, two from France and one from the USA. They are introduced below by country and summarized in table 1. They are also described in depth in the material and methods section of each analysis (chapter 5):

France:

The EPIMOMS study was a population-based case control study designed to study SMM . It was conducted in all maternity and intensive care units of six French regions with a source population of 182,309 parturient women in 2012-2013 with characteristics of women and hospitals similar to the national profile ^{60,65,116}. SMM was first defined via a national expert Delphi consensus process as a global outcome of specific obstetric diagnoses, organ dysfunction criteria, and management interventions. All women who experienced SMM during pregnancy and up to 42 days postpartum were prospectively identified and included, as well as a representative unmatched sample of women who did not experience SMM included after birth. The comprehensive and standardized SMM definition, the

population based study design, and the large number of women with SMM (n = 2,541), were the main strengths of this data set.

The PreCARE prospective multicenter cohort study was designed to study the impact of maternal social deprivation on pregnancies and maternal/neonatal outcomes ^{27,33,70,71}. All women registered to give birth or who gave birth in one of the four maternity units of university hospitals in the socially diverse Paris North area between October 2010 and May 2012 were recruited for the study (n=10,419). SMM was defined as per the study team to allow for comparability with prior studies and consisted of specific obstetric diagnoses and management interventions. The main strength of this study was the inclusion of a large number of immigrant participants from whom detailed social history data were collected. In particular, interpreters were used to overcome language barriers to study inclusion. The role of maternal social vulnerability in affecting pregnancy outcomes in this population was of specific interest. In addition to a large number of available social items collected through interviews with the women maternal social deprivation was characterized by four binary variables measuring different dimensions of deprivation: 1) Social isolation; 2) Poor or insecure housing condition; 3) No work-related household income; 4) Absence of health care insurance. Social deprivation was also characterized by a synthetic semi-quantitative index validated in the 2010 French National Perinatal Survey data ⁹⁰.

USA:

Administrative data from New York City (NYC) were Vital Statistics (VS) birth records linked with New York State discharge abstract data, the Statewide Planning and Research

Cooperative System (SPARCS), for all birth hospitalizations in NYC from 2011-2014 (40 hospitals, approximately 120,000 births per year). This large data set therefore consisted of the detailed medical, social, and billing information routinely collected by doctors and hospitals for all women giving birth in NYC. SMM was defined using a published algorithm from the Centers for Disease Prevention and Controls (CDC) based on diagnoses and procedure codes as well as length of hospital stay ¹⁵. The use of the CDC definition allowed for direct comparability with the vast majority of prior SMM studies conducted in the United States which have also used this definition.

4.2 Cross-national comparisons of severe maternal morbidity

The associations between maternal origin, BMI, and SMM were tested in parallel using the above-described data from the United States and France. This approach was conceptualized based on the potential role played by local context, particularly when examining social risk factors in maternal health. A cross-national approach allowed for a broader and fundamentally more robust investigation than if the relationships were examined in a single limited setting.

Given that SMM is not simply a disease process but a complex grouping of various medical and obstetric pathologies that intersect intimately with non-medical determinants of health, namely social factors (including social policies) and the health system, studies attempting to uncover causal pathways must employ unique approaches to arrive at valid, actionable findings. Analyses of SMM via a cross-country perspective provide a preliminary

insight to the mechanisms by which SMM operates as they serve as natural experiments for examining the convergence of social environment (which varies greatly between countries) and biology (which does not vary significantly)⁴³. Specifically, examining and interpreting associations between social and medical factors in light of key differences between countries, such as socio-medical contexts, population and system characteristics, and social-structural factors may potentially help provide causal explanations for SMM. Additionally, repeating the analyses in different countries provides an opportunity to test for reproducibility.

However, there are obstacles to international comparative research. There may be artifacts secondary to measurement and SMM definitions, as discussed previously in chapter 2. Reproducibility testing may lead to conflicting findings in different countries, which may not be due to true differences and are not always easy to verify or explain. It is important to keep these challenges in mind when interpreting data from international comparisons of health.

Prior studies which have presented cross-national data on SMM have been conducted primarily for the purposes of benchmarking quality or ranking countries by prevalence^{11,19,76,106,112}. To our knowledge, there are no prior cross-national comparisons of SMM causal mechanisms. France and the USA, although both high-income countries, differ in important ways. Their populations have significantly different medical characteristics, for example a higher prevalence of metabolic diseases and obesity in the USA. The social characteristics of the two countries also vary, such as in their demographic

make up and a higher degree of social inequality in the USA⁵⁴. The health system in the USA is largely private with public insurance available to some segments of society leaving approximately 11% of the overall population uninsured¹¹⁷, although all women are typically eligible for health insurance during pregnancy and birth. Conversely, in France there is universal access to healthcare throughout the life course. Notably, the groups at higher maternal risk in both countries are similar in term of their minority status (i.e. Black women in the USA and immigrants from Sub-Saharan Africa in France). It is possible that both groups may similarly suffer negative health consequences, specifically a higher risk of SMM, due to social marginalization, structural racism, and higher rates of medical risk factors.

Examining the outcomes of our analyses in two contrasting socio-medical contexts which nevertheless have similar rates of SMM may provide important insights regarding maternal obesity and SMM risk among mothers who are immigrants and women of color. This may allow for enhanced guidance for future investigations both nationally and globally.

4.3 Main study variables

4.3.1 Outcome: Severe maternal morbidity

The relevance of SMM as a timely outcome of interest in maternal health has been described previously. We specifically examined the outcome of global SMM as well as the component cause of severe preeclampsia. Severe preeclampsia is associated with Sub-

Saharan immigrant status^{94,119,135} as well as maternal obesity¹¹³. Studying SMM as a global indicator is comparable to the mortality approach and gives a big picture of SMM in a given setting. Studying SMM by cause allows for an improved opportunity to explore causal pathways as mechanisms of disease may differ by cause. Different types of data are needed to achieve both of these goals. The specific SMM definitions and sources for each of the three datasets we used are described in full detail in table 1 below, as well as in chapter 5.

4.3.2 Exposure: maternal origin

We selected maternal origin as the main exposure of interest in our investigations as it is a consistent socioeconomic predictor of maternal outcomes in diverse contexts^{3,22}. In our analyses we used self-reported maternal race-ethnicity as the exposure of interest in the American dataset and self-reported maternal place of birth in both French datasets. Specific details regarding how maternal origin was defined, collected, and categorized in each dataset are described in table 1 as well as in Chapter 5.

4.3.3 Mediator: prepregnancy maternal obesity

Elevated BMI or maternal obesity (i.e. BMI \geq 30 kg/m²) has been shown to be associated with SMM in some contexts^{66,72,75,78,91,130}, and is often postulated as a driver of the elevated risk of SMM among minority and immigrant mothers. However, to our knowledge there is currently no data that support this hypothesis. We tested for and quantified a mediation effect of prepregnancy maternal obesity in the association between maternal origin and SMM or severe preeclampsia in the USA and one French dataset.

Details regarding how the mediator was defined, collected, and categorized in both datasets are described in table 1 and in Chapter 5.

4. 4 Elucidating epidemiologic pathways

4.4.1 Directed acyclic graphs

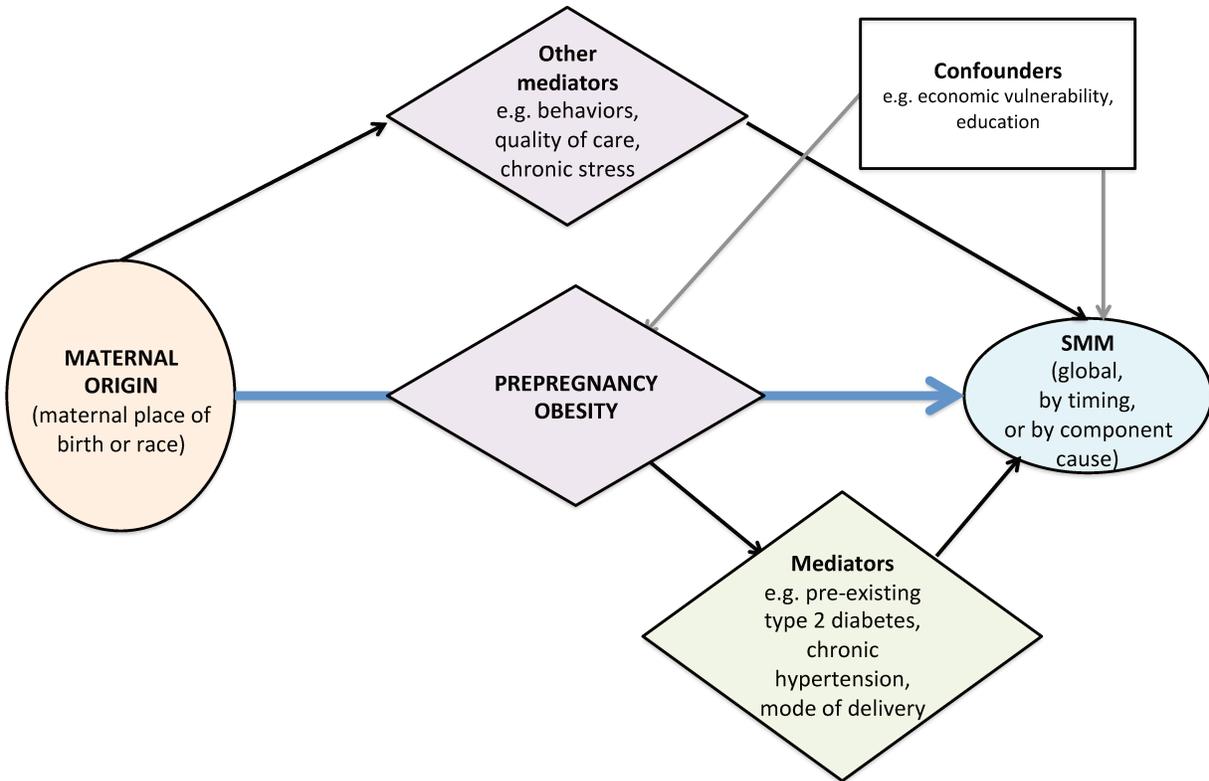
Approximating causality in observational studies requires fulfilling certain assumptions. Particular attention must be paid to limiting bias due to confounding and selection or collider stratification bias⁴. Appropriate identification of exposures, outcomes, antecedents, risk factors, mediators and confounders in the causal pathway is essential. Directed acyclic graphs (DAGs) can be employed as a tool to identify these components in a causal diagram^{7,36,92} and can also help detect the presence of bias^{108,111}. Conceptualizing the causal pathway via DAGs provides guidance on which factors to adjust for, i.e. confounders, and which not to adjust for, i.e. mediators. Adjusting for (or stratifying by, or matching on) mediators in the presence of unmeasured confounders may render conclusions that are over-adjusted ⁴.

For the purposes of this doctoral work, when examining the association between maternal origin and SMM, it is essential to consider the aforementioned risk factors in the framework of a causal diagram. The personal (social, medical) and provider/health system risk factors for which there is credible and sufficient data and biologic plausibility must be defined as per the national context. They must then be individually evaluated to ascertain where they fit on the causal pathway and where they may overlap or interact. Of special

interest are those factors which may be classified as confounders versus mediators. Confounders must be independently associated with the exposure, i.e. maternal origin, and the outcome, i.e. SMM, and must be antecedents of both^{48,97,128}. Mediators are intermediates on the causal pathway and are associated with effects⁶³. When considering an exposure such as maternal origin, given there are no antecedent confounders, we only adjust on confounders of the association between the mediator and outcome.

We present the general DAG that formed the basis of this doctoral dissertation below (figure 2). The individual DAGs used for each of our analyses and sub-analyses are presented in Appendix I. These form the theoretical framework and starting point for our data analyses. They include all known risk factors for SMM and serve primarily to provide an understanding of our model selection processes for our various analyses. They do not represent the models used in our final analyses, which evolved from these initial exhaustive diagrams to arrive at the final functional form of the relationship that fulfills certain assumptions for observational studies^{41,99}. The models were also dependent on the available data. We used a dynamic open source web-based software which allowed us to graphically construct our DAGs to visualize causal effects and testable implications¹¹⁵.

Figure 2. General directed acyclic graph of the association between maternal origin and severe maternal morbidity (SMM)



4.4.2 Employing mediation analyses in obstetric studies

Testing for and quantifying mediation effects when studying SMM has implications for furthering knowledge in the field, as well as possibly practical implications regarding the relative importance of modifiable versus non-modifiable risk factors. The magnitude of

the mediation effect, if it exists, can potentially help rank risks and also provide a hypothetical estimate of disease reduction should a targeted intervention be available. The use of mediation analysis is very recent in the obstetric literature. A few examples of this approach have been published since the completion of this thesis, and some studies have investigated mediation effects on the risk of SMM. A cohort study using administrative data in the USA found that co-morbidities and caesarean birth mediated 13% and 37% the association between obesity and SMM respectively.⁶⁶ Analyses of the EPIMOMS study found a strong mediation effect of multiple pregnancy in the association between in vitro fertilization and SMM ⁶⁵, and a moderate mediation effect of caesarean birth in the association between multiple gestation and SMM ⁸¹. A prospective cohort study in France found a marginal mediating effect of placenta previa in the association between assisted reproductive technologies (ART) and SMM in multiple pregnancies ⁶¹.

For the purposes of our mediation path analyses, the statistical approach we used is based on prior formative work on single mediator analyses by Erikson et al²⁶ which was subsequently further operationalized by Buis¹⁴. We constructed adjusted path analysis logistic regression models to assess the role of prepregnancy obesity as a mediator in the association between maternal origin (race or place of birth/immigrant status depending on the geographic context) and SMM (or component cause). The mediation analyses conceptualized a counterfactual approach, answering the following question:

“What would be the risk of SMM (or component cause) among Black (or immigrant) women if they had the same probability of being obese as White (or non-immigrant) women?”

The results seek to decompose a mediation effect into two quantifiable components:

1. **Direct effect (i.e. non-obesity-mediated):** the proportion of Black (or immigrant) women who develop SMM (or component cause) compared to the counterfactual proportion of White (or non-immigrant) women with the BMI distribution of Black (or immigrant) women.
2. **Indirect effect (i.e. obesity-mediated):** the proportion of White (or non-immigrant) women who develop SMM (or component cause) compared to the counterfactual proportion of White (or non-immigrant) women if they had the BMI distribution of Black or (immigrant) women.

If these comparisons are conducted in the form of log odds ratios, then the total effect equals the sum of the direct and indirect effects.

The terms “direct” and “indirect” effect, although routine terminology in path analysis literature, are misleading since the “direct” effect certainly includes other mediators. It is more accurate to refer to the effects as residual or “non-obesity mediated” (i.e. everything besides obesity) and “obesity-mediated” as noted above.

4.5 Data analysis: general steps

We used logistic regression to model the risk of SMM since our outcome variable was binary in all analyses. Univariable logistic regression models of the main effects were first constructed. DAGs were then used to inform the adjusted multivariable mediation models. Fractional polynomials were used to model continuous variables for which the association was not linear. Tests of relevant interactions were performed between covariables and the exposure. Mediators were subsequently added as appropriate. All path analyses followed the methodology proposed by Buis et al as described above ¹⁴. Stratified subgroup and sensitivity analyses were conducted as needed and are fully described in chapter 5.

In the EPIMOMS analysis, the proportion of women with at least one missing variable was 18.7% in the final multivariable model, therefore multiple imputation was performed for missing data as the missing at random hypothesis was likely, following Rubin's rules¹⁰⁰. Missing data were infrequent in the PreCare and NYC datasets and were omitted from the final analyses. This resulted in no women missing in the final model in the Precare study and 0.2% missing in the NYC analysis.

Table 1: Summary of data sources

	EPIMOMS	PRECARE	NYC/VIS-SPARCS
OUTCOME	<p>Global severe maternal morbidity</p> <p>Definition: National expert consensus criteria*</p> <p>Source: Prospective identification by care providers. Completeness of case ascertainment and timing of SMM occurrence (antepartum, intrapartum/postpartum) verified against birth log books, birth registers, hospital discharge databases, and laboratory records and validated by clinicians.</p> <p>Categories: Binary</p>	<p>Severe preeclampsia</p> <p>Definition: Based on French national clinical guidelines. Preeclampsia plus minimum one of the following criteria: systolic blood pressure >160 mmHg or diastolic blood pressure >110 mmHg, proteinuria >3.5 g/24 h, serum creatinine >100 µmol/l, urine output <20 ml/h, hemolysis, liver transaminitis >3 times upper limit of normal, thrombocytopenia <100 000/mm³, gestational age <32 weeks at onset of disease</p> <p>Source: medical chart review prospectively by research assistants and medical providers</p> <p>Categories: Binary</p>	<p>Global severe maternal morbidity</p> <p>Definition: Based on a published algorithm from the Centers for Disease Control and Prevention and defined as per specific ICD-9-CM billing codes and hospital length of stay**</p> <p>Source: Administrative dataset of NYC birth certificate records linked with hospital discharge abstract data</p> <p>Categories: Binary</p>
EXPOSURE	<p>Prepregnancy body mass index</p> <p>Definition: kg/m²</p> <p>Source: extracted from the medical chart; calculated from self-reported prepregnancy weight and height at the initial prenatal visit</p> <p>Categories: underweight: BMI <18.5 normal: BMI 18.5-24.9 overweight: BMI 25-29.9 obese: BMI ≥30</p>	<p>Maternal place of birth</p> <p>Definition: Mother’s self-reported country of birth</p> <p>Source: Participants’ self-administered questionnaire</p> <p>Categories: France and Europe North Africa Sub-Saharan Africa Other</p>	<p>Maternal race-ethnicity</p> <p>Definition: Combined mother’s self-reported race and Hispanic ethnicity</p> <p>Source: NYC birth certificate administrative database, via mother’s self-completed worksheet***</p> <p>Categories: Non-Hispanic White Non-Hispanic Black Latina Asian Other</p>
MEDIATOR	N/A	<p>Prepregnancy obesity</p> <p>Definition: BMI ≥30 kg/m²</p> <p>Source: abstracted from the medical chart and was calculated by self-reported height and weight at the first prenatal visit</p> <p>Categories: Binary</p>	<p>Prepregnancy obesity</p> <p>Definition: BMI ≥30 kg/m²</p> <p>Source: NYC birth certificate administrative database</p> <p>Categories: Binary</p>

*** EPIMOMS consensus definition of severe maternal morbidity (SMM)**

Items	Criteria (at least one)
Major obstetric bleeding	Volume of postpartum blood loss ≥ 1500 mL Blood transfusion ≥ 4 units RBC Uterine artery embolisation Vascular ligation, compressive uterine sutures Emergency peripartum hysterectomy
Eclampsia	Seizures in a woman previously diagnosed with preeclampsia, and if not, not attributable to another cause
HELLP syndrome	HELLP syndrome* only if associated with hepatic haematoma or rupture *haemolysis, elevated liver enzymes >3 times the normal level and low platelets $<10\,000$
Severe preeclampsia	Preeclampsia** only if it induced a preterm delivery for a maternal indication before 32 weeks gestational age **Defined as hypertension $\geq 140/90$ and proteinuria ≥ 0.3 g/24 h
Placental abruption	Placental abruption associated with a haematological dysfunction criterion
Pulmonary embolism	Clinical symptoms consistent with pulmonary embolism + confirmation with imaging + treatment (imaging: computed tomography or ventilation/perfusion scintigraphy or Doppler; treatment: heparin or thrombolysis or embolectomy)
Stroke	Cerebral imaging showing cerebral infarction or haemorrhage, venous thrombosis, or sub-arachnoid haemorrhage
Cerebral transient ischaemic attack	Neurological deficit with symptoms§ completely resolved within 24 h and normal cerebral imaging, in the absence of associated migraine and confirmed by a neurologist § Monocular blindness, aphasia, hemianopsia, motor, and/or sensory uni- or bilateral disorders
Severe psychiatric disorder	Severe acute psychiatric disorder or acute decompensation of chronic disease (psychosis, major depression, bipolar disorder) and diagnosed by a psychiatrist Suicide attempt
Cardiovascular dysfunction	Cardiac arrest Acute pulmonary oedema with hypoxaemia <60 mm Hg, SaO ₂ $<90\%$, or requiring diuretic treatment Need for continuous IV vasopressor/inotrope drugs Decompensation of a pre-existing cardiopathy with need for specialised management Troponinemia >1 $\mu\text{g/L}$
Respiratory dysfunction	Acute hypoxaemia <60 mm Hg or SaO ₂ $<90\%$, with spontaneous ventilation Mechanical ventilation or non-invasive ventilation in the absence of chronic disease, not related to anaesthesia
Renal dysfunction	Acute renal failure with creatinemia >135 $\mu\text{mol/L}$ Acute oliguria <500 mL/24 h
Neurological dysfunction	Coma, regardless of stage and duration # # Stage 1 coma = impaired consciousness with obtundation and reaction to painful stimuli only
Hepatic dysfunction	Prothrombin time $<60\%$, in the absence of constitutional deficiency Direct bilirubinemia >20 $\mu\text{mol/L}$
Haematological dysfunction	Thrombocytopenia $<50\,000/\text{mm}^3$ in the absence of chronic disorder Acute anaemia <7 g/dL Disseminated intravascular coagulation: platelets $<50\,000/\text{mm}^3$, prothrombin time $<60\%$, or fibrinogen <2 g/l
Emergency surgery apart from childbirth procedure	Secondary hysterectomy Laparotomy for post-delivery complication excluding haematoma or surgical site infection
Admission to intensive care unit	
Maternal death	

*among pregnant women >22 weeks gestational age and up to 42 days postpartum

** Adapted from: Berg, Cynthia J., et al. "Overview of maternal morbidity during hospitalization for labor and delivery in the United States: 1993–1997 and 2001–2005." *Obstetrics & Gynecology* 113.5 (2009): 1075-1081. (Appendix table below)

For hospital length of stay modification see: Callaghan, William M., Andreea A. Creanga, and Elena V. Kuklina. "Severe maternal morbidity among delivery and postpartum hospitalizations in the United States." *Obstetrics & Gynecology* 120.5 (2012): 1029-1036

Appendix. International Classification of Diseases, 9th Revision, Clinical Modification Codes Used to Identify Maternal Morbidity During Hospitalization for Labor and Delivery	
Codes	Morbidity
641.0–641.9	Antepartum hemorrhage (placenta previa, abruptio placenta, hemorrhage with DIC, other and unspecified hemorrhage) excludes hemorrhage in early pregnancy
All 666	Postpartum hemorrhage (third-stage hemorrhage, other postpartum hemorrhage including atony, delayed/secondary postpartum hemorrhage)
642.4–642.7	Mild and unspecified preeclampsia, severe preeclampsia and eclampsia
642.3	Transient hypertension of pregnancy
664.2, 664.3, 664.5	Major perineal laceration (third- and fourth-degree perineal lacerations, vulvar and perineal hematoma)
665.2–665.9	Other obstetric trauma (includes inversion of uterus, cervical laceration, high vaginal laceration, other injury to pelvic organs, joints, or ligaments, pelvic hematoma)
665.0–665.1	Ruptured uterus
646.6, 590, 599.0	Genitourinary infection (pyelonephritis, urinary tract infection)
658.4	Amnionitis
486, all 041, 682	Other infection (unspecified pneumonia, unspecified bacterial infection, abscess)
659.2	Fever (maternal pyrexia during labor, unspecified)
670, all 615	Major puerperal infection (includes endometritis, sepsis, cellulitis, peritonitis, salpingitis)
672	Pyrexia of unknown origin in the puerperium
659.3	Sepsis (generalized infection/septicemia during labor)
648.8	Gestational diabetes (abnormal glucose tolerance test)
674.8–674.9, all 276, 287	Other major puerperal conditions (includes hepatorenal syndrome, postpartum cardiomyopathy, sudden death, fluid/electrolyte abnormality, purpura)
674.5	Peripartum cardiomyopathy (2003–2005)
669.0–669.4, all 998	Other major complications of labor and delivery (includes maternal distress, shock, hypotension, arrest, renal failure, pulmonary insufficiency, surgical complications)
All 668, 349	Anesthetic complications
674.1–674.3	Wound complication
671.3–671.4	Deep venous thrombosis
646.7	Gestational liver disease
643.2	Late vomiting of pregnancy
All 673	Obstetric pulmonary embolism (includes blood clot embolism, amniotic fluid embolism, air embolism)
671.5, 674.0, 430, 431, 436, all 432, 433, 434	Cerebrovascular accident (includes cerebral hemorrhage, embolism, and thrombosis)
642.0–642.2, 642.7, 642.9, all 401	Chronic hypertension
648.5–648.6, all 424, 425	Cardiac disease (excludes cerebral complications)
All 493	Asthma
648.0, all 250	Preexisting diabetes mellitus (excludes abnormal glucose tolerance test)
646.2	Renal disease (unspecified renal disease in pregnancy without mention of hypertension)
74.0–74.2, 74.4, 74.99, 669.70–669.71	Cesarean delivery

OBSTETRICS & GYNECOLOGY

*** Available at: <https://www1.nyc.gov/assets/doh/downloads/pdf/vs/VR203-web.pdf>

Chapter 5: Results

5.1 Associations between maternal obesity and severe maternal morbidity: Findings from the French EPIMOMS population-based study

5.1.1 Summary

Obesity prevalence is increasing in most high-income countries. Emerging evidence suggests that prepregnancy obesity (i.e. BMI \geq 30kg/m²) is an independent modifiable risk factor for SMM. As the previous studies in this area were limited by size and context, we tested for this association via a case-control analysis within a large prospective population-based study of pregnant women conducted in six regions in France between 2012-2013. All women who gave birth at 22 weeks gestational age or greater constituted the source cohort (N=182,309). The exposure of interest was prepregnancy obesity as documented in the prenatal record. The case outcome was defined as experiencing global SMM any time during the pregnancy and up to 42 days postpartum, as per a multi-criteria definition developed by a national expert consensus process (n=2,540). The outcome was further stratified by timing of SMM event (anteartum or intrapartum/postpartum) as well as by component cause. Controls were a 2% unmatched random sample of women who gave birth without SMM selected from the same facilities as cases (n=3,651). Multivariable logistic regression models found an association between prepregnancy obesity and overall SMM (adjusted odds ratio [OR] 1.34, 95% confidence interval [CI] 1.14, 1.59) and anteartum SMM (OR 2.07, 95% CI 1.61, 2.65), but not with intra/postpartum SMM (OR 1.15, 95% CI 0.96, 1.38). Among anteartum SMM cases, severe hypertensive disorders were most strongly associated with obesity (OR 2.50, 95% CI 1.85, 3.40) but the risk of

anteartum SMM due to other causes was also increased among obese women (OR 1.64, 95% CI 1.13, 2.37). Obesity was not associated with severe postpartum hemorrhage (OR 1.12, 95% CI 0.92, 1.37). Our findings underscore the importance of reducing obesity among women of reproductive age. The differential association of obesity by SMM timing and cause has practical clinical implications for prevention possibly via the improvement of antenatal quality of care measures among obese women, such as blood pressure monitoring. Beyond the study objectives, the strong association between Sub-Saharan maternal place of birth and anteartum severe hypertensive disorders (table S3) informed the focus on the SMM component of severe hypertensive disease in the PreCARE study described below.

5.1.2 Article as published

Siddiqui A, Azria E, Howell EA, Deneux-Tharoux C, EPIMOMS Study Group, Langer B, Dupont C, Rudigoz RC, Vendittelli F, Beucher G, Rozenberg P. Associations between maternal obesity and severe maternal morbidity: Findings from the French EPIMOMS population-based study. *Paediatric and perinatal epidemiology*. 2019 Jan;33(1):7-16.

Associations between maternal obesity and severe maternal morbidity: Findings from the French EPIMOMS population-based study

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Abstract

Background: Maternal obesity is increasing. There is growing evidence of its effect on severe maternal morbidity. We assessed prepregnancy obesity as an independent risk factor for severe maternal morbidity by timing and cause.

Methods: We designed a case-control analysis within the EPIMOMS prospective population-based study conducted in six French regions in 2012-2013 (182 309 women who delivered at ≥ 22 weeks). Cases were all women who experienced severe maternal morbidity during pregnancy to 42 days postpartum as per a multicriteria definition derived by national expert consensus ($n = 2540$, severe maternal morbidity prevalence 1.4%). Controls were randomly selected from the same health centres ($n = 3651$). The association between obesity and severe maternal morbidity was assessed from fitting multivariable logistic regression models: overall, by timing (ante-partum and intrapartum/ postpartum), and by cause.

Results: Prepregnancy obesity was associated with overall severe maternal morbidity (adjusted odds ratio [OR] 1.34, 95% confidence interval [CI] 1.14, 1.59) and antepartum severe maternal morbidity (OR 2.07, 95% CI 1.61, 2.65), but not with intra/postpartum severe maternal morbidity (OR 1.15, 95% CI 0.96, 1.38). Among antepartum severe maternal morbidity, severe hypertensive disorders were most strongly associated with obesity (OR 2.50, 95% CI 1.85, 3.40) but the risk of antepartum severe maternal morbidity due to other causes was also increased among obese women (OR 1.64, 95% CI 1.13, 2.37). Obesity was not associated with severe postpartum haemorrhage (OR 1.12, 95% CI 0.92, 1.37).

*On behalf of the EPIMOMS study group, EPIMOMS Study Group members are listed in Appendix.

Conclusion: Obesity is associated with an increased risk of antepartum, but not intra/postpartum, severe maternal morbidity.

KEYWORDS

body mass index, maternal morbidity, maternal obesity, obesity, prepregnancy obesity, severe maternal morbidity

1 | INTRODUCTION

Obesity is a significant health concern among women of reproductive age and trends mirror those of the general population in most high-income countries. Maternal obesity prevalence rates increased from 6.0% to 11.8% between 1998 and 2016 in France and from 17.6% to 20.5% in the United States between 2003 and 2009, with evidence of accelerating incidence.¹⁻³ Obesity during pregnancy is associated with an increased risk of adverse perinatal outcomes and higher health care costs.^{4,5} Maternal outcomes associated with obesity include higher rates of pre-eclampsia and gestational diabetes,⁶⁻⁸ prolonged labour progression,⁹ higher rates of caesarean delivery,^{10,11} and an increased risk for postpartum haemorrhage independent of mode of delivery in some settings.¹²⁻¹⁴ Despite the increased incidence of complications during pregnancy and delivery among obese women, few studies have investigated the effect of maternal obesity on severe complications leading to profound alterations in the mother's health, that is, severe maternal morbidity (SMM).¹⁵⁻¹⁹ These studies have utilised varying definitions of the SMM composite outcome and approaches to case ascertainment. To our knowledge, no study has examined SMM occurrence by timing and few have investigated SMM by cause.

In a population-based case-control study, we examined the association between maternal obesity and SMM overall, by the timing of SMM occurrence (ie, antepartum or intrapartum/postpartum), and by pathologic cause.

2 | METHODS

We performed an unmatched case-control analysis within EPIMOMS, a population-based prospective investigation designed specifically to study SMM in six French regions between May 2012 and November 2013. The study sample was selected from a source population of 182 309 pregnant women receiving care at 119 public maternity units and 136 intensive care units. The source population constituted one-fifth of all deliveries in France, and maternal characteristics were similar to that of the national obstetric population.³ Women ≥ 18 years old who delivered at ≥ 22 weeks of gestational age were eligible for study inclusion. The study was approved by the *Commission Nationale de l'Informatique et des Libertés* (CNIL, no 912210), the French data protection agency.

2.1 | Severe maternal morbidity case and controls

The definition of a SMM event was developed via an extensive national expert Delphi consensus process, with the objective of isolating those maternal complications which result in severe health alteration. The national panel of professionals included obstetricians ($n = 16$), midwives ($n = 5$), anaesthesiologists/intensive care specialists ($n = 8$), and public health specialists ($n = 3$). The process followed a Delphi-Rand design and consisted of two rounds followed by a final plenary session. The level of consensus for each round was fixed at 70%. Once the definition for SMM was finalised, its comprehensiveness was tested via a population-based survey, which was used to study the incidence, the causes, and the risk factors of SMM in six regions across France.

The final EPIMOMS definition of SMM combines diagnostic criteria (major obstetric bleeding, eclampsia, severe pre-eclampsia, pulmonary embolism, stroke, selected psychiatric disorders), organ dysfunction criteria (hepatic, haematologic, respiratory, cardiovascular, renal, neurological), and interventional criteria (admission to ICU, laparotomy after delivery). The EPIMOMS SMM case criteria are detailed in Table 1.

All women who experienced a SMM event in the source population during the study period and were between 22 weeks of gestation and 42 days postpartum were included in the EPIMOMS study. A SMM event was defined as per the EPIMOMS case criteria. They were prospectively identified by care providers, and completeness of case ascertainment and timing of SMM occurrence (ie, antepartum, intrapartum/postpartum) were checked via a review of delivery log books, birth registers, hospital discharge databases, and laboratory records and validated by clinicians who worked at the health centres. Women who experienced more than one SMM event in the antepartum and intra/postpartum periods were only counted once in the analysis of overall SMM. In the EPIMOMS cohort, 2540 women experienced SMM (1.4%) and constituted the case group in this case-control analysis. SMM case inclusion criteria based on organ dysfunction or a management indicator did not necessarily directly correspond to the cause of SMM. Therefore, the SMM causal condition, as identified by the clinician in charge, was also recorded for all cases.

A random 2% unmatched sample of women who delivered at ≥ 22 weeks of gestation without experiencing a SMM event from the same health centres during the study period was selected as the control group ($n = 3651$). Based on an anticipated rate of

TABLE 1 EPIMOMS consensus definition of severe maternal morbidity (SMM)*

Items	Criteria (at least one)
Major obstetric bleeding	Volume of postpartum blood loss ≥ 1500 mL Blood transfusion ≥ 4 units RBC Uterine artery embolisation Vascular ligation, compressive uterine sutures Emergency peripartum hysterectomy
Eclampsia	Seizures in a woman previously diagnosed with preeclampsia, and if not, not attributable to another cause
HELLP syndrome	HELLP syndrome* only if associated with hepatic haematoma or rupture *haemolysis, elevated liver enzymes >3 times the normal level and low platelets $<10\,000$
Severe preeclampsia	Preeclampsia** only if it induced a preterm delivery for a maternal indication before 32 weeks gestational age **Defined as hypertension $\geq 140/90$ and proteinuria ≥ 0.3 g/24 h
Placental abruption	Placental abruption associated with a haematological dysfunction criterion
Pulmonary embolism	Clinical symptoms consistent with pulmonary embolism + confirmation with imaging + treatment (imaging: computed tomography or ventilation/perfusion scintigraphy or Doppler; treatment: heparin or thrombolysis or embolectomy)
Stroke	Cerebral imaging showing cerebral infarction or haemorrhage, venous thrombosis, or sub-arachnoid haemorrhage
Cerebral transient ischaemic attack	Neurological deficit with symptoms§ completely resolved within 24 h and normal cerebral imaging, in the absence of associated migraine and confirmed by a neurologist § Monocular blindness, aphasia, hemianopsia, motor, and/or sensory uni- or bilateral disorders
Severe psychiatric disorder	Severe acute psychiatric disorder or acute decompensation of chronic disease (psychosis, major depression, bipolar disorder) and diagnosed by a psychiatrist Suicide attempt
Cardiovascular dysfunction	Cardiac arrest Acute pulmonary oedema with hypoxaemia <60 mm Hg, SaO ₂ $<90\%$, or requiring diuretic treatment Need for continuous IV vasopressor/inotrope drugs Decompensation of a pre-existing cardiopathy with need for specialised management Troponinemia >1 $\mu\text{g/L}$
Respiratory dysfunction	Acute hypoxaemia <60 mm Hg or SaO ₂ $<90\%$, with spontaneous ventilation Mechanical ventilation or non-invasive ventilation in the absence of chronic disease, not related to anaesthesia
Renal dysfunction	Acute renal failure with creatinemia >135 $\mu\text{mol/L}$ Acute oliguria <500 mL/24 h
Neurological dysfunction	Coma, regardless of stage and duration # # Stage 1 coma = impaired consciousness with obtundation and reaction to painful stimuli only
Hepatic dysfunction	Prothrombin time $<60\%$, in the absence of constitutional deficiency Direct bilirubinemia >20 $\mu\text{mol/L}$
Haematological dysfunction	Thrombocytopenia $<50\,000/\text{mm}^3$ in the absence of chronic disorder Acute anaemia <7 g/dL Disseminated intravascular coagulation: platelets $<50\,000/\text{mm}^3$, prothrombin time $<60\%$, or fibrinogen <2 g/l
Emergency surgery apart from childbirth procedure	Secondary hysterectomy Laparotomy for post-delivery complication excluding haematoma or surgical site infection
Admission to intensive care unit	
Maternal death	

*among pregnant women >22 weeks gestational age and up to 42 days postpartum

SMM of 1%, the size of the control sample was chosen in order to have sufficient statistical power to study the association between various potential risk factors and SMM. Detailed information regarding socio-demographic characteristics, medical and obstetric history, antenatal care, delivery, and obstetric hospitalisation

was collected from the medical chart for all women experiencing SMM and the random sample of women who did not experience SMM. Information regarding facility characteristics and obstetric management was collected via questionnaires administered to maternity unit leaders.

2.2 | Statistical analysis

Categorical prepregnancy body mass index (BMI; kg/m²) was the independent variable of interest in all models (underweight: BMI <18.5; normal weight: BMI 18.5-24.9; overweight: BMI 25-29.9; obese: BMI ≥30). Prepregnancy BMI was extracted from the medical chart and was calculated from self-reported prepregnancy weight and height at the initial prenatal visit. SMM events were described by timing and cause (underlying causal conditions are listed in Table 3), and obesity status. Demographic, medical, and facility characteristics were further described by BMI category among controls only, in order to be reflective of the general population and to assess for potential confounders. Directed acyclic graphs (DAGs) were used to inform the selection of co-variables in the multivariable logistic regression models of SMM outcomes: overall, by timing of occurrence (antepartum and intrapartum/postpartum), and by most common causes. We used the web-based application DAGitty (www.dagitty.net) to create our DAGs (Figure S1). We included only confounders (ie, factors potentially associated with both the exposure and the outcome) in the final multivariable models and not intermediates in the causal pathway between obesity and SMM in order to avoid over-adjusting the measurement of the association between BMI and SMM.²⁰ In particular, pre-existing chronic hypertension and type 2 diabetes were considered to be mediators of the pathway and not confounders and therefore were not controlled for. Confounders in the final analyses included maternal age, parity, prepregnancy tobacco use, maternal place of birth, living alone, and profession. All co-variables were tested for interaction with obesity. Associations between confounders and SMM were additionally of interest as secondary study findings. Fractional polynomials were used to model the nonlinear association between continuous variables considered for inclusion in the model and the risk of SMM in order to increase the flexibility afforded by the family of conventional polynomial models.²¹ We choose the best fitting model for the variables from all polynomial models with combinations of powers from the set (-2, -1, -0.5, 0, 0.5, 1, 2, 3) using the "fp" function in Stata (V.14.0 SE, Stata Corporation, College Station, TX, USA). Age was the only continuous variable we included in the final models, and it did not show any deviation from linearity.

2.3 | Missing data

The proportion of missing data for all variables in the final model was <10% except for maternal place of birth (14%) and profession (11%), and 19% of women had at least one missing variable. The proportion of missing BMI data was 7% among cases and 4% among controls. Multiple imputation using chained equations was performed over 25 cycles to handle missing data assumed to be missing at random (MAR).²²

3 | RESULTS

Characteristics of study participants by case-control status are shown in Table 2. As compared to controls, women experiencing

SMM were more likely to be obese (15% vs 11%). The distribution by obesity class among cases was 65% class 1 (BMI 30.0-34.9 kg/m²), 24% class 2 (BMI 35.0-39.9 kg/m²), and 11% class 3 (BMI ≥40.0 kg/m²). The distribution by obesity class among controls was 67% class 1, 23% class 2, and 10% class 3. Women experiencing SMM were more likely to be older, born in sub-Saharan Africa, be living alone, and have a history of chronic hypertension as well as other pre-existing medical conditions as compared with women who did not experience SMM. They were also more likely to be primiparous and have a history of caesarean delivery, as well as prior obstetrical complications such as hypertension and postpartum haemorrhage. In the current pregnancy, they had higher rates of in vitro fertilisation, multiple gestation, hypertensive disease, and delivered at earlier gestational ages.

In order to identify risk factors associated with obesity that could be possible confounders of the association between obesity and SMM, characteristics of controls were analysed according to their obese or non-obese status (Table S1). Among controls, obese women were more likely to be older, from North Africa, be manual service workers, have a history of chronic hypertension, pre-existing diabetes, multiparous with prior caesarean deliveries, and have prior hypertensive disorders of pregnancy; they were also more likely to have a hypertensive disorder and gestational diabetes in the current pregnancy and were more likely to be induced, have a caesarean delivery, and a higher newborn birthweight. There was no difference in the distribution of BMI category by facility type, level of care, or delivery volume among controls.

The majority of SMM events occurred in intra/postpartum (Table 3). The most common causes of SMM overall were severe haemorrhage and severe hypertensive disorders, with the former accounting for most intra/postpartum SMM cases and the latter for most antepartum SMM cases. Among women experiencing SMM, obese women had higher proportion of antepartum SMM and of severe hypertensive disorders, in particular preeclampsia-related SMM, than non-obese women. Babies born to women experiencing antepartum SMM were more likely to be born preterm as compared to controls or to women experiencing intra/postpartum SMM, primarily as a result of caesarean delivery without a trial of labour (Table S2).

The association between prepregnancy BMI and SMM is shown in Table 4. Prepregnancy obesity was associated with overall SMM and antepartum SMM, but not with intra/postpartum SMM. Among women with antepartum SMM, severe hypertensive disorders had the strongest association with obesity, and this association was mainly driven by preeclampsia-related SMM, but the risk of antepartum SMM from all other causes combined was also increased among obese women. Obesity was not associated with the risk of severe postpartum haemorrhage. Results of the full models with all co-variable adjusted odds ratios and 95% confidence intervals appear in Table S3. Among other risk factors, maternal place of birth was most strongly associated with SMM and sub-Saharan African mothers had an increased risk of SMM at all times.

TABLE 2 Characteristics among women experiencing severe maternal morbidity (SMM) and those not experiencing SMM

	Cases: n (%) n = 2540	Controls: n (%) n = 3651
Prepregnancy body mass index (kg/m ²)		
Mean (standard deviation)	24.5 (5)	23.9 (5)
Underweight (<18.5)	170 (7)	261 (7)
Normal weight (18.5-24.9)	1353 (58)	2137 (61)
Overweight (25-29.9)	474 (20)	724 (20)
Obese (≥30)	357 (15)	395 (11)
Socio-demographic characteristics		
Maternal age (y) [mean (standard deviation)]	31.3 (6)	30.5 (5)
Maternal place of birth		
France	1573 (70)	2313 (76)
Europe	68 (3)	111 (4)
North Africa	234 (10)	316 (10)
Sub-Saharan Africa	245 (11)	173 (6)
Other	141 (6)	150 (5)
Living alone	155 (7)	135 (4)
Profession		
Manual or service workers	150 (7)	174 (5)
Self-employed	47 (2)	81 (3)
Public service, administrative, or sales worker	704 (31)	857 (27)
Intermediate	424 (19)	606 (19)
Professional	424 (19)	677 (21)
Unemployed	534 (23)	818 (26)
Medical history		
Pre-pregnancy tobacco use	472 (20)	774 (22)
Chronic hypertension	70 (3)	30 (1)
Pre-existing diabetes	26 (1)	23 (1)
Any other notable pre-existing medical condition ^a	310 (12)	226 (6)
Obstetric history		
Parity by delivery type		
Primiparous	1235 (50)	1517 (42)
Multiparous without prior caesarean delivery	810 (33)	1641 (46)
Multiparous with prior caesarean delivery	439 (18)	441 (12)
If parous		
Prior caesarean delivery	439 (35)	441 (21)
Prior hypertensive disease of pregnancy	137 (11)	97 (5)
Prior postpartum haemorrhage	113 (9)	83 (4)
Current pregnancy		
In vitro fertilisation	150 (6)	76 (2)
Multiple gestation	207 (8)	59 (2)
Hypertensive disorders of pregnancy		

(Continues)

TABLE 2 (Continued)

	Cases: n (%) n = 2540	Controls: n (%) n = 3651
Normotensive	1997 (80)	3528 (97)
Gestational hypertension	75 (3)	65 (2)
Preeclampsia	434 (17)	57 (2)
Gestational diabetes	231 (9)	273 (8)
Placenta previa or placenta accreta	145 (6)	25 (1)
Antepartum hospitalisation	1026 (41)	576 (16)
Delivery characteristics		
Gestational age (weeks)		
Mean (standard deviation)	36.9 (4.2)	38.9 (2.1)
<28	105 (4)	26 (1)
28-31	312 (13)	35 (1)
32-36	347 (14)	205 (6)
≥37	1720 (69)	3382 (93)
Noncephalic presentation	294 (12)	171 (5)
Labour onset		
Spontaneous	1049 (42)	2649 (73)
Induced	1448 (58)	1000 (27)
Mode of delivery		
Vaginal	820 (33)	2456 (67)
Vaginal instrumental	336 (14)	450 (12)
Caesarean delivery with trial of labour	446 (18)	357 (10)
Caesarean delivery without trial of labour	895 (36)	386 (11)
Newborn characteristics		
Stillbirth and neonatal deaths	136 (6)	31 (1)
Birthweight (g) [mean (standard deviation)]	2888 (990)	3267 (577)
Delivery facility characteristics		
Facility type		
Public teaching hospital	1211 (48)	1095 (30)
Public non-teaching hospital	1022 (40)	1617 (44)
Private hospital	307 (12)	939 (26)
Facility's level of care		
1	419 (17)	932 (26)
2	1010 (40)	1873 (51)
3	1111 (44)	846 (23)
Delivery volume (deliveries per year)		
<1500	573 (23)	1215 (33)
1500-1999	204 (8)	358 (10)
2000-2999	924 (37)	1295 (36)
≥3000	831 (33)	783 (22)

^aHaematologic disease or hemoglobinopathy, psychiatric illness, history of venous thromboembolism, coronary artery disease, cardiomyopathy, congestive heart failure, epilepsy, multiple sclerosis, liver disease including infectious hepatitis, autoimmune disease, inflammatory bowel disease, nephropathy, history of haemodialysis, pulmonary disease, myasthenia gravis, neoplasia, HIV, and any other chronic medical condition.

TABLE 3 Diagnosis of severe maternal morbidity (SMM) cases by timing, cause, and obesity status

	Total	Underweight	Normal weight	Overweight	Obese
	n (%)	n (%)	n (%)	n (%)	n (%)
All SMM cases ^a	2540	170 (7) ^b	1353 (53) ^b	474 (19) ^b	357 (14) ^b
Severe obstetrical haemorrhage	1655 (65)	123 (72)	914 (68)	319 (67)	203 (57)
Severe hypertensive disorder ^d	480 (19)	25 (15)	272 (20)	101 (21)	95 (27)
Preeclampsia	340(13)	17 (10)	175 (13)	71 (15)	77 (22)
Eclampsia	43 (2)	1 (1)	25 (2)	8 (2)	9 (3)
HELLP Syndrome	163 (6)	11(7)	96 (7)	33 (7)	23 (6)
Placental abruption	82 (3)	3 (2)	50 (4)	21 (4)	8 (2)
Sepsis	52 (2)	2 (1)	31 (2)	7 (2)	7 (2)
Decompensation of pre-existing medical condition	108 (4)	3 (2)	50 (4)	14 (3)	14 (4)
Psychiatric disorder	88 (4)	6 (4)	52 (4)	17 (4)	13 (4)
Pulmonary embolus	39 (2)	23 (14)	1 (0)	6 (1)	7 (2)
Cerebrovascular accident	35 (1)	15 (9)	2 (0)	9 (2)	3 (1)
Amniotic fluid embolus	15 (1)	10 (6)	0 (0)	1 (0)	2 (1)
Other	218 (9)	16 (9)	109 (8)	40 (8)	35 (10)
Multiple pathologies	219 (9)	6 (4)	114 (8)	38 (8)	25 (7)
Antepartum SMM cases ^a	598 (24) ^c	28 (17)	288 (21)	110 (23)	121 (34)
Severe obstetrical haemorrhage	83 (14)	3 (11)	48 (17)	10 (9)	15 (12)
Severe hypertensive disorder ^d	320 (54)	12 (43)	156 (54)	73 (66)	76 (63)
Preeclampsia	280 (47)	10 (36)	126 (44)	64 (58)	64 (53)
Eclampsia	24 (4)	1 (4)	7 (2)	5 (5)	7 (6)
HELLP syndrome	81 (14)	4 (14)	43 (15)	18 (16)	13 (11)
Placental abruption	39 (7)	1 (4)	20 (7)	8 (7)	6 (5)
Sepsis	26 (4)	2 (7)	14 (5)	1 (1)	5 (4)
Decompensation of pre-existing medical condition	71 (12)	3 (11)	35 (12)	12 (11)	10 (8)
Psychiatric disorder	54 (9)	4 (14)	24 (8)	10 (9)	5 (4)
Pulmonary embolus	15 (3)	1 (4)	9 (3)	1 (1)	3 (3)
Cerebrovascular accident	17 (3)	1 (4)	7 (2)	6 (6)	1 (1)
Amniotic fluid embolus	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	94 (16)	6 (21)	47 (16)	14 (13)	23 (19)
Multiple pathologies	94 (16)	2 (7)	48 (17)	16 (15)	17 (14)
Intrapartum or postpartum SMM cases ^a	1939 (76) ^c	142 (84)	1065 (79)	364 (77)	236 (66)
Severe obstetrical haemorrhage	1572 (81)	120 (85)	866 (81)	309 (85)	188 (80)
Severe hypertensive disorder ^d	160 (8)	11 (8)	92 (9)	18 (5)	21 (9)
Preeclampsia	87 (5)	7 (5)	49 (5)	7 (2)	13 (6)
Eclampsia	27 (1)	0 (0)	18 (2)	3 (1)	2 (1)
HELLP syndrome	93 (5)	7 (5)	53 (5)	15 (4)	10 (4)
Placental abruption	61 (3)	2 (1)	30 (3)	13 (4)	2 (1)
Sepsis	26 (1)	0 (0)	17 (2)	6 (2)	4 (2)
Decompensation of pre-existing medical condition	28 (1)	0 (0)	15 (1)	2 (1)	2 (1)
Psychiatric disorder	54 (3)	2 (1)	28 (3)	7 (2)	8 (3)
Pulmonary embolus	24 (1)	0 (0)	14 (1)	5 (1)	4 (2)

(Continues)

TABLE 3 (Continued)

	Total	Underweight	Normal weight	Overweight	Obese
	n (%)	n (%)	n (%)	n (%)	n (%)
Cerebrovascular accident	18 (1)	1 (1)	8 (1)	3 (1)	2 (1)
Amniotic fluid embolus	15 (1)	0 (0)	10 (1)	1 (0)	2 (1)
Other	124(6)	10 (7)	62 (6)	26 (7)	12 (5)
Multiple pathologies	122 (6)	4 (3)	66 (6)	22 (6)	8 (3)

^aPercentage total greater than 100 due to possibility of multiple diagnoses.

^bPercentage of total SMM cases (row percentages); NB: total <2540 due to missing BMI data.

^cPercentage of total SMM cases by BMI category (column percentages).

^dPre-eclampsia, eclampsia, HELLP, placental abruption; possibility of multiple diagnoses.

4 | COMMENT

4.1 | Principal findings

We found that maternal obesity is associated with an increased risk of SMM in the antepartum period primarily due to severe hypertensive disorders, with no increased risk of SMM intrapartum or postpartum. The risk of antepartum SMM due to causes other than severe hypertensive disorders was also increased among obese mothers.

4.2 | Strengths of the study

This study had several strengths. The comprehensiveness and high quality of data in the EPIMOMS cohort and rigorous case ascertainment based on expert consensus allowed for more robust results as compared to the prior mixed and often contradictory data on the association between obesity and SMM. Conducting the investigation in France limited confounding bias related to socio-economic status as the health system allows universal access to care, although potential differences in health outcomes due to income are not entirely eliminated. Finally, the EPIMOMS dataset included exhaustive detailed information regarding participants' pregnancies and allowed for a novel analysis of SMM by clinical timing.

4.3 | Limitations of the data

This study was limited by the moderate prevalence of obesity and morbid obesity in France; thus, the findings may not be generalisable to other high-income countries that have a greater prevalence of obesity. In addition to prepregnancy BMI, adiposity and gestational weight gain may be alternate markers of risk, especially in predicting SMM due to severe hypertensive disorders. The use of a composite SMM outcome may in theory bias the results towards null due to the possibility of a heterogeneity of associations. However, it is useful to have the overall SMM composite outcome for comparability with other studies. Furthermore, we did not examine the most common single causes of SMM separately. Despite the relatively large study size, we were unable to study less common causes of SMM, similar to prior

investigations. Finally, only a limited number of socio-demographic confounders were included in the analysis due to data availability, so the potential for unmeasured confounding on the associations remains.

4.4 | Interpretation

Limited previous data exist examining maternal obesity and SMM. A Dutch case-control study of 4561 low-risk pregnant women found a dose-response relationship between overweight, obesity, and morbid obesity and composite SMM outcome.¹⁵ A population-based cohort of 743 630 women in the United States similarly found a dose-response relationship between elevated BMI and composite SMM.¹⁹ A population register-based study of 292 253 singleton births in Finland also reported an increased risk of composite SMM among obese women.¹⁶ A population-based case-control study of 50 597 births in the United States found only a modest association between obesity and SMM.²³ Conversely, two smaller case-control studies of 1443 and 3400 women in the UK¹⁸ and Australia¹⁷, respectively, found no association between maternal obesity and composite SMM. The previous investigations were limited by varying composite SMM case definitions ascertained by administrative/billing data or incomplete clinical information. Of note, the UK,¹⁸ Australian,¹⁷ and one of the US²³ analyses differed from our study by their inclusion in the multivariable model of intermediate variables on the causal pathway between obesity and SMM. The association between obesity and overall SMM outcome in the current investigation is similar to those of the Dutch and Finnish studies mentioned above (OR 1.4, 95% CI 1.1, 1.9 and OR 1.3, 95% CI 1.2, 1.5, respectively).^{15,16} We did not find a dose-response relationship between progressively elevated BMI categories and overall SMM and most sub-categories of SMM in our sample. The exception was antepartum SMM due to severe hypertensive disorders, where a notable dose-response relationship was observed.

The excess risk among obese women of life-threatening maternal morbidity due to a severe hypertensive complication specifically in the antepartum period, and not simply due to preeclampsia regardless of its severity, is an important finding of the current

TABLE 4 Association between prepregnancy maternal body mass index and severe maternal morbidity (SMM) outcomes

	Underweight (BMI <18.5 kg/m ²)		Overweight (BMI 25.0-29.9 kg/m ²)		Obese (BMI ≥30 kg/m ²)	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a
	Overall SMM	1.05 (0.85, 1.28)	1.10 (0.90, 1.37)	1.03 (0.90, 1.18)	1.02 (0.88, 1.17)	1.42 (1.21, 1.66)
Antepartum SMM	0.81 (0.54, 1.21)	0.84 (0.56, 1.28)	1.10 (0.87, 1.40)	1.10 (0.86, 1.41)	2.20 (1.73, 2.79)	2.07 (1.62, 2.66)
Antepartum SMM due to severe hypertensive disorder	0.66 (0.36, 1.20)	0.70 (0.38, 1.28)	1.34 (1.00, 1.80)	1.38 (1.02, 1.87)	2.56 (1.92, 3.43)	2.50 (1.85, 3.40)
Preeclampsia	0.67 (0.35, 1.29)	0.72 (0.37, 1.38)	1.46 (1.07, 2.00)	1.52 (1.10, 2.10)	2.69 (1.96, 3.69)	2.64 (1.89, 3.68)
HELLP syndrome	0.74 (0.26, 2.08)	0.85 (0.30, 2.43)	1.20 (0.69, 2.10)	1.32 (0.75, 2.34)	1.62 (0.86, 3.07)	1.77 (0.92, 3.42)
Placental abruption	0.41 (0.05, 3.02)	0.40 (0.05, 3.03)	1.15 (0.50, 2.63)	1.05 (0.45, 2.46)	1.52 (0.60, 3.81)	1.21 (0.47, 3.11)
Antepartum SMM not due to severe hypertensive disorder	0.98 (0.58, 1.67)	1.00 (0.59, 1.71)	0.83 (0.57, 1.22)	0.82 (0.56, 1.20)	1.80 (1.26, 2.57)	1.64 (1.13, 2.38)
Intrapartum or postpartum SMM	1.11 (0.89, 1.38)	1.18 (0.94, 1.48)	1.01 (0.87, 1.16)	1.00 (0.86, 1.16)	1.20 (1.01, 1.43)	1.15 (0.96, 1.38)
Intrapartum or postpartum SMM due to postpartum haemorrhage	1.13 (0.90, 1.43)	1.20 (0.95, 1.53)	1.03 (0.89, 1.21)	1.03 (0.88, 1.21)	1.18 (0.98, 1.44)	1.12 (0.92, 1.36)
Intrapartum or postpartum SMM not due to postpartum haemorrhage	0.97 (0.63, 1.50)	1.03 (0.66, 1.61)	0.87 (0.65, 1.17)	0.86 (0.64, 1.17)	1.29 (0.93, 1.78)	1.24 (0.89, 1.74)

^aOdds ratios were adjusted for the confounding effects of maternal age, prepregnancy tobacco use, maternal place of birth, living alone, profession, and parity.

investigation. In addition, our results suggest that among the various types of severe hypertensive complications obese women may be at an increased risk of preeclampsia-related SMM and HELLP syndrome-related SMM but not placental abruption-related SMM. The identification of causes of SMM by timing of occurrence during the pregnancy and delivery has practical clinical implications for prevention possibly via the improvement of antenatal quality of care measures among obese women, such as blood pressure monitoring. Indeed, our investigation provides additional evidence in support of the recommendation to carefully monitor blood pressure in obese women during pregnancy, including proper cuff size selection and placement to avoid inaccurate measurements. This may avoid delay in diagnosis of hypertension or preeclampsia in obese women and decrease the risk of evolution of the severe forms of the disease.

Antepartum SMM also leads to an increased rate of caesarean delivery without a trial of labour, and preterm births with a likely increase in neonatal morbidity. This result provides additional insights into the relationship between SMM and preterm delivery; it illustrates the importance of carefully characterising the timing of SMM when studying this association, in which causality can possibly go both ways.²⁴ We found no association between obesity and severe PPH. Previous results on the association between the association between obesity and PPH have been mixed,^{12,14,19,25} although our results are similar to the recent findings by Lisonkova et al¹⁹ in a large population-based sample.

Secondary findings of this study included an independent association between maternal place of birth with obesity among controls and an association specifically between sub-Saharan African maternal place of birth and SMM in the adjusted multivariable analyses, suggesting a socio-demographic component of the pathogenesis of maternal morbidity. These findings are consistent with prior investigations linking SMM risk with maternal origin, race, or ethnicity: sub-Saharan African migrant women have previously been found to have a higher risk of maternal mortality²⁶ and SMM²⁷ in European countries, and in the United States, black and Latina women have disproportionately higher rates of SMM as compared to white women.²⁸⁻³⁰ Previous studies suggest that access and quality of care issues may be implicated in SMM among individuals with known social risk factors.^{31,32}

5 | CONCLUSIONS

Severe maternal morbidity and mortality constitute a notable burden of disease and both are increasing in some developed countries.³³ Identifying modifiable risk factors is therefore necessary. These findings underscore the importance of reducing obesity among women of reproductive age and improving the quality of prenatal care and blood pressure monitoring among obese women. Future investigations should examine the relationship between obesity and other risk factors, such as maternal place of birth, and SMM.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX

EPIMOMS study group members

For the Naitre en Alsace perinatal network: Bruno Langer; For the Rhône-Alpes Aurore perinatal network: Corinne Dupont, René-Charles Rudigoz; For the Auvergne perinatal network: Françoise Vendittelli; For the Basse-Normandie perinatal network: Gaël Beucher; For the MYPA perinatal region, Ile de France region: Patrick Rozenberg; For the Naitre dans l'Est Francilien network, Ile de France region: Lionel Carbillon; For the Paris Nord perinatal network: Elie Azria, Nathalie Baunot; For the 92 Nord perinatal network, Ile de France region: Catherine Crenn-Hebert, Gilles Kayem; For the Lorraine perinatal network: Jeanne Fresson; For the Société Française d'Anesthésie Réanimation (SFAR): Alexandre Mignon; For the Santé Publique pole, Hospices Civils de Lyon: Sandrine Touzet; For the Inserm Epopé research team: Marie-Pierre Bonnet, Marie-Hélène Bouvier-Colle, Anne Alice Chantry, Coralie Chiesa-Dubruille, Catherine Deneux-Tharaux, Aurélien Seco.

Supplemental table 1: Characteristics of controls by BMI category*

	Underweight n(%)	Normal weight n(%)	Overweight n(%)	Obese n(%)
	261 (7)	2,137 (61)	724 (21)	395 (11)
Socio-demographic information				
Age (years) ***	29.9(±)5.7	30.4(±)5.1	30.7(±)5.2	31.2(±)5.4
Place of birth				
France	172 (8)	1408 (62)	418 (19)	262 (12)
Europe	9 (9)	66 (64)	22 (21)	6 (6)
North Africa	19 (6)	151 (50)	89 (30)	43 (14)
Sub-Saharan Africa	9 (6)	91 (60)	34 (22)	18 (12)
Other	8 (6)	90 (63)	30 (21)	16 (11)
Living alone	9 (7)	73 (60)	22 (18)	19 (16)
Profession				
Manual or service workers	10 (6)	80 (47)	48 (28)	31 (18)
Self-employed	5 (6)	45 (57)	16 (20)	13 (17)
Public service, administrative, or sales workers	53 (6)	513 (61)	171 (20)	111 (13)
Intermediate	39 (7)	396 (66)	109 (18)	53 (9)
Professional	50 (8)	464 (70)	108 (16)	41 (6)
Unemployed	76 (10)	416 (54)	181 (23)	102 (13)
Medical history				
Tobacco use	75 (10)	460 (61)	129 (17)	92 (12)
Chronic hypertension	1 (4)	9 (31)	8 (28)	11 (38)
Pre-existing diabetes	1 (4)	3 (13)	8 (35)	11 (48)
Any other notable pre-existing medical condition†	18 (8)	130 (58)	47 (21)	29 (13)
Obstetric history				
Parity by delivery type				
Primiparous	113 (8)	968 (66)	261 (18)	137 (9)
Multiparous without prior cesarean delivery	118 (8)	937 (60)	353 (22)	168 (11)
Multiparous with prior cesarean delivery	26 (6)	210 (50)	101 (24)	80 (19)

If parous

Prior cesarean delivery	26 (6)	210 (50)	101 (24)	80 (19)
Prior hypertensive disease of pregnancy††	6 (7)	38 (42)	22 (24)	24 (27)
Prior postpartum hemorrhage	7 (9)	44 (55)	19 (24)	10 (13)
Current pregnancy				
IVF‡	5 (7)	40 (55)	20 (27)	8 (11)
Multiple gestation	3 (5)	35 (63)	13 (23)	5 (9)
Hypertensive disorders of pregnancy				
None	258 (8)	2,084 (61)	694 (20)	365 (11)
Gestational hypertension	1 (2)	26 (43)	14 (23)	20 (33)
Preeclampsia	2 (4)	27 (49)	16 (29)	10 (18)
Gestational diabetes	11 (4)	111 (42)	71 (27)	74 (28)
Anomalies of placental insertion‡‡	3 (13)	16 (70)	3 (13)	1 (4)
Hospitalized antepartum	41 (7)	327 (58)	112 (20)	81 (14)
Delivery				
Gestational age (weeks) ***	38.6(±)1.9	38.9(±)2.0	38.8(±)2.3	39.1(±)2.0
Gestational age				
<28 weeks	0 (0)	12 (52)	8 (35)	3 (13)
28 to <32 weeks	5 (16)	19 (61)	6 (19)	1 (3)
32 to <37 weeks	17 (9)	117 (61)	39 (20)	19 (10)
>37 weeks	239 (7)	1,988 (61)	670 (21)	372 (11)
Noncephalic presentation	11 (7)	114 (68)	28 (17)	15 (9)
Labor onset				
Spontaneous	204 (8)	1587 (62)	509 (20)	256 (10)
Induced	57 (6)	549 (57)	215 (22)	139 (15)
Mode of delivery				
Vaginal	189 (8)	1453 (62)	477 (20)	244 (10)
Vaginal instrumental	33 (8)	293 (67)	78 (18)	36 (8)
Cesarean delivery with trial of labor	14 (4)	184 (53)	87 (25)	62 (18)
Cesarean delivery without trial of labor	25 (7)	206 (56)	82 (22)	53 (15)
Cesarean delivery	39 (6)	390 (55)	169 (24)	115 (16)

Newborn

Stillbirths and neonatal deaths	1 (4)	16 (57)	10 (36)	1 (4)
Birth weight (g) ^{***}	3,081(±)516	3,245(±)553	3,347(±)598	3,403(±)589

Delivery facility characteristics

Type

Public teaching hospital	81 (8)	666 (62)	199 (19)	124 (12)
Public non-teaching hospital	121 (8)	923 (59)	332 (21)	185 (12)
Private hospital	59 (7)	548 (62)	193 (22)	86 (10)

Level

1	73 (8)	542 (61)	176 (20)	93 (11)
2	122 (7)	1106 (61)	388 (21)	194 (11)
3	66 (8)	489 (59)	160 (19)	108 (13)

Delivery volume (deliveries per year)

<1500	92 (8)	700 (60)	250 (21)	131 (11)
1500-1999	22 (7)	218 (65)	66 (20)	30 (9)
2000-2999	89 (7)	761 (61)	253 (20)	140 (11)
>=3000	58 (8)	458 (60)	155 (20)	94 (12)

*Underweight = BMI <18.5kg/m²; Normal weight = BMI 18.5-24.9kg/m²; Overweight = BMI 25-29.9kg/m²; Obese = BMI > =30kg/m²

**Chi-squared test of independence, Fisher's exact test, or ANOVA

*** Mean +/- standard deviation

†Hematologic disease or hemoglobinopathy, psychiatric illness, history of venous thromboembolism, coronary artery disease, cardiomyopathy, congestive heart failure, epilepsy, multiple sclerosis, liver disease including infectious hepatitis, auto-immune disease, inflammatory bowel disease, nephropathy, history of hemodialysis, pulmonary disease, myasthenia gravis, neoplasia, HIV, & any other chronic medical condition

††Gestational hypertension, preeclampsia, eclampsia, or HELLP syndrome (hemolysis, abnormal liver function tests, and thrombocytopenia)

‡In vitro fertilization

‡‡Placenta previa, placenta accrete

Supplemental table 2: Gestational age at delivery and onset of labor among controls and cases by severe maternal morbidity (SMM) timing

	Antepartum SMM	Intra/postpartum SMM	Controls
	N= 601	N= 1,936	N= 3,651
	n(%)	n(%)	n(%)
Gestational age at delivery (weeks)			
<28	84 (15)	21 (1)	26 (1)
28 to <32	238 (41)	74 (4)	35 (1)
32 to <37	98 (17)	249 (13)	205 (6)
>=37	157 (27)	1,563 (82)	3,382 (93)
Onset of labor			
Spontaneous	87 (15)	962 (50)	2,649 (73)
Induced	92 (16)	461 (24)	614 (17)
Cesarean delivery without a trial of labor	399 (69)	496 (26)	386 (11)

*Chi-squared test of independence

Supplemental table 3: Association between body mass index and severe maternal morbidity (SMM) outcomes – results for all co-variables*

	Overall SMM	Antepartum SMM	Antepartum severe hypertensive disorders	Antepartum SMM not including severe hypertensive disorders	Intrapartum /Postpartum SMM	Postpartum hemorrhage	Intrapartum/postpartum SMM not including postpartum hemorrhage
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Body mass index (ref=Normal weight)							
Underweight	1.10 (0.90,1.37)	0.84 (0.56,1.28)	0.70 (0.38,1.28)	1.00 (0.59,0.71)	1.18 (0.94,1.48)	1.20 (0.95,1.53)	1.03 (0.66, 1.61)
Overweight	1.02 (0.88,1.17)	1.10 (0.86,1.41)	1.38 (1.02,1.87)	0.82 (0.56,1.21)	1.00 (0.86,1.16)	1.03 (0.88,1.21)	0.86 (0.64, 1.17)
Obese	1.34 (1.14,1.58)	2.07 (1.62,2.66)	2.50 (1.85,3.40)	1.64 (1.13,2.38)	1.15 (0.96,1.38)	1.12 (0.92,1.36)	1.24 (0.89,1.74)
Co-variables							
Age	1.04 (1.03,1.05)	1.06 (1.04,1.08)	1.05 (1.03,1.08)	1.07 (1.04,1.09)	1.03 (1.02,1.05)	1.03 (1.02,1.05)	1.04 (1.01,1.06)
Smoking	0.93 (0.81,1.06)	1.28 (1.02,1.60)	1.18 (0.88,1.57)	1.38 (1.00,1.88)	0.83 (0.72,0.97)	0.82 (0.70, 0.96)	0.87 (0.66,1.16)
Maternal place of birth (ref= France)							
Europe	0.99 (0.72,1.38)	0.98 (0.55,1.76)	0.82 (0.38,1.80)	1.21 (0.55,2.69)	1.01 (0.71,1.44)	1.06 (0.74,1.53)	0.83 (0.36, 1.93)
North Africa	1.06 (0.87,1.29)	1.22 (0.88,1.68)	0.98 (0.63,1.53)	1.51 (0.97, .33)	1.01 (0.82,1.26)	0.98 (0.78,1.24)	1.19 (0.79, 1.78)
Sub Saharan Africa	1.95 (1.56,2.43)	2.69 (1.92,3.77)	3.23 (2.16,4.81)	2.03 (1.21,3.40)	1.74 (1.37,2.21)	1.76 (1.37,2.27)	1.73 (1.11,2.68)
Other	1.40 (1.10,1.80)	1.24 (0.79,1.95)	1.59 (0.96,2.62)	0.81 (0.36,1.83)	1.43 (1.10,1.86)	1.30 (0.98,1.73)	1.82 (1.16,2.84)
Living alone	1.42 (1.11,1.83)	1.39 (0.93,2.07)	1.11 (0.66,1.86)	1.79 (1.04,3.06)	1.41 (1.08,1.85)	1.36 (1.01,1.81)	1.67 (1.05,2.66)
Profession(ref=Professional)							
Manual or service workers	1.25 (0.97,1.63)	1.19 (0.75,1.90)	1.37 (0.77,2.43)	0.92 (0.41,2.08)	1.28 (0.97,1.69)	1.21 (0.89, 1.63)	1.53 (0.92,2.56)
Self-employed	0.97 (0.66,1.43)	1.06 (0.54,2.11)	1.19 (0.53,2.64)	0.88 (0.27,2.91)	0.95 (0.62,1.44)	0.91 (0.58,1.43)	1.18 (0.55,2.54)
Public service, administrative, or sales workers	1.41 (1.20,1.66)	1.84 (1.38,2.45)	1.82 (2.16,2.62)	1.87 (0.22,2.87)	1.31 (1.09,1.56)	1.28 (1.06, 1.54)	1.39 (0.98,1.98)
Intermediates	1.19 (1.00,1.42)	1.38 (0.99,1.91)	1.21 (0.79,1.84)	1.62 (1.00,2.61)	1.15 (0.96,1.39)	1.09 (0.90,1.34)	1.37 (0.94,1.97)
Unemployed	1.13 (0.94,1.36)	1.38 (0.99,1.92)	1.24 (0.81,1.88)	1.65 (0.98,2.58)	1.06 (0.87,1.30)	1.03 (0.84,1.28)	1.18 (0.78,1.77)
Parity by delivery type (ref =Multiparous without prior cesarean)							
Primiparous	1.85 (1.58,2.17)	1.42 (1.07, 1.89)	1.63 (1.12,2.37)	1.21 (0.81,1.82)	1.96 (1.65,2.32)	1.92 (1.61, 2.31)	1.97 (1.41,2.75)
Multiparous with prior cesarean delivery	1.95 (1.73,2.21)	2.18 (1.76, 2.70)	2.97 (2.24,3.94)	1.49 (1.10,2.02)	1.87 (1.64,2.14)	1.77 (1.54,2.05)	2.37 (1.83,3.07)

**Number of women included in the final models: Overall SMM: cases= 2,540 controls= 3,651; Antepartum SMM: cases = 598 controls = 3,651; Antepartum SMM due to hypertensive disease: cases = 339 controls = 3,651; Antepartum SMM not due to hypertensive disease: cases = 259 controls = 3,651; Intrapartum or postpartum SMM: cases = 1,939 controls = 3,651; Intrapartum or postpartum SMM due to postpartum hemorrhage: cases = 1,577 controls = 3,651*

5.2 Obesity, a potential mediator of the increased risk of severe preeclampsia among immigrant women in France: results from the PreCARE cohort study

5.2.1 Summary

Severe preeclampsia, a disorder of pregnancy characterized by hypertension, proteinuria, and organ dysfunction, is one of the leading causes of maternal and neonatal mortality and severe morbidity in high-income countries. The prevalence of preeclampsia has been declining in some European countries and Australia but continues to rise in the United States, driven specifically by increasing rates of severe disease. Known social and medical factors associated with an increased risk of developing severe preeclampsia include maternal origin (i.e. immigrant women and minority racial/ethnic groups in Europe and Black and Latina mothers in the United States), and obesity. The findings of the EPIMOMS study described above also suggested a strong association between Sub-Saharan maternal place of birth and antepartum severe hypertensive disease. Notably, maternal obesity rates are increasing globally, and immigrant and minority women have disproportionately higher rates of prepregnancy obesity, suggesting that several risk factors for preeclampsia often co-exist in the same population. However, the precise role of obesity, a modifiable target for disease prevention and treatment, has not previously been well elucidated on the causal pathway. We investigated the extent to which prepregnancy obesity mediates the association between maternal place of birth and severe preeclampsia in the PreCARE cohort of pregnant women in Paris, France (n=9,579). Adjusted path analysis logistic regression models were used to assess the role of prepregnancy obesity as a mediator in the association between maternal place of birth and the development of

severe preeclampsia. Adjusted odds ratios and 95% confidence intervals for the total exposure-outcome association and for the direct and indirect/obesity-mediated components and the indirect/obesity-mediated effect were calculated. Ninety-five (0.99%) women developed severe preeclampsia, 47.6% were non-European immigrants, 16.3% were born in Sub-Saharan Africa, and 12.6% were obese (BMI \geq 30kg/m²). Women experiencing severe preeclampsia were more likely to be from Sub-Saharan Africa (p=0.023) and be obese (p=0.048). Mothers from Sub-Saharan Africa had an increased risk of severe preeclampsia compared to European-born mothers (aOR 2.53, 95% CI 1.39-4.58) and the obesity-mediated indirect effect was 18% of the total risk (aOR 1.18, 95%CI 1.03-1.35). Sub-Saharan African immigrant women have a two-fold higher risk of developing severe preeclampsia as compared to European-born women, one-fifth of which is mediated by prepregnancy obesity. Our results quantify the potential benefit of decreasing obesity among at-risk women.

5.2.2 Article as published

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Maternal obesity and severe pre-eclampsia among immigrant women: a mediation analysis

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We investigated the extent to which pre-pregnancy obesity mediates the association between maternal place of birth and severe pre-eclampsia in the PreCARE cohort of pregnant women in Paris ($n = 9,579$). Adjusted path analysis logistic regression models were used to assess the role of pre-pregnancy obesity as a mediator in the association between maternal place of birth and the development of severe pre-eclampsia. We calculated 1. adjusted odds ratios and 95% confidence intervals for the total exposure-outcome association and for the direct and indirect/obesity-mediated components 2. the indirect/obesity-mediated effect. Ninety-five (0.99%) women developed severe pre-eclampsia, 47.6% were non-European immigrants, 16.3% were born in Sub-Saharan Africa, and 12.6% were obese ($BMI \geq 30 \text{ kg/m}^2$). Women experiencing severe pre-eclampsia were more likely to be from Sub-Saharan Africa ($p = 0.023$) and be obese ($p = 0.048$). Mothers from Sub-Saharan Africa had an increased risk of severe pre-eclampsia compared to European-born mothers (aOR 2.53, 95% CI 1.39–4.58) and the obesity-mediated indirect effect was 18% of the total risk (aOR 1.18, 95% CI 1.03–1.35). In conclusion, Sub-Saharan African immigrant women have a two-fold higher risk of developing severe pre-eclampsia as compared to European-born women, one-fifth of which is mediated by pre-pregnancy obesity. Our results quantify the potential benefit of decreasing obesity among at-risk women.

Pre-eclampsia, a disorder of pregnancy characterized by hypertension and proteinuria, affects 3–5% of pregnancies globally^{1–3} and is one of the leading causes of maternal and neonatal mortality and morbidity in developed countries^{2,4–7}. Severe pre-eclampsia is characterized by higher blood pressures and more profound organ dysfunction than mild pre-eclampsia⁸ and constitutes the largest attributable fraction of severe morbidity due to hypertensive disorders in pregnancy⁵. Overall, the prevalence of pre-eclampsia has been declining in some European countries and Australia but continues to rise in the United States^{5,9,10}. The increase in pre-eclampsia in the United States is driven specifically by higher rates of severe disease: while mild pre-eclampsia declined between 1980 and 2010, from 3.1% to 2.5%, severe pre-eclampsia increased from 0.3% to 1.4%¹¹.

There are known social and medical factors associated with a differential risk of developing pre-eclampsia. Maternal origin has been linked to disparities in rates of pre-eclampsia in various settings. In Europe, immigrant

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women from Sub-Saharan Africa, Latin America, and the Caribbean have a higher risk of pre-eclampsia^{12–14} as have women from minority racial (Black) or ethnic (African and Turkish) groups^{15,16}. In the United States, Black and Latina mothers suffer from disproportionately higher rates of pre-eclampsia as compared to white mothers^{17–20}. Obesity has also been shown to be associated with an increased risk of severe pre-eclampsia²¹. Maternal obesity rates increased from 6.0% to 11.8% between 1998–2016 in France and from 17.6% to 20.5% in the USA between 2003–2009, with evidence of accelerating incidence^{22–24}. Of note, immigrant and minority women have disproportionately increased rates of pre-pregnancy obesity^{23,25}, suggesting that several risk factors for pre-eclampsia often co-exist.

The aforementioned evidence demonstrates strong associations between maternal origin, obesity, and disparities in the development of pre-eclampsia in pregnancy. However the relationship between these risk factors and the development of severe, life-threatening pre-eclampsia is less well established. Furthermore the precise role of obesity, a modifiable target for disease prevention and treatment, has not been well elucidated on the causal pathway²⁶. We hypothesized that obesity may be a mediator in the relationship between maternal origin and the occurrence of severe life-threatening pre-eclampsia. The objective of the current investigation was to test for and quantify this mediation effect.

Methods

Sample. The PreCARE multicenter cohort study was designed to evaluate the association between social deprivation and perinatal outcomes and to investigate the mechanisms of social health inequalities²⁷. All women registered to deliver or who delivered at one of the four participating university hospitals in Paris between October 2010–November 2011 were eligible for study inclusion (n = 10,419). The study was conducted in predominantly immigrant, low-income neighborhoods of Paris. Informed consent was obtained orally at the time of study enrollment and prior to data collection, in accordance with French law. The study was approved by the *Comité de Protection des Personnes*, (CPP Ile de France III, No. 09.341bis), and the *Commission Nationale de l'Informatique et des Libertés* (CNIL), the national French data protection agency on 19 November 2009. All methods were performed in accordance with the relevant guidelines and regulations. Women younger than age 18 (n = 54), not pregnant (n = 1), who had a termination of pregnancy before 20 weeks gestational age (n = 106), delivered elsewhere (n = 210), were lost to study follow up (n = 408), had missing study questionnaire responses (n = 26), missing provider questionnaires (n = 29), or withdrew consent at any time (n = 6) were excluded from the final study sample (n = 9579, 92% of original sample).

Study procedures. Study participants completed a self-administered questionnaire at enrollment and included detailed information regarding their medical antenatal care, psychological and social work consultations, housing and living arrangements, sources of income, public assistance, health insurance type, nationality and, if not a citizen of the European Union, legal status in France. A second similar questionnaire was completed in the postpartum period during the obstetric hospitalization and included additional questions regarding prenatal care utilization. Research assistants and interpreters were available for those who needed assistance with completing the questionnaires or non-French speakers. Questionnaires were also available in the three most common languages among non-French speakers (English, Chinese, and Romanian). Details regarding participants' medical history, current pregnancy, and obstetric hospitalization were collected via medical chart review prospectively by research assistants and medical providers (obstetricians and midwives). Providers also completed detailed questionnaires regarding participants' delivery and postpartum course.

The binary outcome of severe pre-eclampsia was defined as having pre-eclampsia and one or more of the following: a systolic blood pressure >160 mmHg or diastolic blood pressure >110 mmHg, proteinuria >3.5 g/24 h, serum creatinine >100 μmol/l, urine output <20 ml/h, hemolysis, liver transaminitis >3 times upper limit of normal, thrombocytopenia <100 000/mm³, or gestational age <32 weeks at onset of disease. The definition of severe pre-eclampsia used in the current investigation is based on the French guidelines at the time of study protocol preparation²⁸. The exposure of interest in the current analysis was maternal place of birth coded in four categories: France and Europe, North Africa, Sub-Saharan Africa, and other. Pre-pregnancy BMI was abstracted from the medical chart and was calculated by self-reported height and weight at the first prenatal visit. Pre-pregnancy body mass index (BMI) was the mediating factor in the analysis and was coded according to standard clinical categories: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5–24.9 kg/m²), overweight (BMI 25–29.9 kg/m²), and obese (BMI ≥ 30 kg/m²).

Potential confounding variables were either for the causal effect of the exposure on the outcome or of the mediator on the outcome²⁹ and did not include intermediate factors³⁰.

Confounding factors considered were: maternal age as a continuous variable, parity as a binary variable (primiparous or multiparous), and a constructed composite maternal social deprivation variable which was defined as per a previously-validated index and included meeting any one of the following four criteria: being socially isolated, living in poor housing conditions, having no work-related household income, or having no standard health insurance²⁷. Prenatal care utilization and chronic hypertension were not included as confounders in the primary analysis as they are potential mediators in the causal pathway between maternal place of birth and severe pre-eclampsia.

Statistical analysis. Demographic, social, and medical characteristics of participants were described and differences between women who did and did not experience severe pre-eclampsia ascertained using chi-squared tests of independence or Fisher's exact tests for categorical variables, and two sample t-tests or ANOVA for continuous variables (p < 0.05). Since there was no association between being overweight and developing severe pre-eclampsia in our sample, we did not include overweight women in our mediation analysis. Furthermore, as our aim was to isolate the effect of obesity as compared to normal weight, the path analysis was conducted

on a sub-group of the entire study sample which consisted of women who were either normal weight or obese ($n = 6476$)³¹ (31). A path analysis multivariable logistic regression model was used to decompose the total effect of maternal place of birth on severe pre-eclampsia into an indirect effect, that mediated by obesity as compared to a reference with normal weight, and a residual, so called direct, effect not mediated by obesity^{31,32}. The path analysis model conceptualized a counterfactual approach which may theoretically be formulated as the response to the following question: “What would be the risk of severe pre-eclampsia associated with foreign maternal place of birth if foreign-born women had the same probability of being obese as women born in Europe?”. Two estimates of the direct and indirect effects can be made, either based on the answer to the counterfactual question above or on another possible question: “What would be the risk of severe pre-eclampsia associated with foreign maternal place of birth if European-born women had the same probability of being obese as immigrant-born women?”. The two estimates are usually very similar, and if so the direct and indirect (i.e. obesity-mediated) estimates corresponding to the first counterfactual question are reported. The indirect obesity-mediated effect of maternal place of birth on the risk of severe pre-eclampsia was calculated from the regression coefficients obtained via adjusted logistic regression models and was expressed as a percentage of the total effect.

Two sensitivity analyses were performed. The first revised the path analysis mediation model to include an additional adjustment for prenatal care utilization during the pregnancy which was coded in two categories (prenatal care visits as a proportion of what is routinely recommended by gestational age at delivery either $<50\%$ or $\geq 50\%$ ^{33,34}). We conducted this sensitivity analysis to ascertain if treating prenatal care utilization as a confounder as opposed to an intermediate variable changed the obesity-mediated association between maternal place of birth and severe pre-eclampsia significantly. Given legal limitations on the routine collection of data regarding race in France, an additional sensitivity analysis was performed to account for potential differences between maternal place of birth and self-reported ethnic origin by using the latter as the exposure of interest in the path analysis mediation model.

All analyses were performed using Stata, V.14.0 SE (Stata Corporation, College Station, Texas, USA) and add-on models developed by Buis³¹.

Results

Ninety-five out of 9579 women (0.99%) in our sample experienced severe pre-eclampsia during the course of their pregnancies. Differences in the socio-demographic characteristics, medical history, current pregnancy, and delivery characteristics of participants with and without severe preeclampsia are presented in Tables 1 and 2. Mothers experiencing severe pre-eclampsia were more likely to be immigrants from Sub-Saharan Africa, be obese, not be living with the father of the child, suffer from overall social deprivation, have chronic hypertension, and be primiparous ($p < 0.05$). They were also more likely to have had less than 50% of recommended antenatal consultations, conceived via assisted reproductive technologies, have a multiple gestation, be diagnosed with a high risk pregnancy³³, deliver preterm, and have a cesarean delivery ($p < 0.05$). Fetal deaths were higher among participants who developed severe pre-eclampsia ($p < 0.05$). Neonates born to mothers with severe pre-eclampsia were more likely to have low birth weight ($p < 0.05$). Selected characteristics of participants by maternal place of birth are described in Table 3. The prevalence of obesity differed significantly by maternal place of birth and was the highest in women born in Sub-Saharan Africa (Table 3).

There was no association between being overweight and developing severe pre-eclampsia (OR 1.33 95%CI 0.79–2.25), therefore we limited our path analysis to obese versus normal weight women only. The results of the logistic regression multivariable mediation models are presented in Table 4. Immigrant women from Sub-Saharan Africa had a higher risk of developing severe pre-eclampsia in the main analysis, total aOR 2.53, 95%CI 1.39–4.58. In the path analysis, the direct residual effect of this association was aOR 2.14, 95%CI 1.15–3.99 and the indirect effect, i.e. that mediated by obesity, was aOR 1.18, 95%CI 1.03–1.35, which corresponds to an 18% indirect obesity-mediated effect (Fig. 1).

The results of the sensitivity analyses examining the effect of including prenatal care utilization as a control variable found a similar 18% indirect obesity-mediated (Supplementary Table 1). The findings of the sensitivity analysis examining the obesity-mediated effect of self-reported maternal origin, as opposed to maternal place of birth, on severe preeclampsia were similar to that of the principal investigation (Supplementary Table 2).

Discussion

Main findings. We found that women born in Sub-Saharan Africa had more than twice the risk of developing severe pre-eclampsia as compared to women born in Europe. Most notably our results suggest that almost one-fifth of this elevated risk is mediated by pre-pregnancy obesity, while accounting for potential confounders. The latter is a novel finding that provides important insights to the mechanisms by which disparities in the risk of severe life-threatening hypertensive disorders among pregnant women operate along social determinants and offers a target for prevention and treatment, i.e. maternal obesity.

Interpretation. The findings of the current investigation are consistent with previous evidence that immigrant women in Europe from Sub-Saharan Africa or those of African ethnicity have an increased risk of developing severe pre-eclampsia^{13,16}. To our knowledge, there are no prior studies evaluating the role of obesity as a mediator in the relationship between maternal origin and severe pre-eclampsia. Snowden *et al.* examined the independent and joint effects of maternal obesity and race/ethnicity on various perinatal outcomes including pre-eclampsia generally in a large retrospective cohort of all births in California in 2007 ($N = 385,407$)³⁵. Their analysis differed critically from the present study in several ways. The exposure was maternal race, a social construct for which the implications are likely different than maternal place of birth. The outcome was not restricted to severe pre-eclampsia. Furthermore, they used a different statistical approach. Nonetheless we believe it still provides a potential comparison when attempting to understand the relationships between maternal origin,

	All participants N = 9579	Did not experience severe preeclampsia n = 9484 (99.01%)	Experienced severe preeclampsia* n = 95 (0.99%)	p**
Socio-demographic information				
Age (years)	30.8 ± 5.4	30.8 ± 5.4	31.3 ± 5.1	0.343
Maternal place of birth (n,%)				0.023
France + Europe	4979 (52.4%)	4933 (52.5%)	46 (48.9%)	
North Africa	2106 (22.2%)	2093 (22.3%)	13 (13.8%)	
Sub-Saharan Africa	1558 (16.4%)	1533 (16.3%)	25 (26.6%)	
Other	855 (9.0%)	845 (9.0%)	10 (10.6%)	
Length of stay in France				0.256
< 1 year or not living in France	660 (7.5%)	657 (7.6%)	3 (3.4%)	
>= 1 year	3889 (44.2%)	3845 (44.1%)	44 (50.0%)	
Living in France since birth	4259 (48.4%)	4218 (48.4%)	41 (46.6%)	
Language barrier (n, %)				0.836
Yes - total	192 (2.1%)	191 (2.1%)	1 (1.1%)	
Yes - partial	812 (8.7%)	803 (8.7%)	9 (9.9%)	
No	8304 (89.2%)	8,233 (89.2%)	81 (89.0%)	
Living with father of child (n, %)				<0.001
Yes	8129 (85.3%)	8060 (85.4%)	69 (72.6%)	
No	1405 (14.7%)	1379 (14.6%)	26 (27.4%)	
Education (n, %)				0.226
High school diploma	4698 (49.6%)	4645 (49.6%)	53 (55.8%)	
Beyond high school diploma	4772 (50.4%)	4730 (50.5%)	42 (44.2%)	
Overall social deprivation*** (n, %)	3211 (33.6%)	3170 (33.5%)	41 (43.2%)	0.047
Medical history				
Prepregnancy BMI (n, %)				
(collapsed all obese categories)				0.048
Normal weight (BMI 18.5–24.9 kg/m ²)	5380 (59.2%)	5338 (59.3%)	42 (47.2%)	
Underweight (BMI < 18.5 kg/m ²)	534 (5.9%)	526 (5.9%)	8 (9.0%)	
Overweight (BMI 25–29.9 kg/m ²)	2027 (22.3%)	2006 (22.3%)	21 (23.6%)	
Obese (BMI ≥ 30 kg/m ²)	1145 (12.6%)	1127 (12.5%)	18 (20.2%)	
Tobacco use (n, %)	1626 (17.1%)	1612 (17.2%)	14 (14.7%)	0.533
Chronic hypertension (n, %)	152 (1.6%)	140 (1.5%)	12 (12.6%)	<0.001
Obstetric history				
Parity (n, %)				<0.001
Primiparous	4103 (42.9%)	4042 (42.7%)	61 (64.2%)	
Multiparous	5467 (57.1%)	5433 (57.3%)	34 (35.8%)	
<i>Among multiparous participants</i>				
Prior cesarean delivery (n, %)	1179 (12.3%)	1169 (21.5%)	10 (29.4%)	0.593
Prior preeclampsia (n, %)	104 (1.1%)	101 (1.9%)	3 (8.8%)	0.084

Table 1. Socio-demographic characteristics and medical history of participants with and without severe preeclampsia. *Defined as having pre-eclampsia and one or more of the following: a systolic blood pressure >160 mmHg or diastolic blood pressure >110 mmHg, proteinuria >3.5 g/24 h, serum creatinine >100 μmol/l, urine output <20 ml/h, hemolysis, liver transaminitis >3 times upper limit of normal, thrombocytopenia <100 000/mm³, or gestational age <32 weeks. **Chi-squared test of independence or Fisher's exact test for categorical variables, t-test for continuous variables. ***Any of the following: (1) socially isolated (2) poor housing conditions (3) no work-related household income (4) no standard health insurance.

obesity, and pre-eclampsia – particularly in the absence of more congruous prior studies. In the aforementioned investigation, compared with white women, African American women had a higher risk of pre-eclampsia (aOR 1.60, 95%CI 1.48–1.74), as did obese African American women compared to obese white women (aOR 1.45, 95%CI 1.24–1.70). Our findings are broadly consistent with these results. Of interest however, they found an attenuated risk associated with increasing weight, suggesting that BMI is not the only driver of the association between maternal race and pre-eclampsia. The 18% mediation effect of obesity in our study suggests a possibly congruent finding, while additionally quantifying the effect and providing an estimate of what potential reduction in rates of severe pre-eclampsia may be expected by targeting maternal obesity. Since obesity only explains a minor, although important, part of the association between Sub-Saharan place of birth and severe pre-eclampsia, our results also indicate that other factors may be mediating this relationship given the magnitude of the direct effect (82%) which is in fact residual and unexplained. One such candidate mediator may be differential quality of

	All participants N = 9579	Did not experience severe preeclampsia n = 9484 (99.01%)	Experienced severe preeclampsia* n = 95 (0.99%)	p**
Current pregnancy				
Recommended prenatal consultations (% of recommended) [†]				0.008
<50%	273 (2.9%)	266 (2.8%)	7 (7.4%)	
>50%	9271 (97.1%)	9183 (97.2%)	88 (92.6%)	
High risk pregnancy [†]	1867 (19.6%)	1837 (19.5%)	30 (31.9%)	0.002
ART (n, %)	373 (3.9%)	362 (3.8%)	11 (11.6%)	<0.001
Multiple gestation (n, %)	296 (3.1%)	286 (3.0%)	10 (10.5%)	<0.001
Gestational diabetes (n, %)	1006 (10.6%)	993 (10.6%)	13 (13.8%)	0.308
Delivery				
Gestational age (n, %)				<0.001
<28 weeks	95 (1.0%)	86 (0.9%)	9 (9.5%)	
28–37 weeks	1351 (14.1%)	1294 (13.6%)	57 (60.0%)	
>37 weeks	8133 (84.9%)	8104 (85.5%)	29 (30.5%)	
Mode of delivery (n, %)				<0.001
Vaginal birth	7531 (79.7%)	7493 (80.2%)	38 (40.0%)	
Cesarean delivery - without trial of labor	819 (8.7%)	780 (8.3%)	39 (41.1%)	
Cesarean delivery - after trial of labor	1094 (11.6%)	1076 (11.5%)	18 (19.0%)	
Maternal death	0(0.0%)			n/a
Newborn				
Fetal death	79 (0.8%)	72 (0.8%)	7 (7.4%)	<0.001
Intra-uterine demise + stillbirth	49 (0.5%)	48 (0.5%)	1 (1.1%)	0.388
Induced abortion	30 (0.3%)	24 (0.3%)	6 (6.3%)	<0.001
Birth weight (g)				
Birth weight <10th percentile	889 (9.4%)	866 (9.2%)	23 (26.7%)	<0.001
Birth weight <3rd percentile	343 (3.6%)	332 (3.5%)	11 (12.8%)	<0.001
Neonatal death (n, %)	15 (0.2%)	14 (0.2%)	1 (1.1%)	0.133

Table 2. Current pregnancy and delivery characteristics of participants with and without severe preeclampsia. *Defined as having pre-eclampsia and one or more of the following: a systolic blood pressure >160 mmHg or diastolic blood pressure >110 mmHg, proteinuria >3.5 g/24 h, serum creatinine >100 µmol/l, urine output <20 ml/h, hemolysis, liver transaminitis >3 times upper limit of normal, thrombocytopenia <100 000/mm³, or gestational age <32 weeks. **Chi-squared test of independence or Fisher's exact test for categorical variables, t-test for continuous variables. [†]As per the French Haute Autorité de Santé recommendations, 2016.

care for ethnic minorities or immigrants. Indeed, data show that immigrants from Sub-Saharan Africa in France have been shown to have non-medically justifiable delays in prenatal follow up and diagnosis of pre-eclampsia³⁶ and in the United States, differential quality of care for African American mothers who go on to develop severe morbid pregnancy outcomes has been well-documented^{37,38}. Our findings therefore indicate the need not only to reduce pre-pregnancy obesity via pre-conception care, nutrition, exercise, knowledge and access, but also to improve our understanding of other modifiable drivers of severe pre-eclampsia among at-risk minority or immigrant women regardless of their BMI.

Strengths and limitations. Our investigation had several strengths including the prospective study design and a large prevalence of non-European immigrant participants (47.6%), which allowed us to better examine health outcomes in this important subgroup of pregnant women. The high retention rate of 92% and low loss to follow up of the final analyzed sample was a significant strength of this study which limited selection bias in this social cohort study. The dataset included an exhaustive list of social variables from the participant questionnaires, most of which are not otherwise routinely collected in France. The study was conducted in relatively socially deprived neighborhoods of Paris^{27,39} and nearly 11% of participants had a language barrier, representing an important and previously under-investigated population in France. The maternal obesity prevalence (12.6%) was similar to the French national average (11.8%)²⁴, allowing for generalizability in that dimension.

Our study also has limitations. The relatively small number of severe pre-eclamptic outcomes was a limitation of our statistical analysis. Pre-pregnancy BMI was calculated from self-reported weight, which may be inaccurate however more likely to underestimate obesity in our sample and thus the overall effect. Furthermore, the magnitude of this reporting bias is likely to be negligible⁴⁰. The definition of severe pre-eclampsia used in our study is as per the French national clinical guidelines at the time of protocol development, which have since changed²⁸. However this has likely not affected our main results significantly. A more complex mediation model would include factors that could account for the residual or direct effect and allow for a more nuanced understanding of the various mediators of the associations. However we believe focusing our analysis on a single mediator allowed us to not only isolate pre-pregnancy obesity as a risk factor but also to provide a statistically demonstrative

	France + Europe	North Africa	Sub-Saharan Africa	Other	p*
	N = 4979 (52.4%)	N = 2106 (22.2%)	N = 1558 (16.4%)	N = 855 (9.0%)	
Age (years)	30.5 ± 5.2	31.6 ± 5.6	30.9 ± 5.6	30.8 ± 5.5	<0.001
Length of stay in France					<0.001
<1 year or not living in France	76 (1.6%)	293 (16.0%)	190 (14.2%)	95 (13.1%)	
>= 1 year	552 (11.3%)	1544 (84.1%)	1144 (85.8%)	631 (86.9%)	
Living in France since birth	4250 (87.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Language barrier (n, %)					<0.001
No	4801 (96.8%)	1653 (83.9%)	1261 (84.9%)	527 (64.2%)	
Yes - partial	109 (2.2%)	281 (14.3%)	201 (13.5%)	214 (26.1%)	
Yes -total	49 (1.0%)	37 (1.9%)	23 (1.6%)	80 (9.7%)	
Living with father of child (n, %)					<0.001
Yes	4421 (88.9%)	1968 (93.5%)	957 (61.6%)	750 (87.8%)	
No	555 (11.2%)	137 (6.5%)	597 (38.4%)	104 (12.2%)	
Education (n, %)					<0.001
High school diploma	1788 (36.0%)	1238 (59.3%)	1110 (72.3%)	528 (62.5%)	
Beyond high school diploma	3175 (64.0%)	849 (40.7%)	425 (27.7%)	317 (37.5%)	
Overall social deprivation** (n, %)					<0.001
Yes	1039 (20.9%)	823 (39.1%)	937 (60.1%)	377 (44.1%)	
No	3940 (79.1%)	1283 (60.9%)	621 (39.9%)	478 (55.9%)	
Prepregnancy BMI (n, %)					<0.001
Normal weight	3145 (64.9%)	1049 (52.0%)	626 (45.6%)	522 (67.3%)	
Underweight	332 (6.9%)	69 (4.0%)	57 (4.2%)	72 (9.2%)	
Overweight	835 (17.2%)	630 (31.2%)	411 (29.9%)	130 (16.8%)	
Obese	533 (11.0%)	270 (13.4%)	279 (20.3%)	52 (6.7%)	
Parity (n, %)					<0.001
Primiparous	2523 (50.7%)	763 (36.3%)	419 (26.9%)	362 (42.4%)	
Multiparous	2451 (49.3%)	1342 (63.8%)	1138 (73.1%)	492 (57.6%)	
Recommended prenatal consultations (% of recommended) [†]					0.065
<50%	131 (2.6%)	49 (2.3%)	58 (3.7%)	23 (2.7%)	
>50%	4831 (97.4%)	2050 (97.7%)	1494 (96.3%)	831 (97.3%)	

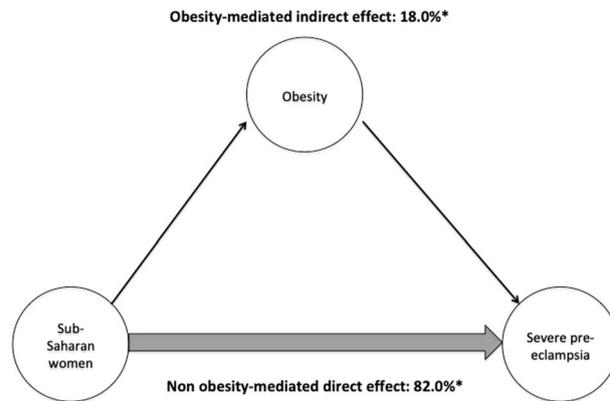
Table 3. Demographic and social characteristics of participants by maternal place of birth. *Chi-squared test of independence or Fisher's exact test for categorical variables, ANOVA for continuous variables. **Any of the following: (1) socially isolated (2) poor housing conditions (3) no work-related household income (4) no standard health insurance. †As per the French Haute Autorité de Santé recommendations, 2016. Excluding missing data for severe pre-eclampsia outcome (n = 29) and maternal place of birth (n = 81).

	Total unadjusted OR (95%CI)	Adjusted for age, parity**, and overall social deprivation***		
		Total adjusted aOR (95%CI)	Direct aOR (95%CI)	Obesity-mediated indirect aOR (95%CI)
N	6476	6473		
Maternal place of birth				
France and Europe	1.00	1.00	1.00	1.00
North Africa	0.77 (0.33–1.81)	0.80 (0.33–1.94)	0.75 (0.31–1.81)	1.07 (1.00–1.14)
Sub-Saharan Africa	2.27 (1.00–5.13)	2.53 (1.39–4.58)	2.14 (1.15–3.99)	1.18 (1.03–1.35)[†]
Other	1.33 (0.47–3.75)	1.34 (0.59–3.06)	1.43 (0.62–3.31)	0.94 (0.86–1.02)

Table 4. Obesity-mediated effect of maternal place of birth on severe preeclampsia*. *Obesity (BMI >= 30 kg/m²); reference: normal weight (BMI 18.5–24.9 kg/m²). **Primiparous or multiparous. ***Any of the following: (1) socially isolated (2) poor housing conditions (3) no work-related household income (4) no standard health insurance. †Indirect effect: 18.0%.

baseline for future, more complex analyses. Finally, generalizability of our results to other countries must be considered carefully given obesity prevalence, health systems, and immigrant and minority health vary considerably by national context.

Immigrant women from Sub Saharan Africa have a twofold higher risk than European-born women of developing severe pre-eclampsia and one fifth of this elevated risk may be mediated by pre-pregnancy obesity, a modifiable risk factor and a potential target for prevention and treatment interventions. While our findings improve



*adjusted for age, parity, and overall social deprivation

Figure 1. Decomposition of the total effect of Sub-Saharan maternal place of birth on the risk of severe pre-eclampsia into a direct effect and an indirect effect mediated through obesity.

our understanding of the complex relationships between maternal origin, obesity, and severe pre-eclampsia, they also highlight the need to better understand other drivers of severe maternal outcomes among immigrant women. Future investigations should focus on better elucidating the role of other modifiable mediators, such as those pertaining to quality of care and the health care system factors in an effort to improve

Data availability

Due to ethical restrictions, data will be made available on request to A. Siddiqui (ayesha.siddiqui@inserm.fr) and subject to receiving appropriate French ethical approval.

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Author contributions

A.S., C.D.T. and E.A. designed the study question and analytic plan. E.A., D.L., T.S., L.M. and C.E. contributed to data acquisition. A.S. conducted data analysis, table and figure generation, and drafted the manuscript. B.K. and N.B. provided statistical expertise. C.D.T., E.A. and E.A.H. provided analytic oversight and edited the manuscript. All authors have seen and approved the final version. The authors have the following conflicts of interest: none.

Competing interests

The authors declare no competing interests.

Additional information

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Supplementary table 1. Sensitivity analysis: Obesity*-mediated effect of maternal place of birth on severe preeclampsia - additional adjustment by prenatal care utilization

N	Total unadjusted OR (95%CI)	Adjusted for: age, parity**, overall social deprivation***, and prenatal care utilization†		
		Total adjusted aOR (95%CI)	Direct aOR (95%CI)	Obesity-mediated indirect aOR (95%CI)
6476		6459		
Maternal place of birth				
France and Europe	1.00	1.00	1.00	1.00
North Africa	0.77 (0.33-1.81)	0.80 (0.36-1.78)	0.75 (0.34-1.65)	1.07 (1.00-1.13)
Sub-Saharan Africa	2.27 (1.00-5.13)	2.52 (1.33-4.74)	2.13 (1.14-3.99)	1.18 (1.04-1.35)††
Other	1.33 (0.47-3.75)	1.34 (0.41-4.36)	1.43 (0.44-4.69)	0.94 (0.88-1.01)

*Obesity (BMI >= 30kg/m2); reference: normal weight (BMI 18.5-24.9kg/m2)

**Primiparous or multiparous

***Any of the following: (1) socially isolated (2) poor housing conditions (3) no work-related household income (4) no standard health insurance

† >50% or <50% of recommended as per the French Haute Autorité de Santé recommendations, 2016

††Indirect effect: 18.0%

Supplementary table 2. Sensitivity analysis: Obesity-mediated effect of self-reported maternal origin on severe preeclampsia

N	Total unadjusted OR (95%CI)	Adjusted for age, parity**, and overall social deprivation***		
		Total adjusted OR (95%CI)	Direct aOR (95%CI)	Obesity-mediated indirect aOR (95%CI)
6469		6466		
Maternal place of birth				
France and Europe	1.00	1.00	1.00	1.00
North Africa	0.76 (0.36-1.61)	0.87 (0.44-1.73)	0.80 (0.41-1.57)	1.08 (1.01-1.17)
Sub-Saharan Africa	2.24 (1.14-4.41)	2.75 (1.32-5.74)	2.34 (1.16-4.74)	1.18 (1.03-1.35)††
Other	1.36 (0.57-3.24)	1.49 (0.49-4.53)	1.55 (0.51-4.69)	0.96 (0.91-1.02)

*Obesity (BMI >= 30kg/m2); reference: normal weight (BMI 18.5-24.9kg/m2)

**Primiparous or multiparous

***Any of the following: (1) socially isolated (2) poor housing conditions (3) no work-related household income (4) no standard health insurance

† >50% or <50% of recommended as per the French Haute Autorité de Santé recommendations, 2016

††indirect effect: 15.9%

5.3 Contribution of Prepregnancy Obesity to Racial and Ethnic Disparities in Severe Maternal Morbidity: NYC/VS-SPARCS study

5.3.1 Summary

SMM is rising in the USA and the high burden of severe maternal outcomes is linked to racial disparities in maternal health. Black women are 2-3 times as likely to experience SMM as compared to White women. New York City (NYC) has a higher SMM rate than the national average, with Black-White racial disparities mirroring national trends. Racial disparities in severe maternal outcomes are multifactorial and not well understood. Black women have twice the rate of prepregnancy obesity ($BMI \geq 30 \text{ kg/m}^2$) as that of White women (40% versus 20%) and, as we confirmed in our EPIMOMS analysis, obesity is associated with SMM. Our objective was to evaluate the role of prepregnancy obesity as a mediator in the association between race-ethnicity and SMM. We conducted an analysis on a population-based retrospective cohort study using 2010-2014 birth records linked with hospital discharge data in New York City. A multivariable logistic regression mediation model on a subgroup of the sample consisting of normal weight and obese women ($n=409,021$) calculated the mediation effect of obesity in the association between maternal race-ethnicity and SMM, and the residual effect not mediated by obesity. A sensitivity analysis was conducted excluding the SMM cases due to blood transfusion. The majority of the remaining cases included in the sensitivity analysis were due to severe hypertensive disease. Among 591,455 live births, we identified 15,158 cases of SMM (256.3 per 10,000 births). The SMM rate among obese women was higher than that of normal weight women (342 vs. 216 per 10,000 births). Black women had a SMM rate nearly three times higher than White women (420 vs. 146 per 10,000 births)

and the SMM rate among Latinas was nearly twice that of White women (285 per 10,000 births). Among women with normal or obese BMI only (n=409,021), Black race was strongly associated with SMM (aOR 3.02, 95%CI 2.88-3.17) but the obesity-mediated effect represented only 3.2% of the total association (aOR 1.03, 95%CI 1.02-1.05). Latina ethnicity was also associated with SMM (aOR 2.01, 95%CI 1.90-2.12) and the obesity-mediated effect was similarly small: 3.4% of the total association (aOR 1.02, 95%CI 1.01-1.03). In a sensitivity analysis excluding blood transfusion, SMM cases found a higher mediation effect of obesity in the association with Black race and Latina ethnicity (15.3% and 15.2% of the total association, respectively). Our findings indicate that prepregnancy obesity, a modifiable factor, is a limited driver of racial-ethnic disparities in overall SMM. However, obesity mediates a more significant part of the association between Black race and Latina ethnicity and severe hypertensive disorders- a finding which is congruent with the results of our PreCARE analysis.

5.3.2 Article as published

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Contribution of Prepregnancy Obesity to Racial and Ethnic Disparities in Severe Maternal Morbidity

Ayesha Siddiqui, MD, MSc, Elie Azria, MD, PhD, Natalia Egorova, PhD, MPH, Catherine Deneux-Tharaux, MD, PhD, and Elizabeth A. Howell, MD, MPP

OBJECTIVE: To evaluate the role of prepregnancy obesity as a mediator in the association between race-ethnicity and severe maternal morbidity.

METHODS: We conducted an analysis on a population-based retrospective cohort study using 2010–2014 birth records linked with hospital discharge data in New York City. A multivariable logistic regression mediation model on a subgroup of the sample consisting of normal-weight and obese women (n=409,021) calculated the mediation effect of obesity in the association between maternal race-ethnicity and severe maternal morbidity, and the

residual effect not mediated by obesity. A sensitivity analysis was conducted excluding the severe maternal morbidity cases due to blood transfusion.

RESULTS: Among 591,455 live births, we identified 15,158 cases of severe maternal morbidity (256.3/10,000 deliveries). The severe maternal morbidity rate among obese women was higher than that of normal-weight women (342 vs 216/10,000 deliveries). Black women had a severe maternal morbidity rate nearly three times higher than White women (420 vs 146/10,000 deliveries) and the severe maternal morbidity rate among Latinas was nearly twice that of White women (285/10,000 deliveries). Among women with normal or obese body mass index (BMI) only (n=409,021), Black race was strongly associated with severe maternal morbidity (adjusted odds ratio [aOR] 3.02, 95% CI 2.88–3.17) but the obesity-mediated effect represented only 3.2% of the total association (aOR 1.03, 95% CI 1.02–1.05). Latina ethnicity was also associated with severe maternal morbidity (aOR 2.01, 95% CI 1.90–2.12) and the obesity-mediated effect was similarly small: 3.4% of the total association (aOR 1.02, 95% CI 1.01–1.03). In a sensitivity analysis excluding blood transfusion, severe maternal morbidity cases found a higher mediation effect of obesity in the association with Black race and Latina ethnicity (15.3% and 15.2% of the total association, respectively).

CONCLUSION: Our findings indicate that prepregnancy obesity, a modifiable factor, is a limited driver of racial-ethnic disparities in overall severe maternal morbidity.

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Maternal mortality in the United States is the highest among developed countries at 17.4 per 100,000 live births.¹ Severe maternal morbidity occurs 100 times more frequently than mortality and is an important indicator for studying obstetric quality and preventing death. Severe maternal morbidity rose



from 49.5 to 144.0 per 10,000 delivery hospitalizations between 1993 and 2014.² The high burden of severe maternal outcomes is linked to racial disparities in maternal health. Black women are three to four times more likely to die in childbirth as compared with White women and 60% of these deaths are preventable.^{3,4} They are also two to three times as likely to experience severe maternal morbidity.^{5,6} New York City has a higher severe maternal morbidity rate than the national average (241.0/10,000 delivery hospitalizations, 2008–2014), with Black-White racial disparities mirroring national trends.⁷

Racial disparities in severe maternal outcomes are multifactorial and not well understood. Conventional wisdom emphasizes differences in clinical comorbidities. For example, Black women have twice the rate of prepregnancy obesity (body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] 30 or higher) as that of White women (40% vs 20%).^{8,9} Some evidence supports an independent association between obesity and severe maternal morbidity.^{10–17}

Given the scarce existing data on how severe maternal morbidity risks operate within the context of disparities, more robust analytic approaches are needed to understand their roles on the causal pathway. Our objective was to elucidate the contribution of prepregnancy obesity to the association between race–ethnicity and severe maternal morbidity.

METHODS

We performed a retrospective cohort study using birth records linked with hospital discharge abstract data for all delivery hospitalizations in New York City from January 2010 to December 2014. The New York State Department of Health and Mental Health conducted the data linkage. Approximately 125,000 live births are registered annually in New York City by the Department of Health and Mental Health's Bureau of Vital Statistics, which issues birth certificates with detailed confidential demographic and medical data of high quality and reliability.¹⁸ The birth certificate data include mother's age, self-reported race and ethnicity, place of birth, education level, health insurance information, and details regarding the pregnancy such as parity, prenatal care, and delivery. A list of all data elements contained in the New York City birth certificate is available at Appendix B of <https://www1.nyc.gov/assets/doh/downloads/pdf/vs/2014sum.pdf>.¹⁹ Almost all (99%) of deliveries in New York City occur in hospitals.¹⁹ The mandatory New York State Department of Health Statewide Plan-

ning and Research Cooperative System monitors and reports on all inpatient hospital discharges, including details regarding length of stay as well as diagnosis and procedure codes.¹⁹ Full data elements can be found at www.health.ny.gov/statistics/sparcs/sysdoc/iptable.htm. New York State Department of Health performs audits to check data quality on a quarterly basis. The data quantity, quality, and validation protocol can be found at https://www.health.ny.gov/statistics/sparcs/training/docs/sparcs_data_quantity_quality_protocol_final.pdf. The match rate in the linked data set was approximately 98%. Multiple births were counted as one delivery.

Maternal race–ethnicity was the independent variable of interest in our analysis. We created this variable by combining self-reported race with self-reported Hispanic ethnicity from the birth certificate and coded it in five categories: non-Hispanic White (we refer to as White), non-Hispanic Black (we refer to as Black), Latina, Asian, and other. Other race was a formal prespecified category on the birth certificate. Birth certificate data regarding maternal race and Hispanic ethnicity have been validated previously.^{20–22} Delivery hospitalizations were ascertained from International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis, procedure, and diagnosis-related group delivery codes from the Statewide Planning and Research Cooperative System.²³ The binary outcome of composite severe maternal morbidity was based on a published algorithm from the Centers for Disease Control and Prevention (CDC) and defined as per specific ICD-9-CM billing codes and hospital length of stay.^{24,25} Prepregnancy BMI is reliably reported on the New York City birth certificate²⁶ and was used to create categorical BMI as the mediator in the analyses, defined as per routine clinical cutoffs: underweight, lower than 18.5, normal weight, 18.5–24.9, overweight, 25–29.9, obese, 30 or higher.²⁷ We excluded improbable prepregnancy BMIs of less than 12 or greater than 55 ($n=4,262$).

Demographic, social, and medical characteristics of participants were described and differences between women who did and did not experience severe maternal morbidity ascertained using χ^2 tests of independence or Fisher exact tests for categorical variables, and two sample *t* tests or ANOVA for continuous variables ($P<.05$). Differences between participants by maternal race–ethnicity and BMI categories were similarly described.

Multivariable logistic regression models were constructed including the mediation effect of maternal



BMI categories in the association between maternal race–ethnicity and severe maternal morbidity. Because our aim was to isolate the effect of obesity as compared with normal weight, the mediation analysis was conducted on a subgroup of the entire study sample that consisted of women who were either normal weight or obese ($n=409,021$).^{2,18,23–30} Using normal BMI as the reference, a path analysis multivariable logistic regression mediation model decomposed the total effect of maternal race–ethnicity on severe maternal morbidity into an indirect obesity-mediated effect and a residual effect not mediated by obesity.^{30,31} Potential variables for inclusion in the analysis were identified by constructing a directed acyclic graph of the main effects, that is, the causal effect of the exposure (race–ethnicity) on the outcome (severe maternal morbidity) and of the mediator (obesity) on the outcome,²⁸ and did not include factors on the causal pathways between them.¹⁷ Prenatal care utilization and certain pre-existing maternal conditions, such as chronic hypertension or diabetes, were not considered for inclusion in the analysis as they are potential intermediates in the causal pathway between maternal race–ethnicity and severe maternal morbidity.

The path analysis model conceptualized a counterfactual approach, which may theoretically be formulated as the response to the following question: “What would be the risk of [severe maternal morbidity] associated with Black race if Black women had the same probability of being obese as White women?” The indirect obesity-mediated effect of maternal race–ethnicity on the risk of severe maternal morbidity was calculated from the regression coefficients obtained using adjusted logistic regression models and was expressed as a percentage of the total effect. We conducted similar analyses for each race–ethnicity category with non-Hispanic White race as the reference. Given a high reported false positive rate of severe maternal morbidity with the ICD-9-CM administrative codes for a blood transfusion,³² likely due to the coding of one- or two-unit transfusions, a sensitivity analysis was conducted using a severe maternal morbidity composite outcome excluding blood transfusion. In the overall data set, missing data were infrequent; variables with the highest rates were prepregnancy BMI (1.6%), and educational level (0.8%). Among the subgroup of normal-weight and obese women included in the model, all participants necessarily had values for BMI and missing data for all other variables were omitted from the final analyses. This resulted in 0.2% of participants missing in the final model. All analyses were performed using Stata,

V.14.0 SE and add-on models developed by Buis.³⁰ The investigation was approved by the Institutional Review Boards of the New York City Department of Health and Mental Hygiene, the New York State Department of Health, and the Icahn School of Medicine at Mount Sinai.

RESULTS

Among 591,455 hospital deliveries in 40 New York City hospitals between 2010 and 2014, we identified 15,158 cases of severe maternal morbidity, a rate of 256.3 per 10,000 deliveries. The severe maternal morbidity rate among obese women was notably higher than among normal-weight women (342 vs 216/10,000 deliveries). Black women had the highest rate of severe maternal morbidity (420/10,000 deliveries), a rate nearly three times higher than that of White women (146/10,000 deliveries), followed by Latina women (285/10,000 deliveries) and Asian women (178/10,000 deliveries). Women who experienced severe maternal morbidity were also more likely to be less than 20 or older than 35, without a high school diploma, unemployed during their pregnancies, have Medicaid insurance, and have pre-existing medical conditions including chronic hypertension and diabetes. Severe maternal morbidity also occurred more often among women who were multiparous with prior cesarean deliveries. In the current pregnancy, women who experienced severe maternal morbidity were more likely to have a multiple gestation, late initiation of prenatal care, hypertensive disorders of pregnancy, gestational diabetes, abnormal placentation, and have conceived through assisted reproductive technologies (Table 1).

Compared with uncomplicated deliveries, deliveries with severe maternal morbidity were more likely to occur preterm or very preterm, have noncephalic presentation, and be by cesarean. Severe maternal morbidity rates were higher in facilities with lower delivery volumes (Table 1).

Socio-demographic differences between participants by race–ethnicity were remarkable for higher levels of education, lower rates of unemployment and lower rates of Medicaid insurance among White mothers as compared with mothers of all other races and ethnicities (Appendix 1, available online at <http://links.lww.com/AOG/C269>). Black and Latina women were also more likely to be overweight or obese, and all race–ethnicity categories were more likely to have history of cesarean delivery as compared with White women (Appendix 1, <http://links.lww.com/AOG/C269>).



Table 1. Characteristics of Women Experiencing Severe Maternal Morbidity and Those Not Experiencing Severe Maternal Morbidity

Characteristic	Total (N=591,455)	Did Not Experience SMM [n=576,297 (97.4)]	Experienced SMM [n=15,158 (2.6)]	P*
Prepregnancy BMI category (kg/m ²)	25.5±10.8	25.5±10.8	26.9±12.6	<.001
Underweight (lower than 18.5)	33,146 (5.7)	32,426 (5.6)	720 (4.8)	<.001
Normal weight (18.5–24.9)	314,047 (54.1)	307,255 (53.3)	6,792 (44.8)	
Overweight (25–29.9)	137,990 (23.8)	134,207 (23.3)	3,783 (25.0)	
Obese (30 or higher)	94,974 (16.4)	91,727 (15.9)	3,247 (21.4)	
Missing	11,298 (1.9)	10,682 (1.9)	616 (4.1)	
Socio-demographic characteristics				
Maternal age (y)	29.6±6.2	29.6±6.1	29.9±6.8	<.001
Maternal age (y) (categorical)				<.001
Younger than 20	28,182 (4.7)	27,237 (4.8)	945 (6.2)	
20–34	424,020 (71.8)	414,250 (71.8)	9,770 (64.5)	
35 or older	132,217 (22.3)	128,214 (22.3)	4,003 (26.4)	
Missing	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Race				<.001
White	185,095 (31.3)	182,386 (31.7)	2,709 (17.9)	
Black	122,067 (20.6)	116,938 (20.3)	5,129 (33.8)	
Latina	177,768 (30.1)	172,693 (30.0)	5,075 (33.5)	
Asian	97,496 (16.5)	95,765 (16.6)	1,731 (11.4)	
Other	1,407 (0.2)	1,365 (0.2)	42 (0.3)	
Missing	7,622 (1.3)	7,150 (1.2)	472 (3.1)	
Foreign born				.208
Yes	274,568 (46.4)	267,455 (46.4)	7,113 (46.9)	
No	316,887 (53.6)	308,842 (53.6)	8,045 (53.1)	
Missing	0	0	0	
Education				<.001
Less than high school	126,668 (21.4)	122,799 (21.3)	3,869 (25.5)	
High school	128,974 (21.8)	125,506 (21.8)	3,468 (22.9)	
Some college or associate degree	127,750 (21.6)	124,285 (21.6)	3,465 (22.9)	
College degree or greater	199,101 (33.7)	195,308 (33.9)	3,793 (25.0)	
Missing	8,962 (1.5)	8,399 (1.5)	563 (3.7)	
Employed during pregnancy				<.001
Yes	286,846 (48.5)	280,472 (48.7)	6,374 (42.1)	
No	296,615 (50.2)	288,340 (50.0)	8,275 (54.6)	
Missing	7,994 (1.3)	7,485 (1.3)	509 (3.3)	
Insurance				<.001
Medicaid	348,936 (59.0)	339,058 (58.8)	9,878 (65.2)	
Private	221,742 (37.5)	217,384 (37.7)	4,358 (28.8)	
Uninsured	7,839 (1.3)	7,555 (1.3)	284 (1.9)	
Other payer	5,902 (1.0)	5,704 (1.0)	198 (1.4)	
Missing	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Medicaid				<.001
Yes	348,936 (59.0)	339,058 (58.8)	9,878 (65.2)	
No	235,483 (39.8)	230,642 (40.0)	4,840 (31.9)	
Missing	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Medical history				
Chronic hypertension	12,498 (2.1)	11,552 (2.0)	946 (6.2)	<.001
Missing	0	0	0	
Pre-existing diabetes	4,968 (0.8)	4,614 (0.8)	354 (2.3)	<.001
Missing	0	0	0	
Any other notable pre-existing medical condition	10,092 (1.7)	9,490 (1.7)	602 (4.1)	<.001
Missing	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Obstetric history				<.001
Parity by delivery type				
Primiparous	260,160 (44.0)	253,879 (44.1)	6,281 (41.4)	
Multiparous without prior cesarean	236,830 (40.0)	232,340 (40.3)	4,490 (29.6)	
Multiparous with prior cesarean	90,882 (15.4)	86,648 (15.0)	4,234 (27.9)	

(continued)



Table 1. Characteristics of Women Experiencing Severe Maternal Morbidity and Those Not Experiencing Severe Maternal Morbidity (continued)

Characteristic	Total (N=591,455)	Did Not Experience SMM [n=576,297 (97.4)]	Experienced SMM [n=15,158 (2.6)]	P*
Missing	3,583 (0.6)	3,430 (0.6)	153 (1.0)	
If parous				
Prior cesarean delivery	90,882 (27.7)	86,648 (27.2)	4,234 (48.5)	<.001
Missing	0	0	0	
Prior preterm delivery	10,664 (1.8)	10,127 (1.8)	537 (3.5)	<.001
Missing	0	0	0	
Current pregnancy				
Conception through ART	7,710 (1.3)	7,334 (1.3)	376 (2.6)	<.001
Missing	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Multiple gestation	11,539 (2.0)	10,557 (1.8)	982 (6.5)	<.001
Missing	0	0	0	
Prenatal care initiation (trimester)				<.001
1st	413,115 (72.3)	403,476 (72.4)	9,639 (68.2)	
2nd	121,317 (21.2)	117,985 (21.2)	3,332 (23.6)	
3rd	37,037 (6.5)	35,868 (6.4)	1,169 (8.3)	
Missing	19,986 (3.4)	18,968 (3.3)	1,018 (6.7)	
Prenatal visits (n)	11.1±3.9	11.1±3.9	10.6±4.5	<.001
Missing	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Hypertensive disorders of pregnancy				<.001
Normotensive	550,774 (93.1)	538,608 (93.5)	12,166 (80.3)	
Nonproteinuric gestational hypertension	14,197 (2.4)	13,721 (2.4)	476 (3.1)	
Preeclampsia	26,483 (4.5)	23,967 (4.2)	2,516 (16.6)	
Missing	1 (0.0)	1 (0.0)	0	
Gestational diabetes	40,944 (6.9)	39,613 (6.9)	1,331 (8.8)	<.001
Missing	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Placenta previa or placenta accreta	4,702 (0.8)	3,772 (0.7)	930 (6.1)	<.001
Missing	0	0	0	
Tobacco use	13,309 (2.3)	12,917 (2.3)	392 (2.7)	<.001
Missing	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Delivery characteristics				
Gestational age (wk)	38.7±2.0	38.7±2.0	37.6±3.3	<.001
Gestational age (wk)				<.001
Less than 28	3,301 (0.6)	2,933 (0.5)	368 (2.4)	
28–31	4,722 (0.8)	4,132 (0.7)	590 (3.9)	
32–36	39,642 (6.7)	37,139 (6.4)	2,503 (16.5)	
37 or more	543,789 (91.9)	532,092 (92.3)	11,697 (77.2)	
Missing	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Noncephalic presentation	25,861 (4.4)	24,542 (4.3)	1,319 (9.0)	<.001
Missing	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Labor onset				.02
Spontaneous	497,276 (85.1)	484,855 (85.1)	12,421 (84.4)	
Induced	87,143 (14.9)	84,846 (14.9)	2,297 (15.6)	
Missing	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Mode of delivery				<.001
Vaginal	373,923 (63.2)	369,587 (64.1)	4,336 (28.6)	
Vaginal instrumental	18,942 (3.2)	18,545 (3.2)	397 (2.6)	
Cesarean with trial of labor	66,341 (11.2)	63,176 (11.0)	3,165 (20.9)	
Cesarean without trial of labor	124,572 (21.1)	117,780 (20.4)	6,792 (44.8)	
Missing	7,677 (1.3)	7,029 (1.3)	468 (3.1)	
Newborn characteristics				
Neonatal death	43 (0.01)	3 (0.0)	40 (0.3)	<.001
Missing	0	0	0	
Birth weight (g)	3,245±563	3,251±554	3,050±807	<.001
Missing	7,036 (1.2)	6,596 (1.1)	440 (2.9)	

(continued)



Table 1. Characteristics of Women Experiencing Severe Maternal Morbidity and Those Not Experiencing Severe Maternal Morbidity (continued)

Characteristic	Total (N=591,455)	Did Not Experience SMM [n=576,297 (97.4)]	Experienced SMM [n=15,158 (2.6)]	P*
Delivery facility characteristics				
Annual delivery volume (quartile)				<.001
1st	150,448 (25.4)	145,013 (25.2)	5,435 (35.9)	
2nd	147,769 (25.0)	143,601 (24.9)	4,168 (27.5)	
3rd	161,097 (27.2)	157,534 (27.3)	3,563 (23.5)	
4th	132,141 (22.3)	130,149 (22.6)	1,992 (13.1)	
Missing	0	0	0	

SMM, severe maternal morbidity; BMI, body mass index; ART, assisted reproductive technologies.

Data are mean±SD or n (%) unless otherwise specified.

* Chi-squared test of independence or two sample *t* test.

Compared with normal-weight women, obese women in our study sample were more likely to be American-born, have a lower level of education, be unemployed, have Medicaid insurance, and have a prior cesarean delivery (Appendix 2, available online at <http://links.lww.com/AOG/C269>). The majority of severe maternal morbidity cases were due to receiving a blood transfusion (202.4/10,000 deliveries), followed by emergent hysterectomy (14.1/10,000 deliveries), and mechanical ventilation (13.6/10,000 deliveries).

In the total population, Black race was associated with composite severe maternal morbidity (odds ratio [OR] 2.95, 95% CI 2.82–3.10) and with obesity (OR 3.90, 95% CI 3.83–3.98), as was Latina ethnicity, but to a lesser extent (Appendix 3, available online at <http://links.lww.com/AOG/C269>). Obesity was also associated with composite severe maternal morbidity (OR 1.60, 95% CI 1.53–1.67) and the association remained significant after adjusting for age, Medicaid insurance, and parity (adjusted odds ratio [aOR] 1.37, 95% CI 1.31–1.43) (Table 2). In the mediation path analysis adjusted for covariables among the subgroup of women with normal or obese BMI only, Black race remained associated with severe maternal morbidity (aOR 3.02, 95% CI 2.88–3.17); however, the obesity-mediated indirect effect was small (aOR 1.03, 95% CI 1.02–1.05) or 3.2% of the total association (Table 3). Latina ethnicity was also associated with severe maternal morbidity (aOR 2.01, 95% CI 1.90–2.12) and the obesity-mediated effect was 3.4% of the total association. When the overweight BMI category was tested as the mediator, the mediation effects were small and not statistically significant (data not shown).

The sensitivity analysis in which blood transfusion severe maternal morbidity cases were excluded revealed similar disparities by race–ethnicity (Appendix 4, available online at <http://links.lww.com/AOG/C269>).

The path analysis found a higher mediation effect of obesity in the association between Black race and the outcome of severe maternal morbidity excluding blood transfusion as compared with the main analysis (15.3% excluding blood transfusion vs 3.2% overall) (Appendix 4, <http://links.lww.com/AOG/C269>). A higher mediation effect was also noted in the sensitivity analysis for Latina ethnicity (15.2% vs 3.4%) (Appendix 4, <http://links.lww.com/AOG/C269>).

DISCUSSION

Black and Latina women had two- to three-fold higher rates of severe maternal morbidity compared with White women even after adjusting for covariables such as Medicaid insurance and maternal education level—social risk factors that are often presumed to be

Table 2. Association Between Categorical Body Mass Index and Severe Maternal Morbidity*

Prepregnancy BMI Category (kg/m ²)	Unadjusted OR (95% CI)	Adjusted aOR (95% CI) [†]
Normal weight (18.5–24.9)	1.00	1.00
Underweight (lower than 18.5)	1.00 (0.93–1.09)	0.99 (0.91–1.07)
Overweight (25–29.9)	1.28 (1.22–1.33)	1.16 (1.11–1.21)
Obese (30 or higher)	1.60 (1.53–1.67)	1.37 (1.31–1.43)

BMI, body mass index; OR, odds ratio; aOR, adjusted odds ratio.

* Logistic regression: n=580,157 for unadjusted analysis, n=574,957 for adjusted analysis.

[†] Adjusted for age (continuous), Medicaid insurance (yes or no), parity (primiparous, multiparous without prior cesarean delivery, multiparous with prior cesarean delivery), education (less than high school, high school, some college or associate degree, college degree or greater).



Table 3. Obesity-Mediated Effect of Maternal Race on Severe Maternal Morbidity*

	Total Unadjusted OR (95% CI)	Total Adjusted aOR [†] (95% CI)	Direct aOR [†] (95% CI)	Obesity-Mediated Indirect aOR [†] (95% CI)
n	409,021	405,578		
Maternal race				
White	1.00	1.00	1.00	1.00
Black	3.02 (2.88–3.17)	2.90 (2.72–3.09)	2.80 (2.63–3.00)	1.03 (1.02–1.05)
Latina	2.01 (1.90–2.12)	1.92 (1.81–2.04)	1.88 (1.77–1.99)	1.02 (1.01–1.03)
Asian	1.25 (1.15–1.35)	1.20 (1.11–1.29)	1.21 (1.12–1.30)	0.99 (0.99–1.00)
Other	2.24 (1.45–3.45)	2.22 (1.62–3.05)	2.20 (1.60–3.02)	1.01 (1.01–1.02)

OR, odds ratio; aOR, adjusted odds ratio.

* Obesity, BMI 30 or higher; reference: normal weight, BMI 18.5–24.9.

[†] Adjusted for age (continuous), Medicaid insurance (yes or no), parity (primiparous, multiparous without prior cesarean delivery, multiparous with prior cesarean delivery), and education level (less than high school, high school, some college or associate degree, college degree or greater).

explanatory for racial–ethnic disparities—as well as age and parity. However, only 3–15% of the association between race or Latina ethnicity and severe maternal morbidity is mediated by prepregnancy obesity, indicating that other factors may be more important when considering interventions to reduce racial disparities in all-cause severe maternal morbidity.

Determinants of severe maternal morbidity can be broadly classified as social or environmental, health system, and individual-level medical characteristics.^{33,34} Individual-level social or environmental factors such as education, insurance, income, and neighborhood poverty account for some of the severe maternal morbidity racial disparity in New York City.^{35,36} Health system factors, such as variation in hospital site and performance, may account for as much as 38–48% of the racial–ethnic disparity in severe maternal morbidity rates in New York City.³⁷ Although there is a growing recognition that structural racism contributes to these disparities,³⁴ previous research has largely focused on individual-level medical characteristics. Characteristics such as age, specific pre-existing medical conditions, and prior cesarean delivery have been shown to be independent risk factors for severe maternal morbidity; however, there is little evidence supporting their role in racial–ethnic disparities.³⁸

Obesity has been postulated as an important modifiable risk factor contributing to racial–ethnic disparities in maternal health. Our current investigation demonstrates that obesity mediates only a small proportion of the association between race–ethnicity and overall severe maternal morbidity. Notably, prior studies examining the association between race–ethnicity and severe maternal morbidity simply employed BMI as a confounder and not as a mediator

(Platner M, Ackerman C, Howland RE, Illuzzi J, Reddy UM, Bourjeily G, et al. 64: The influence of obesity and racial/ethnic disparities on severe maternal morbidity [abstract]. *Am J Obstet Gynecol* 2020;222:S53–4. doi: 10.1016/j.ajog.2019.11.080).^{15,39} Quantifying the mediation effect allowed for a novel theoretical estimation of disease reduction for a modifiable risk factor for severe maternal morbidity.

The majority of severe maternal morbidity in our cohort was ascertained by blood transfusion. When we excluded morbidity from transfusion alone, we found that obesity is a more important mediator of the association between race–ethnicity and other components of severe maternal morbidity such as hypertensive diseases of pregnancy. These findings are consistent with our previous analysis conducted among immigrant women in France in which we found that 18% of the association between Sub-Saharan maternal place of birth and severe preeclampsia was mediated by obesity.⁴⁰

Our study had several strengths. The data set used was large, exhaustive, previously validated, and included a large number of severe maternal morbidity events. The sample was racially and ethnically diverse, as well as population based. The definition of severe maternal morbidity was based on a highly used CDC algorithm; thus, our findings can directly be compared with previous data.

Our study was limited by the reliability of administrative data. Furthermore, severe maternal morbidity is likely underestimated as events occurring after hospital discharge are not included. As noted by others, the CDC definition likely overestimates the rate of severe maternal morbidity due to inclusion of any blood transfusion.³² The sensitivity analysis in



which we excluded all cases of blood transfusion addressed this issue.

Although often attributed to personal medical or behavioral factors, which disproportionately place blame on women of color, current evidence indicates that racial and ethnic disparities in severe maternal morbidity are often due to structural or health system factors rather than modifiable individual-level factors.⁶ Further evaluation of other prominent contributors to maternal morbidity such as the health system, clinician, and structural racism will be necessary to help shape future prevention strategies.

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Table 1: Characteristics of women experiencing severe maternal morbidity and those not experiencing severe maternal morbidity

	Total n=591,455 n(%)	Did not experience SMM n=576,297 (97.4%) n(%)	Experienced SMM n=15,158 (2.6%) n(%)	p*
Prepregnancy body mass-index (kg/m ²) [mean ±standard deviation]	25.5 ±10.8	25.5 ±10.8	26.9 ±12.6	<0.001
Underweight (<18.5)	33,146(5.7)	32,426 (5.6)	720 (4.8)	<0.001
Normal weight (18.5-24.9)	314,047(54.1)	307,255 (53.3)	6,792 (44.8)	
Overweight (25-29.9)	137,990(23.8)	134,207 (23.3)	3,783(25.0)	
Obese (>=30)	94,974 (16.4)	91,727 (15.9)	3,247(21.4)	
Missing	11,298 (1.9)	10,682 (1.9)	616 (4.1)	
Socio-demographic characteristics				
Maternal age (years) [mean ±standard deviation]	29.6 ±6.2	29.6 ±6.1	29.9 ±6.8	<0.001
Maternal age (years) [categorical]				<0.001
<20	28,182 (4.7)	27,237 (4.8)	945 (6.2)	
20-34	424,020 (71.8)	414,250 (71.8)	9,770 (64.5)	
>=35	132,217 (22.3)	128,214 (22.3)	4,003 (26.4)	
Missing	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Race				<0.001
White	185,095 (31.3)	182,386 (31.7)	2,709 (17.9)	
Black	122,067 (20.6)	116,938 (20.3)	5,129 (33.8)	
Latina	177,768 (30.1)	172,693 (30.0)	5,075 (33.5)	
Asian	97,496 (16.5)	95,765 (16.6)	1,731 (11.4)	
Other	1,407 (0.2)	1,365 (0.2)	42 (0.3)	
Missing	7,622 (1.3)	7,150 (1.2)	472 (3.1)	

Foreign born					
	Yes	274,568 (46.4)	267,455 (46.4)	7,113 (46.9)	
	No	316,887 (53.6)	308,842 (53.6)	8,045 (53.1)	
	<i>Missing</i>	<i>0</i>	<i>0</i>	<i>0</i>	
Education					<0.001
	Less than high school	126,668 (21.4)	122,799 (21.3)	3,869 (25.5)	
	High school	128,974 (21.8)	125,506 (21.8)	3,468 (22.9)	
	Some college or associates degree	127,750 (21.6)	124,285 (21.6)	3,465 (22.9)	
	College degree or greater	199,101 (33.7)	195,308 (33.9)	3,793 (25.0)	
	<i>Missing</i>	<i>8,962 (1.5)</i>	<i>8,399 (1.5)</i>	<i>563 (3.7)</i>	
Employed during pregnancy					<0.001
	Yes	286,846 (48.5)	280,472 (48.7)	6,374 (42.1)	
	No	296,615 (50.2)	288,340 (50.0)	8,275 (54.6)	
	<i>Missing</i>	<i>7,994 (1.3)</i>	<i>7,485 (1.3)</i>	<i>509 (3.3)</i>	
Insurance					<0.001
	Medicaid	348,936 (59.0)	339,058 (58.8)	9,878 (65.2)	
	Private	221,742 (37.5)	217,384 (37.7)	4,358 (28.8)	
	Uninsured	7,839 (1.3)	7,555 (1.3)	284 (1.9)	
	Other payer	5,902 (1.0)	5,704 (1.0)	198 (1.4)	
	<i>Missing</i>	<i>7,036 (1.2)</i>	<i>6,596 (1.1)</i>	<i>440 (2.9)</i>	
Medicaid					<0.001
	Yes	348,936 (59.0)	339,058 (58.8)	9,878 (65.2)	
	No	235,483 (39.8)	230,642 (40.0)	4,840 (31.9)	
	<i>Missing</i>	<i>7,036 (1.2)</i>	<i>6,596 (1.1)</i>	<i>440 (2.9)</i>	
Medical history					
Chronic hypertension					<0.001
		12,498 (2.1)	11,552 (2.0)	946 (6.2)	
	<i>Missing</i>	<i>0</i>	<i>0</i>	<i>0</i>	
Pre-existing diabetes					<0.001
		4,968 (0.8)	4,614 (0.8)	354 (2.3)	
	<i>Missing</i>	<i>0</i>	<i>0</i>	<i>0</i>	
Any other notable pre-existing medical condition					<0.001
		10,092 (1.7)	9,490 (1.7)	602 (4.1)	
	<i>Missing</i>	<i>7,036 (1.2)</i>	<i>6,596 (1.1)</i>	<i>440 (2.9)</i>	

Obstetric history					
Parity by delivery type					<0.001
	Primiparous	260,160 (44.0)	253,879 (44.1)	6,281 (41.4)	
	Multiparous without prior cesarean delivery	236,830 (40.0)	232,340 (40.3)	4,490 (29.6)	
	Multiparous with prior cesarean delivery	90,882 (15.4)	86,648 (15.0)	4,234 (27.9)	
	<i>Missing</i>	3,583 (0.6)	3,430 (0.6)	153 (1.0)	
<i>If parous</i>					
	Prior cesarean delivery	90,882 (27.7)	86,648 (27.2)	4,234 (48.5)	<0.001
	<i>Missing</i>	0	0	0	
	Prior preterm delivery	10,664 (1.8)	10,127 (1.8)	537 (3.5)	<0.001
	<i>Missing</i>	0	0	0	
Current pregnancy					
Conception via ART		7,710 (1.3)	7,334 (1.3)	376 (2.6)	<0.001
	<i>Missing</i>	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Multiple gestation		11,539 (2.0)	10,557 (1.8)	982 (6.5)	<0.001
	<i>Missing</i>	0	0	0	
Prenatal care initiation [trimester]					<0.001
	1	413,115 (72.3)	403,476 (72.4)	9,639 (68.2)	
	2	121,317 (21.2)	117,985 (21.2)	3,332 (23.6)	
	3	37,037 (6.5)	35,868 (6.4)	1,169 (8.3)	
	<i>Missing</i>	19,986 (3.4)	18,968 (3.3)	1,018 (6.7)	
Prenatal visits (n) [mean ±standard deviation]		11.1 ±3.9	11.1 ±3.9	10.6±4.5	<0.001
	<i>Missing</i>	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Hypertensive disorders of pregnancy					<0.001
	Normotensive	550,774 (93.1)	538,608 (93.5)	12,166 (80.3)	
	Non-proteinuric gestational hypertension	14,197 (2.4)	13,721 (2.4)	476 (3.1)	
	Preeclampsia	26,483 (4.5)	23,967 (4.2)	2,516 (16.6)	
	<i>Missing</i>	1 (0.0)	1 (0.0)	0	

Gestational diabetes		40,944 (6.9)	39,613 (6.9)	1,331 (8.8)	<0.001
	<i>Missing</i>	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Placenta previa or placenta accreta		4,702 (0.8)	3,772 (0.7)	930 (6.1)	<0.001
	<i>Missing</i>	0	0	0	
Tobacco use		13,309 (2.3)	12,917 (2.3)	392 (2.7)	<0.001
	<i>Missing</i>	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Delivery characteristics					
Gestational age (weeks) [mean ±standard deviation]		38.7 ±2.0	38.7 ±2.0	37.6 ±3.3	<0.001
Gestational age (weeks)					<0.001
	<28	3,301 (0.6)	2,933 (0.5)	368 (2.4)	
	28-31	4,722 (0.8)	4,132 (0.7)	590 (3.9)	
	32-36	39,642 (6.7)	37,139 (6.4)	2,503 (16.5)	
	≥37	543,789 (91.9)	532,092 (92.3)	11,697 (77.2)	
	<i>Missing</i>	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Noncephalic presentation		25,861 (4.4)	24,542 (4.3)	1,319 (9.0)	<0.001
	<i>Missing</i>	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Labor onset					0.02
	Spontaneous	497,276 (85.1)	484,855 (85.1)	12,421 (84.4)	
	Induced	87,143 (14.9)	84,846 (14.9)	2,297 (15.6)	
	<i>Missing</i>	7,036 (1.2)	6,596 (1.1)	440 (2.9)	
Mode of delivery					<0.001
	Vaginal	373,923 (63.2)	369,587 (64.1)	4,336 (28.6)	
	Vaginal instrumental	18,942 (3.2)	18,545 (3.2)	397 (2.6)	
	Cesarean delivery with trial of labor	66,341 (11.2)	63,176 (11.0)	3,165 (20.9)	
	Cesarean delivery without trial of labor	124,572 (21.1)	117,780 (20.4)	6,792 (44.8)	
	<i>Missing</i>	7,677 (1.3)	7,029 (1.3)	468 (3.1)	

Newborn characteristics

Neonatal death		43 (0.01)	3 (0.0)	40 (0.3)	<0.001
	<i>Missing</i>	0	0	0	
Birth weight (g) [mean ±standard deviation]		3,245 ±563	3,251 ±554	3,050 ±807	<0.001
	<i>Missing</i>	7,036 (1.2)	6,596 (1.1)	440 (2.9)	

Delivery facility characteristics

Annual delivery volume (quartiles)					<0.001
	1	150,448 (25.4)	145,013 (25.2)	5,435 (35.9)	
	2	147,769 (25.0)	143,601 (24.9)	4,168 (27.5)	
	3	161,097 (27.2)	157,534 (27.3)	3,563 (23.5)	
	4	132,141 (22.3)	130,149 (22.6)	1,992 (13.1)	
	<i>Missing</i>	0	0	0	

*Chi-squared test of independence or 2 sample t-test

Table 2: Association between categorical body mass index and severe maternal morbidity*

Prepregnancy body mass-index (kg/m ²)	Unadjusted OR (95%CI)	Adjusted [†] aOR (95%CI)
Normal weight (18.5-24.9)	1.00	1.00
Underweight (<18.5)	1.00 (0.93-1.09)	0.99 (0.91-1.07)
Overweight (25-29.9)	1.28 (1.22-1.33)	1.16 (1.11-1.21)
Obese (>=30)	1.60 (1.53-1.67)	1.37 (1.31-1.43)

*Logistic regression, N=580,157 for unadjusted analysis, N=574,957 for adjusted analysis

[†] Adjusted for: age (continuous), Medicaid insurance (Y/N), parity (primiparous, multiparous without prior cesarean delivery, multiparous with prior cesarean delivery), education (Less than high school, high school, some college or associates degree, college degree or greater)

Table 3. Obesity-mediated effect of maternal race on severe maternal morbidity*

	Total unadjusted OR (95%CI)	Total adjusted aOR [†] (95%CI)	Direct aOR [†] (95%CI)	Obesity-mediated indirect aOR [†] (95%CI)
N	409,021	405,578		
Maternal race				
White	1.00	1.00	1.00	1.00
Black	3.02 (2.88-3.17)	2.90 (2.72-3.09)	2.80 (2.63-3.00)	1.03 (1.02-1.05)
Latina	2.01 (1.90-2.12)	1.92 (1.81-2.04)	1.88 (1.77-1.99)	1.02 (1.01-1.03)
Asian	1.25 (1.15-1.35)	1.20 (1.11-1.29)	1.21 (1.12-1.30)	0.99 (0.99-1.00)
Other	2.24 (1.45-3.45)	2.22 (1.62-3.05)	2.20 (1.60-3.02)	1.01 (1.01-1.02)

*Obesity (BMI \geq 30kg/m²); reference: normal weight (BMI 18.5-24.9kg/m²)

[†] Adjusted for age (continuous), Medicaid insurance (Yes or No), parity (primiparous, multiparous without prior cesarean delivery, multiparous with prior cesarean delivery), and education level (Less than high school, high school, some college or associates degree, college degree or greater)

Table S1: Selected socio-demographic and medical characteristics of all participants by maternal race

	White n(%)	Black n(%)	Latina n(%)	Asian n(%)	Other n(%)	p*
	185,095 (31.3)	122,067 (20.6)	177,768 (30.1)	97,496 (16.5)	1,407 (0.2)	
Socio-demographic characteristics						
Maternal age (years) [mean ±standard deviation]	31.3 ±5.7	28.7 ±6.5	27.8 ±6.3	30.7 ±5.2	29.7 ±6.0	<0.001
Maternal age (years) [categorical]						<0.001
<20	2,301 (1.2)	8,696 (7.1)	16,193 (9.1)	890 (0.9)	45 (3.2)	
20-34	127,763 (69.0)	88,414 (72.4)	133,069 (74.9)	73,319 (75.2)	1,049 (74.6)	
>=35	55,031 (29.7)	24,957 (20.5)	28,506 (16.0)	23,287 (23.9)	313 (22.3)	
Missing	0	0	0	0	0	
Foreign born						<0.001
Yes	50,890 (27.5)	51,599 (42.3)	96,740 (54.4)	74,297 (76.2)	882 (62.7)	
No	134,205 (72.5)	70,468 (57.7)	81,028 (45.6)	23,199 (23.8)	525 (37.3)	
Missing	0	0	0	0	0	
Education						<0.001
Less than high school	14,553 (7.9)	24,727 (20.3)	65,221 (36.7)	21,837 (22.4)	222 (15.8)	
High school	34,881 (18.8)	32,831 (26.9)	42,759 (24.1)	18,055 (18.5)	379 (26.9)	
Some college or associates degree	27,525 (14.9)	39,006 (32.0)	44,978 (25.3)	15,807 (16.2)	377 (26.8)	
College degree or greater	107,691 (58.2)	24,816 (20.3)	24,378 (13.7)	41,723 (42.8)	419 (29.8)	
Missing	445 (0.2)	687 (0.6)	432 (0.2)	74 (0.1)	10 (0.7)	
Employed during pregnancy						<0.001
Yes	117,640 (63.6)	59,519 (48.8)	69,419 (39.1)	39,496 (40.5)	659 (46.8)	
No	67,316 (36.4)	62,189 (51.0)	108,170 (60.9)	57,982 (59.5)	744 (52.9)	
Missing	130 (0.1)	359 (0.3)	179 (0.1)	18 (0.0)	4 (0.3)	
Insurance						<0.001
Medicaid	63,504 (34.3)	85,694 (70.2)	139,554 (78.5)	58,995 (60.5)	783 (55.7)	
Private	119,122 (64.4)	30,744 (25.2)	34,039 (19.2)	37,114 (38.1)	585 (41.6)	
Uninsured	1,102 (0.6)	3,403 (2.8)	2,471 (1.4)	811 (0.8)	22 (1.6)	
Other payer	1,367 (0.7)	2,226 (1.8)	1,704 (1.0)	576 (0.6)	17 (1.2)	
Missing	0	0	0	0	0	

Medicaid							<0.001
	Yes	63,504 (34.3)	85,694 (70.2)	139,554 (78.5)	58,995 (60.5)	1,189 (13.2)	
	No	121,591 (65.7)	36,373 (29.8)	38,214 (21.5)	38,501 (39.5)	7,839 (86.8)	
	Missing	0	0	0	0	0	
Medical history							
Prepregnancy body mass-index (kg/m ²)							<0.001
	Underweight (<18.5)	11,103 (6.0)	4,584 (3.8)	5,736 (3.3)	11,484 (11.8)	112 (8.0)	
	Normal weight (18.5-24.9)	122,092 (66.0)	45,967 (38.1)	79,671 (45.3)	65,452 (67.3)	719 (57.1)	
	Overweight (25-29.9)	33,957 (18.4)	35,610 (29.5)	52,643 (29.9)	15,324 (15.8)	371 (26.4)	
	Obese (>=30)	17,204 (9.3)	34,629 (28.7)	37,893 (21.5)	4,970 (5.1)	200 (14.2)	
	Missing	739 (0.4)	1,277 (1.1)	1,875 (1.0)	266 (0.3)	5 (0.4)	
Obstetric history							
Parity by delivery type							<0.001
	Primiparous	85,999 (46.5)	52,572 (43.1)	72,068 (40.6)	48,575 (49.8)	692 (49.2)	
	Multiparous without prior cesarean delivery	528 (39.7)	48,747 (39.9)	74,249 (41.8)	33,483 (34.3)	505 (35.9)	
	Multiparous with prior cesarean delivery	24,295 (13.1)	20,063 (16.4)	30,427 (17.1)	14,835 (15.2)	199 (14.1)	
	Missing	1,273 (0.7)	685 (0.6)	1,004 (0.6)	603 (0.6)	11 (0.8)	

*Chi-squared test of independence or ANOVA

Table S2: Selected socio-demographic and medical characteristics of all participants by BMI category

	Underweight n=33,146 (5.7%)	Normal weight n=314,047 (54.1%)	Overweight n=137,990 (23.8%)	Obese n=94,974 (16.4%)	p*
Socio-demographic characteristics n (%)					
Maternal age (years) [mean ±standard deviation]	28.2 ±6.0	29.7 ±6.1	29.7 ±6.2	29.7 ±6.2	<0.001
Maternal age (years) [categorical]					<0.001
<20	2,189 (6.6)	15,363 (4.9)	6,364 (4.6)	3,912 (4.1)	
20-34	25,608 (77.3)	226,988 (72.3)	99,365 (72.0)	68,958 (72.6)	
>=35	5,349 (16.1)	71,696 (22.8)	32,261 (23.4)	22,104 (23.3)	
Missing	0	0	0	0	
Race					<0.001
White	11,103 (33.5)	122,092 (38.9)	33,957 (24.6)	17,204 (18.1)	
Black	4,584 (13.4)	45,967 (14.6)	35,610 (25.8)	34,629 (36.5)	
Latina	5,736 (17.3)	79,671 (25.4)	52,643 (38.2)	37,893 (39.9)	
Asian	11,484 (34.7)	65,452 (20.8)	15,324 (11.1)	4,970 (5.2)	
Other	112 (0.3)	719 (0.2)	371 (0.3)	200 (0.2)	
Missing	127 (0.4)	146 (0.1)	85 (0.1)	78 (0.1)	
Foreign born					<0.001
Yes	18,037 (54.4)	148,678 (47.3)	68,082 (49.3)	37,530 (39.5)	
No	15,109 (45.6)	165,369 (52.7)	69,908 (50.7)	57,444 (60.5)	
Missing	0	0	0	0	
Education					<0.001
Less than high school	7,286 (22.0)	59,102 (18.8)	34,039 (24.7)	24,600 (25.9)	
High school	7,313 (22.1)	63,379 (20.2)	32,900 (23.8)	24,318 (25.6)	
Some college or associates degree	6,354 (19.2)	60,288 (19.2)	33,451 (24.2)	27,022 (28.5)	
College degree or greater	11,822 (35.7)	130,684 (41.6)	37,222 (27.0)	18,706 (19.7)	
Missing	371 (1.1)	594 (0.2)	378 (0.3)	328 (0.4)	
Employed during pregnancy					<0.001
Yes	14,116 (42.6)	161,777 (51.5)	64,664 (46.9)	45,014 (47.4)	
No	18,715 (56.5)	152,066 (48.4)	73,203 (53.1)	49,829 (52.5)	
Missing	315 (1.0)	204 (0.1)	123 (0.1)	131 (0.1)	
					<0.001

Insurance						
	Medicaid	20,020 (60.4)	168,846 (53.8)	90,775 (65.8)	66,005 (69.5)	
	Private	12,354 (37.3)	138,572 (44.1)	43,533 (31.6)	26,497 (27.9)	
	Uninsured	497 (1.5)	3,794 (1.2)	2,090 (1.5)	1,330 (1.4)	
	Other payer	275 (0.8)	2,835 (0.9)	1,592 (1.2)	1,142 (1.2)	
	<i>Missing</i>	0	0	0	0	
Medicaid						<0.001
	Yes	20,362 (61.4)	171,485 (54.6)	92,396 (67.0)	66,938 (70.5)	
	No	12,784 (38.6)	142,562 (45.4)	45,594 (33.0)	28,036 (29.5)	
	<i>Missing</i>	0	0	0	0	
Obstetric history n (%)						
Parity by delivery type						<0.001
	Primiparous	18,368 (55.4)	155,049 (49.4)	52,466 (38.0)	32,699 (34.4)	
	Multiparous without prior cesarean delivery	11,769 (35.5)	117,664 (37.5)	59,760 (43.3)	39,701 (41.8)	
	Multiparous with prior cesarean delivery	2,850 (8.6)	39,433 (12.6)	24,911 (18.0)	21,946 (23.1)	
	<i>Missing</i>	159 (0.5)	190 (0.6)	853 (0.6)	628 (0.7)	

*Chi-squared test of independence or ANOVA

Table S3: Association between maternal race and severe maternal morbidity (SMM) and Association between maternal race and obesity

Association* between maternal race and SMM (n=591,455)

	OR		95%CI
White	1.00		
Black	2.95	2.82	3.10
Latina	1.98	1.89	2.07
Asian	1.22	1.15	1.29
Other	2.07	1.52	2.82

Association* between maternal race and obesity(n=580,157)**

	OR		95%CI
White	1.00		
Black	3.90	3.83	3.98
Latina	2.67	2.62	2.72
Asian	0.52	0.51	0.54
Other	1.62	1.39	1.88

*Logistic regression univariable analysis **Body mass index \geq 30 kg/m²

Table S4:
Maternal race and severe maternal morbidity without blood transfusion

(sensitivity analysis)

Cases of SMM without blood transfusion by maternal race

	Total hospital deliveries	SMM without blood transfusion			
		Total	%	Rate per 10,000	95% CI
Total	591455	3185	100	53.9	52.0-55.7
White	185095	704	22.1%	38.0	35.2-40.8
Black	122067	1024	32.2%	83.9	78.8-89.0
Latina	17770768	1032	32.4%	58.1	54.5-61.6
Asian	9770496	310	9.7%	31.8	28.3-35.3
Other	1407	8	0.3%	56.9	17.5-96.3

Table S4 – continued

Obesity-mediated effect of maternal race on severe maternal morbidity excluding blood transfusion*

Adjusted for age**, Medicaid insurance***, parity****, and education level*****

	Total unadjusted OR (95%CI)	Total adjusted aOR (95%CI)	Direct aOR (95%CI)	Obesity-mediated indirect aOR (95%CI)
N	409,021	405,578		
Maternal race				
White	1.00	1.00	1.00	1.00
Black	2.24 (2.00-2.50)	2.49 (2.21-2.81)	2.17 (1.90-2.48)	1.15 (1.11-1.19)†
Latina	1.58 (1.38-1.80)	1.85 (1.63-2.09)	1.68 (1.48-1.92)	1.10 (1.07-1.12)††
Asian	0.85 (0.73-1.00)	0.88 (0.76-1.062)	0.91 (0.78-1.04)	0.97 (0.97-0.98)
Other	1.16 (0.45-2.94)	1.26 (0.48-3.33)	1.21 (0.46-3.18)	1.05 (1.03-1.07)

*Obesity (BMI >= 30kg/m2); reference: normal weight (BMI 18.5-24.9kg/m2) **continuous ***Yes or no

****primiparous, multiparous without prior cesarean delivery, multiparous with prior cesarean delivery

*****Less than high school, high school, some college or associates degree, college degree or greater

†Indirect effect: 15.3% ††Indirect effect:15.2%

Chapter 6: Discussion

6.1 Synthesis of main results

Few studies are designed to explore the causal role of individual-level risk factors to explain worse maternal health outcomes among minority women. The investigations which have previously tried to have been inconclusive. In this doctoral work we attempted to better elucidate and quantify the role of one such individual-level risk factor, prepregnancy obesity, as a mediator of the association between maternal origin and SMM in two high-income countries – France and the USA.

Our investigations found similarly positive associations of comparable strength between maternal prepregnancy obesity and global SMM in France and in NYC. As described in Chapter 2, previous studies have suggested such an association. By examining SMM by timing in the EPIMOMS study we found that obesity was associated with SMM in the antepartum, primarily due to hypertensive disease, but not associated with SMM in the intrapartum or postpartum, primarily due to postpartum hemorrhage (PPH) – a novel finding of our analyses. Like some previous studies, we found a dose-response relationship between elevated BMI and global SMM in our NYC data, as well as between elevated BMI and SMM due to blood transfusion. This dose-response relationship was also found for antepartum SMM due to severe hypertensive disorders in the French EPIMOMS study, suggesting causality⁴⁴. We thus advance the findings of previous studies not only by the robustness of our analyses but also by providing greater nuance of causal mechanisms, i.e. that obesity is most likely a risk factor for SMM due to hypertensive disease but not due to

PPH in the French context, and a risk factor for severe PPH requiring transfusion in NYC. Indeed severe obesity in the American context may be a barrier to diligent care for early PPH and also result in a higher tolerance for blood loss, thus increasing both the risk and progression of PPH.

Maternal origin was associated with SMM in both national contexts, confirming a previously well-established finding. In the French PreCARE study women born in Sub-Saharan Africa were more likely than European-born women to experience severe preeclampsia (one type of SMM) and the NYC analysis found that Black and Latina women were more likely than White women to experience global or all-cause SMM. In the French PreCARE study obesity mediated 18% of the association between Sub-Saharan African place of birth and experiencing severe preeclampsia. The mediation analysis conducted on data from NYC examined the mediation effect of obesity in the association between maternal race and global SMM. This effect was 3.2% among Black mothers and 3.4% among Latinas. Excluding blood transfusions as a criterion of SMM and then presumably examining SMM primarily due to severe hypertensive disease resulted in a higher mediation effect of approximately 15% among both Black and Latina women, consistent with the PreCARE findings.

Despite variations in data sources and outcome definitions in both countries, our findings were congruent across contexts. That is, prepregnancy obesity mediates a similar part of the association between Sub-Saharan African origin in France or Black/Latina race in NYC and SMM due to severe maternal hypertensive disease.

6.2 Strengths and limitations

6.2.1 Study populations and data sources

Our investigations employed large contextually representative datasets of high quality. The EPIMOMS study collected comprehensive population-based data regarding participants' pregnancies and obstetric hospitalizations and allowed for a novel analysis of SMM by clinical timing. The PreCARE dataset included a large number of social variables in participant questionnaires, most of which are not otherwise routinely collected in France. The PreCARE study was conducted in socially deprived neighborhoods of Paris and included a significant proportion of participants who did not speak French (11%) and non-European immigrants (47.6%). This was an important distinction as these subgroups of the French population have been previously under-investigated. The high retention rate of 92% limited selection bias in this social cohort investigation. Notably, prepregnancy obesity was ascertained in PreCARE and Epimoms by self-reported weight which has been found to have good accuracy^{13,110} as compared to the first weight measured during prenatal care reported in the obstetrical files as the latter is not standardized by gestational age. The NYC SPARCS-VS sample was racially and ethnically diverse, and population-based. The dataset was limited by the reliability of administrative data.

The relatively small number of SMM cases in EPIMOMS and PreCARE was a limitation, particularly for the analysis of subcategories of SMM causes. The fact that we did not find a dose-response relationship between elevated BMI and some SMM causes, such as sepsis and cardiovascular disease, and only antepartum SMM due to hypertensive disease in the EPIMOMS study may be a result of the small number of these SMM causes included in

the investigation. Prior data does in fact suggest such a link²¹. On the other hand, the NYC SPARCS-VS dataset was large, exhaustive, previously validated, and included a large number of SMM events. Notably, this aspect was counterbalanced by the strengths and limitations of the SMM definitions in the different datasets (see below). The NYC SPARCS-VS dataset had a large number of SMM cases however with heterogeneous SMM case definition and imprecise cause and severity, versus the EPIMOMS and PreCARE datasets had a limited number of SMM cases with more homogeneous SMM definition and precise cause.

6.2.2 Severe maternal morbidity definitions

In our analyses we defined outcomes, whether that of global SMM (in EPIMOMS and NYC SPARCS-VS) or component causes (in EPIMOMS and PreCARE), via previous rigorous validation and consensus procedures^{15,116}. The French EPIMOMS study utilized an innovative approach and further elucidated the role of maternal obesity on the pathway to SMM by the timing of occurrence (in the antepartum mostly due to severe hypertensive disorders). The use of global SMM as the outcome allowed for comparability with the vast majority of the existing literature. The WHO “Maternal Near Miss” (MNM) definition has been used routinely in many SMM studies and is useful from the perspective of allowing comparisons with existing data, however it was not available at the time the EPIMOMS study was conceived. Interestingly, the EPIMOMS consensus definition is quite similar to the WHO MNM but the latter has more severe definition thresholds, thus making it less suitable for high-income countries. The severe preeclampsia outcome used in the PreCARE

study was defined according to standard French clinical guidelines and allowed for direct comparability with previous data. The definition of SMM in the NYC SPARCS-VS dataset was based on a CDC algorithm used in the majority of SMM investigations conducted in the USA, thus also making it ideal for comparability.

Notably, SMM was not a strictly homogenous notion in terms of severity in the American data. There is for instance a gap between SMM due to PPH of 1L of blood loss and SMM due to ICU admission. Also, the CDC SMM definition likely overestimates the rate of severe maternal morbidity due to inclusion of any blood transfusion while also potentially including varying degrees of severity, while the EPIMOMS expert consensus definition attempted to have a similar degree of severity for PPH as well as other SMM causes. The sensitivity analysis in which all cases of blood transfusion were excluded in the NYC SPARCS-VS study addressed the issue of global SMM overestimation however did not rule out the severity issue. Obesity may influence the risk of more severe forms of SMM that cannot be detected by our study design.

Obesity might possibly play a greater role for less prevalent causes of SMM, e.g. thrombotic events or cardiac events, that could not be studied individually in the datasets we used for different reasons: cases from these causes identified in the French data, but too rare to be studied as outcomes; rare-cause SMM cases were theoretically more prevalent in the American data, but they are impossible to isolate given the nature of the definitions.

6.2.3 Causality analysis

From a methodological point of view, we employed a mediation path analysis approach to study the role of obesity in the association between maternal origin and SMM

in the PreCARE and NYC SPARCS-VS data. Previous investigations included obesity as an adjustment variable and not as a mediator. The strengths of our approach included simplicity and a quantitative intuitive assessment of the role of obesity as a mediator. Our approach was limited by not including all BMI categories in the mediation analysis and that we were not able to consider other mediators jointly. Our analyses also did not allow for an accurate assessment of confidence intervals for our quantitative results, thus limiting the theoretical translational value of our findings. Additionally, the proposed path analysis simply provides best estimates of real-world phenomena and is not perfectly precise as one cannot reasonably control for all possible confounders or account for all mediators. During the conception of the current doctoral analysis plan, there existed various published approaches for conducting multiple mediator analyses. However they were significantly complex, difficult to interpret, and there was a lack of consensus regarding the validation of any approach. Given these limitations, we believed focusing our analysis on a single mediator allowed us to not only isolate prepregnancy obesity more accurately as a risk factor, but also to provide a statistically demonstrative baseline for future more complex analyses. More sophisticated mediation path analysis methodologies have been tested in clinical epidemiologic investigations and operationalized via available statistical software since then⁹⁸. These include structural equation modeling for path analysis to accurately quantitatively analyze several categorical and continuous mediators at the same time, calculate latent effects, indirect mediation components, and account for the potential relationships between them^{59,61}. Subsequent investigations of health disparities in SMM should use this approach to better ascertain the relative ranking of effects.

6.2.4 Cross-national approach

The cross-national approach tested for a potential role of social or medical context in influencing the outcome and also provided an opportunity for reproducibility in order to better approximate causality from observational data. Yet there are challenges and limitations to synthesizing results across diverse contexts given considerable variations in obesity prevalence, health systems, and the status of immigrant and minority health. Furthermore, there are country-specific methodological differences which can complicate direct comparisons. Most crucially these include differences in the exposure (maternal origin) and outcome (SMM). However, our results were concordant in the two countries therefore this approach was more a strength than a limitation. Given that obesity primarily operates as a medical variable, we are further reassured that the findings were similar in both contexts. Obesity can also function as a social variable as obese women may face discrimination, for example in the quality of care they receive. Our concordant results indicate that a possible social aspect of obesity is also similar in both contexts.

Notably, unlike in the American data, in the French EPIMOMS study we did not find a dose-response relationship between BMI categories and overall SMM and most sub-categories of SMM. The exception was antepartum SMM due to severe hypertensive disorders, where a clear dose-response relationship was observed. This is likely due to PPH being a major component of global SMM in the NYC data and that obesity is a risk factor for SMM in the American context but not in France. Additionally, it may also be due to a higher prevalence of severe obesity in the USA.

6.3 Furthering an understanding health disparities

Not all health *differences* between groups are health disparities. “Health disparity” is defined specifically as “worse health among socially disadvantaged people” ¹².

Characteristics by which groups differ resulting in health disparities include income, race/ethnicity, immigrant status, mental or physical disability, sexual orientation or gender identity, and geographic location – essentially any factor by which groups are subject to discrimination or have differential access to resources in managing their health risks^{40,127}. Health disparity is an indicator of “health equity”- defined as “social justice in health”, or the degree to which “no one is denied the possibility to be healthy for belonging to a group that has historically been economically/socially disadvantaged” ¹².

As described previously, the association between maternal origin (race or nativity) has been shown to be a strong predictor of SMM globally. The three main analyses in this doctoral dissertation replicate and confirm the importance of this social predictor of maternal health both in France and the USA. Our investigations go a step further to try to understand the mechanism of action of this association by concluding that maternal prepregnancy obesity is a partial mediator of the relationship, specifically of severe hypertensive SMM. This new evidence may be interpreted within a social determinants of health conceptual model by considering the social context, differential exposure, differential vulnerability, and differential consequences for minority mothers ¹³¹. For example from our results we may postulate a role of nutrition, chronic stress, implicit provider bias, and inadequate prenatal screening and monitoring in the pathway from maternal origin to obesity to hypertensive SMM. These and other hypothetical

intermediaries are presently not well understood in how they affect maternal health disparities. For inequalities in SMM due to other causes, our results do not support obesity as a major factor. We hypothesize that this is likely due to the much larger role of social determinants of health for minority mothers, which are currently not well understood.

6.4 Implications for clinical practice and public health policy

Our findings have implications for various stakeholders, including health care facilities, providers, agencies, and individuals. Given the higher prevalence of obesity in the USA as compared to France, the policy implications of our results are plausibly more salient in the USA and can potentially have a greater impact overall.

The identification of obesity as a risk factor for SMM due to hypertensive disease in the antepartum has obvious clinical implications. SMM prevention strategies at the regional or facility level should include improved prenatal quality of care measures among obese women, such as blood pressure monitoring using proper cuff size selection and placement to avoid inaccurate measurements. Our findings may also serve to improve general awareness among providers regarding the magnitude of the overall association, as well as the specific role they may play in differential care and preventing delayed diagnosis or an evolution of more severe hypertensive disease among minority mothers ⁴⁹.

6.5 Research perspectives

Our results support the need to test interventions for obesity reduction to reduce the risk of severe preeclampsia among minority women. Given our findings that maternal obesity is not the main mediator in both countries, future investigations should also

explore other possible mediators of the association between maternal origin and SMM. The roles of other medical risk factors (e.g. pre-existing diabetes, pre-existing hypertension, cardiovascular disease) have been incompletely investigated, and to our knowledge not by path analysis approaches. Psychiatric diagnoses and factors relating to maternal stress should be explored. Social factors such as place of residence, physical security, income, and healthcare access are of significant interest. Structural factors such as racism and implicit bias are essential to consider in health disparities research and have been under-investigated in SMM studies. More nuanced investigations of maternal origin specifics that can affect quality of care, such as linguistic barriers, legal status, years of residence housing, work, cultural factors, racial subgroups (in particular for Asians in the American context)- among others- are needed as adjuncts beyond the traditional race and place of birth categories. The “healthy migrant effect” - of variable applicability in pregnancy outcomes- is also an area meriting further investigation. As mentioned above, the role of BMI as a mediator between origin and other specific causes of SMM should be explored. In the case of rare-cause SMM, a combination of data sources which allow both for the identification of a large number of events (e.g. administrative datasets) and high quality data (i.e. cohort studies) are needed, similar to the approach used in this doctoral work. The role of BMI or obesity as a mediator in the association between other social characteristics (e.g. income, zip code) and SMM needs further study. Given the burden of disease in the USA, there is a need for better quality prospective data from research investigations, not unlike that of EPIMOMS in France, to complement the studies currently done primarily using administrative databases. Given the size and demographic and political heterogeneity of

the USA, such population-based studies would necessarily need to be limited by state or county. Finally, the findings of our work in different contexts highlights the need to standardize minimum core datasets not only towards more harmonious SMM definitions^{45,62,107} but also research methodologies, perhaps via a global consortium.

Publications from the doctoral work

Siddiqui A, Azria E, Howell EA, Deneux-Tharoux C, EPIMOMS Study Group, Langer B, Dupont C, Rudigoz RC, Vendittelli F, Beucher G, Rozenberg P. Associations between maternal obesity and severe maternal morbidity: Findings from the French EPIMOMS population-based study. *Paediatric and perinatal epidemiology*. 2019 Jan;33(1):7-16.

Siddiqui A, Deneux-Tharoux C, Luton D, Schmitz T, Mandelbrot L, Estellat C, Howell EA, Khoshnood B, Bertille N, Azria E. Maternal obesity and severe preeclampsia among immigrant women: a mediation analysis. *Scientific reports*. 2020 Mar 23;10(1):1-9.

Siddiqui A, Azria E, Egorova N, Deneux-Tharoux C, Howell EA. Contribution of Prepregnancy Obesity to Racial and Ethnic Disparities in Severe Maternal Morbidity. *Obstetrics & Gynecology*. 2021 May 1;137(5):864-72.

Presentations

“The risk of severe preeclampsia among immigrant women and the role of maternal obesity: results from the PreCARE cohort study”

Presented in May 2018 to the Obstetrical, Perinatal and Pediatric Epidemiology Research Team, Center for Research on Epidemiology and Statistics Sorbonne Paris Cité at the French National Institute for Health and Medical Research and the Paris-Descartes University

“Obesity and the risk of severe acute maternal morbidity in France: ongoing findings from a case-control study”

Presented in January 2017 to the Obstetrical, Perinatal and Pediatric Epidemiology Research Team, Center for Research on Epidemiology and Statistics Sorbonne Paris Cité at the French National Institute for Health and Medical Research and the Paris-Descartes University

“Obesity and the risk of severe acute maternal morbidity in France: Findings from the EPIMOMS population-based study”

Oral presentation at the annual meeting of the European Board and College of Obstetrics and Gynaecology – Paris 03/2018

“Maternal obesity and severe preeclampsia among immigrant women: A mediation analysis”

Poster presentation at the annual meeting of the European Public Health Association – Marseille 11/2019

“Can obesity explain racial disparities in severe maternal morbidity?”

Poster presentation at the annual meeting of the Society for Maternal Fetal Medicine –USA (remote/virtual conference) 01/2021

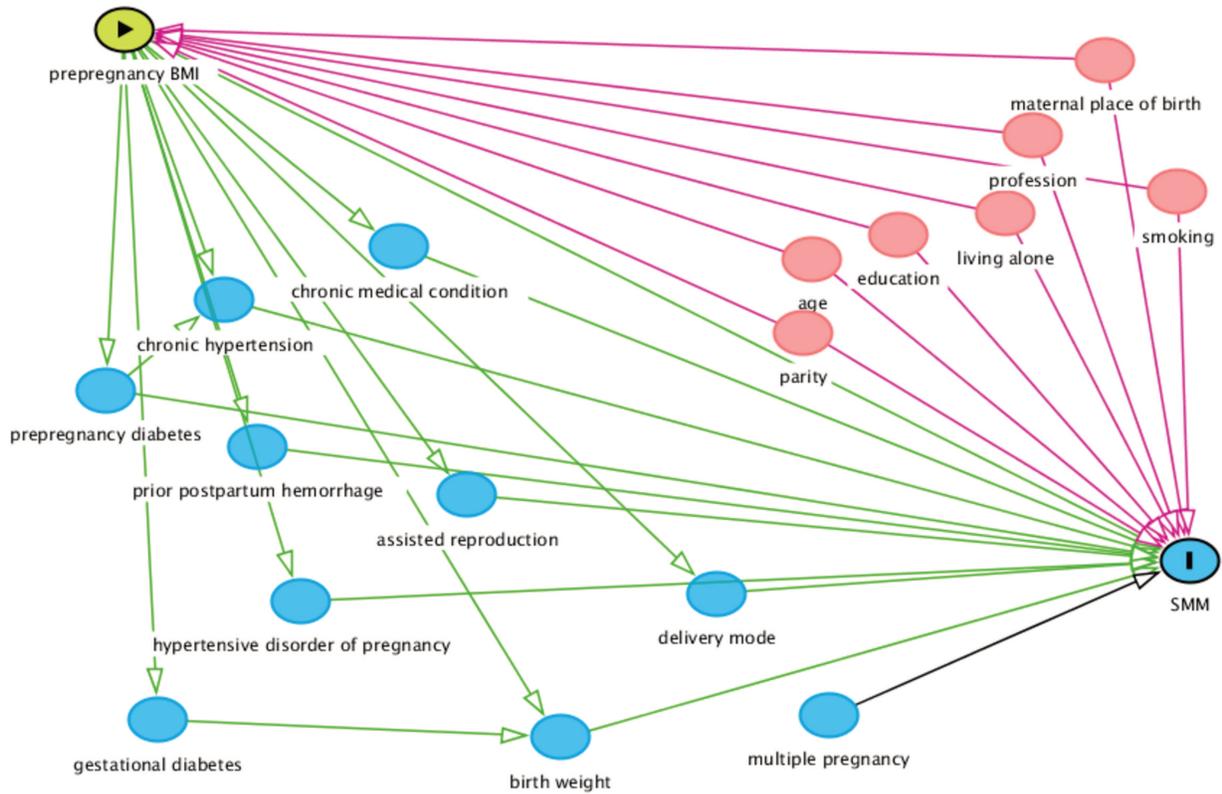
Appendix I: Directed acyclic graphs of individual analyses

Green = exposure or main intermediate variable for mediation analysis

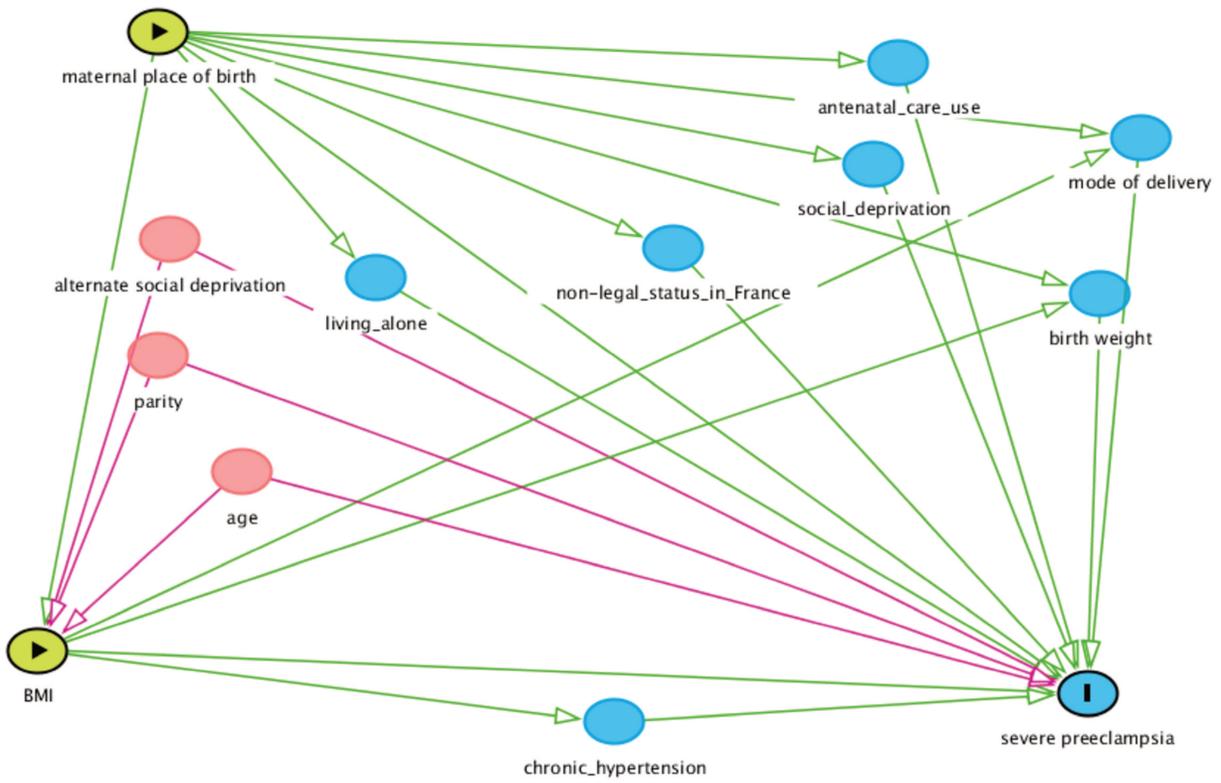
Blue = outcome or intermediate

Red = confounder

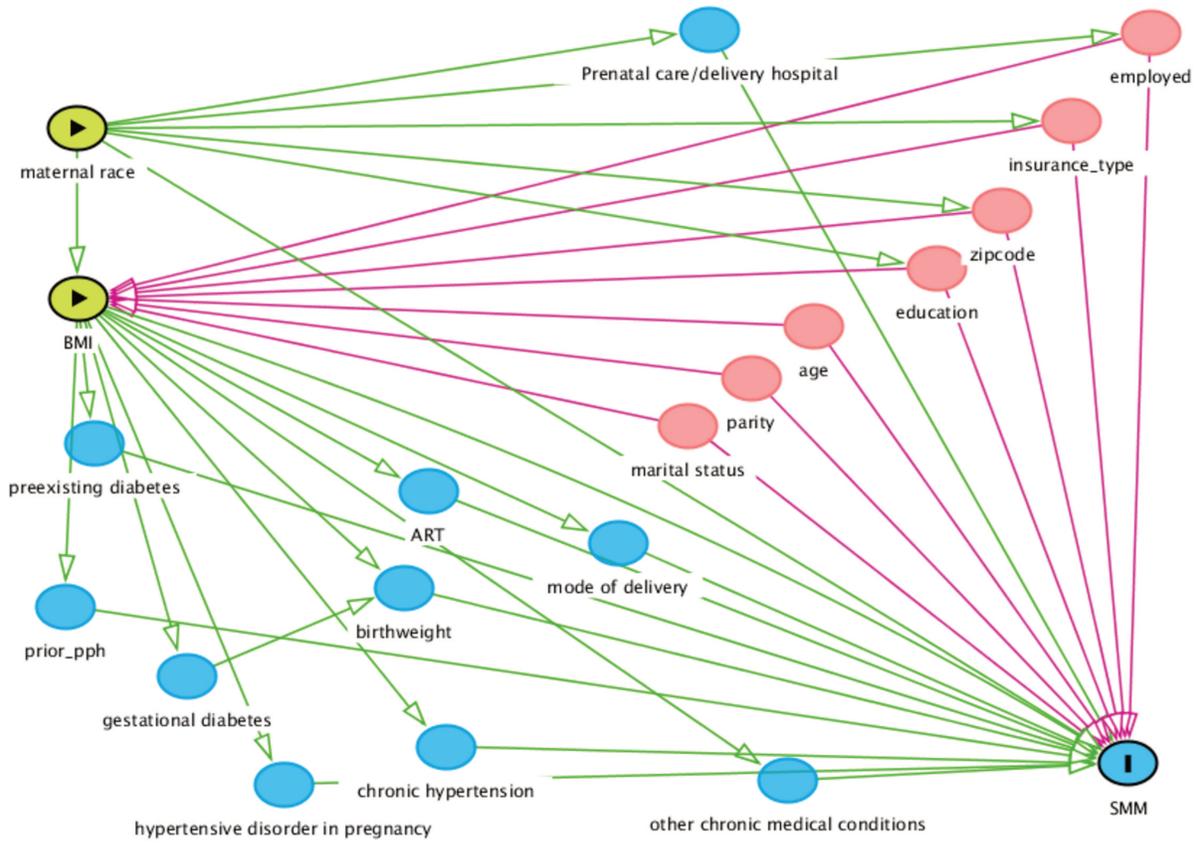
A1: Directed acyclic graph of the EPIMOMS study



A2: Directed acyclic graph of the PreCARE study



A3: Directed acyclic graph of the NYC/VS-SPARCS study



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