Updating Local Birth Weight Percentiles and Statistical Methods Motivated by Challenges in Analysis of Microbiome Studies

by

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ABSTRACT

This dissertation contains two main parts. In part one, I updated the current reference for sex-specific birth weight percentiles by gestational age, overall, and for specific ethnic groups, based on data from all singleton live-birth deliveries from 2005 to 2014 in Alberta, Canada. Crude and corrected estimates for birth weight percentiles, including cut-off values for large for gestational age (LGA) and small for gestational age (SGA), were calculated by sex and sex-ethnic group and gestational age for singleton live births. Birth weights were modelled by gestational age using generalized additive modelling with non-constant variance. The findings show that LGA and SGA cut-offs were lower for females than for males for all gestational ages. The SGA and LGA percentiles were greater for both male and female very preterm infants in Alberta compared to previous national references. Ethnicity-specific LGA and SGA cut-offs for term Chinese and preterm and at-term South Asian infants were consistently lower than those for the general population in Alberta and the previous national reference. South Asian infants had lower birth weights at almost all gestational ages than the other groups. These updated birth weight percentiles presented in this study highlight the differences in SGA and LGA cut-offs among infants from South Asian, Chinese, and the general population, which may be essential for clinical perinatal care.

Part two focused on statistical methods motivated by challenges such as zero inflation, over-dispersion, dimentionality issue, and within-sample correlation in analyzing the infants' gut microbiome data. I first evaluated the performance of three distribution-based models and discussed their ability to accommodate the challenges of gut microbiome data in a comprehensive simulation study with 27 scenarios. In addition, I used each model to analyze a real data set. Sixty-seven percent of our simulation scenarios indicated that the Zero Inflated

Negative Binomial model had a lower mean squared error than the other methods, and the zero-inflated Gaussian mixture model had better statistical power. The real data application on the SKOT (the Danish abbreviation for "Dietary habits and wellbeing of young children.") Cohort I and II dataset showed the effect of maternal obesity on the taxon abundance of infants at 9- and 18-months assessments. Our study showed that univariate zero-inflated negative binomial model and negative binomial-based ManyGLM model could adequately accommodate the challenges in the gut microbiome data without requiring data transformation or normalization, depending on the goal of the study.

Following our comprehensive review study, we proposed a Bayesian Marginal Zero-inflated Negative Binomial (BAMZINB) model, addressing complexities associated with the multivariate structure of the data, inter-variability, heteroscedastic variations, fluctuating library size, high-dimensionality issues, and the zero-inflation in microbiome data. Furthermore, we compared the performance of BAMZINB with- and without- random intercept with two alternative models, the Genewise Negative Binomial Generalized Linear Models (glmFit) implemented in edgeR and the Bayesian hierarchical Generalized Linear Model (BhGLM) implemented in BhGLM package in R software. The results of 32 simulation scenarios showed that BAMZINB models performed as well as BhGLM and glmFit, in estimating average abundance change between groups of interest. The average deviance of the models was different among various simulation scenarios. The application of the BAMZINB model on the real dataset showed the average abundance change in a specific list of bacteria over time for infants born to healthy mothers and those born to obese mothers.

The second part of my dissertation results will help other research groups working on human gut microbiome data better understand the underlying challenges in analyzing the infants' gut

microbiome data. I believe that rather than asking for the best method available for studying the effect of a covariate on taxon abundance, we should make an effort to understand the underlying structure of microbiome data, and adapt an existing method to address statistical assumptions called by the data.

PREFACE

This thesis is an original work by Morteza Hajihosseini under the supervision of Dr. Irina Dinu. In all chapters, I was responsible for conceptualizing the projects, finding public datasets, generating simulated data, conducting data analysis, designing the figures and tables, reviewing the literature, and leading authorship of the manuscripts. Dr. Irina Dinu provided financial support for the projects, conceptualized the project, and helped formulate the manuscripts. Dr. Padma Kaul, Dr. Anamaria Savu, and Dr. Linn Moore provided critical review comments and contributed with manuscript writing for the first project. Dr. Anita Kozyrskyj and Dr. Alireza Saidi-Mehrabad provided microbiological consulting advice for the second and third projects. Dr. Payam Amini assisted with the formulation of statistical theories and consulted statistical concepts for all microbiome projects. Dr. Alireza Saidi-Mehrabad aided with DNA sequence reads pre-process steps for the second and third projects. Data used in chapters 4 and 5 are available from the National Center for Biotechnology Information Sequences Read Archive and European Nucleotide Archive.

Chapter 2 of this dissertation has been published as "**Hajihosseini M**, Savu A, Moore L, Dinu I, Kaul P. An updated reference for age-sex-specific birth weight percentiles stratified for ethnicity based on data from all live birth infants between 2005 and 2014 in Alberta, Canada. Canadian Journal of Public Health. 2022;113(2):272-81. https://doi.org/10.17269/s41997-021-00520-9". I was responsible for conducting the literature review, applying statistical methods to Alberta Vital Statistics-Births Dataset, designing the tables and graphs, and drafting the manuscript. Dr. Padma Kaul was the corresponding author responsible for the concept formulation of the project, study design, and supervision of the research. Dr. Dinu supervised the statistical analysis and representation of the results. Dr. Anamaria Savu and Dr. Linn Moore provided critical review comments and aided with manuscript writing. Canadian Institutes of Health Research funded this project.

Chapter 4 of this dissertation has been submitted as "**Hajihosseini M**, Amini P, Saidi-Mehrabad A, Kozyrskyj A, Dinu I. A Comprehensive Performance Comparison Study of Various Statistical Models that Accommodate Challenges of the Gut Microbiome Data". I was responsible for developing the study, programming, data analysis, simulation study, presenting the results, and drafting the manuscript. Dr. Dinu, Dr. Amini, Dr. Saidi-Mehrabad, and Dr. Kozyrskyj provided

critical review comments and assisted with the microbiological and statistical concepts. All the authors discussed the results and contributed to the final manuscript. Mathematics of Information Technology and Complex Systems (MITACS) funded this project.

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All figures and tables in this dissertation are designed and generated by **Morteza Hajihosseini**. Some components of this dissertation have been used in the following posters and presentations:

Hajihosseini M, Savu A, Moore L, Dinu I, Kaul P. (2020). An Application of Generalized Additive Models to Update Age-Sex-Specific Birth weight Percentiles, Alberta, Canada. The Canadian Statistics Student Conference (Oral presentation).

Hajihosseini M, Khodayari Moez E, Kozyrskyj A, Dinu I. (2018). Comparative evaluation of statistical methods in infant gut microbiome studies. Joint Statistical Meetings (Oral presentation).

I dedicate this dissertation to my parents, siblings, and friends. I am forever extremely grateful for their support through all these years I spent in academic education.

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The School of Public Health has been an excellent environment for graduate students to grow beyond their limitations. I thank each and everyone in the graduate office, staff, faculty members, and my course instructors: Dr. Yan Yuan, Dr. Shelby Yamamoto, Dr. Cameron Wild, Dr. Sentil Senthilselvan, Dr. Candace Nykiforuk, Dr. Jeff Johnson, and Dr. Katerina Maximova. Thank you, University of Alberta, for shaping my career and being my second home for the last five years.

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I end this acknowledgment section by thanking parents and siblings. They have supported me in every aspect of life, including my educational journey, with their unconditional love.

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1.1. Introduction

From 1902 to the 1950s, many studies introduced various criteria to define prematurity (Ballantyne, 1902; Holt & Babbitt, 1915; "The Nursling: The Feeding and Hygiene of Premature and Fullterm Infants," 1906; Opitz, 1913; Pearce, 1919; Schwarz & Kohn, 1921; Talbot et al., 1923; Ylppö, 1919). The criteria were included having a weight that varies from 3 to 4 1/2 lb (Ballantyne, 1902), born before the term, measuring less than 46 cm, or weighed less than 2275 g (Holt & Babbitt, 1915). Prematurity was considered an important contributor to neonatal mortality (Opitz, 1913; Pearce, 1919). In 1919, a Finnish pediatrician proposed the 2500 g cut-off for the first time (Ylppö, 1919). While he provided no scientific justification for this cut-off, it became universally accepted. In 1920, Schwarz and Kohn compared normal infants with low-birth-weight infants using 2500 g or under as a cut-off and found that low-birth-weight infants had ten times the mortality of normal infants in the first month (Schwarz & Kohn, 1921). However, until 1935, there was no universal standard to make morbidity and mortality outcomes of low-birth-weight infants comparable (Capper, 1928; Hess & Chamberlain, 1927; Talbot et al., 1923). In 1935, Dr. Ethel Dunham proposed a standard criterion of prematurity as 2500 g or less regardless of gestational age to facilitate comparison between studies during the American academy of pediatrics conference. From 1935 to 1950, studies used the exact definition with some exceptions (Peckham, 1938; Steiner & Pomerance, 1950). In 1955, Schlesinger and Allaway's study showed that birth weight is a poor indicator of prematurity (Schlesinger & Allaway, 1955).

As the quality of measuring gestational age improved, many studies started to report the distribution of birth weight and gestational age instead of using 2500 g or less as the definition of prematurity (Battaglia et al., 1966; Gruenwald, 1964; Lubchenco, 1976; Silverman et al., 1967; Van den Berg & Yerushalmy, 1966; Wilcox, 2001). At the same time, the literature showed that other population characteristics such as ethnicity, altitude, geographic settings, sex, parity, age,

nutrition, smoking, and SES could modify the relationship between birth weight and adverse outcomes (Brimblecombe & Ashford, 1968; Chase, 1969; Erhardt et al., 1964; Gruenwald, 1964; Kramer, 1987; Lubchenco et al., 1963; Pethybridge et al., 1974; Rooth, 1980; Sansing & Chinnici, 1976; Saugstad, 1981; Staff et al., 1985). Therefore, in the late 1960s, researchers began to use modeling techniques to describe birth weight. The goal was to improve the discrimination of high-risk infants and have a better predictor of neonatal mortality (Brimblecombe & Ashford, 1968).

In 1980, Rooth showed that the universal 2500 g or less cut-off is not appropriate due to differences in mean birth weights between populations (Rooth, 1980). He proposed to use weights less than two standard deviations below the local population as the new cut-off (Rooth, 1980). In 1983, Wilcox and Russell argued that when the cut-off was based on population-specific distribution, they had better discrimination of low-birth-weight infants with a higher risk of mortality (Wilcox & Russell, 1983a, 1983b, 1986). This finding showed the necessity of population-specific birth weight curves. Although increasing birth weight may be an excellent surrogate indicator to reduce infant mortality, it is not in the causal pathway. More recent studies focused on the epidemiology of preterm and small-for-gestational-age (SGA) as casual factors for infants' morbidity and mortality (Katz et al., 2013; Lawn et al., 2010; Lee et al., 2013). Katz *et al.* showed that a higher proportion of preterm deaths occur during the early neonatal period, whereas SGA deaths tend to happen later in infancy (Katz et al., 2013). Starting from the 1990s, researchers began to develop population-based birth weight curves to help categorize high-risk infants (Hughes et al., 2017).

1.2. Definition of SGA and LGA

Population-based standards defined SGA and large-for-gestational-age (LGA) infants as below or above a certain percentile, e.g., 10^{th} and 90^{th}, or below and above two SD of the reference population. World Health Organization (WHO) and the American College of Obstetrics and Gynecology define SGA as those weighting below 10^{th} centile of birth weight by sex for a specific completed gestational age of a given reference population ("ACOG Practice bulletin no. 134: fetal growth restriction," 2013; de Onis & Habicht, 1996b).

The Canadian Perinatal Surveillance System defines SGA as all live birth for which birth weight is below the 10th percentile and LGA as all live birth for which birth weight is above the 90th percentile for sex-specific birth weight for gestational age (Dzakpasu et al., 2019). Several studies used the same percentiles to define SGA and LGA (Adedinsewo et al., 2013; Ahrens et al., 2014; Cantu et al., 2013; Chambers et al., 2013; Dodds et al., 2012; Fell et al., 2012; Huang et al., 2014; Kharbanda et al., 2014; Legge et al., 2014; Ludvigsson et al., 2013; McCowan et al., 2018; Nordin et al., 2014; Olsen et al., 2016; Omer et al., 2011; Pasternak et al., 2012; Richards et al., 2013; Schatz et al., 2011; Sridhar et al., 2013; Steinhoff & Omer, 2012; Steinhoff et al., 2012; Sukumaran et al., 2015; Trotta et al., 2014; van der Maas et al., 2016; Vayssière et al., 2015).

1.3. The importance of studying SGA and LGA infants

Emerging evidence showed the importance of studying the lifelong consequences of being born SGA and LGA. For instance, Ray *et al.* showed that preterm birth (<37 weeks) and SGA infants had higher mortality rates (Ray et al., 2017). Pregnancies affected by preterm birth and SGA are more prone to show placental defection (Ananth & Vintzileos, 2011; Salafia et al., 1995). In addition, Ray *et al.'s* study showed that between 23 to 28 weeks of gestation, the neonatal mortality rate was higher among infants with severe SGA than those without severe SGA (Ray et al., 2017). Moreover, between 29 to 32 weeks, the rates were non-significant. However, significant rates were reported from 33 to 41 weeks (Ray et al., 2017). Moore *et al.* found that Lower than expected birth weight for gestational age increases the risk of Autism Spectrum Disorder (ASD) (Moore et al., 2012). They showed that being SGA and extremely preterm is strongly associated with ASD among children without cognitive impairment (Joseph et al., 2017). Emerging evidence suggests that preterm birth and SGA contribute to an increased risk of ASD (Abel et al., 2013; Johnson et al., 2010; Kuzniewicz et al., 2014; Leavey et al., 2013; Losh et al., 2012; Schendel & Bhasin, 2008).

Infants born with SGA are at increased risk of infection, perinatal respiratory depression, jaundice, polycythemia, hypoglycemia, poor feeding, and hypothermia (Lee et al., 2017). In the Child Health Epidemiology Reference Group (CHERG) study, SGA was associated with an

increased neonatal and post-natal mortality risk (Katz et al., 2013). The risk was higher for preterm SGA infants (Katz et al., 2013). Lee *et al.* study estimated 606,500 neonatal deaths in low- and middle-income countries attributed to SGA in 2012 (Lee et al., 2017). They estimated that 23.3 million infants (19.3%) were born SGA in low- and middle-income countries, and 21.9% of neonatal death were attributed to SGA. Therefore, they concluded that reducing the prevalence of SGA from 19.3 to 10% in low- and middle-income countries could reduce the mortality rate by 9.2% (Lee et al., 2017).

Several studies showed that SGA at birth is associated with cardiovascular diseases (CVD) and type 2 diabetes in adulthood (Barker, 2004; Curhan et al., 1996; Mericq et al., 2005; Norris et al., 2012; Zhang et al., 2014). Infants born with LGA are also at a higher risk of CVD (Curhan et al., 1996). High birth weight is associated with obesity in childhood, related to a higher risk of CVD in adulthood (Gillman et al., 2003; Juonala et al., 2011; Kuhle et al., 2010; Singh et al., 2008). Kuhle *et al*. found that compared to appropriate-for-gestational-age (AGA) infants, SGA and LGA infants had lower and higher significant z-scores of waist circumference and body mass index, respectively (Kuhle et al., 2017). Meta-analysis studies indicated the association between high birth weight and hypertension, or high blood pressure (Mu et al., 2012; Zhang et al., 2013). Kuciene *et al.'s* study found that high birth weight and LGA were associated with high blood pressure among adolescents (Kuciene et al., 2018). A population-based case-control study in the US showed that birth weight of more than 4000 g or being LGA has significantly associated with primary hypertension in adolescents and young adults 15-24 yrs, but not children in 8-14 yrs (Pocobelli et al., 2016). Furthermore, the literature showed that LGA infants are more prone to complications such as hypertension, obesity, insulin resistance, metabolic disorders, and type 2 diabetes later in life (Boney et al., 2005; Chiavaroli et al., 2016; Dyer et al., 2007; Kuciene et al., 2018; Taal et al., 2013; Weissmann-Brenner et al., 2012).

Therefore, studying SGA and LGA infants could help clinicians decide which intervention should be taken to avoid perinatal complications for infants born with SGA and LGA. Also, these measures will allow clinicians, public health researchers, and policymakers to better understand the current status of infants' birth weight in the population.

1.4. The Gestational Age-Specific Birth Weight Charts

The first gestational age-specific birth weight charts were created in 1963 by Lubchenco *et al.* based on all live birth infants admitted to the Colorado General Hospital (Lubchenco et al., 1963) to help clinicians determine when premature infants regain the percentile zone of their birth and classify them as into SGA, LGA and AGA categories. The importance and application of birth weight percentile charts have been discussed widely in the literature. There is an ongoing debate about using national or international charts. The Intergrowth-21st project developed international growth charts based on the assumption that fetal growth is the same across different geographical areas as long as nutrition and health care are provided (Papageorghiou et al., 2014; Stirnemann et al., 2017; Villar et al., 2014). However, the physiological characteristics of populations are different; therefore, population-based national charts seem more appropriate (Alexander et al., 1999; Gardosi, 2014; Gardosi et al., 1995). Hocquette *et al.* study showed that in European countries, national charts discriminate SGA and LGA infants differently from international charts (Hocquette et al., 2021). They found discordance in the classification of SGA and LGA infants between national and international charts (Hocquette et al., 2021). The findings of this study supported the idea of considering population anthropometric characteristics in growth monitoring.

Moreover, a Canadian study by Liu *et al.* showed that after using the local charts, the detection rates for composite mortality and morbidity among SGA infants were higher than using international intergrowth-21st (Liu et al., 2017). They found that the risk of perinatal death for those classified as SGA was based on national charts, but AGA by the international charts was over two-fold more when compared to those classified as AGA by both (Liu et al., 2017). In addition, infants classified as LGA by international charts had a lower risk of mortality than those AGA by both.

Many developed and some developing countries built their own standard national birth weight percentiles charts (Aryal et al., 2012; Dobbins et al., 2012; Kandraju et al., 2012; Kurtoğlu et al., 2012; Olsen et al., 2010; Seaton et al., 2011; Yunis et al., 2007). For example, in 2008, the Netherlands perinatal registry presented new Dutch reference charts for birth weight by gestational age (Visser et al., 2009). In 2015, the Chinese Neonatal Network established a new Birth weight percentile reference using a generalized additive model method used in China (Zhu

et al., 2015). Significant differences in SES, living conditions, and natural environment between north and south China showed the necessity to establish local references (Wu et al., 2022). In 2014, Talge *et al.* updated the US-based birth weight percentiles for gestational age based on 7,818,201 singleton birth from 2009 to 2010 using an algorithm developed by Basso and Wilcox to identify errors in gestational age and reported corrected birth weight percentiles (Nicole M. Talge et al., 2014). In 2018, Norris *et al.* published an updated birth weight percentiles for England and Wales using 1,269,403 singleton births from 2013 to 2014 to assist the national neonatal monitoring program in identifying high-risk infants following birth.

Birth weight percentile charts have various characteristics concerning the population, the sex of the infants, and the time of construction. A birth weight chart could be prescriptive or descriptive. Prescriptive birth weight charts indicate how an individual should grow and descriptive charts show how an individual usually grow (Berkley, 2019). Previous studies showed that compared to descriptive charts, prescriptive charts could improve the identification of SGA infants at risk of adverse outcomes (Ferdynus et al., 2009; Hoftiezer et al., 2016). However, prescriptive charts are based on infants with no risk factor for impaired fetal growth, which is not generalizable to a mixed population with low-and high-risk pregnancies (Lawrence et al., 1989; Niklasson et al., 1991). Some birth weight charts are unisex, failing to account for the existing birth weight difference between males and females (Brenner et al., 1976a; David, 1983; Gruenwald, 1966; Usher & McLean, 1969). Some other charts are more than a decade old and may no longer reflect accurate percentiles for infants born in recent years (Michael S. Kramer et al., 2001). Using outdated standards to screen high-risk neonates may lead to misclassification and mislead clinicians who must decide on interventions and health resource allocations.

Moreover, growth charts in infants can be improved by taking ethnicity into account. Nguyen *et al.* showed similar growth patterns between Australian infants with Vietnamese parents and those in the USA (Nguyen et al., 2004). Comparing growth charts from the US, France, the United Kingdom, Netherlands, and Belgium with the WHO standards revealed lower growth curves. However, after six months, growth curves were higher than reference curves (Rolland-Cachera & Péneau, 2011). Boshari *et al.* performed a systematic review of all birth weight curves between infants of immigrant mothers and those born in their native countries from 2002 to 2007

(Talia Boshari et al., 2013). They found that the infants of mothers who immigrated to Canada weighed more than those born in their native country for almost all countries. Another Canadian study by Ray *et al.* indicated significant differences between the 10^{th}, 50^{th}, and 90^{th} birth weight percentiles of infants of Canadian-born mothers and percentiles of infants born to mothers from each world region, except Western nations and Europe (Ray et al., 2012). These findings confirm the necessity of considering ethnicity for generating local birth weight percentiles.

1.5. Objectives

In Canada, Kramer *et al.* published the national birth weight reference based on all singleton births in the provinces of Canada (except Ontario) born between 1994 and 1996 using the Canadian Birth Database (Michael S. Kramer et al., 2001). This reference has been used in clinical practice and for research purposes ever since (Fenton, 2003; Fenton & Kim, 2013; Luo et al., 2006a; Laura A Magee et al., 2015; Schmidt et al., 2006; Barbara Schmidt et al., 2013; Tyson et al., 2008). However, the population characteristics of Canada have changed over the last two decades. Using an outdated reference could mislead clinical and public health interventions. In Alberta, Robertson *et al.* published local references based on all live births from 1985 to 1998 using Alberta Registries and Vital Statistics (Robertson et al., 2002). This study's birth weight references are outdated as well. The other drawback of this study was the lack of a correction method for possible gestational age errors. There are possible errors in reported gestational age due to inaccurate recall of the last menstrual period, bleeding early in pregnancy, and irregular or delayed menstrual cycles (Gjessing et al., 1999; Kramer et al., 1988; Saito et al., 1972a; Savitz et al., 2002; Yang et al., 2002). Similar studies used various algorithms to flag the erroneous gestational age (Joseph et al., 2001; Parker & Schoendorf, 2002; Platt et al., 2001). In addition, both national (Michael S. Kramer et al., 2001) and local (Robertson et al., 2002) studies did not consider maternal ethnicity.

The goal of the following chapter was to provide an updated reference for sex-specific birth weight percentiles by gestational age, overall, and for specific ethnic groups based on data from all live birth infants between 2005 and 2014 in Alberta, Canada.

Chapter 2 : An Updated Reference for Age-Sex-Specific Birth Weight Percentiles Stratified for Ethnicity Based on Data from All Live Birth Infants between 2005 and 2014 in Alberta, Canada

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2.1. Introduction

For many years, researchers and clinicians have looked at ways to evaluate the relationship between birth weight and gestational age to assess appropriate fetal growth (de Onis & Habicht, 1996a). In 1963, the first gestational age-specific birth weight charts were created to help clinicians identify babies born small for gestational age (SGA), appropriate for gestational age (AGA), or large for gestational age (LGA) (Lubchenco et al., 1963). Numerous studies have confirmed the importance of these markers and have shown that SGA and LGA are associated with an increased risk of severe complications and fetal death (Boghossian et al., 2018; Carter et al., 2018; Charles et al., 2018; Gardosi et al., 2013; Poon et al., 2016; Savchev et al., 2012). One of the most important clinical indicators of potential morbidity, mortality, and developmental delay for a newborn is an extreme deviation from the average birth weight for gestational age (Brenner et al., 1976b; Lubchenco et al., 1963).

In 2001, Kramer et al. (Michael S Kramer et al., 2001) published birth weight curves for babies born in Canada between 1994 and 1996. These have been widely used in Canadian clinical practice, including for the development of Fenton charts for preterm infants (Joseph et al., 2005; Laura A. Magee et al., 2015; Schmidt et al., 2006; B. Schmidt et al., 2013), and for research purposes (Fenton, 2003; Fenton & Kim, 2013; Luo et al., 2006b; Tyson et al., 2008). However, the characteristics of women giving birth in Canada are changing: they are older, heavier, and are more likely to undergo Caesarean-section (c-section) deliveries (Provencher et al., 2018). These factors may influence the gestational age-specific percentiles for SGA (10^{th} percentiles) and LGA (90^{th} percentile). Canada has also experienced significant immigration (Edmonston, 2016) in the last two decades. Statistics Canada reported more than one million people immigrated to Canada between 2006 and 2011 (Canada, 2016). The 2016 Census showed that South Asian and Chinese are the two largest visible minority groups in Canada, constituting 5.6% and 4.6% of the Canadian population respectively (Canada, 2017). This may have implications for Canadian SGA and LGA thresholds. A systematic review published in 2013 showed that term birth weight percentiles are different for infants born to mothers emigrating to Canada than those who were born in their mothers' native countries (T. Boshari et al., 2013). This conclusion was confirmed by a population-based study of 766,688 singletons live births from 2002 to 2007 in Ontario which showed that birth weight curves need to be stratified by the mothers' region of origin for non-Western and non-European nations to avoid misclassification of SGA and LGA (Ray et al., 2012). The last Alberta birth weight percentile reference was based on 556,775 singleton infants and 12,125 twins born between 1985 and 1998 and did not take maternal ethnicity into account (Robertson et al., 2002).

In addition to ethnicity and immigrant status, other factors such as general improvements in health status and changes in population characteristics including socioeconomic status, lifestyle, and diet may contribute to changes in birth weight trajectories. The purpose of the current study is to provide an updated reference for sex-specific birth weight percentiles by gestational age, overall and for specific ethnic groups.

2.2. Materials and Methods

This study was approved by the University of Alberta Research Ethics Board (Pro00056999). The ethics panel determined that the research is a retrospective database review for which subject consent for access to personally identifiable health information would not be reasonable, feasible, or practical.

2.2.1. Population and data linkage

The province of Alberta has an area of 661,848 square kilometers (255,500 square miles), and in 2005 had a population of 3.2 million ("Vital Statistics, Annual Review 2005,"). In 2014, Alberta's population increased to 4.1 million people ("Vital Statistics, Annual Review 2014,"). Live births were identified in the Alberta Vital Statistics-Births Database between January 1st, 2005 and December 31st, 2014. The Vital Statistics-Births Database captures neonatal variables (birth weight, birth order, and sex) and maternal information (age, marital status at delivery, pregnancy type). Using unique personal identifiers, data on the babies from the Alberta Vital Statistics-Births Database were linked with maternal data from the Alberta Health Care Insurance Plan (AHCIP) Registry. We excluded: infants of women who were not Alberta residents at the time of delivery; women who had an incorrect maternal identifier or had gestational age at delivery as missing, <22 weeks, or ≥43 weeks; infants with missing birth weight or sex; and all deliveries resulting in multiple births (twins, triplets, etc.). Maternal ethnicity was established using previously-validated algorithms (Quan et al., 2006; Shah et al., 2010). Briefly, the algorithms were applied to the earliest surname available for each mother in the AHCIP database and used to identify women of Chinese and South Asian ethnicities. All other women in the cohort were categorized as belonging to the general population. We classified preterm infants into three categories including extremely preterm (less than 28 weeks), very preterm (28 to 32 weeks), moderate to late preterm (32 to 37 weeks), and term (more than 37 weeks) based on the World Health Organization (Organization, 2018). Critical percentiles of SGA and LGA are those corresponding to the 10th and 90th percentile of Birth weight at each gestational week.

2.2.2. Statistical analysis

Crude descriptive statistics, including sex-specific percentiles (3rd, 5th, 10th, 50th, 90th, 95th, and 97th), mean, and standard deviation, of birth weights were calculated at each gestational age for each sex, and sex-ethnic group (Supplementary material).

There are several sources of bias in estimating gestational-age specific birth weights. These include inaccurate recall of the date of the last menstrual period (LMP) (Kramer et al., 1988), bleeding very early in pregnancy (Gjessing et al., 1999), as well as, irregular or delayed menstrual cycles (Saito et al., 1972b; Savitz et al., 2002; Yang et al., 2002). Several studies have used various algorithms to flag erroneous gestational ages (Joseph et al., 2001; Parker & Schoendorf, 2002; Platt et al., 2001). We used the method described by Platt *et al.* (2001) to remove data from infants believed to have an incorrectly recorded gestational age (Platt et al., 2001). An expectation-maximization algorithm was used for each infant to calculate the probability that the true gestational age was the recorded gestational age rather than 40 weeks.

Quantile-Quantile plots (QQ-plots) were used to compare the distributions of birth weights and log-transformed birth weight data with normal distributions. We did not see any remarkable deviation from normality. Birth weights were modelled by gestational age using generalized additive modelling (Hastie & Tibshirani, 1995) with non-constant variance due to the uncertainty about the linear relationship between birth weights and gestational age. At each gestational age the birth weight was assumed to be normally distributed with both mean and standard deviation defined as natural cubic splines with seven degrees of freedom for gestational age. Degrees of freedom were obtained by using the likelihood ratio test method of Cantoni and Hastie (2002) for additive models when there is only one predictor (gestational age in here) in the model (Cantoni & Hastie, 2002). Observations were weighted by the square root of the number of infants at each gestational age to account for the different number of infants in each gestational age. The models were fit separately for each sex group and each sex-ethnic group. The model results were used to estimate the percentiles (3rd, 5th, 10th, 50th, 90th, 95th, and 97^{th}), means, and standard deviations of the birth weight distribution at each gestational age by sex and sex-ethnic groups, statistics to be referred to as smoothed statistics. In addition, independent samples T-test with Bonferroni adjustment for multiple comparisons was used to compare mean birth weights in the Alberta cohort with those in the previous national reference (Kramer et al. 2001) at each

gestational age. Crude SGA and LGA cut-offs were also compared between our Alberta cohort 2005-2014 and the Alberta cohort 1985-1998 reported by Robertson et al. (Robertson et al., 2002).

Statistical analysis by sex group was carried for gestational ages 22 to 42 weeks and by sex-ethnic group for gestational ages 33 to 41 weeks to ensure adequate sample size.

All statistical analyses were performed using R (version 3.5.0) (Team, 2014) and packages lmvar (version 1.5.0), and splines (version 3.5.1).

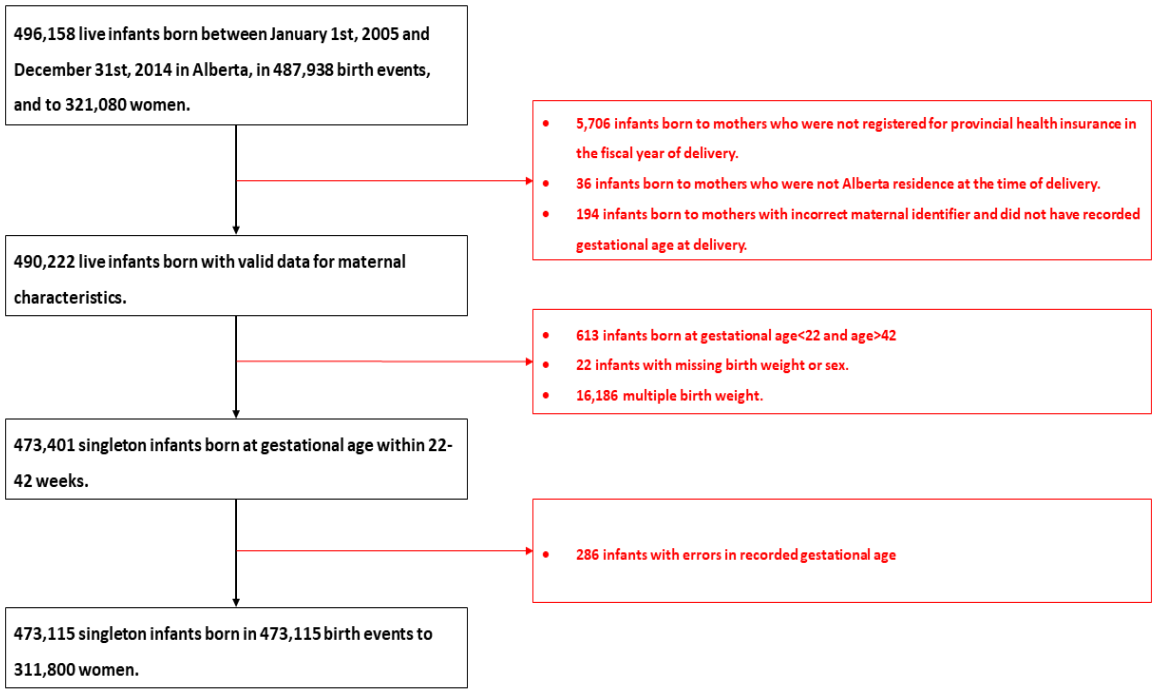

Figure 2-1 This figure shows the process of identifying our cohort before statistical analysis

2.3. Results

2.3.1. Cohort characteristics

Between January 1st, 2005, and December 31st, 2014 there were 496,158 live infants born in 487,938 birth events to 321,080 women (Figure 2-1). We excluded infants born to women not registered for provincial insurance, were non-residents, had incorrect identifiers, or had missing data. We also excluded infants who were born at <22 weeks or ≥43 weeks of gestation, were missing birth weight or sex, or part of a multiple birth event (e.g., twins, triplets). In addition, 286 infants were excluded as a result of applying the Platt *et al.* (2001) EM algorithm to detect possible errors in recorded gestational age. The final study cohort consisted of 473,115 singleton infants born to 311,800 women.

2.3.2. Sex-specific results

Tables 2-1 and 2-2 show smoothed estimates of birth weight percentiles by gestational age and sex. The crude data from which these were derived are presented in supplementary Tables 1-1 and 1-2. The results show that both SGA and LGA (10th and 90th percentiles, respectively) were lower for females than males for all gestational ages and female-male differences ranged from 26.6 to 180.4 grams for the 10^{th} percentile and from 6.7 to 199.7 grams for the 90^{th} percentile. The relative sex-difference (sex-ratio) by gestational age is presented in supplementary Table 3-1.

Table 2-1: Smoothed birth weight (g) percentiles for gestational age, Albertan male singletons born January 1, 2005 and December 31, 2014

Gestational Age (weeks)	n	Percentiles							Mean	SD
		3rd percentile	5th percentile	10th percentile	50th percentile	90th percentile	95th percentile	97th percentile		
22	143	266.6	291.3	329.2	463.0	596.8	634.8	659.4	463.0*	104.4
23	116	355.6	383.8	427.4	580.9	734.5	778.0	806.3	580.9	119.8
24	121	442.1	474.5	524.4	700.4	876.4	926.3	958.6	700.4	137.3
25	139	527.5	564.5	621.6	822.9	1024.2	1081.3	1118.3	822.9	157.1
26	170	613.3	655.5	720.6	950.1	1179.5	1244.6	1286.8	950.1*	179.1
27	220	701.2	749.1	822.9	1083.4	1343.9	1417.7	1465.7	1083.4*	203.2
28	227	793.0	847.1	930.4	1224.5	1518.5	1601.9	1656.1	1224.5*	229.4
29	270	890.8	951.6	1045.1	1374.8	1704.6	1798.1	1858.9	1374.8*	257.3
30	393	997.3	1064.9	1168.9	1536.0	1903.1	2007.2	2074.7	1536.0*	286.4
31	540	1115.1	1189.7	1304.5	1709.5	2114.6	2229.4	2304.0	1709.5	316.1
32	775	1247.4	1328.9	1454.4	1897.0	2339.6	2465.1	2546.5	1897.0	345.4
33	1317	1397.8	1485.8	1621.5	2099.9	2578.3	2713.9	2802.0	2099.9	373.3
34	2238	1569.9	1663.9	1808.8	2319.8	2830.7	2975.6	3069.6	2319.7**	398.7
35	3523	1767.7	1866.8	2019.5	2558.2	3096.8	3249.5	3348.7	2558.2**	420.3
36	7461	1995.0	2098.1	2256.8	2816.7	3376.6	3535.3	3638.4	2816.7**	436.9
37	17292	2255.7	2361.2	2523.7	3096.8	3670.0	3832.5	3938.0	3096.8	447.2
38	43955	2499.1	2602.7	2762.3	3325.0	3887.8	4047.3	4150.9	3325.0**	439.1
39	67240	2674.1	2774.9	2930.1	3477.7	4025.3	4180.5	4281.4	3477.7**	427.3
40	62909	2813.3	2915.0	3071.7	3624.3	4177.0	4333.7	4435.4	3624.3**	431.2
41	32893	2933.0	3036.2	3195.1	3755.4	4315.8	4474.6	4577.8	3755.4**	437.2
42	956	2968.7	3080.2	3251.9	3857.6	4463.2	4634.9	4746.4	3857.6**	472.6

*P<0.05, **P<0.0024 (adjusted for multiple comparisons), Birth weight mean difference compared to Kramer *et al.(Michael S Kramer et al., 2001)*

Table 2-2: Smoothed birth weight (g) percentiles for gestational age, Albertan female singletons born January 1, 2005 and December 31, 2014

Gestational Age, weeks	n	Percentiles							Mean	SD
		3rd percentile	5th percentile	10th percentile	50th percentile	90th percentile	95th percentile	97th percentile		
22	115	217.7	241.4	277.7	405.7	533.7	570.0	593.6	405.7**	99.9
23	91	313.7	341.1	383.3	532.3	681.2	723.4	750.9	532.3*	116.2
24	140	406.0	437.9	486.9	660.0	833.0	882.1	914.0	660.0	135.0
25	135	495.8	532.7	589.5	790.0	990.5	1047.3	1084.2	790.0*	156.4
26	156	584.1	626.6	692.2	923.5	1154.7	1220.3	1262.9	923.5**	180.5
27	175	672.2	721.1	796.3	1061.6	1326.8	1402.0	1450.9	1061.6**	207.0
28	209	762.0	817.6	903.3	1205.4	1507.5	1593.1	1648.8	1205.4**	235.7
29	220	855.5	918.3	1015.0	1356.1	1697.3	1794.0	1856.8	1356.1**	266.2
30	281	955.3	1025.5	1133.6	1515.0	1896.3	2004.5	2074.7	1515.0**	297.6
31	407	1064.4	1142.0	1261.5	1683.0	2104.5	2224.0	2301.6	1683.0**	328.9
32	596	1186.4	1271.0	1401.4	1861.4	2321.3	2451.7	2536.4	1861.4*	358.9
33	884	1325.2	1416.3	1556.5	2051.3	2546.1	2686.4	2777.5	2051.3	386.1
34	1736	1485.0	1581.4	1729.9	2253.9	2777.9	2926.4	3022.9	2253.9	408.8
35	2932	1669.8	1770.3	1924.9	2470.3	3015.8	3170.4	3270.8	2470.3**	425.6
36	6349	1883.7	1986.3	2144.3	2701.7	3259.1	3417.1	3519.7	2701.7**	434.9
37	15414	2129.9	2232.7	2390.9	2949.2	3507.5	3665.8	3768.6	2949.2**	435.6
38	40807	2410.7	2511.5	2666.6	3214.0	3761.4	3916.6	4017.4	3214.0**	427.1
39	65004	2566.1	2663.9	2814.6	3346.1	3877.6	4028.2	4126.1	3346.1	414.7
40	62620	2706.1	2803.9	2954.5	3485.6	4016.8	4167.4	4265.2	3485.6	414.5
41	31083	2809.5	2909.4	3063.3	3606.0	4148.7	4302.5	4402.4	3606.0**	423.5
42	815	2792.8	2902.5	3071.5	3667.5	4263.5	4432.4	4542.1	3667.5	465.1

*P<0.05, **P<0.0024 (adjusted for multiple comparisons), Birth weight mean difference compared to Kramer *et al.(Michael S Kramer et al., 2001)*

2.3.3. Sex-ethnicity-specific results

Figures 2 and 3 show smoothed estimates for 10th and 90th percentiles by gestational age for each sex-ethnic group of infants born at 33 to 41 weeks of gestation. The total number of male infants in the three ethnic groups were: 223,827 in the general population, 8,155 in the Chinese group, and 6,968 in the South-Asian group; and the total number of female infants were 212,787 in the general population, 7,767 in the Chinese group, and 6,349 in the South-Asian group, respectively. The sample sizes varied by the week of gestation and are provided in supplementary Tables 4-1 and 5-1. Birth weight at the 10th and 90th percentiles for South Asian and Chinese ethnic groups were lower than the general population for both sexes. At the 90th percentile, South-Asian and Chinese infants had similar birth weights, regardless of gestational age. However, at the 10th percentile, birth weights among preterm South-Asian infants were much lower than those among preterm Chinese infants. This difference was attenuated among infants born at or over 37-weeks of gestation.

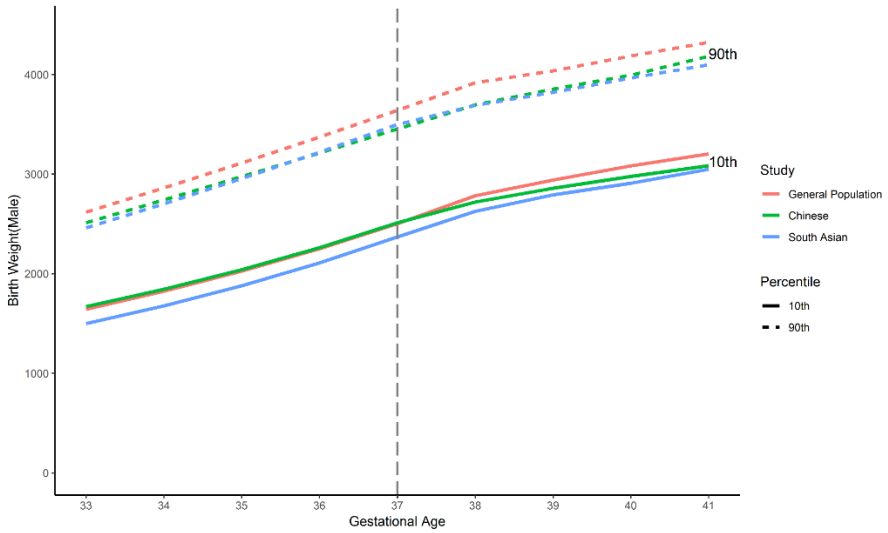

Figure 2-2: This figure shows the smoothed birth weight critical percentiles based on gestational age of mothers and the original ethnicity of mother for male singletons.

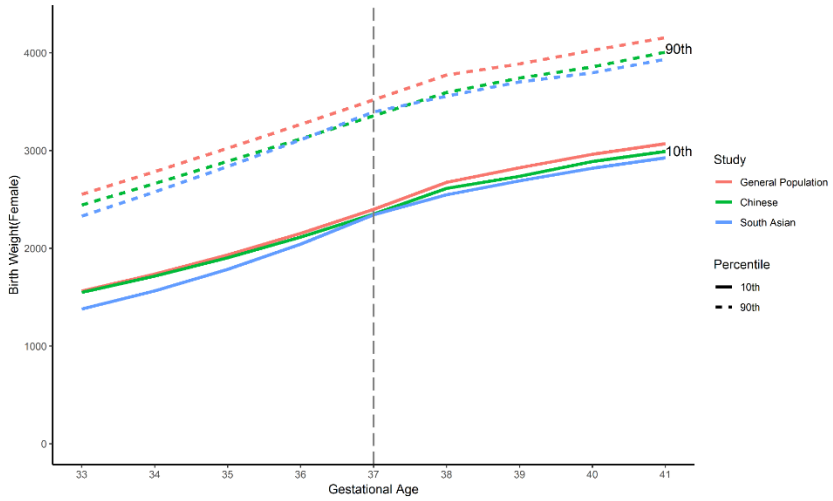

Figure 2-3: This figure shows the smoothed birth weight critical percentiles based on gestational age of mothers and the original ethnicity of mother for female singletons.

2.3.4. Comparison to the previous national reference

Compared to the national reference from 1994-96 (Michael S Kramer et al., 2001), the SGA and LGA values for very preterm male and female infants in our study were slightly greater (Fig 4-1, A and B). After adjusting for multiple comparisons, the mean birth weights of male (at 34-36 and 38-42 weeks) and female (at 22, 26-31, 35-38, and 41 weeks) infants were also significantly different. The largest mean difference for males was 65.5 grams at 28 gestational weeks and 100 grams for females at 29 gestational weeks.

The 90th percentile was lower for preterm and term Chinese infants for both male and female groups. The 10th percentile was only slightly lower for preterm Chinese female infants (Figure 4-1, C and D). Finally, preterm and term South Asian infants had a lower 10th and 90th percentiles for both sexes (Figure 4-1, E and F).

In addition to a national reference, we compared the crude birth weights at 10th, 50th, and 90th percentiles by gestational age in our cohort against those observed in a historical cohort in Alberta. (Robertson et al., 2002) These are provided in supplementary Figure 1-3.

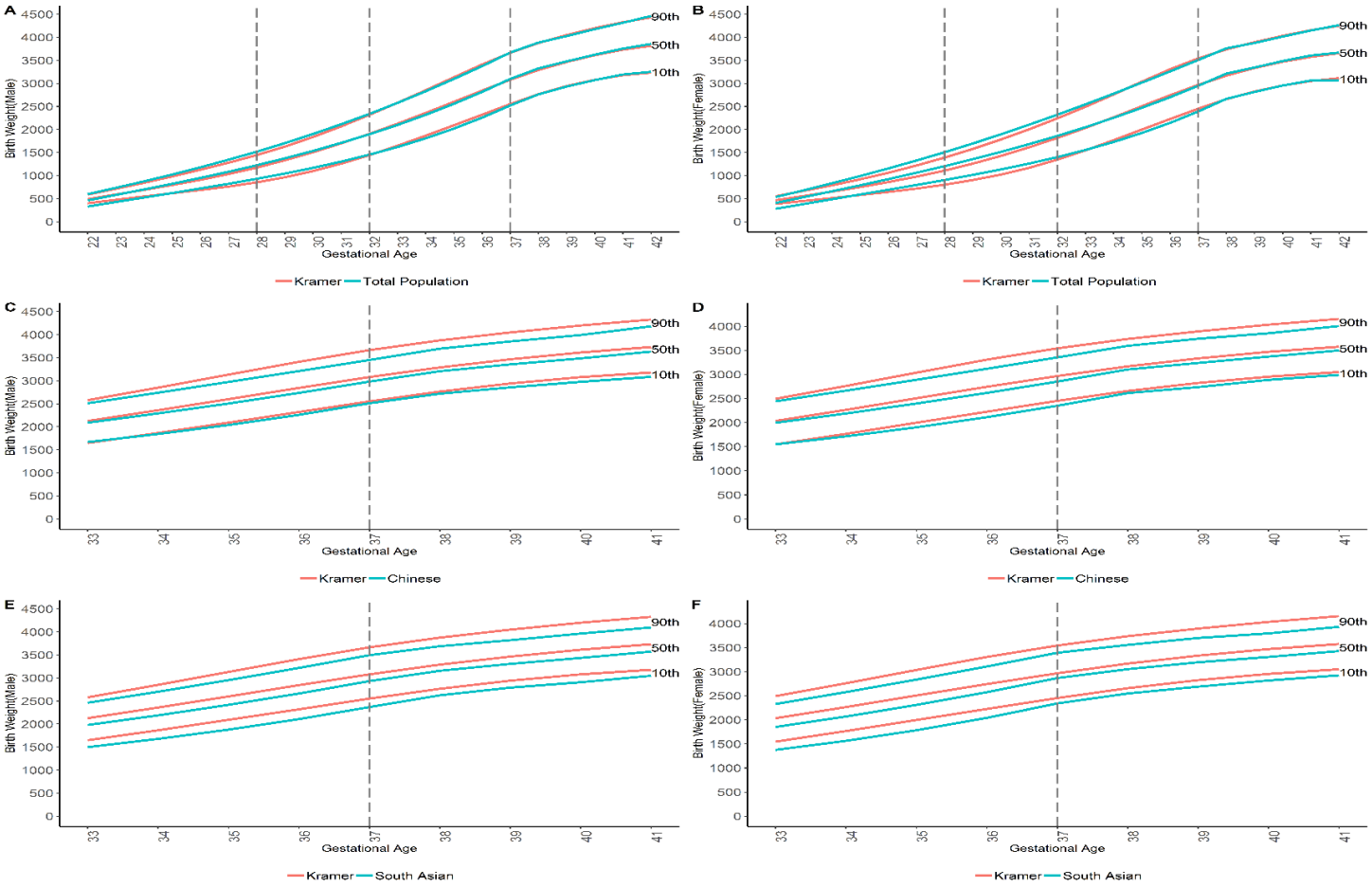

Figure 2-4: This figure shows the Sex-ethnicity-specific critical percentiles of birth weight for gestational age generated based on correction algorithm compared to the previous national reference for male and female singleton live births.

2.4. Discussion

Our study provides a more contemporary reference for both sex- and ethnicity-specific cut-off values for SGA and LGA based on birth weight data from all live-births in Alberta, Canada, between January 1, 2005, and December 31, 2014. We found differences in SGA and LGA cut-offs between male and females infants in the Alberta population. Moreover, as compared to a previous national reference, our results showed greater SGA and LGA values for very preterm infants for both sexes; and smaller SGA and LGA values for South Asian and Chinese ethnic groups.

The results from this study showed that both SGA and LGA were lower for females than males. This is consistent with results of previous studies, including those reported by Skjaerven *et al* (Skjaerven et al., 2000) based on Medical Birth Registry data on more than 1.8 million births from Norway between 1967 and 1998; by Talge *et al* (Nicole M Talge et al., 2014) based on data from the National Center for Health Statistics (USA) on more than 7 million live births between 2009 and 2010; and by Kramer *et al* (Michael S Kramer et al., 2001) based on all live births in Canada (except Ontario) born between 1994 and 1996. Several genetic and physiological factors have been identified as possible contributors to these differences (Voldner et al., 2009). However, less is known about the relative contribution of equity and socioeconomic status on the weight of male and female infants.

Our study showed that LGA was lower for preterm and term Chinese infants for both males and females, and SGA was lower only for preterm Chinese female infants compared to those from the general population. Moreover, preterm and term South Asian infants had lower 10th and 90th percentiles for both sexes. Population projections predict that immigration from Asia will account for 55% of the foreign-born population by 2031 (Edmonston, 2016). These immigration patterns increase the necessity for ethnicity-based analysis of birth weight percentiles. Between 2011 and 2016 in Alberta, there has been a steady increase in the South Asian population (from 4.4% to 5.8%), while the proportion of Chinese immigrants descreased slightly from 4.4% to 4.0% (Canada, 2016; Chui & Flanders, 2013). A study by Ray *et al*. (Ray et al., 2012) showed lower birth weights among term infants born to mothers from each world region except Europe compared to the Canadian general population. However, these patterns have not been found in other countries such as the US, France, and Belguim (Forna et al., 2003; Guendelman et al., 1999).

Using the latest Canadian national or provincial birth weight references to classify Alberta infants born to Chinese or South Asian mothers rather than ethnicity-specific percentiles may increase the risk of misclassification. Mikolajczyk *et al.* indicated that incorporating ethnicity can improve the classification of infants as SGA (Mikolajczyk et al., 2011). Similarly, Ray *et al.* conducted a single-center study on infants born to Canadian East Asian or South Asian mothers which showed that infants in these ethnic-groups are misclassified as SGA at birth (Ray et al., 2009). Hanley *et al.* showed that ethnicity-specific percentiles were more accurate in identifying

infants at higher risk of adverse events than percentiles that did not take into account maternal ethnicity (Hanley & Janssen, 2012). In general, ethnic-specific thresholds have been shown to have better performance in appropriately classifying infants as SGA, AGA, or LGA compared to conventional population-based references (Hanley & Janssen, 2012; Hanley & Janssen, 2013; Kierans et al., 2008).

The comparison between the previous birth weight reference for Canada (Michael S Kramer et al., 2001) and our study showed that SGA and LGA are greater for very preterm infants in Alberta. The LGA was lower for South Asian and Chinese preterm and term infants for both sex groups, and the SGA for South Asian preterm male infants was lower than Chinese male infants compared to the general population in Alberta. These differences could be due to changes in characteristics, such as maternal age of women giving birth in Alberta over the last two decades. Consistent with trends in Canadian births, average maternal age increased steadily in Alberta from 28.3 years old in 2000 to 29.5 years old in 2013. During this time period, the low birth weight rate increased from 5.97% in 2000 to 7.01% in 2013 for women aged 30 to 34 years and from 7.63% to 8.45% for women aged 35 to 39 years (Alberta).

2.5. Limitations

The new sex- and ethnicity-specific cut-off values for SGA and LGA that we estimated could be used for assessing infants born in Alberta, as well as in other parts of Canada. However, the generalizability of our study findings to other parts of the world may be limited due to differences in factors such as ethnicity composition, diet, or socioeconomic status.

Confounding factors such as maternal age at delivery, birth order, parity, and household income were not adjusted for in the current analysis. Further studies with a different study design are needed to complete the causal paths and reveal the important factors that cause differences in SGA and LGA values among infants at the population level (Hernán & Robins, 2006).

Gestational age errors may have impacted our results. However, we used a modified correction method proposed by Platt *et al.* (2001) to reduce the effect of these errors (Platt et al., 2001). This method has been shown to improve measurement of association by deleting extreme

outliers and reducing the chance of misclassification at 40 weeks (Alexander et al., 1996; Arbuckle et al., 1993). We evaluated the normality assumption of birth weight within each gestational age category. This assumption helped us to more precisely estimate deviations from the standard normal. We used previously-validated algorithms by (Quan et al. 2006; Shah et al. 2010) to identify Chinese and South-Asian ethnic groups based on surname. The ethnicity categorization was based on the earliest surname available for each mother in the AHCIP which may change due to marriage, adoption, and other factors. This could lead to misclassification of ethnicity. We categorized all other mothers as belonging to the general population. Better capture of maternal ethnicity data could elucidate birth weight differences among other ethnic groups. The relatively small sample size of Chinese and South-Asian ethnic groups is also a limitation. We limited our comparion for ethnic groups to 33-41 gestational weeks to have at least 30 infants at each gestational age (Supplementary Table 1-4 and 1-5) to provide more stable estimates.

2.6. Conclusion

This study presents sex- and ethnicity-specific SGA and LGA cut-offs by gestational age from a contemporary Canadian cohort. These updated birth weight percentiles highlight the differences in SGA and LGA cut-offs among infants from South-Asian, Chinese and the general population, which may be important for clinical perinatal care. These population driven cut-offs may assist in more accurate classification of infants for public health surveillance.

Chapter 3 : Challenges in Analysis of Microbiome Studies

3.1. Human Gut Microbiome

The first large-scale project to characterize the healthy human microbiome, Human Microbiome Project (HMP), which included 242 healthy humans, was published in two companion papers in Nature (Huttenhower et al., 2012; Methé et al., 2012). The HMP findings showed that stool and oral communities were the most diverse microbial communities regarding the number of different organisms present, and the vaginal community was the least diverse (Methé et al., 2012). Despite such observations, individuals harbor nearly different microbial communities (Huttenhower et al., 2012). The human gut microbiome (GM) studies have attracted much attention recently because of their connection with various diseases and the convenience of fecal sample collection (Eckburg et al., 2005). The human GM is dominated by four major bacterial phyla, including Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria (Ley et al., 2008). The Firmicutes are associated with every intake of food (Turnbaugh et al., 2006), while the Bacteroidetes are capable of degrading complex sugars and proteins into metabolizable short-chain fatty acids (SCFAs) (Ley et al., 2006). There is considerable interest in the microbiome during childhood development both because of the extreme changes undergone during this process and the existing prospects for early-life interventions that could promote health over the infants' lifetime.

Interestingly, the mother's gut microbiome is fundamentally remodeled between the first and third trimesters (Koren et al., 2012). The third-trimester microbiome composition is significantly different from those of the non-pregnant women. The maternal microbiome seeds the infant's first microbial communities, but some arguments exist regarding whether this seeding occurs during birth or prenatally.

3.2. Time of Colonization

The human GM colonization may begin in utero and change over time after birth regarding the diversity and structures (Hollister et al., 2015; Yatsunenko, Rey, Manary, Trehan, Dominguez-Bello, Contreras, Magris, Hidalgo, Baldassano, & Anokhin, 2012). Until recently, it was assumed that colonization begins with birth; however, several studies showed that the placenta, amniotic fluid, fetal membranes, and cord blood from healthy term pregnancies harbor various microorganisms suggesting that colonization starts before birth (Aagaard et al., 2014; Jiménez et al., 2005; Rautava et al., 2012; Steel et al., 2005). Potential sources of these initial bacteria include the vaginal microbiome (Aagaard et al., 2012), bacteria in the uterus (Cowling et al., 1992; Hemsell et al., 1989; Møller et al., 1995), and the maternal digestive track, including the oral cavity (Aagaard et al., 2014). Some studies on healthy term pregnancies showed a low abundance of microbiomes similar to the maternal oral microbiome as the initial sources of fetal exposure to bacteria outside of the uterus (Aagaard et al., 2014; Zheng et al., 2015). However, further detailed studies are needed to characterize the impact of the maternal microbiome on offspring colonization (Greenhalgh et al., 2016).

Several non-human studies suggest that maternal diet (Aagaard et al., 2014; Ma et al., 2014), gestational weight gain (not obesity) (Antony et al., 2015), and maternal stress during pregnancy (Bailey et al., 2004) are associated with the changes in the placental microbiome. The inter-individual variation within GM is much more significant in infants than adults, suggesting that early patterns are not stable but reach a similar endpoint in adulthood (Yatsunenko, Rey, Manary, Trehan, Dominguez-Bello, Contreras, Magris, Hidalgo, Baldassano, & Anokhin, 2012). Compared to adulthood, the GM at birth is less diverse and more variable (Dominguez-Bello et al., 2010; Yatsunenko, Rey, Manary, Trehan, Dominguez-Bello, Contreras, Magris, Hidalgo, Baldassano, & Anokhin, 2012). Culture-based studies indicated a high abundance of Bifidobacterium spp in the neonatal microbiome (Penders et al., 2006), which helps break down dietary carbohydrates and interact directly with host metabolism (Davis et al., 2011). The literature showed that the microbiome of preterm infants exhibits low diversity and abundance of Lactobacillus spp, Bacteroides spp, and Bifidobacterium spp, with some differences persisting until 90 days postpartum (Arboleya, Ang, et al., 2012; Arboleya, Binetti, et al., 2012; Arboleya et al., 2015). The first year of life represents a significant period of development and maturation

of the GM with increase in taxonomic diversity over time with bacteria obtained from breast milk and the environment (Schanche et al., 2015; Thompson et al., 2015).

3.3. Important Factors

Gestational age and mode of delivery are two important factors influencing the neonatal microbiome at birth (Ardissone et al., 2014; Dominguez-Bello et al., 2010). In addition, breastfeeding, antibiotic exposure (Mangin et al., 2010; Penders et al., 2006), number of siblings (Penders et al., 2006), exposure to pets (Nermes et al., 2015), and geography (Matteo Fallani et al., 2010) are affecting GM composition. We discuss some of these factors in the following sub-sections.

3.3.1. Breastfeeding

Human breast milk is a complex fluid that contains necessary bioactive components that shape the microbial composition of an infant's gut (Ballard & Morrow, 2013; Moossavi et al., 2018). Several studies examined the changes in infant gut microbiome composition between breastfed and formula-fed infants (Backhed et al.; M. Fallani et al., 2010; Ho et al., 2018; Albert M Levin et al., 2016; Penders et al., 2006; Stewart et al., 2018). A Dutch birth cohort study on 1032 children at one month of age showed that the colonization rate of E. coli, Clostridium difficile, Bacteroides, and lactobacilli was lower in breastfed infants compared to formula-fed infants (Penders et al., 2006). Another study on European infants at six weeks of age indicated the domination of different bacteria between the two groups. They showed that Bifidobacteria was dominant among breastfed infants, whereas formula-fed infants' microbial composition showed a higher abundance of Bacteroides, Clostridium coccoides, and Lactobacillus (M. Fallani et al., 2010). Moreover, a Swedish study on 98 infants reported that the cessation of breastfeeding shifted the microbial composition toward an adult-like composition (Backhed et al.). Finally, a large international study on 684 infants showed lower diversity and abundance of Bacteroidetes and Firmicutes in breastfed children for up to 6 months, showing that breastfed children had less mature microbial compositions (Ho et al., 2018). In summary, findings from multiple studies

showed that breastfed infants have lower diversity than formula-fed infants, and cessation of breastfeeding is associated with a shift to a more mature gut microbiota composition (Kim et al., 2019).

Although breastfeeding is considered a protective factor against many diseases and disorders such as asthma, obesity, and Type one diabetes (Schack-Nielsen & Michaelsen, 2006), there is contradictory evidence about the protective effect of breastfeeding on the risk of many non-communicable diseases. Inconsistency in the findings of studies evaluating the effects of breastfeeding on the prevention of many diseases could be due to variability in human milk because of diet, duration of breastfeeding and lactation, and infants' response to many elements in the human milk (Munblit et al., 2017). Studies showed that an exclusively breastfed infant has an overall greater diversity of the microbiome when compared to exclusively formula-fed infants (Schwartz et al., 2012). According to the World Health Organization (WHO) recommendations, infants who experienced six months of exclusively breastfeeding have lower long-term morbidity from gastrointestinal and allergic diseases compared to non-breastfed infants (Horta et al., 2007). The UNICEF and WHO recommended that "every infant should be exclusively breastfed for the first six months, with continued breastfeeding for up to two years or longer" (Organization, 2003).

3.3.2. Antibiotic Exposure

Although the large-scale production of the first manufactured antibiotic, Penicillin, is directly responsible for saving hundreds of millions of lives, the inappropriate use of antibiotics in children has become a major public health problem (Rogawski et al., 2017). Viruses, not bacteria, often cause common childhood illnesses such as diarrhea and upper-respiratory-tract infections. Therefore, the prescription of antibiotics in the case of viral infection is ineffective at best (Kutty, 2011). Given that the first three years of life are so important for microbial development, intensive exposure to antibiotics at this time can delay the maturation of normal gut microbiota (Langdon et al., 2016). Antibiotic treatment in children has been associated with an increased risk of many diseases such as obesity (Azad et al., 2014), asthma and allergies (Arrieta et al., 2015; Metsälä et al., 2013), diabetes (Kilkkinen et al., 2006), inflammatory bowel disease (Hviid et al., 2011), and microbial dysbiosis. Antibiotic use is associated with reduced

total bacteria levels (Arboleya et al., 2015; Martin et al., 2016) and decreased gut microbial diversity (Greenwood et al., 2014). The length of exposure to antibiotics has a crucial effect on the severity of the changes in the gut microbial community (Zwittink et al., 2018). A small study of 15 preterm infants examined the short-term effect of antibiotic treatment and showed the level of Bifidobacterium decreased after treatment until week three (Zwittink et al., 2018). The same study indicated that the long-term effect of antibiotic exposure caused a constant decrease in the level of Bifidobacterium up to postnatal week six (Zwittink et al., 2018). In addition, the KOALA study on 1032 infants showed that antibiotic exposure is associated with decreased number of Bifidobacteria and Bacteroides in samples obtained at one month of age (Penders et al., 2006).

3.3.3. Type of Delivery

C-section is one of the important factors associated with dysbiosis in the newborn gut microbiome (Walker, 2017). Vaginally birthed infants have microbial communities closer to the adult vaginal community, whereas infants born by cesarean section have communities more similar to the skin microbiome (Bäckhed et al., 2015; Dominguez-Bello et al., 2010; Francino, 2018). Several studies indicated that bacterial colonization starts before delivery through meconium, umbilical cord blood, fetal membranes, and amniotic fluid (Funkhouser & Bordenstein, 2013; Houghteling & Walker, 2015). The near-term fetus swallows amniotic fluid containing pieces of the vernix caseosa, the waxy skin coating of a fetus made up of short fatty acids (SCFAs), providing a rich medium for the growth of bacteria (Ran-Ressler et al., 2011). When the infant is born, these SCFAs act as the initial probiotics. In contrast, cesarean delivery can disturb the normal colonization of the infant's guts (Fouhy et al., 2012; Penders et al., 2006). The Cesarean (C-section) delivery infant gut microbiome resembles environmental rather than intestinal bacteria, and those bacteria are less diverse (Meghan B Azad, Theodore Konya, Heather Maughan, David S Guttman, Catherine J Field, Radha S Chari, et al., 2013; Jakobsson et al., 2014). Consistent findings showed lower diversity and decreased abundance of Bifidobacterium, Bacteroides, and Lactobacillus in infants born by C-section compared to vaginal birth (Meghan B Azad, Theodore Konya, Heather Maughan, David S Guttman, Catherine J Field, Radha S Chari, et al., 2013; Brumbaugh et al., 2016; Francino, 2018;

Jakobsson et al., 2014; Albert M Levin et al., 2016; Magne et al., 2017; Penders et al., 2006; Sordillo et al., 2017). Moreover, Cesarean birth has been associated with an increased rate of later celiac disease (Decker et al., 2011; Mårild et al., 2012), obesity (Mesquita et al., 2013), and asthma (Thavagnanam et al., 2008), presumably through the microbiome. This association is robust in elective cases rather than emergent Cesarean (Mårild et al., 2012). In a study of birth mode, microbial diversity was the lowest in elective Cesarean compared to emergent Cesarean (Meghan B Azad, Theodore Konya, Heather Maughan, David S Guttman, Catherine J Field, Radha S Chari, et al., 2013).

3.3.4. Pet Exposure

Emerging evidence suggests that having pets at home, especially dogs and cats, can change the microbiome composition of the environment and later the maturing gut microbiome during infancy (Dunn et al., 2013; Fujimura et al., 2016; Fujimura et al., 2010; Gensollen et al., 2016; Johansson et al., 2011; Konya et al., 2014; Maier et al., 2010). Sitarik *et al.'s* study showed that once a dog is introduced to a home, a shift in the microbial composition of the environment is seen within a year of entry, with a large relative abundance of new rare taxa (Sitarik et al., 2018). Detroit WHEALS birth cohort study (Albert M Levin et al., 2016), Canadian Healthy Infants Longitudinal Development Study (CHILD) (Meghan B Azad, Theodore Konya, Heather Maughan, David S Guttman, Catherine J Field, Malcolm R Sears, et al., 2013; Tun et al., 2017), and Danish SKOT 1 cohort study (Laursen et al., 2015b) independently reported changes in the microbial composition of infants gut microbiome related to pet exposure. Levin *et al*. showed that pet exposure was an independent contributor to neonatal microbial composition (Albert M. Levin et al., 2016). Azad *et al.'s* study on a small cohort of 24 infants showed that exposure to pets decreased the relative abundance of Bifidobacteriaceae and increased the abundance of Peptostreptococccceae in the fecal sample collected at four months (Meghan B Azad, Theodore Konya, Heather Maughan, David S Guttman, Catherine J Field, Malcolm R Sears, et al., 2013). In addition, another study on the same cohort (CHILD) with a larger sample size of 746 reported a significant association between pet exposure and enrichment of Oscillospira and Ruminococcus (Tun et al., 2017). Kim *et al.'s* review study concluded that early exposure to furred pets lowers the risk of atopy (having at least one positive skin test or allergen-specific IgE

test to multiple common allergens). At the same time, the effect may be mediated by microbial mechanisms (Kim et al., 2019).

3.4. Gut Microbiome Data

Currently, our understanding of the gut microbial composition is limited to our observations from the collected stool samples analyzed by High-throughput DNA sequencing tools. One common DNA based screening tool used for studying the gut microbiome is amplicon/marker gene-based sequencing and construction of amplicon sequence variants (ASVs), a method for normalizing the errors of the sequencing platforms and Polymerase Chain Reaction (PCR) (Callahan et al., 2017; Callahan et al., 2016; Eren et al., 2013; Tikhonov et al., 2015). This data processing step results in a count table of detected species per sample. The count data (ASV table) has several inherent challenges, such as over-dispersion (or skewness in percentage data) (Shestopaloff et al., 2018; Warton et al., 2012), within-sample negative correlation (Kumar et al., 2018; Mandal et al., 2015; Weiss et al., 2017), and a large number of zeros (Warton, 2005; Xu et al., 2015). Previous simulation studies revealed that statistical methods ignoring over-dispersion, and/or zero-inflation, and/or correlation might result in smaller standard errors, inflated type I errors, and false-positive findings (Brill et al., 2019; Warton et al., 2012).

3.5. Challenges in Analysis of Microbiome Studies

The choice of the method for statistical analysis depends on the properties of the data. The literature has shown that the human gut microbiome data have unique features that are needed to be considered in the statistical analysis to avoid erroneous conclusions about the data and uncertainty in research and practice (Kumar et al., 2018; Shestopaloff et al., 2018; Warton et al., 2012; Weiss et al., 2017). It is widely reported that an essential property of the human gut microbiome data is the high frequency of zeros, also known as zero inflation (Warton, 2005; Xu et al., 2015). The zero counts across samples could be due to either the limitations of sequencing technology in detecting the bacteria with low frequency or the actual absence in the origin environment. The excessive zeros in the data may cause overdispersion, a unique property of count data when the mean and variance of response variables are not equal (Perumean-Chaney et al., 2013). Studies showed that microbiome data have overdispersion, regardless of zero inflation

(Shestopaloff et al., 2018; Warton et al., 2012). Simulations showed that when zero inflation or overdispersion was ignored, parameter estimations were poor, statistically significant findings were missed, and type I error was inflated (Brill et al., 2019; Perumean-Chaney et al., 2013; Warton et al., 2012). Another property of human gut microbiome data is the biological dependency among different bacteria. Microbial co-occurrence network studies showed significant relationships within individual microbes in a healthy gut, leading to biological correlation among microbes (Faust et al., 2012; McGregor et al., 2019).

The conventional analysis methods in human microbiome studies are non-parametric (dis)similarity-based. A distance matrix is a two-dimensional symmetric matrix where all diagonal elements are zero and all positive off-diagonal values (Anderson, 2001). In this approach, the test statistic is obtained by calculating the sum of the squared distances among groups divided by the within-groups sum of squared distances using (dis)similarity matrix and a permutation-based p-value from an empirical distribution. Although many (dis)similarity-based methods are non-parametric, they still need to meet several assumptions (Anderson, 2001; Clarke & Ainsworth, 1993), which are not met by human gut microbiome data. To the best of our knowledge, each distance measure used in (dis)similarity-based methods fails to meet at least one of the properties of the human gut microbiome data (Shestopaloff, 2017; Shestopaloff et al., 2018).

Moreover, most of these methods do not capture the magnitude of the relationship between risk factors and microbiome composition. These limitations may result in incomplete or misleading findings. On the other hand, distribution-based methods are designed to accommodate challenging properties of the human microbiome data that (dis)similarity-based methods failed to address.

3.5.1. (Dis)Similarity-Based Approaches

(Dis)similarity-based approaches or non-parametric methods are prevalent in microbiome studies since they use distance measures to reduce the dimension of the data and permutation tests to detect between-group differences. The most common non-parametric methods are Analysis of Group Similarities (ANOSIM), a non-parametric procedure for testing differences between two or more groups based on a permutation test of among- and within-group similarities (Clarke &

Ainsworth, 1993), and ADONIS the non-parametric version of Permutation-Based Multivariate Analysis of Variance (PERMANOVA) (Anderson, 2001). As we mentioned before, assumptions underlying the use of distances are not always valid because of over-dispersion and zero-inflation features characteristic of microbiome data (Legendre & Legendre, 1998; Rivera-Pinto et al., 2017; Xia & Sun, 2017). Moreover, the simulations show that the permutation procedure is sensitive in detecting differences between groups of interest in the presence of over-dispersion (Anderson, 2001).

3.5.2. Model-Frame Approaches

Recently, many researchers have tried to address the limitations of (dis)similarity-based models by developing different model-frame approaches based on different statistical distributions. Parametric methods use various statistical distributions such as Gaussian, negative binomial, zero-truncated negative binomial, and logistic distributions to address microbiome data features correctly. General Linear Models and their multivariate extension (ManyGLM) (Warton et al., 2012), The Zero-Inflated Gaussian (ZIG) mixture model (Joseph N Paulson et al., 2013), Analysis of Composition of Microbiome (ANCOM) (Mandal et al., 2015), Zero-Inflated Negative Binomial (ZINB) model (Shestopaloff, 2017; Shestopaloff et al., 2018; Xu et al., 2015) are some examples of distribution-based data analysis approaches to microbiome data analysis. Although distribution-based methods deal with the properties of the human gut microbiome data in more sufficient ways than distance-based methods, they have limitations. ANCOM method proposed by Mandal *et al.* (Mandal et al., 2015) requires a certain user-specific threshold for the proportion of zeros to remove before the analysis and ignores overdispersion and within bacteria correlations. The Zero-Inflated Gaussian (ZIG) mixture model (Joseph N Paulson et al., 2013) and ZINB (Shestopaloff, 2017; Shestopaloff et al., 2018; Xu et al., 2015) models are designed to address the excess zeros in the dataset. However, ZIG ignores the overdispersion and within-bacteria correlations, whereas ZINB only ignores within-bacteria correlations. Wartan *et al.* (Warton et al., 2012) proposed the ManyGLM model on microbiome data using the negative binomial distribution for accounting for overdispersion and within-bacteria associations using resampling methods. However, ManyGLM does not adjust for the excess number of zeros in the dataset.

3.6. Objectives

The interest in potential biological and environmental factors associated with gut microbiome composition is becoming increasingly popular as it explains the complexity of biological systems. Microbial co-occurrence network studies showed significant relationships within individual microbes in a healthy gut, leading to biological correlation among bacteria (Faust et al., 2012; McGregor et al., 2019). Although there are debates on the validity of the co-occurrence network approaches in microbiome studies, the importance of taking biological associations into account in the statistical analysis step cannot be neglected (Hirano & Takemoto, 2019). Bayesian marginal models provide a possibility to study the potential factors associated with gut microbiome composition by taking all challenging properties of the data set into account. Although a wide range of statistical techniques is used in the human gut microbiome studies to address its unique properties, Bayesian marginal models remain poorly investigated.

We proposed two studies in the following chapters:
Study 1: Our objective was to analyze the behavior of conventional statistical methods that accommodate challenges of gut microbiome data, such as zero inflation, over-dispersion, and within-sample correlation.

Study 2: We proposed a Bayesian Marginal Zero-inflated Negative Binomial (BAMZINB) model, addressing complexities associated with zero-inflation and multivariate structure of microbiome data.

Chapter 4 : A Comprehensive Performance Comparison Study of Various Statistical Models that Accommodate Challenges of the Gut Microbiome Data

4.1. Introduction

The human gut microbiome includes trillions of symbiotic microbes that colonize the human gut after birth (Donaldson et al., 2016; Gilbert et al., 2018). The gut microbiota has an essential role in maintaining human health. For example, a lack of balance between commensal and pathogenic microorganisms has been shown to play a crucial part in the onset of certain diseases, such as autoimmune and allergic diseases (Mackay, 2020), colorectal cancer (Song et al., 2020), and metabolic disorders (Frazier & Chang, 2020). Factors that could influence disruptions in the human microbiome include the type of delivery (Azad et al., 2016; Meghan B. Azad et al., 2013; Boix-Amorós et al., 2019), formula feeding (Schack-Nielsen & Michaelsen, 2006), and exposure to antibiotics (Langdon et al., 2016), which all may also delay the maturation of normal gut microbiota. This disruption is formally referred to as dysbiosis and is associated with the development of various diseases (Carlson et al., 2018; Kudelka et al., 2016; Lopetuso et al., 2018; Loughman et al., 2020; Mohammadkhah et al., 2018; Schirmer et al., 2018; Sokol et al., 2017). Therefore, studying dysbiosis in gut microbiome composition offers evidence for early disease detection and intervention opportunities (Durack & Lynch, 2018). One of the critical goals in human gut microbiome studies is to identify potential biological and environmental factors associated with dysbiosis in human gut microbiome composition.

Stool samples analyzed by high-throughput DNA sequencing technologies provide a snapshot of the gut microbial community composition. One common DNA-based screening tool used to study the gut microbiome is amplicon sequence variants (ASVs) resolved based on the 16S

rRNA gene. ASV construction is a method for normalizing the errors of the sequencing platforms and Polymerase Chain Reaction (PCR) (Callahan et al., 2017; Callahan et al., 2016; Eren et al., 2013; Tikhonov et al., 2015). This data processing step results in a count table of detected species per sample. Although ASV construction has provided us with new insights regarding the human gut microbial community dynamics, the count data (ASV table) has several inherent challenges, such as over-dispersion (or skewness in percentage data) (Shestopaloff et al., 2018; Warton et al., 2012), within-sample negative correlation (Kumar et al., 2018; Mandal et al., 2015; Weiss et al., 2017), and a large number of zeros (Warton, 2005; Xu et al., 2015). Previous simulation studies revealed that statistical methods ignoring over-dispersion, and/or zero-inflation, and/or correlation might result in smaller standard errors, inflated type I errors, and false positive findings (Brill et al., 2019; Warton et al., 2012). Appropriate statistical models are necessary to measure the effect of risk factors on the gut microbial community while addressing specific challenges inherent to the ASV counts (Shankar, 2017).

Beta diversity in microbiome studies refers to the difference in community structure between samples or groups (Gilbert & Lynch, 2019). The most common statistical methods in microbiome studies to find significant differences in beta diversity are the (dis)similarity-based methods (Xia et al., 2018). These methods come with significant limitations. The choice of (dis)similarity metric is subjective. Various parameters have different power levels, and some metrics cannot detect subtle changes. Another significant limitation is that metric-based methods cannot quantify the magnitude of the association between the covariates and the microbiome composition (Chen & Li, 2013). Additionally, (dis)similarity-based methods showed weak performance in the presence of overdispersion and zero inflation (McMurdie & Holmes, 2013; Joseph N Paulson et al., 2013). These challenges remain the same, even after converting counts to percentages. Simulations showed that applying transformation or normalization methods to converted percentages cannot adequately address the over-dispersion problem, primarily due to rare species (Warton et al., 2012). To the best of our knowledge, each (dis)similarity measure fails to meet at least one microbiota data challenge (Brill et al., 2019; Mandal et al., 2015; Warton et al., 2012).

Recently, many researchers have tried to address the limitations of (dis)similarity-based models by developing model-frame methods. Some examples of parametric model-frame data analysis

include General Linear Models and their multivariate extension (ManyGLM) (Saidi-Mehrabad et al., 2020; Warton et al., 2012), Zero-Inflated Gaussian (ZIG) mixture model (Joseph N Paulson et al., 2013), and Zero-Inflated Negative Binomial (ZINB) model (Mandal et al., 2015; Shestopaloff, 2017; Shestopaloff et al., 2018; Xu et al., 2015). In section *4.2.1* of this chapter, we presented a summary of a number of widely used model-frame methods employed in multivariate and univariate analyses of gut microbiome count data.

Our objective was to analyze the behavior of conventional statistical methods that accommodate challenges of gut microbiome data, such as zero inflation, over-dispersion, and within-sample correlation. We performed a comprehensive simulation study of 27 different scenarios measuring Mean Squared Error (MSE) and statistical power. The rest of the paper is organized into methods, including a description of the simulation study and a real microbiota study application, followed by a results section, including simulations and real data findings, and a discussion section.

4.2. Methods

4.2.1. Review of the Selected Model-Frame Methods

ManyGLM approach proposed by Warton *et al.* (Warton et al., 2012) fits separate univariate negative binomial models for each ASV. It uses likelihood ratio statistics to measure the strength of between-group effects. In microbiome data, we have a large number of outcomes, leading to a large number of univariate negative binomial models and inflation in type I error. ManyGLM models addressed this problem by summing the test statistics and using resampling to test the significance of the multivariate test statistic. This method can handle over-dispersion and correlation between samples appropriately. However, it does not use a zero-inflated adjustment (Brill et al., 2019). These limitations increase the risk of false-positive findings.

The Zero-Inflated Gaussian (ZIG) mixture model proposed by (Joseph Nathaniel Paulson, M Pop, et al., 2013; Joseph N Paulson et al., 2013) follows two steps: (i) normalization; (ii) fitting a zero-inflated log-normal model for each specific outcome (ASV) separately. Simulation studies showed that performing transformation or normalization methods on the microbiome data cannot

address the over-dispersion problem adequately, mainly if the data contains rare species (Warton et al., 2012). Moreover, transformations and standardization methods used as one of the first steps to address sampling biases and library size in microbiome data can change the correlation patterns among ASVs leading to a significant impact on the downstream analyses (Badri et al., 2018). Additionally, ZIG fits a zero-inflated log-normal model for each ASV separately, failing to address within-sample correlation.

The univariate Zero-Inflated Negative Binomial (ZINB) model considers two possible data generation processes for each observation. It uses a binary distribution in the first part to model covariates against zeros or positive values (1 for zeros and 0 for positive values), then fits a negative binomial model for each outcome that includes zeros in the datasets. The main limitation of this method is the restriction of analysis at the univariate level. Shestopaloff et al. (2018) fitted a ZINB model on the presence/absence data using a single OTU at a time. Xu et al. (2015) also fitted the ZINB model on the count microbiome data using an individual bacterium at a time to compare different models that consider zero inflation in their algorithm (Xu et al., 2015).

4.2.2. Simulation study design

4.2.2.1. Data Generation

Microbiome-based studies usually collect more than one outcome. Analyzing multiple outcome variables at the same time is of interest because of the biological within-sample correlation among microbiomes. To do so, several approaches have been introduced. Some approaches evaluate the joint distribution of outcomes using the product of marginal distributions of each outcome or by conditioning one of the others. Copulas are widely used to combine marginal distributions. Copula-based approaches have been frequently utilized to account for the dependence of multiple variables (Kürüm et al., 2018; Smith et al., 2010). There are many copula functions in the literature. The main difference among them is the range of the correlation coefficients. The Gaussian copula has almost the maximum (−1,1) range and was previously reported as a robust copula for most applications (Xue-Kun Song, 2000). Moreover, the Gaussian copula has an attractive property that, as the number of outcomes, p, grows, the amount of

multivariate density parameters also rises in the order p^2, which is the minimum, compared to the other copulas. More advantages of Gaussian copula-based models have been discussed (Embrechts et al., 2001; Trivedi & Zimmer, 2007).

This study used Gaussian Copula to accommodate the correlation among outcome variables. The Gaussian copula conveniently describes a complex relationship (Song et al., 2009).Let Y_1 and Y_2 represent two outcomes random variables, the Gaussian copula function is

$$C(Y_1.Y_2;\rho) = \phi(\phi^{-1}(Y_1).\phi^{-1}(Y_2);\rho) = \int_{-\infty}^{\emptyset^{-1}(Y_1)} \int_{-\infty}^{\emptyset^{-1}(Y_2)} \frac{1}{2\pi(1-\rho^2)^{1/2}} \left\{ \frac{-(s^2 - 2\rho st + t^2)}{2(1-\rho^2)} \right\} dsdt \quad (1)$$

where ϕ is the standard normal cumulative distribution function. The copula we consider here is extended for p outcomes $C\left(Y_1.Y_2 \ldots . Y_p;\rho\right) = \phi\left(\phi^{-1}(F(y_1)).\phi^{-1}(F(y_2)). \ldots . \phi^{-1}\left(F(y_p)\right);\rho\right)$, where $F(y_j); j = 1. \ldots . p$, are the zero-inflated negative binomial cumulative distribution functions.

The zero-inflated negative binomial distribution of a single variable can be written as:

$$p(y=0) = \alpha + (1+\alpha)\left(\frac{\theta}{\mu+\theta}\right)^{\theta} \qquad y = 0$$

$$p(y>0) = (1-\alpha)\left(\frac{\Gamma(y+\theta)}{\Gamma(\theta)\Gamma(y+1)}\right)\left(\frac{\theta}{\mu+\theta}\right)^{\theta}\left(1-\frac{\theta}{\mu+\theta}\right)^{y} \qquad y = 1,2,3,\ldots \quad (2)$$

where $0 < \alpha < 1$ is the probability of an extra zero response, μ is the mean and θ^{-1} is the over-dispersion parameter in the negative binomial distribution. Data generation R code is available in the supplementary material. Given the zero-inflation and over-dispersion in the gut microbiome count data, we reason that zero-inflated negative binomial distribution and Gaussian Copula to incorporate correlation represent the most useful option for data generation.

4.2.2.2. Simulation Parameters

The simulation process includes 27 different scenarios based on the following assumptions: 1) the intensity of over-dispersion (i: θ =0.75 as low, ii: θ =0.3 as medium, and iii: θ =0.1 as high

over-dispersion); 2) the correlation among the response variables (i: ρ=0.2 as low, ii: ρ=0.5 as medium, and iii: ρ=0.8 as high correlation); and 3) the amount of zero-inflation (i:α =0.3 as low, ii: α =0.5 as medium, and iii: α =0.7 as high extra zeros probabilities). The result tables are color-coded as *green* for *low*, *yellow* for *medium*, and *red* for *high* to increase the readability of the table. There was only one binary covariate defined as an indicator of the exposed group, and the probability of a subject coming from the exposed group was set at 50%. We generated 500 subjects and 300 response variables for each simulation scenario.

4.2.2.3. Simulation Steps

Each simulation scenario consisted of the following steps: 1) take 500 random samples from each dataset, with replacement; 2) fit all models; 3) extract and store parameter estimates (slopes), and p-values, 4) compare parameter estimates with the true value β=2 and repeat previous steps for 100 times.

4.2.3. Software and Packages

All statistical analyses were performed in R version 3.6.1 using the phyloseq package (McMurdie & Holmes, 2013) for data preparation, metagenomeSeq package (Joseph Nathaniel Paulson, Mihai Pop, et al., 2013) for the ZIG model, mvabund package (Y. Wang et al., 2020) for ManyGLM model, pscl package (Jackman et al., 2015) for univariate ZINB model. Simulation datasets were generated by using copula (Hofert et al., 2014), mnormt (Azzalini, 2020), and ZIM packages (Yang et al., 2018).

4.2.4. Real microbiome studies applications

ASVs were generated from raw archived sequences with the aid of DADA2 ("High-resolution sample inference from Illumina amplicon data") implemented in the Quantitative Insights into Microbial Ecology (QIIME 2™) pipeline (Bolyen et al., 2019; Callahan et al., 2016). ASVs were assigned to taxonomy via a Naive Bayes classification algorithm using Silva (version 132) as the

reference database from the 515F/806R region of the reference sequences (Quast et al., 2012). The quality filtering threshold based on expected errors was set to 5, and the reverse sequence read length was truncated to 110. The maximum number of reads was used for training the error model. We reported the average abundance difference for Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria at the Phylum level. Laursen et al. study on SKOT Cohorts showed that these four phyla categories were the most dominant groups covering 95% of the data (Laursen et al., 2016). In addition, we extended our investigation to include Actinobacteria, Bacteroidia, Bacilli, Gammaproteobacteria, and Alphaproteobacteria at the Class-level for infants born to healthy mothers and obese mothers from 9 months to 18 months.

The distribution of zeros is shown in supplementary figure 2-1. We used the mean vs. variance graph implemented in the "mvabund" package (Y. Wang et al., 2020) in R. This method was suggested in the Warton et al. (Warton et al., 2012) study to show the overdispersion in supplementary 2-2 in the supplementary material. A positive slope confirms the existence of overdispersion. ICC was calculated using the "ICCbare" function in the "ICC" package in R (Wolak & Wolak, 2015).

4.2.4.1. Application of SKOT Cohorts Data

We used SKOT Cohorts (I and II) to compare three models based on the real-life dataset. SKOT Cohorts include two studies, SKOT I and SKOT II. SKOT is the Danish abbreviation for "Dietary habits and wellbeing of young children." The main goal of SKOT studies was to investigate the relationship between obesity and metabolic syndrome with early diet and growth development. SKOT I included 311 single birth full-term infants with no chronic illness at nine months ±2 weeks of age. All infants' fecal samples were taken at nine months and the second visit at 18 months. SKOT II included 184 infants from obese pregnant mothers who participated in the TOP study (Renault et al., 2014) (Treatment of Obese Pregnant Woman at Hvidovre Hospital in the Copenhagen area) with the same inclusion criteria as the SKOT I study. Similar to SKOT I study, infants in SKOT II studies were examined at 9 (±2 weeks) months and 18 (±4 weeks) months (Laursen et al., 2016). In this study, Sequenced reads and infants' age were downloaded from the National Center for Biotechnology Information (NCBI) with the accession

number SRP052851. We used 465 individuals in the SKOT I and SKOT II study to compare the abundance of specific bacteria at the Phylum and Class levels between healthy and obese mothers at nine months and 18 months.

4.2.5. Performance comparison measures

This study used 27 different simulation scenarios and a real microbiota dataset to compare MSE and power for different statistical methods. The MSE was calculated for ManyGLM, univariate-ZINB, and ZIG models as the average squared difference between the true value (β=2) and its estimate across 100 bootstraps in each scenario. The lower MSE indicates a better estimate for the average change of the outcome variable (Trikalinos et al., 2013).

We fitted ManyGLM, ZIG, and univariate-ZINB models to assess the effect of maternal obesity on the infants' gut microbiome for Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria at the Phylum level and for Actinobacteria, Bacteroidia, Bacilli, Gammaproteobacteria, and Alphaproteobacteria at the Class-level at nine months and 18 months assessments, separately.

4.3. Results

4.3.1. Simulation Study Results

4.3.1.1. Mean Square Error (MSE)

Table 4-1 shows the proportion of observing the lowest MSE among 300 outcome variables in each scenario. Simulation results showed that at low zero-inflation when the within-response correlation is medium, and overdispersion is low/or high, the ZIG model outperformed other methods (scenarios 2 and 8). On the other hand, at the low level of zero inflation and any combination of other challenging situations (scenarios 1-9, except 2 and 8), the univariate ZINB model had a better performance. Moreover, when the zero inflation was at the medium level (scenarios 10-18), the overdispersion was low with low/or medium correlation (scenarios 10-11) ManyGLM and univariate ZINB models showed similar performance compared to ZIG. For

scenarios 12 to 18 (except 15), univariate ZINB models outperformed other methods. The ZIG method also had almost the same performance as univariate ZINB when the correlation was high, while other parameters were at the medium level (scenario 15). At the highest level of zero inflation, when overdispersion was low and correlation was either low, medium, or high, the ZIG model (scenarios 19-21) outperformed other methods. However, when zero inflation was high and overdispersion was medium at all three different levels of correlation (low, medium, and high), univariate ZINB model (scenarios 22-24) outperformed other methods.

Additionally, when zero inflation and overdispersion were high and correlation was low (scenario 25), univariate-ZINB and ZIG models performed the same and better than ManyGLM. When the correlation levels changed to medium, univariate-ZINB had the lowest MSE among all methods tested. ManyGLM showed a better performance when all properties were at their highest level. Generally, univariate ZINB was the best option in 63% (17/27) of scenarios. These results showed the importance of accounting for the properties of the dataset in microbiome data analysis and how the mean square error is impacted.

Table 4-1: The proportion of observing the lowest mean square error (MSE) among 300 response variables in each scenario

Scenario	Zero-inflation	Over-dispersion	Correlation	The proportion of observing the lowest MSE % for each method		
				ManyGLM	Univariate-ZINB	ZIG
1	0.5	0.75	0.2	7%	***52%***	41%
2	0.5	0.75	0.5	24%	19%	***57%***
3	0.5	0.75	0.8	2%	***61%***	37%
4	0.5	0.30	0.2	2%	***97%***	1%
5	0.5	0.30	0.5	1%	***95%***	3%
6	0.5	0.30	0.8	9%	***89%***	3%
7	0.5	0.10	0.2	7%	***91%***	2%
8	0.5	0.10	0.5	9%	28%	***62%***
9	0.5	0.10	0.8	1%	***79%***	20%
10	0.7	0.75	0.2	***49%***	***44%***	7%
11	0.7	0.75	0.5	***45%***	***51%***	4%
12	0.7	0.75	0.8	--	***67%***	33%
13	0.7	0.30	0.2	7%	***89%***	4%
14	0.7	0.30	0.5	4%	***72%***	24%
15	0.7	0.30	0.8	1%	**45%**	***54%***
16	0.7	0.10	0.2	26%	***53%***	20%
17	0.7	0.10	0.5	17%	***64%***	20%
18	0.7	0.10	0.8	15%	***75%***	11%
19	0.9	0.75	0.2	22%	29%	***49%***
20	0.9	0.75	0.5	15%	2%	***83%***
21	0.9	0.75	0.8	6%	14%	***80%***
22	0.9	0.30	0.2	2%	***94%***	4%
23	0.9	0.30	0.5	6%	***85%***	9%
24	0.9	0.30	0.8	11%	***83%***	6%

25	0.9	0.10	0.2	11%	***47%***	***42%***
26	0.9	0.10	0.5	5%	***68%***	27%
27	0.9	0.10	0.8	***71%***	18%	11%

Zero-inflation: 0.5= ”Low”, 0.7= ”Medium”, 0.9= ”High”

Overdispersion: 0.75=”Low”, 0.30=”Medium”, 0.1=”High”

Correlation: 0.2=”Low”, 0.5=”Medium”, 0.8= “High”

4.3.1.2. Statistical Power

Figure 4-1 displays statistical power, specifically the frequency of rejecting the null hypothesis at different thresholds across 100 bootstrap samples in each scenario. Simulation results showed that the ZIG model had the highest power compared to ManyGLM. However, in three scenarios (8, 17, and 26) where the correlation was medium and over-dispersion was high (at various levels of zero inflation), ManyGLM and ZIG showed similar statistical power at various thresholds.

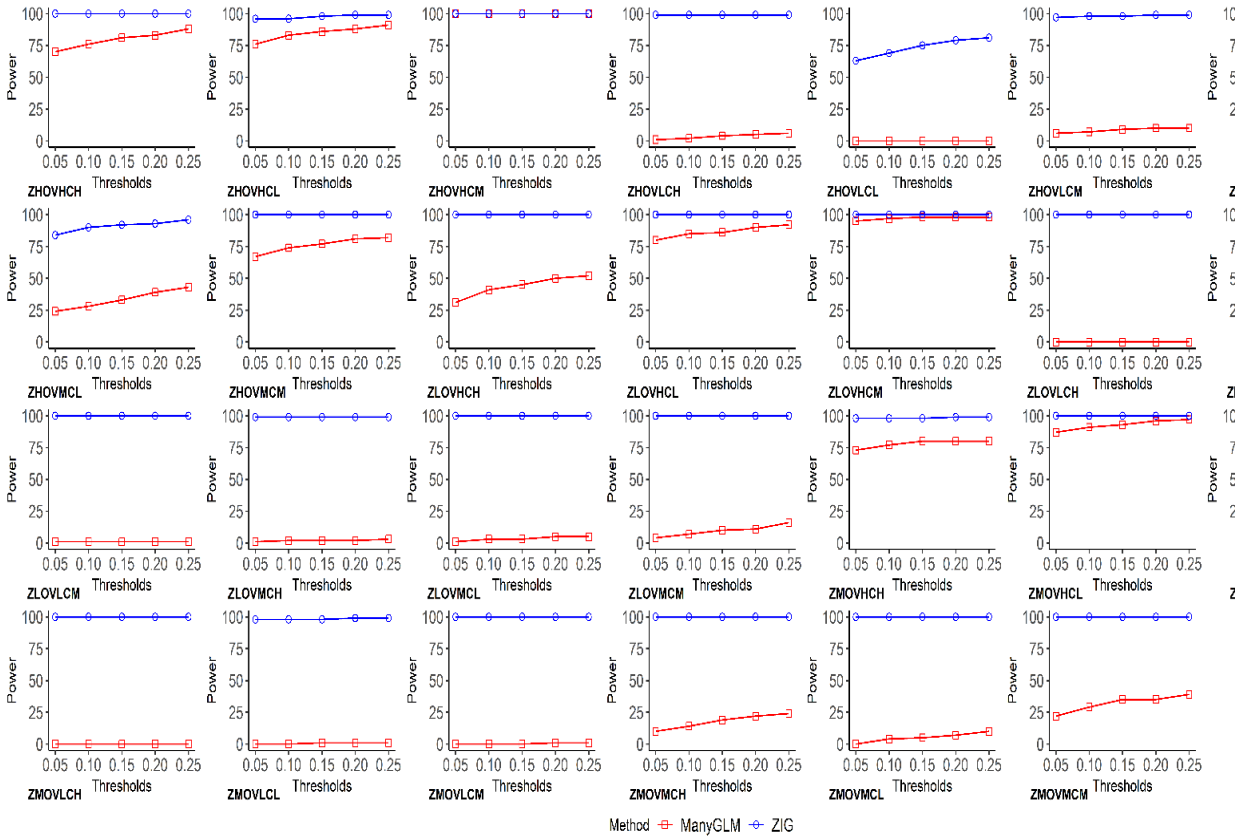

Figure 4-1: This figure shows the statistical power of the simulation study

4.3.2. Real Microbiota Study Results

Table 4-2 shows the effect size (SD) for the average abundance change between infants born to obese mothers and healthy mothers at nine months and 18 months. The comparison results showed that the abundance of Bacteroidetes was lower for infants born to obese mothers at both 9- and 18-months assessment. In addition, the abundance of Firmicutes was lower for infants born to obese mothers at 18 months of assessment. On the contrary, Phylum-level results showed that the abundance of Proteobacteria was higher in infants with obese mothers at both 9 and 18 months. At the Class level, the abundance of Bacteroidia and Bacilli was lower for nine-month infants from obese mothers than healthy mothers. In comparison, the abundance of Gammaproteobacteria was higher for 18 months infants from obese mothers. The distribution of zero values and over-dispersion for ASVs in Phylum- and Class-levels were presented in supplementary figures 2-1 and 2-2.

Table 4-2: The effect size (SD) for the average abundance difference between obese and healthy mothers at nine months and 18 months at the taxon level

Data/Levels	At 9 months			At 18 months		
	ZIG	Univariate-ZINB	ManyGLM	ZIG	Univariate-ZINB	ManyGLM
Phylum						
Actinobacteria	-0.093	-0.073	-0.073	-0.01	0.009	0.009
	(0.132)	(0.044)	(0.044)	(0.133)	(0.018)	(0.018)
Bacteroidetes	-0.987	-0.406	-0.389	-0.364	-0.743	-0.668
	(0.156)*	(0.351)	(0.344)	(0.139)	(0.195) *	(0.21) *
Firmicutes	-0.016	0.19	0.19	-0.077	-0.315	-0.315
	(0.132)	(0.132)	(0.132)	(0.133)	(0.126) *	(0.126)
Proteobacteria	0.62	0.418	0.418	0.405	0.203	0.203
	(0.132) *	(0.152) *	(0.152)	(0.133) *	(0.141)	(0.141)
Class						
Actinobacteria	-0.012	0.009	0.009	-0.092	-0.073	-0.073
	(0.132)	(0.018)	(0.018)	(0.132)	(0.044)	(0.044)
Bacteroidia	-0.492	-0.743	-0.668	-1.017	-0.406	-0.389
	(0.138) *	(0.195) *	(0.21) *	(0.156)	(0.351)	(0.344)
Bacilli	0.386	-0.173	-0.309	-0.309	-0.086	0.198
	(0.269)	(0.132) *	(0.126)	(0.126)	(0.132)	(0.132)
Gammaproteobacteria	0.335	0.218	0.22	0.708	0.423	0.419
	(0.132)	(0.161)	(0.161)	(0.132)	(0.159) *	(0.16) *
Alphaproteobacteria	0.408	0.119	0.108	0.124	0.479	0.386
	(0.139)	(0.182)	(0.198)	(0.151)	(0.254)	(0.269)

*P<0.05

These findings show contradictory results between negative binomial distribution-based and Gaussian distribution-based models. Although effect sizes are almost the same for univariate-

ZINB and negative binomial ManyGLM models, they estimated different p-values. One reason for this phenomenon is the capability of ManyGLM to handle the correlation between samples by using multiple testing techniques discussed in Westfall & Young 1993 to control for family-wise error rates (Westfall & Young, 1993). ManyGLM is also capable of assessing the effect of covariates on the entire composition at the community level at the same time using the "PIT-trap" model-free bootstrap procedure (Warton et al., 2017). We suggest using ManyGLM over univariate-ZINB or univariate-NB based on the advantages mentioned above of NB-based MangGLM. ZIG is a Gaussian distribution-based model that contains two steps, including a cumulative-sum scaling normalization method to adjust issues with sequencing depth and a zero-inflated Gaussian mixture model to assess the effect of covariates on microbiome at the taxon level (Joseph Nathaniel Paulson, M Pop, et al., 2013; Joseph N Paulson et al., 2013). Badri *et al.* indicated that normalization methods, as the first step of analysis for microbiome data, could change the primary correlation pattern among ASVs (Badri et al., 2018). In addition, Warton *et al.* study showed that applying normalization or other forms of transformations to the microbiome data cannot accurately address the mean-variance associations (Warton et al., 2012). Another drawback of using ZIG with the cumulative-sum scaling normalization method is the obligation of adding a pseudocount to the count data prior to estimating the scaling factor to avoid log(0) (Weiss et al., 2017). The nonlinear nature of the Log transformation can change the original distribution of the microbiome data after adding a small pseudocount (Costea et al., 2014; Paulson et al., 2014). In our study, we use 0.001 as a pseudocount for ZIG which could be a reason why it showed different results compared to univariate-ZINB and NB-based ManyGLM.

4.4. Discussion

Many statistical methods have been developed in the literature to compare the changes in the community structure between groups of interest. Some of these methods take the underlying nature of the human gut microbiome data and its unique features into account for analysis. Our study provided evidence about the analytical challenges of gut microbiome data and reviewed the three distribution-based models capable of measuring the effect of covariates on the

individual bacteria or the entire microbial community. Rather than aiming for the best method available for studying the effect of a covariate on taxon abundance, we assessed the performance of three methods under various simulated scenarios and a real dataset. We showed that methods such as ManyGLM, which can handle microbiome data challenges without requiring any normalizations or transformation, are better choices for finding taxon abundance differences between groups of interest, also known as beta diversity, at both community and taxon levels.

A critical question in data analysis is how to choose the appropriate method for every specific study. Sound statistical methods could reduce the risk of false discoveries and help identify the microbial features that discriminate between healthy and unhealthy infants in early life, which allows the scientific community to pursue promising avenues of research and take adequate interventions to prevent diseases in adulthood. We designed a comprehensive simulation study to compare different methods based on MSE for individual bacteria analysis and statistical power for the entire microbiome composition. In addition, we used open-access real data to compare methods at different taxonomic levels.

The microbiome literature has shown that all methods try to scale the variations in one taxon or ASV compared with others. (Dis)similarity-based methods showed improper scaling decisions, leading to misinterpretations and failure to detect differences between groups. On the contrary, it has been shown that Generalized Linear Models (GLMs) can handle mean-variance relationships, zero-inflation, and within-sample correlations in microbiome data (Brill et al., 2019; Shestopaloff, 2017; Warton et al., 2012; Xu et al., 2015). Rather than transforming data to fit the model's assumptions, we should make an effort to understand the underlying structure of microbiome data by adapting an existing method to address statistical assumptions called by the data.

According to our study, some methods can detect the significant risk factors at the community level, whereas others answer the same question at the ASV (or taxon) level. One of the strengths of this study was that we looked at both levels separately in one study. We compared methods based on MSE, calculated by subtracting the estimated effect size from the true value for each ASV level. One reason for choosing MSE was the fact that the effect size in the univariate level analysis was not affected by the within-sample correlation. Therefore, when the analysis was at

the ASV level, univariate-ZINB performed better than the other methods. In contrast, statistical power was considered the comparison criteria at the community level, where standard error and p-values are affected by ignoring within-sample correlation.

In this study, the simulation and real-data application results showed that the univariate-ZINB and ManyGLM models are better options depending on the goal of the study. In addition, ZIG was more prone to convergence issues in the presence of many zeros in the dataset. Further studies need to focus on the methods that can take all of the microbiome data challenges into account and generate unbiased effect sizes with sufficient statistical power.

4.5. Conclusions

Studying dysbiosis in gut microbiome composition helps with the early detection of the disease. It utilizes an appropriate intervention while choosing a proper statistical method, therefore preventing misleading clinical findings and interventions. In a comprehensive comparison study, we have discussed a common problem with the existing methods; more specifically, some of these methods ignore important characteristics of the microbiome datasets. This study showed that some of the more recent methods could accommodate the challenges in the microbiome data without requiring data transformation or normalization.

Chapter 5 : Human Gut Microbiome Data: A Bayesian Marginal Zero-inflated Negative Binomial Regression Model for Multivariate Analyses of Count Data

5.1. Introduction

The advent of high throughput sequencing technologies in parallel with substantial advances in computational, molecular, and quantitative fields has opened new avenues in our understanding of trillions of microbes that call the human intestine home (termed as "human gut microbiome") (Aagaard et al., 2014; Dominguez-Bello et al., 2019; Fan & Pedersen, 2021; Hatzenpichler et al., 2020). In vitro and in vivo studies have shown that the human gut microbiome shape shortly after birth mainly via transmission from the maternal microbial pool (vagina, gut, skin, or breastmilk) and continues to develop until it becomes mature two to three years after the initial colonization (Koo et al., 2020; Milani et al., 2017; Van Daele et al., 2019; S. Wang et al., 2020). Any changes that could disrupt the stability of the healthy gut microbiome, particularly at the early stages of life, could result in severe dysbiosis, which could pave the path for major health issues in adulthood (Cheng et al., 2019; Dogra et al., 2020; Sanders et al., 2021).

For instance, dysbiosis in newly colonized microbes of an infant's gut could result in disorders such as failure to thrive, which have a negative impact on child growth (Robertson et al., 2019). Necrotizing enterocolitis is another common intestinal disease associated with early life dysbiosis, severe intestinal inflammation, and irritable bowel diseases (Ivashkin et al., 2021). Furthermore, a study conducted by Ivashkin and colleagues on patients with irritable bowel syndrome (IBS) showed a link between alteration in the gut microbial community and disruption of the pro-inflammatory, anti-inflammatory cytokines and tight junction proteins expression (Castaner et al., 2018). IBS and some diseases associated with intestinal inflammation are

believed to be one of the long-term side effects of early gut dysbiosis (Turroni et al., 2022). Another prime example of the effect of early gut dysbiosis, which appears later on in life, is obesity (Baothman et al., 2016). A study conducted by Kasai and colleagues showed higher diversity in bacteria in obese individuals compared to non-obese individuals (Kasai et al., 2015). An increase in the abundance of specific microbial taxa has heavily influenced the biological activity of neutrophils, lymphocytes, antigen-presenting cells, and T and B cells (Wu & Wu, 2012). As a result of such substantial influence of the gut microbiome over the human immune system, diseases such as atopy (Petersen et al., 2021), rheumatoid arthritis (Manasson et al., 2020), and nervous system's demyelination-related pathologies (Ma et al., 2019), or Crohn's disease and ulcerative colitis (Liu et al., 2021), have all been suspected to be triggered by changes in gut microbial community structure.

While innovations in next-generation sequencing (NGS) technologies decipher the relationship between the dynamic changes in the human microbiome and various diseases through 16s ribosome RNA gene sequencing or shotgun metagenomics sequencing, the development of statistical methods in microbiome research has not kept up with the same pace. Recent NGS technologies offer a massive amount of sequence reads that provide information about species or bacteria with high resolution (Segata et al., 2012). The statistical methods use this information to assess how species or bacteria are associated with environmental conditions or subjects' characteristics. Microbial abundance can be affected by various confounders. Adjusting for confounders is crucial for a more accurate differential abundance analysis. Furthermore, there may be a clinical need to quantify the association between the microbiome and these confounders (Chen et al., 2021; Kinross et al., 2011; Maier et al., 2018; Zhu et al., 2018). Current literature shows that the analysis of microbial data is complicated due to inherited characteristics of microbiome count data, such as over-dispersion, zero inflation, and fluctuating library size. Fortunately, some of these challenges have been widely studied in the context of microarray and single-cell RNA analysis. For example, library size is suggested to be controlled by implementing a complex normalization technique into the classic Negative Binomial (NB) model, a well-known model for handling over-dispersion. This can be found in R packages such as edgeR (Chen et al., 2014) and DESeq2 (Anders & Huber, 2010; Anders et al., 2013). Another example is implementing a zero-inflated Gaussian mixture model (Zhang et al., 2020) in the metagenomes package to accommodate zero-inflated data in the analysis. Although these tools

seem useful for microbiome data analysis, the assurance of generating precise and unbiased results when utilizing such methods depends on the sample size and multivariate correlation structure of the microbiome data. The common solution for the dimensionality issue in such tools is the utilization of dimension reduction methods and dissimilarity matrices (i.e., principal component or partial least squares). However, relevant information could be lost by selecting a pre-specified number of eigenvalues or factors.

Another set of RNA-seq analysis methods has been recently adapted to microbiome studies. These methods address the dimensionality issue using Markov chain Monte Carlo (MCMC) algorithms. Glmfit function in edgeR package and bglm function in BhGLM package (Yi et al., 2019) are two examples of such tools in genome data analysis. Glmfit function can generate effect sizes for each bacterium as well as the whole microbiome composition (for ecological studies), estimating one common over-dispersion term and adjusting for library size. On the contrary, bglm function is limited to only univariate analysis, generating the result for each bacterium at a time with the estimation of an over-dispersion term per bacterium and adjusting for library size. However, both tools use the classic NB model, therefore not addressing the current zero-inflation issue in the analyses.

Geert Molenberghs and Geert Verbeke discussed mariginal models for discrete longitudinal data and their strength (Geert Molenberghs, 2010). We propose a Bayesian Marginal Zero-inflated Negative Binomial (BAMZINB) model, addressing complexities associated with zero-inflation and multivariate structure of gut microbiome data described above. Our modeling construction includes several advantages. First, BAMZINB can generate results for individual bacterium and the entire microbiome composition. Second, it incorporates zero inflation, over-dispersion, fluctuating library size, and multivariate correlation structure of the microbiome data using the generalized linear model framework. Last, it models the heterogeneity among subjects via a random intercept component. More specifically, the BAMZINB model can perform the differential abundance analysis of responses one by one, focusing on the relationship of interest and simultaneously controlling for the microbiome data's multivariate correlation structure.

As we proceed, the material and method section will further describe the details of the BAMZINB method, the extensive simulation study, and the application of the SKOT Cohorts data (Laursen et al., 2016; Laursen et al., 2017; Laursen et al., 2015a). The results and discussion sections will present the results of simulations and real data application in terms of performance

criteria such as absolute relative bias (ABR) and deviance. An application of BAMZINB compared to glmFit and bglm will be illustrated on data from the SKOT Cohorts study.

5.2. Methods and Materials

5.2.1. Bayesian Marginal Zero-inflated Negative Binomial (BAMZINB)

5.2.1.1. The Joint Zero-inflated Negative Binomial Distribution

Multivariate models are used to accommodate multiple correlated outcomes via statistical model that jointly represents relationships between outcomes and predictors. A broad objective of joint modeling is to provide a framework to ensure valid inferences by accounting for the correlation among the outcome variables. Let Y_1 and Y_2 be random variables representing correlated measurements. While we restrict attention to the case of two outcomes, an extension to a higher dimension is straightforward. In the zero-inflated negative binomial regression model, the objectives are to identify significant factors influencing the zero-inflation count of the bacteria and determine the extent of the effect of potential biological and environmental factors on the mean count of a specific bacteria. Let's assume that Y_1 and Y_2 follow the zero-inflated negative binomial distribution (Eq 1):

$$\begin{cases} p(y=0) = \alpha + (1+\pi)\left(\frac{\theta}{\mu+\theta}\right)^{\theta} & y = 0 \\ p(y>0) = (1-\pi)\left(\frac{\Gamma(y+\theta)}{\Gamma(\theta)\Gamma(y+1)}\right)\left(\frac{\theta}{\mu+\theta}\right)^{\theta}\left(1-\frac{\theta}{\mu+\theta}\right)^{y} & y = 1,2,3,\ldots \end{cases} \quad (1)$$

where $0 < \pi < 1$ is the probability of an extra zero response, μ is the mean and θ^{-1} is the dispersion parameter in the negative binomial distribution. The joint distribution of Y_1 and Y_2 across all *n* samples based on equation 1 is (Preisser et al., 2016):

$$f(\boldsymbol{Y}|\pi.\theta) = \prod_{i=1}^{2}(\prod_{j=1}^{n_i}\left[\pi_i + (1-\pi_i)\left(\frac{\theta_i}{\mu_i+\theta_i}\right)^{\theta_i}\right] I(y_{ij} = 0)\prod_{j=1}^{n_i}\left[(1-\pi_i)\left(\frac{\Gamma(y_{ij}+\theta_i)}{\Gamma(\theta_i)\Gamma(y_{ij}+1)}\right)\left(\frac{\theta_i}{\mu_i+\theta_i}\right)^{\theta_i}\left(1-\frac{\theta_i}{\mu_i+\theta_i}\right)^{y_i}\right] I(y_{ij}>0)) \quad (2)$$

where $\mathbf{Y}=(Y_1, Y_2)$, $\pi_i = (\pi_1, \pi_2)$, $\mu_i = (\mu_1, \mu_2)$ is the mean and $\theta_i = (\theta_1, \theta_2)$. Lambert (Lambert, 1992) and Mullay (Mullahy, 1986) proposed a model for excess zeros and Poisson (or negative binomial) process:

$$logit(\pi_i) = \acute{Z}\alpha \text{ and } Log\,(\mu_i) = \acute{X}\beta \qquad i = 1.2 \quad (3)$$

where Z_{ij} and X_{ij} are the covariates vectors for the j-th individual of the i-th outcome for each process, respectively. In practice, both processes often have the same vector of variables (Z_{ij}=X_{ij}), but not necessarily all the time.

5.2.1.2. Marginal Zero-inflated Negative Binomial (MZINB)

Marginalized zero-inflated count response models are useful when the overall mean of specific bacteria $\mu_i = E[Y_i]$ is of primary interest while $\boldsymbol{\alpha}= (\alpha_0, \alpha_1, \alpha_2)$ models the excess zeros and $\beta = (\beta_0, \beta_1, \beta_2)$ vector represents the overall effect of covariates on the specific bacteria (Martin & Hall, 2017; Preisser et al., 2016). In other words, $\exp(\beta_j)$ represents the multiplicative increase in the mean count for bacteria in the overall population corresponding to a one-unit increase in the covariate x_{ij}. A Multivarite Zero-Inflated Negative Binomial (MZINB) regression model likelihood function for estimation of the (p+q)-vector of distinct parameters (α, β) is introduced within a likelihood framework of one single outcome Y as follows:

$$p(Y|\alpha.\beta.\pi) = \prod_{y_i=0} p(Y=y_i|\alpha.\beta.\pi)\prod_{y_i>0} p(Y=y_i|\alpha.\beta.\pi) = \quad (4)$$

$$\prod_{y_i=0}\left(\frac{e^{Z\prime\alpha}}{1+e^{Z\prime\alpha}} + (\frac{1}{1+e^{Z\prime\alpha}})(\frac{\pi}{\pi+e^{X\prime\beta}})^{\pi}\right)\prod_{y_i>0}\left((\frac{1}{1+e^{X\prime\beta}})(\frac{\Gamma(y+\pi)}{\Gamma(y+1)\Gamma(\pi)})(\frac{\pi}{\pi+e^{X\prime\beta}})^{\pi}(\frac{e^{X\prime\beta}}{\pi+e^{X\prime\beta}})^{y}\right)$$

We changed the format of the dataset to a long data format and defined response variables as an indicator, similar to the format change in the longitudinal datasets for multilevel models. Then, we run simulations, including our proposed method, BAMZINB. We used model residuals' variance-covariance matrix to correlate response variables in BAMZINB. In addition, we used Bayesian estimation methods to cover potentially problematic issues, such as over-parametrization and small sample sizes.

5.2.1.3. Bayesian Parameter Estimates

We needed to specify a prior distribution for parameters in the model to obtain a Bayesian estimation of the unknown parameters in the BAMZINB model. Formulation of an informative prior distribution results from providing good prior information (Park et al., 2010). In this study, we assumed Gamma (a=0.001, b=0.001) distribution for overdispersion parameter, Normal (0, 10e-6) distribution for model parameters, and Normal (0, 10e-6) distribution for zero-inflation parameter. The prior distribution for parameters (α, β, π) is written as the following:

$$p(\alpha.\beta.\pi) = \prod_{y_i=0}\left(\frac{1}{\sigma_{\alpha_i}\sqrt{2\pi}}e^{\frac{-(\alpha_i-\mu_{\alpha_i})^2}{2\sigma^2\alpha_i}}\right)\prod_{y_i>0}\left(\frac{1}{\sigma_{\beta_i}\sqrt{2\pi}}e^{\frac{-(\beta_i-\mu_{\beta_i})^2}{2\sigma^2\beta_i}}\right)\frac{1}{b^{\alpha}\Gamma(\mathrm{a})}\pi^{\alpha-1}e^{-\frac{\pi}{b}} \quad (5)$$

Using the combination of the prior and the likelihood, the posterior of the parameters is found via the following function:

$$p(\alpha.\beta.\pi|Y) = \quad (6)$$

$$\prod_{y_i=0}\left(\frac{1}{1000\sqrt{2\pi}}e^{\frac{-(\alpha_i)^2}{2(1000)}}\right)\prod_{y_i>0}\left(\frac{1}{1000\sqrt{2\pi}}e^{\frac{-(\beta_i)^2}{2(1000)}}\right)\left(\frac{1}{0.001^{0.001}\Gamma(0.001)}\pi^{-0.999}e^{-\frac{\pi}{0.001}}\right)\prod_{y_i=0}\left(\right.$$

$$\left.\left(\frac{1}{1+e^{Z\prime\alpha}}\right)\left(\frac{\pi}{\pi+e^{X\prime\beta}}\right)^{\pi}\right)\prod_{y_i>0}\left(\left(\frac{1}{1+e^{X\prime\beta}}\right)\left(\frac{\Gamma(\mathrm{y}+\pi)}{\Gamma(\mathrm{y}+1)\Gamma(\pi)}\right)\left(\frac{\pi}{\pi+e^{X\prime\beta}}\right)^{\pi}\left(\frac{e^{X\prime\beta}}{\pi+e^{X\prime\beta}}\right)^{y}\right)$$

The posterior distributions were sampled by Monte Carlo Markov Chain (MCMC) (El-Basyouny & Sayed, 2010; Gamerman & Lopes, 2006) techniques available in *JAGZ* (Hornik et al., 2003) using *runjagz* package (Denwood, 2016) in R software. The Bayesian estimated average will be considered as the estimated effect size. The Deviance Information Criteria (DIC) (Spiegelhalter et al., 2002) will be used as a goodness of fit criteria for model performance comparisons.

5.2.2. Simulation

We conducted a simulation study to compare the performance of BAMZINB with two alternative models, the Genewise Negative Binomial Generalized Linear Models (glmFit) (McCarthy et al., 2012) implemented in edgeR package (Robinson et al., 2010) and the Bayesian hierarchical Generalized Linear Model (BhGLM) (Yi et al., 2019) implemented in BhGLM package in R software version 4.0.4 (Team, 2013).

5.2.2.1. Data Generation

We assumed a sample of 300 amplicon sequence variants (ASVs) for 50 and 100 subjects. We generated two sets of data for each simulation scenario with fixed treatment effects: $\beta=0$, representing no signal, and $\beta=2$, indicating a considerable large signal. There was only one binary covariate defined as an indicator of the exposed group, and the probability of a subject coming from the exposed group was set at 50%. **Table 5-1** summarizes the simulation study parameters for 32 scenarios.

Each simulation scenario consisted of the following steps:

1. Take 50 or 100 random samples from each dataset with replacement.
2. Fit four models:
    a. BAMZINB without random intercept,
    b. BAMZINB with random intercept,
    c. glmFit (McCarthy et al., 2012),
    d. BhGLM (Yi et al., 2019).
3. Extract and store parameter estimates and deviances.
4. Compare parameter estimates with the true values.
5. Calculate the average absolute relative bias and deviance.

In this project, the same as our previous chapter, we used Gaussian Copula (Andersen et al., 2015) to accommodate the correlation among outcome variables and zero-inflated negative binomial distribution to generate each response variable (Eq 1).

Table 5-1: The Summary of Simulation Study Parameters

Parameter	Ranges
Sample size, n	50, 100
Number of coefficients	One: 1, categorical (p=0.5)
Effect size, β	Zero: 0, no signal Two: 2, large signal
Over-dispersion	θ: Low= 0.75, Moderate= 0.5
Zero-inflation	α: Low= 0.3, Moderate= 0.5
Correlation	ρ: Low= 0.2, Moderate= 0.5

5.2.2.2. Performance Comparison Measures

We used the ARB as the average difference between the true values and estimated values across 100 bootstrap samples in each scenario. In addition, we used the Deviance Information Criteria (DIC) (Spiegelhalter et al., 2002) to compare the goodness of fit of four models including BAMZINB without random intercept, BAMZINB with random intercept, glmFit (McCarthy et al., 2012), and BhGLM (Yi et al., 2019). We reported the average ARB (SD) and average DIC (SD) among 300 simulated ASVs. Lower ARB and DIC values indicate better estimates and the preferred model.

5.2.3. Application on SKOT Cohort Data

We used SKOT Cohorts (I and II) to show the application of BAMZINB on the real-life dataset. We described details in sections **4.2.4** and **4.2.4.1** in Chapter 4. In this study, we used 465 individuals in the SKOT I and SKOT II study to compare the average abundance change of specific bacteria at the Phylum and Class levels between 9 months and 18 months assessments in each cohort separately.

5.3. Results

5.3.1. Simulation Results

We presented simulation results in two following sections. First, we compared the performance of four models for each scenario presented in Tables 5.2 and 5.3. Then, we compared the performance of the different scenarios for each model in supplementary figures 3-1 to 3-4. The average ARB and average deviance results for each model in different scenarios can be found in **Supplementary Material.**

Table 5-2 shows the average ARB of the estimated simulated effect size for BAMZINB with and without random intercept, BhGLM, and glmFit. For all scenarios, the maximum difference between the average ARB of the BAMZINB models and BhGLM or glmFit was less than 0.22. This result shows that the BAMZINB model performed as well as BhGLM and glmFit.

Table 5-3 shows the average deviance of the models in the simulation study. Average deviance showed the goodness of fit of BAMZINB models (with- and without- random intercept) were better for almost all cases when the signal and sample size were large ($\beta=2$, $n=100$), except for two scenarios when zero-inflation and correlation were medium and at both levels of over-dispersion. In other scenarios, the BhGLM or glmFit had better deviance when there was no signal, and the sample size was low ($\beta=0$, $n=50$), except for four scenarios when zero-inflation was low, over-dispersion was medium, and correlation was medium, when zero-inflation was medium, and correlations were low at both levels of over-dispersion, and when all properties were at the medium level. One of the BAMZINB models performed better in these five scenarios, as mentioned earlier.

Table 5-2: The Average Absolute Relative Bias among 300 Simulated AVSs in the Simulation Study

Zero-inflation	Over-dispersion	Correlation	Effect size, β	Sample size, N	Average Absolute Relative Bias (SD)			
					BAMZINB_ No Random Intercept	BAMZINB+ Random Intercept	BhGLM	glmFit
0.3	0.75	0.2	Zero	50	0.417 (0.374)	**0.394 (0.328)**	0.455 (0.407)	0.423 (0.363)
				100	0.328 (0.256)	0.331 (0.268)	**0.254 (0.202)**	0.268 (0.224)
			Two	50	2.06 (0.505)	2.041 (0.591)	1.996 (0.532)	**1.981 (0.462)**
				100	2.008 (0.391)	2 (0.34)	1.969 (0.463)	**1.949 (0.401)**
0.3	0.75	0.5	Zero	50	0.309 (0.258)	0.309 (0.262)	**0.303 (0.255)**	0.335 (0.28)
				100	0.224 (0.182)	0.213 (0.174)	0.224 (0.183)	**0.212 (0.179)**
			Two	50	1.659 (0.766)	1.674 (0.765)	1.715 (0.768)	**1.604 (0.761)**
				100	**1.564 (0.736)**	1.615 (0.737)	1.62 (0.749)	1.593 (0.737)
0.3	0.5	0.2	Zero	50	0.522 (0.489)	**0.492 (0.385)**	0.506 (0.421)	0.542 (0.513)
				100	**0.273 (0.209)**	0.31 (0.241)	0.284 (0.231)	0.33 (0.273)
			Two	50	1.721 (0.777)	1.667 (0.81)	1.649 (0.849)	**1.597 (0.776)**
				100	2.047 (0.458)	1.984 (0.393)	**1.933 (0.424)**	2.001 (0.516)
0.3	0.5	0.5	Zero	50	0.303	0.299	**0.283**	0.318

				100	(0.309)	(0.225)	**(0.245)**	(0.23)
					0.317	**0.306**	0.354	0.364
					(0.268)	**(0.269)**	(0.275)	(0.319)
			Two	50	2.081	2.079	**1.919**	1.975
					(0.551)	(0.51)	**(0.574)**	(0.552)
				100	**1.608**	1.655	1.621	1.625
					(0.764)	(0.784)	(0.772)	(0.776)
0.5	0.75	0.2	Zero	50	0.633	0.545	**0.537**	0.539
					(0.598)	(0.445)	**(0.61)**	(0.507)
				100	0.358	0.34	**0.331**	0.365
					(0.308)	(0.269)	**(0.265)**	(0.306)
			Two	50	1.618	1.691	1.643	**1.575**
					(0.821)	(0.824)	(0.777)	**(0.79)**
				100	1.646	1.6	1.62	**1.539**
					(0.776)	(0.763)	(0.777)	**(0.795)**
0.5	0.75	0.5	Zero	50	0.363	**0.343**	0.366	0.451
					(0.317)	**(0.319)**	(0.364)	(0.401)
				100	0.295	**0.269**	0.271	0.325
					(0.22)	**(0.217)**	(0.216)	(0.266)
			Two	50	**1.955**	2.035	1.986	2.013
					(0.434)	(0.464)	(0.429)	(0.395)
				100	1.486	1.564	**1.444**	1.539
					(0.803)	(0.849)	**(0.814)**	(0.834)
0.5	0.5	0.2	Zero	50	0.603	0.549	0.524	**0.435**
					(0.547)	(0.552)	(0.487)	**(0.481)**
				100	0.459	0.443	**0.41**	0.436
					(0.399)	(0.36)	**(0.377)**	(0.384)
			Two	50	1.773	1.869	1.822	**1.69**
					(0.95)	(1.028)	(0.892)	**(0.926)**
				100	**1.575**	1.625	1.648	1.632
					(0.772)	(0.773)	(0.79)	(0.802)

0.5	0.5	0.5	Zero	50	0.481 (0.417)	0.457 (0.422)	**0.405 (0.383)**	0.468 (0.408)
				100	0.359 (0.358)	0.403 (0.322)	**0.297 (0.254)**	0.338 (0.32)
			Two	50	1.801 (0.791)	1.749 (0.839)	1.745 (0.774)	**1.594 (0.822)**
				100	1.727 (0.806)	1.674 (0.783)	1.715 (0.829)	**1.583 (0.76)**

Table 5-3: The Average Deviance among 300 Simulated AVSs in the Simulation Study

Zero-inflation	Overdispersion	Correlation	Effect size, β	Sample size, N	Average Deviance (SD)			
					BAMZINB_ No Random Intercept	BAMZINB + Random Intercept	BhGLM	glmFit
0.3	0.75	0.2	Zero	50	23.21 (23.267)	22.541 (21.151)	22.52 (21.327)	**22.47 (21.284)**
				100	45.145 (43.623)	**44.866 (43.42)**	44.95 (43.482)	44.93 (43.471)
			Two	50	62.029 (78.834)	73.346 (114.514)	**54.635 (59.92)**	57.597 (61.56)
				100	**98.65 (9.765)**	105.146 (70.941)	99.511 (10.662)	110.248 (101.446)
0.3	0.75	0.5	Zero	50	25.183 (23.313)	25.512 (23.52)	**25.151 (23.337)**	25.265 (23.525)
				100	**41.884 (40.551)**	42.79 (41.531)	42.337 (41.138)	43.372 (42.089)

			Two	50	27.774 (35.505)	26.195 (32.027)	**24.763 (23.374)**	27.51 (38.83)
				100	55.58 (57.911)	**53.066 (50.362)**	53.596 (50.981)	54.18 (51.984)
0.3	0.5	0.2	Zero	50	22.183 (23.241)	21.81 (22.653)	21.006 (21.245)	**20.759 (20.242)**
				100	**43.231 (41.666)**	43.701 (44.011)	44.084 (43.516)	43.27 (41.73)
			Two	50	**31.225 (62.697)**	35.13 (66.232)	33.363 (63.579)	33.345 (68.432)
				100	**97.125 (106.473)**	120.361 (180.038)	100.118 (108.267)	116.785 (175.243)
0.3	0.5	0.5	Zero	50	**21.587 (20.283)**	22.631 (21.745)	21.731 (20.497)	21.68 (20.566)
				100	53.711 (38.314)	53.527 (37.583)	53.543 (37.538)	**53.461 (37.952)**
			Two	50	55.409 (51.182)	**52.019 (42.644)**	56.483 (73.472)	59.813 (75.561)
				100	53.716 (77.988)	**46.595 (46.451)**	48.324 (53.733)	47.397 (47.013)
0.5	0.75	0.2	Zero	50	**17.345 (18.581)**	17.372 (19.064)	18.156 (20.12)	17.48 (18.211)
				100	37.404 (36.321)	**37.291 (36.239)**	38.004 (37.619)	37.679 (38.046)
			Two	50	45.557 (105.697)	36.61 (76.06)	**33.501 (67.864)**	40.655 (90.208)
				100	46.224 (82.145)	**44.261 (72.867)**	52.69 (96.289)	56.871 (126.317)
0.5	0.75	0.5	Zero	50	30.234 (21.422)	30.005 (20.994)	**29.262 (21.336)**	30.699 (21.67)
				100	84.994	83.364	81.791	**81.762**

					(11.443)	(13.431)	(12.893)	**(11.512)**
			Two	50	30.234	30.005	**29.262**	30.699
					(21.422)	(20.994)	**(21.336)**	(21.67)
				100	68.984	58.118	64.185	**58.008**
					(103.569)	(60.645)	(90.921)	**(56.018)**
0.5	0.5	0.2	Zero	50	**34.438**	39.587	38.566	35.499
					(15.757)	(33.979)	(28.874)	(19.657)
				100	**43.866**	45.853	49.673	47.02
					(31.102)	(36.111)	(48.2)	(39.599)
			Two	50	**35.283**	37.75	40.819	45.822
					(76.951)	(84.385)	(89.961)	(102.464)
				100	56.574	**50.559**	59.399	65.171
					(114.541)	**(104.925)**	(129.781)	(146.331)
0.5	0.5	0.5	Zero	50	17.934	**16.983**	17.053	17.221
					(14.447)	**(14.903)**	(14.494)	(14.9)
				100	42.926	**41.626**	42.681	42.741
					(31.228)	**(29.832)**	(30.294)	(30.506)
			Two	50	29.753	**25.159**	26.767	29.69
					(51.233)	**(39.436)**	(56.673)	(54.827)
				100	43.263	51.5	**41.772**	43.915
					(61.705)	(103.458)	**(56.621)**	(64.84)

5.3.2. SKOT Cohorts Data Results

We showed the application of BAMZINB with a random intercept on the SKOT Cohort I and II data. **Figures 5-1 and 5-2** show the Bayesian mean (SD) abundance difference from 9 months to 18 months for infants from healthy and obese mothers at the Phylum and Class levels.

Figure 5-1 shows that the average abundance for Actinobacteria, Bacteroidetes, and Firmicutes increased, and the abundance of Proteobacteria decreased over time for infants with healthy mothers. Infants with obese mothers showed the same pattern for Actinobacteria and

Proteobacteria. Compared to infants born to healthy mothers, the average abundance of Bacteroidetes had a remarkably lower positive difference for infants from obese mothers from 9 months to 18 months. In addition, the average abundance of Firmicutes decreased over time for infants from obese mothers.

Figure 5-2 shows an increase in the average abundance of Actinobacteria, Bacteroidia, Bacilli, and Gammaproteobacteria and a decrease in average abundance for Alphaproteobacteria over time for infants from healthy mothers. Although Actinobacteria, Bacilli, and Alphaproteobacteria showed the same pattern for infants born to obese mothers, Bacteroidia and Gammaproteobacteria decreased from 9 months to 18 months in infants with obese mothers. In addition, the average abundance change of Alphaproteobacteria was remarkably higher for infants born to obese mothers than infants of healthy mothers over time.

Firmicutes phyla plays an essential role in breaking down the carbohydrates in the infants' gut. Significance changes in Firmicutes and Bacteroidetes abundance over time could be associated with childhood obesity (Bergström et al., 2014; Borgo et al., 2017; Indiani et al., 2018; Scheepers et al., 2015; Xu et al., 2012). Recently, much attention was given to the Firmicutes/Bacteroidetes ratio as a relevant marker of gut microbiome-related diseases (Houtman et al., 2022; Magne et al., 2020; Stojanov et al., 2020; Takezawa et al., 2021), especially in relation to obesity and inflammatory bowel disease (Stojanov et al., 2020; Sutoyo et al., 2020). Evidence shows that maternal microbiota is an initial provider of infants' gut microbiota and this transfer process impacts the newborn's overall physiological condition (Galley et al., 2014; Kozyrskyj et al., 2016). Therefore, maternal obesity could be a potential risk factor for overweight or childhood obesity (Trandafir & Temneanu, 2016). Muller *et al.* study on infants of overweight/obese mothers showed a reduction in Proteobacteria, suggesting that changes in the gram-negative bacteria such as Gammaproteobacteria may cause the vertical transition of maternal microbiota (Mueller et al., 2016). Several studies have found that women who had obesity prior to pregnancy or gained weight during the pregnancy had significantly different gut microbiome than normal-weight pregnant women (Collado et al., 2008; Santacruz et al., 2010).

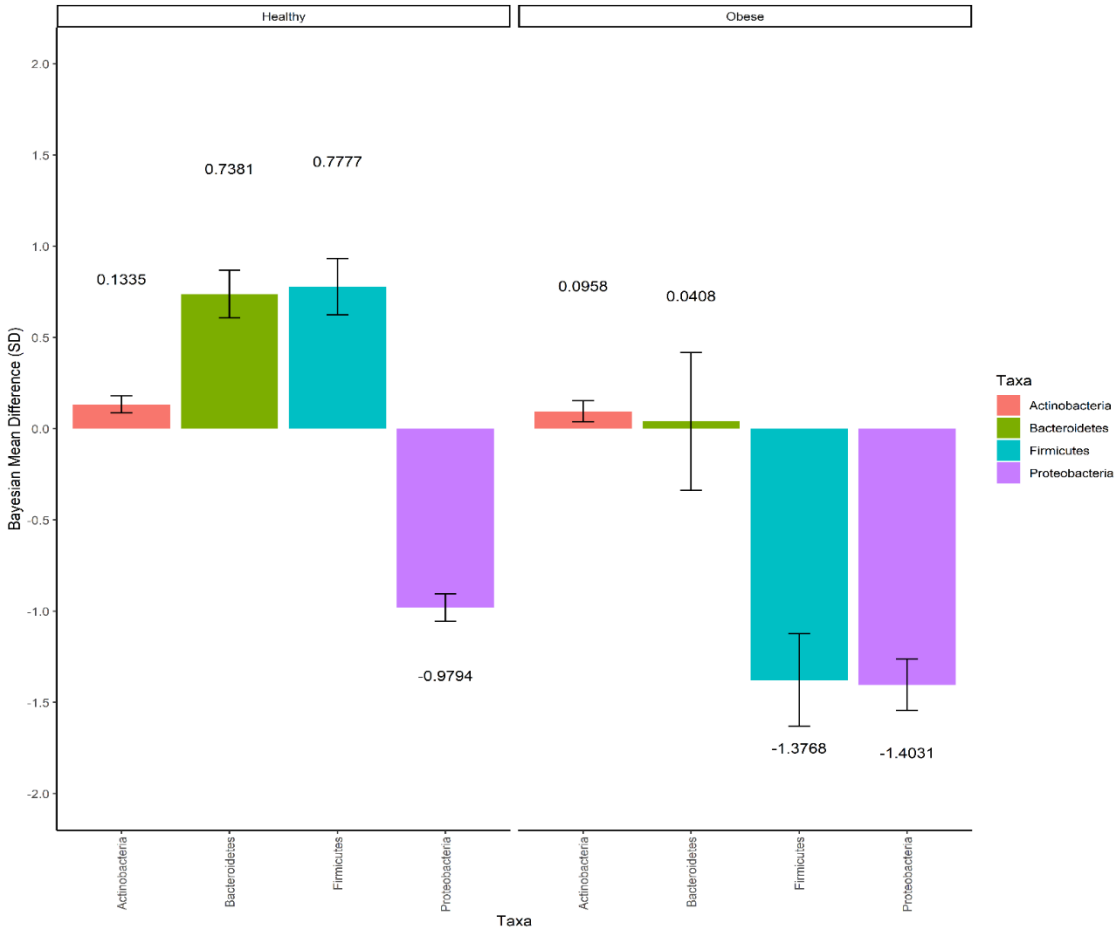

Figure 5-1: This figure shows the average abundance difference for Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria at the Phylum-level for infants from healthy mothers and obese mothers from 9 months to 18 months

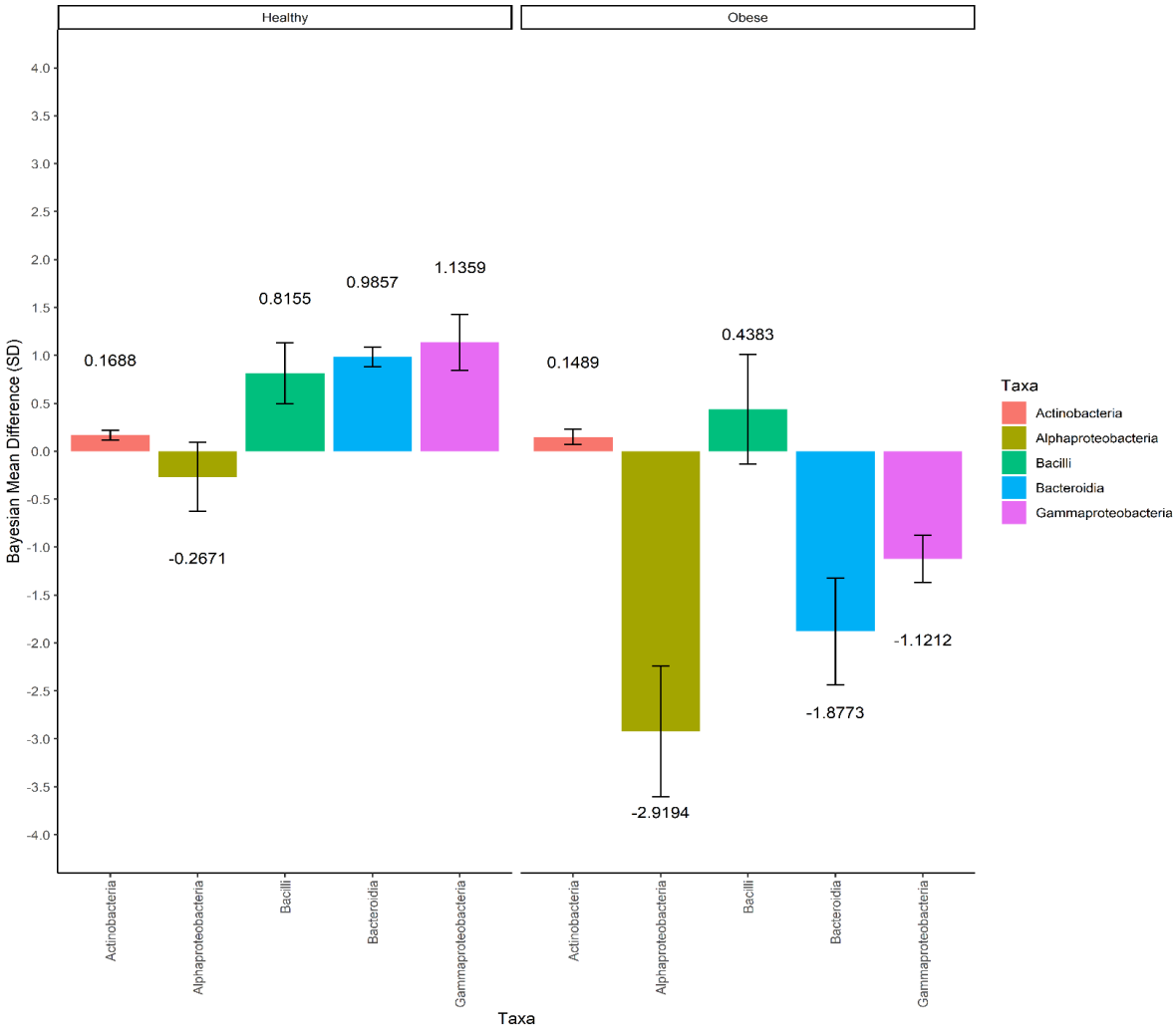

Figure 5-2: This figure shows the average abundance difference for Actinobacteria, Bacteroidia, Bacilli, Gammaproteobacteria, and Alphaproteobacteria at the Class-level for infants from healthy mothers and obese mothers from 9 months to 18 months

5.4. Discussion

We proposed a Bayesian marginal zero-inflated negative binomial (BAMZINB) model for gut microbiome count data. BAMZINB estimates the effects of covariates on microbial composition and each taxon while allowing for incorporating correlations of residuals. Other methods in the literature, such as glmFit (McCarthy et al., 2012), designed to analyze microbiome count data by considering taxon one by one, have heavily depended on the utilization of normalization methods

using the negative binomial distribution (Lin & Peddada, 2020). Tang *et al.* proposed BhGLM to address this issue by using raw counts and incorporating library size as an offset (Yi et al., 2019). However, zero-inflation is one of the proven properties of gut microbiome data, and both BhGLM and glmFit models ignore it by using negative binomial distribution for microbiome count data (Kaul et al., 2017; Silverman et al., 2020).

In addition to taking properties of zero-inflated negative binomial distribution into account, BAMZINB is capable of considering random intercept and library size as modeling parameters. Literature has shown high inter-individual variability of gut microbial composition in the early years of infancy compared to adulthood (Dominguez-Bello et al., 2010; Yatsunenko, Rey, Manary, Trehan, Dominguez-Bello, Contreras, Magris, Hidalgo, Baldassano, & Anokhin, 2012). Generally, the microbial composition tends to be the same for everyone in adulthood. In BAMZINB, we incorporated random intercept to take inter-individual variability into account when analyzing infants' microbiome count data. Although BAMZINB has more advantages than the other two models (theoretically), simulation results showed that the BAMZINB model performed as well as BhGLM and glmFit models with respect to the ARB. One reason for this result could be the difference in the initial values for model parameters. We explained the priors for BAMZINB in section **2.1.3**.. BhGLM offers three priors: Student-t (default), Double-exponential, and mixture Student-t (Yi et al., 2019). In this paper, we used the default priors as Student-t for comparison with BAMZINB and glmFit. Further studies could focus on comparing different priors and comparing them to the other existing models. Deviance was different among 32 scenarios depending on the dataset's properties and sample size.

The real data application on SKOT Cohorts showed a different pattern over time for the average abundance of specific bacteria between infants of healthy mothers and infants of obese mothers. The structure of the SKOT Cohort data required using a random intercept due to changes in gut microbiome composition of infants in early life from 9 to 18 months, given that interpersonal changes are significantly higher in childhood than in adulthood (Yatsunenko, Rey, Manary, Trehan, Dominguez-Bello, Contreras, Magris, Hidalgo, Baldassano, Anokhin, et al., 2012). In addition, the acquisition of zero-inflated negative binomial distribution and unstructured variance-covariance matrix in BAMZINB aided with zero-inflation, over-dispersion, and within-sample correlation issues in infants' gut microbiome data.

Future studies are needed to develop the BAMZINB method to analyze studies with random slopes. Moreover, future studies could compare the results by using different variance-covariance structures for multivariate analyses.

5.5. Conclusion

It has been shown that the gut microbiome data analyses can be affected by the choice of statistical analysis method. This study proposed the BAMZINB method to account for over-dispersion, zero-inflation, multivariate correlation structure, and dimensionality issues in the infants gut microbiome data. We know from previous studies that the consequences of ignoring these features of gut microbiome data cause a lack of precision in estimating effect sizes and loss of statistical power. In this study, we showed and compared the performance of several statistical methods in 32 scenarios and on a real data set. The findings of this study could help other research groups to compare the properties of their dataset with one of the 32 scenarios and make a better decision when choosing a statistical analysis method.

Chapter 6 : Conclusion and Future Directions

6.1. Updating Local Birth Weight Percentiles

The first project (Chapters 1 and 2) aimed to update Alberta's local birth weight percentiles, show the difference among ethnic groups, and highlight the necessity of taking variables such as ethnicity into account when estimating birth weight percentiles in different populations. The reference curves and table presented here are different from the currently available references in several aspects. The main advantages include their time frame, population base, statistical models to correct the potential errors in the reported gestational age, and ethnicity specificity. This reference has differed from current local and national studies in estimating the ethnicity-based curves and tables and comparing those with the national-level reference. In addition, using a contemporary Canadian Cohort is another advantage of the proposed reference. The current national study was conducted on singleton births occurring in all provinces of Canada (except Ontario) between January 1, 1994, and December 31, 1996, without taking ethnicity into account (Michael S. Kramer et al., 2001). Using an outdated reference could cause misclassification of high-risk infants and send a false message to the clinicians responsible for utilizing the most beneficial interventions.

The most recent local reference in Alberta was conducted on singletons and twins born alive in Alberta between 1985 through 1998 (Robertson et al., 2002). Although this reference was based on data from the local population, they did not adjust for ethnicity and errors in the gestational age records. Due to the lack of a correction method for gestational age in the Robertson *et al.* local study, we compared our results only to the national reference study (Michael S. Kramer et al., 2001). We found that LGA thresholds were lower for preterm and term Chinese infants. Therefore, using national reference cause overestimation of AGA and underestimation of LGA infants among male and female preterm and term Chinese infants in Alberta. In addition, our results showed that using national reference misclassifies AGA preterm Chinese female infants as SGA, therefore overestimating SGA infants and underestimation of the AGA group.

Comparing percentiles for the preterm and term South Asian infants with the national showed the same results for both sexes. Classifying these infants with the national reference will underestimate the LGA and overestimate the SGA preterm and term South Asian infants. Yusuf *et al.* conducted a study on 2821,798 Asian Americans and 62,174,875 non-Hispanic-white US live-born infants. They concluded that SGA was higher in Asian American infants than non-Hispanic white infants (Yusuf et al., 2021). They used the US national reference to identify SGA infants using the 10^{th} percentile as the threshold. They mentioned that not using ethnic-specific references to identify SGA infants could be a reason for the difference they found between the two groups, as indicated in other studies (Louis et al., 2015; Seaton et al., 2011; Sletner et al., 2017). I believe the first part of Melby *et al.* paper's title explains the main idea of my first project, "One size does not fit all" (Melby et al., 2019). They examined the appropriateness of using the United States Institute of Medicine (IOM) and Japanese ethnicity-blind guidelines on classifying SGA infants. They argued that the main reason why the IOM guideline is not a reasonable choice for Asian countries could be the lower BMI and Lower gestational weight gain among Asian mothers (Melby et al., 2019). In addition, IOM focused heavily on comparing whites and blacks, and sometimes Hispanic mothers which support the idea of having local or national references instead of using international standards.

In conclusion, having updated local sex- and ethnicity-based birth weight percentiles could prevent misclassification of high-risk infants and help the clinician to take more efficient interventions. Moreover, other research groups could use these updated references to categorize infants as SGA, LGA, and AGA in Alberta in future studies.

There are still questions that remain unanswered and need to be addressed in the future. These include: i) estimating birth weight percentiles for twins, ii) estimating birth weight percentiles for infants whose mother underwent assisted reproductive technology treatments, iii) estimating birth weight percentiles for other categories of a population such as different levels of socioeconomic status or based on immigration status, iv) incorporating comorbidities and characteristics of the mother in the estimation of birth weight percentiles, v) investigating the relationship between ethnic-specific birth weight percentiles and mothers' diet is the pregnancy period, and vi) investigating the causal pathways from ethnicity to SGA and LGA through factors such as maternal BMI, pregnancy gestational weight gain, and socioeconomic status.

6.2. Statistical Methods Motivated by Challenges in Analysis of Microbiome Studies

Classic microbiome-disease-related studies focused on one bacteria or organism related to one disease (Bantock, 1899). However, now we know that imbalances in microbiota are also associated with many diseases and disorders. Reduction or increase in one specific species can change the entire environment and cause adverse effects like inflammation or infection (Belkaid & Hand, 2014). Emerging evidence has shown the potential involvement of the microbiome in almost all health-related complications such as obesity, cardiovascular diseases, cancer, neurocognitive and behavioral disorders, and other types of complications (Ahmadmehrabi & Tang, 2017; Gopalakrishnan et al., 2018; Jamshidi et al., 2019; Maruvada et al., 2017; Rieder et al., 2017; Scott et al., 2019; Shen & Ji, 2019). Analyzing microbiome data is challenging due to its unique properties, including mean-variance association, many zeros, biological correlation, high dimensionality, different sequencing depth, and the multivariate structure. Therefore, it is difficult to suggest a best-practice straightforward statistical method because it is highly dependent on the study's objectives and the underlying nature of the data. However, there has been a tremendous effort to develop methods that facilitate these analyses. The unique characteristics of the microbiome data impose more challenges on the statistical analysis step. The large inter-variability, heteroscedastic variations, and biological variations are not often correctly addressed by the classical Gaussian or log-normal models (Moreno-Indias et al., 2021). Microbiome data tend to be sparse and skewed, with more microbial features than the number of samples.

In chapters 3-5, I focused on the statistical methods in gut microbiome literature, their advantages and limitations, then proposed a Bayesian marginal model based on the negative binomial distribution with zero inflation to address some limitations of current methods. Both studies contained extensive simulation scenarios and applications on an open-access real data set.

The most common approach to finding these associations in microbiome studies is to look for differential diversity analysis, taxa abundance, or functional components between groups of interest. Statistical methods in microbiome studies are evolving to find disease-related associations while addressing the unique features of the microbiome data. In addition, one of the

main limitations of the microbiome studies, in general, is to control for the confounding factors and have a reasonable statistical power (Galloway-Peña & Guindani, 2018). Similar to other studies, the first step is to visualize the data, look for noticeable patterns, and discover potential associations. In microbiome studies, this step includes using dimension reduction methods due to the complexity of the data. The most common visual dimension-reduction methods in microbiome studies are principal coordination analysis (PCoA) and principal component analysis (PCA) (Sudarikov et al., 2017). The next step depends on the objective of each study. One could look at the effect of environmental- or patient-characteristics on the community composition or assess the effect of those variables on a specific taxon. When looking at community composition, multiple statistical methods are mentioned in the literature to find the associations between covariates and community composition. Some of these methods are ANOSIM, PERMANOVA, ANCOM, etc. (Anderson & Walsh, 2013; Mandal et al., 2015). I discussed these methods in section **3.5.1**, Chapter 3. Conventional statistical approaches such as the t-test, Wilcoxon test, ANOVA, or Kruskal-Wallis test are also discussed in the literature (Staley & Sadowsky, 2018; Xia & Sun, 2017). However, none of these methods can take features of microbiome data into account for analysis when the goal is to find the associations between potential risk factors and the microbiome composition. In addition, some of the current statistical tools use traditional techniques with some modifications that do not take into account the inherited biological complexity of the microbiome data by assuming normality (for example, PERMANOVA in the vegan package of R), removing a part of the data due to existence of many zeros or rare species prior to the analysis (for example, ANCOM), or applying normalization methods or adding a pseudocount to avoid Log zero during the process (for example, ZIG in metagenomeSeq package of R). Another categorization of the methods in microbiome literature is distance-based and distribution-based methods. I explained the advantages and limitations of some of the most common methods in each category in section **3.5**, Chapter 3.

In this dissertation (Chapters 3-5), I compared the performance of a Gaussian-based model with two negative binomial-based models. Then, I proposed a different approach to address some of the limitations in those models. The findings in Chapter 4 showed that the NB-based ManyGLM model is capable of taking the mean-variance relationship (heteroscedastic variations) and multivariate structure of the data into account to find the significant predictor of microbial composition at the community level and individual-taxon level at the same time, while

controlling for family-wise error rate. In Chapter 5, I proposed the BAMZINB model to cover the limitations of models such as NB-based ManyGLM. BAMZINB model can answer the same question in the multivariate space using zero-inflated negative binomial distribution and different patterns for variance-covariance matrix (unstructured in this example). BAMZINB can also consider inter-variability by adding a random intercept component into the modeling procedure. Bayesian estimates using the MCMC algorithm in BAMZINB helped with the dimensionality issues of the microbiome data analyses.

There are several gaps in the literature for microbiome data analyses that need to be addressed or developed in the future. I also mentioned some of the recent publications that tried to address these gaps.

i) Machine learning methods are still developing in microbiome literature as they are well-known for feature selection and high-dimension data analyses (Knight et al., 2018). Random Forest, for example, has been found useful for microbiome data analysis to identify important taxa and clinical variables that can predict specific outcomes (Knights et al., 2011). The application of other machine learning algorithms, such as support vector machine, elastic net, and LASSO, has been shown in the literature for analyzing human gut microbiome data (Pasolli et al., 2016).

ii) Sample size calculation for microbiome studies is one of the common challenges. Often in experimental and interventional studies, we need to know the number of required samples prior to the start of the study to achieve a reasonable statistical power later in the downstream analyses. Current methods that exist in the literature are not well developed due to a lack of established metrics to define a suitable magnitude of reasonable and clinically meaningful effect size in microbiome studies (Galloway-Peña & Hanson, 2020). Therefore, determining the required sample size remained an unresolved issue in the microbiome studies. There are web-based applications for power and sample size calculations limited to case-control microbiome studies (Mattiello et al., 2016). Jiang *et al.* study explained three strategies to extract effect size for sample size and power calculations in microbiome studies, including pilot studies, data from prior studies, and simulation studies (Jiang et al., 2022). A recent comprehensive review of strategies and guidelines for conducting power and sample size calculations for microbiome studies can be found in (Jiang et al., 2022).

iii) Another gap in the microbiome studies is the lack of advanced statistical tools for longitudinal analyses. The human gut microbiome has a dynamic nature, especially during childhood (Caporaso et al., 2011; David et al., 2014). More advanced longitudinal methods are needed to elucidate the relationship between taxa, environmental factors, and the host over time. However, one of the advantages of the BAMZINB model is its ability to include multiple time measurements in the analysis. Bokulich *et al.* proposed plugin software for the QIIME2 platform that provides various tools, including mixed models and interactive plots for microbiome longitudinal analysis (Bokulich et al., 2018; Bokulich et al., 2017). Zhang *et al.* introduced a negative binomial mixed model to handle over-dispersion and variability in total reads and dynamic trend and correlation structure among longitudinal samples (Zhang et al., 2018).

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Appendix 1

Supplementary figures and tables for chapter 2

Supplementary Table 1-1: Crude birth weight (g) percentiles for gestational age, Albertan male singletons born January 1, 2005 and December 31, 2014

Gestational Age (weeks)	N	Percentiles							Mean	SD
		3rd percentile	5th percentile	10th percentile	50th percentile	90th percentile	95th percentile	97th percentile		
22	143	286.8	311.0	350.0	496.0	605.6	630.0	635.0	487.9	98.0
23	117	473.8	480.0	510.6	600.0	722.0	772.0	815.6	616.3	158.5
24	121	474.0	512.0	560.0	718.0	830.0	870.0	966.0	708.3	131.7
25	140	570.8	589.8	660.0	800.0	951.0	1080.0	1098.3	822.7	160.1
26	170	520.7	561.7	639.5	900.0	1120.0	1160.0	1258.6	904.1	194.4
27	222	562.6	680.5	801.5	1050.0	1298.5	1399.1	1464.8	1063.3	275.7
28	228	630.0	720.0	820.0	1180.0	1469.0	1556.5	1673.8	1165.0	268.9
29	274	750.0	849.5	930.0	1330.0	1580.0	1687.0	1754.3	1317.6	315.7
30	403	920.0	990.0	1090.0	1510.0	1920.0	2159.0	2491.6	1548.4	442.5
31	548	1044.1	1112.8	1307.0	1699.5	2110.0	2305.6	2507.7	1716.7	385.0
32	784	1192.4	1295.7	1420.0	1900.0	2313.5	2440.0	2596.1	1903.7	376.6
33	1323	1365.0	1460.4	1660.0	2120.0	2552.4	2690.0	2820.4	2115.6	379.0
34	2261	1578.0	1696.0	1860.0	2360.0	2834.0	3005.0	3180.0	2369.4	418.5
35	3547	1760.0	1900.0	2090.0	2590.0	3100.0	3275.0	3450.0	2594.6	428.1
36	7489	2045.0	2153.8	2330.0	2830.0	3410.0	3625.0	3810.0	2859.3	450.9
37	17301	2280.0	2380.0	2535.0	3060.0	3635.0	3832.0	3980.0	3078.1	447.8
38	43970	2550.0	2650.0	2795.0	3300.0	3883.1	4080.0	4214.0	3325.2	439.3
39	67248	2730.0	2820.0	2960.0	3458.0	4020.0	4214.0	4340.0	3477.7	427.3
40	62916	2860.0	2950.0	3095.0	3605.0	4176.0	4360.0	4480.0	3624.3	431.2
41	32895	2980.0	3071.7	3215.0	3740.0	4317.0	4500.0	4620.0	3755.4	437.2
42	961	3019.2	3110.0	3250.0	3830.0	4465.0	4650.0	4816.8	3855.5	473.1

Supplementary Table 1-2: Crude birth weight (g) percentiles for gestational age, Albertan female singletons born January 1, 2005 and December 31, 2014

Gestational Age (weeks)	N	Percentiles							Mean	SD
		3rd percentile	5th percentile	10th percentile	50th percentile	90th percentile	95th percentile	97th percentile		
22	115.00	332.6	352.8	397.0	472.0	563.0	614.5	689.5	480.1	90.6
23	91.00	417.1	447.5	460.0	560.0	675.0	691.5	707.8	564.2	81.8
24	141.00	500.0	502.0	533.0	650.0	770.0	820.0	868.0	662.8	129.3
25	135.00	510.8	580.0	611.6	760.0	900.0	953.0	994.9	759.6	133.8
26	157.00	536.8	568.0	650.0	860.0	1030.0	1126.0	1171.6	872.9	207.3
27	178.00	533.1	584.0	668.5	980.0	1216.0	1301.5	1387.6	986.0	334.7
28	210.00	642.7	707.2	800.0	1100.0	1410.0	1482.7	1500.0	1104.4	240.9
29	225.00	773.0	830.0	904.0	1250.0	1566.0	1750.0	1926.5	1262.5	369.3
30	286.00	810.0	915.0	1055.0	1450.0	1822.5	1945.0	2203.5	1461.2	384.4
31	413.00	1001.2	1038.0	1186.0	1600.0	2038.0	2216.4	2383.2	1612.5	377.6
32	601.0	1170.0	1230.0	1330.0	1820.0	2228.0	2367.0	2570.0	1818.2	376.0
33	887.0	1285.8	1371.5	1540.0	2020.0	2455.0	2620.0	2750.0	2017.8	381.3
34	1751.0	1539.0	1651.0	1815.0	2270.0	2725.0	2932.5	3129.5	2281.1	402.3
35	2948.0	1747.6	1843.1	2006.4	2510.0	3040.0	3261.3	3421.8	2524.5	432.2
36	6365.0	1970.0	2070.4	2220.0	2740.0	3320.0	3520.0	3670.0	2762.5	448.8
37	15421.0	2210.0	2310.0	2450.0	2950.0	3530.0	3725.0	3874.4	2978.2	439.8
38	40813.0	2450.0	2544.6	2685.0	3180.0	3739.0	3925.0	4055.0	3199.3	425.7
39	65007.0	2624.2	2710.0	2840.0	3326.0	3875.0	4050.0	4180.0	3346.1	414.7
40	62626.0	2760.0	2842.0	2977.0	3465.0	4020.0	4195.0	4312.0	3485.7	414.5
41	31085.0	2860.0	2948.0	3080.0	3585.0	4150.6	4339.8	4458.5	3606.0	423.5
42	823.0	2845.0	2928.7	3076.0	3640.0	4241.6	4462.8	4617.4	3664.8	465.5

Supplementary Table 1-3: Smoothed relative sex-difference (M/F) birth weight (g) percentiles for gestational age, Albertan singletons born January 1, 2005 and December 31, 2014

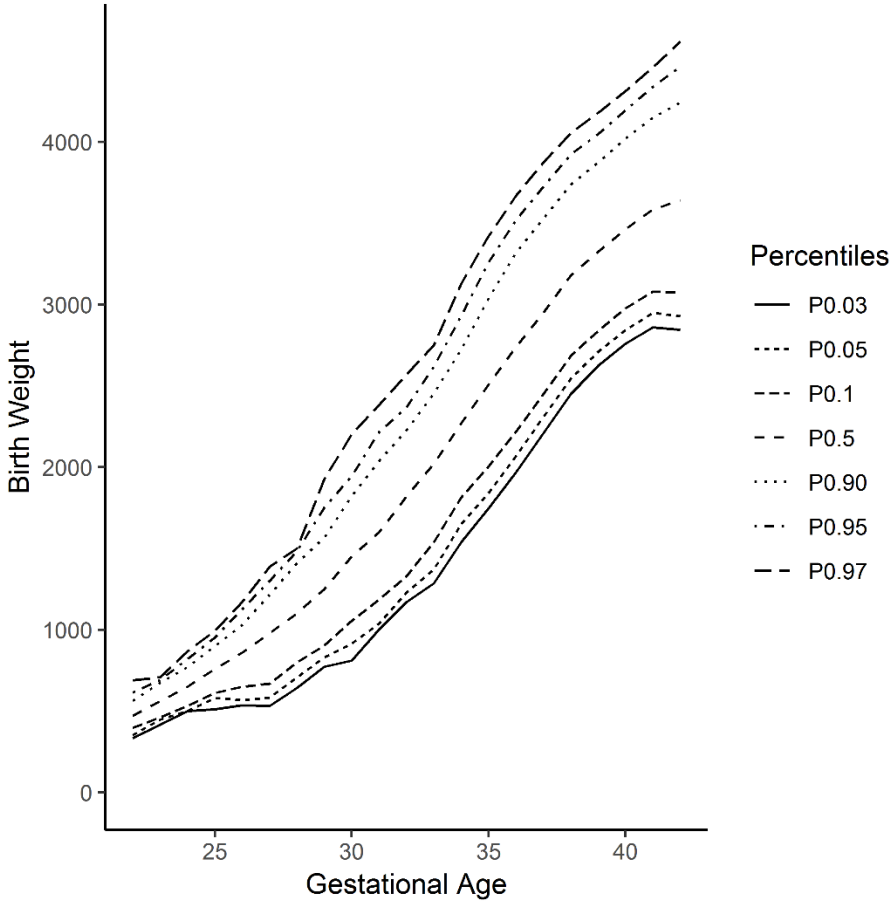
Gestational Age (weeks)	Percentiles						
	3rd percentile	5th percentile	10th percentile	50th percentile	90th percentile	95th percentile	97th percentile
22	1.22	1.21	1.19	1.14	1.12	1.11	1.11
23	1.13	1.13	1.12	1.09	1.08	1.08	1.07
24	1.09	1.08	1.08	1.06	1.05	1.05	1.05
25	1.06	1.06	1.05	1.04	1.03	1.03	1.03
26	1.05	1.05	1.04	1.03	1.02	1.02	1.02
27	1.04	1.04	1.03	1.02	1.01	1.01	1.01
28	1.04	1.04	1.03	1.02	1.01	1.01	1.00
29	1.04	1.04	1.03	1.01	1.00	1.00	1.00
30	1.04	1.04	1.03	1.01	1.00	1.00	1.00
31	1.05	1.04	1.03	1.02	1.00	1.00	1.00
32	1.05	1.05	1.04	1.02	1.01	1.01	1.00
33	1.05	1.05	1.04	1.02	1.01	1.01	1.01
34	1.06	1.05	1.05	1.03	1.02	1.02	1.02
35	1.06	1.05	1.05	1.04	1.03	1.02	1.02
36	1.06	1.06	1.05	1.04	1.04	1.03	1.03
37	1.06	1.06	1.06	1.05	1.05	1.05	1.04
38	1.04	1.04	1.04	1.03	1.03	1.03	1.03
39	1.04	1.04	1.04	1.04	1.04	1.04	1.04
40	1.04	1.04	1.04	1.04	1.04	1.04	1.04
41	1.04	1.04	1.04	1.04	1.04	1.04	1.04
42	1.06	1.06	1.06	1.05	1.05	1.05	1.04

Supplementary Table 1-4: Smoothed birth weight (g) percentiles for gestational age, Albertan male singletons born January 1, 2005 and December 31, 2014 by ethnic group

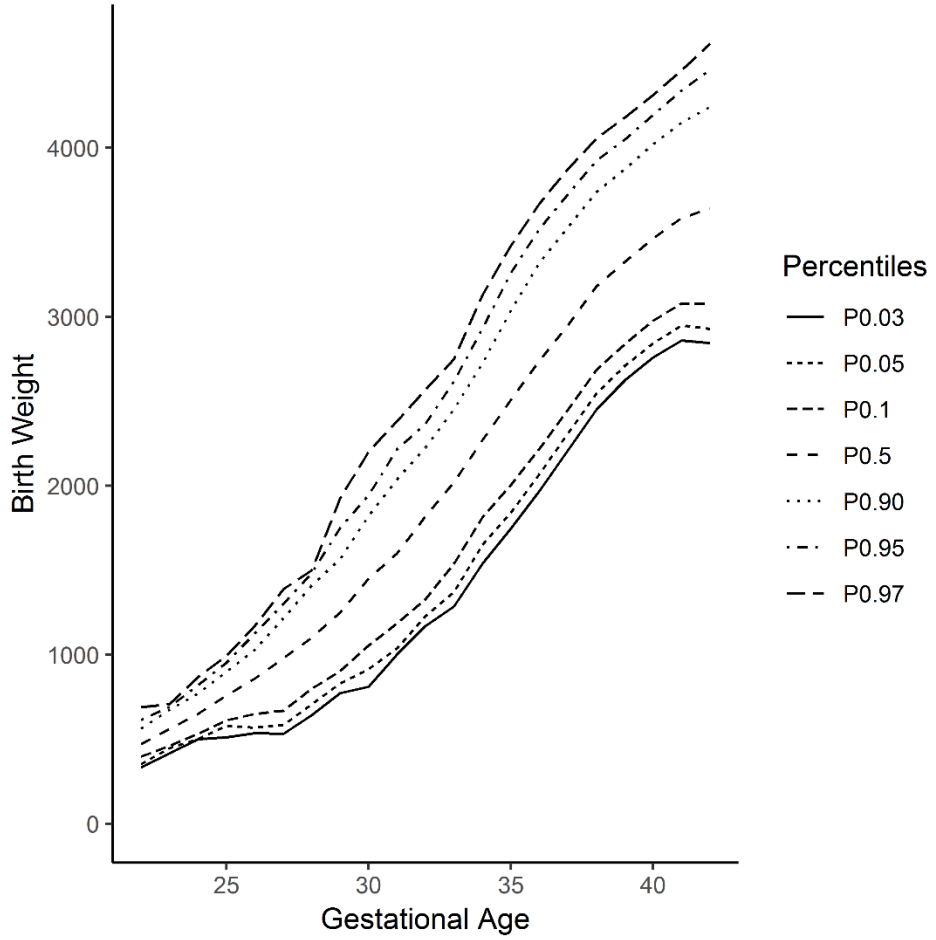
Gestational Age (weeks)	General Population			Chinese			South Asian		
	N	10th percentile	90th percentile	N	10th percentile	90th percentile	N	10th percentile	90th percentile
33	1236	1668	2560	43	1760	2472	44	1464	2436
34	2111	1884	2850	85	1745.2	2652.6	65	1574	2644
35	3308	2090	3104.3	122	2090	2926.1	117	2023	2982.8
36	6955	2340	3425	268	2362.8	3250	266	2147.5	3122.5
37	15970	2545	3648	674	2520	3405.6	657	2383	3500.8
38	40656	2805	3895	1814	2750	3694.1	1500	2645	3660
39	62622	2970	4034	2533	2895.4	3846.4	2093	2815.4	3800
40	59510	3105	4185	1883	2990	3997.4	1523	2920	3997.4
41	31459	3220	4320	733	3100	4190	703	3062.6	4108

Supplementary Table 1-5: Smoothed birth weight (g) percentiles for gestational age, Albertan female singletons born January 1, 2005 and December 31, 2014 by ethnic group

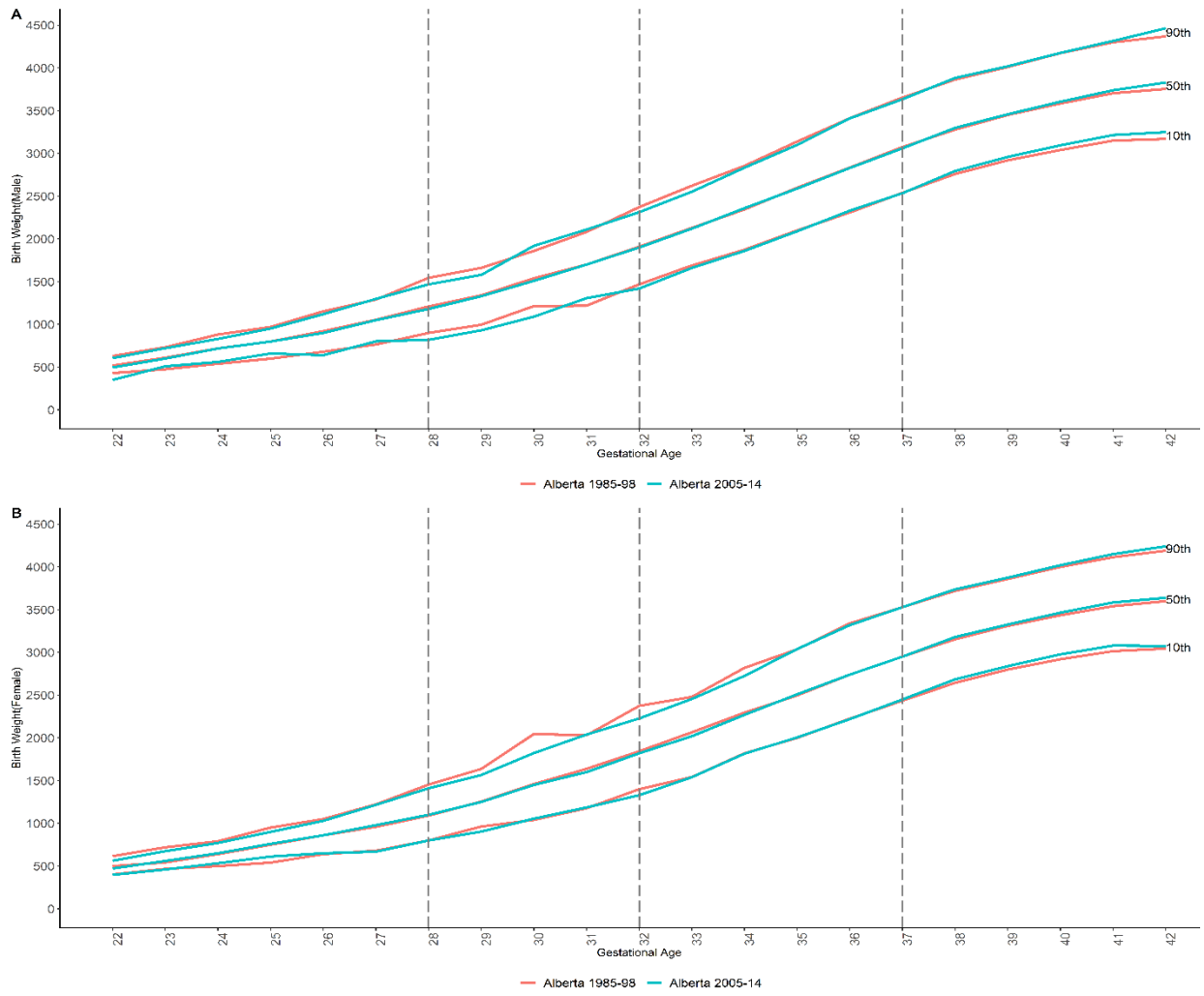
Gestational Age (weeks)	General Population			Chinese			South Asian		
	N	10th percentile	90th percentile	N	10th percentile	90th percentile	N	10th percentile	90th percentile
33	844	1545	2455	24	1536	2287.5	19	1348	2500
34	1650	1820	2730.5	50	1774.1	2606	51	1693	2540
35	2767	2020	3050	102	1854.3	2779	79	1928	2778.4
36	5938	2229.7	3327	217	2206.8	3200	210	2135.8	3080.5
37	14382	2458.1	3540	531	2423	3397	508	2356.3	3423
38	37843	2695	3745	1569	2619.4	3581.4	1401	2570	3560
39	60490	2850	3881	2546	2770	3750	1971	2710	3705
40	59139	2985	4027	1970	2905	3875.5	1517	2823.2	3790
41	29734	3090	4160	758	3013.5	4015.6	593	2935.4	3958



Supplementary Figure 1-1: This figure shows the crude birth weight percentiles based on gestational age of mothers and the original ethnicity of mother for male singletons.



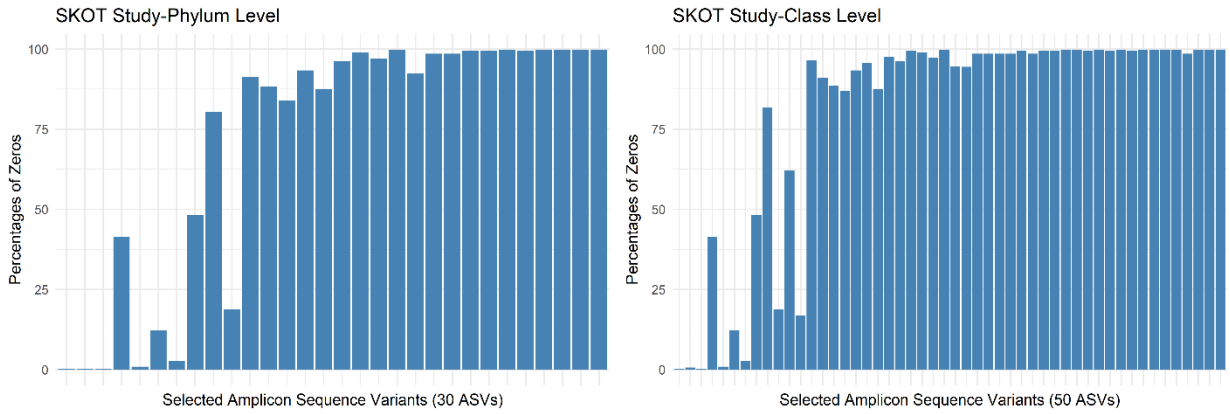
Supplementary Figure 1-2: This figure shows the crude birth weight percentiles based on gestational age of mothers and the original ethnicity of mother for female singletons.



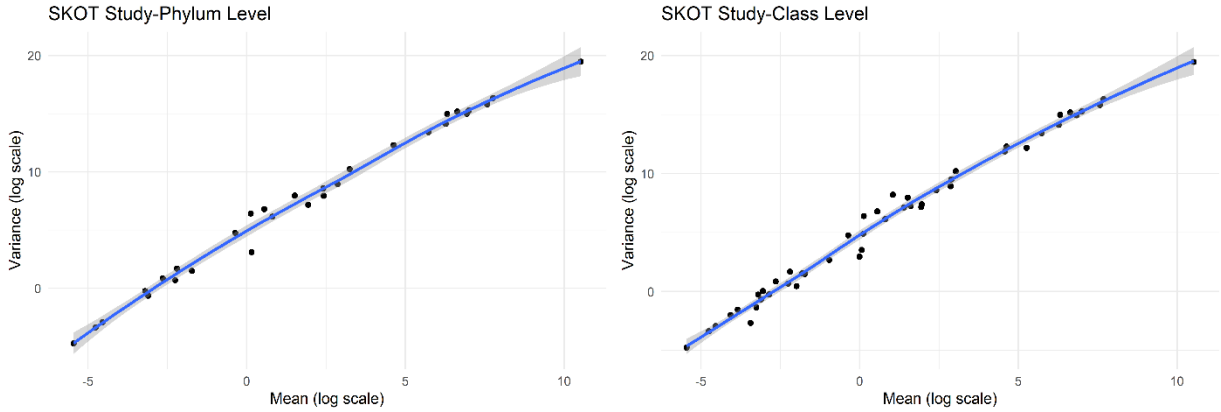
Supplementary Figure 1-3: This figure shows the crude birth weight critical percentiles based on gestational age of mothers compared to the Robertson et al.(Robertson et al. 2002) for male and female singletons.

Appendix 2

Supplementary figures and tables for chapter 4



Supplementary Figure 2-1: This figure shows the distribution of zero values in different levels of SKOT Cohorts study.



Supplementary Figure 2-2: This figure shows overdispersion in different levels of SKOT Cohorts study.

*This graph was suggested by Warton et al. in "mvabund" package to show the overdispersion in the dataset.

*A positive slope between "Log-mean" and "Log-variance" confirms overdispersion.

Supplementary Table 2-1: R Code for Data Generation Step of the Simulation Study

```
rm(list=ls(all=TRUE))
################With Correlated Random Intercepts###
require(foreign)
require(copula)
require(MASS)
require(mnormt)
require(ZIM)
require(erer)
MRgen=function(Dir,Foldername,sets,n,V,B,ZerInf,OvDis,rhoMR)
{
        setwd(Dir)
        D=paste0(getwd(),"/",Foldername)
        Path1=getwd()
i=1
while(i<=sets)
{
Nam=paste0(Foldername,".csv")
        datalist = list()
        C0=0.3
        C1=B
        eta=matrix(0,n,V)
        MR=matrix(0,n,V)
        id=1:n
        group=c(rep(0,n/2),rep(1,n/2))

        for (k in 1:sets)
        {
```

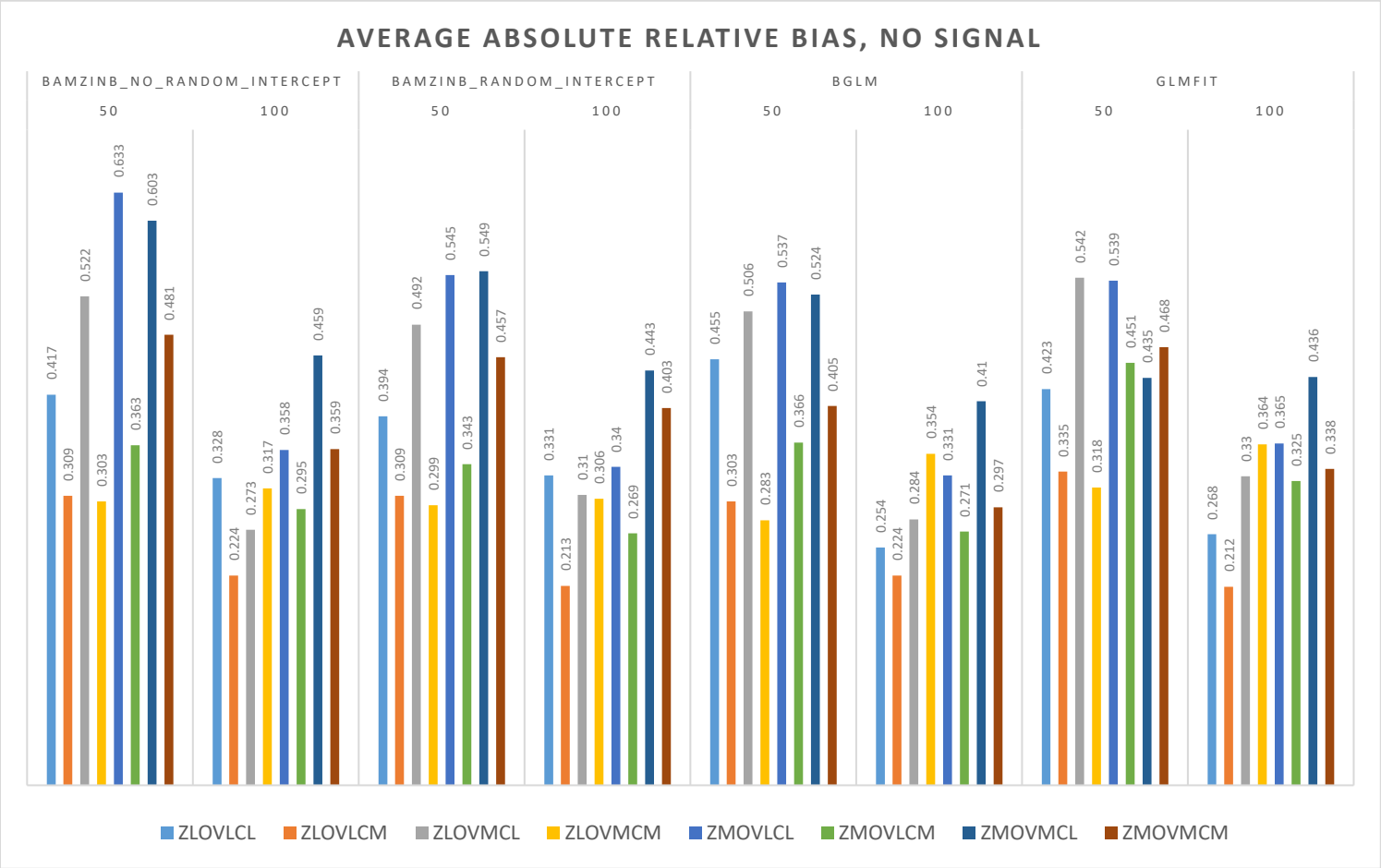
```
            RE=rMvdc(n, mvdc(normalCopula(rep(0,(V*(V-1)/2)), dim = V, dispstr =
            "un"), rep("norm",V),rep(list(list(mean = 0, sd = 1 )),V)))
        for ( j in 1 : V)
        {
            eta[,j]=exp(C0+C1*group+RE[,j])
        }
            teta=t(eta)
        for(q in 1:n)
        {
            MR[q,]=rMvdc(1, mvdc(normalCopula(rep(rhoMR ,(V*(V-1)/2)), dim = V,
            dispstr = "un"),rep("zinb",V),
            rep(list(list(k =OvDis , lambda = mean(teta[,q]), omega =ZerInf )),V)))
        }
            DataG=data.frame(cbind(id,group,MR))
             datalist[[k]] <- DataG
        }
        d = do.call(rbind, datalist)
        D=data.frame(d)
        Path2=file.path(Path1,Nam)
        write.list(list(D),Path2)
i=i+1
}}

Dir="Directory address to save the data sets"
ZerINF=c(0.5,0.7,0.9)
OverDis=c(0.75,0.30,0.10)
Corr=c(0.2,0.5,0.8)
Z=c("L","M","H")
OV=c("L","M","H")
Cor=c("L","M","H")
```

```
for(i in 1:3)
        {
                for(j in 1:3)
                {
                        for(k in 1:3)
                        {
                        nam=paste0("B2","_","Z",Z[i],"OV",OV[j],"C",Cor[k])
        MRgen(Dir,Foldername=nam,sets=1,n=500,V=300,B=2,ZerInf=ZerINF[i],OvDis=
        OverDis[j],rhoMR=Corr[k])
                        }
                }
        }
```

Appendix 3

Supplementary figures and tables for chapter 5

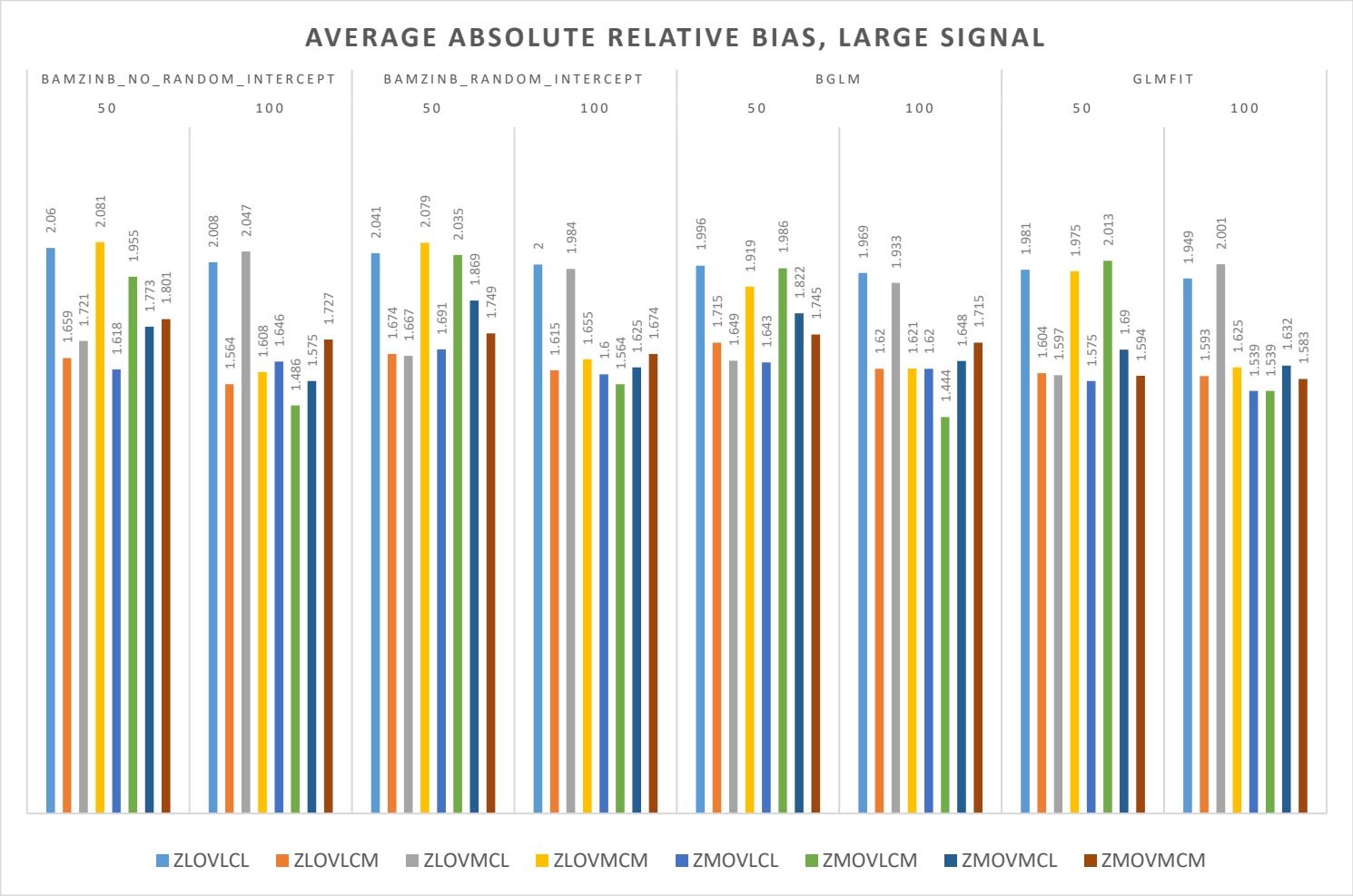


Supplementary Figure 3-1: This Figure shows the average absolute relative bias generated for each scenario by each method assuming no signal

ZL indicates zero-inflation=0.3, ZM indicates zero-inflation=0.5

OVL indicates over-dispersion=0.75, OVM indicates over-dispersion=0.5

CL indicates within-ASVs correlation=0.2, CM indicates within-ASVs correlation=0.5

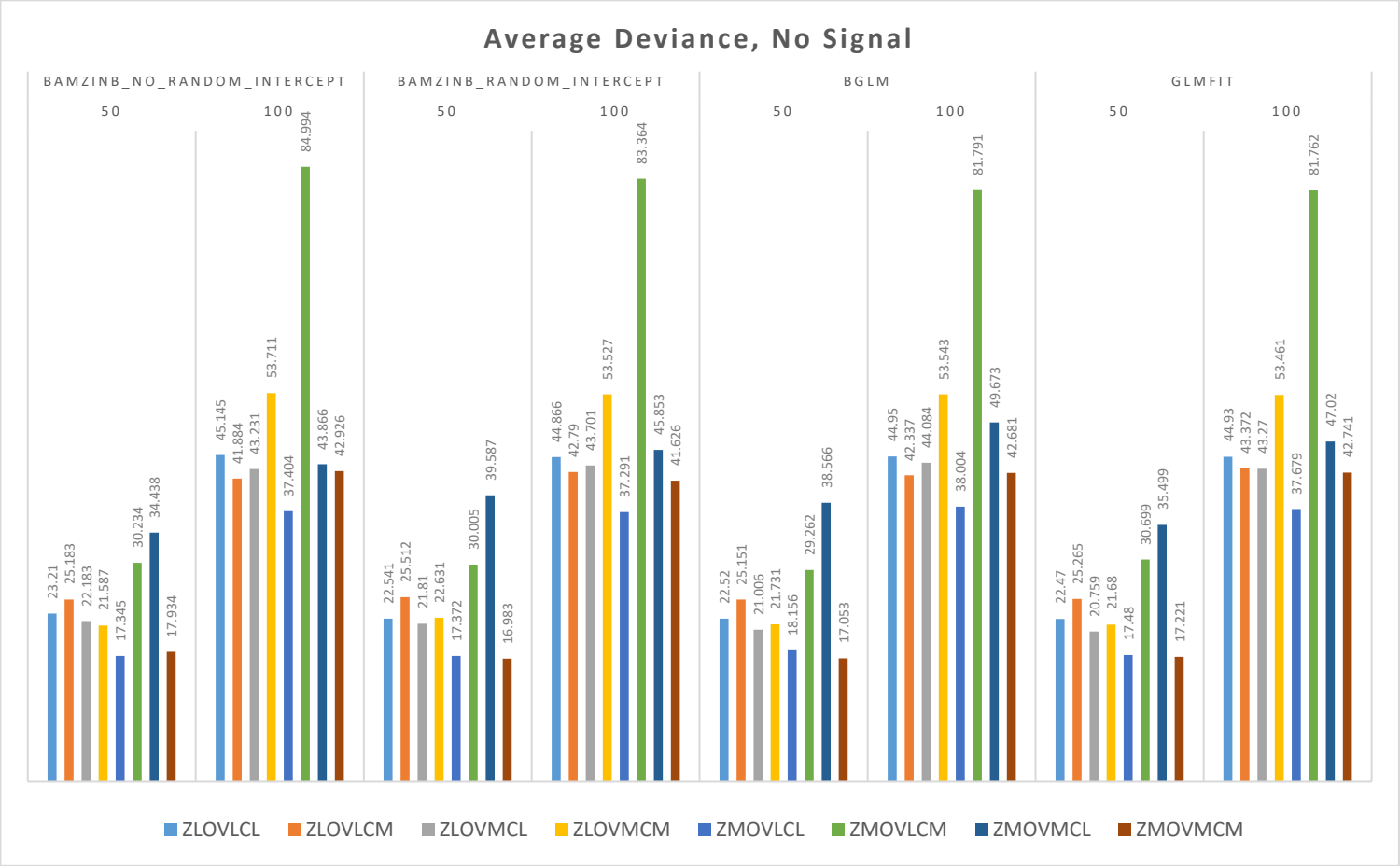


Supplementary Figure 3-2: This figure shows the average absolute relative bias generated for each scenario by each method, assuming a large signal

ZL indicates zero-inflation=0.3, ZM indicates zero-inflation=0.5

OVL indicates over-dispersion=0.75, OVM indicates over-dispersion=0.5

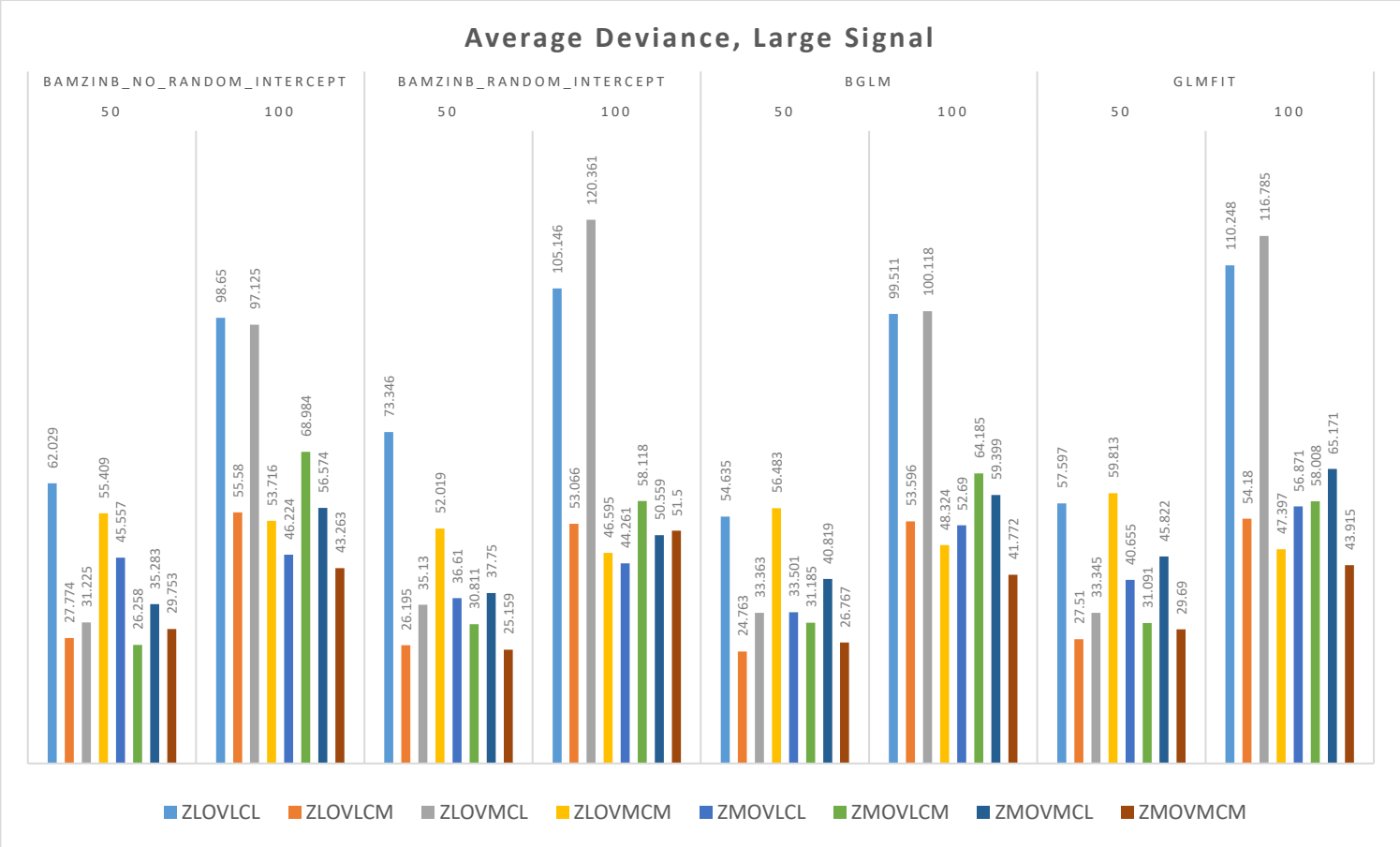
CL indicates within-ASVs correlation=0.2, CM indicates within-ASVs correlation=0.5



Supplementary Figure 3-3: This figure shows the average deviance generated for each scenario by each method assuming no signal

OVL indicates over-dispersion=0.75, OVM indicates over-dispersion=0.5

CL indicates within-ASVs correlation=0.2, CM indicates within-ASVs correlation=0.5



Supplementary Figure 3-4: This figure shows the average deviance generated for each scenario by each method, assuming a large signal

OVL indicates over-dispersion=0.75, OVM indicates over-dispersion=0.5

CL indicates within-ASVs correlation=0.2, CM indicates within-ASVs correlation=0.5