Infant Growth Among Twins: Patterns, drivers, and effects in a cohort with high representation of systematically underserved and marginalized communities, 2005-2021

By

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A DISSERTATION

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ABSTRACT OF THE DISSERTATION

Infant Growth Among Twins: Patterns, drivers, and effects in a cohort with high representation of systematically underserved and marginalized communities, 2005-2021

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The prevalence of twin pregnancies in the United States has risen in the past several decades, driven by use of assisted reproductive technologies and increasing maternal age. However, clinical and epidemiologic research focused specifically on twin pregnancies and children has not kept pace with this increasing prevalence: we currently lack foundational knowledge on several health processes and outcomes that may differ in twins compared to singletons, including growth in early childhood. The rate and pattern of early childhood weight gain is associated with health outcomes including overweight and obesity,[1] cardiovascular disease, and asthma in later life.[2,3] Twins, however, have been largely excluded from growth research for many likely reasons including insufficient sample size and methodological complexity. Utilizing a large electronic health record-based cohort of pregnant people and their children, we assessed differences in patterns of normative early childhood weight gain (0-2 years), associations with gestational weight gain (a critical driver of early childhood weight gain), and associations with childhood body mass index (an important childhood health outcome) in twins compared to singletons born at the same gestational age (GA).

Twins are a distinct population from their singleton counterparts. Although the risks of adverse health outcomes among twin gestations are generally higher than for singletons,[4,5]

associations are complex and sometimes counter-intuitive. And while risks of preterm birth, preeclampsia, and infant death are all higher among twins,[4–7] it is not true that every difference between twins and singletons results from (or is indicative of) some pathological process. For example, it is broadly accepted that some health differences (e.g., in birth weight and GA) exhibited in the twin population probably reflect some degree of physiological difference, rather than solely pathological processes of disease. In many instances, both pathological and health-neutral physiologic differences may be at play. However, differences between twins and singletons are often considered pathological *a priori*. This tendency obscures important information about the health of twins and prevents determination and delivery of optimal care. Therefore, a key aim of this dissertation is to characterize plurality-related differences in health that result from both (a) pathological processes of disease, and (b) physiologic difference. In doing so, we aim to characterize the health of twins on their own terms, without assuming the health of singletons as the automatic default.

In light of this, given the distinct distribution of GA in twins compared to singletons – the GA distribution among twins is left-shifted compared to singletons – we sought to isolate differences between the two groups that were likely driven by inherent differences between twins and singletons, rather than by consequences of GA (e.g., by being born preterm, for the majority of twins). Therefore, we normalized the time scale of early childhood growth by matching twins and singletons on GA. While this was a purposeful decision to address differences in GA, study findings must be interpreted while acknowledging the comparison of a general twin population to a selected (i.e., higher risk) singleton population. This consideration was explored in sensitivity analyses in each aim, which collectively suggested differing patterns of early childhood weight gain, yet similar estimates of associations with gestational weight gain and

with childhood body mass index in a general singleton population compared to the GA-matched singleton population.

My first research aim was to describe normative early childhood weight trajectory among twins and GA-matched singletons. We modeled weight measurements from 0-2 years of age with the Jenss model, a four-parameter mixed effects model that was created to fit growth trajectories from birth to 6-8 years. We report sustained differences in weight trajectory in twins compared to singletons: while twins had a lower starting weight, they underwent more rapid growth in early infancy. Male and female twins caught up to their singleton counterparts in weight at around 6 and 15 months, respectively, and predicted weight at 2 years was nearly identical between groups.

The second aim estimated the impact of gestational weight gain (GWG) throughout pregnancy on early childhood weight trajectory among twins and GA-matched singletons. We standardized GWG using plurality-specific reference charts at 14 weeks, 28 weeks, and delivery. We then used linear regression to model characteristics of early childhood weight gain as a function of GWG z-score at the three timepoints with robust standard errors to account for clustering within twin pregnancies and within matched groups. Our results suggest that GWG throughout pregnancy did not impact early childhood growth equally in twins and singletons, with important sex differences. GWG z-score was not associated with starting weight among twins while it had a positive association among singletons. It was, however, associated with faster early childhood growth in twins, with notable sex differences in the timing of growth: GWG z-score was associated with faster growth in infancy (0-12 months) among female twins and in childhood (12-24 months) among male twins. Among singletons of both sexes, GWG z-

score was not associated with growth in infancy but was associated with faster growth in childhood.

My final aim assessed the relationship between characteristics of early childhood weight gain and childhood body mass index (BMI) among twins and GA-matched singletons. We standardized BMI at 3 and 5 years of age using reference charts provided by the Centers for Disease Control and Prevention. We then used linear regression to model BMI z-score at the two ages as a function of characteristics of early childhood weight gain with robust standard errors to account for clustering within twin pregnancies and within matched groups. We report that characteristics of early childhood weight gain were differentially associated with childhood BMI z-score at ages 3 and 5 in twins compared to singletons. Among singletons, characteristics of early childhood weight trajectory indicative of more rapid growth (higher starting weight, faster growth in infancy, and faster growth in childhood) were associated with higher childhood BMI z-score. In contrast, among twins, characteristics of weight trajectory occurring in infancy were not associated with higher childhood BMI z-score.

Collectively, this body of work highlights that there exist inherent differences between twins and singletons which suggest the need for the establishment of evidence-based twin-specific clinical guidelines for early childhood growth. We describe how normative early childhood weight gain, its drivers, and its effects differ in twins and singletons independent of differences in GA. Results were similar when compared both to a general singleton population and to a singleton population with a similar GA distribution as twins. These findings suggest unique drivers of fetal and early childhood growth in twins, such as epigenetic or metabolic processes, compared to singletons. Further research is needed to understand these drivers and to establish twin-specific clinical guidelines for GWG and early childhood growth. These and

subsequent findings have the potential to greatly impact the care and resulting health of this population.

DEDICATION

To my favorite twins, Jack and Ellis.

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TABLE OF CONTENTS

LIST OF TABLES

Chapter 3

Chapter 4

Chapter 5

Appendices

LIST OF FIGURES

Chapter 3

Chapter 4

Chapter 5

Appendices

LIST OF ABBREVIATIONS

ADVANCE	Accelerating Data Value Across a National Community Health Center Network
ANOVA	Analysis of variance
BMI	Body mass index
BMIz	Body mass index z-score
CDC	Centers for Disease Control and Prevention
CHCO	Community-based health care organization
CI	Confidence Interval
EHR	Electronic health record
FPL	Federal poverty level
GA	Gestational age
GWG	Gestational weight gain
GWGz	Gestational weight gain z-score
HSD	Honestly significant difference
ICD	International Classification of Diseases
MICE	Multiple imputations by chained equations
OR	Odds ratio
PCORnet	National Patient-Centered Clinical Research Network
PROMISE	PReventing Obesity through healthy Maternal gestational weight gain In the Safety nEt
RIWG	Rapid infant weight gain
SD	Standard deviation
SDOH	Social determinants of health
SES	Socioeconomic status

US	United States
WHO	World Health Organization

CHAPTER 1. INTRODUCTION & RESEARCH AIMS

1.1 Introduction

The rate of twin pregnancies in the United States (US) has doubled since 1980 and twins now account for roughly 3% of live births.[8,9] However, research on growth and development specifically in twins has not kept pace with this increasing prevalence. Abundant research has linked rapid early childhood weight gain with later health outcomes, including overweight and obesity, diabetes mellitus, cardiovascular disease, hypertension, asthma, and mortality.[1–3,10–14] Further, growth trajectories among children classified with underweight, normal weight, overweight, or obesity at five years of age are discernible as early as one-week post-birth.[13] Given that children with obesity are highly likely to continue to have obesity into adolescence and adulthood,[15] intervening as early as possible in cases of rapid growth thus can have critical and lasting effects on health for the rest of the life course. Twins, however, have been largely excluded from growth research. The absence of appropriate, twin-specific evidence could lead to erroneous interventions (or non-intervention), with potential health consequences.[16]

Twins exhibit unique fetal growth patterns compared to singletons because they share uterine space[17,18] and experience an average shorter gestational duration;[16,19,20] thus, twins have less space and time, respectively, to grow *in utero.* However, research among non-US-based cohorts of twins reports that twins gain weight more rapidly than singletons in early life,[19,21–24] catching up in weight by mid- to late-childhood. Despite this more rapid weight gain, the prevalence of cardiometabolic outcomes, such as obesity, among twins is not higher, and perhaps is lower, than the prevalence among singletons.[23–25]

Understanding of the inherent differences between twins and singletons that are not due to profound differences in gestational age (GA) was the focus of this dissertation. In 2022, twins

and singletons in the US were born at an average GA of 35.4 and 38.6 weeks, respectively.[26] The final weeks of gestation are critical for fetal growth and achieving optimal birth weight, as can be seen by very rapid fetal weight gain in the final weeks before birth.[27,28] Therefore, uncertainty arises when comparing the postnatal growth of twins and singletons without accounting for GA: that is, whether observed differences are driven by differences in gestational duration (e.g., by being born preterm, for the majority of twins) or by developmental conditions unique to twins. Throughout this work, twins and singletons were matched on GA and sex, thus enabling the comparison of GA-normalized growth by plurality. Inherent in this decision is the comparison of a general twin population to a selected singleton population who were born earlier and had a unique risk profile compared to a general singleton population. This should be considered when interpreting results in this dissertation. Sensitivity analyses were conducted to explore this consideration; results are included in each aim.

This work establishes foundational knowledge regarding early childhood growth among twins and is one of the only studies to describe normative growth among a contemporary cohort of twins in the US. Further, this work will provide evidence needed for developing twin-specific clinical guidelines for pregnancy and childhood, establishing a link between gestational weight gain (GWG) and child growth and the first direct association between characteristics of early childhood weight gain and childhood body mass index (BMI) among twins.

1.2 Dissertation Overview & Research Aims

In Chapter 2, I begin with a review of the literature on early childhood growth in twins and singletons. I review the evidence supporting associations between perinatal exposures and child growth, and between child growth and later health outcomes. Finally, I present the critical gaps

and limitations in the current body of research that hinder our understanding of these associations in a population of twins.

In Chapter 3 (**Aim 1**), I describe normative early childhood weight gain among a population of twins and GA-matched singletons. I utilize data from a large, electronic health record (EHR)-based cohort (the PReventing Obesity through healthy Maternal gestational weight gain in the Safety nEt [PROMISE] study cohort) and apply the Jenss model, a four-parameter mixed effects model that was developed to fit growth trajectories from birth to 6-8 years of age. I provide interpretation and comparison of growth trajectories between twins and singletons that are temporally nuanced and clinically relevant.

In Chapter 4 (**Aim 2**), I estimate associations between GWG at three timepoints during pregnancy and early childhood weight gain among twins and GA-matched singletons. I assess GWG as standardized z-scores, specific to plurality and maternal pre-pregnancy BMI. The outcomes for this Aim are the four parameters from the Jenss model, each of which describe a characteristic of early childhood growth. I estimate effects using multivariable linear regression with robust standard errors to control for clustering within twin pregnancies and within matching group membership.

In Chapter 5 (**Aim 3**), I examine the associations between early childhood weight gain and childhood BMI among twins and GA-matched singletons. The exposures for this Aim are the four parameters from the Jenss model, and the outcomes are standardized BMI z-scores, specific to sex, at 3 years and 5 years of age. Again, I estimate effects using multivariable linear regression with robust standard errors to control for clustering within twin pregnancies and within matching group membership.

In Chapter 6, I conclude with a summary of key study findings, future research directions, and public health implications. The appendices provide supplemental material for the three aims.

CHAPTER 2. REVIEW OF THE LITERATURE

Despite the rapidly rising prevalence of twin births in the United States (US) in the past decades,[8,9] driven by increasing maternal age and use of assisted reproductive technologies, most literature assessing childhood growth has been conducted specifically among singletons. Indeed, most studies specifically exclude twins due to insufficient sample sizes, methodological complexity, and/or because they are a unique subgroup of infants: twins are exposed to unique perinatal factors and exhibit different fetal and postnatal growth patterns compared to singletons. This standard practice has left a significant gap in the literature, leading to a dismal evidence base for health care recommendations and guidelines for twin pregnancies and infants.

The research referenced in sections 2.1-2.3 was conducted specifically among singletons or among a general population (e.g., did not specify if twins were removed).

2.1 Typical Early Childhood Growth In Singletons

Typical growth is not linear; it involves periods of rapid growth (i.e., "growth spurts") separated by periods of little or no growth, and is additionally seasonal, with growth velocities increased during the spring and summer months.[29] Nonetheless, a general understanding of typical growth can be inferred.

Infants born at term (i.e., delivery at ≥37 weeks of gestation) generally lose 5-10% of their birth weight in the few days after birth, and typically regain this weight within 14 days. They then gain between 14 and 30 g/day until three months of age; approximately 20 g/day between three and six months of age; and approximately 10 g/day between six and 12 months of age. This results in the doubling of birth weight by four months of age and the tripling of birth

weight by one year. Birth weight is typically quadrupled by two years, after which children gain approximately 2 kg per year until they reach puberty.[29,30]

2.2 Early Childhood Growth and Later Life Health In Singletons

A vast body of literature has linked early childhood growth with later health outcomes, with overweight and obesity, diabetes mellitus, cardiovascular disease, hypertension, asthma, and mortality, among other conditions, implicated.[1–3,10–14] Rapid infant weight gain (RIWG) in particular has been targeted as a strong risk factor for these morbidities. While several adverse perinatal exposures (e.g., preterm birth or low birth weight) are associated with RIWG, evidence suggests that it is the RIWG itself, not the adverse perinatal exposures, that serves as the precursor to these health conditions later in life.[3,10]

For example, a meta-analysis using data from the United Kingdom, France, Finland, Sweden, the US, and Seychelles reported that every one unit increase in weight standard deviation score from birth to one year of age was associated with a twofold higher odds of childhood obesity (odds ratio [OR] 1.97, 95% confidence interval [CI]: 1.83, 2.12) and 23% higher odds of adulthood obesity (OR 1.23, 95% CI: 1.16, 1.30).[11] Furthermore, a review paper reported that 45 of 46 studies described an association between rapid infant growth and later obesity, and five randomized trials supported a link between slower infant growth and lower risk of later obesity.[12] Body mass index (BMI) growth patterns among children later classified with normal weight, overweight, obesity, and severe obesity at 5 years of age are distinct as early as one week post-birth,[13] indicating the need for early monitoring and potential intervention.

The biologic mechanism underlying the connection between RIWG and adverse cardiometabolic outcomes is likely complex and remains uncertain. However, it has been

proposed that a combination of fetal undernutrition, oxidative stress, inflammation, feeding practice, and maternal metabolism operate through RIWG and influence later cardiometabolic outcomes.[31–33]

Early childhood growth is thus a critical characteristic that has profound implications on public health and clinical practice. Intervening in cases of atypical growth has the potential to directly affect downstream health.

2.3 Determinants of Early Childhood Growth In Singletons

In order to best prevent or intervene in cases of atypical growth, it is critical to understand its determinants. The determinants of child growth can be separated into *pre-pregnancy and pregnancy factors, postnatal factors,* and *social determinants of fetal and child growth.* The determinants outlined here are not exhaustive and were chosen based on volume of evidence and relevance to contemporary US populations.

Pre-Pregnancy and Pregnancy Factors

It is well established that maternal pre-pregnancy health and the intrauterine environment can have lasting effects on offspring health and growth.[34] For example, many studies have reported associations with maternal pre-pregnancy BMI: one meta-analysis reports 264% higher odds of childhood obesity and 80% higher odds of childhood overweight among children whose birthing parent had pre-pregnancy obesity compared to pre-pregnancy normal weight.[35]

Further, a study representing approximately 30% of US births from 2010-2011 found that 64.1% of pregnant people with pre-pregnancy overweight and 63.5%, 54.4%, and 45.8% of pregnant people with pre-pregnancy obesity class I, II, or III, respectively, gained above

recommended gestational weight gain (GWG) guidelines.[36] GWG has implications for infant health and growth. For example, one meta-analysis of 265,270 births from Europe, North America, and Oceania found that 31.6% of the risk of having a large for gestational age infant and 23.9% of the risk of pregnancy complications are attributable to excessive GWG.[37] Because of the patterning of GWG by pre-pregnancy BMI, an interaction effect of these factors with infant growth occurs. One study, for example, among 499 mother-children dyads from Nashville, Tennessee reported that excessive GWG amplified the effect of pre-pregnancy BMI, resulting in a greater elevation of the infant growth curve through the first year of life compared to the effect of pre-pregnancy BMI alone.[38]

Other exposures occurring during pregnancy, such as maternal gestational diabetes mellitus,[39] maternal hypertension,[40,41] fetal growth restriction,[42] maternal cortisol levels,[2] and stressful events during pregnancy[43] have also been shown to be associated with more rapid infant growth.

Postnatal Factors

Several postnatal factors may also affect early childhood growth. One of the most impactful factors is feeding practice. It is recommended by clinical organizations that infants be exclusively breastfed for the first 6 months of postnatal life, with continued breastfeeding alongside the introduction of complimentary foods for at least one year.[44,45] However, in the US, only approximately 25% and 55% of infants are exclusively breastfed or receiving any breast milk by 6 months of age, respectively.[44] Breastfed infants typically grow slower than formula-fed infants,[46–49] likely driven in part by increased protein intake among formula-fed infants,[49] although the composition of breastmilk differs widely between and within mothers (see Gale, et

al.[50] for a review) and other aspects of breastmilk and breastfeeding likely also contribute. Breastfed infants are thus less likely to undergo RIWG and less likely to have overweight or obesity in childhood.[51] Upon the introduction of complimentary foods, the quality of food becomes critical: the early introduction of processed food or sugar-sweetened beverages is associated with higher (i.e., more rapid) weight trajectories and later overweight and obesity.[52–54]

Limited research further supports the association between activity levels of children and their growth, with more active infants having a lower weight trajectory and eventual leaner body size compared to less active infants.[55,56] However, the accurate capture of physical activity in this age group, especially before the development of the ability to walk, is a current limitation of this research.

Social Determinants of Fetal and Child Growth

The aforementioned associations do not take place in a vacuum; they exist within complex societal structures and institutions. Social and political institutions and processes create social class divisions within our society – divisions that influence material and social conditions, termed the social determinants of health (SDOH). The SDOH affect how people are born, live, learn, work, play, and age and, thus, their health and wellbeing throughout their lives. Indicators of these divisions include income, education, occupation, race, ethnicity, sex, and gender.[57] Fetal and infant growth are two examples of health outcomes that are affected by the SDOH.

In 2018, 10.0% of infants born in the US were preterm. This statistic is not consistent, however, across racial and ethnic subgroups: while 9.1% of non-Hispanic White infants were born preterm, 14.1% of non-Hispanic Black infants were born preterm.[58] Preterm infants are born earlier and thus smaller on average compared to term infants, exposing them to greater risk

of RIWG and the associated adverse health outcomes described above. Further, it has been shown that there are racial and ethnic disparities in childhood and adolescent overweight and obesity prevalence, with prevalence as high as 45.9% and 37.8% in Hispanic and Black children and adolescents, respectively, compared to 35.1% in the overall population of children and adolescents in the US.[59,60] These racial and ethnic differences reflect inequitable availability of neighborhood and household resources[61] and racial-based stressors (e.g., systematic racism limiting opportunity for economic growth). And, in a recent systematic review, stronger associations between early life growth and later obesity tended to be observed in study populations that included high proportions of children from low-socioeconomic status (SES) families and of non-White race.[59] Prevalence of breastfeeding is similarly inconsistent across indicators of SDOH, with, for example, parents with more education and with longer parental leave from their job being more likely to initiate and continue breastfeeding compared to those with less education and shorter parental leave, respectively.[62]

It is thus tremendously important to study health and, specifically for this project, early childhood growth, particularly in populations with high prevalence of adverse SDOH. Guidelines for infant growth, however, are largely informed by research from predominately White and moderate-to-high SES populations.[59]

2.4 Early Childhood Growth in Twins

In the US, the Centers for Disease Control and Prevention (CDC) recommends the use of the World Health Organization (WHO) growth standards[63,64] for infants 0 to 2 years of age, and the CDC growth charts[65,66] for children 2 years of age and older. The WHO standards were constructed from an international population of highly selected singletons while the CDC charts

were constructed from nationally representative data from the US and did not differentiate between singletons and multiples. It is common clinical practice to assess twin infant growth using these growth charts, which have been shown to misclassify twins as growth-restricted, given their smaller stature at birth and thereafter.[16] For example, one study reported a prevalence of small for gestational age among twins of 33% when using a reference that was constructed from singleton data, vastly higher than 4% based on a reference that was constructed from twin data.[67]

Twin-specific reference charts for early childhood weight gain have been published, including a 1974 analysis among 584 non-Hispanic White twins from the Louisville, Kentucky area,[68] a 2004 analysis among 4,058 twins from Japan,[69] and a 2008 analysis among 8,318 twins from the Netherlands born in the 1980s and 1990s.[19] The growth charts from the Netherlands are perhaps the most rigorous and the most commonly cited of the three. Compared to the singleton Dutch reference, the authors report sustained differences in weight trajectory between singletons and twins from birth to 2.5 years, with smaller size at birth and faster growth among twins, even after correcting for differences in GA at birth.[19] It is yet unknown if this chart from the Netherlands can serve as an appropriate growth reference for twins in the US. A cursory visual comparison of the Netherlands chart to the CDC weight chart (not shown), which was constructed using data from both singletons and multiples in the US, shows marked differences among the 50th percentile (0 standard deviations) from birth to 12 months for both boys and girls. The differences appear to decrease thereafter until they reach a similar final weight at 30 months. This comparison suggests that twins may grow faster than singletons but highlights the need for a thorough understanding of twin growth in a contemporary and diverse US population – an understanding which has, as yet, been very limited.

2.5 Drivers of Fetal Growth in Twins

Several factors unique to twins affect fetal growth and subsequent child growth among twins. In fact, a US-based, twin-specific fetal growth reference chart has been published,[70] though it has been reported that its clinical use is limited.[71]

Shared Uterine Space and Gestational Age

Twins are born, on average, with a lighter weight compared to singletons.[17] This is due to different fetal growth patterns in twins compared to singletons. While twin and singleton fetuses show similar growth in the first and second trimesters, twins display slower growth beginning around the third trimester likely due to the shared uterine space.[18] However, this conclusion has been contested on the basis of the high compliance of the uterine wall,[17] with some speculating that twins are actually "growth promoted" rather than "growth restricted";[72] that is, because total fetal mass in a twin gestation is larger than fetal mass in an average singleton gestation or, put another way, each individual's birth weight in a twin gestation is more than half of the birth weight of an average singleton. Evidence is still emerging to address this question. Additionally, twins experience an average shorter gestational duration compared to singletons, which does not provide them with the same amount of time to grow *in utero*.[16,19,20]

Mechanisms of Growth

It has further been hypothesized that some of the mechanisms underlying fetal growth in twins are inherently different from those of singletons. For example, studies exploring the effect of fetal reduction in twin pregnancies (i.e., reducing a twin pregnancy to a singleton pregnancy,

either surgically or spontaneously) report slower fetal growth and lower birth weight of the remaining fetus compared to naturally conceived singleton fetuses, even when reduction occurred very early in pregnancy.[7,22,73,74] Similar findings were reported in a study among triplet pregnancies reduced to twin pregnancies compared to naturally conceived twin pregnancies.[75] Additionally, in animal models, twinning has been associated with unique epigenetic changes that potentially alter energy balance regulation and subsequently slow growth of the twin fetuses.[7,76] This suggests that fetal size may be influenced, at least partly, by processes occurring very early in gestation.

Other

Other factors which have been linked to fetal growth among twins include sex of the co-twin (i.e., with infants from unlike-sex twin pairs having higher birth weights than infants from like-sex pairs, for both males and females)[77,78] and zygosity (i.e., genetic similarity between twins, either monozygotic ["identical", 100% shared genes] or dizygotic ["fraternal", 50% shared genes]).[79–81]

2.5.1 Drivers of Early Childhood Growth in Twins

Given that early childhood growth is strongly influenced by fetal growth, the aforementioned factors that affect fetal growth are subsequently associated with early childhood growth among twins. For example, lighter birth weight is associated with more rapid growth among twins born at the same GA.[22]

2.6 Outcomes of Early Childhood Growth in Twins

Previous research has indicated that, though they do grow more rapidly, twins tend to have an average or leaner body size by late childhood and adolescence compared to their singleton siblings or the general population.[22–25] It is unknown whether the prevalence of other health outcomes related to early childhood growth, such as diabetes, cardiovascular disease, hypertension, and asthma, is similarly low in twins despite faster growth in early childhood. One recent study among a large cohort of Israeli twins and singletons reported lower incidence of several respiratory and neurological morbidities by age 18 among twins compared to singletons born at the same GA.[82] Another recent study among a large cohort of Canadian twins and singletons reported higher odds of an adverse composite health outcome (including cognitive, motor, and language development, hearing and vision, cerebral palsy, and death) by age 3 among extremely preterm twins ($23^{0/7}$-$25^{6/7}$ weeks' gestation) but not among preterm twins born at a slightly later gestation ($26^{0/7}$-$28^{6/7}$ weeks' gestation) compared to singletons born at the same GA.[83] However, it is unknown the extent to which early childhood growth is implicated in these relationships.

2.7 Knowledge Gaps in the Research

It is evident that twins and singletons present with different prenatal and postnatal exposures compared to singletons, and that they exhibit different fetal and postnatal growth patterns compared to singletons. However, many gaps in the research remain.

No twin-specific growth reference exists for twins in the US; recommended growth is not described

Twin pregnancies and deliveries are becoming increasingly more prevalent globally due to a higher average maternal age and the use of assisted reproductive technology, and now represent approximately 3% of all pregnancies.[16] It is clear that twins experience a unique intrauterine environment compared to singletons, and thus have unique fetal and child growth compared to singletons.[20] It is common clinical practice, however, to assess singleton and twin child growth in the same manner (i.e., using the WHO and CDC charts described above). While the aforementioned twin-specific growth reference charts from the Louisville, Kentucky area,[68] Japan,[69] and the Netherlands[19] were created to change this practice, they have had no success in clinical practice. A review of the Epic clinical software at our institution revealed no twin-specific growth reference chart available for clinician use (Dr. Alex Foster, Oregon Health & Science University, personal communication, 2023). Additionally, a formal comparison of the international reference charts to US twin data has, to our knowledge, not been conducted, so it is unknown if these charts can serve as a reasonable reference for twins from the US. Further, neither normative nor optimal growth for twins in the US has been described.

There is limited evidence regarding the drivers and effects of infant growth among twins

Research focused on twin pregnancies and subsequent child growth and health has not increased with twins' increasing prevalence. And, much of the very little research examining the relationship between pregnancy factors, such as GWG, with subsequent offspring growth among twins presents with limitations. For example, existing studies assessing the association between GWG and early childhood growth among twins[84–87] are limited in their generalizability to the current US population or did not report on timing of GWG, which has shown to influence perinatal outcomes.[88–90] There is additionally very little research examining how that growth

affects later health outcomes, such as childhood BMI. Only one study to our knowledge has been published which directly assessed the association between early childhood growth and childhood BMI among twins, but it solely assessed RIWG.[22] Given the evidence that twins exhibit different growth patterns compared to singletons, it is expected that its relationship with perinatal factors and with childhood health will additionally differ in twins.

Research that specifically focuses on individuals of lower SES or of minority racial and ethnic groups is sparse

Given the established interconnectedness of the SDOH with growth and health, research is needed to understand these relationships within twins from lower income and racially/ethnically diverse populations.

Contributions of this research

This research seeks to fill these gaps by (1) describing normative early childhood weight trajectory among twins compared to singletons born at the same GA; (2) assessing the association between GWG and early childhood weight trajectory in twins compared to singletons born at the same GA; and (3) estimating the effect of early childhood weight trajectory on child BMI in twins compared to singletons born at the same GA. I utilize data from a recently-constructed electronic health record-based cohort of predominately low-income and racially/ethnically diverse pregnant persons and their children. Collectively, this research aims to better understand normative early childhood weight gain in twins to inform and improve clinical practice, and ultimately impact the health of this increasing population.

CHAPTER 3. RESEARCH PAPER #1

Early childhood weight trajectory differences in twins and gestational-age matched singletons

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3.1 Abstract

Background: Early childhood weight trajectory is an important clinical risk factor for several later health outcomes including weight status, cardiovascular disease, and immune function. However, weight gain research specifically among twin populations remains scant and methodologically challenged, though the prevalence of twins has increased substantially in the past decades.

Objective: The objective of this study was to compare weight trajectories of twin and singleton children 0-2 years of age, independent of differences in gestational age.

Methods: Data are from the PROMISE study, an electronic health record-based cohort of pregnant people and their children from community-based health care organizations in the United States. Infant weight measurements between 0-2 years of age were included. Singletons were matched to twins on gestational age at birth and sex. The Jenss model, a four-parameter mixed-effects model, was used to assess weight trajectories.

Results: Despite matching on gestational age, twins had lower birth weight compared to singletons. However, both male and female twins displayed faster weight gain in infancy compared to their singleton counterparts, catching up in weight at around 6 and 15 months, respectively. Predicted weight at 2 years was nearly identical within plurality groups.

Conclusions: Differences in weight trajectories between twins and singletons 0-2 years of age exist independent of differences in gestational age, with important sex differences, but disappear by 15 months of age. Future research is needed to assess if these patterns continue into later childhood and to assess factors that may be driving differences in weight trajectories between twins and singletons.

3.2 Introduction

Approximately 20% of infants undergo rapid weight gain[91,92] which is associated with greater odds of overweight and obesity,[1] cardiovascular disease, and asthma in later life.[2,3] Slow infant weight gain is also detrimental, associated with outcomes such as poor development of cognitive skills and the immune system.[93] Growth is thus monitored closely during infancy, with interventions introduced in cases of atypical (i.e., rapid or slow) growth. Twins, however, have been largely excluded from growth research. The absence of appropriate, twin-specific evidence could lead to erroneous interventions (or non-intervention), with potential health consequences.[16] Rates of twin pregnancies have doubled since 1980 and now account for approximately 3% of live births in the United States (US).[8,9] Despite this growing prevalence, the understanding of normative early childhood weight gain specifically among twin populations remains scant.

While clinical practice often aligns with evidence that twins are born at a lighter weight compared to singletons, then undergo more rapid weight gain and have comparable weight to singletons by late childhood,[19,20,22–25] this evidence is limited, mixed, and has critical limitations. For example, studies have mixed findings, reporting that differences in weight between twins and singletons disappear by 4 years in the Netherlands,[94] 7-9 years in New York,[22] and 8 years in Kentucky.[25] This prior work lacks representation of contemporary study populations, analyzing data from the 1950s through 1990s, and/or studied non-US cohorts or US cohorts of predominately White infants, raising concerns of generalizability to the current US population[19,20,23–25] where early childhood growth is known to differ by several maternal,[34,35,37] clinical,[39–42] and social factors.[59–62] Additionally, few studies[19,24,25] use longitudinal, provider-recorded weight measurements, which can be more accurate and frequent than parent recall or research visits at specific ages.[20,22,23]

Prenatally, twins exhibit different fetal growth patterns compared to singletons because they share uterine space[17,18] and experience an average shorter gestational duration;[16,19,20] thus, twins have less space and time, respectively, to grow *in utero*. Zygosity and co-twin sex also affect prenatal growth, birth weight, and postnatal growth.[78–81] These factors highlight that twins present with necessarily different exposures and risk factors compared to singletons that may affect early childhood growth.

The different distribution of gestational age (GA) at birth between twins and singletons cannot be disregarded. In 2022, twins and singletons in the US were born at an average GA of 35.4 and 38.6 weeks, respectively.[26] The final weeks of gestation are critical for fetal growth and achieving optimal birth weight.[27] Therefore, complexity arises when comparing the postnatal growth of twins and singletons without accounting for GA: that is, whether observed differences are driven by differences in gestational duration or by developmental conditions unique to twins.

Our objective was to characterize the growth of twin children in our large, electronic health record (EHR)-based cohort, which includes diverse racial and ethnic group representation and children from predominately low-income families. For context, we additionally characterized the growth of singletons with a comparable GA distribution as the twins, therefore aligning the time-scale of early childhood growth, by matching singletons to twins on GA and sex. Even after matching, we hypothesized that, compared to singletons, twins would be born lighter, on average, but experience more rapid growth in early infancy. We also hypothesized sex differences in growth among both twins and singletons, as has been shown in previous research among singletons,[63] with females born smaller and remaining smaller than males through our two-year follow-up period.

3.3 Methods

Study population

The Preventing Obesity Through Healthy Maternal Gestational Weight Gain in the Safety Net (PROMISE) study cohort was derived from EHR data from OCHIN, Inc, supported by the Accelerating Data Value Across a National Community Health Center Network (ADVANCE) Clinical Research Network, a Patient-Centered Outcomes Research Network (PCORnet) member.[95,96] ADVANCE integrates EHR data for community-based health care organizations (CHCOs) from across the US and contains demographic, utilization, and clinical data. The PROMISE study was approved by the [redacted] Institutional Review Board.

The PROMISE cohort contains data from 77,599 pregnancies (among 65,179 individuals) that started between 4/16/2004 and 7/6/2020 in patients 15 years of age or older at pregnancy start and that met the following criteria: GA at delivery between 20 and 42 weeks, available adult height, and had requisite weight measures: pre-pregnancy weight, ≥1 weight measure in the second or third trimester, and ≥1 additional weight measure during pregnancy. Most PROMISE patients lived in California (38.3%) or Oregon (27.2%) while pregnant. Supplemental data from linked[97] birth records, including birth weight and select maternal descriptive variables, were obtained for California and Oregon births. Birthing parents were linked to child(ren)'s EHR data using methods developed and validated by a national PCORnet project[98] and ADVANCE research.[99]

Study variables

Child weight

This study assessed child weight measurements from 0-2 years of postnatal life. Implausible weight values were identified using the "growthcleanR" package in R;[100] only weight values identified as plausible were used in this analysis (2.8% of 1,027,182 weight values removed).

Baseline weight

Baseline weight was defined as the minimum weight among birth weight and clinical visits from postnatal days 0-5. This approach accommodated the monotonic growth model (Jenss model, see Statistical analysis), maximized our sample size, and aligned with prior studies that used the Jenss model,[101,102] although approaches vary.[103–107] Other weight values in the first 5 days of life that were not the minimum value were removed.

Birth weight was ascertained from the birth record (27.4% of twins and 47.1% of singletons); 72.6% of twins and 52.9% of singletons were missing a birth record and therefore missing birth weight. Implausible birth weights were defined with GA- and sex- standardized z-scores calculated from birth weight references for twins[108] and singletons[27] and removed; see Supplementary Materials.

Demographics and health-related variables

Plurality was determined from the birth record if available (46.7%), otherwise by the presence of at least one International Classification of Diseases (ICD)-9 or ICD-10 diagnosis code indicating a twin pregnancy in the birthing parent's EHR (used only to determine twin status; see Supplementary Materials) (1.3%), otherwise by the number of children who shared the same birthing parent and birth date in the EHR (52.1%). The obstetric estimate of GA from

the birth record was used if available (27.2% of twins and 47.0% of singletons); otherwise, GA from the EHR was used (72.8% of twins and 53.0% of singletons).

The following descriptive variables were used to compare twins and singletons in the study population. Parity and maternal education were determined from the birth record and thus were only available for children born in California and Oregon; all other variables were determined from the EHR. Child race and ethnicity are used in this study as descriptive sociodemographic variables that reflect social and cultural differences, including exposure to racism, that can affect health outcomes. Maternal age at the end of pregnancy, preferred spoken language, tobacco use during pregnancy, income as a percentage of the federal poverty level (FPL) reported at the visit closest to pregnancy start, and most prevalent insurance type in the second and third trimesters[109] were also included.

Analytic sample

This study was limited to male and female children linked to a birthing parent in PROMISE (N=55,743) (**Figure 3.1**). The study was further limited to singletons and twins, excluding 30 triplets and 177 children with unclear plurality, then limited to children who had an available baseline weight (44.4% of twins and 24.3% of singletons excluded) and at least one valid weight measurement between five days and two years of life (1.7% of twins and 1.8% of singletons excluded).

Analytic sample: Matching

The distribution of GA among twins is left-shifted roughly three weeks compared to that of singletons.[26] We were interested specifically in assessing differences in early childhood

growth between twins and singletons that were driven by inherent differences, rather than as a consequence of GA. To therefore align the time scale of early childhood growth, singletons were matched to twins on GA (nearest neighbor matching) and sex (exact matching) in a 10:1 ratio, without replacement.[110] However, acknowledging that GA may have different determinants in twins compared to singletons (i.e., early GA may be largely physiological in twins and pathological in singletons[7,111–113]), we conducted a sensitivity analysis that examined early childhood growth in the full population of singletons, described below.

Statistical analysis

Early childhood weight trajectory

We modeled early childhood weight gain using the Jenss model, a four-parameter mixed effects model that was developed to fit growth trajectories from birth to 6-8 years. The model differentiates the pattern of growth into two periods: nonlinear growth during infancy and linear growth in childhood, and has shown to fit childhood growth data well.[102,105,114] We use the terms "infancy" to refer approximately to ages 0-6 months and "childhood" to refer approximately to ages 6 months-2 years. While studies assessing singleton growth have used the Jenss model,[101–103,106,114] we are the first, to our knowledge, to apply this model to a population of twins. The Jenss model fit observed weight values well, providing a similar fit to previous studies.[101,102] See Supplementary Materials for details.

Parameter a from the Jenss model reflects the predicted weight when $t = 0$; parameter c reflects nonlinear growth in early infancy; parameter d reflects the deceleration of growth in late infancy; and parameter b reflects the linear rate of growth in early childhood.[103,105,114] Parameter a cannot necessarily be interpreted as birth weight and is instead referred to as the "starting

value." Our interpretation of parameters b and d reflects their negation in the Jenss model. For example, a greater value (e.g., 5.2 vs. 4.9) for parameter b indicates a lower rate of growth in early childhood (**Figure A1.2**).

Descriptive analysis

All statistics are reported by sex and plurality. Descriptive statistics are reported as means with standard deviations or frequencies with percentages. Statistical differences between groups were tested with the chi-squared test, Fisher's exact test, or one-way analysis of variance (ANOVA).

Parameters estimated by the Jenss model were compared between groups using one-way ANOVA. If significant at the 0.05 level, a *post hoc* Tukey's honestly significant difference (HSD) test was used to determine which groups were statistically significantly different. Predicted weight (kg) and velocity of weight gain (kg/month) were computed at 3 months, 6 months, 1 year, 1.5 years, and 2 years for all groups and descriptively compared. A comparison of fitted trajectories to the median WHO growth standard trajectory for males and females was conducted visually; given recommendations to use a corrected GA of 40 weeks when using the WHO growth standards[115,116] and mean GA of approximately 37 weeks in our sample, the WHO growth standard trajectories were shifted right by three weeks. Analyses were conducted using R version 4.3.2.[117]

Sensitivity analyses

Because most weight measurements occurred in the first 100 days of life (**Figure A1.4**), we conducted a sensitivity analysis which excluded twins and singletons who did not have at

least one weight measurement after 1 year of age. We again matched ten singletons to each twin on sex and GA, constructed the Jenss model, and compared results to the main analysis.

We additionally explored the effect of our matching procedure by constructing the Jenss model on the full sample of singletons in the study population and comparing results to the main analysis.

3.4 Results

The final study sample included 345 male twins, 3,450 GA-matched male singletons, 371 female twins, and 3,710 GA-matched female singletons. Even with GA matching between plurality groups, twins had lower birth weight compared to singletons, regardless of sex (**Table 3.1**). Twins were more likely to be of non-Hispanic Black race; however, the majority of the sample were of Hispanic ethnicity (55.1%-64.4%). Compared to singletons, twins were less likely to be born to primiparous birthing persons and birthing persons with a high school degree or below, though twins had more missingness of these data, and more likely to be born to birthing persons ≥35 years of age and who preferred a language other than English or Spanish (P<0.05 for all). Twins and singletons had similar timing and counts of weight measurements per child, with a median of 10-11 measurements (**Figures A1.4-A1.5**).

Singletons had a higher starting value (parameter a) compared to twins, regardless of sex (**Table 3.2**). Compared to male singletons, male twins underwent more rapid weight gain in infancy (parameter c; 1.66 (95% confidence interval [CI]: 1.61, 1.71) and 1.54 (95% CI: 1.53, 1.56), respectively) and a lower degree of deceleration in their growth rate in late infancy (parameter d; 4.78 (95% CI: 4.71, 4.84) and 4.64 (95% CI: 4.62, 4.65), respectively). Conversely, female twins did not significantly differ in these early life growth parameters

compared to their female singleton counterparts (parameter *c*; 1.48 (95% CI: 1.43, 1.54) and 1.46 (95% CI: 1.44, 1.47), respectively and parameter *d*; 4.79 (95% CI: 4.72, 4.86) and 4.76 (95% CI: 4.74, 4.78), respectively). By early childhood, rate of weight gain was slower among male twins compared to male singletons (parameter *b*; 5.10 (95% CI: 5.03, 5.17) and 5.04 (95% CI: 5.02, 5.06), respectively), while female twins had a nonsignificantly faster rate of weight gain compared to female singletons (5.06 (95% CI: 5.00, 5.13) and 5.12 (95% CI: 5.09, 5.14), respectively). These group differences were statistically significant except where otherwise noted (*post hoc* Tukey's HSD $P<0.05$).

Predicted weights and velocity of weight gain show that male twins had consistently faster growth compared to their singleton counterparts for the first 6 months, while female twins were growing only marginally faster compared to female singletons (**Table 3.3, Figure 3.2**). Male and female twins caught up to and slightly surpassed their singleton counterparts in weight at around 6 and 15 months, respectively. Final predicted weight at 2 years was nearly identical between plurality groups (12.17kg and 12.07kg among male and 11.38kg and 11.30kg among female twins and singletons, respectively).

Comparison with the median WHO growth standard trajectories revealed that observed weight trajectories reasonably followed WHO trajectories, though with male twins consistently at a slightly higher weight compared to the WHO trajectory (**Figure A1.6**).

Sensitivity Analyses

In the sensitivity analysis excluding children without at least one weight measurement after 1 year of age, the fit of the Jenss model and observed trajectories did not meaningfully differ compared to the main analysis (**Table A1.2, Figure A1.7**).

In the sensitivity analysis comparing early childhood weight trajectories of twins to the full sample of singletons, male twins caught up in weight to their singleton counterparts at a later age compared to the main analysis (12 months vs. 6 months) while female singletons did not quite catch up, but predicted weight at 24 months was similar (11.38kg and 11.49kg, respectively; data not shown) (**Table A1.3, Figure A1.8**). These differences were driven predominately by higher starting weight and faster growth in infancy among the full sample of singletons compared to those included in the main analysis.

3.5 Discussion

Our results indicate that differences in growth between twins and singletons exist independent of differences in GA. Though they are born smaller, male twins experience a high rate of weight gain in early infancy, catching up to and surpassing male singletons by 6 months. Female twins grew marginally faster than female singletons, catching up to and slightly surpassing female singletons by 15 months. These findings support our hypotheses: that twins would be born lighter even after matching on GA, that twins would experience more rapid growth in infancy (supported most strongly among males), and that females would remain smaller than males throughout follow-up regardless of plurality.

Previous studies have compared early life growth between twins and singletons with mixed findings. One study among children in the Netherlands reported that the difference in weight between twins and singletons narrowed by 2 years but did not disappear.[19] Other studies reported that differences in weight between twins and singletons disappear by 4 years,[94] 7-9 years,[22] and 8 years.[25] These studies, however, were limited in sample size, generalizability to the US, data generation, and methods used to examine growth. Our study is the first to our

knowledge to apply the Jenss model, a mixed-effects model designed specifically to model early life growth, to a large US population of twins and GA-matched singletons. It is possible that twins in our study caught up in weight earlier than has been reported in previous studies (both when compared to GA-matched singletons and all singletons) for several reasons which may include feeding practices or prevalence of assisted reproductive technologies, both of which have been shown to impact early childhood weight trajectories[46,62,118] but which may differ in our predominately low-income, contemporary US sample. Future research is needed to assess if the patterns identified here remain in later childhood and if the prevalence of health outcomes associated with infant growth (e.g., obesity) is higher in twins compared to singletons because of their more rapid growth.

These results indicate that factors beyond GA differentially influence early childhood growth in twins and singletons; some of these may be factors that are unique to twin pregnancies such as zygosity, chorionicity, and amnionicity. These factors have been shown to affect fetal and postnatal growth among twins with, for example, lower birth weight among monozygotic twins[81] and more disparate postnatal growth trajectories among dizygotic twins.[79,80] Additionally, feeding practices impact weight trajectory, with formula-fed infants growing faster than breastfed infants.[46] We expect the prevalence of breastfeeding to be lower and formula-feeding to be higher among twins compared to singletons,[119] which could be driving the rapid weight gain seen among twins in our study. While we did not have this information for our study population, the contribution of these factors to observed infant growth trajectories is a critical direction for future research.

A notable 44.4% of twins were excluded from our analytic sample due to a missing weight measurement in the first 5 days of postnatal life, compared to 24.3% of singletons.

Correctly linking two child records to one birthing parent rather than identifying the records as duplicates is a known complication of EHR research[120] and is a limitation of these data. However, we do not expect the remaining twin to meaningfully differ from the removed twin, and results can be confidently interpreted on this subset of twins.

Our use of provider-recorded longitudinal weight measurements is a strength of our study. As opposed to parent-reported or study-collected weight measurements, the use of provider-recorded weight measurements allows more varied ages at weight measurements, allowing higher confidence in the fitted trajectory, and a greater average number of weight measurements per child. For example, in a recent study among the Upstate KIDS cohort, children had an average of 5 parent-reported measurements between 0 and 3 years of age;[22] in contrast, children had a median of 10-11 clinician-measured measurements between 0 and 2 years of age in our study.

While matching for GA and sex allowed us to explore differences in early childhood weight trajectory that were not related to differences in GA between twins and singletons, it resulted in a comparison of a general twin population to a highly selected singleton population. That is, singletons included in this analysis had a lower average GA compared to singletons in the overarching study population (37.4 vs. 38.9 weeks). They were therefore born around the preterm classification (37 weeks) and are likely to be a generally higher risk subset with unique risk profiles compared to those in the overarching study population. Indeed, several studies have reported higher morbidity and mortality among singletons compared to twins born at the same GA, suggesting that early GA among singleton pregnancies is largely pathological while early GA among twin pregnancies is largely physiological (i.e., driven by uterine space limitations),[111–113] though other studies have found contradictory evidence.[121,122] However, given

that all groups reasonably followed the median WHO growth standard trajectories, which are considered to be the "gold standard" for infant weight gain,[63] we are not concerned that singleton growth was misrepresented.

3.6 Conclusion

This study has described early childhood weight trajectories in twins compared to singletons independent of differences in GA. We report that both male and female twins grew more rapidly than their singleton counterparts, catching up in weight by 6 and 15 months, respectively. These findings suggest the differential influence of factors beyond GA on early childhood growth in twins compared to singletons.

Table 3.1 Characteristics (column % unless otherwise stated) of the sample of the PROMISE study, by plurality and sex (N=7,876).

	Twins		Singletons		
	Males (N=345)	**Females (N=371)**	**Males (N=3,450)**	**Females (N=3,710)**	***P* value***
Gestational Age at Birth (wks)[a]	37.3 (2.3)	37.2 (2.3)	37.4 (2.2)	37.4 (2.1)	0.28
Birth Weight (grams)[a]	2570 (547)	2440 (549)	3050 (635)	3010 (632)	<0.001
Missing	53.6	46.9	35.9	36.5	
Child Race and Ethnicity					<0.001
Hispanic	55.1	58.2	62.6	64.4	
AA/PI	~4.5	~2.5	4.1	4.1	
NH Black	11.3	14.0	7.3	7.1	
NH White	20.6	19.1	18.8	17.1	
Other	~0.5	~1	1.1	1.3	
Missing	8.1	5.1	6.1	6.1	
Parity[b]					<0.001
1	5.8	7.8	21.0	18.2	
2	15.7	16.2	19.4	19.0	
≥3	24.9	29.1	23.5	26.1	
Missing	53.6	46.9	36.1	36.7	
Maternal age, end of pregnancy (yrs)					<0.001
≤18	~1	~1	4.1	3.2	
19-24	~20	~20	28.3	26.9	
25-34	54.8	51.2	52.1	50.5	
≥35	24.1	27.8	15.5	19.4	
Maternal Preferred Spoken Language					0.01
English	53.6	48.8	49.7	48.5	
Spanish	38.6	42.3	44.9	45.8	

Other	7.8	8.9	~5	5.6	
Missing	0.0	0.0	~0	0.0	
Maternal Education[b]					0.03
High School or Below	30.1	38.0	45.9	47.0	
Some College or College Graduate	~12	~11	15.7	14.1	
Advanced Degree	~2	~2	1.4	1.2	
Missing	55.4	49.1	37.0	37.6	
Maternal Income (% FPL) at Pregnancy Start					0.14
≤50%	22.6	26.4	25.5	25.1	
51-100%	30.4	21.0	22.9	23.7	
101-200%	16.8	17.3	19.8	20.5	
>200%	4.9	5.9	6.4	6.4	
Missing	25.2	29.4	25.4	24.3	
Maternal Insurance During Pregnancy					0.17
Medicaid	86.4	81.9	82.3	82.7	
Medicare/Other Public	~0.5	~1	0.9	0.6	
Private	7.8	11.3	9.0	8.8	
Uninsured	4.1	4.9	7.1	7.1	
Missing	~1	~1	0.6	0.7	
Maternal Tobacco Use During Pregnancy					0.19
Current	7.8	5.7	7.9	8.6	
Former	9.3	14.6	10.9	10.9	
Never	67.5	67.9	66.4	67.1	
Missing	15.4	11.9	14.8	13.5	

Note: Some values hidden due to small cell sizes to retain patient confidentiality.

*: *P* values were determined with the chi-squared test, Fisher's exact test, or one-way analysis of variance.

[a]: Mean (standard deviation) reported.

[b]: High missingness because these data come from birth certificates. Linked birth certificates were not required for inclusion in the study.

AA/PI: Asian American/Pacific Islander. NH: non-Hispanic. "Other" race/ethnicity includes American Indian, Alaska Native, multiple race, "other" race or ethnicity, or unknown race/ethnicity. Wks: weeks. Yrs: years. FPL: federal poverty level.

Table 3.2 Jenss model parameters (estimate (95% confidence interval)) among 7,876 PROMISE study children aged 0-2 years.

Parameter	Twins		Singletons		*P* value
	Males (N=345)	**Females (N=371)**	**Males (N=3,450)**	**Females (N=3,710)**	
a: Starting value	0.91 (0.88, 0.93)	0.86 (0.84, 0.89)	0.98 (0.97, 0.99)	0.97 (0.96, 0.98)	<0.001[1, 3, 4]
c: Growth in early infancy	1.66 (1.61, 1.71)	1.48 (1.43, 1.54)	1.54 (1.53, 1.56)	1.46 (1.44, 1.47)	<0.001[1, 2, 3]
d: Decreasing rate of growth in late infancy	4.78 (4.71, 4.84)	4.79 (4.72, 4.86)	4.64 (4.62, 4.65)	4.76 (4.74, 4.78)	<0.001[2, 3]
b: Linear growth in early childhood	5.10 (5.03, 5.17)	5.06 (5.00, 5.13)	5.04 (5.02, 5.06)	5.12 (5.09, 5.14)	<0.001[2, 3]

Note. Values given as coefficient estimate (standard error). Statistical comparison made with one-way ANOVA. Significance determined with a *P* value < 0.05. The Jenss model is given by $y = e^{a} + e^{-b} * t + e^{c} * \left(1 - e^{-e^{-d} * t}\right)$.

[1]: significant male-female difference among twins.

[2]: significant male-female difference among singletons.

[3]: significant twin-singleton difference among males.

[4]: significant twin-singleton difference among females.

[1, 2, 3, 4]: calculated from *post-hoc* Tukey's honestly significant difference tests.

Table 3.3 Predicted weight and velocity of weight gain at several ages among 7,876 PROMISE study children aged 0-2 years.

Age	Twins		Singletons	
	Males (N=345)	**Females (N=371)**	**Males (N=3,450)**	**Females (N=3,710)**
		Predicted Weight (kg)[a]		
3 months	5.86	5.29	6.00	5.51
6 months	7.72	6.97	7.72	7.12
1 year	9.72	8.88	9.57	8.93
1.5 years	11.02	10.19	10.86	10.17
2 years	12.17	11.38	12.07	11.30
		Predicted Velocity of Weight Gain (kg/month)[b]		
3 months	0.81	0.71	0.77	0.69
6 months	0.48	0.44	0.43	0.42
1 year	0.25	0.25	0.24	0.23
1.5 years	0.20	0.20	0.20	0.19
2 years	0.19	0.19	0.20	0.18

[a]: Predicted weights were calculated by inserting population parameter values into the Jenss model: $y = e^{a} + e^{-b} * t + e^{c} * \left(1 - e^{-e^{-d} * t}\right)$.

[b]: Predicted velocities of weight gain were calculated by inserting population parameter values into the derivative of the Jenss model: $\frac{dy}{dt} = e^{-b} + e^{c-d-e^{-d} * t}$ and multiplying by 30.427 (average number of days per month).

Note. For values of t: 3 months = 91.25 days; 6 months = 182.5 days; 1 year = 365.25 days; 1.5 years = 547.5 days; 2 years = 730 days.

Figure 3.1 Analytic sample derivation.

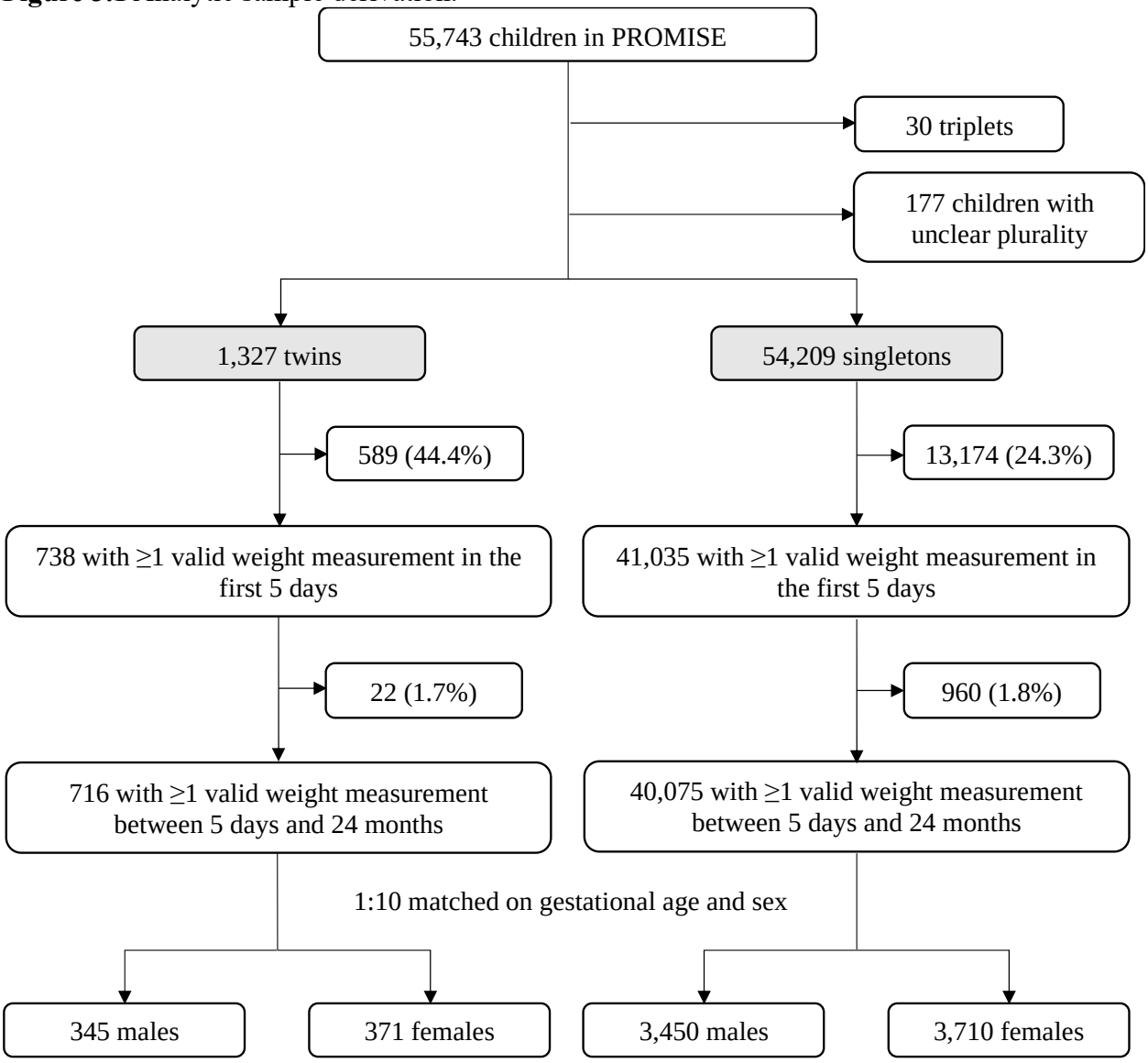
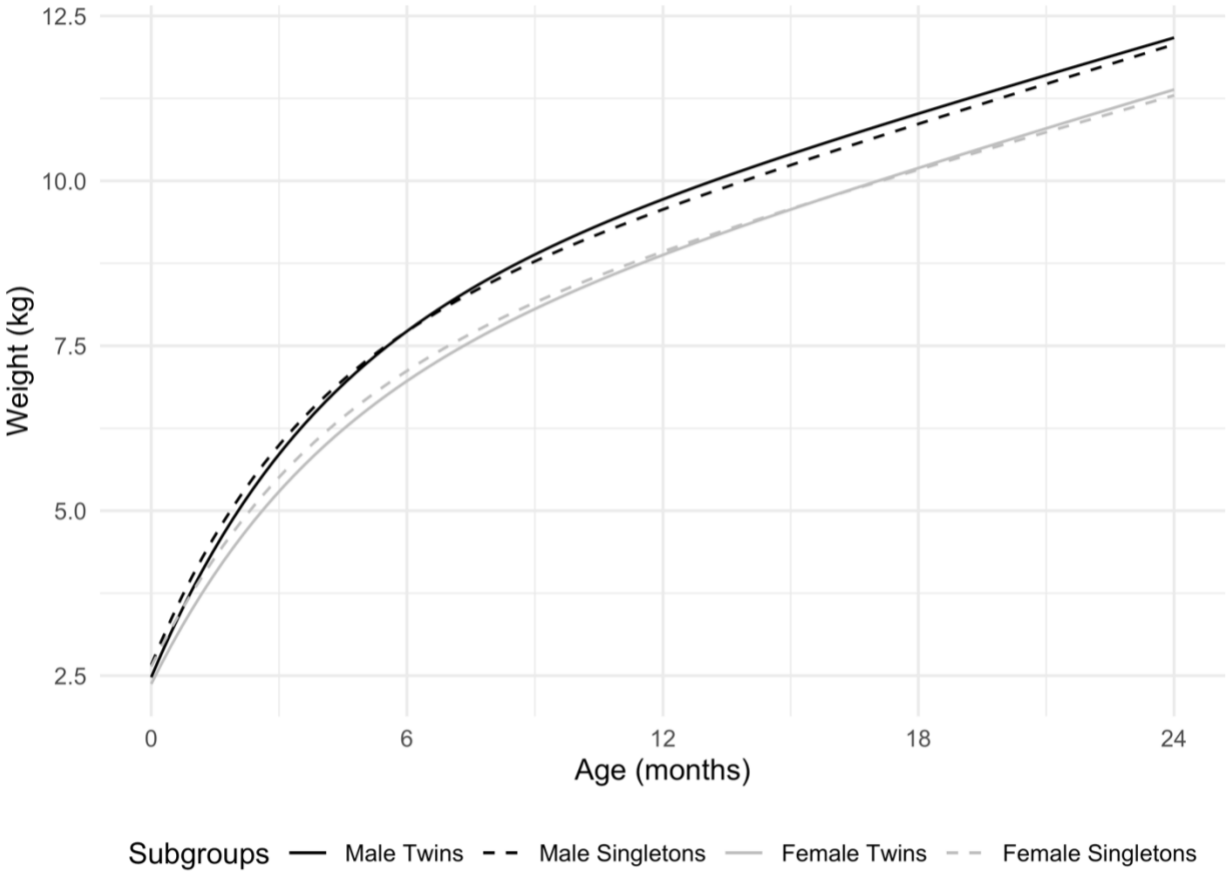


Figure 3.2 Early childhood weight trajectory for 7,876 twin males, twin females, singleton males, and singleton females aged 0-2 years from the PROMISE study.



CHAPTER 4. RESEARCH PAPER #2

Gestational weight gain throughout pregnancy and early childhood weight trajectory between twins and singletons

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4.1 Abstract

Background: Gestational weight gain (GWG) is an important characteristic of pregnancy that supports increased maternal energy requirements and growth of the fetus(es), with important considerations regarding the timing of gain. GWG also affects perinatal outcomes including early childhood weight gain, a risk factor for outcomes including overweight and obesity. Though the rate of twin pregnancies has increased in the past several decades, understanding of GWG and its effects on early childhood weight gain specifically in twin populations is limited.

Objective: The objective of this study was to assess the relationship between timing of GWG during pregnancy and early childhood weight gain among a population of twins compared to singletons independent of differences in gestational age.

Methods: Data are from an electronic health record-based cohort of pregnant people and their children. Twins and singletons were matched on gestational age and sex. GWG z-scores (GWGz) were calculated at 14 gestational weeks, 28 gestational weeks, and delivery. Early childhood weight trajectory between 0-2 years of age was modeled using the Jenss model. Associations between GWGz and early childhood weight trajectory were assessed with linear regression.

Results: Among twins, GWGz was not associated with their starting weight; however, among singletons, GWGz throughout pregnancy had a positive association with starting weight. Among female twins, GWGz throughout pregnancy was positively, though not significantly, associated with growth in early infancy and negatively associated with the decreasing rate of growth at the end of infancy. Among male twins, GWGz throughout pregnancy was not associated with growth until childhood, when it showed a positive and not significant relationship.

Conclusion: GWG may impact early childhood growth differently in twins and singletons, with

important sex differences. Further research is needed to establish guidelines for optimal GWG in twin pregnancies and optimal growth patterns among twin children.

4.2 Introduction

The rate of twin pregnancies has doubled since 1980 and now account for approximately 3% of all live births in the United States (US),[8,9] yet understanding of twin-specific perinatal clinical outcomes and prevention strategies remains limited.[5,123] In particular, while gestational weight gain (GWG) guidelines have been established[124] and are routinely applied to people pregnant with singletons and twins, existing GWG guidelines for twin pregnancies were provisional and based on evidence from a single study.[125,126] The association between GWG and child growth in twins remains largely unexplored.[127]

Among singletons, higher total GWG is associated with greater risk of rapid weight gain in infancy,[36,128–130] and the timing of GWG throughout pregnancy also impacts perinatal outcomes.[88–90] GWG is typically higher in people pregnant with twins compared to singletons, driven by the increased weight of products of conception (e.g., fetal and placental weight) in mid- to late-pregnancy,[131,132] with uncertain effects on child outcomes. While limited research suggests that higher GWG is similarly associated with greater risk of rapid infant weight gain in twins[84–87] as in singletons, existing studies in twins do not assess the timing of GWG,[85–87] and examine non-US twin cohorts,[84–86] limiting generalizability to the US, where early childhood weight trajectories differ markedly by race, ethnicity, and socioeconomic factors.[59]

Moreover, because twins are born, on average, three weeks earlier than singletons,[26] studies in twins must carefully consider gestational age (GA):[133–135] in general, longer gestational duration impacts not only GWG, but also birth weight and, correspondingly, compensatory growth. Indeed, twin children display distinct growth patterns: while they are generally smaller at birth compared to singletons, they gain weight more rapidly, catching up to singletons in weight by late childhood.[19,20,22–25]

In this study, we assessed the relationship between GWG in early-, mid- and late-pregnancy and early childhood weight gain among a large population of twins. For context, we conducted analogous analyses among singletons with a comparable GA distribution, thereby aligning the time-scale of early childhood growth and revealing differential associations driven by differences by plurality, rather than GA. We calculated GWG z-scores (GWGz) at three pregnancy time points – 14 and 28 weeks' gestation and delivery – and assessed nonlinear early childhood growth across four postnatal periods (birth, early infancy, late infancy, and childhood) from 0 to 2 years of age. We hypothesized that high GWGz in early pregnancy would be associated with higher birth weight in both twins and singletons, while high GWGz in mid- to late-pregnancy would be more strongly associated with faster growth in early infancy and higher weight at 2 years among twins compared to singletons given their preexisting tendency toward more rapid growth.

4.3 Methods

Study population

The Preventing Obesity Through Healthy Maternal Gestational Weight Gain in the Safety Net (PROMISE) study cohort was derived from the Accelerating Data Value Across a National Community Health Center Network (ADVANCE) Clinical Research Network, a Patient-Centered Outcomes Research Network site led by OCHIN, Inc.[95,96] ADVANCE integrates outpatient electronic health record (EHR) data for community-based health care organizations from across the US and contains demographic, utilization, and clinical data. The PROMISE study was approved by the Oregon Health & Science University Institutional Review Board.

The PROMISE cohort[136] includes 77,599 pregnancies (among 65,179 individuals) that started between 4/16/2004 and 7/6/2020 in patients 15 years of age or older at pregnancy start and that met the following criteria: GA at delivery between 20 and 42 weeks, available adult height, and with requisite weight measures: pre-pregnancy, ≥1 measure in the second or third trimester, and ≥1 additional measure during pregnancy. Most PROMISE patients lived in California (38.5%) or Oregon (27.2%) while pregnant. Supplemental data, such as birth weight and select maternal factors, were obtained from linked[97] birth record data for California and Oregon births. Pregnancies were linked to child(ren)'s EHR data using methods developed and validated by a national PCORnet project[98] and ADVANCE research.[99]

Study variables

Pregnancy variables

Pre-pregnancy body mass index (BMI) was calculated from height and pre-pregnancy weight. Height was calculated as the median of all adult (≥16 years) height measurements for each individual. Pre-pregnancy weight was defined as the weight closest to pregnancy start date, within 365 days prior and 97 days after. BMI (kg/m^2) was analyzed as a continuous variable in regression models and as a categorical variable for descriptive purposes and for the calculation of GWGz: underweight (<18.5), normal (18.5 to <25), overweight (25 to <30), and obesity class I (30 to <35), II (35 to <40), and III (≥40).

Plurality (singleton, twin) was identified via multiple sources (see Supplementary Materials). First, for linked births, the birth record (46.8%); second, by the presence of at least one International Classification of Diseases (ICD)-9 or ICD-10 diagnosis code indicating a plural pregnancy in the birthing parent's EHR (1.0%; used to determine twin status only); third, by

identifying children who shared the same birthing parent and birth date in the EHR (52.2%). *GA at delivery* was calculated from pregnancy start and end dates ascertained from the EHR and rounded to the last completed week.[136]

GWG was ascertained from maternal weight values recorded during pregnancy, which were cleaned[136,137] and modeled with mixed effects models with a cubic spline (knots at 14 weeks and 28 weeks) stratified by pre-pregnancy BMI category. Resulting model coefficients were used to predict weight at 14 weeks, 28 weeks, and delivery. *GWGz* at 14 weeks, 28 weeks, and delivery were calculated by subtracting pre-pregnancy weight from the predicted weights and comparing to published weight-gain-for-gestational-age z-score charts.[131,138,139] Z-score charts exist separately for singleton[138,139] and dichorionic twin[131] pregnancies and are specific to pre-pregnancy BMI category. As our data source did not contain information on chorionicity, all twin pregnancies were compared to the dichorionic twin reference; see Supplementary Materials.

Child variables

Early childhood weight measurements from 0-2 years were cleaned using the "growthcleanR" package in R[100] and used to construct weight trajectories.

Early childhood weight trajectory was modeled using the Jenss model, a four-parameter mixed effects model that was developed to fit growth trajectories from birth to 6-8 years. The model differentiates the pattern of growth into two periods: nonlinear growth during infancy and linear growth in childhood.[102,105,114] In this study, we use the terms "infancy" to refer approximately to age 0-12 months and "childhood" to refer approximately to age 12 months-2 years.

Parameter a from the Jenss model reflects the predicted weight when $t = 0$; parameter c reflects nonlinear growth in early infancy (approximately 0-6 months); parameter d reflects deceleration in growth at the end of infancy (approximately 6-12 months); and parameter b reflects linear growth in childhood.[103,105,114] Parameter a cannot necessarily be interpreted as birth weight and is instead referred hereafter as the "starting weight." The values for parameters b and d were negated to reflect their negation in the Jenss model and to aid interpretation. For example, a greater value (i.e., less negative) for parameter b indicates a greater rate of growth in early childhood (**Figure A2.2**); see Supplementary Materials. For descriptive purposes, early childhood weight trajectories within GWGz quartiles at each timepoint were visually compared.

Confounders: Maternal demographics and health-related variables

Confounders were defined as variables with prior evidence suggesting effects on both exposure (GWGz) and outcome (early childhood growth) but not on the causal pathway between the two. Unless otherwise noted, confounders were determined from the EHR. Race and ethnicity and preferred spoken language reflect social and cultural differences between groups, including exposure to systemic racism and clinical barriers. Preexisting diabetes and hypertension were defined using ICD-9 and ICD-10 codes; see Supplementary Materials. Health insurance coverage during pregnancy was defined as the most prevalent insurance type in the second and third trimesters.[109] Calendar year at birth was included to control for secular changes and variation in clinical practice throughout the long study period. Pre-pregnancy BMI, maternal age at the end of pregnancy, and income as a percentage of the federal poverty level (FPL) reported at the visit closest to pregnancy start were categorized for descriptive purposes but used

in models as continuous variables. Parity and maternal education were ascertained from the birth record among pregnancies in California and Oregon.

Analytic sample

PROMISE pregnancies linked to at least one child (N=55,190) and with pre-pregnancy normal weight, overweight, or obesity were included; 1,133 (2.1%) of pregnancies with pre-pregnancy underweight were excluded as there are no published GWG references for this group (**Figure 1**). The study was further limited to singleton and twin pregnancies [138 (0.3%) triplet pregnancies or pregnancies with unclear plurality excluded] and pregnancies with calculable and plausible GWGz at 14 weeks, 28 weeks, and delivery [559 (1.0%) pregnancies excluded]. Among male and female children linked to these pregnancies (N=53,805; 1,145 twins and 52,660 singletons), we limited to children with at least one weight measurement between birth and postnatal day 5 [516 (45.1%) twins and 12,699 (24.1%) singletons excluded] and at least one weight measurement between 5 days and 2 years of life [18 (1.6%) twins and 925 (1.8%) singletons excluded]. Those excluded had similar GWGz, maternal pre-pregnancy BMI, and early childhood weight trajectories compared to those included.

Analytic sample: Matching on gestational age

GA at birth has a different distribution among twins (i.e., left-shifted) compared to singletons.[26] While GWGz normalizes GWG by GA, we were interested specifically in differences in the association between GWGz and child growth between twins and singletons that were driven by inherent differences between the two groups, rather than as a consequence of GA (e.g., by being born preterm, for the majority of twins). More specifically, we were interested

in using the twin GA distribution as the standard, rather than using the singleton GA distribution as the standard, and comparing the association between GWGz and GA-normalized infant growth by plurality. Therefore, we aligned the time scale of early childhood growth by matching singletons to twins in a 10:1 ratio on GA (nearest neighbor matching) and sex (exact matching), without replacement.[110] Recognizing that the timing of delivery has different determinants in twins compared to singletons,[7,111–113] with shared drivers that potentially include GWG, we also conducted a sensitivity analysis that examined the full population of singletons, detailed below.

Statistical analysis

Following exploratory analyses showing statistically significant modification of several associations between GWGz and early childhood growth parameters by child sex (*P* for interaction <0.1), all results are reported by sex of the child and plurality. Descriptive statistics are reported as percentages, means with standard deviations, or medians with interquartile ranges.

In a series of 12 linear regression models, we modeled characteristics of early childhood weight trajectory (Jenss model parameters a, b, c, or d) as a function of GWGz at 14 weeks, 28 weeks, or delivery. Models included robust standard errors to control for clustering within twin pregnancies[140] and within matching group membership,[141–143] and an interaction term for plurality group (i.e., male twins, female twins, male singletons, female singletons).

Each model adjusted for above-described confounders; missing data (<1-38.6% missing) were imputed using multiple imputations by chained equations (MICE)[144] (Supplementary Materials). Additionally, models assessing GWGz at 28 weeks and GWGz at delivery adjusted for GWGz at 14 weeks. In the model assessing GWGz at delivery, we were unable to further

adjust for GWGz at 28 weeks given high collinearity (variance inflation factor>5). Analyses were conducted using R version 4.3.2.[117]

Sensitivity Analysis

We explored a sensitivity analysis among pregnancies with complete data to assess confidence in our MICE procedure. We additionally explored modification by pre-pregnancy BMI[38] through stratified analyses (pre-pregnancy normal weight, overweight, and obesity). Finally, we explored the relationship between GWGz and early childhood growth among all singletons in the study population, rather than only those matched to twins on GA.

4.4 Results

The final study sample included 294 male twin and 2,940 GA-matched male singleton children; 317 female twin and 3,170 GA-matched female singleton children. Compared to people pregnant with singletons, those pregnant with twins were more likely to be of non-Hispanic Black race, less likely to have a high school education or below or to be uninsured, and had lower GWGz at 28 weeks and delivery (**Table 4.1**). Absolute change in GWGz throughout pregnancy was similar between plurality groups: GWGz changed substantially between 14 and 28 weeks and minimally between 28 weeks and delivery (**Figure A2.1**). Twin children had lower birth weight compared to singleton children despite matching on GA. Other demographic and clinical characteristics were similar between groups.

Among both twins and singletons, infants whose mothers gained within the fourth quartile for GWGz (14 weeks, 28 weeks, or delivery) grew faster compared to those whose

mothers gained within the first through third quartiles, with marginally higher weight at two years (**Figure 4.2**).

Crude (**Table A2.2**) and adjusted (**Table 4.2, Figure 4.3**) associations were largely similar to each other. Adjusted estimates of the association between a one-unit increase in GWGz at 14 weeks, 28 weeks, and delivery with child growth trajectory characteristics were weak to moderate in magnitude, with distinct associations among twins compared to singletons.

Among male and female twins, higher GWGz throughout pregnancy was not significantly associated with the starting value (parameter a); however, it was positively associated among male and female singletons, with increasing strength of association at each successive GWGz timepoint (e.g., at 14 weeks, 28 weeks, and delivery, β (95% confidence interval [CI]) for male singletons=0.02 (0.01, 0.03), 0.04 (0.02, 0.05), and 0.05 (0.04, 0.06), respectively).

GWGz throughout pregnancy was not associated with growth occurring in infancy (parameter c, nonlinear growth in early infancy and parameter d, decreasing rate of growth in late infancy) among male twins, male singletons, and female singletons. However, among female twins, GWGz throughout pregnancy was positively, though not significantly, associated with nonlinear growth in early infancy (parameter c) and strongly negatively associated with the decreasing rate of growth in late infancy (parameter d) (e.g., at delivery, β (95% CI)=0.05 (0.00, 0.10) and -0.08 (-0.14, -0.01), respectively).

Associations between GWGz throughout pregnancy and linear growth in childhood (parameter b) were similar for twins and singletons, though with wider confidence intervals among twins, reflecting the smaller sample size. Among males, GWGz throughout pregnancy was positively associated with linear growth in childhood, though it did not reach statistical

significance among male twins (e.g., at delivery, β (95% CI)=0.05 (0.00, 0.10)). GWGz was positively associated with linear growth in childhood among females to a lesser extent, reaching statistical significance only in the relationship with GWGz at delivery among female singletons.

Sensitivity Analysis

The complete case analysis among 35.7% of pregnancies did not appreciably change estimates from the main adjusted analysis (**Table A2.3**).

Stratification by maternal pre-pregnancy BMI category (normal, overweight, or obese) revealed slight modification among twins, especially among female twins, though largely with overlapping confidence intervals (**Table A2.4, Figure A2.4**). Notably, GWGz at all three timepoints was significantly associated with starting weight among female twins exposed to maternal pre-pregnancy obesity, while it was not associated among female twins exposed to maternal pre-pregnancy normal weight or overweight, nor among male twins.

Estimates among all singletons in our study population were similar to estimates observed among singletons included in the main adjusted analysis, indicating that associations among singletons were not misrepresented with our matching procedure (**Table A2.5**).

4.5 Discussion

Our results suggest that GWG throughout pregnancy may impact early childhood growth differently in twins and singletons, with important sex differences. In general, GWGz was not associated with starting weight among twins of either sex (except among female twins exposed to maternal pre-pregnancy obesity) while a positive association was observed among singletons. Among female twins, higher GWGz throughout pregnancy was nonsignificantly associated with

more rapid growth in early infancy and significantly associated with less deceleration of growth in late infancy. Among male twins, higher GWGz throughout pregnancy was not associated with growth characteristics until childhood, when it showed a nonsignificant positive association with linear growth. Findings among twins were consistent regardless of the timepoint of the GWGz measure, while among singletons there was some variation for starting weight and, among females, for linear growth in childhood.

These findings partially support our hypotheses. Our hypothesis that high GWGz in early pregnancy would be associated with higher starting weight was supported for singletons but not twins. Our hypotheses that high GWGz in mid- to late-pregnancy would be associated with (a) more rapid growth in early infancy was supported for female twins only, and (b) with higher weight at 2 years was supported for both twins and singletons. Notably, these relationships held regardless of the timepoint of GWGz.

Our findings align with previous research that has reported positive associations between GWG and early childhood growth among twins.[84–86] There are important distinctions between these works and ours: none of the referenced research was conducted in a US population of children, and methodological limitations (e.g., assessing child weight values at ages far apart in time) inhibit utility. To our knowledge, this is the first study to use the Jenss model to assess the association between GWG and early childhood growth, providing temporal granularity needed to investigate potential effects of GWG on the timing of early childhood weight gain. For example, our findings suggest that higher GWGz throughout pregnancy did not increase starting weight among twins. This likely reflects the shared uterine space for twins, such that despite GWG, the uterus may become unable to support further fetal growth. Our findings indicating sex differences in relationships between GWGz and early childhood growth in twins align with sex

differences reported among singletons,[63] which may be driven by the differential production of sex steroids (testosterone and estrogen) in infancy.[145]

Our finding of sustained associations with early childhood growth regardless of the timepoint of GWGz in twin pregnancies, but not in singleton pregnancies, could reflect differences in the composition of GWG in twin pregnancies: the proportion of GWG due to products of conception (e.g., placenta, uterine fluid, fetus) may be higher in twin pregnancies compared to singleton pregnancies. Therefore, it is possible that GWG in singleton pregnancies may be more strongly impacted by maternal exposures and behaviors.[146,147]

Further, the role of GA in this question is complex and warrants discussion. Although it is broadly recognized that conditioning on GA is often inappropriate due to its role as a mediator between prenatal exposures and postnatal outcomes,[148] in this instance we considered GA a time-scale for measuring our outcome (child growth) rather than only a mediator. Our approach for matching on GA addressed this consideration and enabled comparison of GA-normalized infant growth by plurality, but further research should explore alternative approaches. In addition, matching on GA resulted in the comparison of a general twin population to a selected (i.e., likely higher risk) singleton population (born at an earlier GA; 37.2 vs. 38.9 in the overarching PROMISE cohort). However, results from our sensitivity analysis including all singletons did not differ from results from the main analysis, suggesting that associations among singletons were not misrepresented by matching singletons to twins on GA.

There were several limitations in our data source that could be improved in future research in twins. Zygosity or chorionicity, or the higher prevalence of needed medical intervention among twins compared to singletons at a given GA,[149] may confound or mediate, respectively, the relationship between GWG and early childhood growth characteristics among

twins, but were not available in our data. In addition, 45.1% of twins were excluded from the analytic sample because they did not have a weight measurement in the first 5 days of life, compared with 24.1% of singletons. Linking two child records to one birthing parent rather than incorrectly identifying one record as a duplicate and removing it is a known complication in EHR research,[120] but we do not expect this loss of data to differentially skew our results. That is, the remaining twin was not meaningfully different from the lost twin, and our results can still be confidently interpreted on this subset of twins.

These limitations were balanced by several strengths. Our use of longitudinal, provider-recorded weight measurements of both the pregnant persons and their children provided a greater number of weight measurements, more varied GAs (for pregnancy weights) and ages (for child weights) at measurement, and more accurate weight measurements compared to parent-reported data, giving us confidence in our modeling of both GWGz and child growth. Additionally, our large sample size of twins allowed for the examination of sex differences in the studied associations. These findings will be critical in further developing twin pregnancy-specific GWG guidelines, which were provisional upon their publication in 2009 due to limited data.[124]

4.6 Conclusion

Our findings suggest that GWG does not impact early childhood growth equally in twins and singletons. We also report important sex differences: among female twins, higher GWGz throughout pregnancy was associated with faster early infancy growth and less growth deceleration, while among male twins, higher GWGz throughout pregnancy was not associated with growth characteristics until childhood. These associations held regardless of the timepoint

of GWGz. These findings suggest the need for more twin-specific research to better understand optimal GWG among twin pregnancies and optimal growth patterns among twin children.

Table 4.1 Characteristics (column % unless otherwise stated) of the sample of the PROMISE study, by plurality (N=6,506 pregnancies and 6,721 children).

Pregnancy-Level Characteristics		
	Twin (N=396)	**Singleton (N=6,110)**
Race and Ethnicity[a]		
Hispanic	55.6	64.0
AA/PI	~4	4.7
NH Black	14.6	7.6
NH White	21.5	20.0
Other	~1	1.5
Missing	3.0	2.2
Preferred Spoken Language[a]		
English	51.3	48.6
Spanish	40.2	46.1
Other	8.6	~5
Missing	0.0	~0
Education[a]		
High School or Below	30.1	46.4
Some College or College Graduate	~9	15.1
Advanced Degree	~2	1.2
Missing	58.6	37.4
Pre-pregnancy BMI		
Normal	34.3	33.6
Overweight	39.6	32.8
Obesity Class I	14.4	19.1
Obesity Class II	7.1	8.6
Obesity Class III	4.5	6.0
Preexisting Diabetes	~2	2.7
Preexisting Hypertension	4.0	5.3
FPL Closest to Pregnancy Start (%)[a]		

≤50%	19.7	21.1
51-100%	21.5	20.6
101-200%	15.4	16.9
>200%	4.8	5.6
Missing	38.6	35.8
Insurance During Pregnancy[a]		
Medicaid	83.6	82.3
Medicare/Other Public	~1.5	0.8
Private	9.6	9.0
Uninsured	4.5	7.3
Missing	~1	0.7
Age at Pregnancy End (yrs)		
≤18	~1	3.6
19-24	~18	26.9
25-34	55.6	51.3
≥35	25.0	18.2
Parity[a]		
1	6.8	18.8
2	12.4	19.1
≥3	24.0	25.6
Missing	56.8	36.5
GWGz at 14 weeks[b]	-0.6 (0.9)	-0.6 (0.8)
GWGz at 28 weeks[b]	-0.9 (1.1)	-0.5 (1.0)
GWGz at Delivery[b]	-1.0 (1.2)	-0.6 (0.9)
Intrapregnancy absolute difference in GWGz[c]		
Between 14 weeks and 28 weeks	0.5 (0.2, 0.8)	0.4 (0.2, 0.7)
Between 28 weeks and delivery	0.1 (0.1, 0.2)	0.2 (0.1, 0.2)
Child-Level Characteristics		

	Twin		Singleton	
	Male (N=294)	**Female (N=317)**	**Male (N=2,940)**	**Female (N=3,170)**
Gestational Age at Birth (weeks)[b]	37.0 (2.3)	36.9 (2.1)	37.1 (2.0)	37.2 (1.8)
Birth Weight (grams)[b]	2560 (555)	2460 (499)	3020 (610)	2980 (588)
Missing	48.6	40.4	35.9	37.1
Jenss Model Parameters[b]				
a: Starting value	0.9 (0.2)	0.8 (0.2)	1.0 (0.2)	1.0 (0.2)
c: Growth in early infancy	1.7 (0.4)	1.6 (0.4)	1.6 (0.3)	1.5 (0.4)
d: Decreasing rate of growth in late infancy	-4.8 (0.4)	-4.9 (0.5)	-4.6 (0.4)	-4.8 (0.4)
b: Linear growth in early childhood	-5.1 (0.4)	-5.2 (0.5)	-5.0 (0.4)	-5.1 (0.4)

Note: Some values hidden due to small cell sizes to retain patient confidentiality.

[a]: Missingness was imputed for multivariable analyses.

[b]: Mean (standard deviation) reported.

[c]: Median (25th percentile, 75th percentile) reported.

AA/PI: Asian American/Pacific Islander. NH: non-Hispanic. "Other" race/ethnicity includes American Indian, Alaska Native, multiple race, "other" race or ethnicity, or unknown race/ethnicity. BMI: body mass index. FPL: federal poverty level. Yrs: years. GWGz: gestational weight gain z-score.

Table 4.2 Adjusted associations (β (95% confidence interval) between gestational weight gain z-score throughout pregnancy and early childhood weight trajectory parameters by plurality group and child sex (N=6,506 pregnancies and 6,721 children from the PROMISE study).

	Twins		**Singletons**	
	Male	Female	Male	Female
***a*: Starting value**				
GWGz at 14 weeks	0.01 (-0.02, 0.05)	0.00 (-0.03, 0.03)	0.02 (0.01, 0.03)*	0.02 (0.02, 0.03)*
GWGz at 28 weeks	-0.01 (-0.04, 0.02)	0.00 (-0.03, 0.02)	0.04 (0.02, 0.05)*	0.04 (0.02, 0.05)*
GWGz at delivery	0.00 (-0.03, 0.03)	0.01 (-0.02, 0.03)	0.05 (0.04, 0.06)*	0.05 (0.04, 0.06)*
***c*: Growth in early infancy**				
GWGz at 14 weeks	-0.02 (-0.07, 0.03)	0.05 (-0.01, 0.12)	0.00 (-0.02, 0.01)	0.00 (-0.02, 0.01)
GWGz at 28 weeks	-0.01 (-0.06, 0.04)	0.05 (0.00, 0.10)	0.00 (-0.02, 0.01)	0.00 (-0.02, 0.01)
GWGz at delivery	-0.01 (-0.06, 0.04)	0.05 (0.00, 0.10)	0.00 (-0.02, 0.01)	-0.01 (-0.03, 0.01)
***d*: Decreasing rate of growth in late infancy**				
GWGz at 14 weeks	0.03 (-0.03, 0.08)	-0.08 (-0.16, -0.01)*	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.03)
GWGz at 28 weeks	0.01 (-0.04, 0.06)	-0.08 (-0.15, -0.02)*	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.03)
GWGz at delivery	0.01 (-0.04, 0.07)	-0.08 (-0.14, -0.01)*	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.04)
***b*: Linear growth in early childhood**				
GWGz at 14 weeks	0.05 (-0.01, 0.11)	-0.01 (-0.07, 0.06)	0.02 (0.00, 0.03)*	0.00 (-0.02, 0.02)
GWGz at 28 weeks	0.04 (-0.01, 0.10)	0.00 (-0.05, 0.06)	0.02 (0.01, 0.04)*	0.02 (0.00, 0.04)
GWGz at delivery	0.05 (0.00, 0.10)	0.01 (-0.05, 0.07)	0.03 (0.01, 0.06)*	0.02 (0.00, 0.05)*

*: significant at 0.05 significance level.
Estimates reflect associations between a one-unit increase in GWGz and characteristics of early childhood weight trajectory.
All models adjusted for maternal race and ethnicity, preferred spoken language, education, pre-pregnancy body mass index, preexisting diabetes, preexisting hypertension, income as a percentage of the federal poverty level at the start of pregnancy, most prevalent insurance type in the 2nd and 3rd trimesters, age at the end of pregnancy, parity, and year of birth. Models assessing GWGz at 28 weeks and at delivery additionally adjusted for GWGz at 14 weeks.
Robust standard errors were used to control for clustering within twin pregnancies and within matching group membership.

Figure 4.1 Analytic sample derivation.

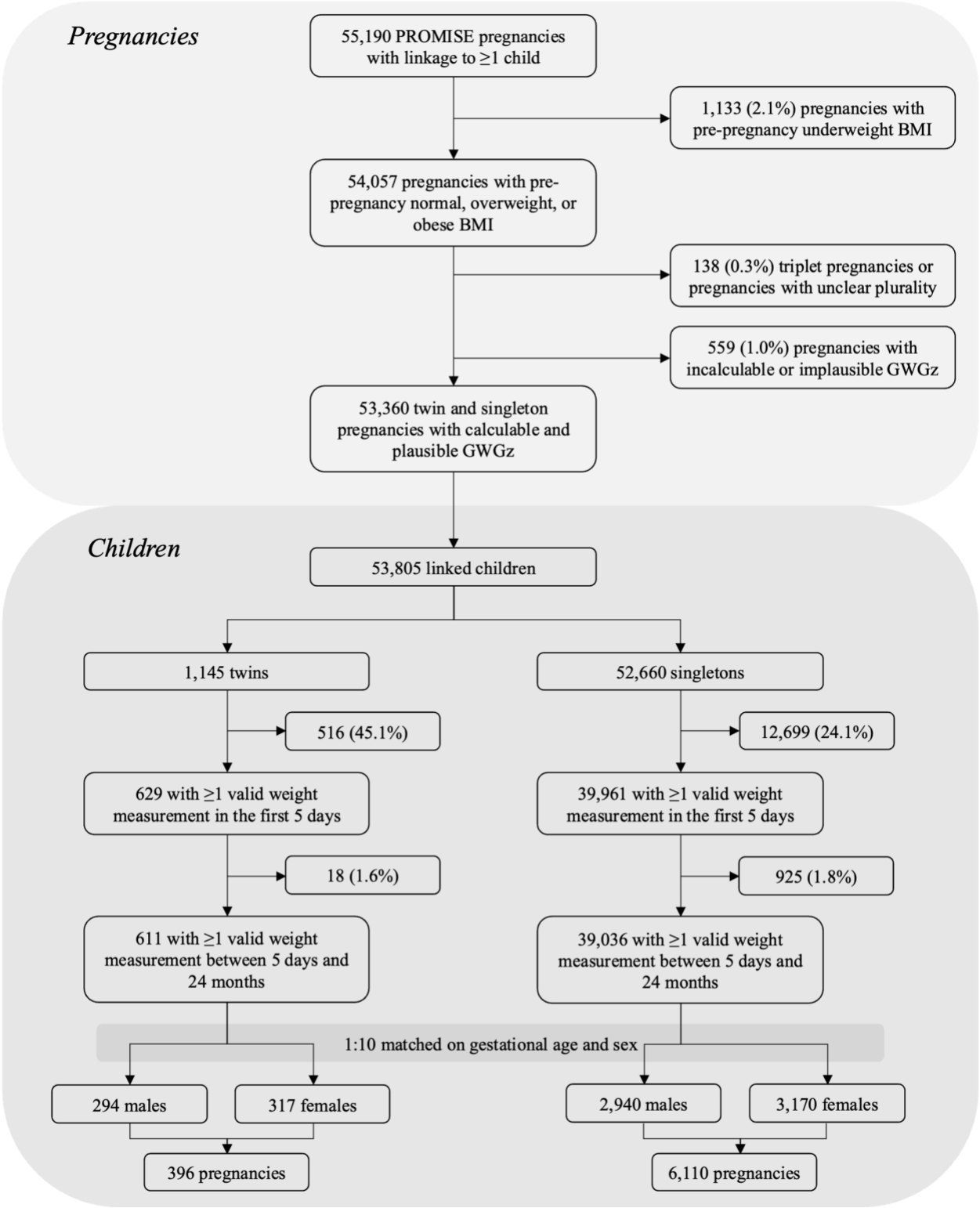


Figure 4.2 Early childhood weight gain patterns within quartiles of GWGz at 14 weeks, 28 weeks, and delivery.

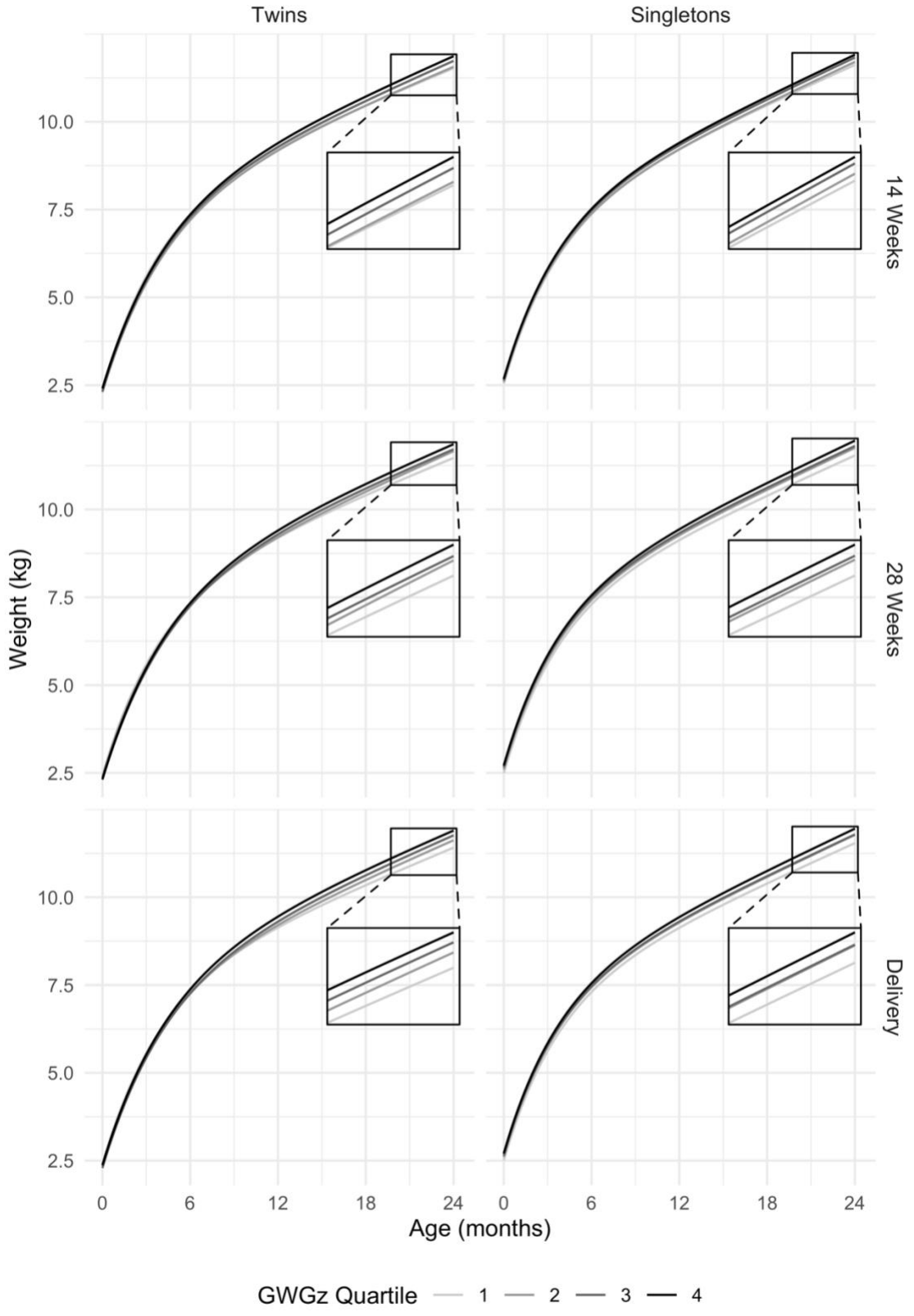
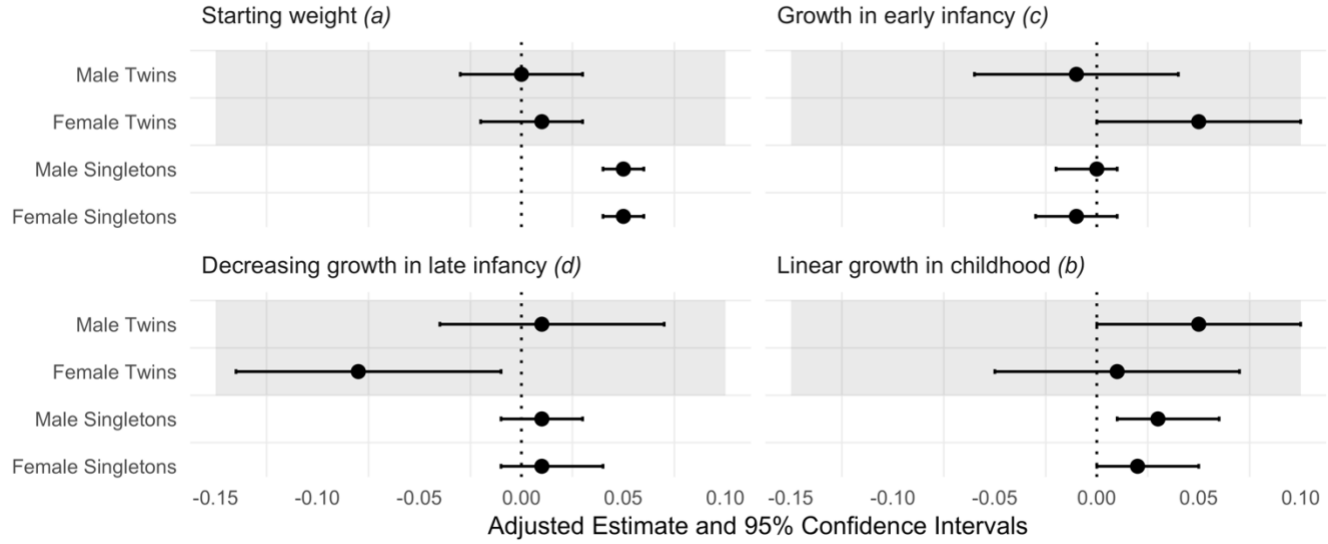


Figure 4.3 Adjusted estimates and 95% confidence intervals of the association between GWGz at delivery with parameters of infant weight trajectories, in children from the PROMISE study (N=6,506 pregnancies and 6,721 children).



Note: Estimates reflect associations between a one-unit increase in GWGz and characteristics of early childhood weight trajectory. Estimates only for GWGz at delivery are shown because of similarity across timepoints. The vertical dotted line shows the null association (0.00). The gray boxes delineate twins from singletons. Estimates adjusted for maternal race and ethnicity, preferred spoken language, education, pre-pregnancy body mass index, preexisting diabetes, preexisting hypertension, income as a percentage of the federal poverty level at the start of pregnancy, most prevalent insurance type in the 2nd and 3rd trimesters, age at the end of pregnancy, parity, and year of birth. Models assessing GWGz at 28 weeks and at delivery additionally adjusted for GWGz at 14 weeks. Robust standard errors were used to control for clustering within twin pregnancies and within matching group membership.

CHAPTER 5. RESEARCH PAPER #3

Infant weight gain patterns are not associated with child body mass index among twins

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5.1 Abstract

Background: Rapid early childhood weight trajectory is a clinical risk factor for health outcomes including overweight and obesity. Twins are born smaller, on average, compared to singletons, and are thus more likely to undergo rapid weight gain. Because twins are smaller at birth compared to singletons even in the absence of an adverse exposure (e.g., preterm birth), it is possible that associations between early childhood weight trajectory and child body mass index (BMI) may differ between twins and singletons.

Objective: The objective of this study was to assess the relationship between characteristics of early childhood weight gain trajectory and child BMI in twins and singletons independent of differences in gestational age.

Methods: Data were from the PROMISE study, an electronic health record-based cohort of pregnant people and their children. Singletons were matched to twins on gestational age and sex. Early childhood weight trajectory between 0-2 years of age was modeled with the Jenss model. Linear regression was used to assess the relationship between characteristics of early childhood weight trajectory and child BMI z-score (BMIz) at 3 and 5 years.

Results: Among singletons, higher starting weight, more rapid growth in early infancy, and more rapid growth in childhood were positively associated with BMIz at 3 and 5 years. However, among twins, only growth in childhood was positively associated with BMIz at 3 and 5 years.

Conclusion: While rapid weight gain in infancy is largely considered a risk factor for childhood overweight and obesity, we found that this assumption does not hold in our population of twin children, both overall and independent of differences in gestational age. The underlying physiology driving early childhood weight gain and eventual BMI may differ in twins compared

to singletons. Further research is needed to assess epigenetic, metabolic, and behavioral drivers of growth and optimal growth patterns among twin children.

5.2 Introduction

The prevalence of twin pregnancies in the United States (US) has increased drastically in the past decades and twins now account for roughly 3% of live births;[8,9] however, twin-specific clinical and epidemiologic research has not kept pace with this increasing prevalence. For example, while abundant research has established a connection between rapid infant weight gain (RIWG) and elevated risk of overweight and obesity in later life,[1,10–12] limited research in this regard has focused specifically on twins.

Twins are born with a lighter weight, on average, than singletons due to unique factors such as the shared uterine space[17,18] and average shorter gestational duration.[16,19,21] They are thus likely to undergo RIWG in the first months of postnatal life to "catch-up" in weight.[19,21–24] However, because twins are born lighter than singletons even in the absence of an adverse exposure (e.g., preterm birth[21]), it is possible that the underlying mechanism driving RIWG, and thus associations with later body mass index (BMI), are also unique to twins.

Specifically, while RIWG is a risk factor for later health outcomes among singletons, it is possible that it is a benign aspect of early childhood growth among twins. For example, a small body of literature suggests that twins grow more rapidly in childhood compared to their singleton siblings or the general population,[19,21–24] while a separate body of literature suggests they tend to have an average or leaner body size by late childhood and adolescence.[22–25] However, there is a need for research that directly and empirically connects RIWG and childhood BMI among twins. As well, several other knowledge gaps remain: whether these prior associations hold in contemporary US populations, in which the current prevalence of childhood[150,151] and adulthood[152,153] obesity is over three times that of the 1960s, when much of the measurements used in previous research were collected; whether associations with specific periods of early

childhood growth exist, which requires numerous repeated measures; and direct examination of associations between early childhood weight trajectories and child BMI among twins.

Stronger evidence is needed to establish twin-specific clinical guidelines for early childhood growth and to establish specific characteristics and periods of growth that may benefit from intervention. In this study, we assessed the relationship between characteristics of early childhood weight gain trajectory between 0-2 years and child BMI z-score (BMIz) at ages 3 and 5 years in a population of twins and singletons born in 2005-2021 in the US. We leveraged an electronic health record (EHR)-based cohort that provided a mean of 12.9 weight measurements per child between 0-2 years of age. We hypothesized that early infancy growth would be less strongly associated with BMIz at 3 and 5 years among twins compared to singletons.

5.3 Methods

Study population

The Preventing Obesity Through Healthy Maternal Gestational Weight Gain in the Safety Net (PROMISE) study cohort is derived from the Accelerating Data Value Across a National Community Health Center Network (ADVANCE), a Patient-Centered Outcomes Research Network site led by OCHIN, Inc.[95,96] ADVANCE integrates outpatient EHR data for CHCOs from across the US which serve predominately publicly insured and uninsured patients and contains demographic, utilization, and clinical data. The PROMISE study was approved by the Oregon Health & Science University Institutional Review Board.

The PROMISE cohort includes 77,599 pregnancies (among 65,179 individuals) that started between 4/16/2004 and 7/6/2020 in patients 15 years of age or older at pregnancy start and that met the following criteria: gestational age (GA) at delivery between 20 and 42 weeks,

available adult height, and that had requisite weight measures: pre-pregnancy, ≥1 measure in the second or third trimester, and ≥1 additional measure during pregnancy. Supplemental data including birth weight and select maternal characteristics were obtained from linked[97] birth record data for California (38.3%) and Oregon (27.2%) births. The birthing parent was linked to child(ren)'s EHR data using methods developed and validated by a national PCORnet project[98] and ADVANCE research.[99] Further details about the PROMISE study cohort can be found elsewhere.[154]

Study variables

Child variables

Plurality was identified from the birth record, if available (46.7%), otherwise by the presence of at least one International Classification of Diseases (ICD)-9 or ICD-10 diagnosis code in the birthing parent's EHR that indicated a twin pregnancy (used to determine twin status only; see Supplementary Materials) (1.3%), otherwise by the number of children who shared the same birthing parent and birth date in the EHR (52.1%). The obstetric estimate of GA from the birth record was used, if available (27.2% of twins and 47.0% of singletons), otherwise the estimate of GA from the EHR was used (72.8% of twins and 53.0% of singletons). Among those with GA from both sources, GA did not substantially differ (Cohen's kappa=0.8).

Child weight and *length/height* measurements from 0-6 years of life were used in this analysis. Implausible values were identified and removed using the "growthcleanR" package in R[100] (2.8% of 1,027,182 weight values removed and 9.1% of 818,967 height values removed). Weight measurements from 0-2 years were used to construct early childhood weight gain trajectories; weight and height measurements from between 2 and <4 years (24 to <48 months)

and between 4 and <6 years (48 to <72 months) were used to calculate BMI at 3 and 5 years, respectively, as described below.

Baseline weight was defined as the minimum weight among birth weight and clinical visits from postnatal days 0-5 and was used as the starting value for early childhood weight trajectory modeling. Other weight values in the first 5 days of life that were not the minimum weight were removed. *Birth weight* was ascertained from the birth record, if available (27.4% of twins and 47.1% of singletons). GA- and sex- standardized z-scores calculated from birth weight references for twins[108] and singletons[27] were used to identify and remove implausible birth weights; see Supplementary Materials.

Early childhood weight trajectory was modeled with the Jenss model, a four-parameter mixed effects model developed to fit weight and height trajectories from birth to 6-8 years and which differentiates the trajectory of growth into two periods: nonlinear growth during infancy and linear growth in childhood.[102,105,114] In this study, the term "infancy" refers approximately to age 0-12 months and "childhood" refers approximately to age 12 months-2 years.

The four parameters from the Jenss model each reflect a characteristic of early childhood weight trajectory: parameter a reflects the predicted weight when $t = 0$; parameter c reflects the nonlinear growth in early infancy (approximately 0-6 months); parameter d reflects the deceleration in growth at the end of infancy (approximately 6-12 months); and parameter b reflects the linear rate of growth in childhood.[103,105,114] Parameter a cannot always be interpreted as birth weight and is hereafter referred to as the "starting value." See Supplementary Materials for details.

BMI at 3 years was calculated from the weight and height measurements closest to 3 years of age, within 2 and <4 years, measured on the same day (mean (standard deviation [SD])

age: 2.9 (0.4) years); BMI at 5 years was similarly calculated, using the weight and height measurements closest to 5 years of age, within 4 and <6 years (mean (SD) age: 4.9 (0.4) years). *BMI percentile* and *BMI z-score (BMIz) at 3 and 5 years* were then calculated by comparing BMI to the Centers for Disease Control and Prevention (CDC) growth reference,[65,155] specific to age and sex and updated in 2022 to include very high BMI values, using the "cdcanthro" package in R.[156] The CDC growth reference was constructed using nationally representative data, which included twins (Robert Kuczmarski, email communication, December 2022). Potentially implausible values were identified with modified BMIz>8 and then manually inspected considering the child's longitudinal weight and height data, as described in recently published recommendations.[156–158] Five and 10 children had potentially implausible BMIz at 3 and 5 years, respectively; however, manual inspection of their data revealed that these values were in accordance with their growth trajectory and, thus, their values were not excluded. BMI percentiles of <5, 5-85, 85-95, and ≥95 were used to define underweight, healthy weight, overweight, and obesity, respectively;[159–161] these categories were used for descriptive purposes only.

Confounders

Confounders were defined as variables which have been shown in existing research to affect both exposure (early childhood weight trajectory) and outcome (BMIz) but are not on the causal pathway between the two. *Parity* (1, 2, ≥3) and *maternal education* (high school or below, some college or college graduate, advanced degree) were identified from the birth record and thus only available for children born in California and Oregon; all other confounders were determined from the EHR.

Maternal pre-pregnancy BMI was calculated from pre-pregnancy weight and the median adult height (≥16 years) for each birthing person; it was categorized for descriptive analysis and for a sensitivity analysis (see below) but examined as a continuous variable in primary analyses. Gestational weight gain (*GWG)* was predicted using all observed maternal weight values during pregnancy, modeled as a cubic spline (knots at 14 and 28 weeks) stratified by pre-pregnancy BMI. *Total GWG* was calculated as the difference between predicted weight at delivery and predicted weight at 0 weeks; and categorized as inadequate, adequate, and excessive according to plurality- and BMI-specific guidelines provided by the Institute of Medicine.[124] *Preexisting or gestational diabetes* and *preexisting hypertension or hypertensive disorders of pregnancy* were defined using International Classification of Diseases (ICD)-9 and ICD-10 codes; see Supplementary Materials. *Maternal age* at the end of pregnancy and mean *family income* as a percentage of the federal poverty level (FPL) reported at clinical visits from 0-2 years were categorized for descriptive purposes but used in analyses as continuous variables. *Child race and ethnicity* reflect social and cultural factors that act through the child, mother, family, and/or neighborhood, including exposure to racism and clinical barriers, that can affect health outcomes. Most prevalent *insurance type* billed at clinical visits from 0-2 years was categorized as Medicaid, private, noncomprehensive (e.g., dental insurance and grant/pilot study coverage), and uninsured. Calendar year of birth was included to control for variation in clinical recommendations and secular changes throughout our long study period.

Multiple imputations by chained equations

Missing covariate data were imputed using multiple imputations by chained equations (MICE),[144] shown to effectively impute data that could reasonably have been observed.[162,163]

Clustering on each twin pregnancy was included to ensure that identical values were imputed for both children from the same pregnancy. See Supplementary Materials for details.

Analytic sample

Among male and female children linked to a PROMISE pregnancy (N=55,743), we limited to twin and singleton children (30 triplets and 177 children with unclear plurality excluded) with a valid baseline weight measurement (44.4% of twins and 24.3% of singletons excluded) and at least one valid weight measurement between 5 days and 2 years of life (1.7% of twins and 1.8% of singletons excluded) (**Figure 5.1**). We further restricted the sample to those who had at least one weight and height measurement from the same clinical encounter between 2 and <4 years (15.7% of twins and 23.3% of singletons excluded). Analysis of BMIz at 5 years (secondary outcome) was conducted in children who also had at least one weight and height measurement from the same clinical encounter between 4 and <6 years (68.3% of twins and 62.8% of singletons). Children in the PROMISE study who were excluded had similar early childhood weight trajectories and BMIz at 3 and 5 years compared to those included in this study.

Analytic sample: Matching

GA affects both early childhood growth[164–166] and child BMI[167,168] and exhibits a distinct distribution among twins compared to singletons (i.e., left-shifted by roughly three weeks[26]). We were interested specifically in the estimation of the effect of early childhood weight trajectory on childhood BMIz that is due to plurality, rather than GA (e.g., by being born preterm, for the majority of twins). Therefore, we aligned the time scale of early childhood growth in twins and

singletons by matching singletons to twins in a 10:1 ratio on GA (nearest neighbor matching) and sex (exact matching), without replacement,[110] resulting in an equal GA distribution between twins and singletons. Because GA has different determinants in twins and singletons[7,111–113] with potentially different effects on health outcomes including early childhood weight gain and child BMI, we additionally conducted a sensitivity analysis to examine associations within the full population of singletons, as described below.

Statistical analysis

Exploratory analyses indicated statistically significant modification by sex in associations between growth characteristics and BMIz at 3 and 5 years (P for interaction <0.1); thus, all results are reported by sex of the child and plurality. Descriptive statistics are reported as percentages or means with SDs.

In a series of eight linear regression models, BMIz at 3 or 5 years was modeled as a function of early childhood weight trajectory characteristics (Jenss model parameters a, b, c, or d). Jenss model parameters were scaled such that estimates and 95% confidence intervals represent the change in BMIz associated with a one-SD increase in the Jenss model parameter. Models included robust standard errors to control for clustering within twin pregnancies[140] and within matched groups,[141–143] and an interaction term for plurality group (i.e., male twins, female twins, male singletons, female singletons).

Minimally adjusted and fully adjusted models were constructed considering the temporal sequence of the growth parameters: the models for parameter a (starting weight) did not include any other growth parameters, while the models for parameters reflecting growth during infancy (parameter c, nonlinear growth in early infancy and parameter d, decreasing growth in late

infancy) included parameter a (starting weight) and the models for the parameter reflecting growth in childhood (parameter b, linear growth in childhood) included parameters a, c, and d.[104]

Fully adjusted models additionally included above-described confounders. Collinearity between variables was identified if the variance inflation factor of variables in the adjusted models was greater than 5; no variables were collinear. Analyses were conducted using R version 4.3.2.[117]

Sensitivity Analysis

We conducted a sensitivity analysis among children with complete data for all confounders in order to assess confidence in our MICE procedure. We additionally conducted a sensitivity analysis to explore modification by maternal pre-pregnancy BMI[169] (normal, overweight, and obesity; underweight was excluded and obesity subclasses were combined due to insufficient sample sizes among twins) in our sample. Finally, we explored the relationship between early childhood weight trajectory and BMIz among all singletons in the study population, rather than only those matched to twins, in order to assess the effect of our matching procedure.

5.4 Results

The final study sample included 227 male twins, 2,270 GA-matched male singletons, 250 female twins, and 2,500 GA-matched female singletons (from 321 twin pregnancies and 4,770 singleton pregnancies). Compared to people pregnant with singletons, people pregnant with twins were more likely to experience inadequate GWG and to be ≥35 years old, and less likely to

be primiparous and to have a high school education or below (though with higher missingness; **Table 5.1**). Twin children were more likely to be of non-Hispanic Black race compared to their singleton counterparts. All early childhood weight trajectory parameters differed between groups, with twins notably having a lower starting weight, despite equal GA between groups, and more growth in early infancy compared to singletons. BMIz at 3 years did not differ between groups; however, BMIz at 5 years was particularly low among male twins.

There was clear patterning of early childhood weight trajectory across BMIz categories at 3 and 5 years in both twins and singletons (**Figure 5.2**). Based on visual inspection, for both ages and both plurality groups, children with an underweight BMIz had the lowest weight trajectory, while children with a healthy, overweight, and obese BMIz displayed sequentially higher trajectories. Notably, average weight trajectory among children with an obese BMIz followed or was slightly below the weight trajectory among those with an overweight BMIz for the first half of follow-up, only showing an increasing rate of weight gain at approximately 12 months of age.

Minimally (**Table A3.3**) and fully (**Table 5.2, Figure 5.3**) adjusted associations were similar. Fully adjusted associations between characteristics of early childhood weight trajectory and BMIz at 3 and 5 years differed between twins and singletons. Among singletons, a one-SD-unit higher starting weight (parameter a) and growth in early infancy (parameter c) were positively associated with BMIz at 3 years (e.g., among males, β (95% confidence interval [95% CI])=0.19 (0.14, 0.24) and 0.16 (0.08, 0.24), respectively). More deceleration in growth in late infancy (parameter d) was not significantly associated with BMIz at 3 years (e.g., among males, β (95% CI)=-0.01 (-0.08, 0.06)); however, linear growth in childhood (parameter b) was positively associated (e.g., among males, β (95% CI)=0.87 (0.80, 0.94)).

Conversely, among twins, early childhood weight trajectory characteristics occurring in infancy (parameters a, c, and d) were not significantly associated with BMIz at 3 years (e.g., among males, β (95% CI)=0.07 (-0.08, 0.22), 0.08 (-0.10, 0.27), and 0.09 (-0.08, 0.25) respectively, though the association was trending positive among males. Only linear growth in childhood (parameter b) showed a significant positive association with BMIz at 3 years (e.g., among males, β (95% CI)=0.79 (0.64, 0.94)).

These findings held for both male and female singletons and twins, and for BMIz at 3 and 5 years.

Sensitivity Analysis

The analysis among children with complete data of all confounders (50.4% for BMIz at 3 years; 62.4% for BMIz at 5 years) did not appreciably change estimates from the main adjusted analysis (**Table A3.4**).

Stratification by maternal pre-pregnancy BMI category (normal, overweight, obese) generally supported our findings and did not reveal any substantial modification in either twins or singletons (**Table A3.5, Figure A3.3**). Notably, growth in early infancy (parameter c) was not associated with BMIz at 3 or 5 years among singleton males or with BMIz at 3 years among singleton females with maternal pre-pregnancy obesity.

Estimates among all singletons in our sample were similar to estimates among GA-matched singletons, indicating that associations among singletons were not misrepresented with our matching procedure (**Table A3.6**).

5.5 Discussion

These results indicate that associations between early childhood weight gain and BMIz in childhood may differ between twins and singletons and exist independent of differences in GA. As expected, among singletons, higher starting weight, faster growth in early infancy, and faster linear growth in childhood were positively associated with childhood BMIz at 3 and 5 years. However, among twins, characteristics of growth occurring in infancy (starting weight, growth in early infancy, and deceleration of growth in late infancy) were not associated with childhood BMIz at 3 or 5 years; only faster linear growth in childhood supported a positive association with childhood BMIz. These findings held for both males and females. Our hypothesis that early infancy growth would be less strongly associated with BMIz at 3 and 5 years among twins compared to singletons was supported by these findings.

This is the first study, to our knowledge, to assess associations between multiple characteristics of early childhood weight trajectory and childhood BMIz in twins compared to singletons. Abundant research conducted among singletons or a general population supports our findings among singletons: namely, that higher starting weight (or birth weight),[170,171] faster catch-up growth in infancy,[1,11,12] and faster growth in childhood[171,172] are positively associated with childhood BMI. Limited research among twins has reported faster rates of weight gain in infancy and early childhood[19,21–24] yet, in separate studies, average or leaner body size in childhood and adolescence[22–25] compared to singletons. However, only one study to our knowledge has assessed the relationship between early childhood weight gain and childhood BMI in twins,[22] which focused on RIWG. Our study builds upon this prior work, examining additional characteristics of early childhood weight gain needed to more fully understand the impacts of early childhood growth and childhood BMI in twins.

Our results support a growing theory in twin research which suggests that the underlying physiology driving fetal growth and eventual birth size in twins differs from that of singletons.[7,17] For example, studies of fetal reduction in twin pregnancies (i.e., reducing a twin pregnancy to a singleton pregnancy, either surgically or spontaneously) report slower fetal growth and lower birth weight of the remaining fetus compared to naturally conceived singleton fetuses, even when reduction occurred very early in pregnancy.[7,22,73,74] Further, in animal models, twinning induces epigenetic changes that potentially alter energy balance regulation and slow the growth of twin fetuses.[7,76] These findings collectively suggest that fetal size among twins may be predetermined, at least partly, by processes occurring very early in gestation and may not be pathologic. Our results extend this research to childhood, suggesting that drivers of early childhood weight gain and childhood BMI may also differ between twins and singletons. Further research is needed to assess epigenetic, metabolic, and behavioral drivers of early childhood weight gain and childhood BMI in twins.

Among the strengths of our study was our use of provider-recorded longitudinal weight and height measurements. Parent-reported child weight and height measurements have been shown to have low concordance with researcher- or provider-measured weight and height measurements,[173,174] and are typically not collected as frequently. For example, a recent study assessing child growth in singletons and twins analyzed a mean of 5 parent-reported weight measurements between 0 and 3 years;[22] in contrast, children in our study had a mean of 12.9 provider-recorded weight measurements between 0 and 2 years. Additionally, our use of the Jenss model allowed us to explore temporally nuanced characteristics of early childhood weight gain and their association with childhood BMIz. As opposed to previous research that used broader measures of early childhood weight gain, such as rate of weight gain between weights

measured far apart in time, our study enabled estimation of effects of growth in developmentally-specific time periods.

Our findings should be interpreted within the context of important limitations and considerations. First, a notable 44.4% of twins, as compared to 24.3% of singletons, were excluded from our analytic sample due to a missing weight measurement in the first 5 days of postnatal life. In a known complication of EHR research, it is possible that we incorrectly classified one of the two child records in a twin pregnancy as a duplicate and removed it, rather than linking both child records to one birthing parent.[120] Secondly, our findings should be interpreted considering our matching procedure, which resulted in the comparison of a general twin population to a highly selected singleton population (i.e., included singletons had a lower mean GA compared to singletons in the overarching PROMISE study cohort, 37.4 vs. 38.9 weeks). However, our sensitivity analysis revealed that associations among all singletons in our study population did not differ from associations among GA-matched singletons. Additionally, those excluded had similar early childhood weight trajectory and BMIz at 3 and 5 years compared to those included in our main analysis, suggesting that the exclusions were not systematic with respect to the study exposure or outcomes, hence selection bias was likely minimal. Finally, our data source had limited information on determinants of early childhood weight trajectory and childhood BMI, such as infant feeding practices[46,175,176] or zygosity.[79–81] The contribution of these factors to the associations reported here is a direction for future research.

5.6 Conclusion

Our findings suggest that early childhood weight gain does not impact childhood BMI in twins and singletons equally. Our findings in singletons align with prior research – specifically, higher starting weight, more rapid catch-up growth in infancy, and more rapid growth in childhood were associated with higher childhood BMIz at 3 and 5 years. In contrast, among twins, neither starting weight nor catch-up growth in infancy were associated with childhood BMIz. These findings suggest differential drivers of early childhood weight gain and childhood BMI in twins and singletons independent of GA. More twin-specific research is needed to better understand epigenetic, metabolic, and behavioral drivers of growth and optimal growth patterns among twin children.

Table 5.1 Characteristics (column %) unless otherwise stated) of the sample of the PROMISE study, by plurality (N=5,091 pregnancies and 5,247 children).

Pregnancy-Level Characteristics		
	Twin (N=321)	**Singleton (N=4,770)**
Pre-Pregnancy BMI		
Underweight	~1	2.1
Normal	29.3	32.5
Overweight	29.6	33.1
Obesity Class I	22.1	18.6
Obesity Class II	12.1	8.2
Obesity Class III	~6	5.5
Hypertension[a]	10.0	11.6
Diabetes[a]	14.6	18.2
Adequacy of GWG[b]		
Inadequate	66.4	39.4
Adequate	20.6	~26
Excessive	13.1	35.0
Missing	0.0	~0
Age at Pregnancy End (yrs)		
≤18	~1	3.9
19-24	~17	26.2
25-34	51.4	51.5
≥35	30.2	18.3
Parity[b]		
1	6.2	18.3
2	12.8	20.1
3 or more	22.4	27.1
Missing	58.6	34.4
Maternal Education[b]		
High School or Below	30.8	50.8

Some College or College Graduate	~7	13.0
Advanced Degree	~2	1.0
Missing	59.8	35.3
Gestational Age at Birth (wks)[c]	37.4 (2.3)	37.2 (2.1)

Child-Level Characteristics				
	Twin		**Singleton**	
	Male (N=227)	**Female (N=250)**	**Male (N=2,270)**	**Female (N=2,500)**
Race and Ethnicity[b]				
Hispanic	55.1	64.8	67.6	69.1
AA/PI	~5	~2	4.1	4.1
NH Black	11.9	14.8	8.0	7.2
NH White	17.6	12.4	15.1	13.6
Other	~1	~1	1.1	1.1
Missing	9.3	4.4	4.1	5.0
Insurance				
Medicaid	90.3	90.4	92.9	93.0
Private	~4	5.2	4.8	4.5
Noncomprehensive	~0	0.0	~0	~0
Uninsured	4.8	~4	2.2	2.2
Missing	0.0	~1	~0	~0
Income (%FPL)[b]				
≤50%	31.7	32.0	27.1	25.8
51-100%	30.8	29.6	30.7	32.3
101-200%	18.1	~16	21.5	20.3
>200%	~4	~4	4.7	5.0
Missing	~16	18.8	15.9	16.6
Jenss Model Parameters[c]				
a: Starting value	0.87 (0.24)	0.83 (0.27)	0.96 (0.21)	0.96 (0.21)

c: Growth in early infancy	1.62 (0.38)	1.47 (0.47)	1.54 (0.36)	1.42 (0.44)
d: Decreasing rate of growth in late infancy	4.72 (0.46)	4.76 (0.50)	4.60 (0.39)	4.69 (0.45)
b: Linear growth in childhood	5.05 (0.43)	5.04 (0.49)	5.00 (0.39)	5.05 (0.44)
BMI at Three Years				
Underweight	~4	4.8	3.7	4.4
Healthy Weight	64.8	64.4	64.2	64.3
Overweight	16.7	15.2	16.2	15.1
Obesity	~15	15.6	15.9	16.2
BMI at Five Years				
Underweight	~1	~1	2.2	2.0
Healthy Weight	37.9	34.8	35.9	36.3
Overweight	~7	~10	10.6	11.4
Obesity	10.1	11.6	14.6	13.6
Missing	43.6	42.8	36.7	36.6
BMIz at Three Years[c]	0.43 (1.10)	0.44 (1.30)	0.47 (1.23)	0.45 (1.18)
BMIz at Five Years[c]	0.44 (1.21)	0.65 (1.22)	0.69 (1.26)	0.68 (1.21)
Missing	43.6	42.8	36.7	36.6

Note: Some values hidden due to small cell sizes to retain patient confidentiality.
[a]: Includes preexisting and gestational.
[b]: Missingness was imputed for analyses.
[c]: Mean (standard deviation) reported.
BMI: body mass index. GWG: gestational weight gain. Yrs: years. Wks: weeks. AA/PI: Asian American/Pacific Islander. NH: non-Hispanic. "Other" race/ethnicity includes American Indian, Alaska Native, multiple race, "other" race or ethnicity, or unknown race/ethnicity. FPL: federal poverty level. BMIz: body mass index z-score.

Table 5.2 Adjusted associations (β (95% confidence interval) between early childhood weight trajectory characteristics and child body mass index z-score at 3 and 5 years by plurality group and child sex (N=5,247 (BMIz at 3 years) and N=3,293 (BMIz at 5 years) children from the PROMISE study).

	Twins		**Singletons**	
	Male	Female	Male	Female
BMIz at 3 years				
a: Starting value	0.07 (-0.08, 0.22)	0.13 (-0.05, 0.30)	0.19 (0.14, 0.24)*	0.15 (0.10, 0.21)*
c: Growth in early infancy	0.08 (-0.10, 0.27)	0.01 (-0.20, 0.23)	0.16 (0.08, 0.24)*	0.13 (0.08, 0.19)*
d: Decreasing rate of growth in late infancy	0.09 (-0.08, 0.25)	-0.02 (-0.21, 0.17)	-0.01 (-0.08, 0.06)	-0.06 (-0.12, 0.00)
b: Linear growth in early childhood	0.79 (0.64, 0.94)*	0.89 (0.71, 1.07)*	0.87 (0.80, 0.94)*	0.87 (0.80, 0.93)*
BMIz at 5 years				
a: Starting value	0.06 (-0.12, 0.24)	0.00 (-0.23, 0.23)	0.14 (0.08, 0.20)*	0.14 (0.08, 0.20)*
c: Growth in early infancy	0.17 (-0.11, 0.44)	-0.09 (-0.34, 0.16)	0.18 (0.10, 0.27)*	0.14 (0.08, 0.21)*
d: Decreasing rate of growth in late infancy	0.00 (-0.23, 0.24)	-0.01 (-0.27, 0.24)	-0.04 (-0.12, 0.05)	-0.09 (-0.16, -0.02)
b: Linear growth in early childhood	0.67 (0.47, 0.87)*	0.92 (0.72, 1.11)*	0.78 (0.70, 0.87)*	0.81 (0.72, 0.89)*

*: significant at 0.05 significance level.
Estimates reflect the change in BMIz for every one standard deviation increase in the early childhood weight trajectory parameter.
All models adjusted for parity, maternal education, maternal pre-pregnancy BMI, total gestational weight gain according to Institute of Medicine guidelines, preexisting or gestational diabetes, preexisting hypertension or hypertensive disorders of pregnancy, maternal age, family income, child race and ethnicity, insurance type, and year of birth.
The models for parameters c and d further adjusted for parameter a while the model for parameter b further adjusted for parameters a, c, and d.
Robust standard errors were used to control for clustering within twin pregnancies and within matching group membership.
BMIz: body mass index z-score.

Figure 5.1 Analytic sample derivation.

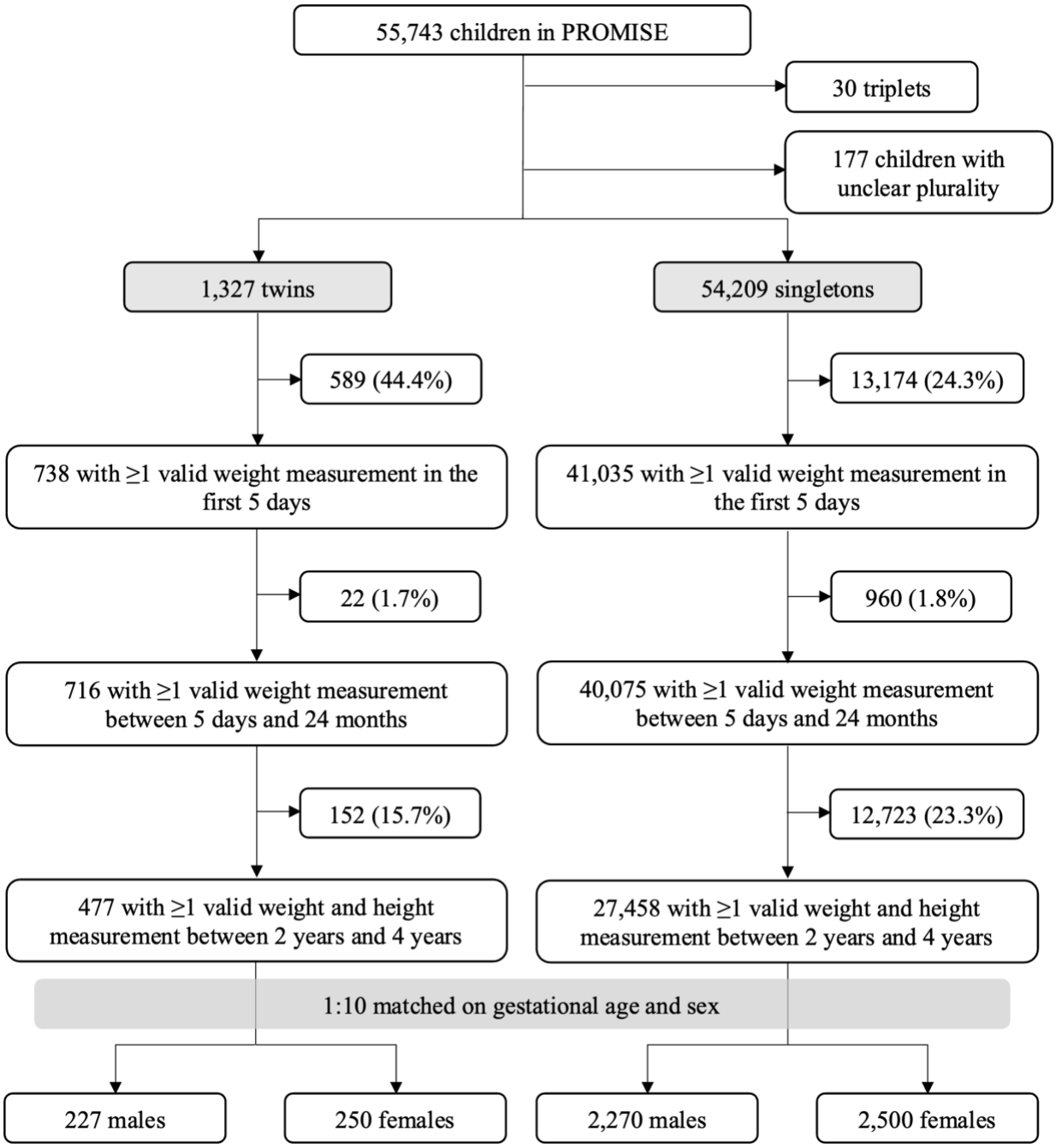
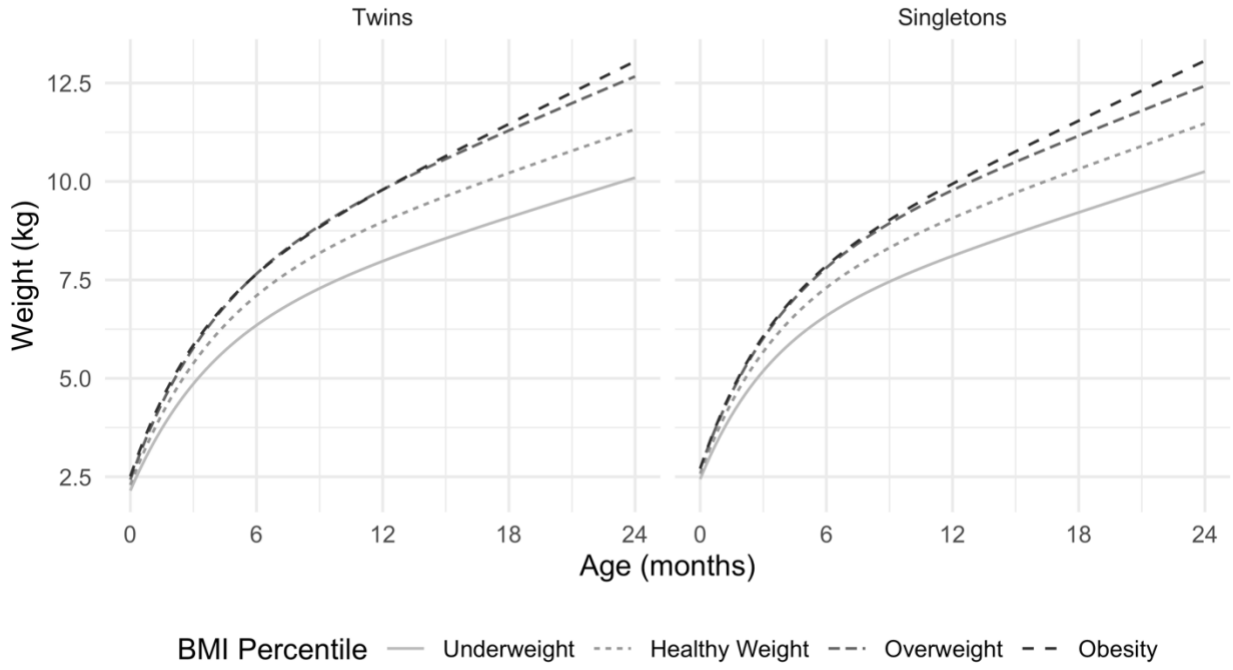
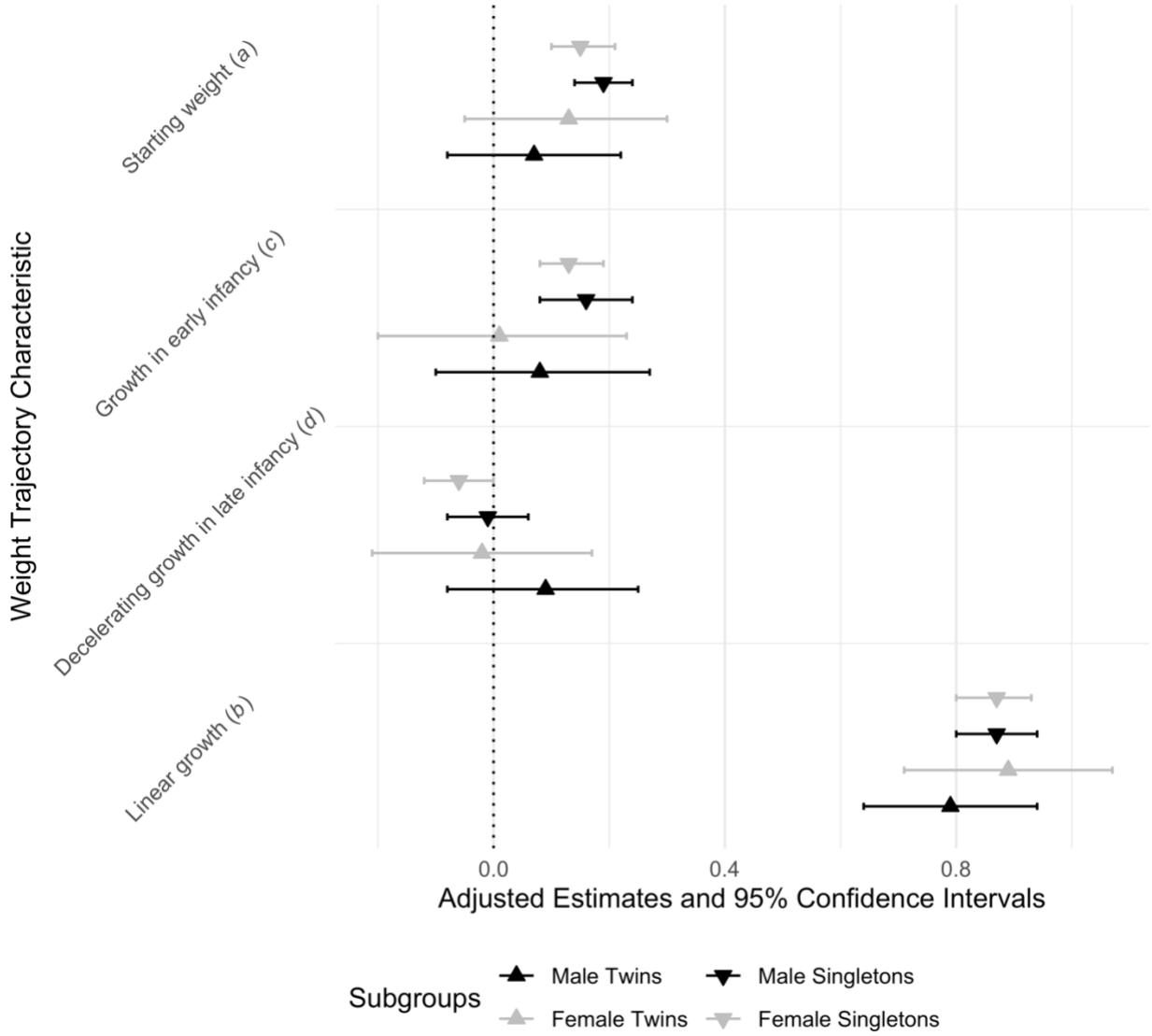


Figure 5.2 Growth patterns from 0-2 years within BMI percentile categories measured at 3 years.



Note: For ease of interpretation, only growth patterns within BMI percentile categories at three years are shown; growth patterns within BMI percentile categories at five years were similar.
BMI: body mass index.

Figure 5.3 Adjusted estimates and 95% confidence intervals of the association between early childhood weight trajectory characteristics and child BMIz at 3 years, in children from the PROMISE study (N=5,247).



Note: the vertical dotted line shows the null association (0.0). All estimates adjusted for maternal parity, education, pre-pregnancy body mass index, gestational weight gain, preexisting or gestational diabetes, preexisting hypertension or hypertensive disorders of pregnancy, and age, family income, child race and ethnicity and insurance, and year of birth. The models for catch-up growth (c) and decelerating growth (d) further adjusted for starting weight (a). The model for linear growth (b) further adjusted for starting weight (a), catch-up growth (c), and decelerating growth (d).
For ease of interpretation, only associations with BMIz at three years are shown; associations with BMIz at five years were similar.
BMIz: body mass index z-score.

CHAPTER 6. SYNTHESIS OF RESEARCH

6.1 Summary

The prevalence of twin pregnancies in the United States (US) has risen substantially in the past several decades. Despite this, clinical and epidemiologic research focused specifically on twin pregnancies and children is scant: we lack foundational knowledge on growth and developmental processes and outcomes among twins. This lack of knowledge does not allow for twin gestations and children to be treated with the most rigorous, evidence-based care and may lead to preventable adverse health exposures and outcomes. Additionally, previous research has accounted for the differing distribution of gestational age (GA) between twins and singletons in various manners, thereby leaving unknown the extent to which observed differences are driven by GA rather than inherent differences between twins and singletons. For example, while one study used a fetal growth chart to assess the size of twins born before the start of postnatal growth charts (i.e., before 40 weeks' gestation),[19] another categorized twins as being small for gestational age or average for gestational age,[22] and another did not clearly explain their treatment of GA.[94] This is important nuance, as this understanding impacts the interpretation of research findings: whether findings among twins are simply driven by their earlier gestational age or whether findings among twins are driven by inherent differences in epigenetics, metabolic processes, etc. The former would suggest that findings in preterm singletons could translate to twins, thus de-emphasizing the recommendation for more twin-specific research, while the latter would support the recommendation for twin-specific research and clinical guidelines.

This dissertation aimed to fill three high-priority research gaps. The first was to describe normative early childhood weight gain among a large population of twins and singletons born at the same GA in the US. The second was to understand the impact of a critical driver of early

childhood weight gain – gestational weight gain (GWG) – among twins and singletons born at the same GA. Finally, the third was to examine whether early childhood weight gain was similarly associated with childhood body mass index (BMI) in twins as in singletons born at the same GA. We utilized data from pregnancy, early childhood (0-2 years), and childhood (3 and 5 years) from a large, recently constructed electronic health record (EHR)-based cohort and applied robust methods to rigorously fill these gaps. This cohort, the PReventing Obesity through healthy Maternal gestational weight gain in the Safety nEt (PROMISE) cohort, contains information on pregnant people and their children with high representation of low-income and publicly insured families.

The results from my dissertation research suggest that there are inherent differences between twins and singletons beyond differences in GA: these could include behavioral, epigenetic, and/or metabolic processes influencing fetal and/or early childhood weight trajectory. In my first aim, I report that, despite matching on GA, twins had lower birth weight compared to singletons. However, both male and female twins underwent more rapid weight gain in infancy compared to their singleton counterparts, catching up in weight at around 6 and 15 months, respectively, and with very similar predicted weights at 2 years.

As in singletons, these results suggest sex differences in early childhood weight trajectory among twins, which was further supported in my second aim: among female twins, GWG z-score (GWGz) throughout pregnancy was most strongly associated with growth in infancy, while among male twins, GWGz was most strongly associated with growth in childhood. Conversely, among singletons, GWGz throughout pregnancy was strongly associated with starting weight and with growth in childhood. The results from my second aim could also reflect differences in the composition of GWG in twin pregnancies compared to singleton pregnancies: the proportion

of GWG due to products of conception (e.g., placental weight) could be higher in twin pregnancies. Therefore, it is possible that GWG in singleton pregnancies may be more strongly impacted by maternal exposures and behaviors than GWG in twin pregnancies.[146,147]

Finally, in my third aim, I report that higher starting weight, more rapid weight gain in infancy, and more rapid weight gain in childhood were positively associated with BMI z-score (BMIz) at 3 and 5 years among singletons; however, among twins, characteristics of early childhood weight trajectory occurring in infancy were not associated with childhood BMIz at 3 or 5 years.

Collectively, results from the three Aims suggest different underlying physiology and/or pathology driving fetal and early childhood weight trajectory in twins and singletons. These results and conclusions were largely supported in sensitivity analyses comparing twins to a general singleton population, rather than matching singletons to twins on GA, collectively suggesting differing patterns of early childhood weight gain in a general singleton population compared to the GA-matched singleton population, yet similar estimates of associations with GWGz and child BMIz.

6.2 Future Research Needs

Many questions remain unanswered and should be prioritized in future research.

First, my data source was limited and did not contain information on critical factors that can markedly influence early childhood weight trajectory: importantly, zygosity[79–81] (the degree of genetic similarity between twins in a pair, either monozygotic [“identical”, 100% shared genes] or dizygotic [“fraternal”, 50% shared genes]) and infant feeding practices.[46–49,51] Future research should explore modification of growth patterns and associations reported throughout my

dissertation by these, and other, factors. This additional understanding will allow for the further refinement of twin-specific clinical recommendations and guidelines.

Second, further research is needed to explore additional outcomes that could be differentially associated with early childhood weight trajectory among twins compared to singletons. This could include cardiovascular disease, adulthood obesity, and asthma. Additionally, further research is needed to explore the sex differences reported here. Studies conducted among singleton populations have reported similar sex differences in growth,[63] which may be driven by the differential production of sex steroids (testosterone and estrogen) in infancy.[145] However, given that previous research has also linked sex of the co-twin to early childhood growth among twins,[77,78] twin-specific research is needed to better understand the underlying driver of these sex differences.

Next, it will be important to explore the underlying physiology/pathology driving differential associations reported between twins and singletons. This could start with animal models (e.g., as in the case of some existing epigenetic studies[76]) and progress to the exploration of behaviors, epigenetics, and metabolic processes in human twin and singleton fetuses and children. For example, the theory that fetal growth is partly predetermined by processes (e.g., epigenetic processes) that occur very early in gestation could be further studied by collecting specimens (e.g., blood) from twin children, from single children born from a reduced pregnancy (i.e., the remaining child from a twin gestation that was reduced to a singleton gestation), and from singleton children and conducting epigenome-wide studies to assess similarities and differences. This understanding of the underlying pathways that differentially affect early childhood growth in twins and singletons may also apply to other health outcomes, such as cardiovascular disease. Results from this suggested body of research would further guide and

refine clinical recommendations and guidelines for optimal early childhood weight trajectory for both twins and singletons, and inform the exploration of suitable interventions (which may differ between twins and singletons). For example, results from this dissertation suggest that more rapid weight gain in infancy may not be associated with childhood body size in twins as it is in singletons. With further support from this suggested body of research, clinical recommendations can be tailored to twin gestations and children with, for example, less emphasis on interventions focused on weight gain in infancy in twins compared to singletons.

Finally, the impact of interventions aimed to reduce adverse health outcomes in twins is an avenue for future research. For example, much research has focused on interventions to promote adequate GWG, with effects on fetal and child growth.[177–180] However, little of this interventional research included people pregnant with twins. Given the findings from my second aim, it is apparent that GWG may impact early childhood growth, and presumably associated health outcomes, differently in twins and singletons; therefore, GWG interventions designed for and conducted within a population of people pregnant with twins is necessary to provide consistent and evidence-based recommendations.

6.3 Impact

Findings from my dissertation suggest inherent differences beyond GA that affect early childhood weight trajectory, its drivers, and its effects in twins compared to singletons. Collectively, findings from my dissertation support a growing theory in twin research which suggests that the underlying physiology/pathology driving fetal growth and eventual birth size in twins differs from that of singletons,[7,17] and extends this theory to early childhood. These findings have the potential to greatly impact clinical care for twin gestations and children, and

suggest the need for twin-specific clinical recommendations regarding the drivers and patterns of early childhood weight trajectory. For example, these findings suggest that early childhood weight trajectory among twins differs from that of singletons for approximately the first year of life, highlighting the need for a growth chart built specifically for twins. Further research is needed to examine the underlying pathways driving childhood growth in twins. Additionally, this research explored normative early childhood weight trajectory among twins; further research is also needed to define optimal weight trajectory that best supports twins' health.

Findings from this dissertation in addition to findings from the suggested body of research outlined above should prove instrumental in the care of twin children. By providing a deep understanding of twin growth in general and in relation to perinatal exposures and childhood health outcomes, we will begin to better understand how clinical recommendations and practice should (or should not) change to better serve this group of infants. These and subsequent findings have the potential to greatly impact the clinical care and resulting lifelong health of this population.

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APPENDICES

Appendix 1. Supplemental material for Chapter 3. Early childhood weight trajectory differences in twins and gestational-age matched singletons.

Appendix 1.A. Details regarding the cleaning of birth weights.

Implausible birth weights were defined as a gestational age (GA)- and sex- standardized z-score of <-5 or >5,[181] calculated from birth weight references for singletons[27] and twins,[108] then omitted (n=42, 0.1% of singletons, n=0 twins). The birth weight reference for twins ends at 40 weeks' GA;[108] 78 twins had a GA beyond 40 weeks and their GA was converted to 40 weeks for this calculation. Because the birth weight reference for twins[108] gives mean and standard deviation values in two-week intervals for GA, mean and standard deviation values for intermediate GAs were imputed (see **Figure S1** and **Table S1**).

Figure A1.1 Birth Weight Reference Imputation for male (A) and female (B) twins.
Imputed values shown in red (mean) and blue (standard deviation).

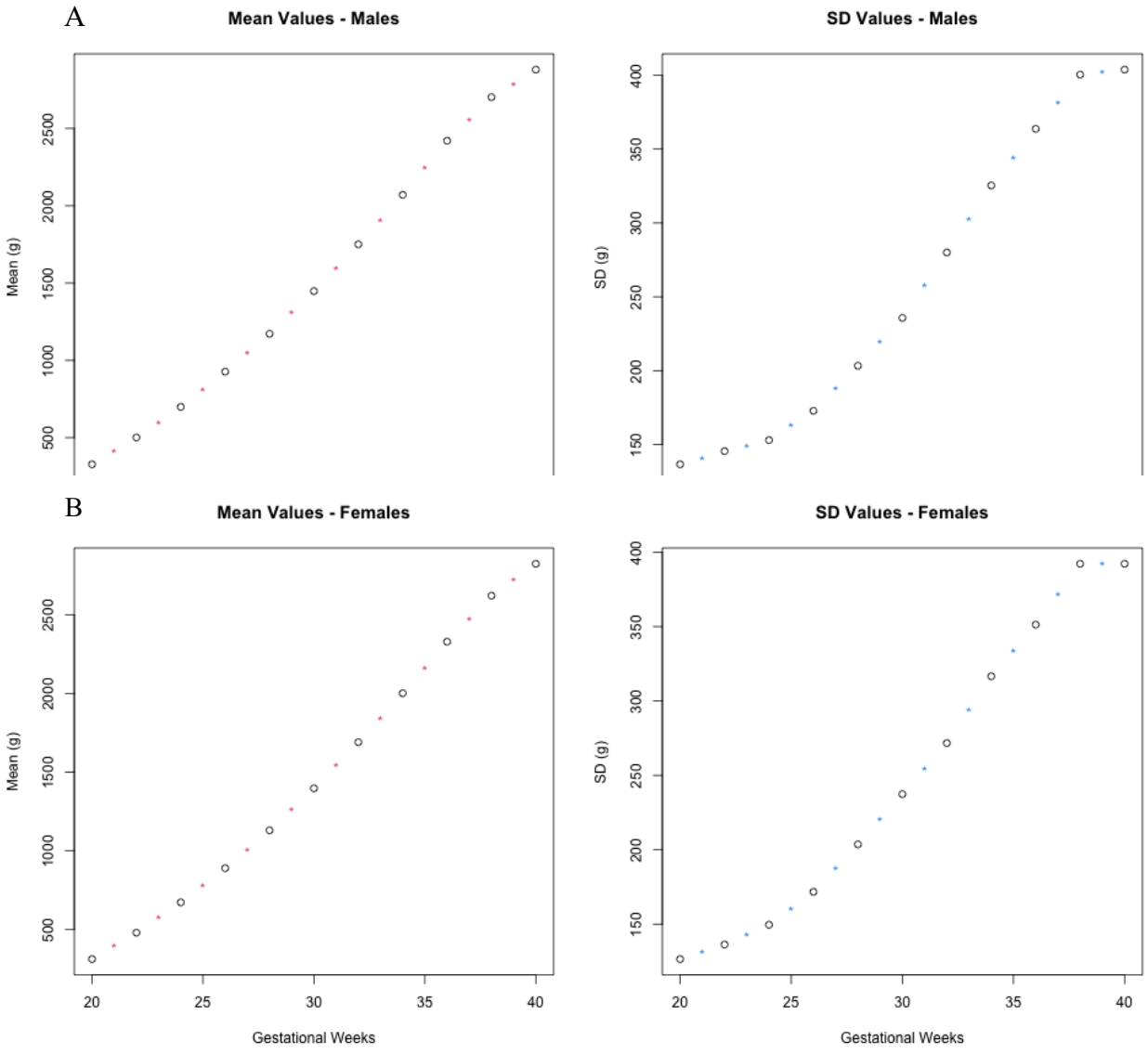


Table A1.1 Published and imputed birth weight values for twins.

	Males		Females	
Week	**Mean (g)**	**SD (g)**	**Mean (g)**	**SD (g)**
20	327.8	136.6	312.4	126.5
21	***414.7***	***141.1***	***396.3***	***131.4***
22	501.5	145.5	480.2	136.3
23	***600.5***	***149.3***	***576.5***	***143.0***
24	699.5	153	672.8	149.6
25	***813.2***	***162.9***	***781.5***	***160.7***
26	926.8	172.8	890.1	171.7
27	***1049.4***	***188.1***	***1010.3***	***187.7***
28	1171.9	203.3	1130.5	203.6
29	***1310.0***	***219.5***	***1263.9***	***220.5***
30	1448.1	235.7	1397.2	237.4
31	***1599.3***	***257.9***	***1543.9***	***254.6***
32	1750.5	280	1690.5	271.7
33	***1910.6***	***302.7***	***1845.9***	***294.2***
34	2070.7	325.4	2001.3	316.6
35	***2245.8***	***344.6***	***2164.9***	***334.0***
36	2420.8	363.7	2328.5	351.3
37	***2561.6***	***382.1***	***2474.6***	***371.8***
38	2702.4	400.4	2620.7	392.2
39	***2791.5***	***402.1***	***2722.0***	***392.2***
40	2880.6	403.8	2823.3	392.2

Published values are given in normal font; interpolated values are given in bolded and italicized font. Published values from Min (2000).[108]

Appendix 1.B. International Classification of Diseases codes to determine twin pregnancies.

Codes from ICD-9 and ICD-10. The presence of at least one code in the pregnant person's EHR with a diagnosis date between pregnancy start and end dates was used to determine twin status. The absence of these codes was not used to determine singleton status; that is, this definition was *only* used to identify twins.

Diagnosis Code	Short Description
O30.00	Twin pregnancy, unsp num plcnta & amnio sacs
O30.001	Twin preg, unsp num plcnta & amnio sacs, first trimester
O30.002	Twin preg, unsp num plcnta & amnio sacs, second trimester
O30.003	Twin preg, unsp num plcnta & amnio sacs, third trimester
O30.009	Twin pregnancy, unsp num plcnta & amnio sacs, unsp trimester
O30.01	Twin pregnancy, monochorionic/monoamniotic
O30.011	Twin pregnancy, monochorionic/monoamniotic, first trimester
O30.012	Twin pregnancy, monochorionic/monoamniotic, second trimester
O30.013	Twin pregnancy, monochorionic/monoamniotic, third trimester
O30.019	Twin pregnancy, monochorionic/monoamniotic, unsp trimester
O30.03	Twin pregnancy, monochorionic/diamniotic
O30.031	Twin pregnancy, monochorionic/diamniotic, first trimester
O30.032	Twin pregnancy, monochorionic/diamniotic, second trimester
O30.033	Twin pregnancy, monochorionic/diamniotic, third trimester
O30.039	Twin pregnancy, monochorionic/diamniotic, unsp trimester
O30.04	Twin pregnancy, dichorionic/diamniotic
O30.041	Twin pregnancy, dichorionic/diamniotic, first trimester
O30.042	Twin pregnancy, dichorionic/diamniotic, second trimester
O30.043	Twin pregnancy, dichorionic/diamniotic, third trimester
O30.049	Twin pregnancy, dichorionic/diamniotic, unsp trimester
O30.09	Twin pregnancy, unable to determine num plcnta & amnio sacs
O30.091	Twin preg, unable to dtrm num plcnta & amnio sacs, first tri
O30.092	Twin preg, unable to dtrm num plcnta & amnio sacs, 2nd tri
O30.093	Twin preg, unable to dtrm num plcnta & amnio sacs, third tri
O30.099	Twin preg, unable to dtrm num plcnta & amnio sacs, unsp tri
Z37.2	Twins, both liveborn
Z37.3	Twins, one liveborn and one stillborn
Z37.4	Twins, both stillborn
Z37.50	Multiple births, unspecified, all liveborn
Z37.60	Multiple births, unspecified, some liveborn
Z37.7	Other multiple births, all stillborn
Z64.1	Problems related to multiparity
651	Twin pregnancy
651.00	Twin pregnancy-unspec
651.01	Twin pregnancy-delivered
651.03	Twin pregnancy-antepart

651.8	Other specified multiple gestation
651.80	Multi gestat NEC-unspec
651.81	Multi gestat NEC-deliver
651.83	Multi gest NEC-antepart
V31	Twin birth, mate liveborn
V31.0	Twin, mate liveborn, born in hospital
V31.00	Twin-mate lb-hosp w/o cs
V31.01	Twin-mate lb-in hos w cs
V31.1	Twin, mate lb-before adm
V31.2	Twin, mate lb-nonhosp
V32	Twin birth, mate stillborn
V32.00	Twin-mate sb-hosp w/o cs
V32.01	Twin-mate sb-hosp w cs
V32.1	Twin, mate sb-before adm
V32.2	Twin, mate sb-nonhosp
V33	Twin birth, unspecified whether mate liveborn or stillborn
V33.00	Twin-NOS-in hosp w/o cs
V33.01	Twin-NOS-in hosp w cs
V33.1	Twin NOS-before admissn
V33.2	Twin NOS-nonhosp
V39	Liveborn, unspecified whether single, twin, or multiple
V39.00	Liveborn NOS-hosp w/o cs
V39.01	Liveborn NOS-hosp w cs
V39.1	Liveborn NOS-before adm
V39.2	Liveborn NOS-nonhosp
V91.0	Twin gestation placenta status
V91.00	Twin gest-plac/sac NOS
V91.01	Twin gest-monochr/monoam
V91.02	Twin gest-monochr/diamni
V91.03	Twin gest-dich/diamniotc
V91.09	Twin gest-plac/sac undet

Appendix 1.C. Details regarding the Jenss model, procedures used to fit the Jenss model, and a summary of model fit.

Jenss model
In order to facilitate model convergence, a parameterization of the Jenss model was used which adds constraints of positivity to the parameters.[105] The equation to model the jth weight measure of the ith child, with y being the weight in kilograms and t being the age in days is thus: $y_{ij} = e^{a_i} + e^{(-b_i)} * t_{ij} + e^{c_i} * \left(1 - e^{\left(-e^{(-d_i)} * t_{ij}\right)}\right)$.

Procedures used
The Jenss model was fit using the SAEMIX package in R. SAEMIX implements a stochastic approximation expectation maximization (SAEM) algorithm for nonlinear mixed-effects models without approximating the likelihood function.[182] To impose minimal assumptions onto the correlation structure of the data, an unstructured variance-covariance matrix was used.

To assess model fit, normalized predicted distribution errors (NPDEs), a simulation-based evaluation tool that accounts for correlated measurements within subjects, were used. Given the number of individuals and observations in this analysis yet with computer limitations, 5,000 simulations were used in the estimation of NPDEs among twins while 10,000 simulations were used among singletons. If the model fit the data well, NPDEs will follow a normal distribution with a mean of 0 and variance of 1; normality was assessed visually using boxplots, histograms, quantile-quantile (QQ) plots, and empirical cumulative distribution function (eCDF) plots.[183,184]

Additionally, weight gain velocity was found by calculating the first derivative of the parameterized Jenss model: $\frac{dy}{dt} = e^{-b} + e^{c-d-e^{-d}*t}$.

Model fit
The Jenss model fit the observed weight values well (see **Figure S2,** next page). The mean and variance of the NPDEs for each group were very close to 0 and 1, respectively. Additionally, visual inspection of the distribution of NPDEs indicated that they reasonably followed a normal distribution though with slight departure from normality at the tails. More variability was seen in NPDEs in the latter months of follow-up as compared to the early months. This could be due to fewer available weight measurements at later ages (**Figures S3-S4**); this was explored in the Sensitivity Analysis; results below (**Tables S2-S4** and **Figures S5-S6**).

The fit of the Jenss model did not markedly improve when we required at least one weight measurement in the latter half of follow-up (see **Tables S2-S4** and **Figures S5-S6**). These findings align with one previous study that used the Jenss model to model weight among singletons aged 0-9 years and reported higher residuals between predicted and observed values in early life (roughly 0-3.5 years) compared to later in follow-up.[102] The Jenss model was designed to model weight trajectories from birth to 6-8 years; it is possible that better fit in later childhood was prioritized over better fit in infancy. Nonetheless, the Jenss model provided a good fit to our data which did not differ by group. Therefore, we are not concerned that the slightly imperfect fit of the Jenss model differentially skewed our interpretation of the results.

Figure A1.2 Visual interpretation of Jenss model parameters.

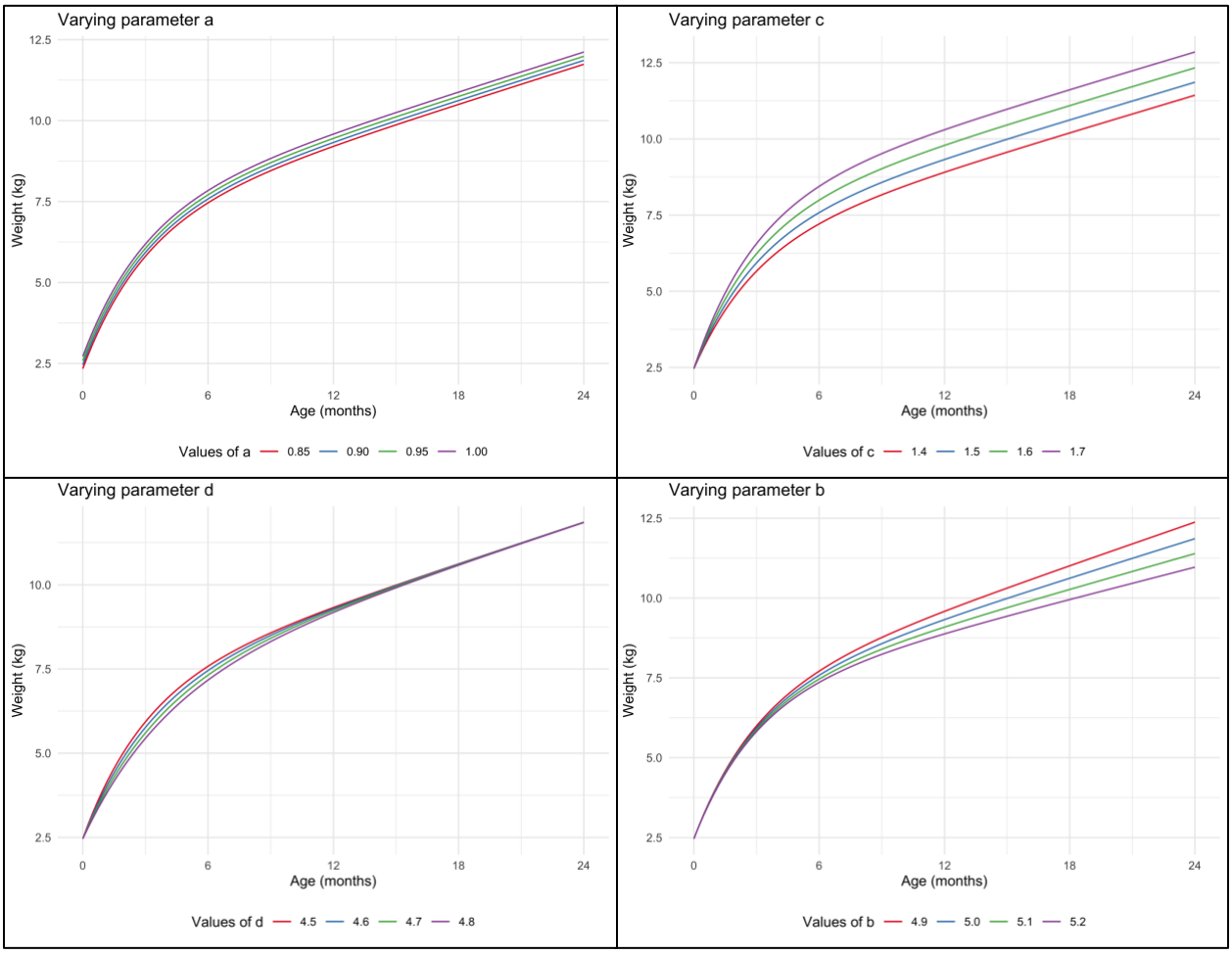
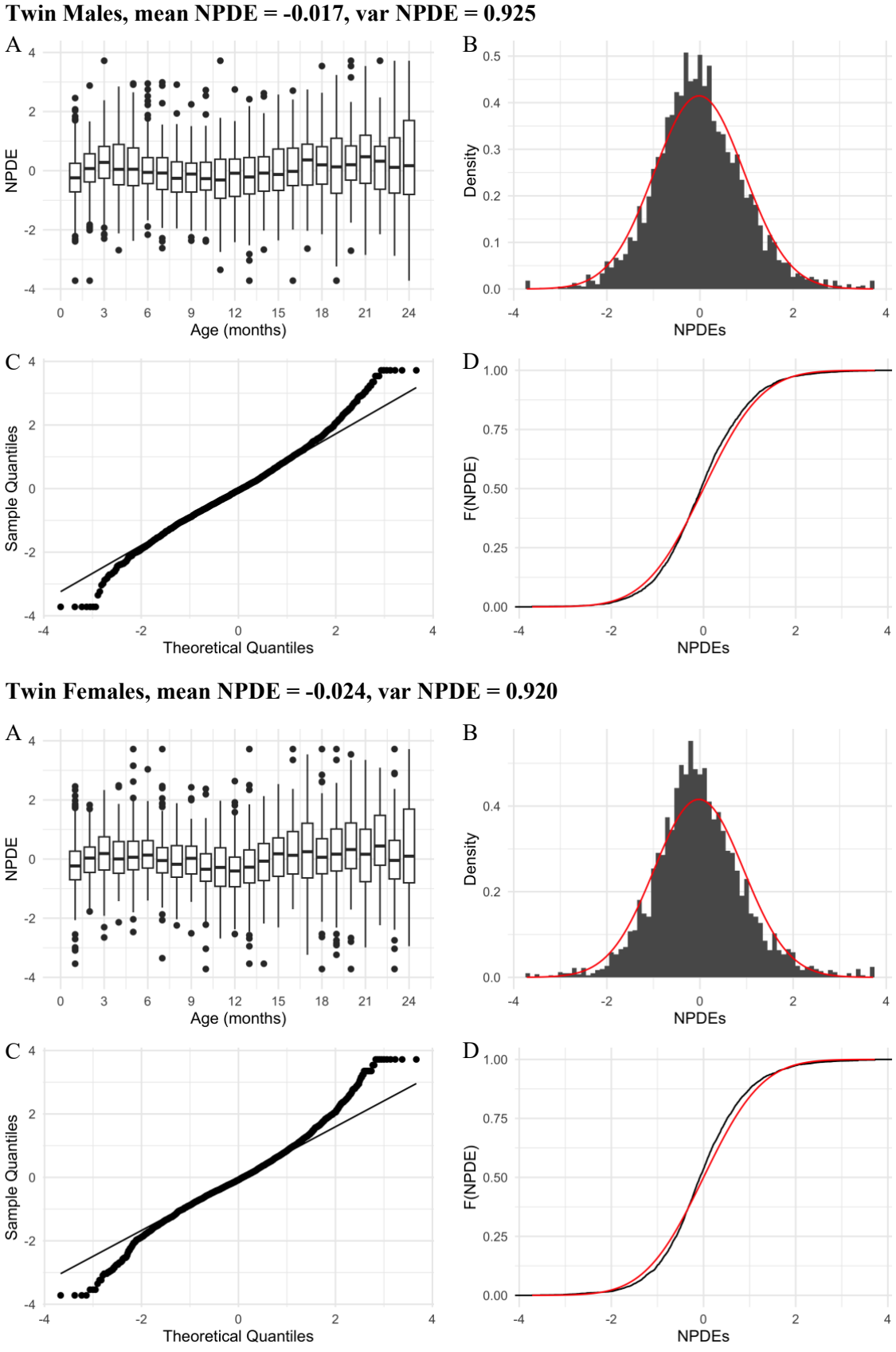
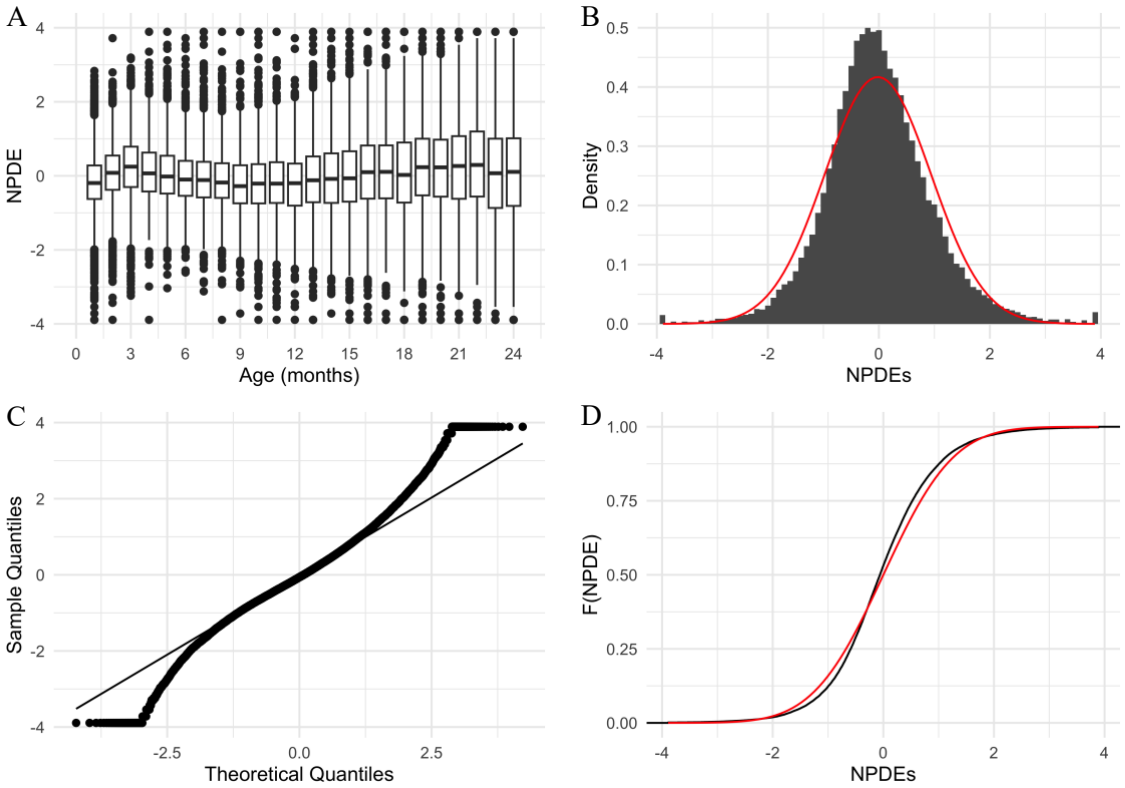


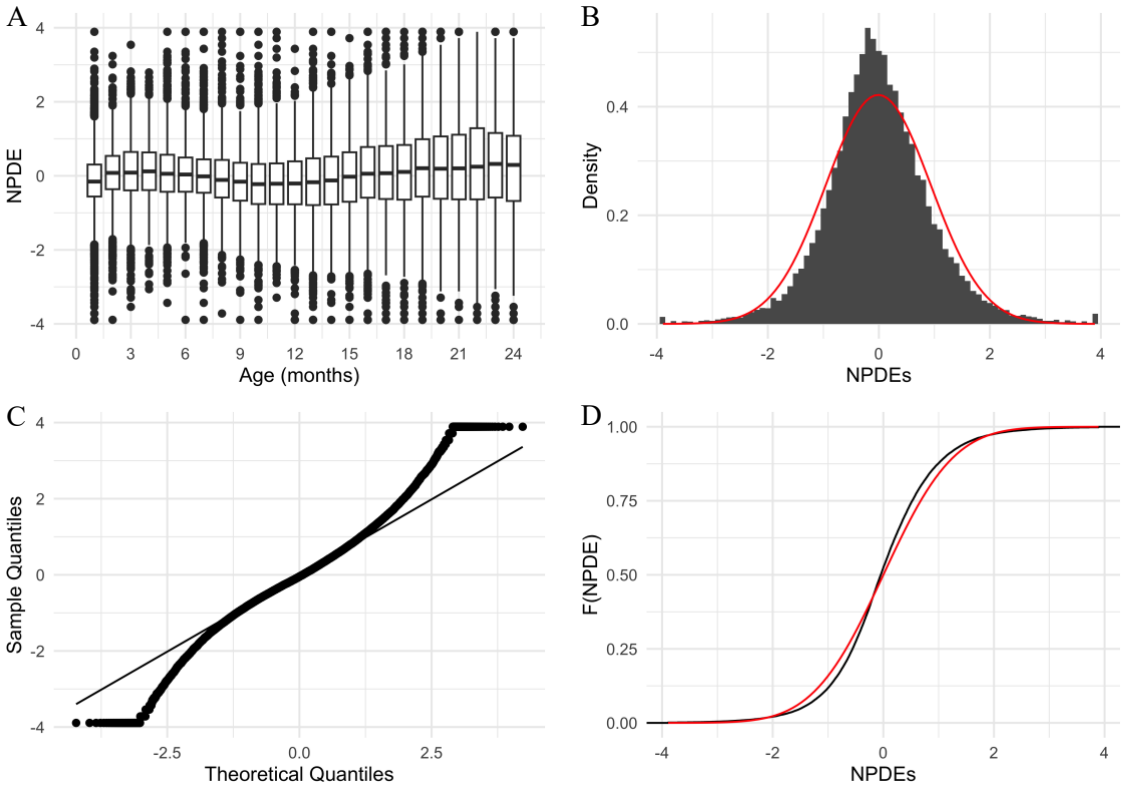
Figure A1.3 (A) NPDE Distribution, (B) Histogram, (C) QQ plot, and (D) eCDF plots to assess normality of NPDEs of the Jenss model. Continued on the next page.



Singleton Males, mean NPDE = -0.018, var NPDE = 0.916



Singleton Females, mean NPDE = -0.011, var NPDE = 0.895



NPDE: normalized prediction distribution errors. Var: variance. QQ: quantile-quantile. eCDF: empirical cumulative distribution function. Red line in histogram and eCDF plots represent the N(0, 1) distribution.

Figure A1.4 Timing of weight measurements, 0-2 years.
Each bin is 10 days.

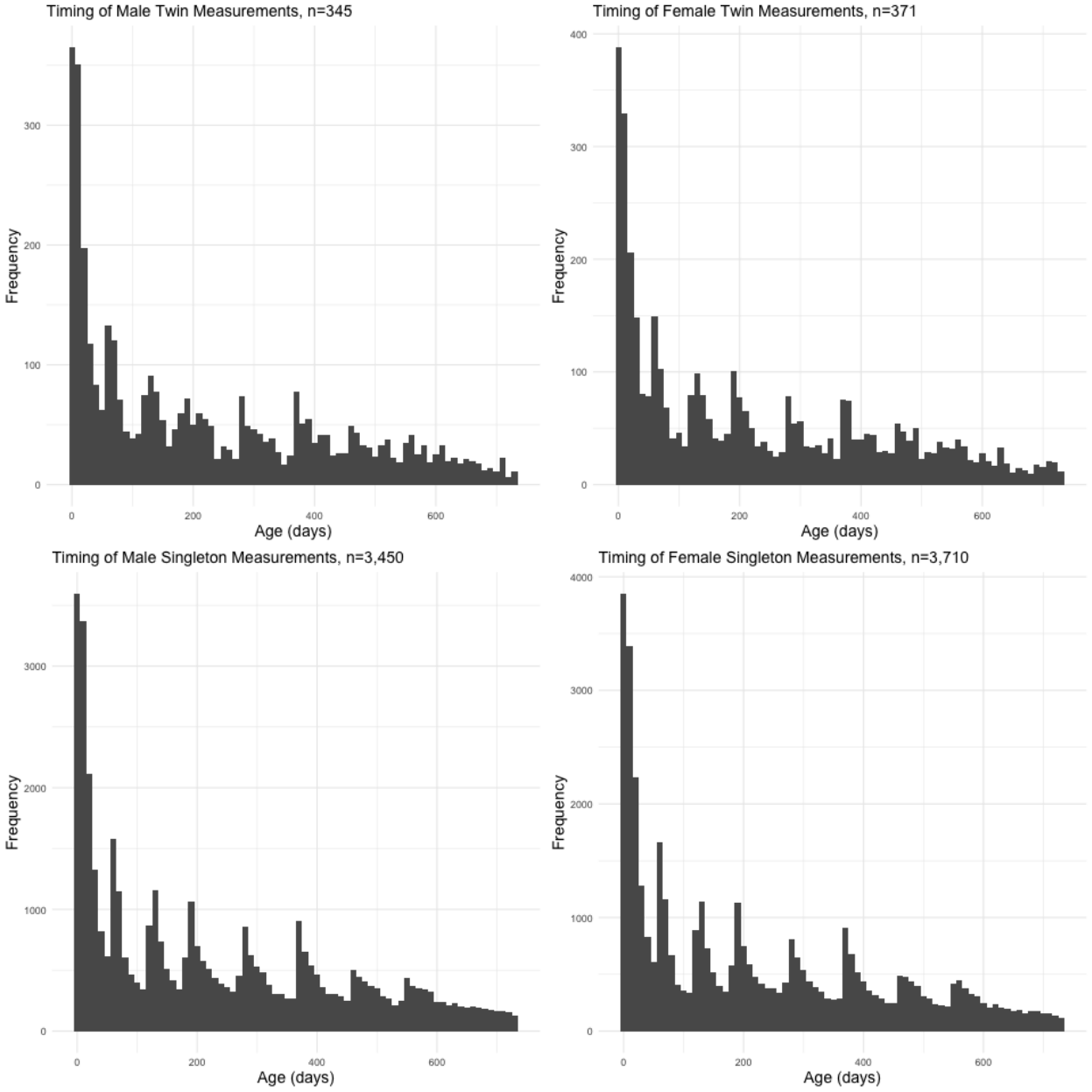
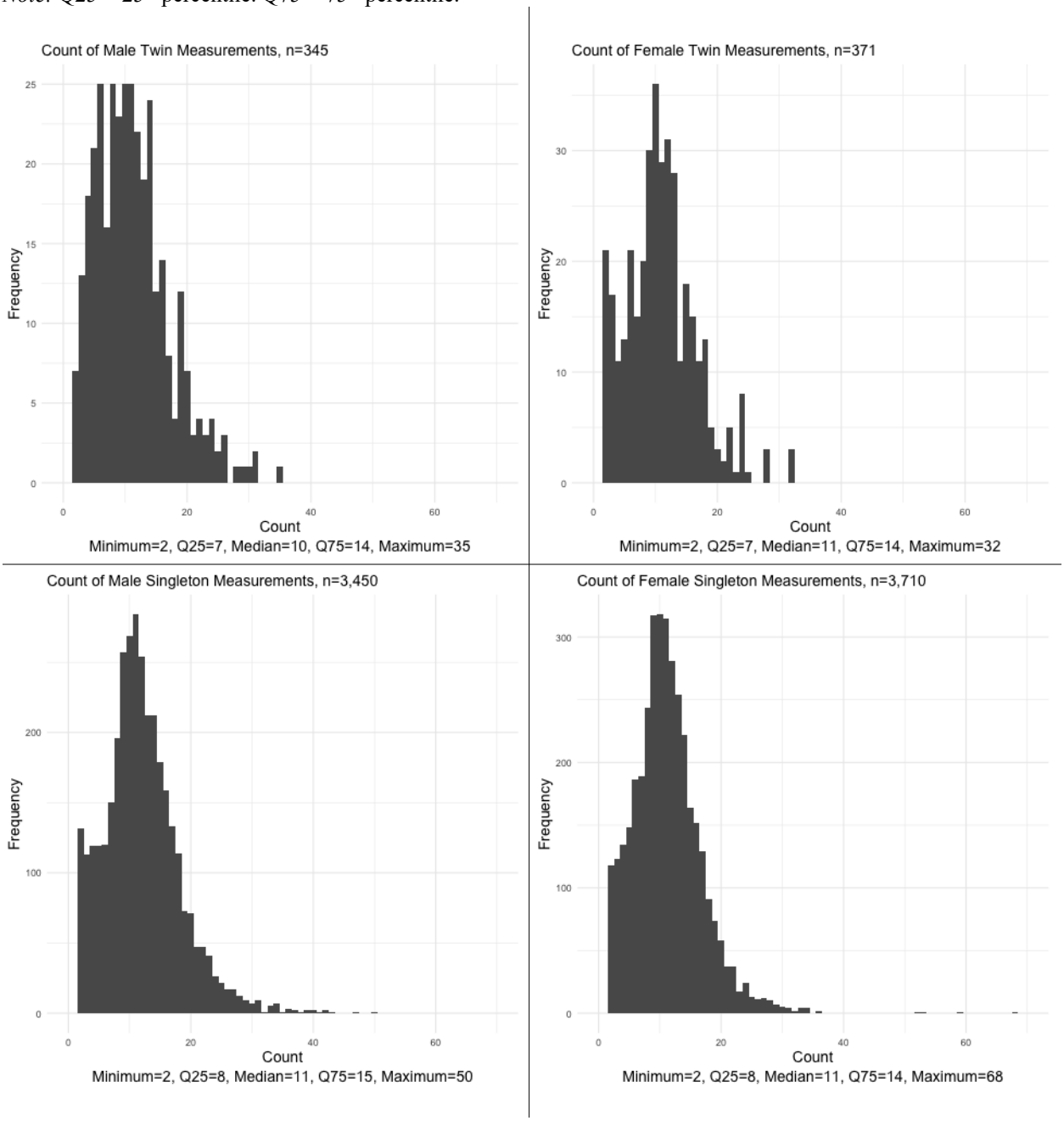
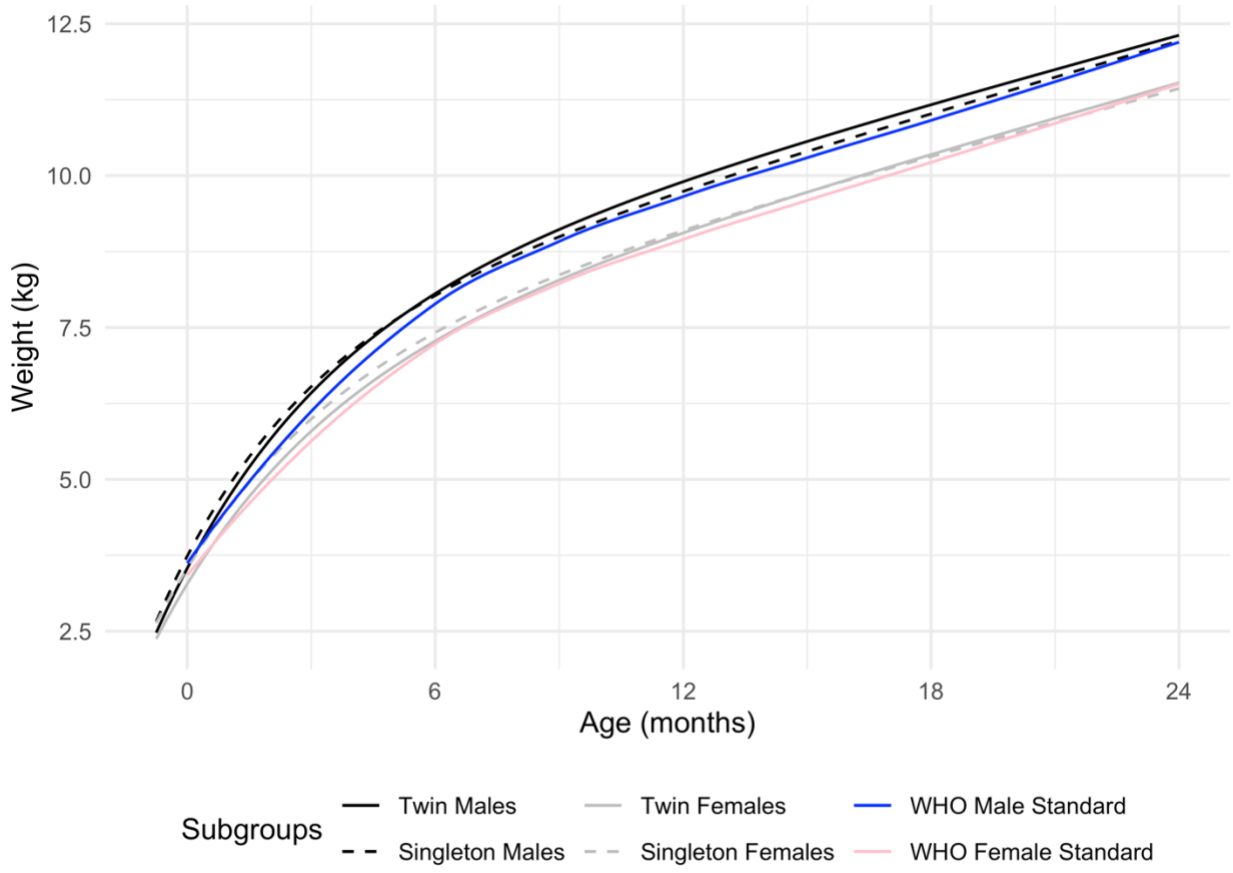


Figure A1.5 Number of weight measurements, 0-2 years.
Each bin is 1 measurement.
Note: Q25 = 25th percentile. Q75 = 75th percentile.



Appendix 1.D. Comparison of early childhood weight trajectories to the WHO growth standards.

Figure A1.6 Early childhood weight trajectories in the analytic sample compared to the median WHO growth standards with correction for gestational age.



WHO: World Health Organization. Values from WHO Multicentre Growth Reference Study Group (2006).[63] Median WHO growth standard trajectories were right-shifted by three weeks, given the mean gestational age of approximately 37 weeks in the analytic sample. It is recommended to use a corrected GA of 40 weeks when using the WHO growth standards.[115,116]

Appendix 1.E. Sensitivity Analysis – Exploring the Timing of Weight Measurements.

Table A1.2 Jenss model parameters among 6,567 PROMISE study children aged 0-2 years included in the sensitivity analysis exploring the timing of weight measurements.

Parameter	Twins		Singletons		*P* value
	Males (N=285)	Females (N=312)	Males (N=2,850)	Females (N=3,120)	
a: Starting value	0.88 (0.85, 0.92)	0.86 (0.82, 0.89)	0.97 (0.96, 0.98)	0.96 (0.96, 0.97)	<0.001[3, 4]
c: Catch-up growth in infancy	1.66 (1.60, 1.71)	1.50 (1.44, 1.56)	1.56 (1.54, 1.58)	1.45 (1.43, 1.47)	<0.001[1, 2, 3]
d: Decreasing rate of growth in late infancy	4.76 (4.70, 4.83)	4.80 (4.73, 4.87)	4.64 (4.62, 4.66)	4.75 (4.72, 4.77)	<0.001[2, 3]
b: Rate of growth in early childhood	5.13 (5.05, 5.20)	5.09 (5.02, 5.16)	5.06 (5.04, 5.08)	5.10 (5.08, 5.12)	<0.001[2]

Note. Values given as coefficient estimate (standard error). Statistical comparison made with one-way ANOVA. Significance determined with a P value < 0.05.

[1]: significant male-female difference among twins.

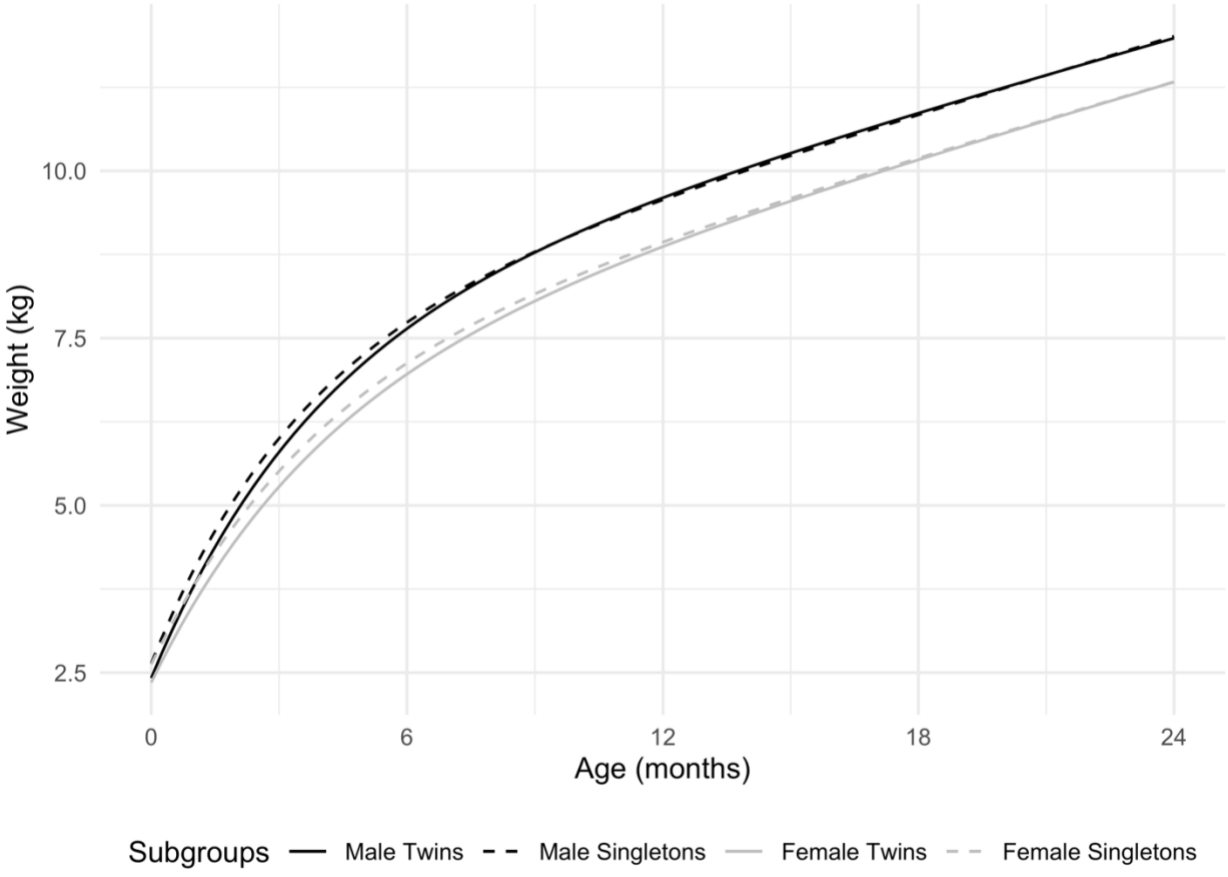
[2]: significant male-female difference among singletons.

[3]: significant twin-singleton difference among males.

[4]: significant twin-singleton difference among females.

[1, 2, 3, 4]: calculated from *post-hoc* Tukey's honestly significant difference tests.

Figure A1.7 Early childhood weight trajectory for 6,567 male twins, female twins, male singletons, and female singletons aged 0-2 years from the PROMISE study included in the sensitivity analysis.



Appendix 1F. Sensitivity Analysis – All Singletons.

Table A1.3 Jenss model parameters (estimate (95% confidence interval)) among 40,791 twins and the full sample of singletons in the PROMISE study aged 0-2 years.

Parameter	Twins		Singletons		*P* value
	Males (N=345)	Females (N=371)	Males (N=20,358)	Females (N=19,717)	
a: Starting value	0.91 (0.88, 0.93)	0.86 (0.84, 0.89)	1.10 (1.10, 1.11)	1.08 (1.08, 1.09)	<0.001[2, 3, 4]
c: Growth in early infancy	1.66 (1.61, 1.71)	1.48 (1.43, 1.54)	1.49 (1.49, 1.50)	1.39 (1.38, 1.39)	<0.001[1, 2, 3, 4]
d: Decreasing rate of growth in late infancy	4.78 (4.71, 4.84)	4.79 (4.72, 4.86)	4.59 (4.58, 4.60)	4.70 (4.69, 4.71)	<0.001[2, 3, 4]
b: Linear growth in early childhood	5.10 (5.03, 5.17)	5.06 (5.00, 5.13)	5.04 (5.03, 5.04)	5.08 (5.07, 5.09)	<0.001[2, 3]

Note. Values given as coefficient estimate (standard error). Statistical comparison made with one-way ANOVA. Significance determined with a P value < 0.05.

[1]: significant male-female difference among twins.

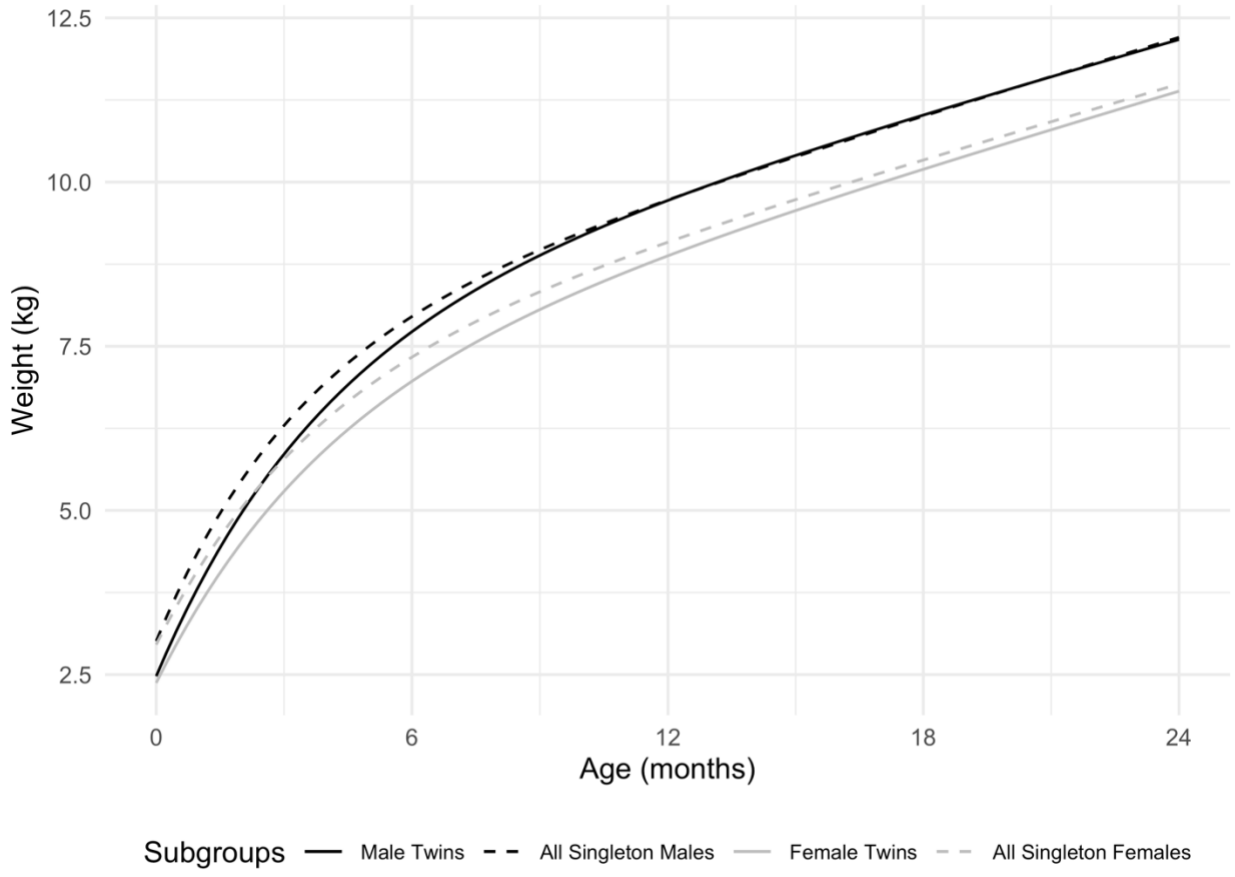
[2]: significant male-female difference among singletons.

[3]: significant twin-singleton difference among males.

[4]: significant twin-singleton difference among females.

[1, 2, 3, 4]: calculated from *post-hoc* Tukey's honestly significant difference tests.

Figure A1.8 Early childhood weight trajectory for male twins, female twins, all male singletons, and all female singletons.



Appendix 2. Supplemental material for Chapter 4. Gestational weight gain throughout pregnancy and early childhood weight trajectory among twins and singletons.

Appendix 2.A. International Classification of Diseases codes to identify twin pregnancies.

Codes from ICD-9 and ICD-10 are given below. The presence of at least one code in the pregnant person's EHR with a diagnosis date between pregnancy start and end dates was used to identify twin pregnancies. The absence of these codes was not used to determine singleton status; that is, this definition was *only* used to identify twins.

Diagnosis Code	Short Description
O30.00	Twin pregnancy, unsp num plcnta & amnio sacs
O30.001	Twin preg, unsp num plcnta & amnio sacs, first trimester
O30.002	Twin preg, unsp num plcnta & amnio sacs, second trimester
O30.003	Twin preg, unsp num plcnta & amnio sacs, third trimester
O30.009	Twin pregnancy, unsp num plcnta & amnio sacs, unsp trimester
O30.01	Twin pregnancy, monochorionic/monoamniotic
O30.011	Twin pregnancy, monochorionic/monoamniotic, first trimester
O30.012	Twin pregnancy, monochorionic/monoamniotic, second trimester
O30.013	Twin pregnancy, monochorionic/monoamniotic, third trimester
O30.019	Twin pregnancy, monochorionic/monoamniotic, unsp trimester
O30.03	Twin pregnancy, monochorionic/diamniotic
O30.031	Twin pregnancy, monochorionic/diamniotic, first trimester
O30.032	Twin pregnancy, monochorionic/diamniotic, second trimester
O30.033	Twin pregnancy, monochorionic/diamniotic, third trimester
O30.039	Twin pregnancy, monochorionic/diamniotic, unsp trimester
O30.04	Twin pregnancy, dichorionic/diamniotic
O30.041	Twin pregnancy, dichorionic/diamniotic, first trimester
O30.042	Twin pregnancy, dichorionic/diamniotic, second trimester
O30.043	Twin pregnancy, dichorionic/diamniotic, third trimester
O30.049	Twin pregnancy, dichorionic/diamniotic, unsp trimester
O30.09	Twin pregnancy, unable to determine num plcnta & amnio sacs
O30.091	Twin preg, unable to dtrm num plcnta & amnio sacs, first tri
O30.092	Twin preg, unable to dtrm num plcnta & amnio sacs, 2nd tri
O30.093	Twin preg, unable to dtrm num plcnta & amnio sacs, third tri
O30.099	Twin preg, unable to dtrm num plcnta & amnio sacs, unsp tri
Z37.2	Twins, both liveborn
Z37.3	Twins, one liveborn and one stillborn
Z37.4	Twins, both stillborn
Z37.50	Multiple births, unspecified, all liveborn
Z37.60	Multiple births, unspecified, some liveborn
Z37.7	Other multiple births, all stillborn

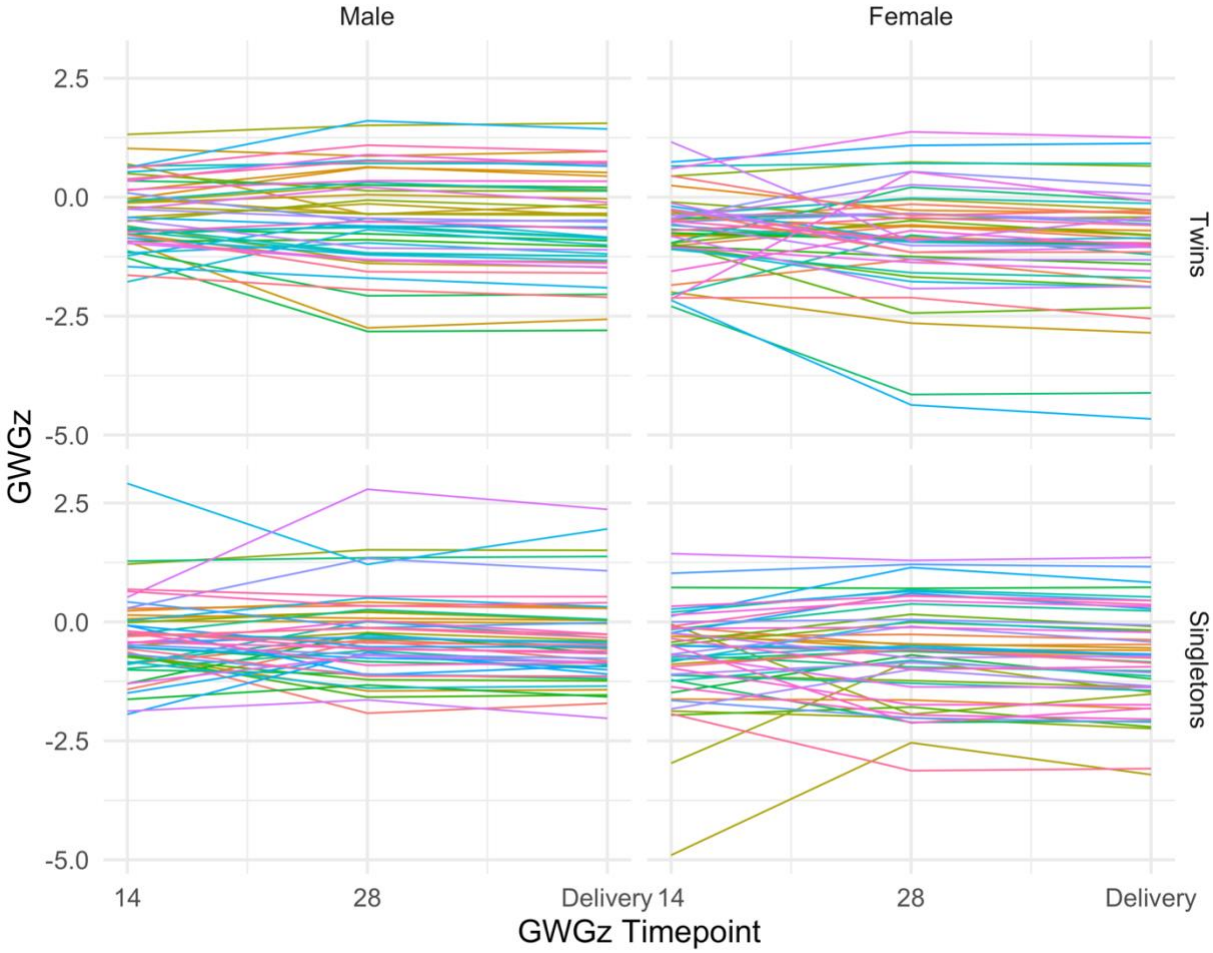
Z64.1	Problems related to multiparity
651	Twin pregnancy
651.00	Twin pregnancy-unspec
651.01	Twin pregnancy-delivered
651.03	Twin pregnancy-antepart
651.8	Other specified multiple gestation
651.80	Multi gestat NEC-unspec
651.81	Multi gestat NEC-deliver
651.83	Multi gest NEC-antepart
V31	Twin birth, mate liveborn
V31.0	Twin, mate liveborn, born in hospital
V31.00	Twin-mate lb-hosp w/o cs
V31.01	Twin-mate lb-in hos w cs
V31.1	Twin, mate lb-before adm
V31.2	Twin, mate lb-nonhosp
V32	Twin birth, mate stillborn
V32.00	Twin-mate sb-hosp w/o cs
V32.01	Twin-mate sb-hosp w cs
V32.1	Twin, mate sb-before adm
V32.2	Twin, mate sb-nonhosp
V33	Twin birth, unspecified whether mate liveborn or stillborn
V33.00	Twin-NOS-in hosp w/o cs
V33.01	Twin-NOS-in hosp w cs
V33.1	Twin NOS-before admissn
V33.2	Twin NOS-nonhosp
V39	Liveborn, unspecified whether single, twin, or multiple
V39.00	Liveborn NOS-hosp w/o cs
V39.01	Liveborn NOS-hosp w cs
V39.1	Liveborn NOS-before adm
V39.2	Liveborn NOS-nonhosp
V91.0	Twin gestation placenta status
V91.00	Twin gest-plac/sac NOS
V91.01	Twin gest-monochr/monoam
V91.02	Twin gest-monochr/diamni
V91.03	Twin gest-dich/diamniotc
V91.09	Twin gest-plac/sac undet

Appendix 2.B. Details regarding the calculation of gestational weight gain z-scores.

Published GWG z-score charts[131,138,139] end at 40 and 41 gestational weeks for singleton pregnancies with pre-pregnancy normal weight and overweight or obesity, respectively; and for twin pregnancies, at 39 and 38 gestational weeks for pre-pregnancy normal weight and overweight or obesity, respectively. GA for deliveries beyond these limits (n=2,573, 4.7%) were converted down to the last available gestational week for the given pre-pregnancy BMI and plurality group for this calculation only. Additionally, the twin GWGz reference did not provide z-score charts for obesity subclasses, so all twin pregnancies with pre-pregnancy obesity were compared to the twin obesity z-score chart, regardless of obesity subclass. The singleton GWGz reference provided z-score charts for obesity subclasses.

GWGz is calculated with the formula: $\frac{log(GWG+c)-\mu}{\sigma}$, where GWG is the GWG in kilograms, c is a constant to ensure nonnegative observations, and μ and σ are the log-transformed mean and standard deviation, respectively;[185] values for c, μ, and σ are specific to each pre-pregnancy BMI, GA, and plurality group and are found in the published references. GWGz at ≥1 of the timepoints (14 weeks, 28 weeks, and delivery) could not be calculated for 274 pregnancies because the constant was not large enough to provide a positive number for the natural log calculation; i.e., $GWG + c$ was negative. Implausible GWGz was defined as GWGz <-5 or >5; 313 pregnancies had at least one implausible GWGz value. 559 pregnancies had either an incalculable GWGz at ≥1 timepoint or an implausible GWGz at ≥1 timepoint, or both (28 pregnancies), and were removed.

Figure A2.1 Intrapregnancy GWGz variation in 50 randomly selected pregnancies per group.



Each color reflects one pregnancy. 50 pregnancies per group were randomly selected for this figure.

Appendix 2.C. Details regarding the Jenss model.

The Jenss model is a four-parameter mixed-effects model that was developed to fit weight and height growth trajectories from birth to 6-8 years. The Jenss model is given by:

$$y_{ij} = a_i + b_i * t_{ij} - e^{c_i + d_i * t_{ij}},$$

Where j is the growth measure of the i^{th} subject, y is the weight measure in kilograms, and t is the age of the child in days. The model differentiates the pattern of growth into two periods.[102,105,114] The first is nonlinear growth during infancy – often a sharp increase in weight in the first months of life followed by a slowly decelerating rate – and is represented by the nonlinear (exponential) term in the model. The second period is linear growth in childhood, represented by the linear terms in the model (i.e., the equation of a straight line, $a_i + b_i * t_{ij}$). The Jenss model is a negatively accelerated exponential that becomes linear at its asymptote.

A parameterization of the Jenss model was used which adds constraints of positivity to the parameters in order to facilitate model convergence.[105] The parameterization is given by:

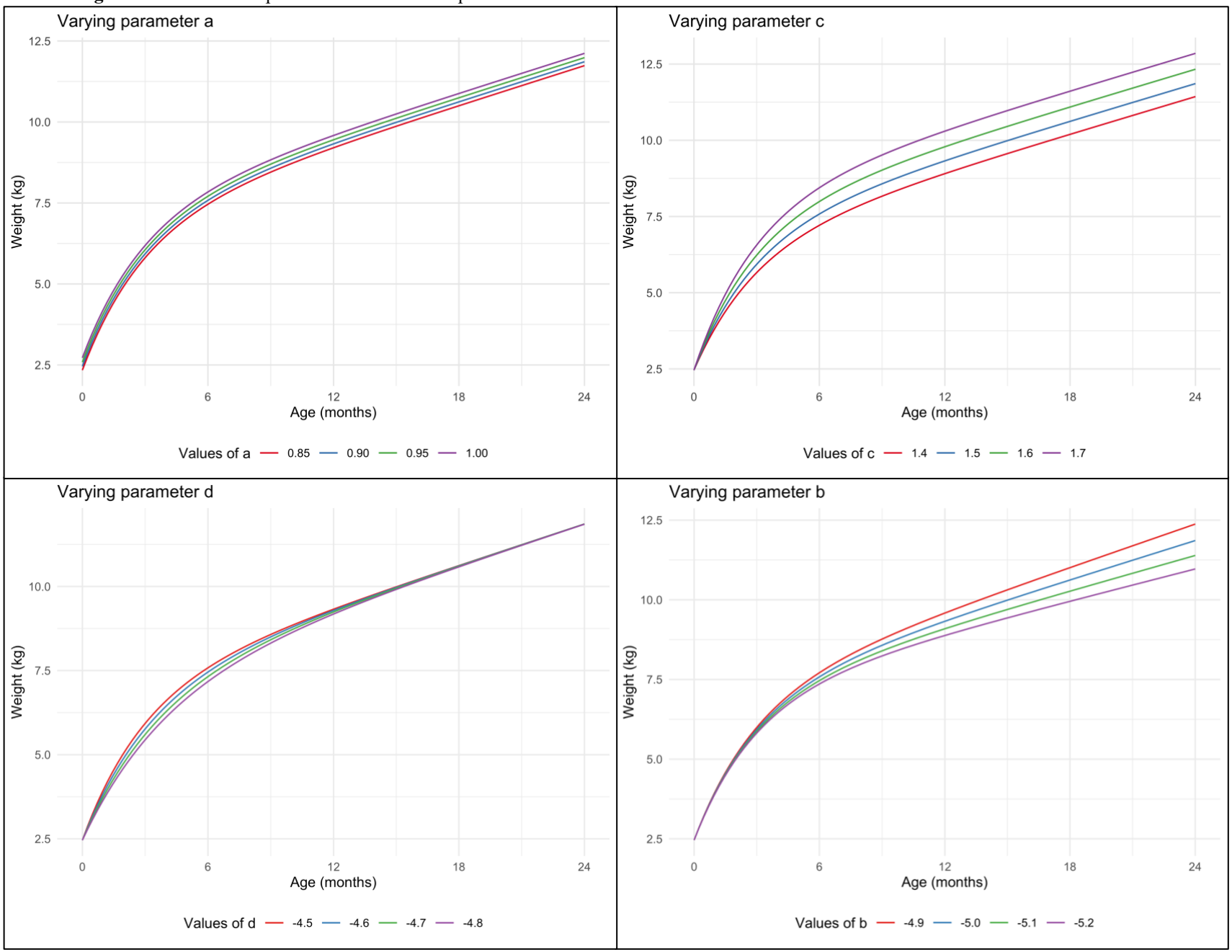
$$y_{ij} = e^{a_i} + e^{-b_i} * t_{ij} + e^{c_i} * \left(1 - e^{\left(-e^{-d_i * t_{ij}}\right)}\right).$$

Each growth parameter given by the Jenss model is the sum of a fixed and a random component. Parameter a reflects the predicted weight when $t = 0$; parameter c reflects growth in early infancy ("catch-up growth"); parameter d reflects the decreasing exponential ("deceleration" in growth at the end of infancy); and parameter b reflects the slope at the asymptote (linear rate of growth in childhood).[103,105,114] Parameter a cannot necessarily be interpreted as birth weight and is instead referred to as the "starting weight."

The Jenss model was fit to our data using the SAEMIX package in R, which implements a stochastic approximation expectation maximization (SAEM) algorithm for nonlinear mixed-effects models without approximating the likelihood function.[182] An unstructured variance-covariance matrix was used. The Jenss model was fit separately for male twins, female twins, male singletons, and female singletons.

We required a baseline weight and at least one other weight measurement for inclusion in this study. *Baseline weight* was defined as the minimum weight among clinical visits from postnatal days 0-5 and, when the birth record was available (30.2% of twins and 47.2% of singletons), birth weight. Other weight values in the first 5 days of life that were not the minimum weight were removed. The baseline weight was used as the starting value for weight trajectory modeling. Implausible birth weights were identified with GA- and sex-standardized z-scores calculated from birth weight references for twins[108] and singletons[27] and removed; see section D of the Supplementary Materials.

Figure A2.2 Visual interpretation of Jenss model parameters.



Appendix A2.D. Details regarding the cleaning of birth weights.

Implausible birth weights were defined as a gestational age- and sex-standardized z-scores of <-5 or >5,[181] calculated from birth weight references for twins[108] and singletons.[27] The birth weight reference for twins ends at 40 gestational weeks; 24 twin children had a gestational age at birth beyond 40 weeks and their gestational age was converted to 40 weeks for this calculation only. Because the birth weight reference for twins[108] gives mean and standard deviation values in two-week intervals for GA, mean and standard deviation values for intermediate GAs were imputed (**Figure A2.2** and **Table A2.1**). 41 singletons and 1 twin were found to have implausible birth weight and their birth weight was removed.

Figure A2.3 Birth weight reference imputation for male (A) and female (B) twins.
Imputed values shown in red (mean) and blue (standard deviation).

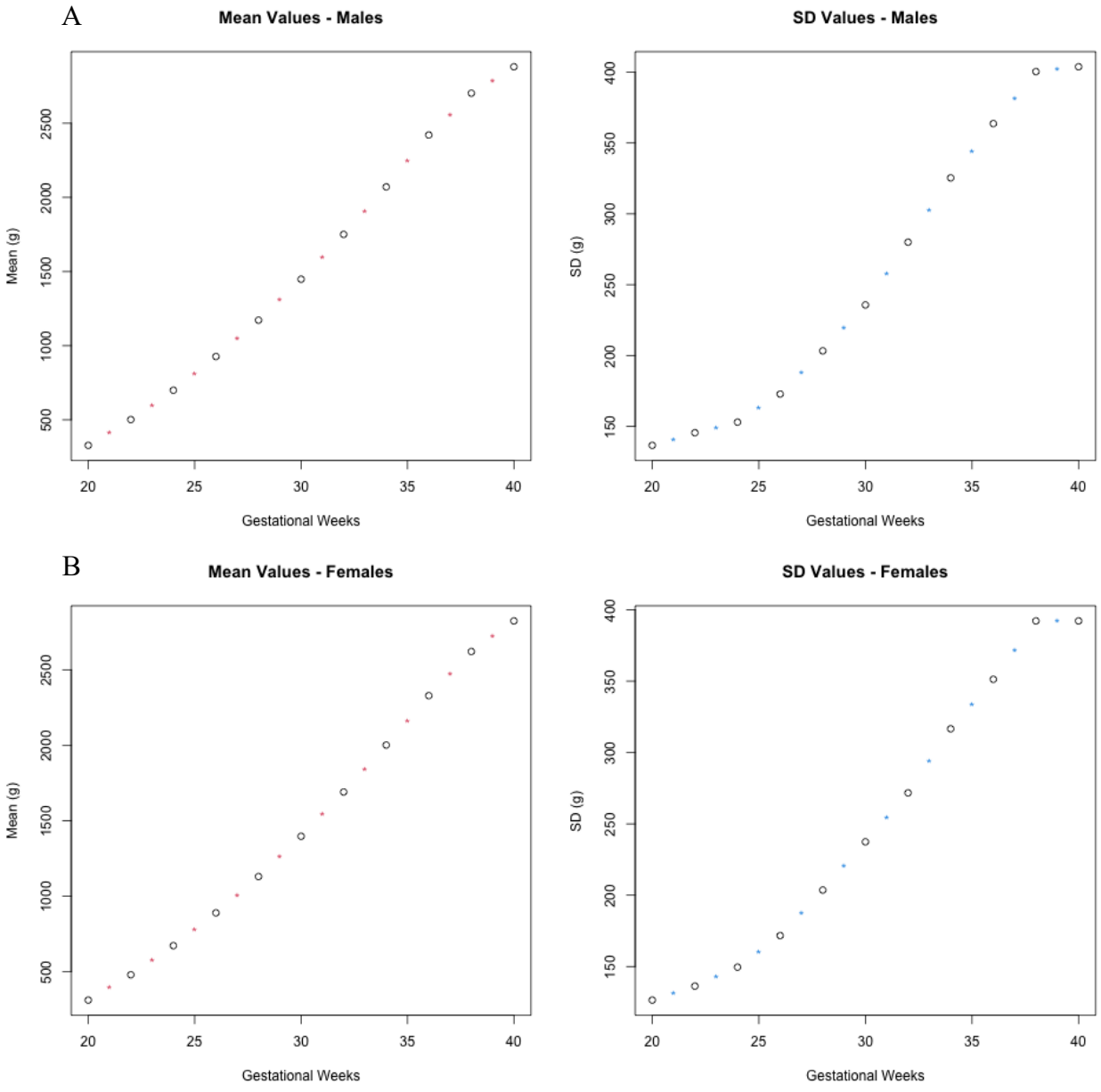


Table A2.1 Published and imputed birth weight values for twins.

	Males		Females	
Week	**Mean (g)**	**SD (g)**	**Mean (g)**	**SD (g)**
20	327.8	136.6	312.4	126.5
21	***414.7***	***141.1***	***396.3***	***131.4***
22	501.5	145.5	480.2	136.3
23	***600.5***	***149.3***	***576.5***	***143.0***
24	699.5	153	672.8	149.6
25	***813.2***	***162.9***	***781.5***	***160.7***
26	926.8	172.8	890.1	171.7
27	***1049.4***	***188.1***	***1010.3***	***187.7***
28	1171.9	203.3	1130.5	203.6
29	***1310.0***	***219.5***	***1263.9***	***220.5***
30	1448.1	235.7	1397.2	237.4
31	***1599.3***	***257.9***	***1543.9***	***254.6***
32	1750.5	280	1690.5	271.7
33	***1910.6***	***302.7***	***1845.9***	***294.2***
34	2070.7	325.4	2001.3	316.6
35	***2245.8***	***344.6***	***2164.9***	***334.0***
36	2420.8	363.7	2328.5	351.3
37	***2561.6***	***382.1***	***2474.6***	***371.8***
38	2702.4	400.4	2620.7	392.2
39	***2791.5***	***402.1***	***2722.0***	***392.2***
40	2880.6	403.8	2823.3	392.2

Published values are given in normal font; interpolated values are given in bolded and italicized font. Published values from Min (2000).[108]

Appendix 2.E. Procedures used to define preexisting diabetes and hypertension.

Preexisting diabetes and hypertension were identified in the electronic health record by searching for specific International Classification of Diseases (ICD)-9 and ICD-10 codes. A list of ICD codes used may be requested by contacting the corresponding author.

Diabetes was identified by first searching the health record for ICD codes related to a diabetes diagnosis, symptoms, or complications at any time since 2000. *Preexisting diabetes* was defined as (1) at least two encounters with at least one ICD-9 or ICD-10 code relating to diabetes before the start of pregnancy; (2) at least one ICD-9 or ICD-10 code relating to diabetes on the patient's Problem List before the start of pregnancy; (3) at least one ICD-10 code specifying pre-existing diabetes during pregnancy; (4) at least two encounters with at least one ICD-9 or ICD-10 code relating to diabetes between week 0 and week 24 of pregnancy; or (5) at least one ICD-9 or ICD-10 code relating to diabetes on the patient's Problem List with a date of onset between week 0 and week 24 of pregnancy.

Hypertension was identified by first searching the health record for ICD codes related to a hypertension diagnosis, symptoms, or complications from the two years prior to the start of pregnancy to the end of week 19 of pregnancy. *Preexisting hypertension* was defined as (1) at least one ICD-9 or ICD-10 code relating to unresolved hypertension on the patient's Problem List; (2) at least two encounters with at least one ICD-9 or ICD-10 code relating to hypertension; or (3) at least two high blood pressure measurements (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) at least one day apart.

Appendix 2.F. Details regarding the multiple imputations by chained equations procedure.

We imputed missing data for four covariates – preferred spoken language, insurance during pregnancy, maternal race and ethnicity, continuous FPL, categorical parity (1, 2, ≥3), and education – which were missing in <1%, <1%, 2.3%, 36.0%, 36.5%, and 37.4% of pregnancies, respectively. Multiple imputations by chained equations has been shown to be valid even with large proportions of missing data (~90%) given data are missing at random and the imputation model is correctly specified.[186] Therefore, we were confident in imputing these confounders; however, a complete case analysis was explored as a sensitivity analysis.

Thirty datasets complete for preferred spoken language, insurance during pregnancy, maternal race and ethnicity, FPL, parity, and education were imputed, each with 20 iterations, and with clustering by pregnancy identification number (i.e., to ensure imputed values were the same for both children within a pregnancy, in the case of twins). These values were chosen given work suggesting that the number of imputed datasets should be roughly equivalent to the percentage of missing data[163] and visual examination of the stability of imputed data when the number of iterations was changed. All regression results were pooled across the thirty datasets.

Each imputed variable used as predictor variables (except itself): race and ethnicity, BMI, education, preferred spoken language, preexisting diabetes, preexisting hypertension, FPL, insurance during pregnancy, age at the end of pregnancy, parity, Jenss model parameters for infant growth (a, b, c, and d), GWGz at 14 weeks, GWGz at 28 weeks, and GWGz at delivery.

Appendix 2.G. Crude Analysis.

Table A2.2 Crude associations (β (95% confidence interval) between gestational weight gain z-score throughout pregnancy and infant weight trajectory parameters by plurality group and child sex (N=6,506 pregnancies and 6,721 children from the PROMISE study).

	Twins		**Singletons**	
	Males	Females	Males	Females
***a*: Starting value**				
GWGz at 14 weeks	0.01 (-0.03, 0.05)	-0.01 (-0.04, 0.02)	0.02 (0.01, 0.03)*	0.03 (0.02, 0.03)*
GWGz at 28 weeks	-0.02 (-0.05, 0.01)	-0.01 (-0.04, 0.01)	0.03 (0.02, 0.04)*	0.03 (0.02, 0.04)*
GWGz at delivery	-0.01 (-0.04, 0.02)	-0.01 (-0.03, 0.02)	0.03 (0.02, 0.04)*	0.03 (0.02, 0.04)*
***c*: Growth in early infancy**				
GWGz at 14 weeks	-0.02 (-0.07, 0.03)	0.06 (0.00, 0.12)	0.00 (-0.01, 0.02)	0.00 (-0.02, 0.02)
GWGz at 28 weeks	-0.01 (-0.06, 0.04)	0.06 (0.00, 0.11)	0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)
GWGz at delivery	-0.01 (-0.05, 0.04)	0.05 (0.00, 0.11)	0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)
***d*: Decreasing rate of growth in late infancy**				
GWGz at 14 weeks	0.02 (-0.04, 0.07)	-0.11 (-0.19, -0.03)*	-0.01 (-0.02, 0.01)	0.00 (-0.02, 0.02)
GWGz at 28 weeks	0.00 (-0.05, 0.05)	-0.10 (-0.17, -0.04)*	-0.01 (-0.02, 0.01)	-0.01 (-0.02, 0.01)
GWGz at delivery	0.00 (-0.05, 0.05)	-0.10 (-0.16, -0.04)*	-0.01 (-0.02, 0.01)	0.00 (-0.02, 0.01)
***b*: Linear growth in early childhood**				
GWGz at 14 weeks	0.05 (-0.02, 0.11)	-0.02 (-0.08, 0.05)	0.02 (0.00, 0.04)	0.01 (-0.01, 0.03)
GWGz at 28 weeks	0.03 (-0.02, 0.08)	-0.01 (-0.07, 0.04)	0.02 (0.00, 0.03)	0.01 (0.00, 0.03)
GWGz at delivery	0.03 (-0.02, 0.08)	-0.01 (-0.07, 0.04)	0.02 (0.00, 0.03)	0.01 (0.00, 0.03)

*: significant at 0.05 significance level.
Robust standard errors were used to control for clustering within twin pregnancies and within matching group membership.

Appendix 2.H. Sensitivity Analysis – Complete Case Analysis.
This sensitivity analysis was conducted to perform a complete case analysis of our adjusted analysis, given the moderately high (38.6% at most) missingness in some confounding variables. Results are largely unchanged from the main adjusted analysis.

Table A2.3 Adjusted associations (β (95% confidence interval) between gestational weight gain z-score throughout pregnancy and infant weight trajectory parameters by plurality group and child sex (N=2,325 pregnancies and 2,404 children from the PROMISE study).

	Twins		**Singletons**	
	Male	Female	Male	Female
***a*: Starting value**				
GWGz at 14 weeks	0.06 (-0.01, 0.12)	0.02 (-0.04, 0.08)	0.02 (0.00, 0.03)	0.03 (0.01, 0.05)*
GWGz at 28 weeks	0.09 (0.04, 0.14)*	0.07 (0.02, 0.11)*	0.05 (0.03, 0.07)*	0.05 (0.03, 0.07)*
GWGz at delivery	0.10 (0.05, 0.15)*	0.08 (0.04, 0.12)*	0.06 (0.04, 0.08)*	0.07 (0.05, 0.09)*
***c*: Growth in early infancy**				
GWGz at 14 weeks	-0.01 (-0.12, 0.10)	0.08 (-0.02, 0.19)	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.03)
GWGz at 28 weeks	-0.05 (-0.14, 0.04)	0.03 (-0.05, 0.12)	-0.02 (-0.05, 0.01)	-0.01 (-0.04, 0.02)
GWGz at delivery	-0.04 (-0.13, 0.05)	0.03 (-0.05, 0.12)	-0.02 (-0.05, 0.02)	-0.01 (-0.05, 0.03)
***d*: Decreasing rate of growth in late infancy**				
GWGz at 14 weeks	0.01 (-0.09, 0.11)	-0.09 (-0.21, 0.02)	-0.01 (-0.04, 0.02)	0.02 (-0.03, 0.06)
GWGz at 28 weeks	0.06 (-0.06, 0.17)	-0.04 (-0.13, 0.05)	0.02 (-0.01, 0.05)	0.02 (-0.01, 0.06)
GWGz at delivery	0.06 (-0.05, 0.16)	-0.03 (-0.12, 0.06)	0.03 (-0.01, 0.07)	0.04 (0.00, 0.07)
***b*: Linear growth in early childhood**				
GWGz at 14 weeks	0.01 (-0.13, 0.14)	0.00 (-0.14, 0.13)	0.02 (-0.01, 0.06)	0.00 (-0.04, 0.04)
GWGz at 28 weeks	0.04 (-0.08, 0.17)	0.02 (-0.09, 0.13)	0.03 (0.00, 0.06)	0.02 (-0.02, 0.05)
GWGz at delivery	0.04 (-0.08, 0.16)	0.03 (-0.08, 0.13)	0.04 (0.00, 0.08)	0.02 (-0.02, 0.06)

*: significant at 0.05 significance level
Adjusted for maternal race and ethnicity, preferred spoken language, education, pre-pregnancy body mass index, preexisting diabetes, preexisting hypertension, income as a percentage of the federal poverty level at the start of pregnancy, most prevalent insurance type in the 2nd and 3rd trimesters, age at the end of pregnancy, parity, and year of birth.
Robust standard errors were used to control for clustering within twin pregnancies and within matching group membership.

Appendix 2.I. Sensitivity Analysis – Stratification by pre-pregnancy BMI.

Table A2.4 Adjusted associations (β (95% confidence interval) between gestational weight gain z-score throughout pregnancy and infant weight trajectory parameters by plurality group, child sex, and pre-pregnancy body mass index.

	Twins		**Singletons**	
	Male	Female	Male	Female
***a*: Starting value**				
GWGz at 14 weeks				
Normal	-0.04 (-0.10, 0.02)	-0.04 (-0.10, 0.01)	0.02 (0.01, 0.03)*	0.02 (0.01, 0.03)*
Overweight	0.05 (0.00, 0.10)	-0.03 (-0.07, 0.01)	0.03 (0.01, 0.05)*	0.03 (0.01, 0.05)*
Obesity	0.00 (-0.06, 0.06)	0.08 (0.03, 0.14)*	0.02 (0.00, 0.04)	0.03 (0.01, 0.05)*
GWGz at 28 weeks				
Normal	-0.03 (-0.06, 0.00)	-0.03 (-0.07, 0.01)	0.06 (0.04, 0.07)*	0.05 (0.04, 0.06)*
Overweight	0.01 (-0.05, 0.07)	-0.03 (-0.08, 0.02)	0.01 (-0.02, 0.03)	0.01 (-0.01, 0.04)
Obesity	-0.02 (-0.06, 0.02)	0.05 (0.01, 0.09)*	0.04 (0.02, 0.05)*	0.04 (0.02, 0.06)*
GWGz at delivery				
Normal	-0.03 (-0.06, 0.01)	-0.02 (-0.07, 0.02)	0.05 (0.04, 0.07)*	0.05 (0.04, 0.06)*
Overweight	0.03 (-0.02, 0.09)	-0.02 (-0.06, 0.03)	0.04 (0.02, 0.06)*	0.04 (0.02, 0.06)*
Obesity	-0.01 (-0.05, 0.03)	0.06 (0.02, 0.10)*	0.04 (0.02, 0.06)*	0.04 (0.02, 0.07)*
***c*: Growth in early infancy**				
GWGz at 14 weeks				
Normal	0.00 (-0.08, 0.08)	0.13 (0.01, 0.25)*	0.00 (-0.03, 0.02)	0.00 (-0.02, 0.03)
Overweight	-0.01 (-0.08, 0.06)	-0.03 (-0.11, 0.06)	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.03)
Obesity	-0.04 (-0.15, 0.08)	0.10 (-0.02, 0.23)	0.01 (-0.02, 0.05)	-0.02 (-0.07, 0.03)
GWGz at 28 weeks				
Normal	-0.05 (-0.11, 0.02)	0.12 (0.04, 0.21)*	-0.02 (-0.04, 0.00)	-0.02 (-0.04, 0.00)
Overweight	0.04 (-0.05, 0.12)	0.01 (-0.07, 0.1)	0.02 (-0.01, 0.04)	0.02 (-0.01, 0.05)
Obesity	0.03 (-0.06, 0.13)	0.02 (-0.09, 0.13)	-0.01 (-0.04, 0.02)	-0.01 (-0.05, 0.02)
GWGz at delivery				
Normal	-0.04 (-0.11, 0.02)	0.13 (0.04, 0.22)*	-0.02 (-0.04, 0.01)	-0.02 (-0.04, 0.01)
Overweight	0.04 (-0.05, 0.12)	0.01 (-0.07, 0.09)	0.01 (-0.02, 0.05)	0.02 (-0.02, 0.06)
Obesity	0.02 (-0.08, 0.12)	0.02 (-0.08, 0.13)	-0.01 (-0.05, 0.03)	-0.01 (-0.06, 0.03)

***d*: Decreasing rate of growth in late infancy**				
GWGz at 14 weeks				
Normal	0.00 (-0.09, 0.08)	-0.18 (-0.37, 0.02)	0.01 (-0.02, 0.03)	0.01 (-0.01, 0.04)
Overweight	0.02 (-0.05, 0.10)	-0.01 (-0.10, 0.07)	0.01 (-0.02, 0.05)	0.00 (-0.04, 0.04)
Obesity	0.04 (-0.11, 0.18)	-0.10 (-0.24, 0.04)	0.01 (-0.03, 0.05)	0.01 (-0.04, 0.06)
GWGz at 28 weeks				
Normal	0.04 (-0.02, 0.10)	-0.18 (-0.32, -0.04)*	0.02 (0.00, 0.05)	0.04 (0.02, 0.07)*
Overweight	-0.02 (-0.12, 0.08)	-0.04 (-0.12, 0.04)	-0.01 (-0.05, 0.02)	-0.02 (-0.06, 0.02)
Obesity	-0.06 (-0.16, 0.03)	-0.03 (-0.15, 0.08)	0.01 (-0.02, 0.04)	0.00 (-0.04, 0.04)
GWGz at delivery				
Normal	0.03 (-0.03, 0.10)	-0.19 (-0.33, -0.04)*	0.02 (-0.01, 0.05)	0.04 (0.01, 0.07)*
Overweight	-0.01 (-0.10, 0.09)	-0.03 (-0.11, 0.05)	0.01 (-0.03, 0.04)	0.00 (-0.04, 0.04)
Obesity	-0.05 (-0.15, 0.05)	-0.04 (-0.15, 0.07)	0.01 (-0.03, 0.05)	0.00 (-0.05, 0.04)
***b*: Linear growth in early childhood**				
GWGz at 14 weeks				
Normal	0.03 (-0.06, 0.13)	-0.05 (-0.16, 0.06)	0.02 (-0.01, 0.04)	-0.01 (-0.03, 0.02)
Overweight	0.04 (-0.05, 0.12)	0.04 (-0.06, 0.14)	0.03 (-0.01, 0.07)	0.02 (-0.02, 0.07)
Obesity	0.04 (-0.11, 0.18)	-0.10 (-0.24, 0.04)	0.01 (-0.03, 0.05)	0.02 (-0.03, 0.07)
GWGz at 28 weeks				
Normal	0.07 (0.00, 0.14)	-0.05 (-0.14, 0.04)	0.03 (0.01, 0.06)*	0.03 (0.01, 0.06)*
Overweight	0.01 (-0.09, 0.11)	0.04 (-0.06, 0.14)	0.02 (-0.02, 0.05)	0.00 (-0.03, 0.03)
Obesity	-0.04 (-0.14, 0.07)	-0.01 (-0.12, 0.11)	0.03 (0.00, 0.06)	0.03 (-0.01, 0.07)
GWGz at delivery				
Normal	0.07 (0.00, 0.14)	-0.05 (-0.14, 0.05)	0.03 (0.00, 0.06)	0.03 (0.00, 0.06)
Overweight	0.03 (-0.07, 0.12)	0.05 (-0.05, 0.15)	0.04 (0.00, 0.09)	0.02 (-0.02, 0.06)
Obesity	-0.02 (-0.13, 0.09)	-0.01 (-0.12, 0.10)	0.03 (-0.01, 0.08)	0.03 (-0.02, 0.08)

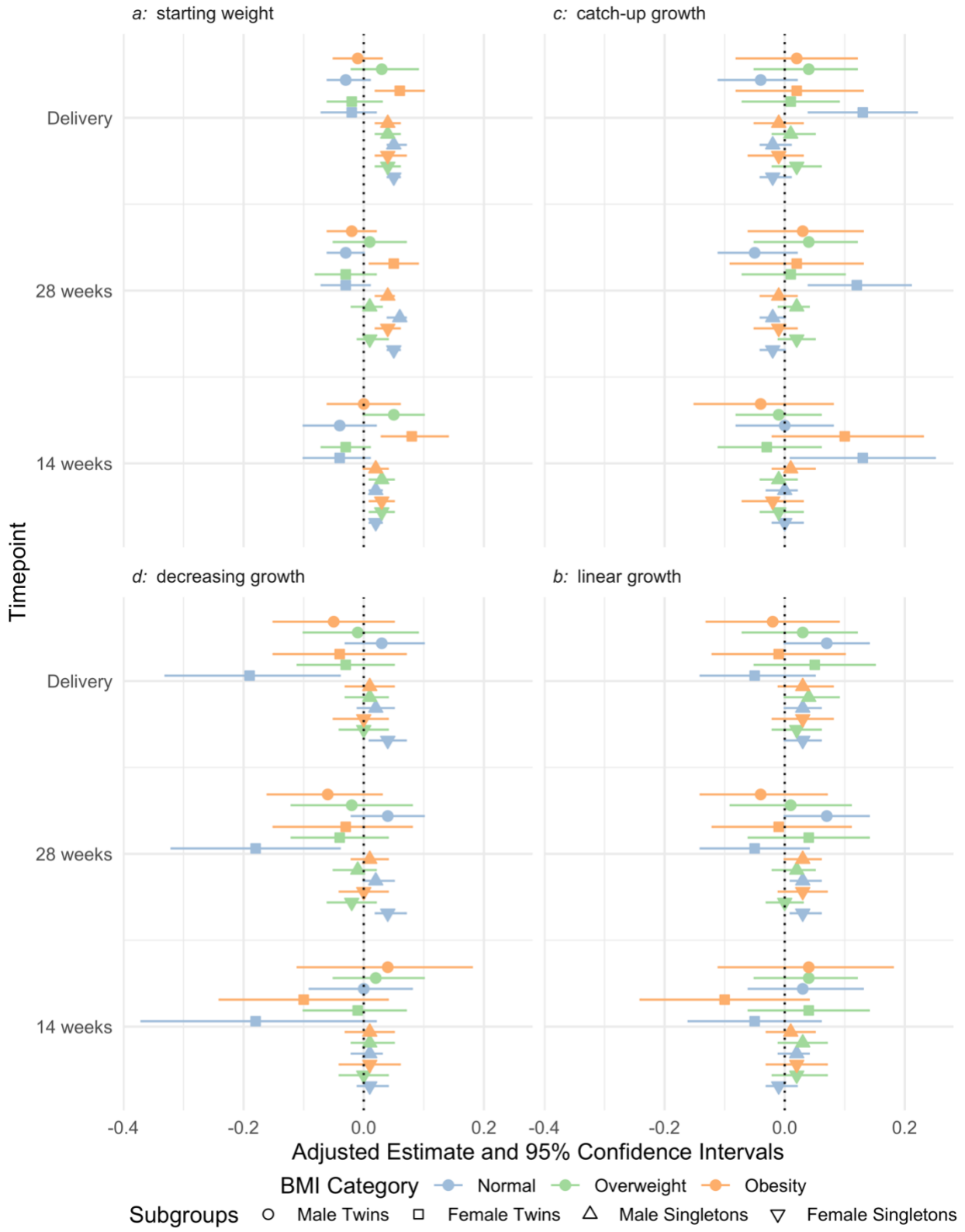
*: significant at 0.05 significance level

All models adjusted for maternal race and ethnicity, preferred spoken language, education, pre-pregnancy body mass index, preexisting diabetes, preexisting hypertension, income as a percentage of the federal poverty level at the start of pregnancy, most prevalent insurance type in the 2nd and 3rd trimesters, age at the end of pregnancy, parity, and year of birth. Models assessing GWGz at 28 weeks and at delivery additionally adjusted for GWGz at 14 weeks.

Robust standard errors were used to control for clustering within twin pregnancies and within matching group membership.

N=2,189 pregnancies with pre-pregnancy normal weight (210 twin and 2,053 singleton); N=2,160 pregnancies with pre-pregnancy overweight (229 twin and 2,003 singleton); N=2,157 pregnancies with pre-pregnancy obesity (172 twin and 2,054 singleton).

Figure A2.4 Adjusted estimates and 95% confidence intervals of the association between GWGz at 14 weeks, 28 weeks, and delivery with parameters of infant weight trajectories, stratified by pre-pregnancy body mass index category.



Appendix 2.J. Sensitivity Analysis – Unmatched Singletons.

This sensitivity analysis was conducted to assess if associations differ among unmatched singletons. Results are largely unchanged from the main adjusted analysis.

Table A2.5 Adjusted associations (β (95% confidence interval) between gestational weight gain z-score throughout pregnancy and infant weight trajectory parameters among singletons, by child sex (N=39,036 pregnancies and 39,036 children from the PROMISE study).

	Singletons	
	Male N=19,824	Female N=19,212
$\boldsymbol{a}$: Starting value		
GWGz at 14 weeks	0.02 (0.02, 0.02)*	0.02 (0.02, 0.02)*
GWGz at 28 weeks	0.04 (0.04, 0.04)*	0.04 (0.04, 0.04)*
GWGz at delivery	0.04 (0.04, 0.05)*	0.05 (0.04, 0.05)*
$\boldsymbol{c}$: Growth in early infancy		
GWGz at 14 weeks	0.00 (-0.01, 0.01)	-0.01 (-0.01, 0.00)*
GWGz at 28 weeks	0.00 (-0.01, 0.01)	-0.01 (-0.02, 0.00)*
GWGz at delivery	0.00 (-0.01, 0.01)	-0.01 (-0.02, 0.00)
$\boldsymbol{d}$: Decreasing rate of growth in late infancy		
GWGz at 14 weeks	0.00 (0.00, 0.01)	0.01 (0.00, 0.02)*
GWGz at 28 weeks	0.01 (0.01, 0.02)	0.02 (0.01, 0.02)
GWGz at delivery	0.01 (0.01, 0.02)	0.02 (0.01, 0.03)
$\boldsymbol{b}$: Linear growth in early childhood		
GWGz at 14 weeks	0.01 (0.00, 0.02)*	0.01 (0.00, 0.02)*
GWGz at 28 weeks	0.02 (0.01, 0.02)	0.02 (0.01, 0.03)
GWGz at delivery	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)

*: significant at 0.05 significance level

Adjusted for maternal race and ethnicity, preferred spoken language, education, pre-pregnancy body mass index, preexisting diabetes, preexisting hypertension, income as a percentage of the federal poverty level at the start of pregnancy, most prevalent insurance type in the 2nd and 3rd trimesters, age at the end of pregnancy, parity, and year of birth.

Appendix 3. Supplemental material for Chapter 5. Infant weight gain patterns are not associated with child body mass index among twins.

Appendix 3.A. International Classification of Diseases codes to identify twin pregnancies.

Codes from ICD-9 and ICD-10 are given below. The presence of at least one code in the pregnant person's EHR with a diagnosis date between pregnancy start and end dates was used to identify twin pregnancies. The absence of these codes was not used to determine singleton status; that is, this definition was *only* used to identify twins.

Table A3.1 International Classification of Diseases codes to identify twin pregnancies.

Diagnosis Code	Short Description
O30.00	Twin pregnancy, unsp num plcnta & amnio sacs
O30.001	Twin preg, unsp num plcnta & amnio sacs, first trimester
O30.002	Twin preg, unsp num plcnta & amnio sacs, second trimester
O30.003	Twin preg, unsp num plcnta & amnio sacs, third trimester
O30.009	Twin pregnancy, unsp num plcnta & amnio sacs, unsp trimester
O30.01	Twin pregnancy, monochorionic/monoamniotic
O30.011	Twin pregnancy, monochorionic/monoamniotic, first trimester
O30.012	Twin pregnancy, monochorionic/monoamniotic, second trimester
O30.013	Twin pregnancy, monochorionic/monoamniotic, third trimester
O30.019	Twin pregnancy, monochorionic/monoamniotic, unsp trimester
O30.03	Twin pregnancy, monochorionic/diamniotic
O30.031	Twin pregnancy, monochorionic/diamniotic, first trimester
O30.032	Twin pregnancy, monochorionic/diamniotic, second trimester
O30.033	Twin pregnancy, monochorionic/diamniotic, third trimester
O30.039	Twin pregnancy, monochorionic/diamniotic, unsp trimester
O30.04	Twin pregnancy, dichorionic/diamniotic
O30.041	Twin pregnancy, dichorionic/diamniotic, first trimester
O30.042	Twin pregnancy, dichorionic/diamniotic, second trimester
O30.043	Twin pregnancy, dichorionic/diamniotic, third trimester
O30.049	Twin pregnancy, dichorionic/diamniotic, unsp trimester
O30.09	Twin pregnancy, unable to determine num plcnta & amnio sacs
O30.091	Twin preg, unable to dtrm num plcnta & amnio sacs, first tri
O30.092	Twin preg, unable to dtrm num plcnta & amnio sacs, 2nd tri
O30.093	Twin preg, unable to dtrm num plcnta & amnio sacs, third tri
O30.099	Twin preg, unable to dtrm num plcnta & amnio sacs, unsp tri
Z37.2	Twins, both liveborn
Z37.3	Twins, one liveborn and one stillborn
Z37.4	Twins, both stillborn
Z37.50	Multiple births, unspecified, all liveborn
Z37.60	Multiple births, unspecified, some liveborn

Z37.7	Other multiple births, all stillborn
Z64.1	Problems related to multiparity
651	Twin pregnancy
651.00	Twin pregnancy-unspec
651.01	Twin pregnancy-delivered
651.03	Twin pregnancy-antepart
651.8	Other specified multiple gestation
651.80	Multi gestat NEC-unspec
651.81	Multi gestat NEC-deliver
651.83	Multi gest NEC-antepart
V31	Twin birth, mate liveborn
V31.0	Twin, mate liveborn, born in hospital
V31.00	Twin-mate lb-hosp w/o cs
V31.01	Twin-mate lb-in hos w cs
V31.1	Twin, mate lb-before adm
V31.2	Twin, mate lb-nonhosp
V32	Twin birth, mate stillborn
V32.00	Twin-mate sb-hosp w/o cs
V32.01	Twin-mate sb-hosp w cs
V32.1	Twin, mate sb-before adm
V32.2	Twin, mate sb-nonhosp
V33	Twin birth, unspecified whether mate liveborn or stillborn
V33.00	Twin-NOS-in hosp w/o cs
V33.01	Twin-NOS-in hosp w cs
V33.1	Twin NOS-before admissn
V33.2	Twin NOS-nonhosp
V39	Liveborn, unspecified whether single, twin, or multiple
V39.00	Liveborn NOS-hosp w/o cs
V39.01	Liveborn NOS-hosp w cs
V39.1	Liveborn NOS-before adm
V39.2	Liveborn NOS-nonhosp
V91.0	Twin gestation placenta status
V91.00	Twin gest-plac/sac NOS
V91.01	Twin gest-monochr/monoam
V91.02	Twin gest-monochr/diamni
V91.03	Twin gest-dich/diamniotc
V91.09	Twin gest-plac/sac undet

Appendix 3.B. Details regarding the cleaning of birth weights.

Implausible birth weights were defined as a gestational age- and sex-standardized z-scores of <-5 or >5,[181] calculated from birth weight references for twins[108] and singletons,[27] and omitted. The birth weight reference for twins ends at 40 gestational weeks; 78 twin children had a gestational age at birth beyond 40 weeks and their gestational age was converted to 40 weeks for this calculation only. Because the birth weight reference for twins[108] gives mean and standard deviation values in two-week intervals for GA, mean and standard deviation values for intermediate GAs were imputed (**Figure S2** and **Table S1**). 42 (0.1%) singletons and 0 twins were found to have implausible birth weight and their birth weight was removed.

Figure A3.1 Birth weight reference imputation for male (A) and female (B) twins.
Imputed values shown in red (mean) and blue (standard deviation).

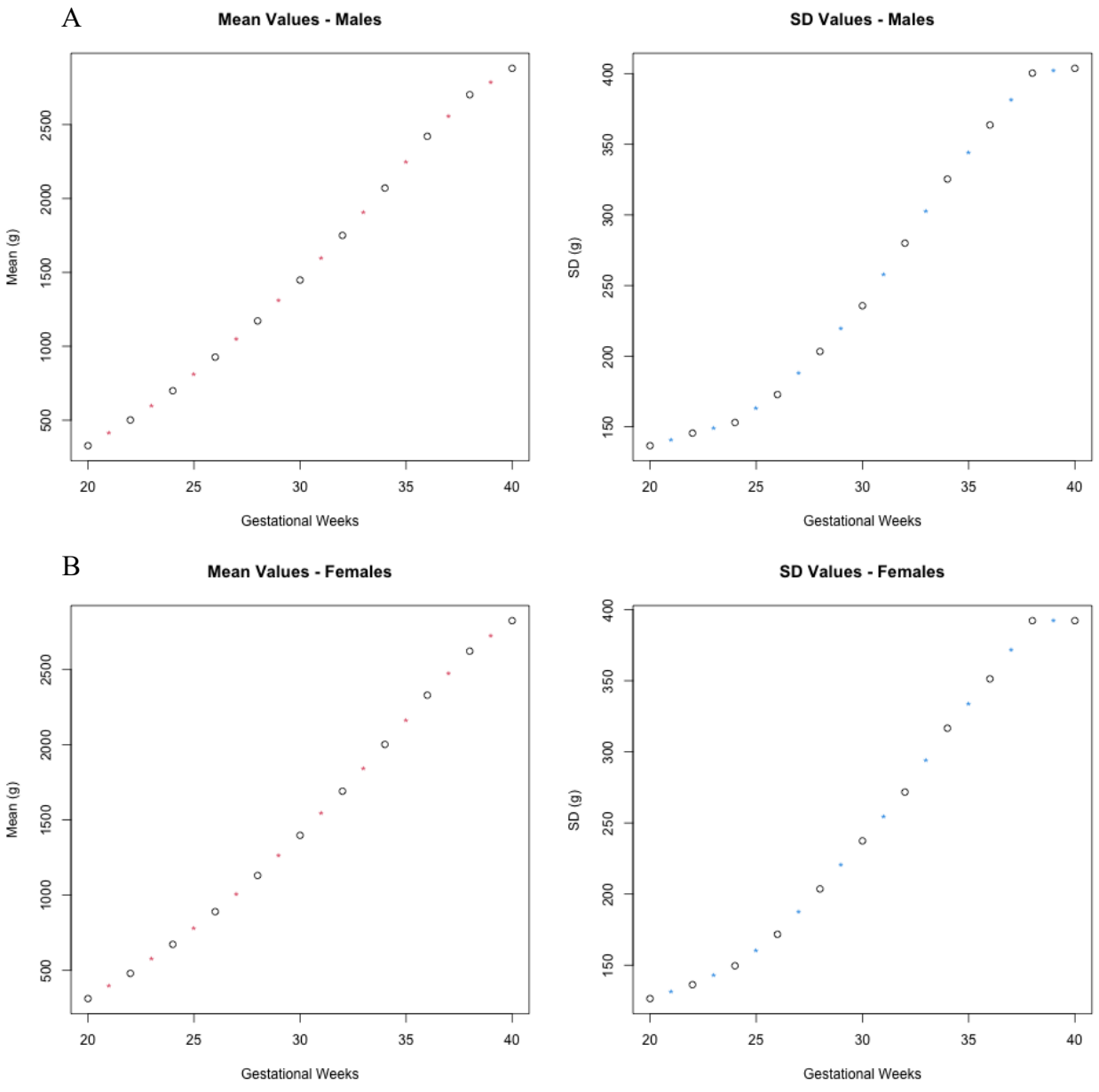


Table A3.2 Published and imputed birth weight values for twins.

	Males		**Females**	
Week	**Mean (g)**	**SD (g)**	**Mean (g)**	**SD (g)**
20	327.8	136.6	312.4	126.5
21	***414.7***	***141.1***	***396.3***	***131.4***
22	501.5	145.5	480.2	136.3
23	***600.5***	***149.3***	***576.5***	***143.0***
24	699.5	153	672.8	149.6
25	***813.2***	***162.9***	***781.5***	***160.7***
26	926.8	172.8	890.1	171.7
27	***1049.4***	***188.1***	***1010.3***	***187.7***
28	1171.9	203.3	1130.5	203.6
29	***1310.0***	***219.5***	***1263.9***	***220.5***
30	1448.1	235.7	1397.2	237.4
31	***1599.3***	***257.9***	***1543.9***	***254.6***
32	1750.5	280	1690.5	271.7
33	***1910.6***	***302.7***	***1845.9***	***294.2***
34	2070.7	325.4	2001.3	316.6
35	***2245.8***	***344.6***	***2164.9***	***334.0***
36	2420.8	363.7	2328.5	351.3
37	***2561.6***	***382.1***	***2474.6***	***371.8***
38	2702.4	400.4	2620.7	392.2
39	***2791.5***	***402.1***	***2722.0***	***392.2***
40	2880.6	403.8	2823.3	392.2

Published values are given in normal font; interpolated values are given in bolded and italicized font. Published values from Min (2000).[108]

Appendix 3.C. Details regarding the Jenss model.

The Jenss model is a four-parameter mixed-effects model that was developed to fit weight and height growth trajectories from birth to 6-8 years. The Jenss model is given by:

$$y_{ij} = a_i + b_i * t_{ij} - e^{c_i + d_i * t_{ij}},$$

Where j is the growth measure of the i^{th} subject, y is the weight measure in kilograms, and t is the age of the child in days. The model differentiates the pattern of growth into two periods.[102,105,114] The first is nonlinear growth during infancy – often a sharp increase in weight in the first months of life followed by a slowly decelerating rate – and is represented by the nonlinear (exponential) term in the model. The second period is linear growth in childhood, represented by the linear terms in the model (i.e., the equation of a straight line, $a_i + b_i * t_{ij}$). The Jenss model is a negatively accelerated exponential that becomes linear at its asymptote.

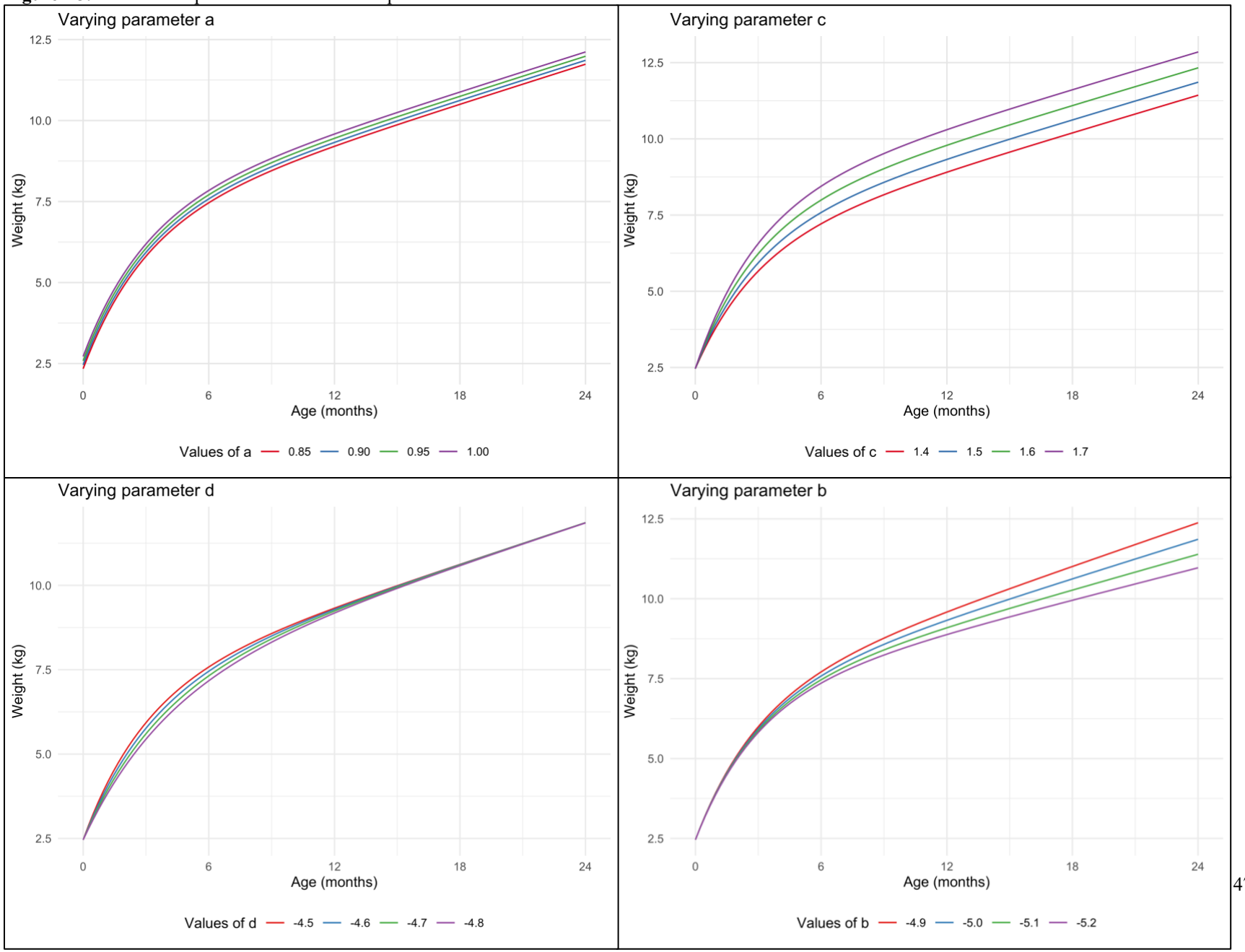
A parameterization of the Jenss model was used which adds constraints of positivity to the parameters in order to facilitate model convergence.[105] The parameterization is given by:

$$y_{ij} = e^{a_i} + e^{-b_i} * t_{ij} + e^{c_i} * \left(1 - e^{\left(-e^{-d_i * t_{ij}}\right)}\right).$$

Each growth parameter given by the Jenss model is the sum of a fixed and a random component. Parameter a reflects the predicted weight when $t = 0$; parameter c reflects the degree of catch-up growth in infancy; parameter d reflects the decreasing exponential ("deceleration" in growth at the end of infancy); and parameter b reflects the slope at the asymptote (linear rate of growth in childhood).[103,105,114] Parameter a cannot necessarily be interpreted as birth weight and is instead referred to as the "starting weight."

The Jenss model was fit to our data using the SAEMIX package in R, which implements a stochastic approximation expectation maximization (SAEM) algorithm for nonlinear mixed-effects models without approximating the likelihood function.[182] An unstructured variance-covariance matrix was used. The Jenss model was fit separately for male twins, female twins, male singletons, and female singletons. See **Figure S1** for a visual interpretation of the four Jenss model parameters, next page.

Figure A3.2 Visual interpretation of Jenss model parameters.



Appendix 3.D. Definitions of preexisting or gestational diabetes and preexisting hypertension or hypertensive disorders of pregnancy.

Preexisting or gestational diabetes and preexisting hypertension or hypertensive disorders of pregnancy were identified in the electronic health record by searching for specific International Classification of Diseases (ICD)-9 and ICD-10 codes. A list of ICD codes used may be requested by contacting the corresponding author.

Diabetes was identified by first searching the health record for ICD codes related to a diabetes diagnosis, symptoms, or complications at any time since 2000. *Preexisting diabetes* was defined as (1) at least two encounters with at least one ICD-9 or ICD-10 code relating to diabetes before the start of pregnancy; (2) at least one ICD-9 or ICD-10 code relating to diabetes on the patient's Problem List before the start of pregnancy; (3) at least one ICD-10 code specifying pre-existing diabetes during pregnancy; (4) at least two encounters with at least one ICD-9 or ICD-10 code relating to diabetes between week 0 and week 24 of pregnancy; or (5) at least one ICD-9 or ICD-10 code relating to diabetes on the patient's Problem List with a date of onset between week 0 and week 24 of pregnancy.

Gestational diabetes was defined as (1) at least one ICD-9 or ICD-10 code relating to GDM on the patient's Problem List during pregnancy; (2) at least one encounter with at least one ICD-10 code relating to GDM during pregnancy; or (3) at least two encounters with at least one ICD-9 code relating to GDM during pregnancy.

Preexisting hypertension was identified by first searching the health record for ICD codes related to a hypertension diagnosis, symptoms, or complications from the two years prior to the start of pregnancy to the end of week 19 of pregnancy. *Preexisting hypertension* was defined as (1) at least one ICD-9 or ICD-10 code relating to unresolved hypertension on the patient's Problem List; (2) at least two encounters with at least one ICD-9 or ICD-10 code relating to hypertension; or (3) at least two high blood pressure measurements (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) at least one day apart.

Hypertensive disorders of pregnancy included gestational hypertension, preeclampsia, and eclampsia. Gestational hypertension was defined at (1) at least one high blood pressure measurement after the end of gestational week 19, with no prior history of high blood pressure; or (2) at least one ICD-9 or ICD-10 code relating to hypertension or gestational hypertension on the patient's Problem List with onset after the end of gestational week 19, with no preexisting hypertension and no preeclampsia. Preeclampsia/eclampsia was defined as (1) at least one ICD-9 or ICD-10 code relating to preeclampsia/eclampsia with onset at any time during pregnancy; (2) at least two encounters with at least one ICD-9 or ICD-10 code relating to preeclampsia/eclampsia at any time during pregnancy; or (3) at least two high blood pressure measurements at least one day apart after the end of gestational week 19, with no prior history of high blood pressure.

Appendix 3.E. Details regarding the multiple imputations by chained equations procedure.

We imputed missing data for six covariates – maternal GWG, child insurance, child race/ethnicity, family FPL, maternal parity, and maternal education – which were missing in 0.01%, 0.1%, 4.7%, 16.4%, 35.7%, and 36.9% of children, respectively. Multiple imputations by chained equations has been shown to be valid even with large proportions of missing data (~90%) given data are missing at random and the imputation model is correctly specified.[186] Therefore, we were confident in imputing these confounders; however, a complete case analysis was explored as a sensitivity analysis.

Thirty datasets complete for all variables were imputed, each with 20 iterations, and with clustering by pregnancy (i.e., to ensure imputed values were the same for both children within a pregnancy, in the case of twins). These values were chosen given work suggesting that the number of imputed datasets should be roughly equivalent to the percentage of missing data[163] and visual examination of the stability of imputed data when the number of iterations was changed. All regression results were pooled across the thirty datasets.

Each imputed variable used as predictor variables (except itself): child sex, child race and ethnicity, plurality, gestational age, maternal education, Jenss model parameters for infant growth (a, b, c, and d), most prevalent insurance between 0-2 years, mean family income as a percentage of the federal poverty level between 0-2 years, maternal BMI, categorical maternal gestational weight gain based on Institute of Medicine recommendations, preexisting or gestational diabetes, preexisting hypertension or hypertensive disorders of pregnancy, maternal age at the end of pregnancy, categorical parity (1, 2, ≥3), and child's BMIz at age 3.

Appendix 3.F. Minimally adjusted estimates.

Table A3.3 Minimally adjusted associations (β (95% confidence interval) between early childhood weight trajectory parameters and child body mass index z-score at 3 and 5 years by plurality group and child sex (N=5,247 (BMIz at 3 years) and N=3,295 (BMIz at 5 years) children from the PROMISE study).

	Twins		**Singletons**	
	Male	**Female**	**Male**	**Female**
BMIz at age 3				
a: Starting value	0.13 (-0.01, 0.28)	0.13 (-0.06, 0.32)	0.21 (0.16, 0.25)*	0.18 (0.12, 0.24)*
c: Catch-up growth in infancy	0.08 (-0.11, 0.28)	0.01 (-0.21, 0.23)	0.16 (0.08, 0.24)*	0.13 (0.07, 0.19)*
d: Decreasing rate of growth in late infancy	0.1 (-0.07, 0.28)	-0.02 (-0.23, 0.18)	-0.01 (-0.09, 0.06)	-0.06 (-0.11, 0.00)
b: Linear growth in early childhood	0.83 (0.67, 0.98)*	0.95 (0.77, 1.13)*	0.91 (0.84, 0.98)*	0.90 (0.84, 0.97)*
BMIz at age 5				
a: Starting value	0.10 (-0.09, 0.29)	0.01 (-0.24, 0.25)	0.17 (0.10, 0.23)*	0.17 (0.11, 0.24)*
c: Catch-up growth in infancy	0.19 (-0.11, 0.49)	-0.11 (-0.39, 0.16)	0.19 (0.10, 0.28)*	0.14 (0.07, 0.21)*
d: Decreasing rate of growth in late infancy	0.01 (-0.24, 0.26)	-0.02 (-0.30, 0.26)	-0.04 (-0.13, 0.05)	-0.09 (-0.15, -0.02)
b: Linear growth in early childhood	0.71 (0.50, 0.93)*	0.99 (0.78, 1.20)*	0.82 (0.74, 0.91)*	0.85 (0.76, 0.93)*

*: significant at 0.05 significance level.
Estimates reflect the change in BMIz for every one standard deviation increase in the early childhood weight trajectory parameter.
Adjusted for previous parameters: the models for parameters c and d adjusted for parameter a, while the models for parameter b adjusted for parameters a, c, and d.
Robust standard errors were used to control for clustering within twin pregnancies and within matching group membership.
BMIz: body mass index z-score.

Appendix 3.G. Sensitivity Analysis – Complete Case Analysis.

Table A3.4 Adjusted associations (β (95% confidence interval) between early childhood weight trajectory characteristics and child body mass index z-score at 3 years and 5 years by plurality group and child sex (N=2,643 (BMIz at 3 years) and N=2,055 (BMIz at 5 years) children with complete data from the PROMISE study).

	Twins		**Singletons**	
	Male	Female	Male	Female
BMIz at 3 years				
a: Starting value	0.11 (-0.19, 0.42)	0.06 (-0.39, 0.52)	0.21 (0.14, 0.29)*	0.17 (0.10, 0.25)*
c: Catch-up growth in infancy	0.08 (-0.20, 0.37)	0.02 (-0.16, 0.21)	0.18 (0.06, 0.30)*	0.14 (0.07, 0.22)*
d: Decreasing rate of growth in late infancy	0.07 (-0.23, 0.36)	-0.12 (-0.38, 0.13)	-0.04 (-0.14, 0.07)	-0.07 (-0.15, 0.00)
b: Linear growth in early childhood	0.82 (0.57, 1.07)*	0.82 (0.63, 1.02)*	0.83 (0.74, 0.93)*	0.84 (0.75, 0.92)*
BMIz at 5 years				
a: Starting value	0.07 (-0.24, 0.37)	-0.02 (-0.52, 0.47)	0.15 (0.06, 0.24)*	0.15 (0.06, 0.23)*
c: Catch-up growth in infancy	-0.09 (-0.41, 0.23)	-0.06 (-0.25, 0.14)	0.22 (0.10, 0.33)*	0.15 (0.06, 0.23)*
d: Decreasing rate of growth in late infancy	0.15 (-0.14, 0.43)	-0.13 (-0.39, 0.13)	-0.07 (-0.18, 0.04)	-0.09 (-0.17, 0.00)
b: Linear growth in early childhood	0.77 (0.53, 1.02)*	0.78 (0.57, 0.98)*	0.72 (0.62, 0.83)*	0.75 (0.65, 0.85)*

*: significant at 0.05 significance level.
Estimates reflect the change in BMIz for every one standard deviation increase in the early childhood weight trajectory parameter.
All models adjusted for parity, maternal education, maternal pre-pregnancy BMI, total gestational weight gain according to Institute of Medicine guidelines, preexisting or gestational diabetes, preexisting hypertension or hypertensive disorders of pregnancy, maternal age, family income, child race and ethnicity, insurance type, and year of birth.
The models for parameters c and d further adjusted for parameter a while the model for parameter b further adjusted for parameters a, c, and d.
Robust standard errors were used to control for clustering within twin pregnancies and within matching group membership.
BMIz: body mass index z-scores.

Appendix 3.H. Sensitivity Analysis – Stratification by maternal pre-pregnancy body mass index category.

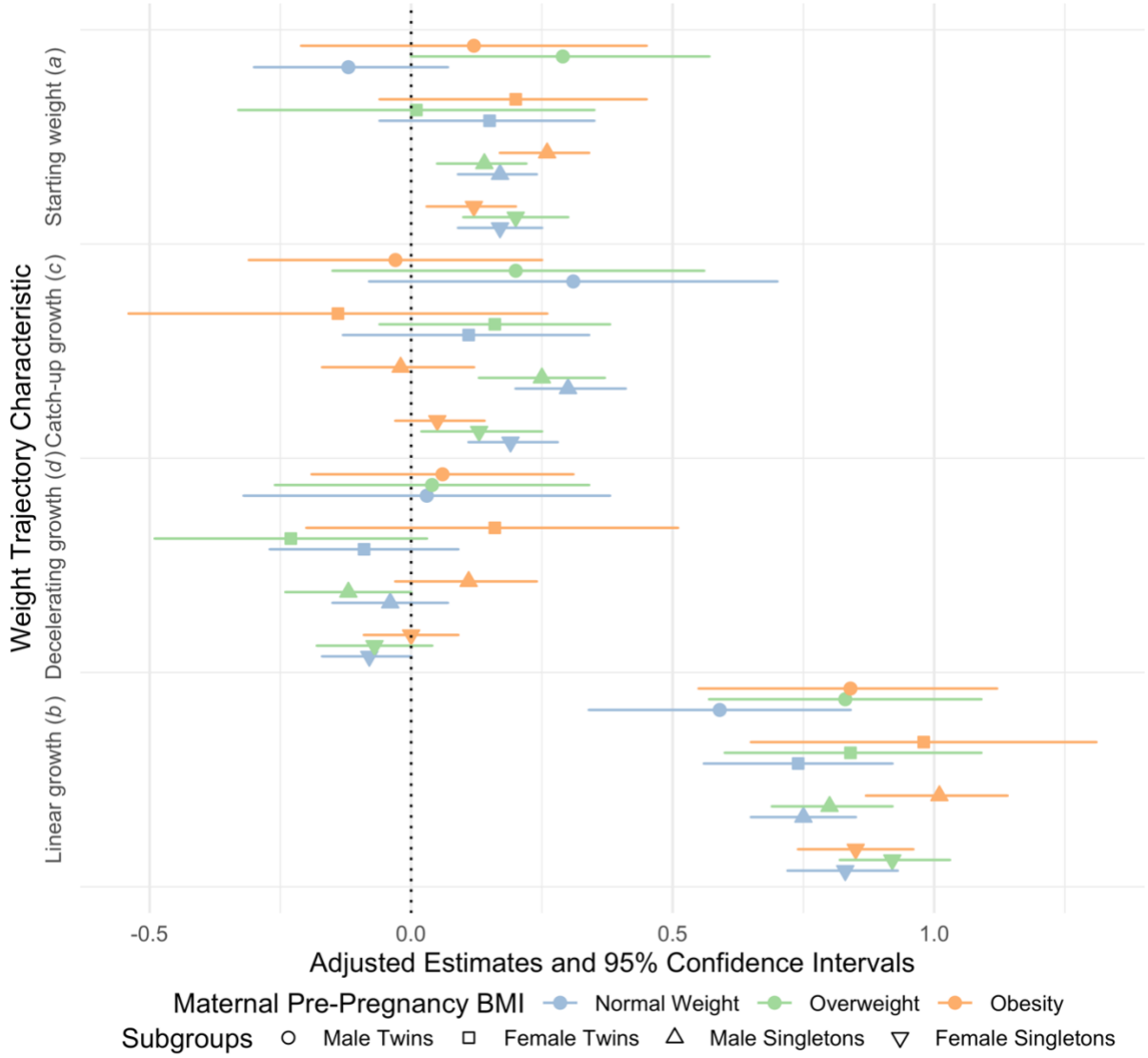
Table A3.5 Adjusted associations (β (95% confidence interval) between early childhood weight trajectory parameters and child body mass index z-score at age 3 and age 5 by plurality group and child sex, stratified by maternal pre-pregnancy body mass index category.

	Twins		**Singletons**	
	Male	Female	Male	Female
BMIz at 3 years				
a: Starting value				
Normal Weight	-0.12 (-0.30, 0.07)	0.15 (-0.06, 0.35)	0.17 (0.09, 0.24)*	0.17 (0.09, 0.25)*
Overweight	0.29 (0.00, 0.57)	0.01 (-0.33, 0.35)	0.14 (0.05, 0.22)*	0.20 (0.10, 0.30)*
Obesity	0.12 (-0.21, 0.45)	0.20 (-0.06, 0.45)	0.26 (0.17, 0.34)*	0.12 (0.03, 0.20)*
c: Catch-up growth in infancy				
Normal Weight	0.31 (-0.08, 0.70)	0.11 (-0.13, 0.34)	0.30 (0.20, 0.41)*	0.19 (0.11, 0.28)*
Overweight	0.20 (-0.15, 0.56)	0.16 (-0.06, 0.38)	0.25 (0.13, 0.37)*	0.13 (0.02, 0.25)*
Obesity	-0.03 (-0.31, 0.25)	-0.14 (-0.54, 0.26)	-0.02 (-0.17, 0.12)	0.05 (-0.03, 0.14)
d: Decreasing rate of growth in late infancy				
Normal Weight	0.03 (-0.32, 0.38)	-0.09 (-0.27, 0.09)	-0.04 (-0.15, 0.07)	-0.08 (-0.17, 0.00)
Overweight	0.04 (-0.26, 0.34)	-0.23 (-0.49, 0.03)	-0.12 (-0.24, 0.00)	-0.07 (-0.18, 0.04)
Obesity	0.06 (-0.19, 0.31)	0.16 (-0.20, 0.51)	0.11 (-0.03, 0.24)	0.00 (-0.09, 0.09)
b: Linear growth in early childhood				
Normal Weight	0.59 (0.34, 0.84)*	0.74 (0.56, 0.92)*	0.75 (0.65, 0.85)*	0.83 (0.72, 0.93)*
Overweight	0.83 (0.57, 1.09)*	0.84 (0.60, 1.09)*	0.80 (0.69, 0.92)*	0.92 (0.82, 1.03)*
Obesity	0.84 (0.55, 1.12)*	0.98 (0.65, 1.31)*	1.01 (0.87, 1.14)*	0.85 (0.74, 0.96)*
BMIz at 5 years				
a: Starting value				
Normal Weight	-0.18 (-0.44, 0.08)	-0.01 (-0.35, 0.32)	0.12 (0.01, 0.22)*	0.16 (0.07, 0.26)*
Overweight	0.33 (0.12, 0.54)*	0.04 (-0.29, 0.38)	0.11 (-0.01, 0.23)	0.19 (0.08, 0.29)*
Obesity	-0.05 (-0.67, 0.57)	-0.03 (-0.41, 0.35)	0.19 (0.09, 0.29)*	0.13 (0.01, 0.25)*
c: Catch-up growth in infancy				

Normal Weight	0.39 (-0.09, 0.86)	-0.01 (-0.44, 0.42)	0.20 (0.08, 0.32)*	0.12 (0.03, 0.22)*
Overweight	0.13 (-0.36, 0.63)	0.12 (-0.09, 0.33)	0.26 (0.10, 0.43)*	0.16 (0.03, 0.29)*
Obesity	0.10 (-0.37, 0.57)	-0.30 (-0.73, 0.14)	0.11 (-0.04, 0.26)	0.13 (0.03, 0.22)*
d: Decreasing rate of growth in late infancy				
Normal Weight	-0.24 (-0.69, 0.22)	-0.20 (-0.66, 0.26)	0.00 (-0.11, 0.12)	-0.09 (-0.18, 0.01)
Overweight	0.09 (-0.21, 0.40)	-0.23 (-0.44, -0.02)*	-0.12 (-0.29, 0.05)	-0.09 (-0.22, 0.04)
Obesity	-0.12 (-0.56, 0.33)	0.22 (-0.19, 0.63)	0.01 (-0.13, 0.16)	-0.08 (-0.19, 0.03)
b: Linear growth in early childhood				
Normal Weight	0.45 (0.10, 0.79)*	0.70 (0.42, 0.98)*	0.66 (0.54, 0.78)*	0.74 (0.62, 0.86)*
Overweight	0.83 (0.57, 1.09)*	0.77 (0.52, 1.02)*	0.69 (0.52, 0.85)*	0.78 (0.65, 0.90)*
Obesity	0.58 (0.17, 1.00)*	1.11 (0.76, 1.46)*	0.96 (0.82, 1.10)*	0.86 (0.69, 1.02)*

*: significant at 0.05 significance level.
Estimates reflect the change in BMIz for every one standard deviation increase in the early childhood weight trajectory parameter.
All models adjusted for parity, maternal education, maternal pre-pregnancy BMI, total gestational weight gain according to Institute of Medicine guidelines, preexisting or gestational diabetes, preexisting hypertension or hypertensive disorders of pregnancy, maternal age, family income, child race and ethnicity, insurance type, and year of birth.
The models for parameters c and d further adjusted for parameter a while the model for parameter b further adjusted for parameters a, c, and d.
Robust standard errors were used to control for clustering within twin pregnancies and within matching group membership.
N=144 twins with maternal pre-pregnancy normal weight; 142 twins with maternal pre-pregnancy overweight; 186 twins with maternal pre-pregnancy obesity; 1551 singletons with maternal pre-pregnancy normal weight; 1581 singletons with maternal pre-pregnancy overweight; 1540 singletons with maternal pre-pregnancy obesity.
BMIz: body mass index z-score.

Figure A3.3 Adjusted estimates and 95% confidence intervals of the association between early childhood weight trajectory characteristics and child body mass index z-score at 3 years, stratified by maternal pre-pregnancy body mass index category.



Note: the vertical dotted line shows the null association (0.0). All estimates adjusted for maternal parity, education, pre-pregnancy body mass index, gestational weight gain, preexisting or gestational diabetes, preexisting hypertension or hypertensive disorders of pregnancy, and age, family income, child race and ethnicity and insurance, and year of birth. The models for catch-up growth (c) and decelerating growth (d) further adjusted for starting weight (a). The model for linear growth (b) further adjusted for starting weight (a), catch-up growth (c), and decelerating growth (d).
For ease of interpretation, only associations with BMIz at three years are shown; associations with BMIz at five years were similar.
BMIz: body mass index z-score.

Appendix 3.I. Sensitivity Analysis – All Singletons.

Table A3.6 Adjusted associations (\beta (95% confidence interval) between early childhood weight trajectory characteristics and child body mass index z-score at 3 and 5 years among singletons, by child sex (N=27,452 (BMIz at 3 years) and N=17,291 (BMIz at 5 years) children from the PROMISE study).

	Singletons	
	Male	Female
BMIz at 3 years	N=13,952	N=13,500
a: Starting value	0.17 (0.15, 0.19)*	0.17 (0.15, 0.19)*
c: Growth in early infancy	0.20 (0.18, 0.22)*	0.13 (0.11, 0.15)*
d: Decreasing rate of growth in late infancy	-0.05 (-0.07, -0.03)*	-0.04 (-0.06, -0.02)*
b: Linear growth in early childhood	0.82 (0.80, 0.84)*	0.87 (0.85, 0.90)*
BMIz at 5 years	N=8,795	N=8,496
a: Starting value	0.15 (0.12, 0.17)*	0.14 (0.11, 0.16)*
c: Growth in early infancy	0.17 (0.15, 0.20)*	0.13 (0.10, 0.15)*
d: Decreasing rate of growth in late infancy	-0.03 (-0.05, 0.00)*	-0.04 (-0.07, -0.02)*
b: Linear growth in early childhood	0.70 (0.67, 0.72)*	0.73 (0.70, 0.76)*

*: significant at 0.05 significance level.
Estimates reflect the change in BMIz for every one standard deviation increase in the early childhood weight trajectory parameter.
All models adjusted for parity, maternal education, maternal pre-pregnancy BMI, total gestational weight gain according to Institute of Medicine guidelines, preexisting or gestational diabetes, preexisting hypertension or hypertensive disorders of pregnancy, maternal age, family income, child race and ethnicity, insurance type, and year of birth.
The models for parameters c and d further adjusted for parameter a while the model for parameter b further adjusted for parameters a, c, and d.
BMIz: body mass index z-score.