**Distribution Agreement**

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

_____ _____

Kirsten A. Herrick Date

Maternal Anthropometry and Adverse Perinatal Outcomes in Chinese Women

By

Kirsten A. Herrick

Doctor of Philosophy

Division of Biological and Biomedical Sciences

Nutrition and Health Sciences

| | |
|---|---|
| K.M. Venkat Narayan<br>Advisor | Adolfo Correa<br>Committee Member |
| Michele Marcus<br>Committee Member | Reynaldo Martorell<br>Committee Member |
| Usha Ramakrishnan<br>Committee Member | David F. Williamson<br>Committee Member |

Accepted:

Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

Date

# Maternal Anthropometry and Adverse Perinatal Outcomes in Chinese Women

By

Kirsten A. Herrick

B.A. The University of Tennessee, 1999

MSc, The London School of Hygiene and Tropical Medicine, 2002

Advisor: K.M. Venkat Narayan, M.D., M.Sc., M.B.A.

An abstract of

A dissertation submitted to the Faculty of the James T. Laney

School of Graduate Studies of Emory University in partial

fulfillment of the requirements for the degree of

Doctor of Philosophy

in

Division of Biological and Biomedical Sciences

Nutrition and Health Sciences

2011

ABSTRACT

Maternal Anthropometry and Adverse Perinatal Outcomes in Chinese Women

By

Kirsten A. Herrick

Low birth weight, macrosomia and cesarean delivery confer serious consequences to mothers and infants. Epidemiological evidence associates maternal anthropometry, namely height, pre-pregnancy body mass index (BMI), and gestational weight gain (GWG) with the adverse outcomes: low birth weight (LBW), macrosomia and cesarean delivery (CD) in Europoid populations. However there is a dearth of information on these associations among Chinese women which may not function identically as observed in Europoid populations. For example, rates of CD in China are among the highest of any developing country at 46%. The prevalence of LBW is uncharacteristically low for a developing country, roughly 3%. Macrosomia, at the opposite end of the birth weight spectrum, has yet to see a large increase.

Using data from a large prospective cohort of pregnant women (n=247,831) we found that recommendations for GWG, derived in the US population, did not adequately identify Chinese women at risk of CD or delivering a macrosomic infant; however, they satisfactorily identified women at risk of delivering a LBW infant. To understand why the recommendations were not well suited for Chinese women, we undertook an examination of maternal pre-pregnancy BMI and height and focused solely on the outcome of CD. We found that the risk for CD increased at a considerably lower pre-pregnancy BMI than previously thought. Additionally, the impact of GWG on CD depends on pre-pregnancy BMI, such that high GWG is more deleterious in heavier women compared with leaner women. Maternal height was also found to increase the risk of CD; however, we were unable to identify a threshold where risk increased dramatically.

Adverse pregnancy outcomes are important endpoints and predictors of future health for both mothers and infants. Development of appropriate guidelines for maternal anthropometry is a good investment since the period prior to and during pregnancy provides an opportunity to mitigate risk factors for adverse pregnancy outcomes. Additional research is needed to develop adequate GWG guidelines tailored for Chinese women. Research should focus on the impact of the changing distribution of body weight and the growing prevalence of obesity in China.

# Maternal Anthropometry and Adverse Perinatal Outcomes in Chinese Women

By

Kirsten A. Herrick

B.A. The University of Tennessee, 1999

MSc, The London School of Hygiene and Tropical Medicine, 2002

Advisor: K.M. Venkat Narayan, M.D., M.Sc., M.B.A.

A dissertation submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

In

Division of Biological and Biomedical Sciences

Nutrition and Health Sciences

2011

# Acknowledgements

The process of obtaining my doctoral degree has been an exercise in persistence, a test of my resolve, and one of the hardest fought battles I've ever voluntarily signed up for. I would not have had the courage to continue had it not been for the many individuals along the way who gave of their time and support. Thank you to my committee members, Venkat Narayan, Adolfo Correa, Michele Marcus, Reynaldo Martorell, Usha Ramakrishnan, and David Williamson for your guidance and expertise. I would like to extend a special thank you to my adviser, Venkat Narayan, who had enough faith in my abilities to turn me loose on a project of my choice, allowed me to complete my degree remotely after my family moved to Virginia, seemed to be available via email at virtually any hour, and who generously funded the majority of my stipend when grant proposals were declined.

I am also grateful to three honorary committee members, RJ Berry, Dana Flanders, and David Kleinbaum, who were generous with their time. Your involvement immeasurably enriched my learning experience. I would like to recognize Nana Gletsu for her support as a colleague and in her role as the Director of Graduate Studies for the program. Thank you to my classmates Reena Oza-Frank, Mary Beth Weber, Jean Welsh, Jessica Marcinkevage, Stephanie Hinkle, Beth Imhoff, and Suzanne Judd. You always provided a compassionate ear. Some of you even put me up and fed me on a few occasions, making the process easier when I was far from home. Thanks to Stephan Brown, my 'PhD Buddy'. Our bi-monthly Skype meetings kept me honest and on track. Thank you to my parents who were my constant cheerleaders, and to my brother Tim for your continual overwhelming encouragement. Finally, my deepest appreciation goes to my husband, Carson, who was unwavering in his support. When you joked that *I* will be the 'doctor', but *you* have had all the 'patience', it was not far from the truth. I could not have done it without you.

# Table of Contents

# List of Tables

# List of Figures

# Chapter 1 Introduction

The impact of maternal anthropometry, i.e., pre-pregnancy body mass index (BMI) and gestational weight gain (GWG), on obstetric outcomes has been well documented in Europoid populations [1]. Low maternal pre-pregnancy BMI and low GWG have negative impacts on infant outcomes: infant mortality, low birth weight (LBW) and preterm delivery [2]. Pregnancy in a climate of excess is also not without risk. Mothers with excess GWG may experience gestational diabetes, preeclampsia, cesarean delivery (CD) [3] and weight retention after childbirth [4-6]. Maternal obesity creates an intra-uterine environment that impacts fetal development and hence future generations. It is associated with an increased risk of metabolic syndrome [7, 8], childhood obesity [9, 10], and diabetes [11] in the offspring.

Recommendations for GWG were developed by the Institute of Medicine (IOM) and first published in 1990 [2] and then revised in May 2009 [1]. Their overarching goals are to balance adequate weight gain to optimize fetal growth, and hence infant outcomes, and to promote maternal health by reducing pregnancy complications and minimizing maternal weight retention. These recommendations are based on mainly white women, living in the United States post the nutrition transition. In the US, roughly 40%  women start pregnancy overweight [12] and exceed recommended limits for pregnancy weight gain [13]. The IOM's recommendations are intended for use with US populations. Their application to women in developing countries, who may be shorter or thinner than US women, is less well established.

China has one of the world's most rapidly growing economies and currently has the largest population of any nation in the world, followed closely by India [14]. The economic changes over the past half century have laid the foundation for demographic, epidemiologic, and nutritional transitions. As China moves through the nutrition transition, diseases of overnutrition are appearing alongside diseases of undernutrition [15] and potentially within the same

individual. Additionally, over the past decade, Chinese immigrants have been one of the largest migrant groups to the United States, second only to immigrants from Mexico [16]. Because of past and present malnourishment, there is potential for Chinese women, both new immigrants to the US and, especially, women in China, to enter pregnancy undernourished, manifesting as maternal stunting alone or in combination with low pre-pregnancy BMI. Additionally, Chinese women are typically shorter, start pregnancy with a lower BMI, and gain less weight in pregnancy compared to US women [13].

The analyses in this dissertation sought to address the uncertainty surrounding the association between maternal anthropometry and adverse pregnancy outcomes among Chinese women. We chose to focus on three measures of maternal anthropometry: height, pre-pregnancy BMI and GWG, and three different adverse perinatal outcomes: LBW, macrosomia and CD. We examined the following questions:

- Are the IOM's recommendations appropriate for Chinese women, when evaluating LBW, macrosomia and CD?
- What is the relationship between pre-pregnancy BMI and CD in this Chinese population?
    - Is there evidence of a threshold effect of pre-pregnancy BMI?
    - Does pre-pregnancy BMI modify the association between GWG and CD?
- What is the relationship between maternal height and CD in this Chinese population?
    - Is there evidence of a threshold effect of maternal height?
    - Does maternal height modify the association between GWG and CD?
- What is the relative importance of maternal anthropometry to the risk of CD?

To accomplish our goals we were privileged to analyze the China-US Collaborative Project for Neural Tube Defect Prevention. It is a rare and underutilized source of data on pregnancy and perinatal outcomes among Chinese women. It was collected as dramatic changes

were beginning in earnest in China. It was undertaken to evaluate whether the maternal use of 400 micrograms of folic acid, taken before and during the first trimester of pregnancy was successful at preventing neural tube defect-affected pregnancies. From September 1993 through December 1996, all pregnant women or women planning marriage registered with the pregnancy monitoring system. At registration, physical measurements were taken, and questionnaires on reproductive history, general health and socio-economic status were administered. Women were followed throughout pregnancy and through six weeks postpartum [17, 18]. This data set is unparalleled in its ability to examine pregnancy and perinatal outcomes in this understudied population.

The following chapters will review the epidemiology of common adverse pregnancy outcomes: LBW, macrosomia, and CD (Chapter 2); review the association of maternal anthropometry and these outcomes (Chapter3); and provide details on the study design, data collection, data management, and analytical issues unique to this data set (Chapter 4). The remaining chapters report the main findings of this dissertation (Chapters 5, 6, & 7), and summarize the findings, conclusions and implications of this research (Chapter 8).

Chapters 5, 6 and 7 present the analyses of this dissertation. They focus on maternal anthropometry and its association with three adverse perinatal outcomes: LBW, macrosomia, and CD. First, we examine the performance of current US recommendations for adequate GWG by pre-pregnancy BMI, on our study population (Chapter 5). Next, we take a detailed look at the association between pre-pregnancy BMI and the risk of CD for the presence of a threshold effect, and further examine whether current definitions of overweight are similar to this threshold (Chapter 6). Finally, we describe the magnitude and direction of the association between maternal height and CD. We estimate the relative importance of maternal pre-pregnancy BMI, height, GWG and infant birth weight to understand whether different measures of maternal anthropometry are a better predictor of CD risk in this population (Chapter 7).

In a population of China's size (one-fifth of the earth's total population), the association between GWG and maternal and infant health outcomes will impact the health of future generations on a massive scale. This may be of particular importance for the rapidly growing new immigrant groups in the US and countries passing through the nutritional transition. The primary goal of this research is to add to our understanding of maternal anthropometry and adverse pregnancy outcomes among Chinese women, an important and understudied population. We hope that findings from this dissertation highlight the need for continued maternal and perinatal research in this population; as this dissertation captures a snapshot of women in a unique position: pregnant on the backdrop of dramatic epidemiologic transitions. Evidence based recommendations for GWG in pregnancy for women in developing countries are sorely needed. Identifying associations between maternal anthropometry and adverse pregnancy outcomes in developing countries is important for (a) understanding ways in which they differ from developed countries, (b) developing appropriate recommendations, and (c) developing prevention strategies and health policy to support healthy pregnancies for mothers and their infants, through pregnancy and beyond.

# Chapter 2 Literature Review: Epidemiology of Adverse Perinatal Outcomes

Maternal health, objectively measured by the maternal mortality ratio (MMR), a ratio of the number of maternal deaths per 100,000 live births, is an important indicator of health status [19]. It features as one of the 8 Millennium Development Goals [20]. Despite the recognition of maternal mortality as an important adverse perinatal outcome, it is a rare event and thus much of the published research focuses on its proxies: low birth weight (LBW), preterm birth, intrauterine growth restriction (IUGR), and congenital defects [21]. They are considered proxies of maternal mortality, especially where maternal nutrition is concerned, in that they are less severe summary measures of the multifaceted public health problem that includes long-term malnutrition, illness, and poor pregnancy care[22]. We chose to focus on LBW. Interestingly, the rate of LBW in China is low, more characteristic of a developed country [23], so we also chose to look at its counter: macrosomia, or high birth weight. Finally, as high rates of cesarean delivery (CD) are an increasing concern in developing countries [24], China among them, we have included CD in the following analysis.

## Low Birth Weight

The World Health Organization (WHO) defines low birth weight (LBW) as <2500 g (5.5 lbs) at birth [22]. Birth weight is determined by the duration of gestation and the rate of growth [25]. LBW is often associated with being physiologically immature and can manifest as poor suckling reflexes, increased susceptibility to infection, and low fat deposits, and is therefore associated with increased morbidity and mortality [26]. Studies have demonstrated that LBW infants are 20 times more likely to die, compared with their normal weight counterparts [22]. LBW, however, is a heterogeneous descriptor that indicates prematurity, either by time, termed

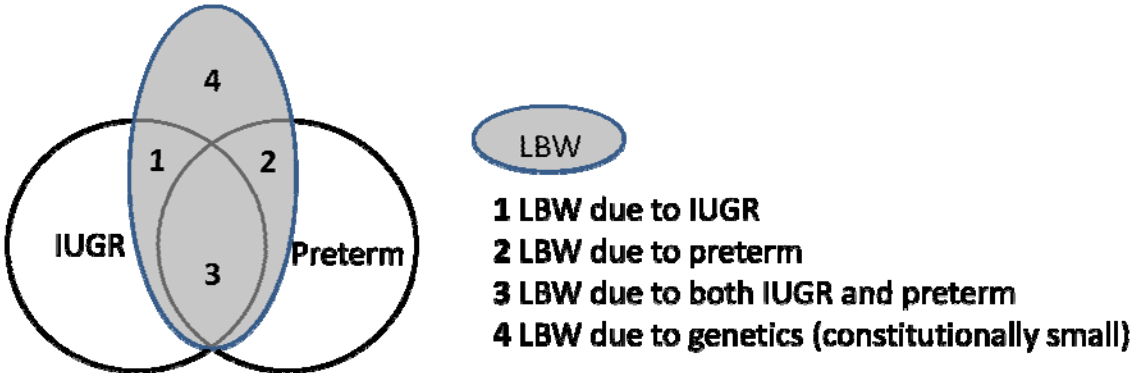
'preterm', (born before 37 weeks completed gestation), or rate of growth, termed 'intrauterine growth restricted' infants (IUGR).

The consequences of preterm and IUGR are different. Preterm infants are at an increased risk of death [21]. Significant organ system development occurs in the last weeks of pregnancy; therefore preterm infants that do survive birth may suffer short and long-term morbidities, principally in brain or lung function, but also in the immune and gastrointestinal systems, kidneys, eyes, and skin [27]. In contrast, infants that are growth restricted are at an increased risk of stillbirth [28, 29], and may suffer from short-term problems with hypoglycemia and hypocalcaemia [30]. Long-term morbidities such as diabetes and cardiovascular disease have also been found to be associated with IUGR infants as they age into adulthood [31].

IUGR is operationalized and measured by its proxy, small-for-gestational age (SGA). SGA is defined as a birth weight below the $10^{th}$ percentile for gestational age based on sex-specific curves from a reference population [21]. Although SGA and IUGR are often used interchangeably, they are not equivalent. Some SGA infants are constitutionally small, born to smaller parents, whereas other SGA infants are also IUGR and therefore be at higher risk of poor outcomes and would benefit the most from interventions to prevent morbidity and mortality. SGA indicates infants *at risk* of adverse outcomes due to small size, whereas IUGR infants have suffered an insult during development that manifests differently depending on the timing and severity of the insult [32].

LBW infants can be preterm, IUGR, both preterm and IUGR, or neither preterm nor IUGR. Figure 2-1 shows the relationship between LBW, preterm birth, and IUGR.

**Figure 2-1 Relationship between LBW, IUGR and Preterm**




Distinguishing between the types of LBW is hampered by the lack of specificity in the definition of SGA to identify IUGR, and by the reliance on gestational age to determine preterm birth. In developing countries, the use of ultrasound technology in early pregnancy to estimate fetal age is not routine [21]. Additionally, there is no international standard for the determination of SGA, so the use of different reference populations will identify different infants at risk of adverse outcomes [33]. Although recent studies have demonstrated that infants born below the 3$^{rd}$ percentile of gestational age adjusted, sex-specific reference curves have the most significant morbidly, [34, 35] without a standard reference population, the individuals identified as below the 3$^{rd}$ percentile change depending on the reference population used.

An estimated 20 million LBW infants are born worldwide and over 95% occur in developing countries [22]. LBW infants represent 7% of all births in developed countries, compared to 16% in developing countries [22]. However, there is large variation in rates of LBW within developing regions of the world. For example, in south-central Asia, where rates are the highest, 27% of all births are classified as LBW. In south-eastern Asia, the rate is halved, at 12% [22]. Within China, estimates vary widely as well, with more urban areas reporting lower rates

compared to rural areas. A national survey in China, completed in 1998, reported rates of LBW in urban and rural areas were 4.2% and 6.3%, respectively [36]. By comparison, rates of LBW in the United States are 8%, one of the highest in the developed world [37]. Although rates of LBW in China are low, due to the size of China's population a 3% rate of LBW represents roughly 1 million infants per year.

Traditionally, higher rates of LBW in developing countries are driven by high rates of IUGR, whereas LBW in developed countries are driven by high rates of preterm births [30]. The primary determinants of LBW in developed countries are multiple births resulting from fertility treatments and 'indicated preterm birth', due to fetal distress, suspected growth restriction, maternal preeclampsia and placental abruption [37]. In developing countries, where the majority of LBW is due to IUGR, the primary determinants are maternal nutritional status before and during pregnancy, race/ethnicity, maternal smoking habits, malaria infection, primiparity, pregnancy induced hypertension, and genetic abnormalities[30].

## Macrosomia

The term 'macrosomia' refers to a large infant at birth. There is no single, standard definition of macrosomia. In the literature, common definitions are infants with birth weights greater than or equal to 4000 g, 4500 g, and even 5000 g [38-41]. Unless otherwise noted here, 'macrosomia' refers to any infant born $\geq$ 4000g. Large for gestational age (LGA) is another term used to describe the oversized fetus, and similar to SGA, it uses sex and age-specific cut-offs from a reference population, and defines infants above the 90$^{th}$ centile as LGA and at risk of adverse outcomes[42].

Both women and their infants are at risk of adverse outcomes, during and after birth, if an infant is macrosomic. The main risks during labor arise from cephalopelvic disproportion, where the fetal head is too large to pass through the mothers pelvic outlet [43]. Common maternal

complications that arise during labor are: prolonged labor, 3rd and 4th degree perineal lacerations [44], and CD, and its associated complications, such as postpartum hemorrhage and infection [40]. Birth trauma is also a risk for the macrosomia infant. Shoulder dystocia, where the infant head is delivered, but the anterior shoulder gets stuck behind the pubic bone, requires physical manipulations to release the infant and allow delivery. Physical manipulations can cause injury to the brachial plexus or facial nerves and fractures to the clavicle and occasionally the humerus [44]. In rare cases, the infant may asphyxiate because of compression on the umbilical cord while stuck in the birth canal [43]. Future health risk for macrosomic infants include overweight, diabetes, metabolic syndrome and cancer later in life [45, 46].

The reported prevalence of macrosomia varies substantially from country to country and this variation cannot be solely attributed to the use of different definitions of macrosomia. In his review, Chauhan et al. reported that the prevalence of macrosomia ranged from 1% to 28%. Nigeria, Pakistan, Thailand and Taiwan were among the countries with the lowest prevalence (<3%), in contrast to Denmark and the Republic of Croatia where the prevalence exceeds 20% [40]. The United States has experienced a decline in the rate of macrosomia, from 9.1% to 7%, between 1990 and 2005, respectively [47]. Chauhan [40] and others[47] have speculated that multiple gestations secondary to assisted reproductive technology, older maternal age, routine testing for gestational diabetes, and obstetric interventions such as induction of labor and CD could be driving this decrease.

Reports on the prevalence of macrosomia in China vary. Estimates over a 7-month period in 1987 from the Prince of Wales Hospital in Hong Kong, China, showed roughly a 5% rate of macrosomia among singleton, cephalic presentation infants [48]. In a study of CD by maternal request, covering 1994-2006 in selected counties/cities in two southeastern provinces in China (Zhejiang and Jiangsu), Zhang et al. reported a 7.0-7.7% prevalence of macrosomia [49]. A more

recent study, representative of all births in Shenyang province in northeast China, reported a 9.6% prevalence of macrosomia from January to June 2009 [50].

There are many risk factors for fetal macrosomia; however, not all fetal macrosomia is detrimental. The highest infant survival rates are associated with birth weights between 3,500 – 4,499 grams [51]. Some large infants are constitutionally large due to genetic influences. Factors contributing to fetal macrosomia include: maternal obesity, high pre-pregnancy weight, high GWG, diabetic pregnancies, previous macrosomic infant, multiparity, male fetal sex, high pre-pregnancy height, high maternal/paternal birth weight, advanced maternal age and congenital disorders [41, 44, 52]. Of these, only the first three are potentially modifiable [53].

## Cesarean Delivery

Williams Obstetrics defines CD as, "the birth of a fetus through incisions in the abdominal wall (laparotomy) and the uterine wall (hysterotomy)"[43]. It is performed when a vaginal delivery would put either the infant or the mother's health at risk. CD can be subdivided into elective or intrapartum, differentiated by when in the course of pregnancy the decision to perform a CD was made. 'Intrapartum' or 'emergency' refers to a CD occurring after labor has started. An elective or planned CD describes the situation where, prior to the onset of labor, a pregnant woman may request or a physician may recommend a CD due to the presence of medical indications.

In the United States, rates of CD have increased, from roughly 4.5% of all births in 1970 to 31.1% in 2006 [54]. They continue to rise; the most recent figure from 2008 estimates that 32.3% of all births in the United States were CD [55]. It is the most common major surgery for women in the United States [56]. Population-based studies in China have reported increases in CD in the last three decades, from 5% to 23%. Similar increasing trends have been observed in

hospital-based, urban areas where rates ranged from 26% to 63% in the late 1990's [24]. These figures are well above the WHO recommended range of 10-15% [57].

It's unclear what is driving the increase in CDs observed internationally, although the maternal belief that CD is safer [58] and less painful [59, 60] than a vaginal birth appears to be responsible for some of the increase. Changes in physician's beliefs and practices may also play a role [61-63]. Despite these beliefs, conclusive evidence exists that demonstrates increased morbidity and mortality for both mothers and infants when CD is performed without clear medical indications.

In 2005, the WHO undertook a comprehensive study to examine maternal and fetal morbidity and mortality associated with CD. They found that compared with vaginal delivery, women undergoing either an elective or intrapartum CD experienced twice the risk of maternal morbidities, including admission to the intensive care unit, blood transfusion, hysterectomy, and a hospital stay of more than 7 days. They were also up to five times more likely to require antibiotic treatment after delivery. The study also looked at neonatal mortality and morbidities. Analysis was stratified by presentation; cephalic presentation vs. breech or other presentations. CD was protective against fetal death for breech presentation, compared with a vaginal delivery. However, compared with vaginal delivery, CD with cephalic presentation nearly doubled the risk for a stay in the neonatal intensive care unit for 7 days or more, and increased the risk for neonatal mortality up to hospital discharge [64]. CD has also been shown to decrease initiation of breastfeeding[65].

A previous CD is a major medical indication for a CD. For women with a previous CD, uterine rupture is the outcome most commonly associated with maternal and neonatal morbidity, and in catastrophic cases, mortality [66]. Because the presence of this one risk factor is so strong, the remaining discussion is limited to risk factors associated with primary CD, or CD for women giving birth for the first time. As previously mentioned, the presence of medical indications is a

common reason for a physician to recommend an elective or planned CD. A study by Gregory and colleagues used 1995 delivery discharge records from California to identify indications for elective primary CD. They list 31 clinical indications derived from International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). 'Malpresentation' increased the relative risk (RR) of CD by 25 times (confidence interval (CI): 24.24-25.49), compared to women delivering vaginally. 'Other uterine scar' was the second most common indication for CD, increasing the RR of CD 15 times (CI: 14.30-16.53). Other indications increasing the RR of CD by 5 times or more, compared to a vaginal birth included: asthma, severe hypertension, herpes, multiple gestation, maternal soft tissue condition, anomaly or abnormal chromosomes, obstetrical shock and pulmonary embolism[67].

The increase in CD is mediated by increases in the risk factors discussed above, as well as changes in maternal [58-60] and physician preference [61, 62]. It is unclear whether changes in medical indications or personal preferences are driving the increase in CD, but some explications for change in medical indications have been suggested. Maternal age at childbirth is increasing, overall and among women delivering their first child [54]. Advanced maternal age (>35 years) is associated with CD [54]. The prevalence of obesity has been increasing both in the US [68] and in China [69] and increased fat deposition in the maternal pelvis due to increasing obesity has been hypothesized as a cause of malpresentation [70-72]. The ability to track changes in indications for CD in developing countries, such as China is hampered by the lack of standards for reporting [73]. Thus, it is difficult to tease out the determinants of CD and identify measures to reduce CD.

## Summary

LBW, macrosomia, and CD are adverse perinatal outcomes that carry with them short and long term consequences for both mothers and their infants. The prevalence of these outcomes

in China has historically matched that of other developing countries. However, rapid changes are occurring in China, including dramatic shifts in lifestyle and food availability that ultimately affect maternal nutritional status. It is unclear if changes in maternal anthropometry will impact rates of LBW, macrosomia and CD as did similar changes that occurred in the developed world over half a century ago.

# Chapter 3 Literature Review: Epidemiology of Maternal Anthropometry and Adverse Perinatal Outcomes

A woman's nutritional status, namely her body composition, diet and metabolic state before and during pregnancy determine her ability to deliver nutrients to her fetus for optimal growth [74, 75]. Maternal diet has been shown to affect infant birth size, but the effect is modest, explaining 3-5% of variance in birth weight [25, 76, 77]. Maternal anthropometry, namely GWG, pre-pregnancy BMI and height, are all proven determinants of fetal growth and cesarean delivery. A review of these associations follows. Figure 3-1 presents the general conceptual framework of this dissertation, highlighting the potential determinants, outcomes and effect modifiers of GWG. Arrows signify causal associations and lines without arrows ending in a short hash indicate potential effect modification.

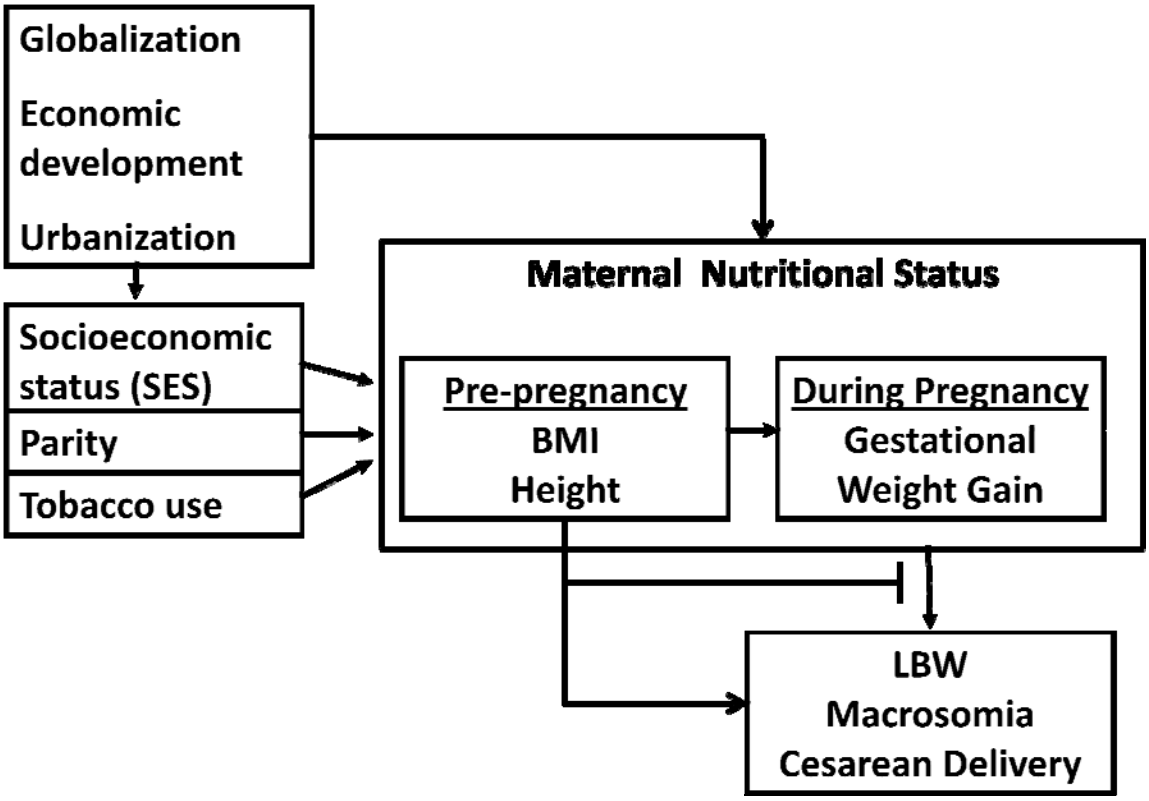



**Figure 3-1 Conceptual Framework**

## Body Mass Index

Body mass index, calculated by dividing height in meters by the square of weight in kilograms, is used to estimate a healthy weight for a given height. BMI is a measure of body composition and is divided into classes, with increasing BMI being associated with increasing adiposity. The classes defined by the WHO are: <18.5, 18.5-24.9, 25-29.9, and ≥30 for underweight, normal weight, pre-obese, and obese, respectively [78]. Obesity is a strong independent risk factor for diabetes, stroke, heart disease and some cancers [79-81]. The association between all-cause mortality and BMI suggests a J or U-shape [79, 82, 83].

Pre-pregnancy overweight (25 ≤BMI<30) and obesity (BMI≥30) carry greater risks of gestational hypertension, preeclampsia and gestational diabetes [84-88]. Birth weight increases with pre-pregnancy BMI as does the prevalence of emergency CD, large-for-gestational-age infants, gestational diabetes and preeclampsia [89-91]. A retrospective study of over 60,000 Chinese women delivering singleton infants in Hong Kong showed a 2.15 increased risk in emergency CDs for women with a pre-pregnancy BMI ≥30. This study also showed a 4 fold increase in gestational diabetes and preeclampsia in the same women [87]. Low pre-pregnancy BMI is associated with the delivery of low birth weight infants [3, 92] and preterm delivery [93]. Among obese women, there is an increased risk of CD and associated morbidities resulting from: failed induction, labor abnormality, fetal distress, and abnormal presentation [94, 95]. Increased risk of caesarean delivery among obese women may be partially due to higher rates of delivery of large for gestational age neonates, or neonates who were born at a birth weight greater than the $90^{th}$ percentile [96]. In addition to caesarean delivery, obese women are also at an increased risk of postpartum hemorrhage [94]. Maternal obesity also creates an intra-uterine environment that impacts fetal development and hence future generations. It is associated with an increased risk of metabolic syndrome [7, 8], childhood obesity [9, 10], and diabetes [11] in the offspring.

Although few Chinese women can be characterized as obese (BMI ≥30), obesity in China is increasing. In 1991, 13.4% of women were classified as overweight (BMI ≥ 25), rising to 26.2% in 2004 [6]. In 2002, a national survey in China of both urban and rural respondents aged 18 and over reported 18.8% of women were overweight, and 3.4% were obese [97]. Conservative estimates therefore suggest that one-fourth of the child-bearing population in China today enters pregnancy with a higher than recommended pre-pregnancy BMI. In addition to the differing distribution of obesity in Chinese populations as compared to the US population, Asians have an increased percentage body fat at a lower BMI, compared with their White counterparts [98]. There is also evidence that the relationship between BMI and percentage body fat is different for different racial/ethnic groups among individuals of Asian background [99]. Asian women typically start pregnancy at a lower BMI compared with American women [13].

It is clear that obesity is important to obstetric outcomes in Chinese women. However, multiple definitions of obesity are in use. In 2002 the WHO convened an expert consultation on BMI in Asian populations. They recommended the use of additional BMI cut-off points until enough evidence was collected to determine whether, and at what point, different cut-offs were needed for different ethnic/racial groups. The BMI cut-off points they recommended are: 23, 27.5, 32.5 and 37.5 kg/m$^2$, positioned between the traditional BMI cut-off points (<18.5, 18.5-24.9, 25-29.9, and ≥30 kg/m$^2$) [100]. Concurrently, the Working Group on Obesity in China (WGOC) proposed the following BMI categories: 24.1-27.9 kg/m$^2$ for overweight and ≥28 kg/m$^2$ for obesity [101]. A study of 29,303 Chinese women, in Hong Kong, assessed maternal obesity and associated risk of adverse pregnancy outcomes. The study concluded that the Asian-specific BMI categories recommended by the WHO [100], (< 18.5, 18.5-22.9, 23- 24.9, 25- 27.4, 27.5-30, ≥ 30) may be appropriate for obstetric outcomes [87]. In contrast, a study in Shenyang province, China, used the BMI cut-off points suggested by the WGOC. They found that pre-pregnancy overweight (BMI 24.1-27.9 kg/m$^2$) and obese (≥28 kg/m$^2$) were associated with gestational

hypertension, preeclampsia, gestational diabetes, and preterm premature rupture [50]. Adding to the uncertainty surrounding the BMI level where risk for adverse pregnancy outcomes becomes significant, these studies focus only on women in urban areas; however, roughly half of China's population lives in rural areas [102]. Due to these differences, considerable controversy exists regarding appropriate BMI cut-off points for Chinese.

## Gestational Weight Gain

Gestational weight gain (GWG) is a potentially modifiable and easily measured risk factor associated with pregnancy. It results from the gain of maternal tissues and products of conception (i.e., fetus and placenta). Two common calculations are found in the literature: 'total' GWG and 'net' GWG. Total GWG is calculated by subtracting weight before conception from weight before delivery. Net GWG is calculated by subtracting infant birth weight from total GWG. It can be further refined by subtracting placental weight and amniotic fluid weight, although these are rarely available. Unless otherwise noted, GWG refers to total GWG.

Recommendations for total GWG have changed over the past century. In the 1930s and 1940s women were advised to limit their weight gain to no more than 6.8 kg (15 lb) [103, 104] for fear of toxemia and a difficult birth due to cephalopelvic disproportion. However, it was also recognized that GWG could be used as an indicator of maternal nutritional status, which in turn, influences fetal growth. Davis noted that mean birth weight increased from 3100 g to 3600 g when GWG increased from 7 kg (15 lb) to 13.6 kg (30 lb) [105]. Several large studies showed that a GWG of 12.5 kg (27.5 lbs) resulted in the birth of a "physiologically normal" infant [106].

Thus, in 1970 in the United States, recommendations were published advising a GWG of 24 lbs and a range from 20 to 25 lbs [107]. In 1990, the Institute of Medicine (IOM) published revised recommendations recognizing that *body composition before* and *weight gain during*

pregnancy have independent but additive effects on maternal and infant outcomes [2]. Thus, the 1990 recommendations used pre-pregnancy BMI as an index whereby women are grouped and further recommended to categories of appropriate weight gain. The newest iteration of the recommendations (see Table 3-1), published in May 2009, has refined the BMI categories and added advice for women who start pregnancy obese [1] reflecting the US context where in 2004, 33% of women aged 20 years and older were obese [108].

**Table 3-1 BMI categories and recommended GWG**

| BMI Categories ($kg/m^2$) | GWG (kg) | GWG (lbs) |
|---|---|---|
| Underweight, < 18.5 | 12.5 - 18 | 28 - 40 |
| Normal, 18.5 – 24.99 | 11.5 - 16 | 25 - 35 |
| Overweight, 25.0 – 29.9 | 7 - 11.5 | 15 - 25 |
| Obese, ≥ 30 | 5 - 9 | 11 - 20 |

Although the best outcomes are observed when women follow the recommendations, few women are able to do so [109]. In the US, women typically start pregnancy overweight and exceed recommended limits for pregnancy weight gain. Gains outside the recommendations are associated with negative outcomes. High GWG is associated with an increased risk of caesarean delivery [110], transient hypertension [111], preeclampsia [112], and macrosomia [44, 52, 113]. Low GWG is associated with neonatal mortality resulting from low birth weight [114].

## Height

Height attainment is a function of genetics and environmental influences [115] such as nutrition, illness and socioeconomic status during critical windows of growth. Growth failures during these critical windows (the first two years of life, and to a lesser extent, during the pubertal

growth spurt), represent missed opportunities that cannot be made up once missed [116, 117]. Adult height is therefore a proxy for nutrition in childhood. Thus, a women faced with undernutrition in childhood may reach her adulthood shorter than her genetic potential. In addition to reduced standing height, malformations and smaller pelvis size can result from undernutrition in childhood [118, 119].

There are contradictions in the literature about the usefulness of maternal height in predicting adverse perinatal outcomes. First, some argue for height acting on a continuum rather than at a threshold below which the risk for negative outcomes increases significantly [120-122]. Second, those evaluating a threshold often do not agree on the threshold for 'short maternal stature' : <145cm [117], <150 cm [123], <155cm [124, 125], <157 or <62 in [1, 121, 126-128]. Third, studies evaluating height often do so without simultaneously considering the effects of pre-pregnancy BMI and pregnancy weight gain.

Despite the uncertainties in the literature, maternal height has been found to be associated with adverse perinatal outcomes. In developing countries, maternal height has been shown to have an independent effect on infant birth weight, with increased height correlating with modest increases in birth weight (~15 gram increase for every 1 cm increase in height) [129-132]. However, studies in US populations have not demonstrated an effect of maternal height independent of maternal body size [133-135]. Evidence has clearly indicated an association between short stature and an increased risk of CD [120, 123, 125, 136, 137]. Depending on the definition of short stature and the referent group used, the odds of CD ranges from a 50% increase in odds, comparing women less than 1.57 m tall with women 1.57-1.73 meters tall (OR 1.56, CI: 1.32-1.85) [126] to a 2.7-fold increase in odds for CD among women <1.53 m tall compared to a referent group of women >1.60 m (OR: 2.7, CI: 2.30-3.19) [122].

## Effect Modification

To this point, the discussion has focused on the main effects of GWG, pre-pregnancy BMI and maternal height on the incidence of LBW, macrosomia and CD. However, pre-pregnancy BMI and maternal height may acts as effect-measure modifiers of the association between GWG and the three outcomes under study. An effect modifier, also referred to as an interaction term, is a variable that changes the magnitude of the exposure across levels of that variable [138]. For example, if a high GWG was protective against LBW among adolescent mothers and also found to increase the incidence of LBW among women of advanced maternal age (>35 years), then we would say that maternal age is an effect modifier of the association between GWG and LBW. If we had neglected to account for the effect modification and reported the overall effect of age, the net effect might show no association between GWG and LBW. This is clearly erroneous.

Recommendations for adequate weight gain for the US population are specific to categories of pre-pregnancy BMI, and have associated ranges of GWG [1]. The presentation of the recommendations in this way highlights the well-documented association between GWG and pre-pregnancy BMI. Specifically, as pre-pregnancy BMI increases, GWG decreases [1, 2]. In addition to this association, the literature has documented that BMI modifies the effect of GWG on different outcomes. The interaction between pre-pregnancy BMI and GWG in relation to birth weight is generally viewed as modest [1] stemming from a very thorough analysis of data from the Danish National Birth Cohort. In this analysis, Nohr et al. found the effect of BMI on the association between GWG and birth weight to be of "minor clinical significance, except for the risk of SGA in underweight women with low gain". Among these women, the risk of delivering an SGA infant was more than five times the risk for an underweight woman with a normal GWG [139].

The majority of studies that have examined the association between GWG and route of delivery have demonstrated that as GWG increases, so does the risk of CD; however, only one has assessed whether pre-pregnancy BMI modifies this association [140]. In a study of over 7,000 women from the New Jersey Pregnancy Risk Assessment Monitoring System (PRAMS) from 2002 to 2005, Jain et al. did not find any evidence of effect modification by pre-pregnancy BMI on the association between GWG and CD. However, the authors note that due to their small sample size the study was insufficiently powered to detect any effect modification less than a doubling of risk [141].

There is a dearth of research on the role of maternal height as an effect modifier. We could find only three studies that examined any interaction effects. Witter et al. tested for an interaction between birth weight and height on the outcome of CD [126] and found no association. Pickett et al. reported that height did not modify the association between pregnancy weight gain and infant birth weight [121]. Using data from the Pregnancy Risk Assessment Monitoring System (PRAMS), Dietz et al., reported that height did not modify the association between pre-pregnancy BMI and CD [128]. All of the above studies used data from US populations and none found any significant effect modification by maternal height in a variety of variable combinations. The relationship between maternal height and perinatal outcomes has been documented in well-nourished or even over-nourished populations. This may not be relevant to developing nations, where rapid nutritional transition[1] [142, 143] may lead to childhood stunting

---

***[1] Nutrition Transition***

The nutrition transition describes changes in energy intake and expenditure that occur as communities become more urbanized. The transition is gradual and can occur at a different pace in different communities within the same country and even region. Before the transition, undernutrition and strenuous physical labor are common, and after, lack of food is rare and sedentary occupations are more prevalent. It often appears alongside demographic and epidemiologic transitions and is characterized by classical shifts observed at a population level: from infectious to chronic disease, from high fertility and mortality to low fertility and mortality. The United States began this transition in the 1950s, in contrast to China which is currently undergoing the transition. The nutritional state of women before and during pregnancy differs based on whether their community has passed through this transition. Pre-pregnancy height and weight reflect maternal nutritional status before pregnancy, in contrast to GWG which represents changes in maternal nutritional status throughout pregnancy.

in addition to adult obesity. [144]. Childhood stunting can, in turn, lead to reduced maternal height which, when combined with obesity, may compound the risks for adverse pregnancy outcomes.

## Summary

It is unclear whether the application of 2009 IOM pregnancy weight gain recommendations to Chinese women is appropriate. The prevalence of overweight and obese (BMI ≥ 25) among women in China, 13.4% in 1991 and 26.2% in 2004, still lags behind the rest of the world [6]. Chinese women are also typically shorter, start pregnancy with a lower BMI and gain less weight in pregnancy compared to US women [13]. Other differences associated with ethnicity may also play a role. Asian populations have a higher percentage of body fat at a lower BMI than Western populations [98, 145-148]. Thus Asians are at in increased risk of cardiovascular disease at a lower BMI. Consequently, the IOM's recommendations may be inappropriate for non-Whites [2].

The association between pre-pregnancy BMI and GWG and negative pregnancy outcomes observed in Caucasian populations needs confirmation in Chinese populations. The appropriate definitions of overweight and obesity, relevant to pregnancy outcomes, and the associated GWG need further investigation. Further, the additional impact of maternal height requires more thorough investigation, especially given China's rapid development and progress through the nutrition transition. Also, research investigating the potential effect modification of pre-pregnancy BMI and maternal height on the associations between GWG and adverse pregnancy outcomes in Europoid populations is limited and inconclusive. Documenting such effects or lack of effects among Chinese women will add to our general understanding of the association in all women. Finally, gaining a better understanding of the interplay between measures of maternal anthropometry in the Chinese population will provide a basis for developing adequate GWG recommendations and help prevent chronic disease in this population

as well as in the Chinese immigrant population in the US. This research will assist policy makers with planning future health care capacity and promoting a healthy population.

# Chapter 4 Methods

The body of work represented in this dissertation uses data from the China-US Collaborative Project for Neural Tube Defect Prevention [17, 18]. Details presented below are common to all of the analytical chapters (Chapter 5, Chapter 6 and Chapter 7). Analytical chapters also present methods relevant to each analysis in greater detail.

## Study Background

In 1992, the United States Public Health Service recommended that all women who could become pregnant take a daily dose of 400 μg of folic acid to reduce their risk of having an infant with a neural tube defect [149]. The Centers for Disease Control and Prevention (CDC) and Beijing Medical University evaluated whether the maternal use of 400 micrograms of folic acid, taken before and during the first trimester of pregnancy was successful at preventing neural tube defect-affected pregnancies. To accomplish this, a prospective surveillance system was established in 28 city/county sites in four provinces in China, two northern (Hebei and Shanxi) and two southern (Zheijiang and Jiangsu). All pregnant women and women planning marriage were required to register with the pregnancy-monitoring system that documented prenatal care and delivery. The goal was to document both the maternal use of folic acid prior to and during the first trimester of pregnancy and the cases of neural tube defects in her offspring.

The cohort assembled captured all women registering between October 1993 and September 1995 (285,536 women), and whose pregnancy ended on or before December 31, 1996 (277,287 or 97%) [17, 18]. At the end of the first year, the ability of each city/county site to capture all pregnancies was evaluated. Seven city/county sites were unable to keep up with number of women, and were dropped from follow-up. All of the city/county sites in Shanxi were dropped and therefore are not part of the analysis. Thus, the final analysis includes data from 21 city/counties in Hebei, Zheijiang, and Jiangsu.

All women who registered with the pregnancy monitoring system were *asked* to purchase pills containing 400 μg of folic acid and were therefore not randomized by pill-taking status. Compliance was assessed by village health workers who visited each woman monthly and recorded the number of pills (0-31) remaining at the end of each month during the first trimester. Pill-taking habits during their first trimester were classified as: periconceptional, late starting, early discontinuation, and non-use of folic acid. Village health workers also asked about menstrual cycles at these monthly visits and data for the last menstrual period (LMP) was derived from this information.

At the time of registering, women participated in an examination which included physical measurements and biochemical tests. Weight and height were measured and women were administered a questionnaire to collect information about their reproductive history, personal and family history of disease, and socioeconomic status. Throughout their pregnancy, women have a maximum of 12 recorded, prenatal contacts with the surveillance system. During these visits, blood pressure and weight were measured and women provided urine samples that were screened for the presence of protein and glucose. Symptoms and complications of pregnancy were also recorded. Characteristics of delivery, fetal measurements, and the presence of birth defects were collected at birth. The last point of contact for women and their infants was at 6 weeks postpartum. The presence of birth defects was again collected at this visit.

After excluding loss to follow-up and those for whom the neural tube defect status of the fetus or infant could not be determined, 247,831 pregnant women remained in the cohort for continued study.

## Sample Population

From the 247,831 women who remained in the study, we defined our eligible sample as primiparous, ethnically Han Chinese women with no preexisting chronic disease or spousal

consanguinity, registering with the pregnancy monitoring systems prior to their LMP, delivering a single infant without birth defects at 24-43 completed weeks of gestational age (N=153,534) (Figure 4-1). We further restricted the sample to women who registered before their LMP to ensure that we captured pre-pregnancy weight and were able to calculate pre-pregnancy BMI. Thus, 80,058 women were eligible for analysis before implausible and missing covariates were assessed.

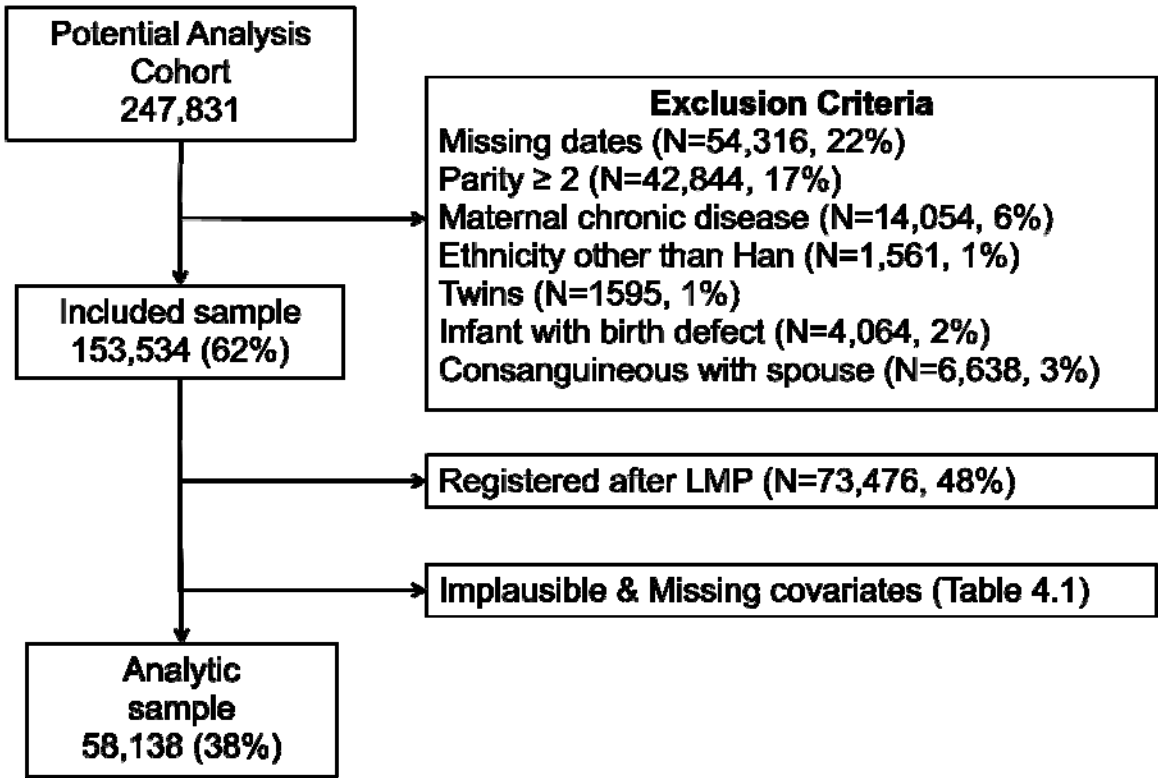



**Figure 4-1 Defining the eligible analytic sample**

We then defined our analytical sample by excluding records with missing or extreme values for the following variables (exclusions are non-mutually exclusive): pre-pregnancy weight (<34 kg or >69 kg) (N=961), pre-pregnancy height (<147 cm or >173 cm) (N=7,986), last prenatal weight (<41 kg or >94 kg) (N=12,540), BMI (<13 kg/m$^2$) (N=8,779), GWG (loss of more than 5% of pre-pregnancy body weight, or a gain of more than 50% of pre-pregnancy body

weight) (N=14,030), maternal age at delivery (N=0), sex of infant (N=128), maternal education (N=189) , maternal occupation (N=61) and method of delivery (N=1,700) (See Table 4-1). Extreme values were defined as any value falling outside mean ± 3standard deviations (SD) for each anthropometric variable. Maternal height received special consideration when identifying missing and extreme values. As it was potentially measured twice, once pre-pregnancy, and again in the first trimester, measurements were considered replicates, as changes in height are negligible during the measurement period. Where two measurements were present, if they differed by more than 2 cm, they were considered unreliable and treated as missing. Additionally, implausible values were defined for unlikely combinations of birth weight and gestational age (n=1,881), as defined by Alexander et al. [150]. The majority (80%) of women provided physical measurements 7 months before their LMP. For the analysis, we assumed that pre-pregnancy weight represents weight at conception. Our final analytical sample included 58,138 (38%) women.

**Table 4-1 Excluded missing and extreme values**

| | Outliers | | Unreliable | | Missing | | Total | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| Maternal height | 389 | 0.49 | 7,544 | 9.43 | 53 | 0.07 | 7,986 | 9.98 |
| Pre-pregnancy weight | 731 | 0.91 | - | - | 230 | 0.29 | 961 | 1.20 |
| Last prenatal weight* | 536 | 0.67 | - | - | 12004 | 14.99 | 12,540 | 15.66 |
| Pre-pregnancy BMI | 2 | 0.00 | - | - | 8777 | 10.96 | 8,779 | 10.97 |
| GWG | 905 | 1.13 | - | - | 13125 | 16.39 | 14,030 | 17.52 |
| Maternal age | - | - | - | - | 0 | 0.00 | 0 | 0.00 |
| Sex of infant | - | - | - | - | 128 | 0.16 | 128 | 0.16 |
| Maternal education | - | - | - | - | 189 | 0.24 | 189 | 0.24 |
| Maternal occupation | - | - | - | - | 61 | 0.08 | 61 | 0.08 |
| Mode of delivery | - | - | - | - | 1700 | 2.12 | 1,700 | 2.12 |

*Missing can also be due to both answer not present and time outside accepted time range

**Table 4-2 Characteristics of mothers and infants included and excluded from the analytical sample[1]**

| | Excluded subjects N=95,396 | | Analytical sample N=58,138 (38%) |
|---|---|---|---|
| | No. of records with available data[2] | Values | Values |
| **Maternal characteristics** | | | |
| Age (y) | 95395 | 24.6 ± 2.30[3] | 24.4 ± 1.81 |
| Height (cm) | 80416 | 158.9 ± 4.24[4] | 158.9 ± 4.11 |
| Pre-pregnancy weight (kg) | 89543 | 51.5 ± 5.67 | 51.4 ± 5.30 |
| BMI (kg/m$^2$) | 78131 | 20.4 ± 2.04 | 20.3 ± 1.89 |
| Final prenatal weight (kg) | 89266 | 62.8 ± 6.73 | 63.2 ± 6.34 |
| Pregnancy weight gain (kg) | 67095 | 11.2 ± 4.64 | 11.8 ± 4.52 |
| Cesarean Delivery | 91955 | 20.8 | 21.2 |
| North Region | 95396 | 13.5 | 15.1 |
| Education | 95069 | - | - |
| High school or college | - | 11.9 | 12.7 |
| Junior high school | - | 63.8 | 66.1 |
| Elementary or none | - | 24.3 | 21.1 |
| Occupation | 95275 | - | - |
| Farmer | - | 59.9 | 55.3 |
| Factory worker | - | 34.3 | 39 |
| Other | - | 5.8 | 5.8 |
| **Infant Characteristics** | | | |
| Male sex | 95147 | 51.7 | 51.4 |
| Birth weight (g) | 93515 | 3287.7 ± 423.97 | 3290.1 ± 403.77 |
| Gestational duration (wks) | 94882 | 39.8 ± 1.80 | 39.9 ± 1.53 |
| Macrosomia | 93515 | 5.6 | 5.3 |
| LBW | 93515 | 2.4 | 1.9 |

[1] LBW, low birth weight. Data are from the China-US Collaborative Project for Neural Tube Defect Prevention. All comparisons between excluded and included subjects were significant at P<0.0001 with the exception of cesarean delivery (P=0.0471), male sex (P=0.3561), and macrosomia (P=0.0019).

[2] A total of 95,369 (62%) of eligible records were excluded from the analytical sample because of missing or implausible data.

[3] Mean ± SD (all such values).

[4] Percentage (all such values).

## Data Challenges

The exposures and outcomes of interest in this dissertation were relatively untouched since their collection. As such, a great deal of time and effort was dedicated to dealing with challenges that arose from the state of the data. In the following sections we document the steps taken to clean the data, how missing data were characterized and what techniques were employed to cope with it, and finally we address measurement error and the way it shaped the analyses presented in this dissertation.

### *Data cleaning*

Data unique to each mother-child pair were collected in paper booklets pre-coded for computer data entry. A data entry program that prevented duplicate record entry was used to create an electronic record; however, no variables were double-entered. Additionally, although range checks were built into the program, it was later learned that most of the range checks of dates had been disabled. The variables pertinent to the original study question, documenting the efficacy of 400 micrograms of folic acid in the first trimester to reduce the incidence of neural tube defects, were cleaned and cross-checked. These variables mainly included dates and the presence of neural tube defects. Later other variables were checked and corrected until the missing rate reached 0.5%.

As the main exposure variables for this analysis are GWG, BMI, and maternal height, data quality of the anthropometric data was important. GWG and BMI were derived from weight and height which were measured during the course of the study. Measurements were collected pre-pregnancy, before 13 completed weeks of gestation (first trimester), and up to 2 weeks prior to delivery (delivery). Weight was potentially measured three times, once pre-pregnancy, once in the first trimester and lastly at delivery. To be included in the study, a woman had to have three measurements: a height measurement, a pre-pregnancy weight and a delivery weight. The timing

of these measurements in absolute terms (i.e., in reference to the study period) and in relative terms (i.e., in reference to last menstrual period) also required data cleaning.

Guiding principles were defined for data cleaning. A measurement was accepted as correct, unless data cleaning processes demonstrated otherwise. Identifying potential errors was a multi-step and iterative process. First, all variables were checked for normal distribution. Second, outliers were identified using mean and standard deviation (SD) as an internal standard. Mean and SD were calculated for height and weight at each measurement occasion. Values 3 SD from the mean were excluded: they represented less than 1% of the available data, but still too many to evaluate individually. Values within 3 SD of the mean were considered 'acceptable' in this step. Third, data entry errors were identified where replicate or sequential measures were present. Rules for identifying errors were tailored to the measurement (detailed in Appendix A). Fourth, contextual definitions were used to remove any implausible values for composite variables, such as GWG and BMI. For example, a woman might have a height and weight value labeled as 'acceptable' by outlier identification, but the calculated BMI might be extremely low. Women with a pre-pregnancy BMI below 13 $kg/m^2$ were excluded from the analysis (n=2).

### *Missing data*

Missing data are common phenomena in epidemiologic research. The scale of attrition tends to be magnified as the duration of the research period increases, as there are more opportunities for non-participation. Reasons for attrition can be innocuous, such as the subject was sick on the day of interview or equipment malfunctions. If however the reason for attrition is related to the outcome of interest, then attrition may bias research conclusions. It is therefore recommended that the reason for missing variables be evaluated before proceeding with any analysis [151]. Based on the reason for missingness, appropriate techniques can be employed to reduce bias in the data.

Missing data is commonly classified as missing completely at random (MCAR), missing at random (MAR), missing not at random (MNAR). MCAR means that the probability of missingness is unrelated to any of the other study variables. The previous example of equipment malfunction falls under the heading of MCAR. If data is MAR, missingness is related to a study variable, but not the outcome under study. An example of MAR given by Sanders et al. is: "(A)n elderly person may have more difficulty getting to an appointment to complete the study questionnaire because of age (a measured variable) but not because of his or her level of depression (the outcome being measured)" [152]. Finally, data can be MNAR. In this instance, missingness is related to the outcome [151, 153].

There are numerous ways to deal with missingness. An underlying assumption required to apply methods to assess missingness is that at minimum, it is MAR [152]. The most common technique to deal with missingness is listwise deletion which *assumes* attrition is not occurring in a biased manner [152]. This technique is the standard procedure used in statistical packages. In this instance, the lack of information on any variable specified in the analytical technique, such as regression, causes the whole case to be deleted from the analysis. This method results in the greatest loss of power due to the loss of potentially informative values from other variables and the reduced sample size. Mean substitution is probably the second most popularly employed technique used to deal with missing data. The unfortunate side-effect of mean substitution is the reduction of the standard deviations around the mean, so the true variability of the sample is lost. Other more laborious techniques exist, such as hot-decking; however, with the advent of statistical packages that can manipulate large datasets, these have fallen out of favor [152]. The new technique gaining support is the use of multiple imputations of chained equations (MICE). Assuming you have missing values for more than one variable, as is often the case in large cohort studies, MICE can be employed to use patterns in the data you have, to make a 'best guess' at values for the data you do not have. Operationally, this involves building a good fit regression model based on the data you do have. It becomes 'chained' by predicting the variable with the

fewest missing first, then using this newly imputed variable as a predictor for the regression of the next variable with the fewest missing values until a series of regression equations are chained together to result in a data set with no missing values [154].

Table 4-2 demonstrates one method commonly employed to assess differences in those who are included in a study and those who are excluded. Although there are statistical differences between the two groups, due to the large sample size, the differences have no biological significance. Missingness was therefore assumed to be MAR and listwise deletion was employed to cope with it as the sheer size of the data ensure enough statistical power to look for biologically relevant differences.

### *Measurement error*

While missing data deal with information that is not present, measurement error deals with the validity of information that is present. The main objective of the original pregnancy monitoring system was to document pill-taking practice of folic acid supplements and incidence of neural tube defects. Maternal and infant anthropometry were collected routinely, but not as a study focus. Delivery information was also collected; however, standardized definitions to describe progress of labor and interventions used and why, were not employed. Additionally, resources were not used to ensure data quality of these variables. For example, computerized survey data collection programs have built in range checks that can improve data quality by reducing random data entry error. This tool improves the quality of the data before data cleaning even begins. Finally, measurement protocols, which often reduce systematic errors, were not standardized between study sites.

Measurement error can be assessed in multiple ways. Where anthropometry is measured, rather than reported, it is possible to avoid respondent bias. Respondent bias has been linked to underreporting of weight and over reporting of height in certain situation [155]. However, measurement error still exists in the form of human error and digit preference. Human error can

be assessed where duplicate values are present for the same variable. In this situation, it is possible to identify pairs of values wildly different from each other. Maternal height was measured on two occasions, and was found to differ by more than 2 cm on 13,598 (6.6%) occasions, of a total of 207,321 pairs of measurements. As noted above, when this occurred for maternal height, the values were considered unreliable and treated as missing. Another form of error commonly found in epidemiologic research is digit preference among continuous variables. Digit preference describes the tendency to report 0, 5 or even numbers, such that the frequency of a preferred digit exceeds the expected 10% [156]. Digit preference can reduce the power of statistical analyses [157] and is therefore important to assess when choosing variables to include in an analysis. Exposure variables maternal height and weight, and potential perinatal outcome measurements such as birth weight, birth length and head circumference were assessed for digit preference.

Tables 4-3 and 4-4 show the frequency of digit preference for infant and maternal anthropometry, respectively. The terminal digits assessed were millimeter (mm) for head circumference, centimeter (cm) for birth length, and 100 grams (grms) of birth weight. Birth length shows considerable heaping at 0, while values for head circumference are concentrated at 2-5. The frequency of digits for birth weight reflects a distribution closer to that expected if digit preference is not operating. Pre-pregnancy weight and height measurements demonstrate a preference for values ending in 0 and 5, however it was slight. All of the maternal measures were deemed acceptable for use, while only birth weight had the required data quality for use in the analysis.

**Table 4-3 Frequency of terminal digit for infant measurements**

| Terminal digit | Head circumference | | Birth Length | | Birth weight | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| . | 11385 | 4.6 | 10598 | 4.3 | … | … |
| 0 | 9427 | 3.8 | 115420 | 46.6 | 36662 | 15.4 |
| 1 | 7314 | 3.0 | 21169 | 8.5 | 21608 | 9.1 |
| 2 | 31379 | 12.7 | 14901 | 6.0 | 28459 | 12.0 |
| 3 | 54581 | 22.0 | 4543 | 1.8 | 20834 | 8.8 |
| 4 | 88648 | 35.8 | 3862 | 1.6 | 22771 | 9.6 |
| 5 | 29844 | 12.0 | 8517 | 3.4 | 34444 | 14.5 |
| 6 | 8914 | 3.6 | 5757 | 2.3 | 18828 | 7.9 |
| 7 | 2800 | 1.1 | 9010 | 3.6 | 19305 | 8.1 |
| 8 | 2261 | 0.9 | 28082 | 11.3 | 17327 | 7.3 |
| 9 | 1278 | 0.5 | 25972 | 10.5 | 17636 | 7.4 |

**Table 4-4 Frequency of terminal digit for maternal measurements**

| Terminal digit | Pre-pregnancy weight | | Height | | Last prenatal weight | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| . | 62633 | 25.3 | 54108 | 21.8 | 19740 | 8.0 |
| 0 | 35654 | 14.4 | 44076 | 17.8 | 28789 | 11.6 |
| 1 | 13872 | 5.6 | 10106 | 4.1 | 20661 | 8.3 |
| 2 | 18322 | 7.4 | 16692 | 6.7 | 23649 | 9.5 |
| 3 | 15326 | 6.2 | 13391 | 5.4 | 22460 | 9.1 |
| 4 | 14486 | 5.9 | 13263 | 5.4 | 21453 | 8.7 |
| 5 | 29674 | 12.0 | 23975 | 9.7 | 26779 | 10.8 |
| 6 | 13951 | 5.6 | 16595 | 6.7 | 21131 | 8.5 |
| 7 | 13294 | 5.4 | 13827 | 5.6 | 21433 | 8.7 |
| 8 | 16581 | 6.7 | 29180 | 11.8 | 22121 | 8.9 |
| 9 | 14038 | 5.7 | 12618 | 5.1 | 19614 | 7.9 |

## Statistical Challenges

The objective of the dissertation was to examine the relationships between maternal anthropometry and adverse pregnancy outcomes. Several statistical techniques were required to deal with the unique challenges presented in addressing these questions with data from the China-

US Collaborative Project for Neural Tube Defect Prevention. The following sections summarize issues relating to estimating relative risk for common outcomes and the implementation and utility of spline analysis to identify threshold effects. We also address two common statistical challenges related to the study of pregnancy outcomes: part-whole correlation between GWG and birth weight, and duration of gestation.

### *Estimating measures of association for common outcomes in cohort studies*

For binary outcomes, logistic regression is a standard procedure in most statistical packages which can be easily implemented and adjusted for several confounders and/or continuous covariates. The measure of association calculated from a logistic regression model is an odds ratio (OR). Another commonly used measure of association for binary outcomes is the risk ratio (RR). There is considerable debate in the literature concerning the conditions under which one measure is preferred over the other [158-160]. Proponents of RR argue that its interpretation is intuitive and easier to grasp than OR. The mathematical properties of OR and RR demonstrate that when the outcome under study is rare (< 10%), the OR approximates the RR, so it does not matter if you calculate the OR, one can still report the RR [159, 160]. But if an outcome does not meet the rare disease assumption then the OR will be further away from 1 than the RR [161]. One outcome, CD, was not rare in our study population (22%), so in this situation, calculating the OR and interpreting it as a RR is clearly wrong. Generalized linear regression models, such as log-binomial, Poisson regression with a robust error variance, and 'copy' method can be used to calculate RR directly[162]. All of these methods avoid the bias associated with the over-simplistic adjustment proposed by Zhang and Yu [163].

We used logistic models to approximate RR for the outcomes of LBW and macrosomia in Chapter 5. As noted above, the outcome of CD did not meet the rare disease assumption, and therefore logistic models were not appropriate. We used log-binomial models to estimate RR of CD in Chapters 5 and 6. However, in Chapters 5 and 7 we experienced two common problems

associated with log-binomial models: failure to converge, especially with continuous covariates and unrelated to co linearity, and out of bound estimates for predicted probabilities made this procedure [164, 165]. We therefore used Poisson regression with a robust error variance to estimate the RR and 95% confidence intervals (CI) for CD [166] in Chapters 5 and 7.

### *Spline analysis*

We were interested in describing the association between maternal anthropometry and adverse pregnancy outcomes. If present, we were also interested in identifying any threshold effects. One analytical technique employed to assess this is spline analysis. It has been used to characterize the variation in risk of adverse birth outcomes within traditional categorization of maternal pre-pregnancy BMI [167]. Traditional categorical analysis suffers from numerous shortcomings that can be avoided with the use of spline regression. By grouping continuous variables into categories, power is lost [168]. Individuals at the extremes of the distribution are hidden among the lower-risk members of the group. Intracategory variation is assumed to be zero, which presents an unrealistic model of risk. Additionally, there is discontinuity between category endpoints as risk is allowed to jump at the endpoints [138]. Spline analysis allows the analyst to fit a sequence of regression lines along a non-linear relationship; it offers a considerable amount of flexibility over and above a single regression line. Similar to categorical analysis, the continuous predictor is categorized, and a separate spline term is used for each category. Unique to spline analysis is the ability to specify the power of the spline. Thus, depending on the relationship desired within a category, linear, quadratic or cubic functions can be specified. The common endpoints between the categories are termed ‘knots’. A full spline model uses a series of segments connected at knots, thereby removing the unrealistic jump in risk often seen in categorical analysis [169]. Quadratic and cubic splines can become unstable in the end categories, especially if open-ended [170]. To combat this, one or both of the end categories can be ‘restricted’ to a line segment, rather than a curve.

We utilized spline regression in Chapter 6, to describe in detail the magnitude and direction of the association between pre-pregnancy BMI and risk of CD, controlling for GWG and other covariates and confounders. Initial characterization of the data suggested a possible threshold effect of pre-pregnancy BMI, making spline analysis best suited for further investigation. This is in contrast to the analysis using maternal height as a predictor of CD risk. In this analysis presented in Chapter 7, the relationship between maternal height and risk of CD was not suggestive of a threshold effect, making spline analysis unnecessary.

### *Part-whole correlation*

When both the independent (GWG) and dependent (birth weight) variable share a common component, correlations between the two are overestimated. Thus, the distinction between 'total' GWG and 'net' GWG is important if both GWG and birth weight are included in the same analysis. Net weight gain is calculated by subtracting birth weight from GWG. Net GWG removes the part-whole correlation because there is no overlap between net GWG and birth weight [171, 172]. However, both GWG and net GWG have their uses. In clinical setting total GWG is often used as a screening tool to identify women and infants at risk for poor outcomes due to weight gain outside what is considered 'physiologically normal'. Net GWG would be useless in this setting as it could not be calculated until after the infant was born, at which point nothing could be done to alter outcomes. Net GWG is the preferred calculation for use in analytical studies as it avoids a statistical phenomenon called part-whole correlation. We chose to use GWG for the analyses in chapters 5 and 6 since we were interested in GWG as a predictor to identify women at risk of poor outcomes. We used net GWG in chapter 7 as we were specifically interested in understanding the relative contribution of net GWG and birth weight to the risk of CD.

### *Duration of gestation*

Total GWG, net GWG and birth weight are dependent on the duration of gestation. Studies of GWG and birth weight therefore require assessment of gestational duration to determine whether a given birth weight is appropriate for a given gestational age. Typically, gestational age is estimated by the woman's LMP, recorded at the first prenatal visit. Measurement error is inherent in estimated gestational age because it is an estimate rather than a directly observed event. It also suffers from recall bias as the time between the event and reporting the event increases. Recall bias can be reduced with the use of early ultrasounds and minimizing the time between LMP and first prenatal visit. Failure to control for duration of gestation can result in spurious conclusions, biased either towards or away from the null, depending on whether gestation was estimated shorter or longer than its true value.

# Chapter 5 Institute of Medicine's Recommendations, Low Birth Weight, Macrosomia and Cesarean Delivery among Chinese Women

Kirsten A. HERRICK[1], Song LI[2], Usha RAMAKRISHNAN[3], KM Venkat NARAYAN[3], Li HAO[2], Yinghui LIU[2], Robert J. BERRY[4], Zhu LI[2]

[1] Nutrition and Health Sciences Program, Graduate Division of Biological and Biomedical Sciences, Emory University, Atlanta, GA,

[2] National Center of Maternal and Infant Health, Beijing, People's Republic of China

[3] Emory University, Hubert Department of Global Health

[4] CDC, National Center on Birth Defects and Developmental Disabilities

## Abstract

***Objective:*** To examine the risk of macrosomia (birth weight ≥ 4000g), cesarean delivery (CD), and low birth weight (LBW) associated with pre-pregnancy BMI and gestational weight gain (GWG) in Chinese women using the latest recommendations for adequacy by the US Institute of Medicine (IOM).

***Methods:*** All pregnant women from 21 counties/cities in three provinces (Hebei, Zhejiang and Jiangsu) in China registered with a perinatal health system. We restricted analysis to Han Chinese women aged 15-46 years, delivering a singleton infant by December 31, 1996 with pre-pregnancy BMI measured (N=58,138). GWG was described as below, within and above the IOM's recommendations for underweight (<18.5 kg/m$^2$), normal weight (18.5-24.9 kg/m$^2$) and overweight (25-29.9 kg/m$^2$) women. GWG was also divided into 6 categories of weight gain: <8.5, 8.5-11.4, 11.5-13.4, 13.5-15.4, 15.5-17.9 and ≥18 kg. Multivariable logistic and log-binomial regression models were estimated for three outcomes: LBW, CD and macrosomia. Models were adjusted for pre-pregnancy BMI, GWG, gestational age, sex of infant, region of residence, maternal age, education and occupation.

***Results:*** The incidence of CD, macrosomia and LBW were 21.2%, 5.3% and 1.9%, respectively. The relative risk (RR) of LBW followed the expected pattern, being highest among underweight and normal weight women with low GWG or GWG below the IOM's recommendations. Pre-pregnancy BMI did not modify the relationship between GWG and LBW. The magnitude of adjusted RR for macrosomia and GWG above IOM recommendations was greatest for underweight women (RR: 2.3; 95% CI: 1.79-2.95) and lowest for overweight women (RR: 2.1; 95% CI: 1.17-3.76), when compared with gains within the IOM recommendations. The opposite pattern was observed for GWG above the IOM's recommendation and CD: effect was stronger for overweight women RR 1.5 (95% CI:1.12-1.89) and weakest for underweight women RR 1.2

(95% CI: 1.11-1.34), respectively (p for interaction =0.001). The RR of CD and macrosomia increased with GWG; this increase was significant even though gains were still within the recommended range of GWG for pre-pregnancy BMI.

***Conclusions:*** This large population-based study of Chinese women suggests that the new IOM recommendations include gestational weight gain ranges that are associated with increased risk of macrosomia and CD for Chinese women.

## Introduction

The Institute of Medicine (IOM) recently published revised guidelines on adequate GWG [1]. In addition to standardizing pre-pregnancy BMI cutoffs to those used by the World Health Organization (WHO), they introduced a range of adequate weight gain for obese women. The authors of the new guidelines carefully point out that they are intended for women in the United States, and suggest that their application to women in other developed countries may also be appropriate. However, their application to other women, namely women with limited access to prenatal care or those who start pregnancy shorter or thinner than American women is uncertain.

Chinese women are, on average, two centimeters shorter than American women, 158 cm [173] vs. 160 cm [174]. They also typically start pregnancies thinner than American women [13]. Despite these differences, associations between pre-pregnancy BMI and GWG and adverse pregnancy outcomes found in Europoid populations are also found in studies among Chinese women. Leung and others reported an increased risk of CD, preterm delivery, and large-for-gestational-age (LGA) as pre-pregnancy BMI increased [87]. In a recent study among Chinese women in Shenyang Province, China, the risk of macrosomia (birth weight ≥ 4000g), preeclampsia, and gestational hypertension also increased with both increasing pre-pregnancy BMI and increasing rate of weight gain [50].

To our knowledge, there have been no reports of the performance of the IOM's new recommendations within populations of Chinese women. We undertook the current study to understand whether they can be applied as is, or perhaps with modification, to Chinese women. In this paper we examine the association between categories of GWG and low birth weight (LBW) (<2500g), macrosomia (≥ 4000g) and CD within maternal pre-pregnancy BMI categories. We also examined the associations between these outcomes and GWG below and above the new IOM recommendations for adequate pregnancy weight gain.

## Methods

### *Study design*

We used data from the China-US Collaborative Project for Neural Tube Defect Prevention, a public health campaign conducted in 21 counties/cities in three provinces in China; one Northern (Hebei) and two Southern (Zhejiang and Jiangsu). All pregnant women and women who were planning a marriage were registered with the pregnancy monitoring system, which serves as the primary data source for prenatal care and pregnancy outcomes in these three provinces (N=247,831). At the time of registering, women provided information on age, completed years of maternal education, maternal occupation, region of residence, ethnicity, family and personal history of chronic disease and previous obstetric history. Height and weight were measured prospectively. Pregnancies were followed through 6 weeks postpartum and perinatal outcomes were collected at delivery.

### *Study participants*

We defined our analytical population as primiparous, ethnically Han Chinese women with no preexisting chronic disease or spousal consanguinity, registering with the pregnancy monitoring systems prior to their last menstrual period (LMP), delivering a single infant without birth defects at 24-43 completed weeks of gestation (N=73,476, 48%). We excluded records with missing or extreme values for the following variables (exclusions are non-mutually exclusive): pre-pregnancy weight (<34 kg or >69 kg) (N=961), pre-pregnancy height (<147 cm or >173 cm) (N=7,986), last prenatal weight (<41 kg or >94 kg) (N=12,540), BMI (<13 kg/$m^2$) (N=8,779), GWG (loss of more than 5% of pre-pregnancy body weight, or a gain of more than 50% of pre-pregnancy body weight) (N=14,030), maternal age at delivery (N=0), sex of infant (N=128), maternal education (N=189) , maternal occupation (N=61) and method of delivery (N=1,700) (See Table 4-1). Extreme values were defined as any value falling outside mean ± 3standard deviations (SD) for each anthropometric variable. Additionally, implausible values were defined for prenatal body mass index (BMI): less than 13 kg/$m^2$ (n=3) and unlikely combinations of birth

weight and gestational age (n=1,881), as defined by Alexander et al.[150]. Our final analytical sample included 58,138 (38%) women. No statistical differences were found between those included and not included in the analysis (data not shown).

### *Measurements*

We calculated BMI at registration with the pregnancy monitoring system by dividing weight (kg) by height-squared (m) ($kg/m^2$). Pre-pregnancy BMI was categorized according to the IOM recommendations: underweight (<18.5 $kg/m^2$), normal weight (18.5-24.9 $kg/m^2$), overweight (25-29.9 $kg/m^2$) and obese (≥30 $kg/m^2$). Only two women had a pre-pregnancy BMI> 30 $kg/m^2$. We therefore restricted the analysis to women with a BMI < 30 $kg/m^2$. The mean number of weeks between pre-pregnancy measurement and the LMP was 16 ±13 (range 0 to 52 weeks). 80% of women provided physical measurements 7 months before their LMP. For the analysis, we assumed that pre-pregnancy weight represented weight at conception. A sub analysis showed that weight at registration increased as the interval between registration and the LMP decreased. The mean increase was 0.6 kg over the year before LMP. These findings are similar to those found by Winkvist et al. [175] and appear to be representative of a population going through the nutrition transition [176, 177]. This trend may lead to a slight underestimation of pre-pregnancy weight and BMI at conception.

We calculated GWG as the difference between maternal pre-pregnancy weight and weight at last prenatal visit, which occurred less than 2 weeks before delivery. Two different characterizations of GWG were used. First, GWG was categorized as below, within and above, according to the IOM recommendations. Gains within the IOM recommendations were defined as 12.5-18 kg, 11.5-16kg and 7-11.5 kg, for underweight, normal weight and overweight women, respectively. Second, to examine the change in risk with successive gains in kilograms, we divided GWG into 6 groups, which were devised to roughly correspond to the IOM weight gain categories, <8.5, 8.5-11.4, 11.5-13.4, 13.5-15.4, 15.5-17.9 and ≥18kg.

CD included all cesarean births, regardless of medical indication or maternal request. As the analytical population was limited to primiparous women, no repeat CDs are included in the analysis. Standard definitions were used to define LBW: birth weight <2500g and macrosomia: birth weight ≥4000g.

Covariates were chosen *a priori* based on a review of the literature [140]. All analyses were adjusted for maternal age, sex of infant, region of residence, completed years of maternal education and maternal occupation and gestational age. We estimated RRs and 95% CI. Interaction between GWG and pre-pregnancy BMI was assessed separately for all three outcomes. Statistical significance for interaction was set at $p<0.01$. All analyses were preformed with SAS software (version 9.2; SAS Institute, Cary, NC). The ethics committee at the Peking University Health Science Center in China approved the study and the analysis used only de-identified data.

### *Statistical analysis*

Separate logistic models were used to examine the association between GWG (in categories by kg and by IOM recommendations) and LBW and macrosomia. Because both outcomes were rare (<10%), the odds ratio (OR) approximates the risk ratio (RR) reported in the text. Because CD was not rare in our study, we initially used log-binomial models to estimate RR of CD. However, we experienced two common problems associated with this procedure: failure to converge, especially with continuous covariates, and out of bound estimates for predicted probabilities [164, 165]. We therefore used Poisson regression with a robust error variance to estimate the RR and 95% confidence intervals (CI) directly for CD [166].

## Results

The incidence of CD was 21.2%. Macrosomia occurred in 5.3% of infants, and overall 1.9% of infants were classified as LBW. LBW decreased with increasing pre-pregnancy BMI. Macrosomia followed the opposite trend, increasing with increasing pre-pregnancy BMI. CD was

stable for underweight and normal weight women, but increased for overweight women (Table 5-1). GWG varied by pre-pregnancy BMI. Underweight and normal weight women gained more than overweight women, however overweight women were more likely to gain above IOM recommendations. Lean women were more likely to have a high school or college education. Pre-pregnancy BMI also varied by maternal occupation. Farmers were more likely to be overweight and factory workers were more likely to be underweight. The majority of women were between the ages of 20 and 30. There was suggestion of an increase in BMI for women aged 20-25, and an opposite trend for women aged 25-30.

In general, the incidence of macrosomia and CD increased with increasing pre-pregnancy BMI and GWG. The incidence of LBW followed the opposite trend, decreasing as pre-pregnancy BMI increased. Increasing GWG had a similar effect on LBW for underweight and normal weight women; however, for overweight women the gradient was no longer observed (Figures 5-1 through 5-6).

Pre-pregnancy BMI modified the association between IOM recommendations and macrosomia (p=0.005) and CD (p=0.001), but not LBW (p=0.121). To maintain continuity between outcomes and because the *a priori* interest was how the IOM recommendations perform in a Chinese population, we present results stratified by standard BMI cut offs. Women with gains above the IOM recommendations doubled the risk of macrosomia across all categories of pre-pregnancy BMI, (RR: 2.3, 95% CI: 1.79-2.95 underweight, RR: 2.1, 95% CI: 1.90-2.30 normal weight and RR: 2.1, 95% CI: 1.17-3.76 overweight) (Table 5-2), when compared with women gaining within the IOM recommendations. The magnitude of adjusted RR for macrosomia and GWG above IOM recommendations was greatest for underweight women (RR: 2.3; 95% CI: 1.79-2.95) and lowest for overweight women (RR: 2.1; 95% CI: 1.17-3.76), compared with gains within the IOM recommendations.

The trend for CD was similar, although the magnitude was not as great; RR: 1.2 (95% CI: 1.11-1.34), RR: 1.3 (95% CI: 1.26-1.37) and RR: 1.5 (CI: 1.12-1.89) for underweight, normal and overweight women, respectively. The effect of pre-pregnancy BMI on the association between GWG by IOM recommendations and CD was in the opposite direction from macrosomia: greatest for overweight women and lowest for underweight women. Gains below the IOM recommendations were associated with an increased risk of delivering a LBW infant, 2.0 (95% CI: 1.52-2.71) among underweight and RR: 1.9 (95% CI: 1.55-2.23) among normal weight. The number of overweight women delivering a LBW infant was too small to make stable estimates.

GWG was categorized into 6 groups that roughly corresponded to the IOM weight gain ranges: <8.5, 8.5-11.4, 11.5-13.4, 13.5-15.4, 15.5-17.9 and ≥18kg. Grouping GWG this way allowed us to examine changes in risk *within* the broad IOM categories. The shaded areas in tables 5-3 through 5-5 represent GWG within the IOM's recommended range. Bolded values within the shaded range highlight weight gains within the IOM recommendations that show a statistically significant increase in risk. Women with gains between 11.5-13.5kg served as the referent, as this corresponds with the low end of the recommended range for normal weight women.

Gains above 15.4 kg conferred an increased risk of both macrosomia and CD for underweight women. The adjusted RR for macrosomia with a GWG between 15.5-17.9 kg, was 1.8 (95% CI: 1.22-2.54), and for gains equal to or greater than 18 kg, the adjusted RR was 3.2 (95% CI: 2.27-4.51) (Table 5-3). Equivalent adjusted RR for CD among underweight women were 1.3 (95% CI: 1.15-1.46) and 1.4 (95% CI: 1.23-1.56). For normal weight women with GWG of 13.5-15.4 kg (within the recommended range), the risk of macrosomia was 1.2 (95% CI: 1.06-1.39). The equivalent adjusted RR for CD among normal weight women was 1.2 (95% CI: 1.09-1.22).

For overweight women, gains within the recommended range appeared to be protective of macrosomia, CD and LBW. Gains below the IOM recommendations were associated with an increase risk of LBW for underweight and normal weight women. Gains between 8.5-11.4 kg increased the adjusted RR of LBW, RR 1.5 (95% CI: 1.02-2.20) compared to women with pregnancy weight gains between 11.5-13.4kg. For both underweight and normal weight women, gaining less than 8.5 kg during pregnancy increased the risk of delivering a LBW infant to more than twice the risk of a woman gaining between 11.5-13.5kg, 2.5 (95% CI; 1.69-3.77) and 2.2 (95% CI:1.75-2.80), respectively.

There was a statistically significant interaction between pre-pregnancy BMI and GWG in 6 categories for the outcome of macrosomia (p=0.0004). The magnitude of effect of the adjusted RR for women gaining 15.5 -18 kg, compared with gaining 11.5-13.4 was greatest for overweight women (RR: 3.8; 95% CI: 1.35-10.95) and lowest for underweight women (RR: 1.8; 95% CI: 1.22-2.54). The effect appears to be in opposite directions for women gaining >18 kg, compared with gaining 11.5-13.4, where equivalent figures were lowest for overweight women (RR: 2.4; 95% CI: 0.74-7.98) and greatest for underweight women (RR: 3.2; 95% CI: 2.27-4.51). However, this should be interpreted with caution as data are sparse for overweight women gaining ≥15.5 kg. No statistically significant interactions were found between GWG in 6 categories and LBW (p= 0.17) or CD (p=0.37).

## Conclusions

Findings from this large cohort of Chinese women confirm that maternal GWG is associated with LBW, macrosomia and CD. Similar to other studies [12, 113], our results indicate the gains outside the IOM recommendations confer increased risk of adverse pregnancy outcomes. We also demonstrated that similar to the study by Dietz et al. [113], gains within, but at the high end of the IOM recommendations, are associated in an increased risk macrosomia and CD. Pre-pregnancy BMI did not consistently modify the association between GWG and LBW,

macrosomia and CD. The effect of GWG described by categories of gain or by IOM recommendations was found to be strongest among underweight women and weakest among overweight women. The interaction effect was observed to be in the opposite direction for CD: the effect of GWG was found to be strongest for overweight women and weakest for underweight women when GWG was described by IOM categories of GWG.

The lack of consistent interaction between pre-pregnancy BMI and categories of GWG for the outcome of macrsomia could be a function of the narrow distribution of pre-pregnancy BMI found within our study population. The mean pre-pregnancy BMI was 22 $kg/m^2$. Although 58,138 women is a large sample, only 735 (1.3%) women were classified as overweight. Additionally, we were unable to investigate these associations in obese women as only two women had a pre-pregnancy BMI$\geq$30 $kg/m^2$, and were therefore excluded from the analysis. We may not have had the power to detect the interaction in this group, especially since we further reduced the statistical power by categorizing continuous variables [178]. The lack of consistent interaction between BMI and GWG in this population needs further study. If BMI is not an important predictor because of little variation in this population, then other predictors of maternal nutritional status before pregnancy should be considered. Maternal height has been shown to be associated with birth weight [121, 126] and CD [122, 127].

Our study is not without limitations. CD represents 'total' cesarean deliveries, as it was not possible to distinguish between maternal requests for cesarean and medically indicated cesarean deliveries. We also limited the analysis to primiparous women, so these results may not be applicable to multiparous women. This study probably underestimates current rates of CD. More recent studies in China have estimated the total cesarean rate to be about 46% [179]. Another limitation is that measurement of maternal anthropometry was not the original aim of the study. Measurement tools and protocols were not standardized between study sites. This will introduce random misclassification, biasing results towards the null. The data were collected from

1993-1997, and overweight and obese (BMI ≥ 25 kg/m$^2$) were scarce – less than 2% in the current study. More recent estimates from 2005 in Hong Kong, suggest obesity is becoming more common, 15.8%, in urban settings [87]. The rapid changes occurring in China may limit the generalizability of our findings.

A strength of this study is its large population-based dataset, with exposure and outcome measures collected prospectively. This study design eliminates recall bias. Maternal anthropometric data were objectively measured, instead of self-reported. Additionally, pre-pregnancy BMI and GWG were calculated with true pre-pregnancy weight, instead of weight after pregnancy was established. This study also presents data from a very large, understudied population, but one that may provide insight into pregnancy as a country rapidly modernizes.

The use of the 2009 IOM recommendations in this population of Chinese women highlights the gaps in our knowledge. Due to the narrow distribution of pre-pregnancy BMI, the standard BMI cutoff points may not be appropriate. Too many women are lumped into a rather large BMI category, 18.5-25 kg/m$^2$. There are Asian-specific [100], Chinese [101] and pregnancy-related [13] BMI categorizations in the literature, but to our knowledge, the BMI categories relevant for short term and long term pregnancy outcomes have not be objectively derived for Chinese women.

In the most recent advice for adequate weight gain in pregnancy, the IOM stressed the importance of balancing short and long-term consequences for both mothers and infants. While CD and infant weight are important consequences to consider, maternal weight retention and childhood obesity should also be considered. Balancing and interpreting multiple outcomes for both mothers and infants is a challenge. For China, LBW appears to be less of a problem. However, with a population so large, an incidence of 2% translates into nearly 1 million infants at risk of serious morbidities and mortalities. China is rapidly changing though, and if the obesity

epidemic witnessed in other modern countries affects China and women enter pregnancy heavier and gain more weight, perhaps for this population, balancing the reduction in LBW will not be as serious as a concern.

Further studies are needed to understand the impact that maternal anthropometry before and during pregnancy has on short and long term pregnancy outcomes in Chinese women. Our results indicate that restricting weight gain may not increase the risk of LBW, as lower gains within the IOM recommendations do not appear to be associated with increased risk of LBW. We found that gains above the IOM's recommendation may result in higher percentages of macrosomia and CD. We demonstrated among underweight and normal weight women, the risk of CD and macrosomia increase within GWG ranges that are traditionally associated with minimal risk. These findings question the application of the IOM's recommendations to Chinese women, especially given the adverse perinatal and chronic conditions associated with CD and macrosomia.

**Table 5-1 Characteristics of women by pre-pregnancy BMI**

| | Pre-pregnancy BMI (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <18.5 N=9,797 | | 18.5-24.9 N=47,606 | | 24.9-29.9 N=735 | | Total | |
| | N | % | N | % | N | % | N | % |
| **LBW (<2500g)** | 287 | 2.9 | 795 | 1.7 | 11 | 1.5 | 1,093 | 1.9 |
| **Macrosomia (≥4000g)** | 335 | 3.4 | 2,660 | 5.6 | 73 | 9.9 | 3,068 | 5.3 |
| **Cesarean delivery** | 2,129 | 21.7 | 9,994 | 21.0 | 196 | 26.7 | 12,319 | 21.2 |
| **Weight gain (kg)** | | | | | | | | |
| <8.5 | 1,038 | 10.6 | 11,062 | 23.2 | 364 | 49.5 | 12,464 | 21.4 |
| 8.5-11.4 | 2,119 | 21.6 | 12,521 | 26.3 | 176 | 24.0 | 14,816 | 25.5 |
| 11.5-13.4 | 1,891 | 19.3 | 8,342 | 17.5 | 83 | 11.3 | 10,316 | 17.7 |
| 13.5-15.4 | 1,843 | 18.8 | 6,586 | 13.8 | 60 | 8.2 | 8,489 | 14.6 |
| 15.5-17.9 | 1,527 | 15.6 | 4,706 | 9.9 | 30 | 4.1 | 6,263 | 10.8 |
| ≥18 | 1,379 | 14.1 | 4,389 | 9.2 | 22 | 3.0 | 5,790 | 10.0 |
| **Weight gain by IOM recommendations** | | | | | | | | |
| Below | 4,103 | 41.9 | 23,583 | 49.5 | 254 | 34.6 | 27,940 | 48.1 |
| Within | 4,315 | 44.0 | 15,610 | 32.8 | 284 | 38.6 | 20,209 | 34.8 |
| Above | 1,379 | 14.1 | 8,413 | 17.7 | 197 | 26.8 | 9,989 | 17.2 |
| **Age (y)** | | | | | | | | |
| <20 | 3 | 0.0 | 24 | 0.1 | . | . | 27 | 0.1 |
| 20-25 | 6,708 | 68.5 | 34,372 | 72.2 | 540 | 73.5 | 41,620 | 71.6 |
| 25-30 | 3,012 | 30.7 | 12,624 | 26.5 | 180 | 24.5 | 15,816 | 27.2 |
| 30-35 | 68 | 0.7 | 549 | 1.2 | 15 | 2.0 | 632 | 1.1 |
| >35 | 6 | 0.1 | 37 | 0.1 | . | . | 43 | 0.1 |
| **Mother's Education** | | | | | | | | |
| High school or college | 1,774 | 18.1 | 5,579 | 11.7 | 46 | 6.3 | 7,399 | 12.7 |
| Junior high school | 6,162 | 62.9 | 31,810 | 66.8 | 476 | 64.8 | 38,448 | 66.1 |
| Elementary or none | 1,861 | 19.0 | 10,217 | 21.5 | 213 | 29.0 | 12,291 | 21.1 |
| **Mother's occupation** | | | | | | | | |
| Farmer | 4,537 | 46.3 | 27,083 | 56.9 | 500 | 68.0 | 32,120 | 55.3 |
| Factory worker | 4,445 | 45.4 | 18,014 | 37.8 | 215 | 29.3 | 22,674 | 39.0 |
| Other | 815 | 8.3 | 2,509 | 5.3 | 20 | 2.7 | 3,344 | 5.8 |
| **Region** | | | | | | | | |
| North | 478 | 4.9 | 8,132 | 17.1 | 182 | 24.8 | 8,792 | 15.1 |
| South | 9,319 | 95.1 | 39,474 | 82.9 | 553 | 75.2 | 49,346 | 84.9 |

**Table 5-2 Adjusted* risk ratio for macrosomia, CD and LBW by IOM categories and pre-pregnancy BMI**

| | Weight gain by Institute of Medicine recommendations | Pre-pregnancy BMI (kg/m$^2$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Underweight | | | Normal weight | | | Overweight | | |
| | | RR | CI LO | CI HI | RR | CI LO | CI HI | RR | CI LO | CI HI |
| Macrosomia | BELOW | 0.4 | 0.27 | 0.50 | 0.5 | 0.41 | 0.51 | 0.7 | 0.36 | 1.40 |
| | WITHIN | 1.0 | | | 1.0 | | | 1.0 | | |
| | ABOVE | 2.3 | 1.79 | 2.95 | 2.1 | 1.90 | 2.30 | 2.1 | 1.17 | 3.76 |
| | | RR | CI LO | CI HI | RR | CI LO | CI HI | RR | CI LO | CI HI |
| CD | BELOW | 0.8 | 0.71 | 0.84 | 0.7 | 0.69 | 0.74 | 0.7 | 0.53 | 0.99 |
| | WITHIN | 1.0 | | | 1.0 | | | 1.0 | | |
| | ABOVE | 1.2 | 1.11 | 1.34 | 1.3 | 1.26 | 1.37 | 1.5 | 1.12 | 1.89 |
| | | RR | CI LO | CI HI | RR | CI LO | CI HI | RR | CI LO | CI HI |
| LBW | BELOW | 2.0 | 1.52 | 2.71 | 1.9 | 1.55 | 2.23 | 0.4 | 0.07 | 2.47 |
| | WITHIN | 1.0 | | | 1.0 | | | 1.0 | | |
| | ABOVE | 0.5 | 0.24 | 0.92 | 0.5 | 0.38 | 0.74 | 1.2 | 0.23 | 5.98 |

**Adjusted for pre-pregnancy BMI, maternal age at delivery, maternal education, maternal occupation, region of residence, sex of infant and weeks of gestation

### Table 5-3 Adjusted* risk ratio of macrosomia by categories of GWG and pre-pregnancy BMI

| Weight gain (kg) | Pre-pregnancy BMI (kg/m$^2$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | UNDERWEIGHT | | | NORMAL WEIGHT | | | OVERWEIGHT | | |
| | RR | CI LO | CI HI | RR | CI LO | CI HI | RR | CI LO | CI HI |
| **<8.5** | **0.3** | **0.12** | **0.60** | **0.4** | **0.30** | **0.42** | 0.5 | 0.25 | 1.22 |
| **8.5-11.4** | **0.5** | **0.31** | **0.80** | **0.7** | **0.57** | **0.75** | 0.8 | 0.36 | 1.98 |
| **11.5-13.4** | 1.0 | | | 1.0 | | | 1.0 | | |
| **13.5-15.4** | 1.1 | 0.78 | 1.69 | **1.2** | **1.06** | **1.39** | 1.3 | 0.48 | 3.73 |
| **15.5-17.9** | **1.8** | **1.22** | **2.54** | **1.8** | **1.58** | **2.08** | **3.8** | **1.35** | **10.95** |
| **≥18** | **3.2** | **2.27** | **4.51** | **2.8** | **2.49** | **3.23** | 2.4 | 0.74 | 7.98 |

### Table 5-4 Adjusted* risk ratio of cesarean delivery by categories of GWG and pre-pregnancy BMI

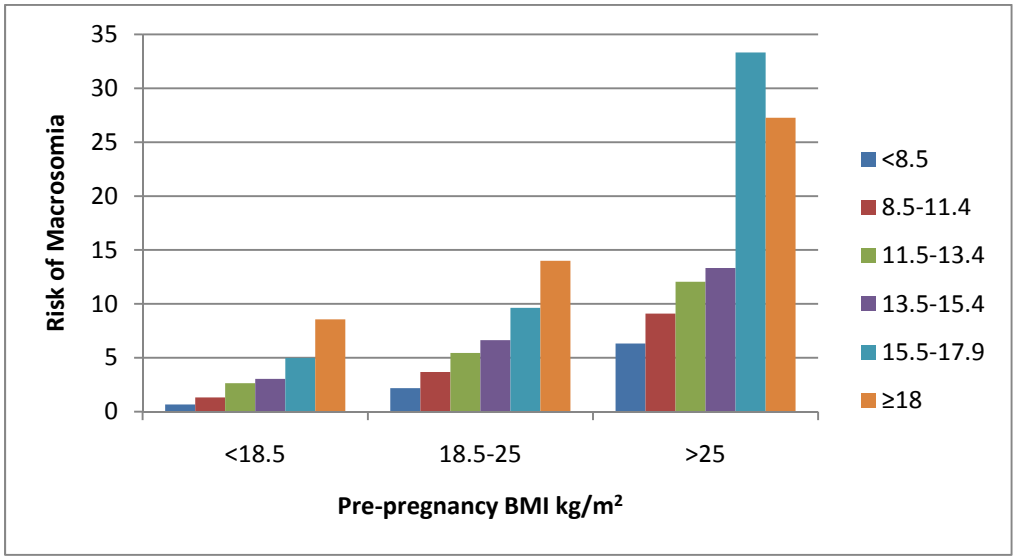
| Weight gain (kg) | Pre-pregnancy BMI (kg/m$^2$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | UNDERWEIGHT | | | NORMAL WEIGHT | | | OVERWEIGHT | | |
| | RR | CI LO | CI HI | RR | CI LO | CI HI | RR | CI LO | CI HI |
| **<8.5** | **0.7** | **0.60** | **0.85** | **0.7** | **0.66** | **0.74** | 0.7 | 0.51 | 1.11 |
| **8.5-11.4** | 0.9 | 0.78 | 1.01 | **0.8** | **0.79** | **0.89** | 1.1 | 0.75 | 1.72 |
| **11.5-13.4** | 1.0 | | | 1.0 | | | 1.0 | | |
| **13.5-15.4** | 1.0 | 0.92 | 1.18 | **1.2** | **1.09** | **1.22** | **1.7** | **1.10** | **2.56** |
| **15.5-17.9** | **1.3** | **1.15** | **1.46** | **1.3** | **1.23** | **1.38** | **2.1** | **1.33** | **3.18** |
| **≥18** | **1.4** | **1.23** | **1.56** | **1.5** | **1.45** | **1.62** | **2.3** | **1.47** | **3.58** |

### Table 5-5 Adjusted* risk ratio of low birth weight by categories of GWG and pre-pregnancy BMI

| Weight gain (kg) | Pre-pregnancy BMI (kg/m$^2$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | UNDERWEIGHT | | | NORMAL WEIGHT | | | OVERWEIGHT | | |
| | RR | CI LO | CI HI | RR | CI LO | CI HI | RR | CI LO | CI HI |
| **<8.5** | **2.5** | **1.69** | **3.77** | **2.2** | **1.75** | **2.80** | 0.3 | 0.05 | 1.95 |
| **8.5-11.4** | **1.5** | **1.02** | **2.20** | 1.1 | 0.88 | 1.45 | 0.3 | 0.03 | 2.35 |
| **11.5-13.4** | 1.0 | | | 1.0 | | | 1.0 | | |
| **13.5-15.4** | **0.5** | **0.30** | **0.86** | 0.7 | 0.54 | 1.04 | 0.4 | 0.03 | 5.46 |
| **15.5-17.9** | 0.8 | 0.50 | 1.40 | **0.5** | **0.32** | **0.75** | | | |
| **≥18** | **0.4** | **0.18** | **0.74** | **0.5** | **0.32** | **0.78** | | | |

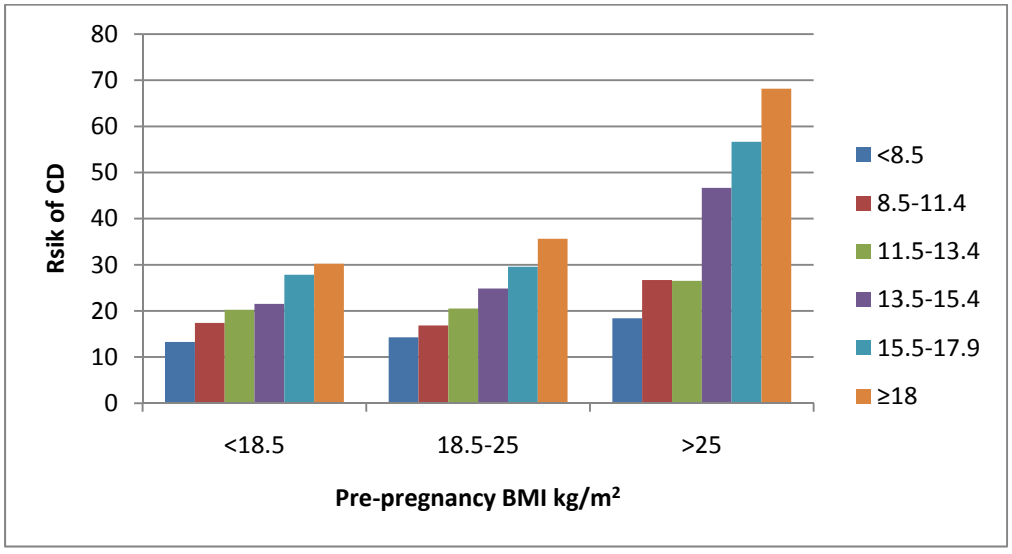
*Adjusted for pre-pregnancy BMI, maternal age at delivery, maternal education, maternal occupation, region of residence, sex of infant and weeks of gestation

**Figure 5-1 Risk of macrosomia by pre-pregnancy BMI and categories of GWG**



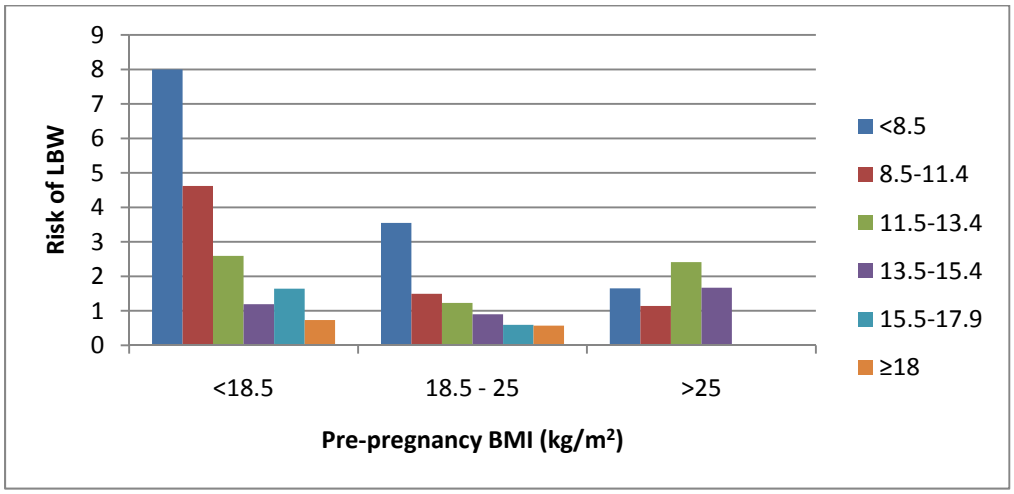

Categories of GWG: <8.5, 8.5-11.4. 11.5-13.4, 13.5-15.4, 15.5-17.9, ≥18 kg
CD, cesarean delivery; BMI, body mass index

**Figure 5-2 Risk of cesarean delivery by pre-pregnancy BMI and categories of GWG**



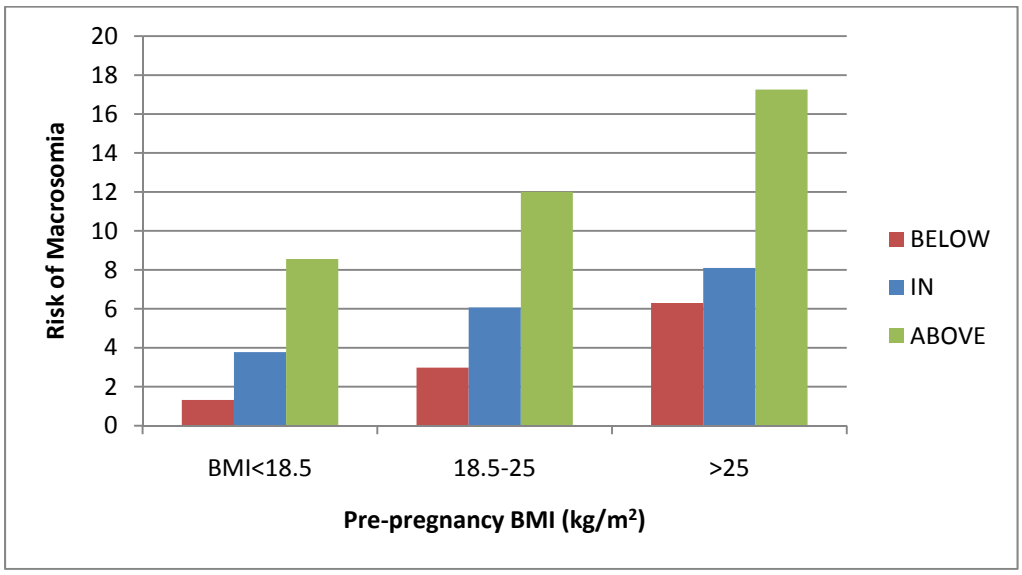

Categories of GWG: <8.5, 8.5-11.4. 11.5-13.4, 13.5-15.4, 15.5-17.9, ≥18 kg
CD, cesarean delivery; BMI, body mass index

**Figure 5-3 Risk of low birth weight by pre-pregnancy BMI and categories of GWG**



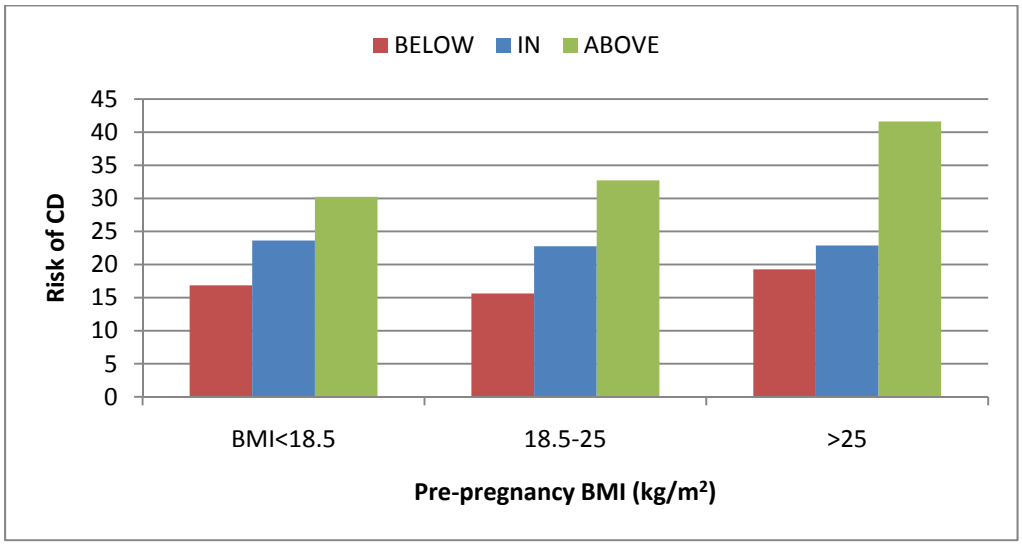

Categories of GWG: <8.5, 8.5-11.4. 11.5-13.4, 13.5-15.4, 15.5-17.9, ≥18 kg
CD, cesarean delivery; BMI, body mass index, LBW, low birth weight

**Figure 5-4 Risk of macrosomia by pre-pregnancy BMI and IOM recommendations**



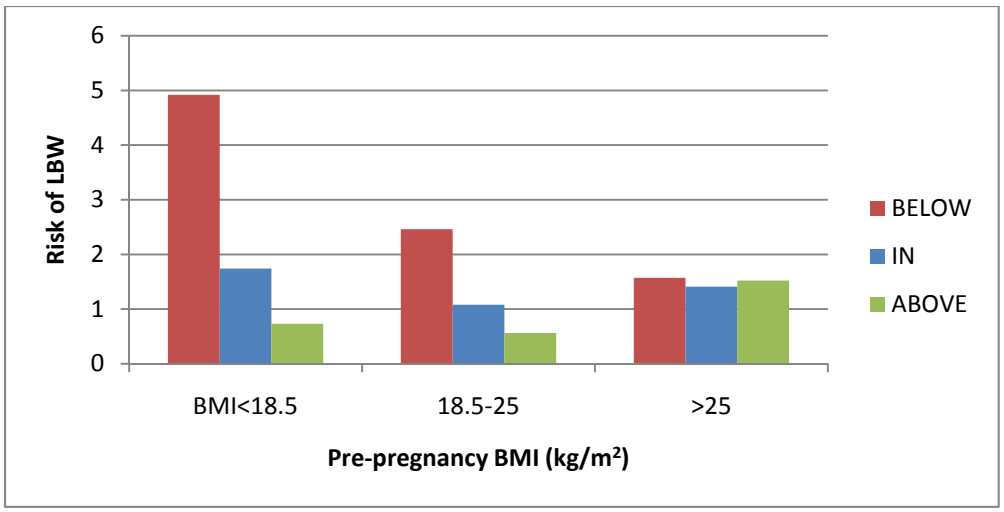

BMI, body mass index; IOM, Institute of Medicine

**Figure 5-5 Risk of cesarean delivery by pre-pregnancy BMI and IOM recommendations**




BMI, body mass index; IOM, Institute of Medicine

**Figure 5-6 Risk of low birth weight by pre-pregnancy BMI and IOM recommendations**




LBW, low birth weight; BMI, body mass index; IOM, Institute of Medicine

# Chapter 6 Maternal Anthropometry and Risk of Primary Cesarean Delivery among Chinese Women

Kirsten Herrick[1], Song Li[2], KM Venkat Narayan[3], Li Hao[2], Yinghui Liu[2], David F. Williamson[3], DG Kleinbaum[4], Michele Marcus[4], Adolfo Correa[6], Robert J.Berry[6], Zhu Li[2]

[1]Nutrition and Health Sciences Program, Graduate Division of Biological and Biomedical Sciences, Emory University, Atlanta, GA,

[2] National Center of Maternal and Infant Health, Beijing, Peoples' Republic of China

[3]Emory University, Hubert Department of Global Health, Atlanta, Georgia

[4] Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia

[5] CDC, National Center on Birth Defects and Developmental Disabilities

## Abstract

***Background***: Recommendations for gestational weight gain (GWG) are based on Europid populations and may not be appropriate for women of Chinese origin, as they are typically shorter and gain less weight in pregnancy.

***Objectives:*** Our goal was to examine the relationship between pre-pregnancy BMI, GWG and primary cesarean delivery (CD) among Chinese women. We also assessed the use of various BMI cut-off points (WHO/IOM, Asian and Chinese) to identify if a best fit categorization exists using the present data.

***Design:*** We used data from the China-US Collaborative Project for Neural Tube Defect Prevention, a pregnancy monitoring system established in 21 counties/cities in three provinces in China, (Hebei, Zhejiang and Jiangsu) from 1993-1996. We identified 58,138 primiparous, Han Chinese women delivering a singleton infant for analysis. Unadjusted relative risk (RR) of primary CD was evaluated by single unit increases in pre-pregnancy BMI to describe the pattern of risk. Using spline models to evaluate best fit, four categorizations of obesity were compared: WHO (<18.5, 18.5-24.9 and ≥ 25kg/m$^2$), Asian-specific (<18.5, 18.5-22.9, 23-24.9, 25-27.4 and ≥27.5 kg/m$^2$), Chinese (<18.5, 18.5-23.9, 24.27.9, ≥28 kg/m$^2$) and our empirically derived categorization (<22 and ≥ 22 kg/m$^2$). Interactions between BMI and GWG were assessed in the best fit model and presented stratified pre-pregnancy BMI and quintiles of GWG (<8, 8.0-10.4, 10.5-12.9, 13.0-14.9 and ≥15 kg).

***Results:*** The unadjusted RR of primary CD was vacillated between 0.8 and 1.2 as pre-pregnancy BMI increased until BMI=22 kg/m$^2$. The RR of CD was two times greater for a mother with a pre-pregnancy BMI of 28 kg/m$^2$ compared to a referent of 22 kg/m$^2$. Using spline analysis we empirically identified BMI=22 kg/m$^2$ as a threshold in the association between pre-pregnancy BMI and risk of CD. Excess risk of CD was present for women with a pre-pregnancy BMI≥22 kg/m$^2$ gaining more than 13 kg of weight in pregnancy.

***Conclusions:*** Data from this large population-based study of Chinese women suggests a lower BMI threshold of 22 kg/m$^2$, rather than 25 kg/m$^2$, as suggested by the WHO, may be more appropriate to define obesity for risk of CD. Ranges of GWG may also need to be revised downward.

## Introduction

Cesarean deliveries (CD) have been increasing globally and represent a significant proportion of all births nationally. In the United States, the rate increased from 20.7% in 1996 to 31.1% in 2006 [55]. Rates can also vary wildly within a country depending on access to care: in Brazil 80% of private sector births, which account for one quarter of all births, are CD. This is in sharp contrast to the public sector where CD comprises 28% of all births [180]. Similar to Brazil, rates of CD in China are variable and high; a recent estimate puts the overall CD rate at 46.2% [179], but they can vary from 22.5% to 63.2% depending on the setting [181].

Consequences of CD can be substantial: in 1995 in the US, the average cost of a vaginal delivery was $3,038, compared with $7,241 for a cesarean delivery [182]. CD is a major surgery that carries with it risk of infection and injury to other organs, and is associated with a longer recovery time than a vaginal birth[183]. Babies delivered by CD are also at increased risk of respiratory distress syndrome, compared to their vaginally delivered counterparts [179]. Mother/infant bonding and establishment and maintenance of breastfeeding may also suffer after a CD [65]. Maternal demand [24, 60] and physician preference [61-63] are two hypothesized reasons for the increase. However, there is also evidence supporting the association between increased risk of CD and high pre-pregnancy BMI [87, 184, 185] and excessive GWG [1, 140].

Recommendations for adequate GWG were developed in the United States by the Institute of Medicine (IOM) in 1990 [2] and revised recently in 2009 [1]. Pre-pregnancy BMI based on the WHO's categorization of obesity, <18.5, 18.5-24.9, 25-29.9 and ≥ 30 kg/m$^2$ for underweight, normal weight, overweight and obese, respectively [186], determine the recommended range of GWG. The recommended GWG for an underweight, normal, overweight and obese women are: 12.5-18.0, 11.5-16, 7.0-11.5 and 5.0-9.0 kg, respectively [1]. However, these recommendations are based on well-nourished, American women and their application to

women who are shorter or thinner than American women or even members of American minority ethnic or racial groups is uncertain.

There are multiple categorizations of BMI for Asian populations. In 2002 the WHO Expert Consultation on BMI in Asian Populations recommended additional BMI cut-off points until enough evidence was collected to determine whether, and at what point, different cut-offs were needed for different ethnic/racial groups. The BMI cup-off points they recommended are: 23, 27.5, 32.5 and 37.5 kg/$m^2$, positioned between the traditional BMI cut-off points (<18.5, 18.5-24.9, 25-29.9 and ≥30 kg/$m^2$) [100]. Concurrently, the Working Group on Obesity in China (WGOC) proposed the following BMI categories: 24.1-27.9 kg/$m^2$ for overweight and ≥28 kg/$m^2$ for obese [101]. A study of 29,303 Chinese women in Hong Kong concluded that Asian-specific BMI cut-off points may be appropriate for obstetric outcomes [87]. In contrast, a study in Shenyang province, China, used the BMI cut-off points suggested by the WGOC [50]. These studies focus on women in urban areas; however, more than half of China's population lives in rural areas [102].

In a large prospective cohort study, we examined the relationship between pre-pregnancy BMI and primary CD among Chinese women. We also assessed the use of various BMI cut-off points (WHO/IOM, Asian, Chinese and our empirically derived categorization) to identify a threshold effect of BMI. We examined quintiles of GWG (<8, 8.0-10.4, 10.5-12.9, 13.0-14.9 and ≥15 kg) with 3 BMI groups (<18.5, 18.5-24.9, ≥25 kg/$m^2$) and 2 BMI groups (<22, ≥22 kg/$m^2$) to capture interaction effects. Finally we report ranges of GWG associated with our empirically derived BMI threshold.

## Methods

### *Study design*

We used data from the China-US Collaborative Project for Neural Tube Defect Prevention, a public health campaign that demonstrated 400 mcg of folic acid taken daily in the

first trimester of pregnancy reduced the risk of neural tube defects[17, 18]. It was conducted in 21 counties/cities in three provinces in China, one Northern (Hebei) and two Southern (Zhejiang and Jiangsu). All women who were pregnant or were planning a marriage registered with the pregnancy monitoring system. This source serves as the population from which we drew our sample (N=247,831). At the time of registering, women provided information on completed years of maternal education, maternal occupation, region, ethnicity, and family and personal history of chronic disease. Information on age and previous obstetric history were collected prospectively. Height and weight were measured. Data on perinatal outcomes (i.e., final maternal weight before delivery, mode of delivery and infant birth weight) were collected at delivery.

### *Study participants*

Our analysis included primiparous, ethnically Han Chinese women with no preexisting chronic disease or spousal consanguinity, who had registered with the pregnancy monitoring systems prior to their last menstrual period (LMP), and delivered a single infant without birth defects at 24-43 completed weeks of gestation (N=73,476, 48%). We excluded records with missing or extreme values for the following variables (exclusions are non-mutually exclusive): pre-pregnancy weight (<34 kg or >69 kg) (N=961), pre-pregnancy height (<147 cm or >173 cm) (N=7,986), last prenatal weight (<41 kg or >94 kg) (N=12,540), BMI (<13 kg/$m^2$) (N=8,779), GWG (loss of more than 5% of pre-pregnancy body weight, or a gain of more than 50% of pre-pregnancy body weight) (N=14,030), maternal age at delivery (N=0), sex of infant (N=128), maternal education (N=189) , maternal occupation (N=61) and method of delivery (N=1,700) (See Table 4-1). Extreme values were defined as any value falling outside mean ± 3 standard deviations (SD) for each anthropometric variable. Additionally, implausible values were defined for prenatal body mass index (BMI): less than 13 kg/$m^2$ (n=3) and unlikely combinations of birth weight and gestational age (n=1,881), as defined by Alexander et al.[150]. Our final analytical sample included 58,138 (38%) women. No statistical or biologically relevant differences in age,

height, pre-pregnancy weight or BMI, GWG or infant birth weight were observed between women and infants include and not included in the study (data not shown).

### *Measurements*

Registration for all women took place before LMP, mean 16 ±13 standard deviation (SD) weeks before LMP (range 0 to 52 weeks). The majority (80%) of women provided physical measurements 7 months before their LMP. We assumed that pre-pregnancy weight represented weight at conception. Maternal height and weight were measured at registration and we calculated pre-pregnancy BMI by dividing weight by height-squared. Last prenatal weight was measured a maximum of 2 weeks before delivery and always before delivery. GWG was calculated by subtracting pre-pregnancy weight from the last prenatal weight. Covariates were chosen *a priori* based on a review of the literature [140, 187, 188]. All analyses were adjusted for maternal age, sex of infant, region, completed years of maternal education and maternal occupation.

The outcome of interest was CD. Method of delivery was recorded at birth as: crown vaginal, partial breech, breech extraction, vacuum, forceps, CD before labor, CD after labor, embryotomy, other and unknown. We collapsed all cesarean deliveries into one category for analysis, regardless of medical indication or maternal request. As the analytical population was limited to primiparous women, no repeat CDs are included in the analysis.

### *Statistical analysis*

The risk of CD was common in our study (21.2%). Odds ratios (OR) would therefore overstate the relative risk (RR) [161] and were therefore inappropriate. There are many proposed methods to estimate adjusted RR for common outcomes [161, 163, 166]. For our purposes, the log-binomial method is the best choice as it is easily implemented in SAS and directly estimates RR. Using PROC GENMOD (specifying a binomial distribution and log link function) we performed exploratory log-binomial regression models to examine the association between CD

and continuous BMI (as linear and quadratic) as well as the categorical BMI (as defined by three standards: WHO, Asian Specific and Chinese). All analyses were completed using SAS software (version 9.2; SAS Institute, Cary, NC). De-identified data was approved for use by the ethics committee at the Peking University Health Science Center in China and Emory University, Atlanta, GA.

### *Spline regression*

Spline analysis has been used to elucidate variation of risk of adverse birth outcomes within traditional categorization of maternal pre-pregnancy BMI [167]. Traditional categorical analysis suffers from numerous shortcomings that can be avoided with the use of spline regression. Some of these shortcomings include: power loss due to grouping and loss of within category variation of risk (unrealistic model of risk) [178]. Additionally, there is discontinuity between category endpoints as risk is allowed to jump at the endpoints of the categories [189].

Regression splines are a type of semi-parametric generalized linear model where one of the continuous variables is modeled with piecewise polynomials or splines and treated non-parametrically, and the other covariates are modeled parametrically [190]. Splines allow a considerable amount of flexibility. Although the continuous predictor is essentially categorized with polynomials in regression splines, the common endpoints between the categories, termed 'knots', are connected. Separate spline terms are used for each category. The power of the spline terms – linear, quadratic, cubic, or some other function – can be independently specified. A full spline model uses a series of connected segments, thereby removing the unrealistic jump in risk often seen in categorical analysis [169, 170]. Quadratic and cubic splines can become unstable in the end categories, especially if open-ended. To combat this, one or both of the end categories can be 'restricted' to a line segment, rather than a curve [169].

We fit multivariable models with linear, unrestricted and restricted quadratic spline terms for BMI. We tried splines with 1 to 4 knots, consistent with the number and location of cut-off

points in the different BMI categorizations compared. Data were too sparse to fit a knot point at BMI=30 kg/m$^2$ (only 2 women in the study population had a BMI≥30 kg/m$^2$). For this reason, the maximum number of knot points for the WHO/IOM categorization was 2: (18.5 and 25 kg/m$^2$) and 4 knots for the Asian-Specific categorization (18.5, 23, 25 and 27.5 kg/m$^2$). All restricted quadratic models were restricted at the highest knot.

We assessed model fit for all multivariable models by comparing the Akaike Information Criterion (AIC). The model with the smallest AIC indicates the best-fit [190]. Based on model fit, we calculated adjusted estimates of the association of BMI and risk of CD using the chosen model. A BMI of 22 kg/m$^2$ was selected at the reference level for all calculations of relative risks as this value is within what is considered the 'normal' range for Chinese women and it is close to the study population mean of 20 kg/m$^2$.

We were interested in the potential interaction effects between GWG and pre-pregnancy BMI. We tested whether the BMI-by-GWG combinations for WHO and the empirically defined categorization of obesity and quintiles of GWG (<8, 8.0-10.49, 10.5-12.9, 13.0-15.49 and ≥15.5 kg) represented distinct risk levels. Similar to Dietz et al.[191] we implemented this test by constructing 9 interaction terms for the empirically defined categorization and 14 interaction terms for the WHO categorization of obesity. Each set of interaction terms was tested in a separate model. The likelihood ratio test was found to be highly statistically significant for both sets of interaction terms (P<0.00001).

## Results

Table 6-1 shows the demographics of the study population (mean ± SD or %) overall and by quintiles of BMI. On average, BMI at registration was 20.3 ± 1.89 kg/m$^2$. The mean age of mothers at delivery of the study infant was 24.4 (SD 1.81) years. The average height was 159 ± 4.11 cm. 51% of the offspring were male. The proportion of women with no formal education or elementary education only, increased with increasing BMI. The distribution of maternal

occupation also changed as BMI increased. In the 1st quintile, roughly equal proportions (47%) of women reported working as a farmer or factory worker. By the 5th quintile of BMI, 63% of women reported working as a farmer in contrast to 33% who reported working in a factory. As BMI increased the proportion of women from the North also increased, from 4% to 22%. The frequency of CD was fairly steady at 21% until the 5th quintile, (BMI>21.8 kg/m$^2$) where proportion increased to 22.3% of all births.

Categorization of pre-pregnancy BMI in quintiles provided an incomplete picture of the variation in CD in the last quintile. The last quintile represented nearly 10,000 women and spans a BMI range of roughly 22-30 kg/m$^2$. Therefore, we visually inspected the data by plotting the unadjusted relative risk of CD for each single unit of BMI, using a BMI of 22 kg/m$^2$ as the referent. Figure 6-1 illustrates the curvilinear association between pre-pregnancy BMI and the risk of CD. Using unadjusted bivariate log-binomial models, we performed a likelihood ratio test for the null-hypothesis that the quadratic term of the unadjusted model was equal to zero ($\alpha$=0.05). The hypothesis was rejected ($Chi^2$=31.746, p<<0.0001), further confirming the non-linear BMI-CD association. This informed the choice of spline models considered to identify the best fit model.

Table 6-2 presents the AIC statistics for adjusted models with different characterizations of BMI: continuous, quadratic, categorical and two spline models: quadratic and restricted quadratic for each of the three different categorizations of BMI. We fit an additional linear spline model with a knot at BMI=22 kg/m$^2$ based on *post hoc* evaluation of Figure 6-1. Of the log-binomial models, a quadratic model displayed the best fit. Among the spline models, the best fit was achieved by a linear spline with a single knot at 22 kg/m$^2$, AIC=56065.92. However, restricted regression spline models fit with 2 knot points at the WHO and Chinese cut-offs have very similar AIC values, 56066.41 and 56066.24, respectively. These models are statistically indistinguishable and when graphed, their curves were qualitatively consistent (Figure 6-2).

We tried alternative single knot points (BMI=21 and 23 kg/m$^2$) and also tried forcing an additional knot point at BMI=27 and BMI=28 kg/m$^2$, but were unable to identify an alternative that reduced the AIC statistic further (data not shown). Our *a priori* interest was whether a threshold effect of pre-pregnancy BMI was observed when considering CD. We therefore carried forward the results from the regression spline model indentifying a single knot point at BMI=22 kg/m$^2$, and thus two categories. We then compared this empirically derived categorization with the current IOM recommendations, based on the WHO categorization of BMI with knot points at BMI=18.5 and 25 kg/m$^2$ and thus three categories [1].

Analysis to this point has not included GWG as a predictor of CD risk. Using separate models to test the interaction of pre-pregnancy BMI and GWG, we tested for interaction between GWG, in quintiles, and pre-pregnancy BMI using the two different categorizations of pre-pregnancy BMI. We constructed 9 interaction terms for the empirically defined categorization and 14 interaction terms for the WHO categorization of obesity. The likelihood ratio test was found to be highly statistically significant for both sets of interaction terms ($P<0.00001$). The referent category for the empirically defined categorization of BMI was women with a pre-pregnancy BMI <22 kg/m$^2$ gaining 10.5-12.9 kg weight in pregnancy. Similarly, the referent category for the WHO categorization of BMI was women with a pre-pregnancy BMI between 18.5-24.9 kg/m$^2$, gaining 10.5-12.9 kg. This range of GWG was chosen as the referent as it is at the low end of the recommended GWG range for normal weight women based on the revised IOM recommendations [1].

The effect of GWG on CD was stronger for women with a higher pre-pregnancy BMI; for the empirically defined categorization (BMI≥22 kg/m$^2$) and the WHO categorization (25 kg/m$^2$) (Tables 6-3 and 6-4). The adjusted RR of CD for women with a pre-pregnancy BMI < 22 kg/m$^2$ gaining between 13-14.9 kg during pregnancy was 1.0 (95% CI: 0.97-1.09) compared with an adjusted RR of 1.2 (95% CI: 1.03-1.35) for women with a pre-pregnancy BMI ≥ 22 kg/m$^2$

gaining the equivalent amount of weight in pregnancy. Similar findings were observed for women gaining ≥15 kg in pregnancy using BMI=22 kg/$m^2$ to divide the two categories. Using the WHO categorization of pre-pregnancy BMI, only women with the highest gains (≥15kg) experienced statistically significant increase in RR: 1.13 (95% CI: 1.05-1.23) for underweight (BMI<18.5kg/$m^2$), 1.12 (95% CI: 1.04-1.19) for normal weight (18.5≤ BMI<24.9 kg/$m^2$) and 1.42 (95% CI: 1.18-1.71) for overweight women (25≤BMI<30 kg/$m^2$). Figures 6-2 and 6-3 present the adjusted RR of CD by quintiles of GWG and the two different categorizations of BMI. Using the empirically derived categories, risk of CD for women with a BMI≥22 kg/$m^2$ is significantly higher than risk for women with a BMI<22 kg/$m^2$ within the 4$^{th}$ quintile of GWG. The difference approaches significance for the last quintile (Figure 6-2). A similar plot using the WHO categorization of obesity demonstrates that there is an overlap of RR in all quintiles (Figure 6-3).

In Table 6-5, we compare the mean (±SD) and percentile values of GWG, stratified by the BMI threshold identified through spline analysis. We restricted to the sample to only those women with 'good outcomes', namely delivery of a healthy infant with a birth weight ≥2500g, but less than 4000g, delivered vaginally. The average GWG for women starting pregnancy with a BMI<22 kg/$m^2$ was 11.9 ±4.20 kg and 9.3±4.60 kg for women with a pre-pregnancy BMI≥22 kg/$m^2$. Using the 25$^{th}$ and 75$^{th}$ percentiles, new ranges of adequate GWG were defined as 9.0 and 14.5kg and 6.5 and 12 kg, for women with a pre-pregnancy BMI<22 and ≥22, respectively. Figure 6-4 shows the comparison between the newly defined GWG and the IOM's recommended weight gain. There was considerable overlap between the two schemas; however, the empirically derived schema was shifted towards lower ranges.

## Discussion

This research presents new findings on the associations between maternal anthropometry and the risk of primary CD in a Chinese population. We empirically defined BMI cut-off points

relevant for CD. To our knowledge, this is the first time this has been done. We used descriptive plots and fit statistics from spline models to identify BMI=22 kg/$m^2$ as a threshold beyond which the risk of CD increased more rapidly. We also found a statistically significant interaction between GWG and BMI. Our empirically defined cut-off points were better at identifying distinct trajectories of risk as GWG increased. Lastly, we presented GWG associated with 'good outcomes' and found them to be shifted lower than comparable ranges from the IOMs recommendations.

This study benefited from a large sample size and sufficient power to investigate complex interactions. Maternal height and weight were measured prospectively, therefore avoiding recall bias associated with remembering body size in the past. Detailed information was also collected on birth outcomes. However, this study was limited by the data quality, as there was no standardization of measurement techniques between study sites. Great care was taken to exclude unreliable measurements, resulting in a reduction in sample size to 38% of the original cohort. The external validity of the study is also uncertain as the data are over 15 years old.

We used spline models to identify the best fit categories of increase in risk of CD. There are other similarly flexible alternative methods we could have employed, such as fractional polynomial regression [169]. We chose to use splines based on an *a priori* decision and other examples from the literature [167, 192, 193]. Splines have been criticized as being too sensitive to exposure misclassification [190]. However, splines are *locally* sensitive, so while highs or lows at the extremes of the data could be viewed as too influential or due to sparse data, alternatively they could be viewed as clues to associations at the extremes of the data [190].

We selected the best-fit spline model using the AIC statistic. This approach is straightforward to implement; however, when AIC values are similar between comparison models, as was the case for our analysis, it is difficult to distinguish one model from another. It

may be that there is not a uniquely best model because risk increases gradually and there are no clear thresholds of changes in risk. Alternatively, because of sparse data at high values of pre-pregnancy BMI, we were unable to fit knot points in this region, where true and biologically important increases in risk may exist. We were therefore forcing knots in an area of the distribution where the there were no true differences in risk. Future studies that included more women with a pre-pregnancy BMI$\geq$ 30 kg/m$^2$ would allow for knot points in this region, which might make knots in the lower BMI range (22$\leq$BMI$\leq$25) unnecessary and help elucidate the relationship between BMI and risk of CD among Chinese women.

Another shortcoming of this analysis is the lack of a comparable analysis in a Europoid population. Similar analyses in another population might identify similar difficulties in identifying a single best model. This would indicate that the methodology, rather than the population the method was used in, was not well suited for the identification of threshold points. However, spline methodology has been successfully used in similar analyses [167, 192, 193]. Alternatively, the suggestion of a threshold effect of pre-pregnancy BMI may be wishful thinking on our part, and the risk of CD may increase linearly with pre-pregnancy BMI. On the larger scale, distinct pre-pregnancy BMI categories associated with increased risk of adverse outcomes must include and balance competing risk for mother and infants in the short term and over a lifetime (i.e., infant low birth weight and maternal post-partum weight retention and childhood obesity).

Results from the current study identified a potential threshold effect of pre-pregnancy BMI and the risk of CD. The threshold identified (BMI<22 kg/m$^2$) suggests that risk increases earlier than reported in other populations. The latest revision of the IOM's recommendations [1] utilize pre-pregnancy BMI categories identical to the WHO's categories for BMI [186]. They indicate an increase of risk at a pre-pregnancy BMI = 25 kg/m$^2$, three BMI points higher than we found. This could be related to the finding that Asians have an increased percentage body fat at a

lower BMI, compared with their White counterparts [98]. However our threshold was also below Asian [100] and Chinese [101] cut-off points for increased risk, 23.5 and 24 kg/m$^2$, respectively. This might reflect the different outcomes under study. We focused on CD, a perinatal outcome, in contrast to cardiovascular disease risk and mortality risk.

Uncertainty also surrounds appropriate ranges of GWG for Chinese women. In addition to entering pregnancy with a lower BMI, Asian women typically gain less weight in pregnancy, compared with American women [13]. Our results support this statement; however, we identified different BMI categories and ranges of GWG, lower than reported in the literature. Wong et al. used data from 504 women in a university hospital in Hong Kong, described as having 'good pregnancy outcomes' to derive recommendations for GWG. They identified the following BMI categories and associated ranges of GWG: BMI <19 kg/m$^2$, GWG: 13-16.7 kg; BMI 19-23.5 kg/m$^2$, GWG: 11-16.4 kg; and BMI >23.5 kg/m$^2$, GWG: 7.1-14.4 kg [13]. One of the reasons for the difference between our findings and those of Wong et al. could be the setting: Hong Kong vs. eastern China. However, we still identified GWG ranges that were shifted towards lower gains.

Pre-pregnancy BMI and GWG are associated with the risk of CD among Chinese women. This is but one adverse outcome to consider when deriving recommendations for adequate weight gain in pregnancy. Both the short term consequences and future chronic disease potentials for mothers and their infants need to be balanced. In China, the task is complicated by the rapid modernization and increase in obesity prevalence that has occurred over the last two decades [15, 194]. These changes will no doubt have an impact on developing recommendations for GWG.

Despite the future challenges, China is in a fortunate position. The prevalence of obesity still lags behind other developed countries. This presents an opportunity to stave off the adverse consequences of obesity and excess GWG if public health policy can produce appropriate recommendations and educational material to inform women and their physicians, and this information actually results in real behavioral change. Both pre-pregnancy BMI and GWG are

modifiable, and prevention of unhealthy pre-pregnancy BMI and GWG translates into savings for both individuals and health care systems.

**Table 6-1 Sociodemographic characteristics of mother-infant pairs by maternal pre-pregnancy BMI**

| | BMI kg/m$^2$ | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Quintile 1 BMI<18.6 | | Quintile 2 18.7 ≤ BMI < 19.6 | | Quintile 3 19.7 ≤ BMI < 20.6 | | Quintile 4 20.7 ≤ BMI < 21.7 | | Quintile 5 BMI ≥ 21.8 | | Total | |
| | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| **Male** | 5757 | 51.42 | 5961 | 51.38 | 6386 | 51.12 | 5712 | 51.05 | 6088 | 52.22 | 29904 | 51.4 |
| **Mother's Education** | | | | | | | | | | | | |
| High school or college | 2018 | 18.02 | 1631 | 14.06 | 1651 | 13.22 | 1213 | 10.84 | 886 | 7.6 | 7399 | 12.7 |
| Junior high school | 7048 | 62.95 | 7728 | 66.61 | 8389 | 67.15 | 7548 | 67.45 | 7735 | 66.35 | 38448 | 66.1 |
| Elementary or none | 2130 | 19.02 | 2243 | 19.33 | 2452 | 19.63 | 2429 | 21.71 | 3037 | 26.05 | 12291 | 21.1 |
| **Mother's occupation** | | | | | | | | | | | | |
| Farmer | 5215 | 46.58 | 6025 | 51.93 | 6987 | 55.93 | 6550 | 58.53 | 7343 | 62.99 | 32120 | 55.3 |
| Factory worker | 5049 | 45.1 | 4831 | 41.64 | 4788 | 38.33 | 4113 | 36.76 | 3893 | 33.39 | 22674 | 39.0 |
| Other | 932 | 8.32 | 746 | 6.43 | 717 | 5.74 | 527 | 4.71 | 422 | 3.62 | 3344 | 5.8 |
| **Region** | | | | | | | | | | | | |
| North | 556 | 4.97 | 1311 | 11.3 | 2146 | 17.18 | 2177 | 19.45 | 2602 | 22.32 | 8792 | 15.1 |
| South | 10640 | 95.03 | 10291 | 88.7 | 10346 | 82.82 | 9013 | 80.55 | 9056 | 77.68 | 49346 | 84.9 |
| **Cesarean Delivery** | 2450 | 21.9 | 2400 | 20.7 | 2586 | 20.7 | 2279 | 20.4 | 2604 | 22.3 | 12319 | 21.2 |
| | Mean | Std | Mean | Std | Mean | Std | Mean | Std | Mean | Std | Mean | Std |
| **Maternal age at birth** | 24.5 | 1.71 | 24.4 | 1.74 | 24.3 | 1.8 | 24.3 | 1.84 | 24.3 | 1.96 | 24.4 | 1.81 |
| **Maternal height (cm)** | 159.1 | 4.2 | 159.3 | 3.95 | 158.9 | 4.04 | 159.0 | 4.1 | 158.6 | 4.25 | 159.0 | 4.11 |
| **Gestation duration** | 39.8 | 1.57 | 39.9 | 1.51 | 39.9 | 1.5 | 40.0 | 1.53 | 40.0 | 1.55 | 39.9 | 1.53 |
| **Birth weight (g)** | 3216.7 | 408.94 | 3269.3 | 403.19 | 3294.5 | 392.91 | 3314.1 | 391.33 | 3353.3 | 410 | 3290.1 | 403.77 |
| **BMI (kg/m$^2$)** | 17.8 | 0.72 | 19.2 | 0.3 | 20.18 | 0.28 | 21.2 | 0.32 | 23.1 | 1.1 | 20.3 | 1.89 |
| **GWG (kg)** | 13.21 | 3.99 | 12.58 | 4.24 | 11.99 | 4.33 | 11.25 | 4.5 | 10.01 | 4.82 | 11.8 | 4.52 |

**Figure 6-1 Unadjusted risk ratio of primary cesarean delivery, by pre-pregnancy BMI**

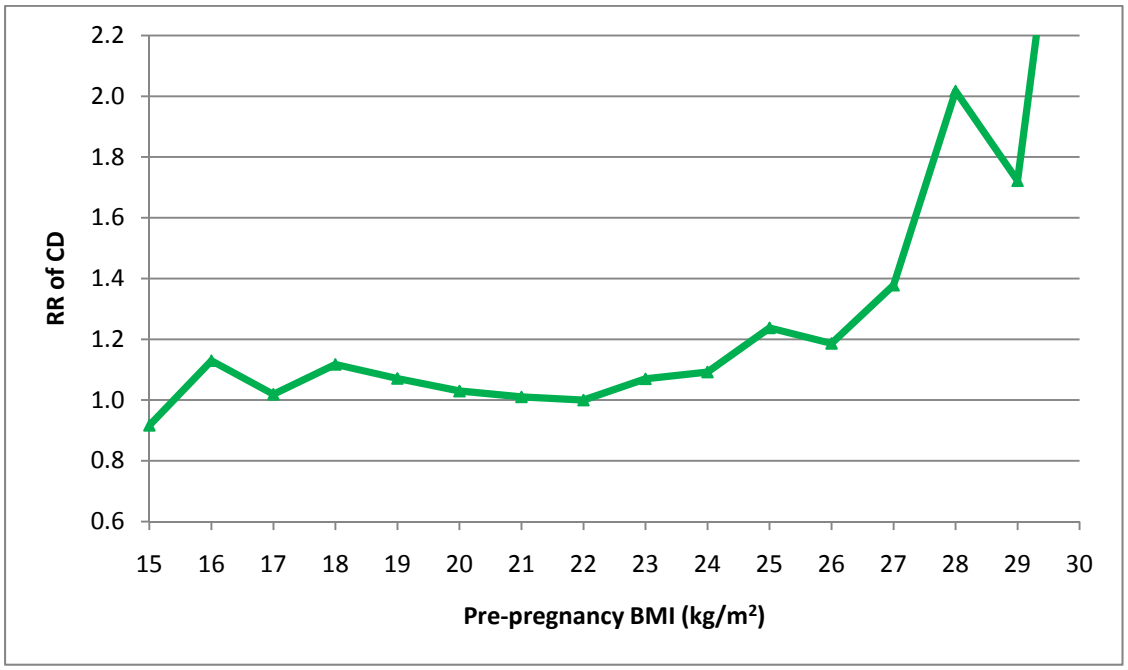
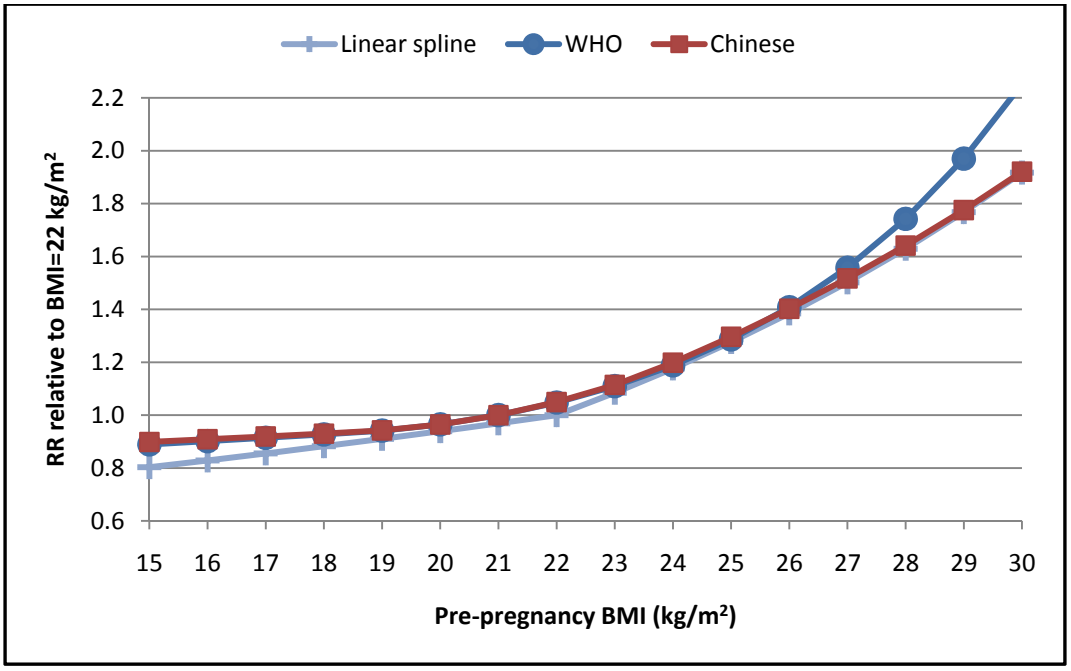


**Table 6-2 Akaike Information Criterion (AIC) values for fully adjusted* models, by characterization of BMI**

| Characterization of BMI | | Model details category / knot points | AIC |
|---|---|---|---|
| **Continuous** | | | |
| | Continuous | --- | 56076.44 |
| | Quadratic | --- | 56066.51 |
| **Categorical** | | | |
| | WHO/IOM categories | 18.5, 25 | 56144.99 |
| | Asian Specific categories | 18.5, 23, 25, 27.5 | 56097.10 |
| | Chinese categories | 18.5, 24, 28 | 56110.08 |
| **Splines** | | | |
| Visual inspection decile plot | Linear | 22 | 56065.92 |
| WHO/IOM | Quadratic, 2 knots | 18.5, 25 | 56070.35 |
| | Restricted, Quad 2 knots* | 18.5, 25 | 56066.41 |
| Asian Specific | Quadratic, 4 knots | 18.5, 23, 25, 27.5 | 56073.42 |
| | Restricted, Quad 4 knots* | 18.5, 23, 25, 27.5 | 56069.95 |
| Chinese | Quadratic, 3 knots | 18.5, 24, 28 | 56070.08 |
| | Quardratic, 2 knots | 18.5, 24 | 56068.21 |
| | Restricted, Quad, 3knots* | 18.5, 24, 28 | 56068.20 |
| | Restricted, Quad, 2 knots | 18.5, 24 | 56066.24 |

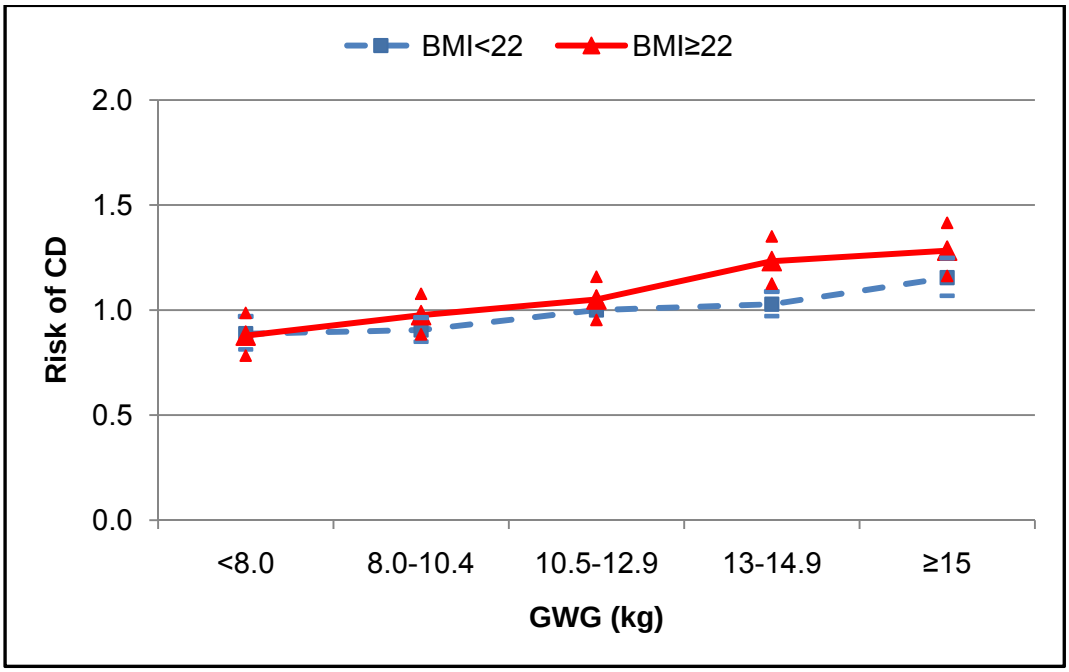
*Adjusted for maternal education, occupation, region of residence, sex of infant, duration of gestation and maternal age at birth

**Figure 6-2 Comparison of estimates of the adjusted* RR characterizing pre-pregnancy BMI and risk of CD among Chinese Women**




*Adjusted for maternal education, occupation, region of residence, sex of infant, duration of gestation and maternal age at birth

**Figure 6-3 Adjusted* RR of CD by gestational weight gain and objectively derived BMI**




GWG, gestational weight gain, CD, cesarean delivery; BMI, body mass index

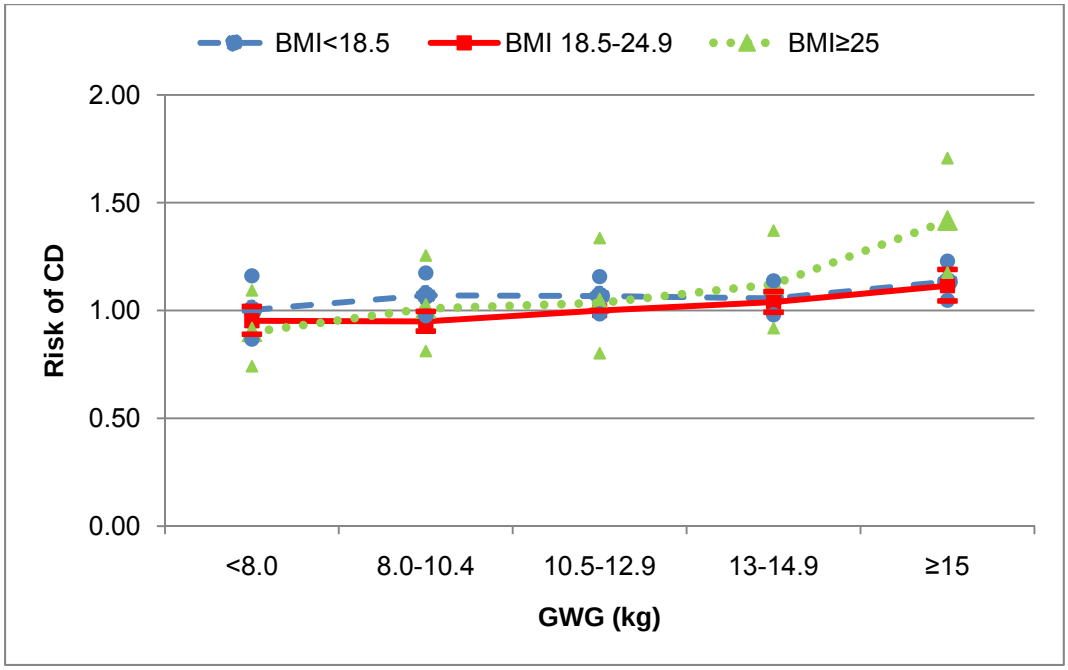
*Adjusted for maternal education, occupation, region of residence, sex of infant, duration of gestation and maternal age at birth

**Table 6-3 Adjusted RR of CD by pre-pregnancy BMI and GWG for objectively derived BMI**

| GWG (kg) | BMI<22 | | | | BMI≥22 | | |
|---|---|---|---|---|---|---|---|
| | RR | CI lo | CI hi | | RR | CI lo | CI hi |
| **<8.0** | **0.9** | **0.81** | **0.97** | | **0.9** | **0.78** | **0.99** |
| **8.0-10.4** | **0.9** | **0.85** | **0.96** | | 1.0 | 0.88 | 1.08 |
| **10.5-12.9** | | Reference | | | 1.1 | 0.95 | 1.16 |
| **13-14.9** | 1.0 | 0.97 | 1.09 | | **1.2** | **1.13** | **1.35** |
| **≥15** | **1.2** | **1.07** | **1.25** | | **1.3** | **1.16** | **1.42** |

*Adjusted for maternal education, occupation, region of residence, sex of infant, duration of gestation and maternal age at birth

**Figure 6-4 Adjusted* RR of CD by gestational weight gain and WHO defined BMI categories**




GWG, gestational weight gain, CD, cesarean delivery; BMI, body mass index

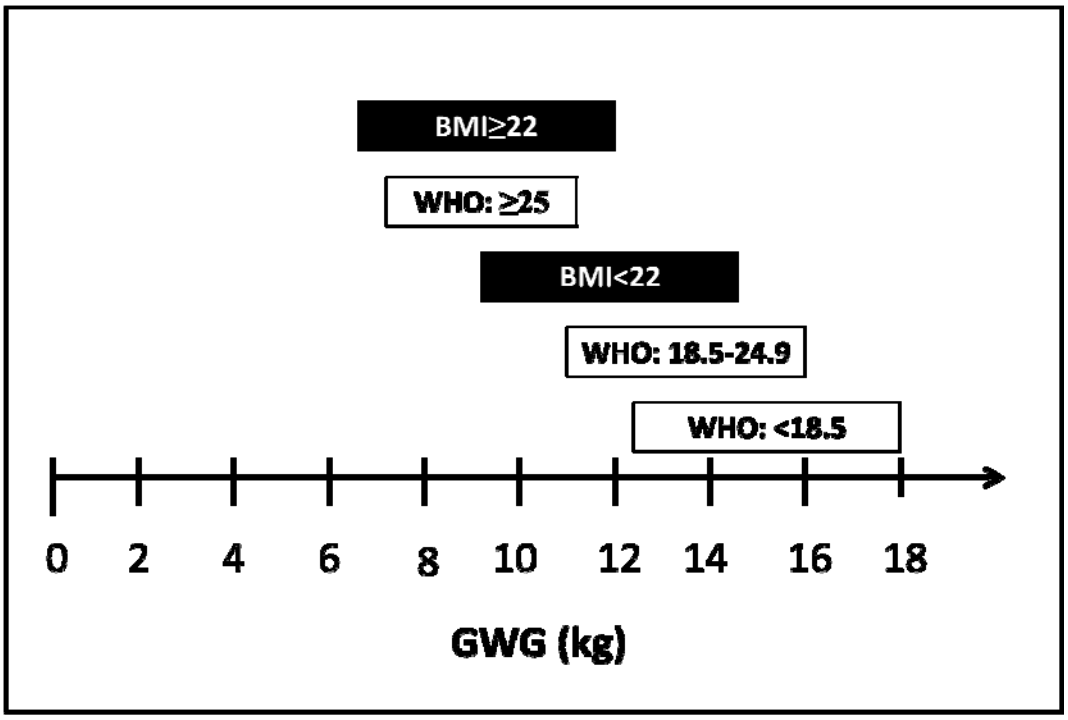
*Adjusted for maternal education, occupation, region of residence, sex of infant, duration of gestation and maternal age at birth

**Table 6-4 Adjusted* RR of CD by gestational weight gain and WHO defined BMI categories**

| GWG (kg) | BMI<18.5 | | | 18.5≤BMI<25 | | | 25≤BMI<30 | | |
|---|---|---|---|---|---|---|---|---|---|
| | RR | CI lo | CI hi | RR | CI lo | CI hi | RR | CI lo | CI hi |
| **<8.0** | 1.0 | 0.87 | 1.16 | 1.0 | 0.89 | 1.02 | 0.9 | 0.74 | 1.09 |
| **8.0-10.4** | 1.1 | 0.98 | 1.17 | 0.9 | 0.90 | 1.00 | 1.0 | 0.81 | 1.25 |
| **10.5-12.9** | 1.1 | 0.98 | 1.16 | | Reference | | 1.0 | 0.80 | 1.34 |
| **13-14.9** | 1.1 | 0.98 | 1.14 | 1.0 | 0.99 | 1.09 | 1.1 | 0.92 | 1.37 |
| **≥15** | **1.1** | **1.05** | **1.23** | **1.1** | **1.04** | **1.19** | **1.4** | **1.18** | **1.71** |

*Adjusted for maternal education, occupation, region of residence, sex of infant, duration of gestation and maternal age at birth

**Figure 6-5 Range of GWG by WHO and empirically derived categorization**




GWG, gestational weight gain; CD, cesarean delivery; BMI, body mass index

**Table 6-5 Gestational weight gain for good outcomes, stratified by pre-pregnancy BMI**

| Pre-pregnancy BMI, (kg/m$^2$) | N | GWG (kg) | | | |
|---|---|---|---|---|---|
| | | mean ± SD* | 25th percentile | 75th percentile | 10th, 90th percentile |
| <22 | 35,493 | 11.9 ± 4.20 | 9 | 14.5 | 7, 17 |
| ≥22 | 7,584 | 9.3 ± 4.60 | 6.5 | 12 | 4,15 |

GWG, gestational weight gain; BMI, body mass index

# Chapter 7 Maternal height and the risk of cesarean delivery in a population of Chinese women

Kirsten A. HERRICK[1], Song LI[2], Reynaldo Martorell[3], DG Kleinbaum[4], KM Venkat NARAYAN[3], Li HAO[2], Yinghui LIU[2], Robert J.BERRY[5], Zhu LI[2]

[1]Nutrition and Health Sciences Program, Graduate Division of Biological and Biomedical Sciences, Emory University, Atlanta, GA

[2] National Center of Maternal and Infant Health, Beijing, Peoples' Republic of China

[3]Emory University, Hubert Department of Global Health, Atlanta, Georgia

[4] Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia

[5] CDC, National Center on Birth Defects and Developmental Disabilities, Atlanta, Georgia

## Abstract

***Background:*** The results of studies examining the association between maternal and fetal body size and delivery complications have been mixed. Few studies have examined these associations among Asian women. The purpose of this study is to assess the association between maternal height, pre-pregnancy body-mass-index (BMI), net gestational weight gain (net GWG) and newborn birth weight on risk of cesarean delivery (CD) among Han Chinese women, and to determine if maternal height modified the effect of net GWG on CD risk.

***Methods:*** Data for our study come from the pregnancy-monitoring system established to test the efficacy of 400 mcg of folic acid to reduce the incidence of neural tube defects in China. Our sample included primiparous ethnic Han women, aged 15-46 y who had, prior to marriage, registered with the monitoring system in 21 counties/cities in the Chinese provinces of Hebei, Zhejiang and Jiangsu, and became pregnant with a single infant between October 1, 1996 and December 31$^{st}$, 1996. After excluding those with extreme and missing covariates our final sample included 58,138 women. Pre-pregnancy BMI (< 22 and ≥22 kg/m$^2$), maternal height (<156, 156.0-157.9, 158.0-159.9, 160.0-161.9, ≥ 162 cm), net GWG (<4.9, 4.9-7.3, 7.4-9.4, 9.5-12.1, ≥12.1 kg) and infant birth weight (g) were evaluated as predictors of risk of CD. We assessed interaction between net GWG and maternal height on the risk of CD. Log binomial regression models were used to estimate the relative risk (RR) of CD. We also calculated Z-scores to allow for comparison of effects between the various predictors. Estimates were adjusted for parity, sex of infant, region, education and occupation.

***Results:*** The risk of CD increased monotonically as maternal height decreased. Maternal height did not modify the association between net GWG and risk of CD. Among women with a pre-pregnancy BMI≥22 kg/m$^2$, for a 1 Z-score in net GWG (4.4kg), the risk ratio (RR) of CD was 1.28 (95% CI: 1.24-1.32). One Z-score increase in maternal height (4.1 cm) was associated with a

RR of CD of 0.85 (95% CI: 0.83-0.88). The risk of CD increased 18% (95%CI: 1.12-1.24) for every 1.9 kg/$m^2$ unit change in BMI, and increased 20% with a 403 g increase in birth weight.

***Conclusions:*** Results from this large, prospective study of Han Chinese women confirm previous findings that the risk of CD increases gradually with increases in maternal height. We found no evidence of an interaction between maternal height and net GWG. Maternal height may be an important predictor of the risk of CD, independent on pre-pregnancy BMI.

## Introduction

Maternal height represents the accumulation of a lifetime of nutritional experiences [195] and is an important predictor of birth outcomes [25]. In developing countries short maternal stature is associated with an increased risk of CD due to pelvic restriction [131]. However, there are contradictions in the literature about the usefulness of maternal height in predicting CD. First, some argue for height acting on a continuum rather than at a threshold below which the risk for CD increases significantly [120-122]. Second, those evaluating a threshold often do not agree on the threshold for 'short maternal stature' : <150 cm [123], <155cm [124] [125], <157 or <62 in [1, 121, 126-128]. Third, studies evaluating height often do so without adjusting for potential confounding by pre-pregnancy BMI and GWG or considering the possible effect modification of the association between GWG and risk of CD by maternal height. Due to the inconsistencies in the literature, it is difficult to understand the relative importance and interplay between maternal height, pre-pregnancy BMI and GWG in predicting birth outcomes.

The goal of this paper is to examine the contributions of: net GWG, pre-pregnancy BMI, maternal height and infant birth weight on the risk of CD among a large prospective cohort of Chinese women. Specifically, we wished to: (1) quantify the magnitude and direction of the association between net GWG and maternal height, (2) determine if maternal height is an effect measure modifier of the relationship between net GWG and CD, (3) examine the relationship for a threshold of height below which the risk of CD accelerates, and (4) determine the relative contribution of net GWG, pre-pregnancy BMI, maternal height and infant birth weight on the risk of CD.

## Methods

### *Data source*

We used data from the China-US Collaborative Project for Neural Tube Defect Prevention, a public health campaign conducted in 21 counties/cities in three provinces in China,

one Northern (Hebei) and two Southern (Zhejiang and Jiangsu). All pregnant women and women who were planning a marriage were registered with the pregnancy monitoring system, which serves as the primary data source for prenatal care and pregnancy outcomes in these three provinces (N=247,831). At the time of registering, women provided information on completed years of maternal education, maternal occupation, region, ethnicity, and family and personal history of chronic disease. Information on age, height, weight and previous obstetric history were collected prospectively. Women were followed through delivery when information on the infant and birth was recorded.

### *Study population and sample size*

We defined our analytical population as primiparous, ethnically Han Chinese women with no preexisting chronic disease or spousal consanguinity, registering with the pregnancy monitoring systems prior to their last menstrual period (LMP), delivering a single infant without birth defects at 24-43 completed weeks of gestation (N=73,476, 48%). We excluded records with missing or extreme values for the following variables (exclusions are non-mutually exclusive): pre-pregnancy weight (<34 kg or >69 kg) (N=961), pre-pregnancy height (<147 cm or >173 cm) (N=7,986), last prenatal weight (<41 kg or >94 kg) (N=12,540), BMI (<13 kg/$m^2$) (N=8,779), GWG (loss of more than 5% of pre-pregnancy body weight, or a gain of more than 50% of pre-pregnancy body weight) (N=14,030), maternal age at delivery (N=0), sex of infant (N=128), maternal education (N=189) , maternal occupation (N=61) and method of delivery (N=1,700) (See Table 4-1). Extreme values were defined as any value falling outside mean ± 3 standard deviations (SD) for each anthropometric variable. Additionally, implausible values were defined for prenatal BMI: less than 13 kg/$m^2$ (n=3) and unlikely combinations of birth weight and gestational age (n=1,881), as defined by Alexander et al. [150]. The mean number of weeks between pre-pregnancy measurement and the LMP was 16 ±13 (range 0 to 52 weeks). The majority (80%) of women provided physical measurements 7 months before their LMP. For the

analysis, we assumed that pre-pregnancy weight represented weight at conception. Our final analytical sample included 58,138 (38%) women.

### *Exposures*

Weight and height were measured at registration and BMI was calculated by dividing weight by height-squared. Height was categorized into the following quintiles: <156.0, 156.0-157.9, 158.0-159.9, 160.0-161.9, ≥162 cm. Pre-pregnancy BMI was dichotomized at BMI=22 kg/m$^2$ based on previous analysis of this cohort that identified this as a threshold point for the association between pre-pregnancy BMI and risk of CD (See Chapter 6). GWG was calculated as the difference between maternal pre-pregnancy weight and weight at last prenatal visit, which occurred 2 weeks or less, before delivery. Net GWG (GWG - infant birth weight) was used so that the independent effect of infant birth weight and net GWG could be assessed as they relate to the risk of CD. We divided net GWG into quintiles, <4.9, 4.9-7.3, 7.4-9.4, 9.5-12.1, ≥12.1 kg.

### *Covariates*

Covariates were chosen *a priori* and included factors determined from a review of the literature [50, 112, 196, 197] to be associated with any of our exposures of interest and our outcome, having a cesarean birth. All analyses were adjusted for the following self-reported indicators: sex of infant, region of residence (North or South), maternal education (elementary or none, junior high school and high school or college) and maternal occupation (factory worker, farmer, or other).

### *Statistical analysis*

The outcome of CD was not rare. Use of adjusted odds ratios in this situation 'overstates' the relative risk [161]. There are numerous methods (log binomial, Poisson regression with a robust error variance, and the 'copy' method) [162] to avoid the bias associated with the overly-simplistic adjustment proposed by Zhang and Yu [163]. Separate log binomial models were used initially, however when convergence issues were encountered (unrelated to co-linearity) we used

Poisson regression with a robust error variance to estimate the relative risk (RR) and 95% confidence intervals (CI) directly [166]. We tested for effect modification of the association between net GWG and CD risk by maternal height. Statistical significance for interaction was set at $p<0.01$. We also expressed our anthropometry variables in Z-score units: net GWG (NGWGZ), maternal height (MHTZ), pre-pregnancy BMI (BMIZ) and birth weight (BWTZ). By doing so, we could compare them directly and assess their relative importance to the outcome of CD [198].

All analyses were preformed with SAS software (version 9.2; SAS Institute, Cary, NC). De-identified data was approved for use by the ethics committee at the Peking University Health Science Center in China and Emory University, Atlanta, GA.

## Results

Table 7-1 presents maternal and obstetric characteristics by quintiles of maternal height. The incidence of CD increased with decreasing height. 19% of the tallest women (>162 cm) compared to 26% of the shortest women (<156cm) delivered by cesarean. Net GWG increased with increasing height, from 7.9kg in the first quintile, to 9.1 kg in the fifth quintile. Birth weight also increased with increasing height. Infants born to the shortest women were nearly 200 grams lighter than infants born to the tallest women: 3186g vs. 3376 g, on average. Maternal age at delivery and gestational age at delivery did not vary by quintiles of height.

Figure 7-1 presents the cross-classified risk of CD by quintiles of maternal height and net GWG. A clear gradient in risk of CD is visible from the tallest women (>162 cm) with the lowest weight gain (<4.9kg), with a risk of CD of 12% compared to a 39% risk of CD among the shortest women (<156 cm) gaining the largest net GWG (<12.1 kg). However, the interaction for height in the lowest quintile (<156 cm) and net GWG in the highest quintile (≥12.1 kg) was not significant.

Previously, work in this sample demonstrated a meaningful interaction between GWG and pre-pregnancy BMI on the risk of CD (See Chapter 6). The adjusted RR of CD for women

with a pre-pregnancy BMI < 22 kg/m$^2$ gaining between 13-14.9 kg during pregnancy was 1.0 (95% CI: 0.97-1.09) compared with an adjusted RR of 1.2 (95% CI: 1.03-1.35) for women with a pre-pregnancy BMI ≥ 22 kg/m$^2$ gaining the equivalent amount of weight in pregnancy. Equivalent figures for women gaining ≥15 kg were: RR 1.2 (95% CI: 1.07-1.25) and RR 1.3 (95% CI: 1.16-1.42), respectively, using BMI=22 kg/m$^2$ to divide the two categories. Table 7-2 summarizes the multivariable regression models for the risk of CD, with all women, and also stratified by BMI. Having a high school or college education increased the risk of CD in the non-stratified model (RR: 1.18, CI: 1.13-1.23). After stratification, the effect of education was attenuated for women with a pre-pregnancy BMI≥22 kg/m$^2$ (RR: 1.12, CI: 1.00-1.26). Maternal occupation as a farmer was slightly protective of CD (RR 0.89, CI 0.86-0.92), but the effect was lost among the women with a higher pre-pregnancy BMI after stratification. Stratification strengthened the effect of pre-pregnancy BMI on the risk of CD for women with a pre-pregnancy BMI≥22 kg/m$^2$. The effect of GWG was virtually unchanged by stratification. In the non-stratified and lower pre-pregnancy BMI group, women in the first two quintiles of height experienced a roughly 20% increased risk in CD. After stratification however, maternal height below158 cm was no longer associated with an increased risk of CD.

Maternal height, pre-pregnancy BMI, net GWG and infant birth weight were considered the main predictors of the risk of CD. By using Z-scores of each of these variables, we were able to compare the contribution of each. All four exposures were significant ($p<0.0001$), however the relative contribution of pre-pregnancy BMI differed after stratification. Net GWG was the strongest predictor of the risk of CD, followed by infant birth weight. The relative contribution of pre-pregnancy BMI surpassed that of maternal height in the risk of CD among women with a higher pre-pregnancy BMI (Table 7-3). For women with a pre-pregnancy BMI≥22 kg/m$^2$, one Z-score increase in net GWG (4.4kg) increased the risk of CD by 28%. One Z-score increase in maternal height (4.1 cm) decreased the risk of CD by 15%. The risk of CD increased by 18% with

a 1.9 kg/m$^2$ unit change in BMI which translates to a 5 kg change in weight for the average height woman in our sample (158 cm). The risk of CD increased 20% with for a 403 g increase in birth weight.

## Discussion

Our results confirm previous findings that the risk of CD increases gradually as height decreases, with no clear threshold where the risk of CD increases more rapidly [120-122]. No biologically significant interactions were observed between net GWG and maternal height. Our study adds to knowledge by demonstrating that net GWG, infant birth weight, maternal pre-pregnancy BMI and maternal height are important predictors in the risk of CD. A new finding of this research is that the increased risk of CD due to maternal height (<156 cm) was lost among women with a pre-pregnancy BMI≥22 kg/m$^2$ in our sample. Among women less than 156 cm tall, the risk of CD for women with a pre-pregnancy BMI <22 kg/m$^2$ the RR was 1.29 (95% CI 1.22-1.37), compared with RR 1.08 (0.98-1.20) for women with a pre-pregnancy BMI ≥22 kg/m$^2$.

We expected an interaction between the shortest height and highest net GWG. Poor maternal nutritional status, borne out by stunting coupled with excess gain, might lead to excess fetal growth, or soft tissue dystocia. Both of which have been shown to be associated with an increased risk of CD [70-72]. It may be that the distribution of maternal height was too narrow to demonstrate the interaction or that GWG was not so excessive as to cause this complication. Alternatively, the association doesn't exist in this data. Interestingly, we found that for women beginning pregnancy with a pre-pregnancy BMI ≥22 kg/m$^2$, BMI was as strong, or stronger, a predictor of risk of CD than maternal height. At a pre-pregnancy BMI above 22 kg/m$^2$ there is no impact of maternal height on the risk of CD, which lends support to the lack of separate recommendations for women of short stature in the US population [1], but also indicates that for developing countries where pre-pregnancy BMI is low, height may be an important predictor of the risk of CD.

A strength of this study is the use of prospective data from a large sample of women which allowed for the exploration of potential interactions over the range of maternal height, pre-pregnancy BMI and net GWG, rather than arbitrarily categorizing continuous variables. Our study is also the first of which we are aware to report on the relative contribution of maternal anthropometry to the risk of CD among a population of Chinese women.

Our study is not without limitations. Random measurement error is a possibility as anthropometric measurements were not part of the original study design and therefore measurement protocols were not standardized across study sites. This type of error would bias away from the null [199]. A subanalysis showed weight at registration increased as the interval between registration and the LMP decreased. The mean increase was 0.6 kg over the year before LMP. These findings are similar to those found by Winkvist et al. [175] and appear to be representative of a population going through the nutrition transition [200]. This trend may lead to a slight underestimation of pre-pregnancy weight and BMI at conception, which in turn would lead to a minor tendency to bias away from the null.

Records did not contain sufficient information to exclude, or analyze separately, women who developed pregnancy complications such as gestational diabetes, pregnancy induced hypertension and other risk factors for CD. To attempt to assess any bias this might have introduced, we limited the analysis to intrapartum cesarean deliveries. No difference in relative risks or final conclusions was observed (data not shown). However, even limiting the analysis to women undergoing a CD after labor has begun is unable to assess physician attitude or maternal preference for CD. In this population, CD was available to all women and requests for CD would have been granted. Further research evaluating beliefs and preferences surrounding CD is warranted. Lastly, great economical changes have occurred in China since data for this study were collected. While we feel that our results are generalizable to areas of China where

overweight and obesity are still relatively rare, care should be taken when extrapolating these results to China as a whole.

This study has implications for assessing risk of CD among Chinese women. First, we demonstrated that height may be an important factor to consider when identifying women at risk of CD. We did not find an interaction between maternal height and net GWG. These findings need to be replicated in other studies and repeated in the Chinese population as modernization continues. Further research is needed to determine whether height should be considered in addition to pre-pregnancy BMI when devising recommendations for pregnancy weight gain among Chinese women.

**Table 7-1 Characteristics of women and their infants by quintiles of height**

| | Maternal Height (cm) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <156 | | 156-158 | | 158-160 | | 160-162 | | >162 | | Total | |
| | N=11,550 | | N=7,718 | | N=11,194 | | N=13,628 | | N=14,048 | | N=58,138 | |
| | N | % | N | % | N | % | N | % | N | % | N | % |
| **Cesarean Delivery** | 3003 | 26.0 | 1706 | 22.1 | 2370 | 21.2 | 2602 | 19.1 | 2638 | 18.8 | 1,093 | 21.2 |
| **LBW** (<2500g) | 363 | 3.14 | 161 | 2.09 | 207 | 1.85 | 206 | 1.51 | 156 | 1.11 | 3,068 | 1.9 |
| **Macrosomia** (>4000g) | 351 | 3.04 | 291 | 3.77 | 562 | 5.02 | 744 | 5.46 | 1120 | 7.97 | 12,319 | 5.3 |
| **Male infants** | 5946 | 51.48 | 4014 | 52.01 | 5729 | 51.18 | 6967 | 51.12 | 7248 | 51.59 | 29904 | 51.4 |
| **Mother's Education** | | | | | | | | | | | | |
| High school or college | 1290 | 11.17 | 965 | 12.5 | 1306 | 11.67 | 1701 | 12.48 | 2137 | 15.21 | 12.7 | 7,399 |
| Junior high school | 7226 | 62.56 | 5065 | 65.63 | 7497 | 66.97 | 9288 | 68.15 | 9372 | 66.71 | 66.1 | 38,448 |
| Elementary or none | 3034 | 26.27 | 1688 | 21.87 | 2391 | 21.36 | 2639 | 19.36 | 2539 | 18.07 | 21.1 | 12,291 |
| **Mother's occupation** | | | | | | | | | | | | |
| Farmer | 6606 | 57.19 | 4332 | 56.13 | 6269 | 56 | 7766 | 56.99 | 7147 | 50.88 | 55.3 | 32,120 |
| Factory worker | 4375 | 37.88 | 2928 | 37.94 | 4344 | 38.81 | 5118 | 37.56 | 5909 | 42.06 | 39.0 | 22,674 |
| Other | 569 | 4.93 | 458 | 5.93 | 581 | 5.19 | 744 | 5.46 | 992 | 7.06 | 5.8 | 3,344 |
| **Region: North** | 1349 | 11.68 | 1220 | 15.81 | 1666 | 14.88 | 2627 | 19.28 | 1930 | 13.74 | 15.1 | 8,792 |

**Table 7-1 Characteristics of women and their infants by quintiles of height (continued)**

| | Maternal Height (cm) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **<156** | | **156-158** | | **158-160** | | **160-162** | | **>162** | | Total | |
| | **N=11,550** | | **N=7,718** | | **N=11,194** | | **N=13,628** | | **N=14,048** | | N=58,138 | |
| | Mean | Std | Mean | Std | Mean | Std | Mean | Std | Mean | Std | Mean | Std |
| **Maternal age at birth** | 24.4 | 1.79 | 24.3 | 1.8 | 24.4 | 1.8 | 24.4 | 1.84 | 24.3 | 1.82 | 24.4 | 1.81 |
| **Maternal height (cm)** | 153.2 | 2.14 | 156.6 | 0.55 | 158.4 | 0.52 | 160.2 | 0.43 | 164.3 | 2.24 | 159.0 | 4.11 |
| **Pre-pregnancy BMI (kg/m$^2$)** | 20.5 | 2.01 | 20.3 | 1.9 | 20.3 | 1.89 | 20.4 | 1.85 | 20.2 | 1.8 | 20.3 | 1.89 |
| **Gestational weight gain (kg)** | 11.1 | 4.26 | 11.5 | 4.36 | 11.8 | 4.45 | 11.9 | 4.59 | 12.4 | 4.71 | 11.8 | 4.53 |
| **Net weight gain (kg)** | 7.9 | 4.17 | 8.3 | 4.29 | 8.5 | 4.37 | 8.6 | 4.52 | 9.1 | 4.63 | 8.5 | 4.44 |
| **Gestational age at delivery (wk)** | 39.9 | 1.61 | 39.9 | 1.55 | 39.9 | 1.54 | 40.0 | 1.51 | 40.0 | 1.48 | 39.9 | 1.53 |
| **Birth weight (g)** | 3185.8 | 401.18 | 3254.0 | 391.78 | 3287.4 | 398.97 | 3312.4 | 393.03 | 3376.1 | 404.79 | 3290.1 | 403.77 |

**Figure 7-1 Unadjusted Risk of Cesarean Delivery cross-classified by maternal height and net gestational weight gain quintiles**

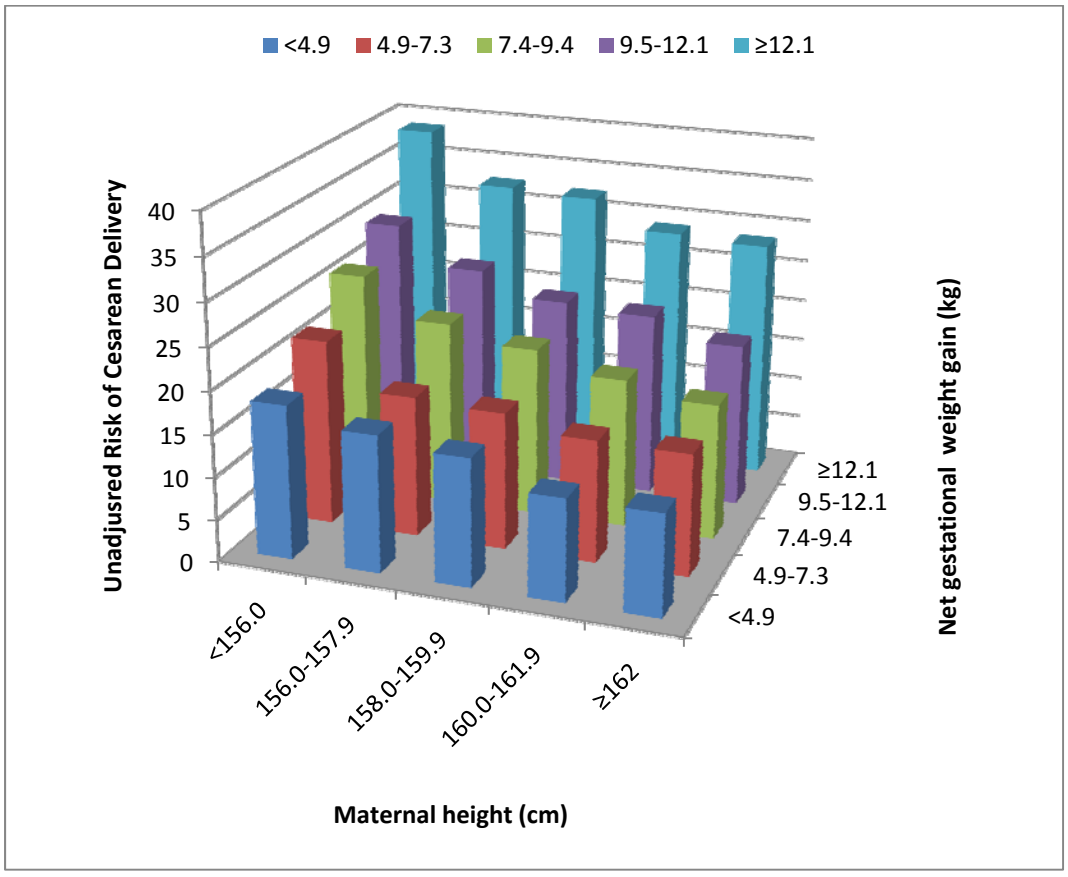


**Table 7-2 Multivariable log-binomial regression models for the risk of primary cesarean delivery**

| | Model 1 Not Stratified | | | Model 2 BMI<22 kg/m$^2$ | | | Model 2 BMI≥22 kg/m$^2$ | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variable** | RR | 95% CI | | RR | 95% CI | | RR | 95% CI | |
| Mother's Education | | | | | | | | | |
| High school or college | 1.18 | 1.13 | 1.23 | 1.19 | 1.13 | 1.25 | 1.12 | 1.00 | 1.26 |
| Junior high school | 1.00 | | | 1.00 | | | | | |
| Elementary or none | 0.89 | 0.86 | 0.93 | 0.88 | 0.84 | 0.93 | 0.91 | 0.85 | 0.99 |
| Mother's occupation | | | | | | | | | |
| Farmer | 0.89 | 0.86 | 0.92 | 0.87 | 0.84 | 0.91 | 0.95 | 0.88 | 1.02 |
| Factory worker | 1.00 | | | 1.00 | | | | | |
| Other | 1.25 | 1.18 | 1.31 | 1.27 | 1.19 | 1.34 | 1.12 | 0.97 | 1.30 |
| North Region | 0.19 | 0.17 | 0.21 | 0.19 | 0.17 | 0.22 | 0.19 | 0.16 | 0.22 |
| Male infant | 1.11 | 1.08 | 1.14 | 1.10 | 1.06 | 1.14 | 1.10 | 1.08 | 1.13 |
| Pre-pregnancy BMI (kg/m$^2$) | 1.08 | 1.07 | 1.09 | 1.06 | 1.05 | 1.07 | 1.16 | 1.08 | 1.24 |
| Net GWG (kg) | | | | | | | | | |
| <4.9 | 0.68 | 0.64 | 0.72 | 0.71 | 0.66 | 0.76 | 0.60 | 0.54 | 0.67 |
| 4.9-7.3 | 0.82 | 0.78 | 0.87 | 0.84 | 0.79 | 0.89 | 0.75 | 0.67 | 0.84 |
| 7.4-9.4 | 1.00 | | | 1.00 | | | | | |
| 9.5-12.1 | 1.15 | 1.09 | 1.20 | 1.14 | 1.08 | 1.20 | 1.18 | 1.06 | 1.32 |
| ≥ 12.1 | 1.51 | 1.44 | 1.58 | 1.53 | 1.45 | 1.61 | 1.43 | 1.28 | 1.60 |
| Maternal height (cm) | | | | | | | | | |
| <156 | 1.24 | 1.18 | 1.31 | 1.29 | 1.22 | 1.37 | 1.08 | 0.98 | 1.20 |
| 156.0-157.9 | 1.06 | 1.01 | 1.12 | 1.08 | 1.02 | 1.15 | 0.99 | 0.88 | 1.11 |
| 158.0-159.9 | 1.00 | | | | | | 1.00 | | |
| 160.0-161.9 | 0.92 | 0.88 | 0.96 | 0.94 | 0.89 | 0.99 | 0.86 | 0.78 | 0.96 |
| ≥ 162.0 | 0.82 | 0.79 | 0.86 | 0.84 | 0.80 | 0.89 | 0.76 | 0.69 | 0.85 |

**Table 7-3 Relative risk of cesarean delivery, stratified by pre-pregnancy BMI**

| | BMI <22 kg/m$^2$ | | | | BMI ≥ 22 kg/m$^2$ | | | |
|---|---|---|---|---|---|---|---|---|
| | RR | P-value | 95% CI | | RR | P-value | 95% CI | |
| NWTGZ | 1.25 | <.0001 | 1.22 | 1.27 | 1.28 | <.0001 | 1.24 | 1.32 |
| MHTZ | 0.83 | <.0001 | 0.82 | 0.85 | 0.85 | <.0001 | 0.83 | 0.88 |
| BMIZ | 1.08 | <.0001 | 1.05 | 1.10 | 1.18 | <.0001 | 1.12 | 1.24 |
| BWTZ | 1.17 | <.0001 | 1.15 | 1.20 | 1.20 | <.0001 | 1.16 | 1.24 |

*Adjusted for maternal education, occupation, region of residence, sex of infant, parity, duration of gestation and maternal age at birth

# Chapter 8 Summary and Conclusions

## Main findings

This dissertation assessed the association of maternal anthropometry before and during pregnancy and three adverse pregnancy outcomes: LBW, macrosomia and CD in a population of Chinese women. This work comes at critical time, as there is scant information on these associations among Chinese women and their infants, yet the growing public health challenge of obesity in China [201, 202] and its associated morbidities is gaining recognition [148, 203]. Due to the sheer size of China's population, the fiscal burden on individuals and government poses a pressing concern.

The first goal of this work was to establish the fit of the IOM's recommendations for Chinese women. We found that gains above the IOM's recommendations were associated with an increased risk of macrosomia and CD, and gains below the IOM's recommendations were associated with an increased risk of LBW. Further we found that high gains that were still within the IOM's recommendations were associated with an increased risk of macrosomia and CD for both underweight and normal weight women. We did not find a consistent modification of the association between GWG and adverse pregnancy outcomes by pre-pregnancy BMI.

The lack of consistent interaction between pre-pregnancy BMI and GWG coupled with the ill-fit of the IOM's recommendations led us to consider alternative measures of maternal pre-pregnancy body size that might be a better indicator of risk. Given that there are many categorizations for obesity in the literature, we hypothesized that the standard cut-offs used in the IOM's recommendations ($<18.5$, 18.5-24.9, 25-29.9, $\geq 30$ kg/m$^2$) was partly to blame for the ill-fit between the recommendations and the Chinese population. Thus, we explored other cut-offs in the second analysis. We also considered that pre-pregnancy BMI was not the appropriate measure to describe maternal nutritional status before pregnancy given that the distribution of BMI was

quite narrow among Chinese women. Therefore, we examined maternal height as a marker of risk of CD, as it encapsulates past nutritional exposures that might be more informative than nutritional exposures concurrent with becoming pregnant. The third analysis explored this hypothesis.

As previously mentioned, the first analysis demonstrated that the IOM's recommendations did not adequately fit Chinese women. In addition, previous literature has demonstrated that there are multiple definitions of overweight and obesity for Chinese populations [100, 101]. Our goal with the second analysis was to describe in detail the association between pre-pregnancy BMI and the risk of CD. We were specifically interested in examining the association for threshold effects that might suggest pre-pregnancy BMI cutoff points that are associated with increased risk of CD. We choose to limit our focus to CD, as this outcome is common in our population, and rates of CD have dramatically increased recently in China.

Using spline models, we examined the data for the presence of a threshold effect by pre-pregnancy BMI when the outcome under consideration was CD. We also compared the fit of models using different categorizations of obesity. We found that current categorizations of obesity, Chinese[101], Asian or international [100], did not fit the data any better than our empirically derived categorization with a single knot point at a BMI of 22 $kg/m^2$. We felt however that our empirically derived categorization deserved further investigation. Women were stratified into two groups based on their pre-pregnancy BMI, < $22kg/m^2$ (normal weight) and $22 \leq BM < 30$ $kg/m^2$ (overweight), and the interquartile range of GWG was described for women with 'good outcomes', i.e., vaginal delivery of infants that were neither LBW nor macrosomic. We then compared this interquartile range (IQR) to the IOM recommendations for adequate pregnancy weight gain for normal and overweight women. Using this empirically derived categorization of obesity, we found that the range for GWG was similar among overweight

women in both categorizations, but the IQR was shifted towards lower gains for normal weight women.

We also explored a different hypothesis when considering measures of maternal anthropometry as predictors of CD. In the third analysis we evaluated the contribution of maternal height to the risk of CD. The distribution of BMI was quite narrow in our population, so we hypothesized that variations in maternal height might be more informative. China is rapidly modernizing. The population is shifting from rural to more urban areas, shedding diets high in fruits and vegetables for fast food diets characterized by high fat and high sugar [204, 205]. Additionally, physical activity patterns are changing from very active to sedentary [194, 205, 206]. Because of the rapid shift, the population is straddling this change. The current environment is obesogenic, which may be in sharp contrast to childhood environments characterized as sufficient, or for some, deficient [207]. Thus, physiologically, the women in our study spent their formative years in relatively lean times compared to the excesses of today. This contradiction may add an excess burden on pregnancy. One way to examine this is to look for variation in adverse pregnancy outcomes by height and compare the relative contribution of height with other risk factors.

In the evaluation of height, we chose to separate the maternal and infant components of GWG and use net GWG and infant birth weight. By doing this, it is possible to see the contribution of each to the risk of CD. Another innovation in this analysis was to transform the exposure variables into Z-scores. By using Z-scores, we were able to calculate the relative importance of net GWG, BMI, birth weight and maternal height to the risk of CD. All four exposures were important; however, the relative importance of pre-pregnancy BMI was greater for women who began pregnancy heavier: adjusted RR 1.1 (95% CI: 1.05-1.10) and 1.2 (95% CI: 1.12-1.24), for BMI<22 and BMI≥22 kg/m$^2$, respectively. Net GWG was the strongest predictor of the risk of CD, followed by infant birth weight. The relative importance of pre-pregnancy BMI

also surpassed that of maternal height in the risk of CD among women with a higher pre-pregnancy BMI. This analysis demonstrated that the contribution of maternal height on the risk of CD may only be relevant for women who start pregnancy both short and lean.

The associations examined in this dissertation add to our understanding of the link between maternal anthropometry before and during pregnancy and adverse pregnancy outcomes. However, maternal anthropometry only explains some of variation in adverse outcomes; there are other explanations. Maternal anthropometry is only a proxy for the complex processes that occur during pregnancy. Pre-pregnancy BMI and GWG may be poor proxies for what is happening. Perhaps different physical measurements such as skin fold or blood analytes would better gauge and indicate risk. In addition to imprecise measurement, there is always the possibility for unmeasured confounding in survey data.

## Limitations

Discussions to this point have assumed a biological pathway between exposures and outcomes. For objective measures such a birth weight, biology is clearly the appropriate pathway. It is possible that for CD, a psycho-social model that accounts for mothers', doctors' and societies' view of pregnancy and birth could account for the variation in the risk of CD. A recent study of urban births in China found that the increase in CD from 1998 to 2002 was partially due to nonmedical causes [208]. Another study found that maternal request was the driving factor for increasing rates of CD in southeast China between 1994 to 2006 [49]. One study cited the place of delivery as a potential risk factor for CD, attributing 69% of the increase in CD from1993 to 2002 to the increase in institutional births [24]. A very small qualitative study identified the following factors as influencing a Chinese women's choice to have an elective CD include: belief that medicalization of birth is a sign of wealth, avoidance of risk and pain, cultural beliefs surrounding birth on auspicious days, convenience, and desire to exercise choice [59]. It was not possible, given our data, to assess the impact of these potentially important risk factors for CD.

Measurement of maternal and infant anthropometry was not the original aim of the study; so there was no standardization of measurement techniques between study sites. This can result in digit preference, also discussed in Chapter 4, which can cause both systematic and random error [209]. On the scale of a large cohort study, the effect is increased 'noise' in the data, or less power to discern true associations from spurious ones.

The data collection for the study lacked rigorous protocols to ensure data quality. Data were not double-entered and although the data entry program had range checks, those entering the data often turned this function off, so simple range checks and miss-key checks that are common and routine with computer-based data collection systems were not utilized consistently. The lack of this quality check increases the potential for random errors and dramatically increases the time spent to prepare data for analysis after collection.

Despite our best efforts to exclude or control for known confounders, unmeasured confounding is still a possibility. Maternal anemia in pregnancy was not controlled for, but might affect maternal pre-pregnancy weight, and hence pre-pregnancy BMI and GWG. It has been shown to increase the incidence of LBW [210] and, if severe, to lead to CD [211]. By not controlling for anemia, we may have overestimated the incidence of LBW and CD. There may be additional confounders unique to this population that have yet to elucidated as there are a lack of studies on this population.

We restricted the analysis to primiparous women. As a group, primiparous women deliver lighter infants and gain more weight in pregnancy compared with their multiparous counterparts [1]. Multiparous women, in contrast, are more likely to start pregnancy with a higher BMI as they have the potential for post-partum weight retention. By restricting the analysis in this way, we did not need to adjust for parity or investigate potential interactions between parity and GWG or pre-pregnancy BMI, nor remove women with repeat CD from the analysis where CD

was the outcome. However, our results may not be generally applicable to multiparous women. We speculate that had we included multiparous women in the analysis, estimates of RR for LBW, macrosomia and CD would be virtually unchanged because GWG and pre-pregnancy BMI move in opposite directions for primiparous and multiparous women.

The external validity of the results is also questionable. At the time of analysis, the data were already 15 years old. Due to the dramatic changes that have been occurring in China, the results we report may no longer apply. At the time of the study, the narrow distribution of maternal pre-pregnancy BMI made it impossible to identify a potential upper limit for overweight. Replication of these results is needed to determine if ethnic differences or economic development are important in explaining the differences observed in this population.

## Strengths

Despite the limitations, this dissertation has many strengths. It uses data that was truly population based, so selection bias is not a problem. The data were also based on a large sample. Even after defining the analytic population and excluding missing and implausible values the sample was of sufficient size to examine interactions. The one instance where interaction could not be adequately assessed may be due to the narrow distribution of pre-pregnancy BMI and thus was an artifact of the population under study, not a limitation of the data. This dissertation also presents data that were collected prospectively, eliminating any responder bias that might result from recalling facts about the past.

The most significant strength of this dissertation is the elucidation about pregnancy outcomes and associated risk factors in an understudied group. No comparable study of Chinese women exists. These data have never been explored in this way before. The work from this dissertation begins to fill gaps in our understanding about pregnancy in Chinese women. This is important not only for China, but for the United States; especially in states where Chinese women represent large fractions of the non-white ethnic population, for example, Hawaii and California.

Lastly, because this dissertation captures women on the cusp of the nutrition transition, as a country modernizes and can no longer be described as a low-income or developing country, this work may shed light on pregnancy in other developing countries poised to start this transition. There is potential to improve pregnancy outcomes for women and babies around the world, not just in China.

## Challenges to Studying Pregnancy

There are a myriad of challenges that any study of pregnancy may encounter. Typically, studies of pregnancy are rare. One of the reasons for this is the ethical concerns. Pregnant women are considered a vulnerable population so special guidelines dictate their study. It is unethical to withhold treatment if it is known to provide benefit. Plus, there are two subjects under study in pregnancy: mother and infant. Sometimes there are competing risks. Studies of pregnancy are also expensive, due to the time involved to follow a pregnancy from start to finish. Additionally, short term outcomes must be balanced with the potential for chronic conditions. The fetal origin of adult disease hypothesis [31] has highlighted the importance of long term follow-up of infants. For these reasons, many studies enroll pregnant women once pregnancy is well established (into the second trimester) or data is collected retrospectively. Both of these study designs suffer from many limitations. Resources are not endless and it is difficult to collect all of the data desired. Finally, pregnancy entails a complex orchestration of many biochemical events. In truth, it is not well understood. Maternal anthropometry is a proxy for what is happening and may not be the best predictor to study.

The work in this dissertation has highlighted the importance of CD for China, as rates continue to climb, and additionally because of the consequences for mothers and their infants. The WHO has stated that there is little benefit to CD rates above the conservative rate of 10-15% [57]. Recent estimates put China's rate of CD at 46% [179], well above the recommended level. Within our study, the indications for CD were poorly recorded and we found few studies of

pregnancy and birth in China that recorded sufficient detail to untangle the causal factors of CD in China. Without good information on the precipitating factors for CD it is impossible to disentangle cesarean by choice from cesarean by medical necessity. Without this critical information, it is impossible to design policy and interventions to reduce rates of CD.

## Public Health Significance and Policy Implications

### *Data gaps and future studies*

The work from this dissertation highlights the lack of timely data on pregnancy and adverse outcomes in China as the country rapidly modernizes. In addition to balancing maternal and infant risks, both short and long term outcomes must be considered when developing recommendations for adequate GWG. There is scant research that addresses these concerns among Chinese women.

Recommendations for the US population have been developed over the past 40 years, with the most rigorous investigation taking place in the past two decades. The IOM's recommendations still have gaps and require re-evaluation as the US population changes. Recommendations for the Chinese population can build off of what is known from the IOM recommendations, but more studies are required that specifically focus on Chinese and Asian populations. The literature has already demonstrated that body fat is proportionally higher at a similar BMI among Asians, compared to Caucasian populations, and impacts cardiovascular disease risk [145]. It is not a leap to suggest that it might also impact pregnancy negatively, as pregnancy presents a short-term metabolic challenge which might be exaggerated with excess body fat.

First and foremost, the results from our work need to be replicated in China with contemporary data. The impact of low maternal height may be less important as obesity increases, and as China puts famine and under nutrition well into the past. Perhaps other measures of maternal nutritional status, such as waist and hip circumferences or skin fold thickness should be

evaluated. We may have observed a cohort effect that is relevant to other countries as they move through the epidemiologic transition, but after which, it no longer applies.

A future study would be designed with specific aims to capture pre-pregnancy weight, pre-pregnancy waist and hip circumference, sequential pregnancy weight measurements and perinatal outcomes, with plans to re-visit mothers and their infants five, ten and 15 years into the future. We would also suggest extending the utility of the pregnancy monitoring system from which this data were derived, and designing a follow-up study to examine some of the long term outcomes of child health. These studies would use data capture software that has built-in range and implausible value checks would greatly increase data quality. In addition, we would recommend the development and use of study protocols to standardize measurement and documentation techniques.

In addition to repeating the study, we would include blood samples to objectively measure metabolic disturbances. Gestational diabetes is associated with a myriad of pre and postnatal risks, including preeclampsia [212], and increased risk of LGA and macrosomic infants and subsequent CD [213-215]. There is also growing evidence to demonstrate that gestational diabetes is a risk factor for cardiovascular disease (CVD) [216]. Mothers with gestational diabetes are at an increased risk of later diabetes [217] and components of the metabolic syndrome [218]. Candidate analytes for measurement include: oral glucose tolerance tests (OGTT), lipid profile: total cholesterol, LDL, HDL and triglycerides, and inflammatory markers like C-reactive protein.

Over the course of preparing this research, it became apparent that both medical indication and personal preference, on the part of pregnant women and their physicians, motivated the decision to have a CD. The WHO has previously published that there is no medical benefit of CD rates above 10-15% [57]. However, rates of CD worldwide far exceed this figure, and in China, national estimates are around 46% [179]. The risk factors for CD therefore are

many and require very different action to reduce rates. Currently, there are few studies that record pregnancy in enough detail to differentiate between truly medically indicated CD from those motivated by fear of a painful birth [59, 219, 220] and fear of litigation [221] for example. The lack of good data on this aspect of birth could be due to the lack of appropriate qualitative tools to understand the decision process that leads to a CD.

### *Policy implications*

There is insufficient evidence to argue for or against developing Chinese -specific guidelines for adequate GWG. As the section above suggests there are considerable gaps in our understanding. The work in this dissertation presents a detailed look at the relationship between maternal anthropometry and the risk of any CD, and briefly touches on two other outcomes: LBW and macrosomia. These are only parts of the whole pictures. Chinese-specific recommendations of GWG must be evidence based. Plus, they should both include and balance competing risks for mothers and infants in the short term and over a lifetime, for example, infant low birth weight, preterm birth, maternal post-partum weight retention and childhood obesity, to name a few. In addition to filling gaps in our knowledge about the relationship between maternal anthropometry and adverse pregnancy outcomes, there are difficulties interpreting and weighing multiple outcomes.

One approach to balancing competing risks evidenced in the literature is the presentation of adjusted absolute risks for multiple adverse outcomes [139, 222]. Nohr et al. evaluated the trade-offs between mothers and infants with respect to BMI and GWG, for the following outcomes: SGA, LGA, emergency CD, and postpartum weight retention. This technique allows direct comparison between multiple outcomes, but assumes equal weighting of each outcome. It is left up to the discretion of the policy maker or researcher to decide what is the acceptable level of risk for each outcome. More discussion in the literature is needed to standardize how outcomes are weighted so that synthesis of results is possible and repeatable.

The development of evidence-based policy is further challenged by the need to translate research into public health messages. Our results suggest that different categorizations of pre-pregnancy BMI, with lower BMI cut-offs may be required for pregnancy outcomes in contrast to cardiovascular disease (CVD) outcomes. However, pregnant women are a transitory subgroup of all women, and devising separate recommendations based on pregnancy outcomes sends a confusing public health message and would make policy development difficult at best.

## Summary

In summary, the studies presented in this dissertation examined the association between maternal nutritional status: height, pre-pregnancy BMI and GWG, and three adverse perinatal outcomes: LBW, macrosomia and CD. Our findings suggested that the IOM's recommendations adequately minimize risk of LBW. However, we also found that the risk of macrosomia and CD increase within the IOM's recommended ranges and the standard cut-offs for BMI do not adequately capture the increase in risk of CD. We identified maternal height as an important predictor of CD risk, for women of short stature, with low pre-pregnancy BMI; this warrants future investigation.

Chinese women exhibit characteristics unique to their ethnicity and stage of national economic development that may justify modification of GWG guidelines for Chinese women. Modifications should consider the changing population distribution of body weight and prevalence of obesity in China. Our findings contribute to the understanding of pregnancy in a climate of modernization and the changes that accompany it. More research is needed to develop appropriate anthropometric guidelines targeted at Chinese women that are relevant to pregnancy. Evidence based guidelines are the first step in developing public health policies that prevent proximal and long term adverse outcomes for mothers and babies. We assert that investment at this level will reduce the burden of future chronic disease for both individuals and health care systems.

## References


1. Institue of Medicine (IOM), *Weight Gain During Pregnancy: Reexamining the Guidelines*. 2009, Washington, D.C.: The National Academies Press.

2. Institute of Medicine, *Nutrition during Pregnancy Part I: Weight gain Part II: Supplements*. 1990, National Academy Press: Washington, DC.

3. Doherty, D.A., et al., *Pre-pregnancy body mass index and pregnancy outcomes.* Int J Gynaecol Obstet, 2006. **95**(3): p. 242-7.

4. Gunderson, E.P., B. Abrams, and S. Selvin, *The relative importance of gestational gain and maternal characteristics associated with the risk of becoming overweight after pregnancy.* Int J Obes Relat Metab Disord, 2000. **24**(12): p. 1660-8.

5. Delisle, H.F., *Poverty: the double burden of malnutrition in mothers and the intergenerational impact.* Ann N Y Acad Sci, 2008. **1136**: p. 172-84.

6. Dearth-Wesley, T., H. Wang, and B.M. Popkin, *Under- and overnutrition dynamics in Chinese children and adults (1991-2004).* Eur J Clin Nutr, 2008. **62**(11): p. 1302-7.

7. Boney, C.M., et al., *Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus.* Pediatrics, 2005. **115**(3): p. e290-6.

8. Hirschler, V., et al., *Maternal waist circumference and the prediction of children's metabolic syndrome.* Arch Pediatr Adolesc Med, 2007. **161**(12): p. 1205-10.

9. Whitaker, R.C., *Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy.* Pediatrics, 2004. **114**(1): p. e29-36.

10. Dubois, L. and M. Girard, *Early determinants of overweight at 4.5 years in a population-based longitudinal study.* Int J Obes (Lond), 2006. **30**(4): p. 610-7.

11. Dabelea, D., et al., *Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships.* Diabetes, 2000. **49**(12): p. 2208-11.

12. Margerison Zilko, C.E., D. Rehkopf, and B. Abrams, *Association of maternal gestational weight gain with short- and long-term maternal and child health outcomes.* Am J Obstet Gynecol, 2010. **202**(6): p. 574 e1-8.

13. Wong, W., et al., *A new recommendation for maternal weight gain in Chinese women.* J Am Diet Assoc, 2000. **100**(7): p. 791-6.

14. U.S. Census Bureau, *International Database*. 2008.

15. Popkin, B.M., et al., *Trends in diet, nutritional status, and diet-related noncommunicable diseases in China and India: the economic costs of the nutrition transition.* Nutr Rev, 2001. **59**(12): p. 379-90.

16. *United States Department of Homeland Security. Yearbook of Immigration Statistics: 2007*. 2008, Washington, D.C: U.S. Department of Homeland Security, Office of Immigration Statistics.

17. Berry, R.J. and Z. Li, *Folic acid alone prevents neural tube defects: evidence from the China study.* Epidemiology, 2002. **13**(1): p. 114-6.

18. Berry, R.J., et al., *Prevention of neural-tube defects with folic acid in China. China-U.S. Collaborative Project for Neural Tube Defect Prevention.* N Engl J Med, 1999. **341**(20): p. 1485-90.

19. Wildman, K. and M.H. Bouvier-Colle, *Maternal mortality as an indicator of obstetric care in Europe.* Bjog, 2004. **111**(2): p. 164-9.

20. Islam, M. and S. Yoshida, *MDG 5: how close are we to success?* Bjog, 2009. **116 Suppl 1**: p. 2-5.

21. Kramer, M.S., *The epidemiology of adverse pregnancy outcomes: an overview.* J Nutr, 2003. **133**(5 Suppl 2): p. 1592S-1596S.

22. United Nations Children's Fund and World Health Organization, *Low Birthweight: Country, regional and global estimates.* 2004, UNICEF: New York, NY.

23. Xu, B. and P. Rantakallio, *Low birth weight in China and Finland.* Scand J Soc Med, 1998. **26**(1): p. 10-7.

24. Sufang, G., et al., *Delivery settings and caesarean section rates in China.* Bull World Health Organ, 2007. **85**(10): p. 755-62.

25. Kramer, M.S., *Determinants of low birth weight: methodological assessment and meta-analysis.* Bull World Health Organ, 1987. **65**(5): p. 663-737.

26. Ashworth, A., *Effects of intrauterine growth retardation on mortalty and morbidity in infants and young children.* European Journal of Clinical Nutrition, 1998. **52**(S1): p. S34-S42.

27. Behrman RE, B.A., ed. *IOM, Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Preterm birth: Causes, consequences, and prevention.* 2007, National Academies Press: Washington, DC.

28. Froen, J.F., et al., *Risk factors for sudden intrauterine unexplained death: epidemiologic characteristics of singleton cases in Oslo, Norway, 1986-1995.* Am J Obstet Gynecol, 2001. **184**(4): p. 694-702.

29. Kramer, M.S., et al., *Impact of intrauterine growth retardation and body proportionality on fetal and neonatal outcome.* Pediatrics, 1990. **86**(5): p. 707-13.

30. Semba, R.D. and M.W. Bloem, *Nutrition and health in developing countries*. 2nd ed. Nutrition and health series. 2008, Totowa, NJ: Humana Press. xxiii, 931 p.

31. Barker, D.J.P., *Mothers, Babies and Health in Later Life*. 1998: Churchill Livingstone, Edinburgh.

32. Godfrey, K.M. and D.J. Barker, *Fetal nutrition and adult disease.* Am J Clin Nutr, 2000. **71**(5 Suppl): p. 1344S-52S.

33. de Onis, M. and J.P. Habicht, *Anthropometric reference data for international use: recommendations from a World Health Organization Expert Committee.* Am J Clin Nutr, 1996. **64**(4): p. 650-8.

34. McIntire, D.D., et al., *Birth weight in relation to morbidity and mortality among newborn infants.* N Engl J Med, 1999. **340**(16): p. 1234-8.

35. Minior, V.K. and M.Y. Divon, *Fetal growth restriction at term: myth or reality?* Obstet Gynecol, 1998. **92**(1): p. 57-60.

36. Lin, L., et al., *Sampling survey on low-birth weight in China in 1998.* Zhonghua Yu Fang Yi Xue Za Zhi, 2002. **36**(3): p. 149-53.

37. Goldenberg, R.L. and J.F. Culhane, *Low birth weight in the United States.* Am J Clin Nutr, 2007. **85**(2): p. 584S-590S.

38. Langer, O., *Fetal macrosomia: etiologic factors.* Clin Obstet Gynecol, 2000. **43**(2): p. 283-97.

39. *Fetal macrosomia. ACOG Technical Bulletin Number 159--September 1991.* Int J Gynaecol Obstet, 1992. **39**(4): p. 341-5.

40. Chauhan, S.P., et al., *Suspicion and treatment of the macrosomic fetus: a review.* Am J Obstet Gynecol, 2005. **193**(2): p. 332-46.

41. Grassi, A.E. and M.A. Giuliano, *The neonate with macrosomia.* Clin Obstet Gynecol, 2000. **43**(2): p. 340-8.

42. Ferber, A., *Maternal complications of fetal macrosomia.* Clin Obstet Gynecol, 2000. **43**(2): p. 335-9.

43. Cunningham, F.G. and J.W. Williams, *Williams obstetrics*. 23rd ed. 2010, New York: McGraw-Hill Medical. xv, 1385 p.

44. Zamorski, M.A. and W.S. Biggs, *Management of suspected fetal macrosomia.* Am Fam Physician, 2001. **63**(2): p. 302-6.

45. Henriksen, T., *Nutrition and pregnancy outcome.* Nutr Rev, 2006. **64**(5 Pt 2): p. S19-23; discussion S72-91.

46. Harder, T., et al., *Birth weight and subsequent risk of type 2 diabetes: a meta-analysis.* Am J Epidemiol, 2007. **165**(8): p. 849-57.

47. Martin, J.A., et al., *Births: final data for 2005.* Natl Vital Stat Rep, 2007. **56**(6): p. 1-103.

48. Cheung, T.H., A. Leung, and A. Chang, *Macrosomic babies.* Aust N Z J Obstet Gynaecol, 1990. **30**(4): p. 319-22.

49. Zhang, J., et al., *Cesarean delivery on maternal request in southeast China.* Obstet Gynecol, 2008. **111**(5): p. 1077-82.

50. Chen, Z., et al., *Prepregnancy body mass index, gestational weight gain, and pregnancy outcomes in China.* Int J Gynaecol Obstet, 2010. **109**(1): p. 41-4.

51. Martin, J.A., et al., *Births: final data for 2006.* Natl Vital Stat Rep, 2009. **57**(7): p. 1-102.

52. Heiskanen, N., K. Raatikainen, and S. Heinonen, *Fetal macrosomia--a continuing obstetric challenge.* Biol Neonate, 2006. **90**(2): p. 98-103.

53. Voldner, N., et al., *Modifiable determinants of fetal macrosomia: role of lifestyle-related factors.* Acta Obstet Gynecol Scand, 2008. **87**(4): p. 423-9.

54. MacDorman, M.F., F. Menacker, and E. Declercq, *Cesarean birth in the United States: epidemiology, trends, and outcomes.* Clin Perinatol, 2008. **35**(2): p. 293-307, v.

55. Hamilton, B.E., J.A. Martin, and S.J. Ventura, *Births: preliminary data for 2008.* Natl Vital Stat Rep, 2010. **58**(16): p. 1-18.

56. DeFrances, C.J. and M.N. Podgornik, *2004 National Hospital Discharge Survey.* Adv Data, 2006(371): p. 1-19.

57. *Appropriate technology for birth.* Lancet, 1985. **2**(8452): p. 436-7.

58. Wagner, M., *Choosing caesarean section.* Lancet, 2000. **356**(9242): p. 1677-80.

59. Lee, L.Y., E. Holroyd, and C.Y. Ng, *Exploring factors influencing Chinese women's decision to have elective caesarean surgery.* Midwifery, 2001. **17**(4): p. 314-22.

60. Lei, H., S.W. Wen, and M. Walker, *Determinants of caesarean delivery among women hospitalized for childbirth in a remote population in China.* J Obstet Gynaecol Can, 2003. **25**(11): p. 937-43.

61. Minkoff, H., et al., *Ethical dimensions of elective primary cesarean delivery.* Obstet Gynecol, 2004. **103**(2): p. 387-92.

62. Bailit, J.L., J. Schulkin, and N.V. Dawson, *Risk-adjusted cesarean rates: what risk factors for cesarean delivery are important to practicing obstetricians?* J Reprod Med, 2007. **52**(3): p. 194-8.

63. Habiba, M., et al., *Caesarean section on request: a comparison of obstetricians' attitudes in eight European countries.* Bjog, 2006. **113**(6): p. 647-56.

64. Villar, J., et al., *Maternal and neonatal individual risks and benefits associated with caesarean delivery: multicentre prospective study.* Bmj, 2007. **335**(7628): p. 1025.

65. Perez-Rios, N., G. Ramos-Valencia, and A.P. Ortiz, *Cesarean delivery as a barrier for breastfeeding initiation: the Puerto Rican experience.* J Hum Lact, 2008. **24**(3): p. 293-302.

66. *ACOG Practice bulletin no. 115: Vaginal birth after previous cesarean delivery.* Obstet Gynecol, 2010. **116**(2 Pt 1): p. 450-63.

67. Gregory, K.D., et al., *Using administrative data to identify indications for elective primary cesarean delivery.* Health Serv Res, 2002. **37**(5): p. 1387-401.

68. Flegal, K.M., et al., *Prevalence and trends in obesity among US adults, 1999-2008.* Jama, 2010. **303**(3): p. 235-41.

69. *The burden of overweight and obesity in the Asia-Pacific region.* Obes Rev, 2007. **8**(3): p. 191-6.

70. Barau, G., et al., *Linear association between maternal pre-pregnancy body mass index and risk of caesarean section in term deliveries.* Bjog, 2006. **113**(10): p. 1173-7.

71. Crane, S.S., et al., *Association between pre-pregnancy obesity and the risk of cesarean delivery.* Obstet Gynecol, 1997. **89**(2): p. 213-6.

72. Young, T.K. and B. Woodmansee, *Factors that are associated with cesarean delivery in a large private practice: the importance of prepregnancy body mass index and weight gain.* Am J Obstet Gynecol, 2002. **187**(2): p. 312-8; discussion 318-20.

73. Stanton, C. and C. Ronsmans, *Recommendations for routine reporting on indications for cesarean delivery in developing countries.* Birth, 2008. **35**(3): p. 204-11.

74. Jackson, A.A., *Nutrients, growth, and the development of programmed metabolic function.* Adv Exp Med Biol, 2000. **478**: p. 41-55.

75. Duggleby, S.L. and A.A. Jackson, *Relationship of maternal protein turnover and lean body mass during pregnancy and birth length.* Clin Sci (Lond), 2001. **101**(1): p. 65-72.

76. Mathews, F., P. Yudkin, and A. Neil, *Influence of maternal nutrition on outcome of pregnancy: prospective cohort study.* Bmj, 1999. **319**(7206): p. 339-43.

77. Kramer, M.S., *Balanced protein/energy supplementation in pregnancy.* Cochrane Database Syst Rev, 2000(2): p. CD000032.

78. World Health Organization, *Obesity and overweight.* Fact sheet No.311, 2006.

79. Gu, D., et al., *Body weight and mortality among men and women in China.* Jama, 2006. **295**(7): p. 776-83.

80. Must, A., et al., *The disease burden associated with overweight and obesity.* Jama, 1999. **282**(16): p. 1523-9.

81. Krauss, R.M., et al., *Obesity: impact of cardiovascular disease.* Circulation, 1998. **98**(14): p. 1472-6.

82. Flegal, K.M., et al., *Excess deaths associated with underweight, overweight, and obesity.* Jama, 2005. **293**(15): p. 1861-7.

83. Hu, F.B., et al., *Adiposity as compared with physical activity in predicting mortality among women.* N Engl J Med, 2004. **351**(26): p. 2694-703.

84. Bhattacharya, S., et al., *Effect of Body Mass Index on pregnancy outcomes in nulliparous women delivering singleton babies.* BMC Public Health, 2007. **7**: p. 168.

85. Denison, F.C., et al., *Maternal obesity, length of gestation, risk of postdates pregnancy and spontaneous onset of labour at term.* Bjog, 2008. **115**(6): p. 720-5.

86. Driul, L., et al., *Prepregnancy body mass index and adverse pregnancy outcomes.* Arch Gynecol Obstet, 2008. **278**(1): p. 23-6.

87. Leung, T.Y., et al., *Trends in maternal obesity and associated risks of adverse pregnancy outcomes in a population of Chinese women.* Bjog, 2008. **115**(12): p. 1529-37.

88. Weiss, J.L., et al., *Obesity, obstetric complications and cesarean delivery rate--a population-based screening study.* Am J Obstet Gynecol, 2004. **190**(4): p. 1091-7.

89. Lynch, C.M., et al., *Obesity and mode of delivery in primigravid and multigravid women.* Am J Perinatol, 2008. **25**(3): p. 163-7.

90. Sarkar, R.K., et al., *The incidence and impact of increased body mass index on maternal and fetal morbidity in the low-risk primigravid population.* J Matern Fetal Neonatal Med, 2007. **20**(12): p. 879-83.

91. Kabali, C. and M.M. Werler, *Pre-pregnant body mass index, weight gain and the risk of delivering large babies among non-diabetic mothers.* Int J Gynaecol Obstet, 2007. **97**(2): p. 100-4.

92. Tsukamoto, H., et al., *Risk factors for small for gestational age.* Pediatr Int, 2007. **49**(6): p. 985-90.

93. Hauger, M.S., et al., *Prepregnancy weight status and the risk of adverse pregnancy outcome.* Acta Obstet Gynecol Scand, 2008. **87**(9): p. 953-9.

94. Sebire, N.J., et al., *Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London.* Int J Obes Relat Metab Disord, 2001. **25**(8): p. 1175-82.

95. Baeten, J.M., E.A. Bukusi, and M. Lambe, *Pregnancy complications and outcomes among overweight and obese nulliparous women.* Am J Public Health, 2001. **91**(3): p. 436-40.

96. Castro, L.C. and R.L. Avina, *Maternal obesity and pregnancy outcomes.* Curr Opin Obstet Gynecol, 2002. **14**(6): p. 601-6.

97. Ministry of Health, Ministry of Science, and and Technolog National Bureau of Statistics, *The nutrition and health status of the Chinese people 2002.* 2004, Personal communication: Chen Chunming International Life Science Institute(ILSI) Focal Point in China Rm 903 Chinese Center for Disease Control and Prevention 27 Nan Wei Road, Beijing 100050 China Tel:86-10-6317 0892 or 86-10-8315 9165 Fax:86-10-8315 9164

98. Wang, J., et al., *Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements.* Am J Clin Nutr, 1994. **60**(1): p. 23-8.

99. Deurenberg, P., M. Deurenberg-Yap, and S. Guricci, *Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship.* Obes Rev, 2002. **3**(3): p. 141-6.

100. WHO expert consultation, *Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies.* Lancet, 2004. **363**(9403): p. 157-63.

101. Zhou, B., *[Predictive values of body mass index and waist circumference to risk factors of related diseases in Chinese adult population].* Zhonghua Liu Xing Bing Xue Za Zhi, 2002. **23**(1): p. 5-10.

102. WHO. *WHO Western Pacific Region Country Context: China*. [cited 2010 December 30]; Available from: http://www.wpro.who.int/countries/2010/chn/.

103. Bingham, A.W., *The prevention of obstetric complications by diet and exercise.* Am J Obstet Gynecol, 1932. **23**: p. 38-44.

104. McIlroy, A.L. and H.E. Rodway, *Weight-changes during and after pregnacny with special reference to early diagnosis of toxaemia.* J Obstet Gynaecol. Br. Empire, 1937. **44**: p. 221-244.

105. Davis, C.H., *Weight in pregnancy; its value as a routine test.* Am J Obstet Gynecol, 1923. **6**: p. 575-581.

106. Hytten, F.E. and I. Leitch, *The Physiology of Human Pregnancy, 2nd ed.* 1971, Oxford: Blackwell Scientific Publications. 599.

107. NRC, *Maternal Nutrition and the Course of Pregnancy. Report of the Committee on Maternal Nutiriton, Food and Nutrition Board.* 1970, National Academy of Sciences: Washington, D.C. p. pp. 241.

108. Ogden, C.L., et al., *Prevalence of overweight and obesity in the United States, 1999-2004.* Jama, 2006. **295**(13): p. 1549-55.

109. Abrams, B., S.L. Altman, and K.E. Pickett, *Pregnancy weight gain: still controversial.* Am J Clin Nutr, 2000. **71**(5 Suppl): p. 1233S-41S.

110. Stotland, N.E., L.M. Hopkins, and A.B. Caughey, *Gestational weight gain, macrosomia, and risk of cesarean birth in nondiabetic nulliparas.* Obstet Gynecol, 2004. **104**(4): p. 671-7.

111. Saftlas, A., et al., *Prepregnancy body mass index and gestational weight gain as risk factors for preeclampsia and transient hypertension.* Ann Epidemiol, 2000. **10**(7): p. 475.

112. Cedergren, M., *Effects of gestational weight gain and body mass index on obstetric outcome in Sweden.* Int J Gynaecol Obstet, 2006. **93**(3): p. 269-74.

113. Dietz, P.M., W.M. Callaghan, and A.J. Sharma, *High pregnancy weight gain and risk of excessive fetal growth.* Am J Obstet Gynecol, 2009. **201**(1): p. 51 e1-6.

114. Taffel, S.M., *Maternal weight gain and the outcome of pregnancy: Unites States, 1980. Vital and Health Statistics, Series 21, No. 44. DHHS Publ. No. (PHS) 86-1922.* 1986, National Center for Health Statistics, Public Health Service, U.S. Department of Health and Human Services: Hyattsville, MD. p. 25 pp.

115. Tanner, J.M., *Growth as a measure of the nutritional and hygienic status of a population.* Horm Res, 1992. **38 Suppl 1**: p. 106-15.

116. Shrimpton, R., et al., *Worldwide timing of growth faltering: implications for nutritional interventions.* Pediatrics, 2001. **107**(5): p. E75.

117. Christian, P., *Maternal height and risk of child mortality and undernutrition.* Jama, 2010. **303**(15): p. 1539-40.

118. Bernard, R.M., *The shape and size of the female pelvis.* Edinb Med J, 1952. **59**(2): p. 1-15.

119. Tague, R.G., *Do big females have big pelves?* Am J Phys Anthropol, 2000. **112**(3): p. 377-93.

120. McGuinness, B.J. and A.N. Trivedi, *Maternal height as a risk factor for Caesarean section due to failure to progress in labour.* Aust N Z J Obstet Gynaecol, 1999. **39**(2): p. 152-4.

121. Pickett, K.E., B. Abrams, and S. Selvin, *Maternal height, pregnancy weight gain, and birthweight.* Am J Hum Biol, 2000. **12**(5): p. 682-687.

122. Chan, B.C. and T.T. Lao, *The impact of maternal height on intrapartum operative delivery: a reappraisal.* J Obstet Gynaecol Res, 2009. **35**(2): p. 307-14.

123. Kara, F., N. Yesildaglar, and D. Uygur, *Maternal height as a risk factor for Caesarean section.* Arch Gynecol Obstet, 2005. **271**(4): p. 336-7.

124. Sheiner, E., et al., *Maternal obesity as an independent risk factor for caesarean delivery.* Paediatr Perinat Epidemiol, 2004. **18**(3): p. 196-201.

125. Wongcharoenkiat, N. and D. Boriboonhirunsarn, *Maternal height and the risk of cesarean delivery in nulliparous women.* J Med Assoc Thai, 2006. **89 Suppl 4**: p. S65-9.

126. Witter, F.R., L.E. Caulfield, and R.J. Stoltzfus, *Influence of maternal anthropometric status and birth weight on the risk of cesarean delivery.* Obstet Gynecol, 1995. **85**(6): p. 947-51.

127. Shepard, M.J., et al., *Maternal anthropometric factors and risk of primary cesarean delivery.* Am J Public Health, 1998. **88**(10): p. 1534-8.

128. Dietz, P.M., et al., *Population-based assessment of the risk of primary cesarean delivery due to excess prepregnancy weight among nulliparous women delivering term infants.* Matern Child Health J, 2005. **9**(3): p. 237-44.

129. Prentice, A.M., et al., *Increased birthweight after prenatal dietary supplementation of rural African women.* Am J Clin Nutr, 1987. **46**(6): p. 912-25.

130. Lechtig, A., et al., *Influence of maternal nutrition on birth weight.* Am J Clin Nutr, 1975. **28**(11): p. 1223-33.

131. Martorell, R., et al., *Maternal stature, fertility and infant mortality.* Hum Biol, 1981. **53**(3): p. 303-12.

132. Habicht, J.P., et al., *Relationship of birthweight, maternal nutrition and infant mortality.* Nutr Rep Int, 1973. **7**(5): p. 533-46.

133. *Maternal anthropometry for prediction of pregnancy outcomes: memorandum from a USAID/WHO/PAHO/MotherCare meeting.* Bull World Health Organ, 1991. **69**(5): p. 523-32.

134. Rush, D., H. Davis, and M. Susser, *Antecedents of low birthweight in Harlem, New York City.* Int J Epidemiol, 1972. **1**(4): p. 375-87.

135. Frisancho, A.R., J.E. Klayman, and J. Matos, *Newborn body compositon and its relationship to linear growth.* Am J Clin Nutr, 1977. **30**(5): p. 704-11.

136. Kirchengast, S. and B. Hartmann, *Short stature is associated with an increased risk of Caesarean deliveries in a low risk population.* Acta Medica Lituanica, 2007. **14**(1): p. 1-6.

137. Camilleri, A.P., *The obstetric significance of short stature.* Eur J Obstet Gynecol Reprod Biol, 1981. **12**(6): p. 347-56.

138. Rothman, K.J. and S. Greenland, *Modern epidemiology*. 2nd ed. 1998, Philadelphia, PA: Lippincott-Raven. xiii, 737 p.

139. Nohr, E.A., et al., *Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy.* Am J Clin Nutr, 2008. **87**(6): p. 1750-9.

140. Viswanathan, M., et al., *Outcomes of maternal weight gain.* Evid Rep Technol Assess (Full Rep), 2008(168): p. 1-223.

141. Jain, N.J., et al., *Maternal obesity: can pregnancy weight gain modify risk of selected adverse pregnancy outcomes?* Am J Perinatol, 2007. **24**(5): p. 291-8.

142. Caballero B, Popkin BM, and (eds), *The Nutrition Transition: Diet and Disease in the Developing World*. 2002, London: Academic Press.

143. Popkin, B.M., *Understanding the nutrition transition.* Urban Health Newsl, 1996(30): p. 3-19.

144. Barquera, S., et al., *Coexistence of maternal central adiposity and child stunting in Mexico.* Int J Obes (Lond), 2007. **31**(4): p. 601-7.

145. Deurenberg-Yap, M., S.K. Chew, and P. Deurenberg, *Elevated body fat percentage and cardiovascular risks at low body mass index levels among Singaporean Chinese, Malays and Indians.* Obes Rev, 2002. **3**(3): p. 209-15.

146. He, M., et al., *Body fat determination by dual energy X-ray absorptiometry and its relation to body mass index and waist circumference in Hong Kong Chinese.* Int J Obes Relat Metab Disord, 2001. **25**(5): p. 748-52.

147. Nguyen, T.T., et al., *Optimal cutoff values for overweight: using body mass index to predict incidence of hypertension in 18- to 65-year-old Chinese adults.* J Nutr, 2008. **138**(7): p. 1377-82.

148. Li, R., et al., *Relationships between indices of obesity and its cardiovascular comorbidities in a Chinese population.* Circ J, 2008. **72**(6): p. 973-8.

149. *Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects.* MMWR Recomm Rep, 1992. **41**(RR-14): p. 1-7.

150. Alexander, G.R., et al., *A United States national reference for fetal growth.* Obstet Gynecol, 1996. **87**(2): p. 163-8.

151. Schafer, J.L. and J.W. Graham, *Missing data: our view of the state of the art.* Psychol Methods, 2002. **7**(2): p. 147-77.

152. Saunders, J.A., et al., *Imputing missing data: A comparison of methods for social work researchers.* Soc Work Res, 2006. **30**(1): p. 19-31.

153. Pigott, T.D., *A review of methods for missing data.* 2001. **7**(4): p. 353.

154. White, I.R., P. Royston, and A.M. Wood, *Multiple imputation using chained equations: Issues and guidance for practice.* Stat Med, 2011. **30**(4): p. 377-99.

155. Rowland, M.L., *Self-reported weight and height.* Am J Clin Nutr, 1990. **52**(6): p. 1125-33.

156. Buller, A.J., et al., *Digit preference in Goldmann applanation tonometry: the hedgehog effect.* Am J Ophthalmol, 2005. **140**(3): p. 527-9.

157. Hessel, P.A., *Terminal digit preference in blood pressure measurements: effects on epidemiological associations.* Int J Epidemiol, 1986. **15**(1): p. 122-5.

158. Cook, T.D., *Advanced statistics: up with odds ratios! A case for odds ratios when outcomes are common.* Acad Emerg Med, 2002. **9**(12): p. 1430-4.

159. Schmidt, C.O., T. Kohlmann, and P. Cummings, *When to use the odds ratio or the relative risk?* Int J Public Health, 2008. **53**(3): p. 165-7.

160. Cummings, P., *The relative merits of risk ratios and odds ratios.* Arch Pediatr Adolesc Med, 2009. **163**(5): p. 438-45.

161. McNutt, L.A., et al., *Estimating the relative risk in cohort studies and clinical trials of common outcomes.* Am J Epidemiol, 2003. **157**(10): p. 940-3.

162. Greenland, S., *Model-based estimation of relative risks and other epidemiologic measures in studies of common outcomes and in case-control studies.* Am J Epidemiol, 2004. **160**(4): p. 301-5.

163. Zhang, J. and K.F. Yu, *What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes.* Jama, 1998. **280**(19): p. 1690-1.

164. Localio, A.R., D.J. Margolis, and J.A. Berlin, *Relative risks and confidence intervals were easily computed indirectly from multivariable logistic regression.* J Clin Epidemiol, 2007. **60**(9): p. 874-82.

165. Blizzard, L. and D.W. Hosmer, *Parameter estimation and goodness-of-fit in log binomial regression.* Biom J, 2006. **48**(1): p. 5-22.

166. Zou, G., *A modified poisson regression approach to prospective studies with binary data.* Am J Epidemiol, 2004. **159**(7): p. 702-6.

167. Gilboa, S.M., A. Correa, and C.J. Alverson, *Use of spline regression in an analysis of maternal prepregnancy body mass index and adverse birth outcomes: does it tell us more than we already know?* Ann Epidemiol, 2008. **18**(3): p. 196-205.

168. Greenland, S. and C. Poole, *Interpretation and analysis of differential exposure variability and zero-exposure categories for continuous exposures.* Epidemiology, 1995. **6**(3): p. 326-8.

169. Greenland, S., *Dose-response and trend analysis in epidemiology: alternatives to categorical analysis.* Epidemiology, 1995. **6**(4): p. 356-65.

170. Greenland, S., *Historical HIV incidence modelling in regional subgroups: use of flexible discrete models with penalized splines based on prior curves.* Stat Med, 1996. **15**(5): p. 513-25.

171. Gunderson, E.P. and B. Abrams, *Epidemiology of gestational weight gain and body weight changes after pregnancy.* Epidemiol Rev, 1999. **21**(2): p. 261-75.

172. Selvin, S. and B. Abrams, *Analysing the relationship between maternal weight gain and birthweight: exploration of four statistical issues.* Paediatric and perinatal epidemiology, 1996. **10**(2): p. 220-34.

173. Yang, X.G., et al., *[Study on weight and height of the Chinese people and the differences between 1992 and 2002].* Zhonghua Liu Xing Bing Xue Za Zhi, 2005. **26**(7): p. 489-93.

174. McDowell, M.A., et al., *Anthropometric reference data for children and adults: U.S. population, 1999-2002.* Adv Data, 2005(361): p. 1-5.

175. Winkvist, A., et al., *Weight-gain patterns from prepregnancy until delivery among women in Central Java, Indonesia.* Am J Clin Nutr, 2002. **75**(6): p. 1072-7.

176. Brown, J.E., S.A. Kaye, and A.R. Folsom, *Parity-related weight change in women.* Int J Obes Relat Metab Disord, 1992. **16**(9): p. 627-31.

177. Winkvist, A., K.M. Rasmussen, and L. Lissner, *Associations between reproduction and maternal body weight: examining the component parts of a full reproductive cycle.* Eur J Clin Nutr, 2003. **57**(1): p. 114-27.

178. Greenland, S., *Avoiding power loss associated with categorization and ordinal scores in dose-response and trend analysis.* Epidemiology, 1995. **6**(4): p. 450-4.

179. Lumbiganon, P., et al., *Method of delivery and pregnancy outcomes in Asia: the WHO global survey on maternal and perinatal health 2007-08.* Lancet, 2010. **375**(9713): p. 490-9.

180. Potter, J.E., et al., *Women's autonomy and scheduled cesarean sections in Brazil: a cautionary tale.* Birth, 2008. **35**(1): p. 33-40.

181. Betran, A.P., et al., *Rates of caesarean section: analysis of global, regional and national estimates.* Paediatr Perinat Epidemiol, 2007. **21**(2): p. 98-113.

182. U.S. Agency for Healthcare Research and Quality. *HCUPnet, Healthcare Cost and Utilization Project. Rockville, MD.* [cited 2011 January 1]; Available from: http://hcupnet.ahrq.gov/.

183. Belizan, J.M., F. Althabe, and M.L. Cafferata, *Health consequences of the increasing caesarean section rates.* Epidemiology, 2007. **18**(4): p. 485-6.

184. Pang, M.W., et al., *A longitudinal observational study of preference for elective caesarean section among nulliparous Hong Kong Chinese women.* Bjog, 2007. **114**(5): p. 623-9.

185. Pang, S.M., et al., *Determinants of preference for elective caesarean section in Hong Kong Chinese pregnant women.* Hong Kong Med J, 2007. **13**(2): p. 100-5.

186. *Obesity: preventing and managing the global epidemic. Report of a WHO consultation.* World Health Organ Tech Rep Ser, 2000. **894**: p. i-xii, 1-253.

187. Cogswell, M.E., et al., *Gestational weight gain among average-weight and overweight women--what is excessive?* Am J Obstet Gynecol, 1995. **172**(2 Pt 1): p. 705-12.

188. Edwards, L.E., et al., *Pregnancy in the underweight woman. Course, outcome, and growth patterns of the infant.* Am J Obstet Gynecol, 1979. **135**(3): p. 297-302.

189. Rothman, K.J., S. Greenland, and T.L. Lash, *Modern epidemiology*. 3rd ed. 2008, Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. x, 758 p.

190. Rosenberg, P.S., et al., *Quantifying epidemiologic risk factors using non-parametric regression: model selection remains the greatest challenge.* Stat Med, 2003. **22**(21): p. 3369-81.

191. Dietz, P.M., et al., *Combined effects of prepregnancy body mass index and weight gain during pregnancy on the risk of preterm delivery.* Epidemiology, 2006. **17**(2): p. 170-7.

192. Simhan, H.N. and L.M. Bodnar, *Prepregnancy body mass index, vaginal inflammation, and the racial disparity in preterm birth.* Am J Epidemiol, 2006. **163**(5): p. 459-66.

193. Bodnar, L.M., et al., *The risk of preeclampsia rises with increasing prepregnancy body mass index.* Ann Epidemiol, 2005. **15**(7): p. 475-82.

194. Monda, K.L., et al., *China's transition: the effect of rapid urbanization on adult occupational physical activity.* Soc Sci Med, 2007. **64**(4): p. 858-70.

195. Silventoinen, K., *Determinants of variation in adult body height.* J Biosoc Sci, 2003. **35**(2): p. 263-85.

196. Merchant, K.M., J. Villar, and E. Kestler, *Maternal height and newborn size relative to risk of intrapartum caesarean delivery and perinatal distress.* Bjog, 2001. **108**(7): p. 689-96.

197. Merchant, S.S., et al., *Effect of prepregnancy body mass index and gestational weight gain on birth weight.* J Pak Med Assoc, 1999. **49**(1): p. 23-5.

198. Martorell, R., et al., *Weight gain in the first two years of life is an important predictor of schooling outcomes in pooled analyses from five birth cohorts from low- and middle-income countries.* J Nutr, 2010. **140**(2): p. 348-54.

199. Flegal, K.M., P.M. Keyl, and F.J. Nieto, *Differential misclassification arising from nondifferential errors in exposure measurement.* Am J Epidemiol, 1991. **134**(10): p. 1233-44.

200. Brown, J.E., et al., *Influence of pregnancy weight gain on the size of infants born to underweight women.* Obstet Gynecol, 1981. **57**(1): p. 13-7.

201. Reynolds, K., et al., *Prevalence and risk factors of overweight and obesity in China.* Obesity (Silver Spring), 2007. **15**(1): p. 10-8.

202. Wildman, R.P., et al., *Trends in overweight and obesity in Chinese adults: between 1991 and 1999-2000.* Obesity (Silver Spring), 2008. **16**(6): p. 1448-53.

203. Popkin, B.M., et al., *Measuring the full economic costs of diet, physical activity and obesity-related chronic diseases.* Obes Rev, 2006. **7**(3): p. 271-93.

204. Zhai, F., et al., *Prospective study on nutrition transition in China.* Nutr Rev, 2009. **67 Suppl 1**: p. S56-61.

205. Popkin, B.M. and S. Du, *Dynamics of the nutrition transition toward the animal foods sector in China and its implications: a worried perspective.* J Nutr, 2003. **133**(11 Suppl 2): p. 3898S-3906S.

206. Monda, K.L., et al., *Longitudinal relationships between occupational and domestic physical activity patterns and body weight in China.* Eur J Clin Nutr, 2008. **62**(11): p. 1318-25.

207. Guldan, G.S., *Asian children's obesogenic diets-time to change this part of the energy balance equation?* Res Sports Med, 2010. **18**(1): p. 5-15.

208. Tang, S., X. Li, and Z. Wu, *Rising cesarean delivery rate in primiparous women in urban China: evidence from three nationwide household health surveys.* Am J Obstet Gynecol, 2006. **195**(6): p. 1527-32.

209. Wen, S.W., et al., *Terminal digit preference, random error, and bias in routine clinical measurement of blood pressure.* J Clin Epidemiol, 1993. **46**(10): p. 1187-93.

210. Ren, A., et al., *Low first-trimester hemoglobin and low birth weight, preterm birth and small for gestational age newborns.* Int J Gynaecol Obstet, 2007. **98**(2): p. 124-8.

211. Levy, A., et al., *Maternal anemia during pregnancy is an independent risk factor for low birthweight and preterm delivery.* Eur J Obstet Gynecol Reprod Biol, 2005. **122**(2): p. 182-6.

212. Carpenter, M.W., *Gestational diabetes, pregnancy hypertension, and late vascular disease.* Diabetes Care, 2007. **30 Suppl 2**: p. S246-50.

213. Nordin, N.M., et al., *Comparison of maternal-fetal outcomes in gestational diabetes and lesser degrees of glucose intolerance.* J Obstet Gynaecol Res, 2006. **32**(1): p. 107-14.

214. Crowther, C.A., et al., *Effect of treatment of gestational diabetes mellitus on pregnancy outcomes.* N Engl J Med, 2005. **352**(24): p. 2477-86.

215. Agarwal, M.M., et al., *Gestational diabetes screening of a multiethnic, high-risk population using glycated proteins.* Diabetes Res Clin Pract, 2001. **51**(1): p. 67-73.

216. Marcinkevage, J.A. and K.M. Narayan, *Gestational diabetes mellitus: Taking it to heart.* Prim Care Diabetes, 2010.

217. Ben-Haroush, A., Y. Yogev, and M. Hod, *Epidemiology of gestational diabetes mellitus and its association with Type 2 diabetes.* Diabet Med, 2004. **21**(2): p. 103-13.

218. Metzger, B.E., *Long-term outcomes in mothers diagnosed with gestational diabetes mellitus and their offspring.* Clin Obstet Gynecol, 2007. **50**(4): p. 972-9.

219. Saisto, T. and E. Halmesmaki, *Fear of childbirth: a neglected dilemma.* Acta Obstet Gynecol Scand, 2003. **82**(3): p. 201-8.

220. Simkin, P., *The experience of maternity in a woman's life.* J Obstet Gynecol Neonatal Nurs, 1996. **25**(3): p. 247-52.

221. Murthy, K., et al., *Association between rising professional liability insurance premiums and primary cesarean delivery rates.* Obstet Gynecol, 2007. **110**(6): p. 1264-9.

222. Nohr, E.A., et al., *Pregnancy outcomes related to gestational weight gain in women defined by their body mass index, parity, height, and smoking status.* Am J Clin Nutr, 2009. **90**(5): p. 1288-94.

# Appendix A: Data Cleaning & Variable Definition

There were no protocols in place when the data were collected to do range checks or identify data entry errors for the anthropometric data. Additionally, this data has not been cleaned since it was collected. As the main exposure variables for this analysis are gestational weight gain (GWG), body mass index (BMI), and maternal height (HT), data quality of the anthropometric data is important. GWG and BMI were derived from weight and height which were measured during the course of the study. Measurements were collected pre-pregnancy, before 13 completed weeks of gestation (first trimester), and up to 2 weeks prior to delivery (delivery). Weight was potentially measured three times, once pre-pregnancy, once in the first trimester and lastly at delivery. To be included in the study, a woman had to have three measurements: a height measurement, a pre-pregnancy or first trimester weight and a delivery weight. The timing of these measurements in absolute terms (i.e., in reference to the study period) and in relative terms (i.e., in reference to last menstrual period) also required data cleaning.

*Guiding principles for data cleaning*

A measurement was accepted as correct, unless data cleaning processes demonstrated otherwise. Identifying potential errors is a multi-step and iterative process. First, all variables were checked for normal distribution. Unless otherwise noted, all anthropometry measures were normal. Second, outliers were identified with an internal standard. Mean and standard deviation (SD) were calculated for height and weight at each measurement occasion. Values 3 SD from the mean were excluded as they represented less than 1% of the available data, but still too many to evaluate individually. Values within 3 SD of the mean were considered ‘acceptable’ in this step. Third, data entry errors were identified where replicate or sequential measures were present. Rules for identifying errors were tailored to the measurement (detailed below). Fourth, contextual definitions were used to remove any implausible values for composite variables, such as GWG

and BMI. For example, a woman might have a height and weight value labeled as 'acceptable' by outlier identification, but the calculated BMI might be extremely low. Women with a pre-pregnancy BMI below 13 kg/$m^2$ were excluded from the analysis.

**Dates**

This was a longitudinal study with variable entry and exit dates. This necessitated careful consideration of dates for both entry into the study and time between events, for example time between LMP and delivery for calculation of gestational age. First, missing variables were identified and then valid date ranges were identified. SAS records dates as integers that indicate the days since January 1, 1960. Dates before this reference date are negative, and dates after, are positive. Table 1 shows the missing values and frequency for each of the important date variables in the study. Once values were labeled 'missing', the minimum and maximum values were examined to identify implausible values based on the last acceptable delivery date for inclusion into the study (December 31, 1996). Table 2 below shows the values and frequency of implausible dates.

**Table 1 Missing values for Important Dates**

| Variable | Label | SAS value | SAS format | N |
|---|---|---|---|---|
| PMEXAM | Date of Premarital Exam | -21549 | 01 Jan 1901 | 97,987 |
| REGDATE | Date of Registration | -21549 | 01 Jan 1901 | 7 |
| NEWLMPD | Date of Last Menstrual Period (LMP) | -137775 | 14 OCT 1582 | 1,861 |
| FPEXAM | Date of First Trimester Exam | -21549 | 01 Jan 1901 | 3,344 |
| FPEXAM | Date of First Trimester Exam | -21914 | 01 JAN 1900 | 3 |
| LPNEXAM | Date of Last Prenatal Exam | -137775 | 14 OCT 1582 | 17,286 |
| DDATE | Date of Delivery | -21549 | 01 Jan 1901 | 40 |

| Table 2 Minimum and Maximum Values of Important dates for Identification of Implausible Values | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Variable** | **SAS Min** | **SAS format** | **Decision** | **SAS Max** | **SAS format** | **Decision** | **N** |
| PMEXAM | 11689 | 02 Jan 1992 | OK | 13595 | 22 Mar 1997 | Implausible | 3 |
| NEWLMPD | 11721 | 13 Apr 1984 | Implausible | 13342 | 24 Apr 1997 | Implausible | 4 |
| FPEXAM | 12054 | 01 Jan 1993 | OK | 13885 | 06 Jan 1998 | Implausible | 37 |
| LPNEXAM | 12304 | 08 Sept 1993 | OK | 13877 | 29 Dec 1997 | Implausible | 41 |
| DDATE | 12327 | 01 Oct 1993 | OK | 13514 | 31 Dec 1996 | OK | 0 |

| Table 3 Implausible values for Time Intervals (in weeks) | | | | | |
|---|---|---|---|---|---|
| **Variable** | **Description** | **N possible** | **Limits** | **N excluded** | **%** |
| Time1 | Weeks between premarital exam and LMP | 142,959 | Time1>-52; Time1<14 | 19,481 | 13.6 |
| Time2 | Weeks between first prenatal exam and LMP | 239,016 | Time2<14 | 58,322 | 24.4 |
| Time3 | Weeks between last prenatal exam and delivery | 230,504 | Time 3≤2 | 25,960 | 11.2 |

**Time**

The concept of time, indicating time between significant events is also important. Missing and implausible dates had to be removed from the data and limits were applied to create sensible eligibility criteria. Pre-pregnancy measurements were limited to those taken less than one year prior to LMP. Prenatal measurements were limited to those before 13 completed weeks of gestation (Table 3).

**Height**

Height was potentially measured twice, once pre-pregnancy, and again in the first trimester. Height measurements were considered replicates, as changes in height are negligible during the measurement period. Height accrual is minimal once a female has reached puberty and the analytical population will include women aged 16 and older, therefore eliminating the possibility of positive height changes. Negative height change associated with pregnancy, such as lordosis (exaggerated forward curvature of the lumbar and cervical spine) is minimal overall, and negligible in early pregnancy (before 13 completed weeks gestation). Negative height change associated with aging occurs beyond the third decade of life and have been shown to be around 3 inches over a lifetime (7.62 cm) (Baltimore Longitudinal Study of Aging), and therefore not applicable to women of child-bearing age.

The distribution of both measurements of height was normal. Outliers were defined as values below mean minus 3 SD (1.43 m or 56.3 in) and above mean plus 3 SD (1.73 m or 68.1 in). All outliers were labeled as ‘missing’ for the purposes of the analysis. Height measurements for less than 0.5% (n=969) of all women were considered outliers.

Table 4 below summarizes the actions taken to identify valid values of height. Nearly half (49%) of all women had two measurements of HT taken. Of these, 71% had identical values for both measurements. This value was therefore labeled 'acceptable' and used in all analyses as a valid height measurement. Where the difference between the two values was less than 2 cm, the values were averaged, labeled 'acceptable' and used in all analyses as valid height (18%). For the remaining 10%, the difference between the two values was larger than 2 cm. These values were therefore considered unreliable and labeled as 'missing'. 35% of all women had only one height measurement taken: premarital (26%) and 1st trimester (74%). As previously stated, when only one measurement was present, this value was accepted as correct at this step. 16% of women had no value for height recorded.

Once all data cleaning processes were complete for maternal height, 78% of women (N=193,723) had a valid measurement of height.

**Table 4 Data Cleaning Methods for Maternal Height (MHT)**

| Condition | Action | N | Frequency (%) |
|---|---|---|---|
| No MHT measurement recorded | Label 'missing' | 40,511 | 16.35 |
| Premarital MHT measured only | Label 'acceptable' | 22,627 | 10.91 |
| 1st trimester MHT measured only | Label 'acceptable' | 64,056 | 30.90 |
| Both premarital and 1st trimester MHT present | | 120,638 | 48.68 |
| Premarital HT = 1st trimester MHT | Label 'acceptable' | 85,862 | 41.42 |
| Difference between premarital and 1st trimester MHT is less than or equal to 2 cm | Average values, label as 'acceptable | 21,178 | 10.22 |
| Difference between premarital and 1st trimester MHT is more than 2 cm | Unreliable, label as 'missing' | 12,629 | 6.09 |
| Premarital MHT or 1st trimester HT are greater than 3 SD from respective means | Outlier, label as 'missing' | 969 | 0.47 |

**Weight**

Weight was potentially measured twice, once pre-pregnancy, around the time of registration (MWT_PM) and again during the first prenatal visit (MWT_FP). In contrast to height where multiple measures were considered replicates, weight is expected to change over time and with pregnancy. For this reason, different rules were devised to determine acceptable values of weight. Additionally, weight could not be considered independent of time. Pairs of weight and time had to be considered to identify acceptable values of weight: MWT_PM and TIME1 and MWT_FP and TIME2. Normality was assessed and outliers identified (mean ± 3SD) for both MWT_PM and MWT_FP. Both measurements of maternal weight followed a normal distribution.

**Table 5 Descriptive Statistics and Outlier Values for MWT_PM and MWT_FP**

| | N | MIN | MEAN | SD | MAX | MEAN - 3SD | MEAN + 3SD |
|---|---|---|---|---|---|---|---|
| **MWT_PM (m)** | 143,009 | 1.00 | 1.59 | 0.05 | 1.97 | 1.45 | 1.73 |
| **MWT_FP (m)** | 184,594 | 1.00 | 1.59 | 0.05 | 2.17 | 1.45 | 1.73 |

As previously mentioned, TIME values more than 52 weeks before, or more than 13 completed weeks after LMP were considered invalid, and by association, weight values at these times were also considered invalid. It was necessary to devise a way to simplify the dataset with respect to weight and time measurements by storing all the necessary information in a single data column, as opposed to 15 separate columns. Four indicator variables were created (denoting the presence or absence of the value), one for each of the following: MWT_PM, MWT_FP, TIME1 and TIME2. Instead of coding “0” absence and “1” presence, each indicator variable was assigned a unique constant that was a power of 2 (i.e., 1, 2, 4 and 8). By summing cumulatively over each woman’s line of data, it was possible to determine the combination of values present for each woman, as the sums of any combination of powers of 2 are unique. The table below demonstrates

this property of the sums of powers of 2 and lists the data cleaning methods taken to identify acceptable values of maternal weight.

Let

F_MWT_PM= 1
F_TIME1= 2;
F_MWT_FP= 4;
F_TIME2= 8;
RESULT= 0;

**Table 6 Data Cleaning Methods for Maternal Height (MWT)**

| Power of 2 Sum | Condition | Action | N | (%) |
|---|---|---|---|---|
| 0 | No valid measure of TIME1, TIME2, MWT_PM or MWT_FP | Label 'missing' | 35,679 | 14.4 |
| 1 | MWT_PM recorded | Label 'missing' | 7,399 | 2.99 |
| 2 | Valid TIME1 only | Label 'missing' | 185 | 0.07 |
| 3 | MWT_PM recorded and TIME1 is valid: **use MWT_PM** | Label 'acceptable' | 8,066 | 3.25 |
| 4 | MWT_FP recorded | Label 'missing' | 8,487 | 3.42 |
| 5 | MWT_PM and MWT_FP recorded but TIME1 and TIME2 are missing or outside valid range | Label 'missing' | 2,425 | 0.98 |
| 6 | MWT_FP recorded and TIME1 is valid, but TIME2 is missing or outside valid range | Label 'missing' | 53 | 0.02 |
| 7 | MWT_PM and MWT_FP recorded and TIME1 is valid: **use MWT_PM** | Label 'acceptable' | 4,405 | 1.78 |
| 8 | Valid TIME2 only | Label 'missing' | 5,524 | 2.23 |
| 9 | MWT_PM recorded and TIME2 is valid, but TIME1 is missing or outside valid range | Label 'missing' | 597 | 0.24 |
| 10 | Valid TIME1 and TIME2 only | Label 'missing' | 229 | 0.09 |
| 11 | MWT_PM recorded and TIME1 and TIME2 are valid: **use MWT_PM** | Label 'acceptable' | 6,959 | 2.81 |
| 12 | MWT_FP recorded and TIME2 is valid: **use MWT_FP** | Label 'acceptable' | 54,376 | 21.94 |
| 13 | MWT_FP and MWT_PM recorded and TIME2 is valid : **use MWT_FP** | Label 'acceptable' | 8,985 | 3.63 |
| 14 | MWT_FP recorded TIME1 and TIME2 are valid: **use MWT_FP** | Label 'acceptable' | 648 | 0.26 |
| 15 | MWT_PM and MWT_FP recorded, TIME1C and TIME2C are valid | **See below** | 101,759 | 41.06 |
| | OUTLIERS FOR MWT_PM OR MWT_FP | Label 'missing' | 2,055 | 0.83 |

Decoding the powers of 2 was straightforward except when all 4 variables were present. For all other scenarios, only one weight and time pair were valid. 101,759 (41%) of women had two

values of maternal weight. For nearly all of these women, one measurement was before LMP and the second measurement was after LMP, but before 13 completed weeks of gestation. Where there was no difference in the two measurements of maternal weight, MWT_PM was labeled as 'acceptable' and TIME1 was used as the time of measurement. For the remaining cases with two measurements, 42% lost weight and 32% gained weight between MWT_PM and MWT_FP.

**Table 7 Data Cleaning Methods for Maternal Weight (MWT) When All 4 Variables Are Present**

| Power of 2 Sum | Condition | Action | N | (%) |
|---|---|---|---|---|
| 15 | No weight change between MWT_PM and MWT_FP: **use MWT_PM** | Label 'acceptable' | 25,924 | 25.48 |
| 15 | Weight loss from MWT_PM to MWT_FP | See below | 42,706 | 41.97 |
| 15 | Weight gain from MWT_PM to MWT_FP | See below | 33,129 | 32.56 |

Ideally, weight measurement would be recorded at LMP. But as this is not usually possible, the convention is generally to accept any measurement that occurs at some point prior to LMP and before 13 completed weeks of gestation. This convention is very lenient and can maximize sample size; however, it can introduce error depending on when a woman has her weight measured relative to LMP.

*Before LMP:* Among women of child-bearing age, weight change has been shown to vary by affluency. In more affluent societies, women gain 0.35 kg/year when they are not pregnant (Brown et al 1982). Among women in less affluent societies, studies of weight gain are rarer. In one study, women in Indonesia gained 0.7 kg/year (Winkvist 2000). This rate is greater than women in affluent societies, and the authors conjectured that the rate may represent a society experiencing the nutrition transition. The literature demonstrates that including women with a weight measurement before LMP could introduce systematic error, as weight appears to gradually

increase with time. This trend would bias results towards the null because pre-pregnancy weight, BMI and GWG would be underestimated.

*After LMP:* Pregnancy weight gain after LMP until 13 completed weeks of gestation is typically regarded as minimal (source). In practice however, and on the population level, weight change can appear random. Some women gain weight during the first trimester, while others gain little to no weight until the second and third trimester. There are also groups of women who experience weight loss in early pregnancy due to nausea, or in rare cases, hyperemisis. Thus, including women with a weight measurement after LMP can introduce non-systematic bias, commonly referred to as noise. This would bias results towards the null and could also reduce precision.

With these biases in mind, two approaches were developed to cope with the situation where all four variables were present. The first approach, hereafter referred to as "LMP", chooses the value closest to LMP as the valid value, regardless of whether it falls before or after LMP. The second approach, hereafter referred to as 'pre-pregnancy', chooses to the value that was recorded pre-pregnancy. Initially, the LMP approach was considered to be the best estimate of weight at conception. When this rule was applied to the data, the majority of values selected as valid were those taken after LMP. Due to the variable nature of weight change after LMP in the first trimester, and the random error introduced by this method, the approach was reconsidered. The pre-pregnancy approach was then used and sub analyses were undertaken to assess the merits of this approach over the LMP approach. By design, pre-pregnancy values were selected over values after LMP. 50% of women had a weight measurement less than 13 weeks before their LMP. Similar to what was shown in the literature, when the average weight by week was plotted, a slight increasing trend was observed as week of measurement approached LMP from before LMP. After LMP, the increasing trend continued, at a slightly steeper slope (See plot 1 – page 7 below). A similar plot for the LMP approach was constructed. Unlike what was expected, a slight

*decreasing* trend in maternal weight was observed prior to LMP. Additionally, dispersion was highly variable, further calling into question the validity of this approach.

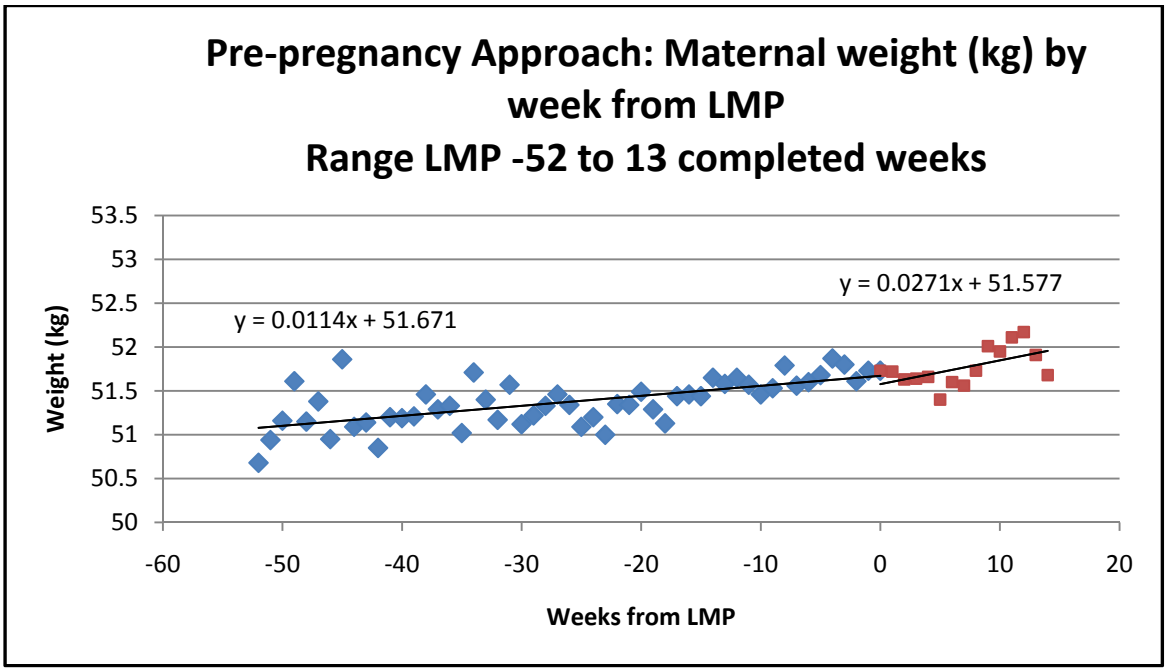
The decision was made to use the pre-pregnancy approach. Additionally, as the error associated with this approach was deemed systematic, adjustments could be made to account for this. By using the estimate for the slope of the line, it was possible to multiply the slope value by the number of weeks from LMP the measurement was taken, and add this to the raw weight to calculate the adjusted weight. A further sub-analysis was undertaken to understand that level of misclassification that might occur in choosing the raw vs. the adjusted maternal weight.

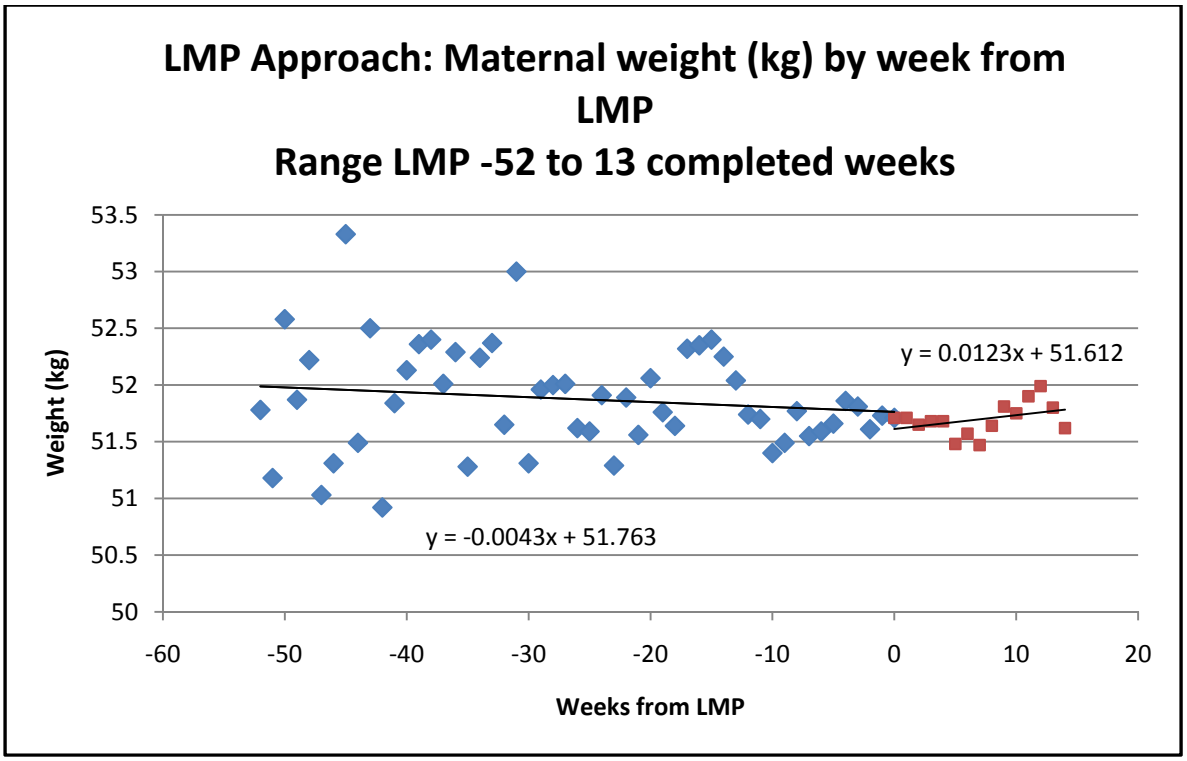
**BMI**

BMI was calculated using the standard definition, $kg/m^2$. Extremes of weight and height had already been excluded before BMI was calculated. BMI values were calculated for 172,129 (69.5%) women, it was normally distributed. The mean BMI was 20.5 $kg/m^2$, ranging from 12.5 to 30.1$kg/m^2$. Mean ± 3SD were considered as potential cut-off values for identifying valid values of BMI. The lower BMI cut-off point was 14.4 $kg/m^2$ and the upper value was 26.6 $kg/m^2$. Chronic energy deficiency (CED) is typically defined as any BMI below 15 $kg/m^2$. A BMI between 13-15 $kg/m^2$ corresponds to a range of 48-55% of ideal body weight and is considered the lowest amount of body fat compatible with life. A conservative view of cleaning BMI was taken and only women with a BMI<13 were labeled ‘invalid’ (N=3). All other values were considered ‘valid’.

**GWG**

GWG was calculated by subtracting pre-pregnancy weight from the last prenatal weight. Only valid values of pre-pregnancy and last prenatal weight were considered in the calculation. Last prenatal weight was valid up to 2 weeks before delivery. GWG was normally distributed, with mean 11.4 kg, ranging between -20kg loss to a 46 kg gain before implausible values were re-assigned to missing (n=158,657). Implausible values were defined as those that represented a loss of more than 5% of pre-pregnancy weight or a weight gain of more than 50% of pre-pregnancy weight. 615 (0.4%) women lost more than 5% of their pre-pregnancy weight and 1301 (0.8%) women gained more than 50% of their pre-pregnancy weight between LMP and delivery. Once invalid values were re-assigned to missing, the mean GWG was 11.3 kg, ranging from -20 kg to 28kg.




LMP Approach: Maternal weight (kg) by week from LMP
Range LMP -52 to 13 completed weeks
Weight (kg)
53.5
53
52.5
52
51.5
51
50.5
50
-60
-50
-40
-30
-20
-10
0
10
20
Weeks from LMP
y = 0.0123x + 51.612
y = -0.0043x + 51.763