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The Relationship of Macronutrient Intake with Growth in Children with Type 1 Diabetes Mellitus

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THE RELATIONSHIP OF MACRONUTRIENT INTAKE WITH GROWTH IN CHILDREN WITH TYPE 1 DIABETES MELLITUS

BY

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DISSERTATION ACCEPTANCE PAGE
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This dissertation is approved as a creditable and independent investigation by a candidate for the Doctor of Philosophy degree and is acceptable for meeting the dissertation requirements for this degree. Acceptance of this does not imply that the conclusions reached by the candidate are necessarily the conclusions of the major department.

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Dedication

To the courageous children and their families, whose selfless contribution to this study serves to guide us towards a brighter future for children facing this challenging diagnosis. Your resilience and sacrifice in the face of Type 1 diabetes will have a profound impact on the lives of those yet to be diagnosed. With heartfelt gratitude, this dissertation is dedicated to you, for your invaluable contribution to advancing our understanding toward a brighter, healthier future for all.

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ABBREVIATIONS

AA	amino acid
ADA	American Diabetes Association
AI	adequate intake
AIC	Akaike Information Criterion
ALA	alpha linolenic acid
AMDR	Adequate Macronutrient Distribution Range
aPHV	age at peak height velocity
BCAA	branch chain amino acid
BEE	basal energy expenditure
BFE	basic fixed effect
BMI	Body Mass Index
BMR	basal metabolic rate
BRE	basic random effect
CDC	Center for Disease Control
CHO	carbohydrate (dietary)
CM	covariate model
CNS	central nervous system
DCCT	Diabetes Control and Complication Trial
DGA	Dietary Guidelines for Americans
DHA	docosahexaenoic acid
DHHS	Department of Health and Human Services
DIAAS	digestible indispensable amino acid score
DLW	double labeled water
DONALD	Dortmund Nutritional and Anthropometric Longitudinally Designed Study
DRI	Dietary Reference Intakes
EAR	estimated average requirements
ECHO	Environmental Influences on Child Health Outcomes
ECoG	energy cost of growth
EER	estimated energy requirements
EFA	essential fatty acid
EPA	eicosapentaenoic acid
FA	fatty acid
FAH	final adult height
FAO	Food and Agriculture Organization
FAOSTAT	Food and Agriculture Organization Statistical Database
FAT	fat (dietary)
fat	body or tissue fat
FE	fixed effect

FFM	fat-free mass
FFQ	food frequency questionnaire
FM	fat mass
GAM	generalized additive model
GH	pituitary growth hormone
GH/IGF-1	growth hormone/insulin-like growth factor hormone 1 axis
HAZ	height for age z-score
HbA1c	glycated hemoglobin
HFKD	high fat ketogenic diet
IAAO	indicator amino acid oxidation
IDAA	indispensable amino acids
IGF-1	Insulin-like growth factor 1
IOM	Institute of Medicine
IRB	Institutional Review Board
LA	linoleic acid
LBM	lean body mass
LCD	low carbohydrate diet
LEAD	Lifecourse Epidemiology of Adiposity & Diabetes Center
LRT	likelihood ratio test
MUFA	monounsaturated fatty acid
NB	nitrogen balance
NG	Nutritional Geometry
NHANES	National Health and Nutrition Examination Survey
NIDDK	National Institute of Diabetes and Digestive Diseases
NIH	National Institutes of Health
NLME	nonlinear mixed effects model
PAL	physical activity level
PDCAAS	protein digestibility corrected amino acid score
PEM	protein energy malnutrition
PFAA	perfluoroalkyl acids
PHV	peak height velocity
PRO	protein (dietary)
protein	tissue or body protein
PUFA	polyunsaturated fatty acid
RCT	randomized controlled trial
RDA	recommended dietary allowance
RE	random effect
ROUT	robust regression and outlier removal
RSA	response surface analysis
RSM	response surface mapping
SD	standard deviation

SES	socioeconomic status
SFA	saturated fatty acid
SRE	selected random effect
SSB	sugar sweetened beverage
T1DM	type 1 diabetes mellitus
TE	total energy
TEE	total energy expenditure
TEF	thermic effect of food
TOT	total caloric intake (equivalent to total energy)
UL	tolerable upper intake level
USDA	United States Department of Agriculture
WAZ	weight for age z-score
WHO	World Health Organization
WHZ	weight for height z-score

ABSTRACT

THE RELATIONSHIP OF MACRONUTRIENT INTAKE WITH GROWTH IN CHILDREN WITH TYPE 1 DIABETES MELLITUS

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Child growth, a sensitive metric of overall health, results from the intricate interplay of nature and nurture. While the importance of nutrition in child growth is well-established, growth trajectories exhibit substantial individual variability, influenced by sex and age, and often characterized by nonlinear patterns. Inadequate nutrition or disease can hinder growth, with potential for recovery upon proper nutrition or acute disease resolution. However, chronic disease or persistent malnutrition may lead to permanent growth perturbation. Notably, before the advent of insulin, chronic stunting and wasting were hallmarks of Type 1 diabetes mellitus (T1DM), though the specific impacts under modern standard of care remain incompletely understood.

The three primary macronutrients—protein, carbohydrate, and fat—contribute to growth by supplying calories for total energy. Among healthy children, the roles of each macronutrient in physical growth are well-defined. Dietary protein uniquely supports linear and somatic growth through its dual energy-yielding and nitrogen-obtaining properties. Fatty acids from dietary fat are essential for neurological growth and development. Conversely, any direct role of dietary carbohydrate in growth beyond energy provision is minimal. Whether these macronutrient roles are altered in the presence of T1DM remains unclear. Additionally, recommendations for macronutrient distribution in children, as defined by the Acceptable Macronutrient Distribution Range

(AMDR), were primarily extrapolated from adults and not tailored for diseased populations.

This dissertation first provides context by examining the relationship between macronutrient intake and height growth in healthy children. Subsequent chapters explore growth and nutrition in children with T1DM undergoing standard insulin therapy. Longitudinal descriptive analyses, utilizing nonlinear mixed effects modeling, revealed that these children may experience earlier puberty onset and achieve taller final adult heights compared to their non-T1DM peers. Nutritional Geometry (NG) was applied to uncover disease-, sex-, and age-specific relationships between macronutrient distribution and physical height growth. Findings suggest a significant positive main effect association between fat intake and maximal height in boys, but not girls. However, no relationships with z-height were observed in boys or girls, suggesting macronutrient distribution is unrelated to normal growth in this population. The findings underscore NG's potential to inform disease-specific AMDR recommendations for optimal child growth.

Chapter 1: Dietary Macronutrients and Child Height: A Narrative Review

INTRODUCTION

Francis Galton's well-known concept of *nature versus nurture* provides an elegant way to think about child growth. Though unknown to Galton, we now know about epigenetics, namely that the nurture aspect can affect the nature aspect. The two are dynamically interwoven, no longer considered pitted against one another. The primary impacts on growth and development in children involve a complex interplay between *nature* (hormones, genetics, and metabolism) and *nurture* (environment, socioeconomics, and nutrition). This review will explore both the *nature and nurture* aspects of child growth, focusing on the nutritional impacts of macronutrients on linear height.

Studies have explored the genetic/ethnic, socioeconomic, and nutritional predictors of adult height across world populations.[1,2] As expected, genetic/ethnic factors correlated closely with adult height. However, among 45 nations of European background, including the U.S., the primary factor in stature was nutrition-related[2]. Data across 152 nations, including developing countries, further suggests the primary importance of nutrition.[1] Worldwide, socioeconomic factors correlated mildly with height, but the strongest correlates were protein (PRO) quantity and quality.[1,2] These data indicate that while genetic and socio-economic factors are important to stature worldwide, nutrition also plays an important role.

Stagnant growth is considered an adaptive response to inadequate nutrition, making the ability of a child to grow a good indicator of overall health.[3,4] Growth is complicated by the variability in growth rates of infants and children as linear growth occurs in *spurts*, even in healthy children. The timing of the initiation and duration of the

growth spurt is also highly variable, as is the onset of puberty. If a child is undernourished, growth slows as an adaptive response to decrease protein synthesis, the basal metabolic rate (BMR), and physical activity level (PAL).[5] Additionally, the presence of disease may result in alterations in growth patterns. This slowing of growth may be temporary in cases of acute illness or long-term if chronic disease or undernutrition is present. Adaptive slowing may occur with catch-up at the reintroduction of adequate nutrition; however, permanent perturbation of growth due to the sustained presence of disease or lack of caloric or specific macronutrient availability may result in shorter stature, termed *stunting*. Growth deceleration has an upper limit where 1) prolonged suboptimal nutritional intake (namely PRO); 2) poor nutritional absorption (diseases of intestinal nutrient malabsorption or parasitic infections); or 3) decreased substrate deposition (altered cellular glucose uptake as occurs in uncontrolled diabetes) may result in a permanently reduced stature.

Nutrition science has excelled at identifying overt deficiencies and toxicities of single nutrients and defining total energy expenditure (TEE) at various life stages; however, understanding the impact of specific dietary macronutrient patterns on health is complicated by their interrelated (collinear) nature. The Dietary Reference Intakes (DRI) and associated Adequate Macronutrient Distribution Ranges (AMDR) were developed by the Institute of Medicine (IOM) of The National Academies to provide a set of reference values for macronutrient intakes for total energy (TE), carbohydrate (CHO), fiber, fat (FAT), fatty acids (FA), cholesterol, protein (PRO), and amino acids (AA). The document was developed for healthy individuals to define a macronutrient range that will "confer decreased risk of disease and provide the most desirable long-term health benefits

to apparently healthy individuals."[3(p.39)] Even for adults, data on the impact of macronutrients on health was limited at the time of the release of the current DRI, now nearly two decades old. As will be discussed, the DRI and AMDR for children were primarily extrapolated from adult data.

The effects of nutrition on child growth in the context of overweight/obesity have received much attention over the previous two decades. However, this hyper-focus on obesity outcomes has missed "*the forest for the trees*" regarding child growth, as nutritional impacts on linear height have been largely ignored. Many studies have collected height data to calculate body mass index (BMI) but failed to report height-specific outcomes. In light of this, this review will attempt to synthesize the available literature on the potential impacts of macronutrients on stature, exploring how *nature and nurture* influence linear child growth. The *nature* facet will include a review of the 1) hormonal, genetic, and metabolic contexts, and the *nurture* aspect will explore the 2) environmental, socioeconomic, and nutritional factors of linear child growth. Particular focus will be on the methods utilized for the current dietary recommendations for children, with a detailed examination of the potential impacts of the three primary dietary macronutrients on linear growth, excluding obesity.

NATURE: Hormones, Genetics, and Metabolism

Hormones

Growth is driven through the growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis. The primary hormones involved in growth include the sex hormones estrogen and testosterone, the pituitary growth and gonadotropic hormones, and the

thyroid hormones. Deficiencies or overproduction of these various hormones can result in an alteration of normal growth patterns.

Thyroid hormone is needed for normal continual growth and brain function. Thyroid deficiency, when treated, results in catch-up growth but does not appear to play a role in the adolescent growth spurt.[6,7] It is well known that the pituitary growth hormones (GH) drive linear growth during puberty, as GH is known to have net effects on the breakdown of adipose and the buildup of body tissue.[8] Produced mainly by the liver, IGF-1 increases the amount of protein deposited in muscle and decreases the amount of fat deposited, resulting in an increase in lean body mass (LBM) and a decrease in fat mass (FM). The sex hormones, testosterone and estrogen, are known to stimulate GH secretion[7]. Therefore, in children, the primary sex hormones bring about the changes of adolescence and are responsible for most of the growth spurt by impacting GH. In boys and girls, respectively, increased testosterone and estrogen during puberty induce secretion of GH and hepatic production of IGF-1.[5,7,9] Circulating IGF-1 stimulates growth in all cellular systems of the body but is particularly important for skeletal muscle and bone deposition.[7] Levels of IGF-1 can, however, be altered by other factors besides nutrition, such as physical activity[10] and stress.[11] Levels also change over time as children grow.[12]

The GH/IGF-1 axis plays a primary role in metabolic homeostasis by impacting gluconeogenesis, glycogenolysis, and lipolysis.[13] Clinically, insufficient nutrition or disorders of the axis can result in inadequate child growth. Serum IGF-1 is a standard screening tool for stunting, defined as low height for age z-score (HAZ) since levels are sensitive to acute and chronic nutritional status and potential GH disorders.[14] It is known

that chronic energy or PRO malnutrition results in GH resistance and decreased IGF-1 levels.[14]

Linear height in puberty outpaces bone deposition. In a large longitudinal study of healthy adolescents, linear height increased substantially faster than bone mineral content accrued, with a large proportion of bone deposition taking place after adult height was achieved.[15] The deposit of bone before height accrual highlights that growth, at least in linear height and bone accumulation, is driven by hormones and not the availability of substrate for bone.

Genetics

The primary role of genetics in growth, particularly in height accretion in adolescence, is widely accepted.[16] Genetics and ethnicity predict ~25-50% of interindividual variability in body composition and height by one estimate[5] and ~41-71% by another.[17] In a longitudinal Finnish twin cohort study, genetics explained ~72-81% of the variation in height in boys and 65-86% for girls, while environmental factors, including diet, were estimated to explain just 5-23% of the variation in height.[18] A study using National Health and Nutrition Examination Survey (NHANES) data revealed that ethnicity and birth weight are strongly associated with height for age z-score (HAZ).[19] These data suggest that most of the variation in height within populations results from genetic variation (*nature*). In contrast, the remaining variation can be attributed to environmental factors, such as dietary intake and socioeconomic factors (*nurture)*.

While obesity is outside the scope of this review, children with obesity are taller on average and hit puberty earlier than their lean peers due to earlier onset of epiphyseal growth plate maturation; however, final adult heights (FAHs) are similar.[20–22] A large

observational study found that children with obesity were taller than their peers at ages 6-8 years old.[21] However, they then exhibited a reduction in circulating levels of IGF-1, insulin, and leptin during puberty, thereby reducing growth velocity so that FAH was similar to non-obese controls. These observations suggest that while dietary factors can alter the progression of linear height in children, some other setpoint element, likely genetic potential, plays a primary role in FAH. Depending on age, growth patterns and velocities may be altered by dietary intake and hormonal status, but genetic potential is a primary driver of FAH.

Metabolism

The metabolic flexibility of the human is supported by the capacity of the body to produce and utilize two primary fuels physiologically: glucose and ketones. The human body can *de novo* synthesize most of the types of lipids and all the glucose needed for homeostasis.[3,23] Aside from n-6 and n-3 polyunsaturated fatty acids (PUFA), there are no specific requirements for FAT or CHO in the diet.[3] However, while the human body can synthesize some AAs *de novo*, nine AAs must be obtained through dietary PRO intake, termed the indispensable amino acids (IDAA). Dietary PRO provides nitrogen to make the non-essential AAs and is required for tissue repair and new cell production, a vital component of growth. Only about half of the body's nitrogen stores can be mobilized before death occurs, highlighting the unique importance of PRO.[24,25] In comparison, practically all the lipid stores of the body can be mobilized without detrimental effects.[25,26]

Production and utilization of glucose and ketones as fuel sources act in concert daily in any given individual. Glucose metabolism pathways produce and metabolize

glucose for body tissues. Ketone production occurs during periods of fasting, such as during the night, periods of starvation, or in the absence of dietary CHO. Some organs prefer a particular fuel source over the other, but most organs of the body, including the brain, can utilize either glucose or ketones for fuel.[23,24,26] There is much variation among the organs regarding which fuel source is preferred or optimal.[27] However, extensive discussion of this topic is beyond the scope of this paper.

Endogenous glucose production can be accomplished from dietary FAT and PRO. Glucose production via glycogenolysis (glycogen breakdown in the liver) and gluconeogenesis (*de novo* glucose synthesis in the liver and kidney) can produce needed glucose.[24] In adults, it has been reported that about half of glucose in circulation comes from glycogenolysis and half from gluconeogenesis.[28] However, in adolescents, Sunehag et al. found that ~64-69% of glucose production comes from gluconeogenesis.[29] Gluconeogenesis utilizes PRO to produce needed glucose because FAs cannot be converted very *efficiently* to glucose, from which came the biochemist's mantra that '*you can't make sugar from fat.'* Further, FAs cannot be utilized as fuel for the brain because they are bound to albumin in plasma which cannot pass the blood-brain barrier. Because gluconeogenesis primarily uses PRO to produce glucose, this PRO can come from dietary PRO or body tissue protein. In the absence of dietary PRO, to spare this tissue protein, the priority of the liver shifts to ketone production from lipid stores. Without dietary CHO, gluconeogenesis preferentially breaks down dietary PRO to spare tissue protein to produce glucose.[23]

It is well known that the body tightly regulates blood glucose levels with only ~4g (~1 teaspoon) of glucose in the entire bloodstream at any given time.[30] Data collected a

century ago in adults showed that gluconeogenesis can make ~0.56g glucose for every gram of animal PRO ingested.[31] Estimates of the totality of the various gluconeogenic substrates produce ~100-200 g/day of glucose in adults.[23] Glucose production rates in adolescents and prepubertal children have been recorded as 12.5-13.1 and 19.4-21.2 µmol/kg/min, respectively; see g/day estimates below.[29] Further, isocaloric/isonitrogenous diets containing 30% versus 60% CHO were similar in total glucose production from gluconeogenesis.[29]

Doing the math: In an adolescent weighing 100 lbs at 13 µmol/kg/min, the estimated daily total endogenous glucose production is ~153 g/day. A 50 lb prepubertal child at 20 µmol/kg/min would produce an estimated ~118 g/day of endogenous glucose.

The brain is the most energy-greedy of all the organs, requiring an estimated 50-60% of the glucose energy of the body[27] and 20% of the body's total energy expenditure (TEE).[32] Therefore, if the adult brain requires ~130g/day of glucose, the argument can be made that the process of hepatic glucose production is adequate and remarkably well-matched with the needs of the brain for glucose. Research has demonstrated that the brain can utilize ketone bodies and lactate as alternative fuels. Notably, the monocarboxylate transporter mechanisms by which ketones and lactate cross the blood-brain barrier have been identified.[33,34] Plasma levels of ketone bodies are transported and metabolized by the brain in a dose-dependent manner.[35,36]

The ability to endogenously produce glucose or ketones for the brain, and whether it is optimal to do so, gets to the center of the disagreement among nutritional physiologists. Regardless, advances in understanding ketone metabolism in the brain

bring questions to the long-held view that the brain can only utilize glucose and thus must have constant access to CHO in the diet.

Recent research highlights that child metabolism is dynamic with age. The 12-year EARLYBIRD study, which followed children from ~5 to 18 years old, showed complex glucose metabolism alterations and amino/fatty acid molecular changes across time.[37] As children progressed through puberty, there was a shift away from fat oxidation resulting in reduced ketogenesis and increased blood glucose levels. However, while the study involved extensive evaluation of metabolic markers across time, no dietary intake data were collected. The changes in metabolism observed at puberty could reflect a change in macronutrient intake during adolescence. Indeed, it is known that U.S. children increase CHO intake in adolescence to the highest level of all age groups across the lifespan.[38]

A study conducted in prepubertal and adolescent children by the United States Department of Agriculture (USDA) suggested a similar pattern of change in metabolism with child age. Insulin sensitivity and glucose effectiveness were age, but not sex-dependent, with prepubertal children having about double the insulin sensitivity as adolescents.[29] These studies suggest that the child's metabolism may differ from that of adults and change dynamically as children grow. Considering this may have important implications given that current child dietary recommendations are primarily based on extrapolation from adult data.

Metabolic and Altered Growth States

The absence of all macronutrients (i.e., low PRO, low FAT, low CHO) is defined as caloric energy starvation or *marasmus*. It is unknown how much glucose can be produced through gluconeogenesis in the absence of dietary PRO before tissue protein

stores are affected. However, nitrogen balance (NB) studies in adults suggest that without CHO in the diet, 100-150g of daily PRO is required for adequate substrate for gluconeogenesis to produce needed glucose.[39] During starvation and without PRO and CHO in the diet, once fat stores have been depleted and no more ketones are produced, tissue protein is lost until death occurs. The loss of body condition is termed wasting, defined as a low weight-for-age z-score (WAZ).

In the absence of dietary PRO and FAT (i.e., low PRO, low FAT, HIGH CHO), a disease of young children called *kwashiorkor* can develop. Kwashiorkor occurs when there is an adequate caloric intake, but the diet is specifically deficient in PRO, as opposed to *marasmus,* in which total calories are inadequate. Protein has metabolic roles in pH and fluid balance. The extreme lack of PRO in kwashiorkor results in an osmotic imbalance that causes skin edema and "potbelly" due to liver enlargement. Generally, PRO deficiency adversely affects the organs, brain, and immune system, increasing the risk of infections. The condition typically develops once a child transitions from breast milk, which provides required AAs, to a diet high in CHO but lacking in PRO. Another form, protein-energy malnutrition (PEM), can also occur in elderly adults and children with chronic disease, impacting immune and organ function. However, PEM in the U.S. is more often associated with marasmus (total caloric deficiency) than kwashiorkor, though it is not unheard of in developed countries.[40]

In the absence of dietary FAT and CHO (i.e., HIGH PRO, low FAT, low CHO diet), humans can enter "rabbit starvation," also known as "protein poisoning." Rabbit starvation occurs when the diet consists primarily of PRO and is named for the cautionary statements in World War II-era survival manuals for soldiers to not exclusively consume

rabbits in survival situations. Starvation can occur even in the presence of more than sufficient calories from dietary PRO, as the liver has a limited capacity to convert excess nitrogen to urea. This upper limit is estimated to be ~35% PRO (~175g PRO in a 2000 calorie diet), but no human studies have examined this threshold. This level fits with anthropological data from pre-agricultural man, estimated to have ingested ~35% of calories from PRO.[41,42] However, despite the adverse effects of excessive PRO in the diet, the DRI has not set an UL for PRO.[3]

The absence of dietary CHO in the diet (i.e., HIGH PRO, HIGH FAT, and low CHO diet) was common to northern sea-faring nations such as the Inuit.[43,44] As discussed, the lack of CHO in the diet is managed by the presence of endogenous physiological mechanisms to produce needed glucose and ketones. Indeed, the DRI text states, "the lower limit of dietary carbohydrate compatible with life apparently is zero, provided that adequate amounts of PRO and FAT are consumed."[3(p.275)] When the diet is absent of dietary PRO and CHO (i.e., low PRO, HIGH FAT, low CHO), this defines a high-fat ketogenic diet (HFKD). This diet is well-researched for the treatment of intractable epilepsy in children. As discussed, some PRO in the diet is presumably required to produce glucose via gluconeogenesis for the brain.

Excessive caloric intake with an abundance of all three macronutrients, especially CHO and FAT (i.e., HIGH PRO, HIGH FAT, HIGH CARB), essentially defines overnutrition. Overnutrition is known to contribute to metabolic syndrome[45] and obesity[46] in children.

The human metabolism is remarkably flexible but with limitations. Humans utilize glucose as the primary fuel source if all three primary macronutrients are present

in the diet. If CHO is absent from the diet, the human body will endogenously produce needed glucose and ketones as fuel sources. Arguments about what is optimal will always ensue.

NURTURE: Environment, Socioeconomics, and Nutrition

Environment

Environmental exposure to toxins, heavy metals, or pesticides can negatively affect child growth. Lead is one of the most common toxins affecting children. Children exposed to e-waste with elevated plasma lead levels had lower physical growth with lower weight, height, and BMI.[47] Similarly, Ugandan children exposed to metal mixtures had lower HAZ, with 62% of this effect specifically attributed to lead.[48] Stunting was associated with pesticide exposure in a case-control study of 160 children in an agricultural area of Indonesia.[49]

In low to middle-income countries, dietary sources of mycotoxin exposure contribute to malnutrition and growth impairment.[50] Blood biomarkers of aflatoxin exposure in children aged 6 to 12 years in Kenyan children were associated with wasting but not stunting.[51] However, Guatemalan children exposed to aflatoxin in maize were associated with decreased HAZ.[52]

Among developed countries, exposures to endocrine disruptors and perfluoroalkyl acids (PFAAs) in the environment may be of increasing concern. In the Jersey Girls Study, urine mycoestrogens were detectable in 78.5% of 163 girls aged 9-10 years old.[53] Among the girls with detectable levels, these levels were associated with decreased HAZ and WAZ at menarche. Bisphenol A (BPA) from plastics also affects height in children. Among 754 Chinese children aged 9-18 years old, urine BPA and HAZ were inversely

associated in boys but not girls.[54] A study of NHANES children 3-11 years old, detected significant associations of PFAA and PFAA mixtures with decreased HAZ in boys.[55]

Many studies report associations between childhood maltreatment and obesity, but the exploration of height is limited. For example, adverse childhood experiences, such as bullying, were found to be associated with BMI in 10-year-olds[56] and increased waist-to-hip ratio in adults.[57] In the National Survey of Children's Health, obesity was associated with having more adverse childhood experiences.[58] However, impacts on height have also been reported, as clinical psychosocial short stature has been described in Japanese children exposed to physical abuse.[59] One study reported that stunting and wasting in children were associated with neglect.[60] Taken together, these studies highlight the importance of a positive social environment for child growth.

Socioeconomics

Socioeconomic and demographic factors have known impacts on child growth and development.[61] Socioeconomic status (SES) may impact growth via many factors, such as lack of access to medical care, the increased prevalence of disease, or decreased food access. Severe deprivation in early childhood was associated with permanent stunting among adoptees, with low HAZ found to be specific to females, with particular impacts on height velocity and FAH.[62] In a study utilizing NHANES data, the Poverty Income Ratio and HAZ were strongly associated.[19]

Within-countries, a low SES and unhealthy dietary pattern were associated, with this relationship maintained across 12 countries.[63] These unhealthy diet patterns may contribute to the lack of specific micronutrients,[64] known to affect growth in children.[65,66] Worldwide, the presence of iron deficiency anemia is of primary importance, impacting

growth and development in children. However, while no less critical, iron deficiency primarily affects psychomotor development rather than growth in terms of height.[67] The World Health Organization (WHO) considers low iron to be of central importance. The WHO explicitly cites the causes as low iron availability in plant-based foods and poor iron absorption due to parasitic infections.[68] Many studies in developing nations utilize iron or anemia status as a proxy for PRO intake when studying stunting. In Sub-Saharan Africa, for example, anemia prevalence in children was ~60%, but only ~7% in U.S. children.[64]

However, a meta-analysis of studies that treated children under 5 year old in developing nations with single nutrients, including iron, vitamin A, or zinc, showed that only zinc had a small positive effect on child growth.[69] Further, a systematic review of over 200 studies that utilized fortification of *multiple* micronutrients in children showed improvement of serum micronutrient concentrations but non-significant impacts on growth.[70] These data suggest that replacing these micronutrients has little effect on growth in the absence of a complete diet. Thus, this further highlights the importance of total energy (TE) and macronutrient intake, as these directly impact micronutrient availability and absorption.

Nutrition

Guideline Determination Methods: The Dietary Reference Intakes (DRI)

The set of reference values for micro- and macronutrients developed by the IOM, collectively known as the Dietary Reference Intakes (DRI), provide the estimated average requirement (EAR), recommended dietary allowance (RDA), adequate intake (AI), and tolerable upper intake level (UL). These collective DRIs were then used by the USDA and the Department of Health and Human Services (DHHS) to set the Dietary Guidelines

for Americans (DGA) and are communicated to the general U.S. public using MyPlate. A significant portion of current recommendations for child caloric intake and macronutrient distribution are extrapolated from adult data. Therefore, understanding how the IOM defines the DRI for children first requires understanding how it is defined in adults.

Total Energy Expenditure (TEE) Calculations

The most recent version of the DRI determined total energy expenditure (TEE), essentially the "*caloric cost of living*," from the gold-standard doubly labeled water (DLW) method followed by stepwise multiple linear regression to predict TEE based on age, gender, height, and weight. The DLW method measures TEE in free-living individuals[71] and represents the sum of the basal metabolic rate (BMR), thermic effect of food (TEF), thermoregulation, and physical activity. Stable isotopic forms of water are administered orally, and the disappearance rate from body fluids is monitored, typically for 7-21 days.

Disappearance rates are used to calculate carbon dioxide (CO_2) production and thus, TEE. Consequently, TEE is the energy *expended* during the oxidation of energy-yielding nutrients to water and CO_2. For the DRI, data was compiled from ~20 investigators contacted from the literature who provided data across genders, ages, body weights, heights, and PALs. Further, the data included normal-weight children (n=525), normal-weight adults (n=407), children with overweight/obesity (n=319), and adults with overweight/obesity (n=360).[3] Data were evaluated using non-linear regression to produce recommendations based on 1611 individuals.

There is a substantial effect of gender on energy expenditure throughout the lifespan.[3,72] TEE is estimated at four different PALs in the DRI. PAL is determined by dividing the TEE by the basal metabolic rate (BMR) as calculated using the Basal Energy

Expenditure (BEE), making PAL a function of the ratio of TEE to BEE, creating a standardized set of ratios to define the level of activity into four categories. *The PAL categories are defined here.*[3]

PAL = TEE/BEE

sedentary (PAL 1.0-1.39)

low active (PAL 1.4-1.59)

active (PAL 1.6-1.89)

very active (PAL 1.9-2.5)

Energy Requirement Calculations in Children

TEE was calculated from data directly collected using DLW in adults and children with and without obesity. However, TEE does not consider the energy needed for tissue deposition, as TEE represents the energy *expended*. The estimated energy requirements (EER) were developed to provide a standardized prediction algorithm for estimating the TE required for energy balance. For children, this must include energy for somatic growth. Therefore, when the EER was determined for growing children, the energy cost of growth (*ECoG)* was added to the TEE for a given child's age and sex. The EER algorithm, which includes TEE in its mathematics, uses multiple factors, including sex, age, weight, height, and physical activity, to make predictions for normal weight, healthy individuals. Therefore, the primary energy expenditures in children can be simplified to include the summation of 1) BMR, 2) physical activity, and 3) ECoG. The largest component, ~60-70% of EER, comes from the BMR, which can be considered the *basal cost of living*.[73] The second-largest component is physical activity comprising ~30-

40% of EER.[73] The final component is the *ECoG*, estimated to be just ~3-4% of the EER in children over the age of 1 year.

Two components comprise the ECoG in children; the energy required to synthesize the new tissue and the energy deposited/stored within the newly acquired tissue.[73] Essentially, the ECoG quantifies the cost of energy deposition of body tissue fats and proteins because glucose content within the deposited tissue is negligible. The ECoG was calculated in children recovering from malnutrition to be ~4-6 kcal/g of tissue deposited, with ~1 kcal/g of that being the synthesis component.[74] Similarly, Butte et al. estimated the ECoG at 4.8 kcal/g in a 1989 study of infants across multiple body composition studies.[75] Therefore, the consensus is that the average energy cost of tissue synthesis and deposition is ~5 kcal/g tissue deposited.[76] More recently, Butte et al. quantified the ECoG in healthy children as a percentage of TEE. The ECoG is ~35% of TEE at 1 month of age, drops to just ~8% of TEE by 4 months, and ~3% of TEE by 1 year of age.[77,78] The ECoG remains around 3% until the pubertal growth spurt, when it increases to ~4% of TEE.[77,78] Nutritionally, the DRI concluded that ECoG is only of concern during the first few months of life.[3] Indeed, the ECoG, at just 3-4% of the TEE, is negligible compared to the BMR and physical activity. In the DRI, the regression equation estimates the ECoG at just ~20-30 kcal/day for a growing teenager.[3] Despite this, humans accrue up to 50% of their adult weight[5,79] and 15% of their adult height with >90% of total adult bone mass during puberty.[5] This remarkable increase in body size is despite the minimal ECoG because hormones[80,81] and genetics[5,82] play primary roles in growth.

Practical Example: Using the tables provided in the DRI, a sedentary 15-year-old, 115 lbs (52kg), 63.8 inch tall female has a TEE of 1706 kcal/day. The same individual with a very active PAL would have a TEE of ~1000 more kcal at 2845 kcal/day. For comparison, the ECoG for this very active child in a growth spurt at 4% of TEE would be estimated at just 114 kcal/day.

Because physical activity is the second-largest component encompassing ~30-40% of TEE, it dramatically impacts energy requirements. Inadequate energy intake for an extended period will reduce physical activity to decrease TEE adaptively. If a child is chronically undernourished, growth slows as an adaptive response to decrease BMR, protein synthesis (i.e., the contribution of proteins for the ECoG), and physical activity.[5] Data from studies show that physical activity increases with age but does not vary significantly by sex,[71] and PAL estimates for boys and girls aged 6-16 years can be calculated as 0.025 X age + 1.40.[83] Young children generally have a *low active* PAL of ~1.4 that gradually increases to an *active PAL of* ~1.75 by age 18 years.[71] The lower PAL of younger children is explained despite their observed *non-stop body motion* by being in a smaller, less energy-hungry body. Adolescents may have an *active* or *very active* PAL during middle and high school sports, particularly if they are engaging in exercise or weight training. Therefore, the impact of PAL on EER may be among the highest of a given individual's lifetime during adolescence. Physical activity is generally considered beneficial for growth[84] and the prevention of obesity.[85] However, being overweight or obese is not associated with a lower PAL[71] because higher body mass results in increased TEE, keeping the ratio of TEE to BEE (i.e., PAL) elevated. A review study concluded that physical exercise does not negatively impact child growth.[86] Physical activity and

height were not associated in an NHANES study of 6116 U.S. children aged 2d-18 years old.[19]

Acceptable Macronutrient Distribution Range (AMDR) Determination

Calculating energy requirements in a whole organism is more straightforward than determining optimal macronutrient distribution. The AMDR is primarily based on NHANES III oral survey food frequency questionnaire (FFQ) data, representing *habitual* and not necessarily *optimal* intakes. Survey data has inherent issues,[87,88] particularly with the underreporting of foodstuffs perceived as unhealthy and overreporting of those perceived as healthy.[89] The IOM embraced data that reported *reasonable agreement* in adults between DLW and FFQ.[3] However, this DLW/FFQ relationship has recently been questioned in adults,[90] older adults,[91,92] and adolescents.[93] In children, the method is reported to be largely accurate at the group level but not for the individual.[94–96] Across 15 studies, underreporting by FFQ in children varied by a wide range from 2% to 59% compared with DLW,[94] and may be due to issues unique to FFQ in children, such as lack of child-specific portion sizes.[97]

The IOM states that for "many of the macronutrients, there are few direct data on the requirements of children. In this case, the EARs and RDAs for children are based on extrapolations from adult values".[3(p.25)] Only infants aged 0 to 6 months were able to be directly defined due to availability of exclusive breast milk intake data. Infants 7 to 12 months and toddlers aged 1 to 3 years were interpolated from the younger infants getting milk. For children aged 4 to 8 years, the DRI cites that "For many nutrients, a reasonable amount of data is available on nutrient intake and various criteria for adequacy..."[3(p.32)] Still, the ability to directly measure data in this age group varied by macronutrient. AMDRs for adolescent children aged 9 to 17 years were extrapolated from adult data,

with statistical adjustments for projected somatic growth needs.[3] Depending on age group and macronutrient, AMDR in children is based on direct measurement, extrapolation from adult data, or interpolation from infants. The following section will summarize the foundation for each macronutrient's current DRI for children. A detailed exploration of studies investigating the individual macronutrient intakes of total PRO, FAT, and CHO and their relationships with height will be introduced separately.

Dietary PRO

PRO represents a unique and important macronutrient for child growth. Growth can be thought of as a net deposition of protein (meaning that the rate of anabolism must be greater than that of catabolism). Two important unique properties of PRO must be considered. First, there is no capacity to store dietary PRO, and as such, there is no dedicated storage organ beyond synthesized muscle tissue. Second, no non-PRO foods can be converted into body tissue protein. These properties create the necessity for daily PRO intake, and over-ingestion of PRO does not enable storage for the future, though it can still contribute to TE. While the contribution of PRO to the TE in the diet is lower compared to FAT and CHO, it is simultaneously essential for acquiring nitrogen, contributing to tissue structure and metabolic function. Like all mammals, humans must obtain this nitrogen from their diet to capture dietary nitrogen as body protein. For the growing child, nitrogen accumulation, and thus, growth can be measured by monitoring outcomes in child weight and height. The inability to store protein combined with its unique dual *energy-yielding and nitrogen-obtaining* properties makes daily dietary PRO intake essential in the human diet.

The DRI RDAs specific to PRO intake in children were calculated based on the NB method. NB is interpreted as '*the point at which intake is equivalent to excretion*,' representing the EAR plus a safety factor. A correction for the ECoG in children then reveals the RDA. The RDA represents a *minimum* daily need for protein to maintain short-term NB in healthy people with moderate physical activity[3]. However, DRI recommendations for total PRO intake in children were not based on direct NB child measurement but extrapolation from adult data and interpolation from infant data. A primary reason for this was that the NB method requires a minimum of three days for each protein level challenge and collecting all urine and feces during this time. Further, it is unethical to underfeed children to determine appropriate linear ranges.

The NB method for determining PRO requirements is based on "*structural maintenance requirements*." It does not account for protein's many metabolic roles (i.e., proper pH and fluid balance, hormone and enzyme production, immune function, or energy contribution).[98] Therefore, NB determines a minimum requirement only and does not take into account all of the growth and metabolic needs of children, although some algorithmic adjustment for somatic ECoG was made. Currently, the AMDR provides recommendations for a practical range of PRO intakes in a complete diet, with child ranges considerably above the RDA, set at 10-30% of calories. However, in clinical and nutrition practice, PRO recommendations in children are commonly prescribed based on the RDA, intended to represent minimum, not optimum, levels.[99] Since the publication of the DRI, new methods for determining PRO needs indicate that PRO requirement may be higher in children than determined by previous NB methods[100] and will be discussed in the next section.

The need for dietary PRO for human growth and development is well established.[101–103] While PRO plays a role in development, there is a widely accepted causal role of PRO in linear height. PRO intakes below 0.79-1.12 g/kg depending on age have been reported to restrict linear growth in children.[104] In a study of 1-year-olds, protein synthesis was highly dependent on dietary PRO intake, with protein synthesis about half that of intake.[105] The rate of tissue protein synthesis is very high in neonates to support rapid growth.[106] It is known that PRO increases fat-free mass (FFM) in children and adolescents[107] and that adequate PRO intake is needed for body composition and FFM in young adults.[108]

A prospective study of 229 healthy children 6-18 years of age assessed the impact of long-term dietary PRO intake on bone.[109] PRO intake was positively associated with periosteal circumference, cortical area, bone mineral content, and polar strength strain index, underscoring the net anabolic effect of PRO on bone. The presence of adequate muscle, facilitated by dietary PRO intake, further enables bone development through biomechanics.[110] The body is constantly making and breaking down tissue protein, with body protein turnover in adults calculated to be ~210 g/day,[111] with similar World Health Organization/Food and Agriculture Organization of the United Nations (WHO/FAO) estimates in children.[112] Data on direct protein turnover is limited at most stages of child growth. However, data comparing prepuberty to puberty suggests that proteolysis and protein oxidation (protein breakdown mechanisms) are lower in puberty with no difference in protein synthesis.[113] It is accepted that protein turnover decreases across the lifespan, from birth to old age. Proteins that are degraded can be recycled, but this is not 100% efficient.[114] Calculations of the minimum dietary PRO required/day to maintain

NB in adults from standard NB methods were 32-46 g by one estimate[111] and 56g/day by another.[115] Protein turnover in pubertal children with FFM of 45 kg and mean age of ~13.6 years old has been reported to be ~1.0 g/day/kg of FFM,[113] estimated at ~45 g/day.

Lack of PRO in the diets of children in developing countries is known to be causative for stunted growth. In the developing world, parasitic infections are a driver of chronic and acute illnesses. Increased catch-up height in children after diarrheic illness was improved with higher PRO levels in the diet.[116] The presence of parasites and disease increases the PRO requirement due to decreased absorption and altered immune response, reducing the utilizable PRO. Further, PRO source and quality in these regions may be lacking in addition to PRO quantity, contributing to the need for higher PRO intakes to increase utilizable PRO. A study that examined stunting in children across multiple regions and countries revealed that utilizable and not total PRO was the statistically significant factor.[117]

Recall that RDA minimum PRO recommendations for children were based on NB data extrapolated from adults and corrected for tissue growth using algorithms. Recent advances in more minimally invasive PRO requirement measurement methods have enabled direct data to be collected in children. The indicator amino acid oxidation (IAAO) method has been validated against NB methods in swine,[118] children,[119–121] and adults.[122–125] One of the primary reasons that limited data had been collected from children using the NB method is the requirement of a minimum of three days for each PRO level challenge and the collection of all urine and feces across the entire time window. With IAAO, subjects are fed graded amounts of stable carbon-13 (^{13}C) labeled IDAAs, and the breath is monitored for the appearance of the carbon-13 labeled carbon

dioxide ($^{13}CO_2$), requiring just 3-4 hours of sampling. A study was performed in 2011 in which healthy 6 to 11 year old children were evaluated using IAAO.[126] Mean PRO requirements were determined to be nearly double the current RDA.[127] The calculations for the EAR (mean) and RDA (population safe) equivalents in the study revealed 1.3 and 1.55 g/kg/day, respectively, contrasted with the 0.76 and 0.95 g/day of current DRI recommendations for the age group. Additional studies using IAAO suggest that current recommendations for PRO in the diet of adults are also drastically underestimated by as much as 30-50%, suggesting a need for 1.5-2.2 g/kg/day.[100] The potential role of total PRO on HAZ will be explored later in this review.

Dietary PRO quality has the potential to impact child growth in important ways, given the primary role of the IDAA in muscle, bone, and organ tissue synthesis. There are well-established dose-response relationships between muscle protein synthesis and blood levels of the IDAA in young adults[128] and the elderly.[129] Extensive research has explored which and how much IDAA and BCAA are required to retain muscle mass in the elderly. However, dose-response relationships regarding the impact on child growth have been chiefly understudied in healthy children in each age group. Studies have been limited without a method to determine which specific BCAA and IDAA, and their levels, are deficient.

The DRI states the importance of 'high-quality PRO' for growth in children, but tools to define this specific to the growing child were limited to animal-based research methods at the time. From 1991 to 2013, the WHO/FAO consensus was to utilize the protein digestibility corrected amino acid score (PDCAAS) to evaluate PRO quality. This method considered the AA composition, digestibility, and bioavailability, producing a

score based on the most limiting AA.[130] Using the IDAA requirements of a single reference, defined as a growing 2 to 5-year-old child, digestibility/absorption sampling was taken from the feces of mice for calculation. However, the last 30 years have brought forward critical concerns with the PDCAAS method.[130]

Recently, agreement on the best method to define PRO quality has shifted from the PDCAAS to the digestible indispensable amino acid score (DIAAS). Concerns with PDCAAS methods prompted the FAO in 2013 to announce a preference for the new method. DIAAS is superior because instead of being based on a single reference child, it is based upon the IDAA requirements adjusted for age (as determined from NB). Further, instead of sample results being taken from the feces of mice, they are collected from the ileum of pigs, which are more physiologically similar to humans.[131–133] Multiple studies report improvement in the accuracy of DIAAS over PDCAAS,[134] prompting the change in consensus by the WHO/FAO.

Recall that the DIAAS is adjusted for age based on NB data. Given child-specific concerns about NB methods and recent IAAO research proposing higher PRO requirements, the DIAAS method also has limitations. Another metric for PRO quality has been proposed using the IAAO PRO quantity method. The IAAO method can also evaluate the bioavailability and, thus, quality of various AA-containing foods.[125,135] Unlike DIAAS, IAAO can be collected non-invasively and in humans, which is a distinct advantage, particularly for child studies. The IAAO PRO quality method has been validated in swine,[136] humans,[137,138] and specifically children[126] and can also evaluate individual foodstuffs. Moreover, evaluating foods based on preparation and ultra-processing methods is possible. For example, the bioavailability of peas and uncooked

peas was 88% versus 55%, respectively.[136] Recent data suggests that while food processing may have a limited effect on animal PRO bioavailability, the effect may be more pronounced for plant PRO.[139] In humans, the method has enabled the investigation of which foodstuffs can be combined to improve specific AA bioavailability.[138,140] Advantages include a minimally invasive means for determining specific IDAA bioavailability and total PRO requirement in a given human subject. In healthy 6-11 year old children, the method enabled direct measurement of a branched-chain amino acid (BCAA) and specific IDAA requirements.[126] For example, the IAAO method determined that BCAA requirements were higher in children with liver disease than in healthy children,[141] highlighting the potential for improvement of growth outcomes in critically ill children. The field of PRO quality evaluation in human subjects is changing rapidly, and even improvements on IAAO using multiple stable isotopes are being proposed.[142]

Dietary FAT

Fats have critical biological functions in addition to being a rich energy source. Broadly, FAs serve as ligands and in ligand synthesis for receptors that regulate bodily functions impacting inflammatory, neurological, and insulin pathways. FAs also play key roles in cholesterol and lipoprotein metabolism, directly impacting cell signaling and gene expression. In children, FAs are crucial for growth and development. However, unlike PRO, which is known to have specific impacts on linear growth, FAT plays a more significant role in nervous tissue development. Among the FAs, the human body synthesizes both saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs). Thus, no AI, EAR, or RDA is set for these two fat categories. SFA and MUFA are vital

for energy and cell membrane function and are the primary FATs in human breast milk.[143,144]

However, two specific polyunsaturated fatty acids (PUFAs) cannot be made by the body and are required in the diet: linoleic acid (LA) and alpha-linolenic acids (ALA). As such, AIs have been established specifically for these essential fatty acids (EFAs) but not broadly for total FATs, MUFAs, or PUFAs. As deficiency of LA and ALA is rare in the U.S., the AI is defined by U.S. median intakes. LA and ALA are important eicosanoid precursors that make hormones and autocrine/paracrine mediators, regulating cell and tissue functions. Less studied, the body synthesizes omega-9 MUFAs, and their role in human health is less clear, so no AI or RDA is set. Omega-3 FAs are particularly important for children as they support nerve and brain development. ALA serves as the precursor to two other important omega-3 FAs: docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Indeed, the lipid membranes of the brain, central nervous system (CNS), and retina are primarily comprised of DHA. All of these critical roles of FAT impact child development.

FAT is a major source of energy for humans at all stages. However, it is vital in newborns, as breast milk FAT is the primary energy source. As explained with the ECoG concept, the first few months of life require as much as ~35% of TEE for growth, thus the high FAT content of breast milk supplies ~40-50% of TE.[145] Studies in infants suggest that diets with <22% energy from FAT restricts infant growth.[146] Therefore, the AI for FAT in infants is set from known quantities of FAT in breast milk. However, once children are beyond approximately 6 months of age and supplementation of breastfeeding with complementary foods beings, the proportion of FAT required in the diet becomes

more difficult to quantify. AI has been determined for infants up to 12 months of age using habitual average intakes from the Continuing Survey of Food Intakes by Individuals.[3] After 1 year of age, the DRI concluded "…no effect on the level of dietary fat on growth when energy intake is adequate"[3(p.810)] and did not set an AI for total FAT over 1 year of age, with AMDR set based on interpolation and extrapolation. Known infant breast milk macronutrient content and habitual intakes for children 1 to 3 years old, were used to set FAT AMDR at 30-40%. For children 4 to 18 year old, the AMDR for FAT is 25-30%, based on habitual intakes and extrapolation from adults.

FAT plays a primary role in CNS development rather than linear growth. However, the studies the DRI cited[146–155] for recommendation determination exclusively focused on growth. Low-fat diets in children have been reported to be associated with deficiency of the fat-soluble vitamins.[155] Further, data suggests that children metabolize fat differently than adults, as pre-pubertal children have higher fat oxidation rates relative to TEE than adults.[156] While the development of the CNS, differences in fat metabolism, and micronutrient deficiencies are outside the scope of this review, these are no less important to child health. Importantly, these were also not considered in developing recommendations for FAT in the DRI.

As mentioned, the AI for ALA and LA were set based on habitual intakes in the U.S. since deficiency of these EFAs is non-existent in developed countries. However, an investigation of the association of HAZ with the various FA blood levels was explored in several developing countries in populations with high stunting prevalence. HAZ was compared in 307 Ghanaian children aged 2-6 years old. While 30% of the population was stunted, EFA deficiency of ALA and LA was not associated with HAZ.[157] However, total

omega-3 and omega-9, but not omega-6, were inversely associated with stunting. Another study found an association of omega-6, but not omega-3, with HAZ in 6 to 10-year-old Ugandan children.[158] However, in Malawian children, HAZ was associated with low serum concentrations of both omega-3 and omega-6.[159] Further study of the impact of specific FAs is warranted. The potential impact of total FAT on HAZ will be explored in-depth later in this review.

Dietary CHO

Dietary CHO can serve as a primary energy source for the body. Simple sugars and starches can enter the bloodstream quickly after ingestion. Therefore, dietary CHO is an obvious source of TE which can contribute to overall child growth. But endogenous glucose and not dietary CHO is the ultimate supplier of the cellular energy that contributes to growth. Unlike PRO and FAT, there is no identified physiological requirement of CHO in the diet specific to child growth other than the contribution to TE.

Recommendations for CHO intake in children were not considered in the context of child growth but rather the availability of glucose for the brain. As in adults, the IOM reasons that the continuous availability of glucose for the brain is essential, and humans should not rely on endogenous glucose production to supply such glucose. It has been determined that the adult human brain requires ~110-140 g/day of glucose.[24,27] The RDA, therefore, advises a minimum of 130 g/day of dietary CHO for adults and children to prevent the *requirement* for additional endogenous glucose (or ketone) production.[3] The provided rationale is that the amount of dietary PRO required to support adequate endogenous glucose production for the body approaches "the theoretical maximal rate of gluconeogenesis from amino acids in the liver."[3(p.288)] This interpretation is despite

contradictory statements elsewhere in the DRI that "The lower limit of dietary carbohydrate compatible with life apparently is zero, provided adequate amounts of protein and fat are consumed."[3(p.275)] An RDA of 130 g/day translates to ~30% of calories in a 2000 calorie diet. Still, the AMDR for CHO is 1.5-2X that amount at 45-65% of calories for children. In practice, AMDR CHO recommendations reflect the balance needed to meet energy needs once "acceptable" amounts of PRO and FAT have been consumed. Whether this amount of dietary CHO is optimal for human health is unknown.

Importantly, a distinction must be made between dietary CHO and glucose. In children, adequate CHO intakes were determined for the different age groups based on limited studies available at the time and largely reflect NHANES III data for *habitual* intakes. Recommendations were determined from intakes by age group combined with extrapolation of estimates for brain needs from adult data. At the time of the DRI release, the amount of endogenous glucose production from protein catabolism in children was unknown, but is now known.[29] However, the current recommendations in children are based on extrapolation of adult endogenous glucose production data to children, setting the present RDA for children of all age groups at a minimum of 130 g/day of CHO. Again, this level is consistent with the DRIs rationale that the CHO intake should be high enough to prevent the necessity of endogenous glucose production from PRO.

While there is a clear contribution of CHO in terms of TE, CHO lends no dietary essentiality as it does not directly contribute any amino or fatty acids for physiological functions. Thus, no published studies explore the *specific* necessity of CHO in the diet for child growth. Association studies, foundational to hypothesis generation, have shown either none or lower associations of height outcomes with CHO than PRO or FAT and

will be explored in more detail later in this review. Known causal mechanisms of PRO in growth have primarily resulted in nutritional epidemiology studies targeted to investigate PRO. Available studies, including many randomized controlled trials (RCTs), explore the association of CHO intake with obesity but not growth.

At the time of the release of the DRI, data were limited on the impact of CHO *quality* on human health, concluding that there was a lack of evidence in healthy individuals for recommendations of a CHO-specific glycemic index. Methods to evaluate CHO quality, such as glycemic index and load concepts, have received exhaustive study over the last 20 years, particularly in diabetes.[160] Overall, evidence has accumulated that a higher glycemic index may negatively impact human health,[161] but the extent of impact has high interindividual variability.[162,163]

While obesity is outside the scope of this review, it should be noted that overconsumption of simple CHOs, including sugars and starches, is as implicated in children as it is in adults. High total and added sugar[164] and sugar-sweetened beverage[165] (SSB) intake in childhood has been associated with increased obesity risk. Alarmingly, a study of 2353 children aged 12 years old, showed associations between consumption of one or more SSB daily with retinal microvascular alteration, a marker of cardiovascular disease risk.[166]

An RCT in pre-pubertal children reported that slow digesting versus rapid digesting CHO increased endogenous CHO oxidation rates, suggesting that slower digesting CHO could have positive health benefits.[167] Few explorations of CHO-specific impacts on growth have been reported. However, a 2008 PEDIATRICS paper by Ruottinen et al., involving 543 children aged 7 months to 9 years old, showed that

improved longitudinal child growth was associated with low versus high sucrose intake.[168]

Of particular beneficial focus has been dietary fiber intake, necessary for overall adult human health,[169] principally through the support of the gastrointestinal flora.[170] For example, in a large meta-analysis, dietary fiber showed a relationship with critical non-communicable disease outcomes.[161] In children, the relationship between dietary fiber and digestive health has had limited study,[171] with an overall lack of data from clinical studies to support the extrapolation of fiber benefits from adults to children.[172] In another publication by Ruottinen et al. in 2010 of data from the same prospective trial involving 543 children, weight and height were similar among three levels of fiber intake, suggesting a limited impact of fiber on child growth.[173]

Regardless of the three primary CHO sources, sugar, starch, or fiber, studies of their individual associations with linear growth are few, with associations in children with obesity receiving some attention.[174–176] Additional exploration of these associations with specific diseases and obesity is beyond the scope of this review. In practice, children are recommended to consume maximal fiber and minimal simple CHOs, similar to adult recommendations. However, whether the overconsumption of simple CHOs impacts child linear growth remains unexplored in healthy children.

Literature Search: Macronutrient Relationships with Linear Growth

Nutritional interventions are not commonly tested in healthy children without obesity or disease. While there is value in interpreting data from RCTs in children with overweight/obesity, the extrapolation of the results to growth for healthy child populations has limited relevance. Further, such studies seldom include healthy control

groups from which to glean information. While BMI is commonly a focus of studies in children with obesity, linear height is rarely explicitly reported as a primary outcome.

Thus, high-level studies on the specific impact of altered macronutrient distribution on linear growth in healthy children are largely nonexistent. Indeed, a recent systematic review by the Dietary Patterns Subcommittee of the USDA 2020 Dietary Guidelines Advisory Committee (the Subcommittee) concluded that "No evidence is available to determine a relationship between diets based on macronutrient distribution consumed during childhood and growth, size, body composition, and risk of overweight/obesity."[177(p.9)] However, this conclusion reflected the lack of available studies due to a limited inclusion criterion in their review. The Subcommittee restricted their review to include studies of healthy children in which "at least one macronutrient proportion was outside of AMDR for CHO, FAT, and/or PRO, …." Given the wide ranges of the AMDR, no studies met this inclusion criteria leading to the conclusion of 'no available evidence.' Thus, these restrictions effectively excluded all studies that explored habitual intake associations of individual macronutrients with linear child growth, e.g., excluded all available nutritional epidemiology on the subject.

For the current search, we did not include such restrictions. We expanded the scope to explore associations of individual macronutrients and/or macronutrient distribution with stature in children, regardless of whether macronutrients were outside of AMDR. We only excluded studies that did not report these associations with linear height or stunting (i.e., many studies only reported BMI but not linear height association outcomes even though height data was also collected to calculate BMI). No assumptions were made to define "healthy populations" or exclude "unhealthy

populations" other than to exclude studies in children with clinical overweight/obesity, diagnosed medical disease, or abnormal blood pathologies (e.g., hyperlipidemia).

Therefore, observational studies across populations *designed to detect obesity/overweight or stunting* were included if linear height metric associations with macronutrients were reported. Studies are presented with a focus on linear height outcomes and without discussion of weight/BMI outcomes. Findings in rural or developing nations, where child stunting was present, were reviewed as these populations present the unique opportunity to detect variation in macronutrient associations with growth. Nutritional influences on height were assumed to result from differences in 1) total energy (TE) intake and/or 2) the influence of each individual macronutrient (PRO, CHO, or FAT) and/or 3) the relative distribution of such macronutrients. Literature searches included Google Scholar and PubMed and incorporated international studies as long as they were reported in English. Included studies and generalized conclusions about the association with height appear in **Table 1.1** in the order of their appearance in this section.

Macronutrient and Total Energy Associations with Height

World View

To examine the big picture of height worldwide, Grasgruber et al. in 2020 investigated the association of food supply with male FAH.[1] The Food and Agriculture Organization Corporate Statistical Database (FAOSTAT) of the United Nations across 152 populations was utilized.[1] In addition to TE (calories/day/per capita), PRO for 28 individual food items and total PRO (each as g/day/per capita), in addition to %PRO in the diet, were evaluated for associations with FAH. As expected, TE had a strong positive correlation ($r = +0.70$) with male height, underscoring that total caloric availability is

important for FAH. However, total dairy PRO (r = +0.75) and total PRO (r = +0.71) also exhibited similarly strong correlations. The correlation of %PRO in the diet was r= +0.59. Unfortunately, the other macronutrients (total CHO and total FAT) were not reported, only the foodstuff PROs. The most negative correlate with height was rice protein (r = -0.67), with combinations of grain PROs resulting in even more strongly negative correlations. Animal, plant, and total PRO correlations with FAH were r = +0.68, +0.03, and +0.71, respectively. All calculations were repeated in females with similar trends. Further analysis led authors to suggest that the differences in height in developing countries were associated with PRO *quantity* and TE. In Europe and developed countries, PRO *quality* largely explained height differences. In light of this conclusion, the studies presented next will be organized by whether TE was likely adequate or inadequate.

Macronutrient Studies in Low-Income Populations (i.e., TE may not be adequate)

The relationship of diet with HAZ in developing nations was explored using data previously collected from rural populations in Guatemala (n=878) and the Philippines (n=3080) of children 6 to 24 months old.[178] In 1969-1977, these populations exhibited high percentages of children with stunting, so the Institute of Nutrition of Central America and Panama performed a nutritional supplementation trial. Some villages were randomly selected to receive a high PRO supplement and some an alternative PRO-devoid supplement. Data on height and dietary intake were collected from the children every 2-3 months. In 2016, a retrospective study was performed to explore associations of macronutrients with height across the populations (i.e., not evaluated by the PRO

supplementation group). While TE was associated with height, specifically total PRO, not total FAT nor total CHO was strongly associated with height.

Another study in developing countries explored associations of stunting prevalence with dietary intake across 18 Latin American countries in children under 6 years old.[146] FAOSTAT and the UN Subcommittee on Nutrition collected the data used in the study in 1996-1997. Using simple linear correlation models, TE, PRO, and FAT associations with the prevalence of stunting were -0.529, -0.563, and -0.520, respectively. Unlike the previous study, total FAT was also found to be associated with HAZ, and the association of animal FAT with stunting prevalence was -0.539. Unfortunately, associations with total CHO were not reported. This study suggests that FAT, in addition to TE and PRO, may be important to height in children in the developing world. The authors suggest that diets with <22% of energy from total FAT and <45% animal FAT may even restrict growth.

Similar associations were detected in a U.S. longitudinal observational study reviewing data collected in Depression Era 1930s Boston among 64 Caucasian boys. The study observed that higher total PRO and total FAT intakes resulted in taller FAH.[179] Specifically, in childhood, the intake of total FAT and animal PRO, but not vegetable PRO, was positively associated with FAH. Again, no exploration of total CHO was performed. Unlike other studies, however, there was no association of height with TE. Further, there was a clear association of birth length/childhood height with FAH, maintaining the expected impacts of genetics. Given that these data were collected during the Great Depression and into WW II, we can speculate that this population may have been more like those of developing countries.

Another study of Depression Era Boston was conducted in girls rather than boys. Using data collected originally in the 1920s to 1940s, a retrospective multiple regression analysis was performed in 2000.[180] The analysis included 67 Caucasian girls followed from birth to age 18 years old, for which height and dietary intake were collected annually. Stepwise linear regression was used to evaluate whether preschool (aged 1 to 5 years old) and school-age (aged 6-8 years old) dietary variables were associated with adolescent outcomes. The most predictive multiple regression model was one in which more TE and animal PRO resulted in higher peak growth velocity. However, no modeling was attempted to determine the independent relationship of TE on height or the independent relationship of individual macronutrients on height.

Macronutrient Studies in High-Income Populations (i.e., TE likely adequate)

In contrast to the Depression Era Boston studies, a study of modern-day Boston children showed no association between early childhood PRO intake and childhood height.[181] Among 1165 children, using linear regression, the β(95% CI) for HAZ per 10g PRO intake increase from early childhood to early teen was barely positive, with +0.07 and +0.05, for boys and girls, respectively. Further, animal versus plant PRO showed no statistically significant associations with height outcome. Notably, this population had very high mean PRO intakes at ~3.77 g/kg/day, well above both EAR and RDA and at the maximal end of AMDR. The study did not report the association between TE and height. Given the high PRO intake in this study and the prevalence of overnutrition in the U.S., we can speculate that the TE of this population was more than adequate, perhaps differentiating these children from the Depression Era Boston studies.

Additional studies explored mid-childhood height outcomes instead of FAH. Among 2154 twins in the United Kingdom Gemini cohort, there was no association of PRO intake collected at 21 months of age with height at 36 and 60 months of age.[182] TE and other macronutrient associations were not explored. In a prospective Netherlands cohort study, dietary intakes were collected in 3565 children at 1 year of age, and height was measured repeatedly until 9 years of age.[183] Linear mixed modeling found that total PRO, animal PRO, vegetable PRO, and individual IDAAs were all associated with greater height. Animal PRO had a higher association with height than vegetable PRO. In a Danish study involving 105 girls and boys 10 years of age, the association of TE and PRO with height was assessed.[184] There was only a moderate correlation between total PRO and height (r=0.378) and TE with height (r=0.337).

A large cross-sectional 2007-2014 NHANES study with 6116 U.S. children 2-18 years old tested if HAZ was associated with intakes of TE, PRO, CHO, or FAT.[19] HAZ was positively associated individually with caloric intakes of TE, total PRO, total CHO, and total FAT, though individual association statistics were not reported. But, as macronutrient distributions were almost identical across HAZ tertiles, there was no association of %PRO, %CHO, or %FAT with HAZ. While this suggests that TE, and not the distribution of that energy, is associated with HAZ in U.S. children, without variation in macronutrient distribution, this conclusion is limited.

Among modern European populations, a recent publication of the German DONALD study investigated the relationship between TE and total PRO on FAH.[185] Multilinear regression models showed that long-term PRO or animal PRO intake each explained about 80% of the adult height variance in girls and 70% in boys. Interestingly,

there was a strong association of total PRO ($R^2 = 0.80$) and animal PRO ($R^2 = 0.82$) with adult height in females but no association of either variable in males. Though the strength of the association was not reported, TE intake was stated to be associated with height. Unfortunately, no associations of the other macronutrients with height were explored. This study highlights that sex differences need consideration.

A small number of association studies focused on FAT in developed nations. A comparison of FAT intakes of <30%, 30-34.9%, and >34.9% were evaluated in children from birth to 8 years old with no significant differences in height.[147] Similarly, there was no difference in height in preschoolers across FAT quintiles in a cohort of 215 Hispanic children aged 3-4 years followed for ~2 years.[154]

A series of intervention studies using low-FAT diet RCTs were conducted in the 1990s in Finland. A study published in the Lancet of 1062 young infants aged 7 months were randomized to an intervention or control group and monitored out to 13 months of age.[150] The intervention group families received intensive dietary advice to feed their babies a "low-FAT" diet of 30-35% of energy from FAT with an unrestricted diet in the control group. The authors concluded that there were no differences in height between groups at 13 months. However, while the FAT gram intakes at 13 months were statistically different ($p=0.008$), they may not have been metabolically different. The mean %FAT intakes of the intervention and control were similar at 26.2% and 27.9%, respectively, at the 13-month endpoint. Effectively, both groups at 13 months were "low-FAT" by study definition, preventing clear conclusions. A follow-up study of the same cohort at 2- and 3 years of age was published in PEDIATRICS in 1997 with continued intensive dietary advice of a "low-FAT" diet.[152] There was more difference in %FAT

between intervention and control at 2 years (29.9% vs. 32.8%) and 3 years (30.8% vs. 33.2%) with no differences in height between groups. However, the other macronutrients were not reported. Finally, a third follow-up study was published in the American Journal of Clinical Nutrition (AJCN) in 1999 using associations across the study population rather than by the original intervention category.[149] Children were evaluated using regression at 13 months, 3 years, and 5 years and sorted into five FAT intake groups. Growth was not significantly different throughout the study period among FAT intake groups, with the lowest, mean, and highest FAT intakes of 25.8%, 32.1%, and 37.1%, respectively, at 5 years. However, unlike the earlier two publications,[150,152] intakes of the other macronutrients were reported but not evaluated for associations with height. In the lowest FAT intake group, children at 13 months ingested proportionally more PRO than children in the other FAT groups. However, there were no differences in PRO intake among the other FAT intake groups at 5 years. The highest FAT intake group had lower CHO intake consistently across time points. All FAT intake groups and ages in the study were similar in key vitamins, minerals, and FAs. In contrast, studies of the longitudinal effects of macrobiotic diets (low-FAT, vegetarian) in the Netherlands in children 0-10 years old were shown to inhibit growth in children under 18 months.[186–188] However, diets in these studies were shown to be deficient in TE, PRO, and key vitamins.

Discussion of Macronutrient Associations with Linear Growth

Most of the presented studies in low-income populations investigated PRO, and all reported associations with height outcomes. Studies in high-income populations show less consistency and strength of associations of PRO with height. Further, one study reported sex differences of HAZ with PRO, which were not evaluated in other studies.

Among low-income populations, the role of FAT on height is unclear as some studies showed a clear association and others did not. Among high-income countries, a single study detected an association of FAT with reduced height in children, but also reported inadequate TE, PRO, and key vitamins.

A series of longitudinal low-FAT RCTs, which began in infancy, detected no statistical differences in height among FAT intakes out to 5 years of age and reported dietary adequacy. Only two studies explored and reported associations of CHO with height, with one reporting no association and the other detecting an association but did not report the statistical strength of the association. Associations of TE with height were explored in low-income countries, with clear associations of TE on height, as only one study failed to find an association. However, TE was less explored and reported in high-income countries, with only one study testing and finding an association. Studies that evaluated mid-childhood growth utilizing HAZ may reflect alterations in growth patterns that may or may not eventually impact FAH**.** A few studies explored all three individual macronutrient relationships with height. However, none reported the correlation coefficients for all three macronutrients with height, preventing comparison of the strength of association. *Unfortunately, no studies were found that investigated and reported results for the complete macronutrient distribution to understand the whole diet's potential impacts on growth outcomes.*

As discussed, associations of the individual macronutrients, particularly PRO, with height were more evident among low- versus high-income. Grasgruber et al.[1] suggested in their world FAOSTAT analysis that differences in FAH in developing countries were strongly associated with TE and total PRO intake after controlling for SES

and genetics. In contrast, in developed countries, PRO quality/type was more strongly associated. Among the presented studies, this premise holds, as there were clear and consistent associations between total PRO and height outcomes in low-income countries. This association was less consistent among high-income countries, and the detection of associations of total PRO with growth disappeared in studies in which total PRO intakes were known to be high. As such, it is plausible that PRO quantity versus quality may differentially affect height depending on whether TE is adequate.

OVERALL DISCUSSION

Growth can be considered ~75% *nature* and ~25% *nurture.* Of the ~75% that is *nature*, hormones, metabolism, and genetics play key roles in child growth. However, of the ~25% of *nurture*, socioeconomics, environment, and nutrition are also very important. After exploration of each of these *nature* and *nurture* aspects of child growth, the central focus of this review was to explore the latter, that is, potential nutritional impacts on child growth. The nutritional aspect was examined, focusing on the three primary macronutrients and height outcomes for a clear and targeted search.

Diets are a complex mixture of foods with PRO, CHO, and FAT. The DRI text states this "imposes some limits on the type of research that can be conducted to ascertain causal relationships."[3(p.53)] There are obvious reasons that nutrition studies have traditionally been observational across populations. Nevertheless, the impact of macronutrients and macronutrient distribution is achievable with RCTs.[189] Indeed, many studies in the last two decades since the release of the DRI have explored the role of macronutrients in children with obesity. However, there is a shortage of high-quality studies on the topic of healthy children without obesity. Among the many studies

presented in this review, a single cohort of 1062 children represented the only RCTs that manipulated macronutrient intake and explored height outcomes. As discussed, in the Finnish low-FAT infant RCTs, no differences in height were detected out to 5 years of age.[149] Additional follow-up studies were published when the same cohorts reached 13 years old[190] and adulthood.[191] At these follow-ups, however, the focus had shifted from growth to obesity and, unfortunately, did not report subsequent height outcomes with FAT intake. This shift of focus from growth to obesity in children, happening throughout child research, may be missing important aspects of child health. Additionally, focusing on single macronutrients without considering macronutrient distribution prevents a comprehensive understanding of the impact of the whole diet.

Biologically, the goal of the mature individual is longevity, while the goal of the young individual is proper growth and development. Notably, that which provides optimal longevity and reduces the risk of disease in adults may not be appropriate for optimal growth and development in children. Given these opposing goals, the prevailing dogma that "what is good for the adult should also be good for the child" requires critical reassessment. The current DRI for macronutrients is very similar for adults and children. It is acknowledged that different macronutrient distributions for different optimal outcomes are likely to change dynamically across the lifespan, making recommendations complex. Nevertheless, precision nutrition for the growing child is an appealing and important goal. At the least, the opposing biological goals and dynamic changes in child metabolism call for serious questions about the continued extrapolation of adult data for AMDR and RDA to children.

The requirement of dietary PRO for growth in every genus/species, including humans, is well established. Across the animal kingdom, more dietary PRO is required in the young than the mature. Namely, in species ranging from the *C. elegans* worm to the mouse to primates, a higher PRO intake as a percent of calories is required in the young in the growth phase than in the adult phase of life. In animal agriculture and pet care, this is also widely known. In contradiction, the DRI AMDR PRO ranges are lower for children than adults. Further, RDA for PRO in children and adults is set at an identical value despite their biological differences. Recent literature has addressed how the current RDA for PRO is at odds with AMDR recommendations.[99] The AMDR seeks to provide PRO ranges in the context of a complete diet and recommends PRO intake to be a minimum of 10% and a maximum of 30% of calories in children over 4 years of age. However, the upper range of AMDR for PRO in children is seldom clinically applied as the RDA and not the AMDR is widely used to define PRO intakes for children. The *USDA DRI Calculator for Healthcare Professionals* (which references the IOM DRI [3]) exemplifies this contradiction: https://www.nal.usda.gov/fnic/dri-calculator/.[192] Despite the posted statement that "DRI amounts are set at levels to meet the nutrient requirements of almost all healthy people," suggesting the calculator uses AMDR, the calculator instead yields PRO values consistent with the RDA, intended to be a minimum. Returning to our example 15-year-old, 115#, 63.8", very active female child, using the above calculator, is recommended to consume 44g of PRO and 2845 total calories per day, equivalent to just 176 calories or 6.2% of total calories from PRO. This recommended PRO intake just meets this minimum range at

~0.84g/kg or 6.2% of total calories from PRO, which does not meet the minimum 10% requirements of AMDR for PRO.

For iteration, the RDA estimates the lowest intake level that meets the NB requirement of nearly all individuals. More simply, the RDA reflects the absolute minimum level of PRO that must be ingested to avoid loss of body nitrogen. However, as discussed, NB data specific to children and adolescents is lacking, and the values used in the DRI were extrapolated from adults and interpolated from infants.[3,193] The DRI report also states that due to issues with the NB method, it should no longer be considered the gold standard, but then fails to utilize other evidence to derive the RDA for PRO in children.[3] Thus, a valid concern is that NB may not be maintained if a child eats only to the current RDA.

Values calculated for PRO requirements derived from newer IAAO methods fit better than NB methods with habitual intakes in the U.S. and worldwide. American adults consume an average of 65-100 g/day[194] translating to ~1.68-2.4 g/kg/day with a worldwide average of ~68 g/day.[195] The World Resources Institute proclaims, "People are eating more PRO than they need, especially in wealthy regions." Yet, even in the world's poorest regions, habitual PRO intakes exceed the current minimum RDA requirements. In 90% of the world's countries, PRO intake far exceeds the RDA, suggesting that there is a biological basis for these "higher" habitual PRO intakes. It seems highly unlikely that across all the world's populations of genetic, dietary, economic, and cultural diversity that 90% of the world population is "over-consuming" PRO. The overconsumption of PRO seems highly unlikely, given the high prevalence of kwashiorkor in many developing countries.

Therefore, there are several important concerns specific to PRO recommendations proposed 1) that the RDA and AMDR may be inaccurate for children due to extrapolation from adult NB data, 2) that the RDA is confusing in that the consumer (or even healthcare professional) may believe that the RDA indicates an optimal intake of PRO, and 3) that the lack of clarity prompts clinical professionals to seldom stray from recommending RDA PRO minimums. These issues merit attention, given the importance of PRO for growth and development in children.

CONCLUSION

The human metabolism is remarkably flexible and dynamic across the lifespan. Needed glucose or ketones are endogenously produced depending on the macronutrient content of the diet. Children need just ~3-4% of the EER, an estimated 114 calories/day, in a pubertal growth spurt for somatic growth. This amount is minimal compared with the energy required for the daily cost of living and physical activities.

All three primary macronutrients contribute to growth by providing calories for TE. However, through this review, evidence suggests 1) a causal role for PRO in somatic and linear growth, 2) an essential role of FAT in neurological growth and development rather than stature, and 3) that beyond TE, CHO is unlikely to play a direct role in linear growth, nor development. PRO provides AAs and IDAAs, FAT provides FAs and EFAs, and CHO provides no essentiality.

In a 1970 AJCN article exploring child growth, Dugdale and Hewitt eloquently hypothesized that there was a nutritional basis for the pattern of growth in childhood but with genetic interaction in height growth.[196] They posited that the protein available after energy needs are met is principal to growth in height and muscle; total calories are

fundamental to fat deposition, and genetic factors set a ceiling on height growth which is maximized when nutrition is optimized. While simple, these tenets appear to hold even after 50 years of investigation. *Based on the research presented in this review, we propose that if TE intake is adequate and PRO minimums are met, children will reach their genetic height potential.*

TABLES

Table 1.1

Table 1.1: Studies included in literature search examining the relationship between macronutrient intake and height growth. NR denotes no report of result.

				Income									Positive Association with Height?			
ref#	**author**	**year data**	**year pub**	**low**	**high**	**study location**	**#participants**	**ages**	**gender**	**goal**	**design**	**method**	**PRO**	**FAT**	**CHO**	**TE**
1	Grasgruber	1995-2013	2020	mixed	mixed	152 world countries	152 countries	adults	M F	protein on FAS	observational	population assocaitions	yes	NR	NR	yes
178	Puentes	1969-1977	2016	yes	no	Guatemala & Philippines	3958	6-24 mos	M F	macros on height	observational	associations	yes	no	no	yes
146	Uauy	1996-1997	2000	yes	no	18 Latin American	18 countries	<6yo	M F	FAT on stunting	observational	population associations	yes	yes	NR	NR
179	Alimujiang	1930s	2018	yes	no	U.S. Boston	64	to adult	M	macros on height	observational	longitudinal association	yes	yes	NA	no
180	Berky	1920s-1940s	2000	yes	no	U.S. Boston	67	to adult	F	macros on height	observational	longitudinal association	yes	NR	NR	yes
181	Switkowski	modern	2019	no	yes	U.S Boston	1165	to teen	M F	protein on HAZ	observational	longitudinal association	weak	NR	NR	NR
182	Pimpin	modern	2016	no	yes	U.K Gemini Twins	2154	36 & 60 mos	MF	protein on height	observational	longitudinal association	no	NR	NR	NR
183	Braun	modern	2016	no	yes	Netherlands	3565	1-9 yo	M F	protein on height	observational	longitudinal association	yes	NR	NR	NR
184	Hoppe	modern	2000	no	yes	Denmark	105	10 yo	M F	protein on height	observational	cross sec assocations	yes	NA	NA	yes
19	Kim	modern	2021	no	yes	U.S. NHANES	6116	2-18 yo	M F	macros on HAZ	observational	cross sec assocations	yes cal, no %	yes cal, no %	yes cal, no %	yes
185	Hua	modern	2022	no	yes	Germany DONALD	189	3-17 yo	M F	protein on FAS	observational	longitudinal association	yes F, no M	NR	NR	yes
147	Boulton	1990s	1995	NR	NR	Australia	140	0-8 yo	M F	Fat on height	observational	longitudinal association	NR	no	NR	no
154	Shea	1986-1989	1993	no	yes	Hispanic	215	3-4 yo	M F	Fat on height	observational	longitudinal association	NR	no	NR	NR
150	Lapinleimu	1990s	1995	no	yes	Finland	1062	7-13 mos	M F	low fat intervention on height	RCT	intervention association	NR	no	NR	NR
152	Niinikoski	1990s	1997	no	yes	Finland	1062	2 and 3 yo	M F	low fat intervention on height	RCT	intervention association	NR	no	NR	NR
149	Langstom	1990s	1999	no	yes	Finland	1062	5 yo	M F	Fat on height	RCT	longitudinal association	NR	no	NR	NR
186*	Dagnelie	1980-1990s	1994	no	yes	Netherlands	243	0-10 yo	M F	macrobiotic diet on height	observational	mixed longitudinal	yes	NR	NR	NR
187*	Dagnelie	1980-1990s	1991	no	yes	Netherlands	110	4-18 mos	M F	macrobiotic diet on height	observational	mixed longitudinal	yes	yes	NR	yes
188*	Dagnelie	1980-1990s	1994	no	yes	Netherlands	110	4-18 mos	M F	advice increase fatty fish & dairy	"intervention"	mixed longitudinal	yes	NR	NR	no

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Chapter 2: Longitudinal Analysis of Physical Growth in Children with T1DM: The Potential Impacts of Disease Duration and Blood Glucose Control

ABSTRACT

Background: Child growth is an important and sensitive metric of overall child health, yet the specific impacts of Type 1 diabetes mellitus (T1DM) on growth metrics remain unclear. Even with modern interventions, children with T1DM have historically exhibited poor glycemic control, measured by glycated hemoglobin (HbA1c). High HbA1c and early age of diagnosis have the potential to alter growth patterns.

Objective: To investigate the long-term effects of Type 1 diabetes mellitus (T1DM) on child growth patterns, specifically focusing on height, weight, and the timing and tempo of growth.

Participants: The analysis included 1516 children with etiologic T1DM, followed from ages 2 to 20 years (71% white, 53% female) with a mean age of diagnosis of 9 years.

Study Design & Statistical Analysis: A longitudinal analysis using nonlinear mixed effects (NLME) statistical models was employed to describe the growth trajectories of children with T1DM. This approach allowed for the evaluation of sex-specific, individual and population-level growth metrics, including timing (age at takeoff), tempo (slope at takeoff), and upper asymptotic height and weight. The potential impact of disease duration and glycemic control on growth metrics was also explored.

Results: Children with T1DM showed differences in growth metrics compared to reports of children without T1DM, including earlier age of growth takeoff. Although stunting and wasting rates may be cause for clinical concern, final adult heights (FAH) in both boys and girls were predicted to be taller. Disease duration was found to have a greater negative impact on FAH than HbA1c levels.

Conclusion: This study highlights the potential for long-term effects of T1DM on child growth, with implications for earlier puberty onset and taller FAH. Although glycemic control is an important factor in growth, modeling suggests that disease duration has a more significant impact. The mechanisms involved in these altered growth patterns remain to be elucidated.

BACKGROUND

Growth and growth rate (height velocity) are standard clinical metrics for child health. Poor blood glucose control in children with Type 1 diabetes mellitus (T1DM) has known negative effects on diabetes-specific health outcomes detectable even at a young age.[1–5] Before the invention of insulin, early studies reported that the disease profoundly impacted growth, making stunting and wasting hallmarks of the disease.[6] Once insulin became available, alterations in growth were attributed to poor blood glucose control.[7,8] However, these early studies pre-dated the landmark Diabetes Control and Complication Trial (DCCT), modern blood glucose control methods, and robust study design and analysis. Post-DCCT reviews conclude that impacts on growth metrics in children with T1DM are remarkably inconsistent,[9,10] despite generally improved HbA1c levels. More recently, studies have suggested that the lack of blood glucose control can negatively impact final adult height (FAH) and was primarily related to whether the diagnosis was before or after puberty.[11,12] However, the precise quantification of longitudinal impacts on growth in children with T1DM remains unclear. The present analysis describes the longitudinal growth profile of children with etiologic T1DM.

The *timing* and *tempo* of growth provide context for growth dynamics in children. James Tanner coined these foundational metrics for growth in children, which still bear

his name.[13] Of particular physiological interest to Tanner was the *tempo* of the adolescent growth spurt for which the age at peak height velocity (aPHV) and the peak height velocity (PHV) could be utilized to define the *timing* and *rate* of growth, respectively. These important growth metrics can be easily extracted from cross-sectional data of child populations using readily available metrics of linear height. However, the current clinical definition of the Tanner stage is based on the presence of specific secondary sex characteristics.[14] Therefore, in the individual-participant clinical context, the *timing* of growth is often interpreted as the Tanner stage of a child compared to peers. In terms of *tempo*, the clinical interpretation considers a child's progression from Tanner stage 2 to menarche/spermarche compared to peers.

Unfortunately, adequate Tanner data, particularly for both sexes, is often absent when studying child populations. As discussed, aPHV and PHV can be calculated from cross-sectional height data, giving important descriptive clues about child growth. However, more advanced longitudinal statistical modeling can be employed using these same basic growth metrics to calculate the *timing* and *tempo* of growth in the absence of Tanner scores. Therefore, the present analysis sought nonlinear mixed effects (NLME) modeling to calculate the *timing* and *tempo* of growth in a longitudinal rather than cross-sectional fashion.

In a longitudinal and population data context, instead of relying on Tanner scores, *timing* can be interpreted more directly as the age at which specific growth milestones are met compared to their same-sex peers. In logistical statistical modeling, *timing* can be represented by an inflection point (i.e., age) at which half of child growth has occurred. Similarly, *tempo* can be considered as the rate of progress of growth (i.e., how fast or

slow the child or population is growing at a specific point) represented as the slope at the same inflection point defined with *timing*. Importantly, *timing* and *tempo* apply regardless of physical sexual development stage (i.e., Tanner), making the metrics relevant to both girls and boys without knowledge of primary and secondary sex characteristics or the onset of menarche/spermarche. NLME can also calculate the FAH, an additional standard clinical metric for evaluating maturation outcomes that does not rely on secondary sex characteristics.

In the present analysis, NLME modeling enabled a mathematically robust determination of the nonlinear dynamic process of child growth. An NLME model was adapted from Marceau et al.,[15] including coefficients for FAH, *timing*, and *tempo* of the population by sex. The modeling enabled the exploration of both fixed and random effects and the inclusion of covariates of interest to T1DM. Traditional cross-sectional growth metrics such as PHV and aPHV were explored descriptively outside the model. Further, analysis of stunting and wasting provided an understanding of potential growth dysfunction in populations.

The goal of this analysis is largely descriptive. However, undertaking this dataset was driven by the central hypothesis that the presence of T1DM may negatively impact growth. Given the early-age diagnosis of the disease,[16] the long-term[17] and early onset[18] of adverse health outcomes of the overall population, and the inability of children to meet American Diabetes Association (ADA) HbA1c goals,[19] we hypothesize that growth metrics may be negatively affected in children with T1DM. Further, we hypothesize that blood glucose control and disease duration may adversely affect physical height and weight metrics.

METHODS

Data Acquisition

Data was obtained from a two-decade-long multicenter longitudinal study of children diagnosed with diabetes. The study was conducted from ~2000 to 2020 by the Center for Disease Control and Prevention (CDC) and the National Institute of Diabetes and Digestive Diseases (NIDDK) of the National Institutes of Health (NIH). Study centers were located in five states: Colorado, Ohio, Washington, South Carolina, and California, with the coordinating center located in North Carolina.

The present secondary data analysis was approved by the coordinating center, and data were obtained through the Lifecourse Epidemiology of Adiposity & Diabetes (LEAD) Center at the Colorado School of Public Health of the University of Colorado (IRB#CRV018). Data were received in de-identified form and deemed exempt from oversight by South Dakota State University IRB (#IRB-2210012-EXM). The present analysis is focused on physical child growth metrics encompassing height and weight.

Participants

The methods for data collection from participants have been described previously.[20] Briefly, anthropomorphic and demographic data were collected via surveys, and clinical data were collected by medical personnel at study visits. Surveys obtained self-reported information on income, race, and education.[21–23] At initial enrollment, blood was drawn for diabetes autoantibodies and utilized to confirm etiologic T1DM. Study visits included a brief physical examination with the collection of height and weight. Blood was drawn for HbA1c testing at each study visit with specifics for the laboratory analysis methods as previously reported.[20]

Participant data were collected across time, with a maximum of six visits across childhood, with data collected at baseline, one-year, two-year, and five-year follow-up, with two later cohorts collected at approximately five-year intervals. Only participants with etiologic T1DM were included in the present analysis and were enrolled after diagnosis. The majority of participants were within one year of diagnosis at baseline enrollment. No exclusions were made to restrict participants with a particular disease duration to enable consideration as a covariate in models. Data were restricted to participants whose exact age was known between 2 and 20 years. Physiologically implausible data and outliers were detected using robust regression and outlier removal (ROUT),[24] a *non-ad-hoc* method for outlier detection and removal, with slight modifications described below. The ROUT method detects outliers specific to the statistical model being fit. **Table 2.1** reflects baseline data removed of outliers using ROUT after fitting the fixed-effects-only HEIGHT and WEIGHT NLME models for each sex. As the longitudinal and repeated-measures nature of growth is an important aspect of the present analysis, participants without at least two visit time points were excluded. **Supplement 2.1** depicts the inclusion and exclusion flowchart. Two separate NLME statistical models were applied, one for HEIGHT and one for WEIGHT for each sex. Each analysis reflects the pattern of child growth across the ages of 2 and 20, with an NLME model-fitted to represent the average growth of the population.

Measures

Age and age of diagnosis

A precise date of birth was not provided in the dataset due to patient protection protocols. However, the exact age of diagnosis was provided for a subset of participants,

and disease duration was provided for all participants. Due to the age-dependent nature of growth, only those participants with the exact age of diagnosis were utilized for analysis. Therefore, child age was calculated as age at diagnosis added to the disease duration.

Height

Logically, height cannot decrease across time; however, decreases in height were noted in the dataset. Therefore, decreases in height of up to 2.5 cm were presumed to be due to measurement error and converted to zero. All other height decreases of more than 2.5 cm were deemed physiologically implausible and removed. Mean height is reported by age for each sex in **Tables 2.2A, 2.2B, 2.3A,** and **2.3B**.

Weight

Unlike height, weight can decrease over time. Therefore, weight-related outliers were only removed using ROUT. Mean weight is reported by age for each sex in **Tables 2.2A, 2.2B, 2.3A,** and **2.3B**.

Growth rate

Height velocity was calculated as the difference in height as a ratio to the difference in age between visits. By definition, height velocity cannot be negative. Therefore, any mildly negative height velocity values were converted to zero before analysis (i.e., these resulted from the negative height values of up to -2.5 cm deemed as acceptable measurement error described above, which had remained in the dataset). The height velocity was calculated for a given individual directly from height, and a mean height velocity was reported by age and sex in **Tables 2.2A, 2.2B, 2.3A,** and **2.3B**. The mean PHV and aPHV were also calculated and reported as a single mean value for boys and girls.

Disease Duration

The disease duration was provided in the dataset to the nearest month. Duration was not restricted in the analysis, although 66.1% of children in the dataset were enrolled within one year of diagnosis. Disease duration was explored as an explanatory covariate in the models for any potential relationship between disease duration and growth outcomes.

Blood glucose

The HbA1c was collected within approximately one month of growth metric collection. HbA1c was used as an explanatory covariate to explore any potential relationship between blood glucose control and growth outcomes.

Stunting and Wasting

Z-scores were provided in an already-calculated form from the LEAD Center and were based on CDC 2000 growth charts. Stunting and wasting parameters were calculated based on z-score using height-for-age (HAZ) and weight-for-height (WHZ) z-scores. The severity of stunting and wasting were calculated using the standard deviation (SD) of z-scores with marginal, moderate, and severe stunting classified as -2<HAZ<-1, -3<HAZ<-2, and HAZ<-3, respectively. Similarly, marginal, moderate, and severe wasting was classified as -2<WHZ<-1, -3<WHZ<-2, and WHZ<-3, respectively. Total stunting or wasting was defined as the SD of HAZ or WHZ<-1 (that is, the sum of marginal, moderate, and severe stunting) representative of the rate of each metric at each one-year age interval. Total burdens, which can be thought of as the longitudinal prevalence or the proportion of time with stunting or wasting, were each calculated as the

total number of stunted or wasted cases divided by the total number of person-years across ages 2 to 20 years.

Data Analysis

Statistical Model Selection

Multiple models for child growth analysis have been reported in the literature, but there is no consensus on the ideal model. Physiologically, child growth follows a nonlinear pattern.[25,26] Even Tanner suggested a nonlinear pattern when describing puberty as occurring in "spurts."[27] Nonlinear, rather than linear models, have been reported to model child growth more accurately.[15,28,29] Not only is growth in physical height and weight known to occur "in spurts," it also exhibits a logistic curve pattern. Growth data from children with T1DM in the present dataset is longitudinal. However, the interval between participant samples is inconsistent, and the data is unbalanced. The use of NLME modeling is ideal for unbalanced, repeated measurement data with irregular intervals. Repeated measurements of height and weight are inherently autocorrelated (height at a given timepoint for an individual is related to height at a later timepoint, i.e., not intra-individual independent). Thus, models including random effects (REs), enable the incorporation of individual-to-individual (inter-individual) and within-individual (intra-individual) variability. NLME models enable flexibility for modeling such data signatures by accommodating more than one source of random variability in the data, with the potential for modeling REs of intercepts and slopes.

The variability of REs in nonlinear models has a similar interpretation of residual variance in linear models; that is, if the SD of the RE is high, then the inclusion of the RE does not improve the model. Alternatively, if the SD of the RE decreases, then the

inclusion of the RE contributes to model improvement. This principle and the Akaike Information Criterion (AIC) were utilized to determine the best models. In the present study, models were attempted, including REs for intercepts and slopes and combinations thereof. However, all selected models included REs exclusively for intercepts, as all RE slope models failed to converge, suggesting overparameterization. All models were given initial values to aid in convergence. The best statistical models were chosen based on the ability to converge, model-fit using residuals, evaluation of change in SD with the addition of each coefficient RE, and the lowest AIC. Covariates of interest were added to models for comparison after choosing the best primary RE model for each metric of interest (HEIGHT or WEIGHT). Comparison of the basic fixed effects (BFE) vs. basic random effects (BRE) vs. selected random effects (SRE) models was performed using *post hoc* likelihood ratio tests (LRT) with a Probability > $\chi 2$, and a p-value < 0.05 was considered significant for improvement in model-fit. SRE vs. SRE covariate models (CM) were also compared to identify if the inclusion of explanatory covariates improved model-fit. All data handling, modeling, and model graphing were primarily performed in Stata18, though some graphs were created in GraphPad Prism v10. Graphical depiction of RE models were smoothed using the -*lowess*- command in Stata. The NLME modeling was performed using -*menl* -*, a* function that employs maximum likelihood least-squares regression with error distributions assumed to be Gaussian.

Outlier Detection and Removal

Inter-individual outliers were identified using the ROUT method for nonlinear regression.[24] The *non-ad-hoc* ROUT method was applied to detect inter-individual outliers by fitting each sex-specific BFE -*menl*- model and setting the false discovery rate

Q-value to 1%. All Stata code for the ROUT method and NLME models is provided in **Supplement 2.2.**

HEIGHT and WEIGHT Models

The NLME logistic HEIGHT and WEIGHT models utilized are physiologically relevant and interpretable. The model was proposed by Grimm and Ram[30] et al. in 2007 and applied by Marceau et al.[15] in 2011, hereafter referred to as the Marceau model. The four-coefficient Marceau model enables the calculation of a lower asymptote representing the initial height (or weight), an upper asymptote representing the FAH or asymptotic weight, a growth slope or *tempo* at the inflection point when 50% of growth has occurred, and a centering term which represents the age or timing at this inflection point, commonly considered the age at pubertal takeoff. The statistical formula and a graphical explanation of the models and their coefficients are depicted in **Figure 2.1**.

The basic Marceau model with FEs (i.e., without REs) was used to visualize model prediction and graphing of individual and predicted whole population growth trajectories, run separately for HEIGHT and WEIGHT for each sex. Once a Marceau model for each metric with the inclusion of REs was chosen, this model was used for subsequent analyses involving the potential explanatory covariates of duration and HbA1c. **Table 2.4** depicts the various Marceau models and their reported AICs. Models containing covariates and their statistical comparison are also reported in **Table 2.4**.

RESULTS

Cross-Sectional Analysis Results

Baseline Participant Characteristics

Baseline demographic and anthropomorphic data of participants at enrollment are shown in **Table 2.1**. The analysis study population was 73.5% white, and 81.1% of children had a household member who attended at least some college. The average age at enrollment was 9.9±3.5 years, with an age of diagnosis of 9.0±3.5 years and a mean HbA1c of 7.61±1.41%. The mean birthweight of participants was 3393±589g. **Table 2.1** also reports these metrics by sex.

Descriptive Growth Patterns

The mean annual physical growth parameters for participants aged 2 to 20 are reported for boys in **Tables 2.2A** and **2.2B** and for girls in **Tables 2.3A** and **2.3B**. Included are annual mean metrics for disease duration (years), height (cm), height velocity (HV, cm/year), height z-score, height-for-age z percentile, weight (kg), BMI z-score, BMI z percentile, and HbA1c (%).

As expected, the mean height in boys and girls increased steadily across childhood. In boys and girls, the mean maximal height appears to be reached around age 15-16 years. In the context of height velocity, boys exhibit the expected bi-phasic growth pattern in which a high growth rate is present in early childhood, then levels off until a second growth spurt occurs around 12-14 years and begins to slow after about age 15. In girls, early childhood growth rates were higher than in boys and retained at a higher level, without an apparent growth spurt in the early teens nor a decline in height velocity until after age 13. The calculated mean PHV and aPHV for boys was 5.49±2.37 cm/year at

14.12±3.42 years of age. In girls, the mean PHV was 4.84±2.66 cm/year at 13.39±3.43 years of age.

For z-score metrics, the mean height z-score illustrates normal or above normal average height (HAZ>0) across childhood in both sexes. Similarly, the mean BMI z-score also depicts normal or above normal average weight (WHZ>0) across childhood. However, there is a trend of decreased height z-score in males, but not in females, after age 10. In contrast, the BMI z-score in females increases over time after age 10, but this trend is absent in boys.

Stunting and Wasting Rates

To further investigate descriptive growth phenomena, the stunting and wasting rates were explored and included in **Tables 2.2** and **2.3**. Across both sexes, most stunting and wasting were classified as marginal (-2<HAZ<-1). In boys, stunting rates were highest at younger ages, improved during mid-childhood, and increased again during the late teen years, creating a convex pattern. In girls, a different pattern of increased stunting rates appeared around age 6-7 but declined and reappeared in the early teen years before dropping again in the late teens, creating a concave pattern. For wasting, rates among boys were highest at age 4-7, declined, and then increased again in the late teen years. For girls, wasting rates overall were lower than boys but had similarly high rates during the toddler years. However, wasting rates peaked at age 12 in girls and continued to improve as they approached adulthood. Stunting and wasting rates across ages 2 to 20 years are depicted in graphical form in **Figure 2.2**. The total burden of stunting (HAZ<-1) and wasting (WHZ<-1) in males was calculated to be 8.35% and 6.85%, respectively, and 8.89% and 4.38% in females.

Blood Glucose Control

In boys and girls, mean HbA1c was largely stable from ages 3 to 8; however, began to climb thereafter (**Table 2.3A and 2.3B**). Girls had more significant increases in blood glucose at an earlier age than boys, with girls having a mean HbA1c above ~8.3% by age 11. However, boys did not exceed ~8.3% until age ~13 years. Further, girls had a mean HbA1c of 9.6% in their 19th year compared with 9.0% in boys.

Longitudinal Analysis Results

As discussed, growth in children is nonlinear. As such, the exploration of descriptive patterns and population averages is inadequate for understanding the complexities of growth. Further, such cross-sectional analysis has limited utility for studying any potential impacts of explanatory variables (covariates) on longitudinal growth outcomes. Therefore, NLME models were developed to enable a more precise assessment of height and weight trajectories across time.

Fixed Effects Model Results

For height in boys, the BFE model (i.e., without REs) resulted in a height *tempo* slope coefficient (α) of +0.309 at the age at takeoff *timing* (λ) of 9.3 years of age. The initial height (β_0) was 92cm, and the FAH (β_1) was 183 cm. For height in girls, the BFE model reported a higher slope (α) of +0.408 at an earlier age (λ) of 8.2 years compared to boys. The initial height in girls was higher than in boys, with a β_0 of 94 cm and an expected lower FAH (β_1) of 167 cm.

For weight in boys, the BFE model resulted in a weight *tempo* slope coefficient (α) of +0.360 at a *timing* (λ) of 12.2 years of age. The initial weight (β_0) was 16.3 kg with an asymptotic weight of 81.2 kg. Weight in girls had a slope (α) of +0.424 with a *timing*

takeoff (λ) of 11.3 years. In girls, the initial weight (β_0) was 17.1 kg, and the final weight (β_1) was 72.3 kg.

Results for each BFE HEIGHT and WEIGHT model are reported in **Table 2.4.**

Random Effects Model Results

All models which included REs for slope, failed to converge. However, models including REs for intercepts, converged well. Values for each coefficient in the models and the AICs are presented in **Table 2.4.** After consideration of models including intercept REs for each coefficient and combinations thereof, a SRE intercept model which enabled all four coefficients (β_0, β_1, λ, and α) to vary by each individual participant in the HEIGHT and WEIGHT models each resulted in the best (lowest) AIC. The inclusion of intercept REs resulted in the improvement of model-fit AIC in both HEIGHT and WEIGHT models over BFE and BRE models. All RE models exhibited statistical improvement of model-fit by LRT over BFE models (p=0.000).

The SRE models are plotted for males and females in **Figures 2.3** and **2.4,** respectively. These plots depict individual growth trajectories in light gray (n=710 male, n=806 female). The solid black line represents the predicted mean of the SRE trajectory by sex using each associated NLME model for HEIGHT or WEIGHT.

For height in boys, the SRE model reported a height *tempo* slope (α) of +0.331, age of takeoff (λ) of 9.6 years, initial height of 96 cm, and FAH (β_1) of 182 cm. For height in girls, the SRE model reported a higher *tempo* slope (α) of +0.460 than boys but at an earlier *timing* age (λ) of 8.6 years. The initial height in girls was higher than in boys, with a β_0 of 98.7 cm but an expected lower FAH (β_1) of 166 cm.

For weight in boys, the SRE weight *tempo* slope (α) was +0.416 at a *timing* age (λ) of 12.2 years, with an initial weight (β_0) of 17.8 kg and a final weight (β_1) of 79.0 kg. The weight slope (α) was higher in girls than boys at +0.495 at a takeoff age (λ) of 11.3 years. In girls, initial and final weight, β_0 and β_1, was 17.6 kg and 71.4 kg, respectively.

These age of takeoff (λ) results illustrate that height takeoff precedes weight takeoff by ~2.5 years in both girls and boys.

Covariate Model Hypothesis Testing

Poor glycemic control (as measured by HbA1c) and disease duration are hypothesized to negatively impact growth outcomes in children with T1DM. To explore this, these two factors were investigated as explanatory variables (covariates) in each resulting SRE HEIGHT and WEIGHT model for each sex. The impacts of each covariate on each available coefficient (β_0, β_1, λ, and α) were explored in each SRE model. These data are presented in **Table 2.4**, and impacts on FAH (β_1) are graphed in **Figures 2.5** and **2.6**. Coefficients for the initial height, β_0, were not explored as the average age of diagnosis was ~10 years. Comparisons of SRE models with and without each covariate were evaluated for model improvement by LRT and the results are reported in **Table 2.4.**

HbA1c Covariate

Exploration of the hypothesized impact of the HbA1c covariate on the upper height asymptote (β_1) in boys resulted in a coefficient term of -0.339, suggesting that for every 1% increase in HbA1c, FAH was reduced by 0.339 cm. In girls, this coefficient was -0.209, suggesting that for every 1% increase in HbA1c, FAH was reduced by 0.209. For weight in boys, the coefficient term was -1.496, suggesting that for every 1% increase in HbA1c, the upper asymptotic weight was reduced by 1.496 kg. In girls, this

value was -1.146, suggesting that for every 1% increase in HbA1c, the upper asymptotic weight was reduced by 1.146. All SRE β1 covariate models for HEIGHT and WEIGHT significantly differed from the SRE model without covariates as determined by LRT ($p<0.009$). The results suggest that HbA1c may have some impact on FAH and asymptotic weight in children with T1DM.

The HbA1c covariate impact on the slope *tempo* (α) on height was nearly zero in males and females at -0.001 and +0.008, respectively, suggesting that blood glucose control has no impact on height *tempo*. The LRT for the α HEIGHT covariate model in girls was statistically different from the SRE model ($p<0.001$), indicating model improvement with the inclusion of the HbA1c covariate for *tempo*. The impact of HbA1c on weight *tempo* in boys was -0.010 with model-fit $p<0.004$. This value was +0.009 in girls, but the model-fit was insignificant with $p=1.000$. Taken together, HbA1c may improve model-fit, but near-zero coefficient values suggest little impact of HbA1c on height or weight *tempo*.

Finally, the HbA1c covariate for height *timing* (λ) resulted in a coefficient of +0.029 in males and +0.011 in females, suggesting that for each 1% increase in HbA1c, the *timing* of age of height takeoff was delayed by just 11 and 4 days in males and females, respectively. As such, there was no significant difference in the LRT between the SRE model and the height *timing* HbA1c covariate model in either sex. For the HbA1c covariate for weight, the *timing* coefficient (λ) resulted in longer delays with coefficients of +0.144 and +0.085 in males and females, suggesting delays of 53 and 31 days per 1% increase in HbA1c, respectively. These weight *timing* models were

statistically significantly different from the SRE model ($p<0.002$). However, whether this slight timing delay is physiologically relevant is questionable.

Graphical depictions of the impact of the HbA1c covariate on FAH can be seen in **Figure 2.5**. This graph has been restricted in scale to enable visualization of the differences in FAH. Note that despite negative coefficients for height β_1 in boys and girls, and the detection of model improvement with the inclusion of the HbA1c covariate, there is little graphical impact of HbA1c on FAH in either sex.

Disease Duration Covariate

The disease duration covariate produced more strongly negative coefficient values for FAH in both sexes than the HbA1c covariate but did not affect *tempo* and *timing* of height. Duration as a covariate for β_1 resulted in an FAH coefficient of -0.666 and -0.773 in males and females, suggesting that FAHs were reduced by 0.695 and 0.798 cm, respectively, for each additional year of disease duration. LRT showed statistical significance compared with SRE models in boys and girls for duration as a covariate for FAH ($p=0.000$). Graphs of the disease duration covariate on FAH can be seen in **Figure 2.5** alongside the HbA1c covariate model. To provide physiological context, **Figure 2.6** depicts in-sample covariate model predictions with 2, 4, 6, and 8-year disease durations for FAH in boys and girls. Too few participants had durations beyond 8 years to explore longer duration prediction impacts due to the average age of diagnosis of ~10 years.

Duration as a covariate for male upper asymptotic weight (β_1) resulted in a coefficient of -1.006, which was statistically different from the SRE model via LRT ($p=0.000$). The duration covariate model for the female upper asymptotic weight (β_1) was -1.111 ($p=0.000$).

The duration covariate impact on the height *tempo* (α) in males were, as with HbA1c, nearly unaffected with coefficient terms of +0.002 (p=1.000). The height *tempo* model failed to converge for females. The duration covariate models for male weight *tempo* (α) resulted in a coefficient of +0.014 but did not improve the model-fit (p=1.000). For girls, this coefficient was +0.021 but was significant (p=0.000). Duration covariates for height *timing* (λ) coefficients in males and females were +0.070 and +0.063, respectively; however, neither model was significant for improving the model-fit. Finally, the model for the duration covariate for weight impacts on *timing* (λ) was +0.093 and +0.072 in males and females, respectively, but both resulted in no improvement in model-fit (p=1.000).

Together, these results suggest that disease duration has more impact on FAH than HbA1c, though HbA1c may have more impact on asymptotic weight than duration. However, both explanatory covariates have little impact on the *tempo* or *timing* of height or weight.

DISCUSSION

Obesity has been a primary focus of much of the research conducted relative to children with diabetes. We chose height growth as the primary focus of the present analysis, with particular attention on potential negative height outcomes. In the presented analysis, both cross-sectional and longitudinal data were investigated. The analysis presented here provides important information about the complex growth dynamics in children with T1DM. In addition to cross-sectional mean annual growth metrics, stunting and wasting metrics were explored. Next, we plotted individual growth trajectories overlaid with NLME models for HEIGHT and WEIGHT to enable visualization and

calculation of average growth metrics in this population. Finally, we explored HbA1c and disease duration as explanatory covariates for potential impacts on growth metrics.

Pediatric growth charts developed by the CDC from cross-sectional population data are relied upon for individual patient monitoring. In our analysis, we chose to explore stunting and wasting using z-scores. Of note, the CDC does not have guidance for stunting and wasting based on z-scores, but instead, describes just two categories: *underweight* and *short stature,* defined as $<5^{th}$ percentiles. However, these are intended for cross-sectional population-wide surveillance, not for understanding the potential growth dynamics of a specific disease-state. Similarly, the WHO defines stunting and wasting as height or weight as -2SD below the population mean. We argue that CDC and WHO definitions are not appropriate or sensitive enough to detect alterations of growth patterns relevant to the individual participant in the clinical setting. As such, we expanded our analysis categories to include *marginal, moderate, and severe* stunting and wasting categories. These categories enabled more sensitive detection and a clearer understanding of this population's potential growth abnormalities.

Utilizing the three categories, we found many children with stunting and wasting rates in the marginal categories, which may have been missed using CDC or WHO definitions. While it is true that most children in this study population were normal or above normal for height and weight, detecting at-risk children is critically important for early clinical intervention. The high *marginal* stunting rates in boys are particularly concerning, though the NLME model predicted FAH exceeding NHANES at-large American population means.[31] Still, this does not mean that stunting and wasting are not clinical concerns in T1DM, as FAH is but one metric. Stunting and wasting can have

short-term impacts on health, such as increased risk for infection[32] and decreased cognitive development.[33] Long-term impacts include increased risks for chronic diseases,[34] obesity,[35] and decreased bone density.[36] Further, alteration of pubertal patterns may contribute to social and mental health abnormalities.[37] Whether the stunting and wasting in this population contribute to the long-term adverse diabetic-specific health outcomes in individuals with T1DM is unknown. Nonetheless, even temporary alterations of growth patterns are clinically relevant. Critically, close monitoring and early detection of stunting and wasting may enable mitigation of any potential long-term negative health consequences.

The present longitudinal analysis was accomplished using a physiologically relevant and interpretable NLME model. The classical use of linear regression or analysis of variance (ANOVA) is inappropriate for the nonlinear patterns of longitudinal child growth. Polynomial modeling is common but does not enable physiological interpretability; the coefficients do not provide clinically translatable values. Therefore, we chose an NLME model for several reasons. First, logistical modeling has long been used to understand the complex dynamics of biological growth.[38] Second, utilizing a mixed-effects model provided flexibility to accommodate inter- and intra-individual differences in growth across time. Our SRE versus BFE models showed clear improvement as detected by AIC and *post hoc* model-fit analysis. Third, the coefficients in nonlinear regression could be interpreted similarly to linear regression. That is, interpretation is dependent on the context and units of measure. In the present study, the Marceau model utilized readily available, non-subjective, and commonly collected

metrics of clinical health, namely height (cm), weight (kg), and age (years). The outcome coefficients could be directly interpreted in these same unit measures.

The metrics of primary clinical importance in our NLME model are arguably the FAH (β_1) and age at takeoff (λ), as these metrics are readily available for the U.S. population. A review published by Abbassi in the journal Pediatrics in 1998 compiled growth data from multiple cross-sectional and longitudinal studies of U.S. children[39] and will be used for comparison here.

The mean FAH reported by Abbassi was ~177 cm and ~161 cm for boys and girls, respectively,[31] lower than the ~182 cm and ~165 cm (β_1) heights reported in our SRE model analysis, suggesting that our study population may be taller than the U.S. population at large. Interestingly, our SRE model reported an age of takeoff (λ) of 9.6 years for boys and 8.6 years for girls, which differs with the reported age of takeoff in U.S. children of ~11 and 9 years.[39] The earlier age of takeoff could explain an increased FAH, that is, if growth began earlier and was sustained for longer, perhaps altering the *tempo*. While the *tempo* (α) slope was an important metric produced by our model, unfortunately, it can only be determined from longitudinal and not cross-sectional analysis, which makes comparison to U.S. child growth data impossible without running a corresponding NLME model. Notably, this population's mean age of diagnosis was 9.4 years in males and 8.8 years in females, corresponding closely with the model prediction of age of takeoff of 9.6 and 8.6 years for boys and girls, respectively. Whether an earlier age of takeoff for this population compared with the U.S. population at large is related to disease onset is indeed interesting.

An additional benefit of NLME modeling is the ability to test covariates of interest in models for hypothesized impacts on each growth-specific coefficient. Covariate coefficients in NLME have the utility to not only explore negative versus positive effects on an outcome but also share straightforward interpretations in terms of unit measure. For example, the HbA1c covariate models produced negative height and weight coefficients for FAH and exhibited statistically significant improvement in model-fit as determined by LRT. However, centimeter units were used in the NLME models, and as such, coefficient values for β_1, while negative, were small, suggesting little physiological impact of HbA1c on FAH. Further, graphing of the complete HbA1c covariate height model showed almost no difference compared with the SRE model.

We are not the first to hypothesize that disease duration and lack of blood glucose control may negatively impact growth in children with T1DM. Work by Holl et al. suggested that age of diagnosis and long-term metabolic control reduce height and delay growth, concluding that reaching FAH depended on whether T1DM was diagnosed before or after puberty.[11] Others have also reported that growth is more impacted in children diagnosed before puberty.[12] Indeed, our data support this conclusion, as longer disease duration was associated with lower FAH (β_1) and delayed age at takeoff (λ). Importantly, our modeling enabled the quantification of these effects using covariate models.

For duration as a covariate, coefficient values were more strongly negative than HbA1c as a covariate. Graphing of duration supported a larger physiologic impact on FAH than HbA1c. Further, utilization of the principle of coefficient interpretability enabled quick estimates of the impact of duration on FAH. For example, assuming a child

has reached their FAH and has had T1DM for 6 years, with a duration coefficient of -0.7 cm (i.e., the FAH is reduced by 0.7 cm for each year of disease duration), this results in a child that is predicted to be 0.7 X 6 cm = 4.2 cm = ~1.5 inches shorter. The authors propose that this level of estimated reduction in height for the average child with T1DM is physiologically and clinically relevant. Indeed, the fact that any effect is detectable is critical to understand, as growth is widely accepted as a sensitive metric of child health.

HbA1c and disease duration as covariates are arguably multicollinear. As such, we explored each separately as explanatory variables to clarify their respective influences. However, the true impact of HbA1c may logically be "hidden" within the disease duration. It is conceivable that the more substantial impact of duration on FAH than HbA1c on FAH is related to "metabolic load," that is, exposure to higher blood glucose levels for longer. Future modeling could explore this relationship, among other potential covariates, such as the potential impacts of diet. Importantly, our code is provided so that others can compare their data using the NLME modeling.

Several limitations of the present analysis must be acknowledged. First, we acknowledge that no attempts were made to control for any socioeconomic or demographic factors in the NLME modeling. Future use of these modeling methods should incorporate appropriate controls to ensure that model predictions are accurate relative to physiologic outcomes.

Second, due to patient protection protocols, the dataset did not provide exact birth dates for participants. Ages were provided for all participants but were unfortunately rounded down to the nearest year. Knowledge of the exact age is critical for model-fit and accuracy. Fortunately, one of the later cohorts reported the exact disease duration and age

of diagnosis, making the calculation of the exact age possible for a subset of participants. Unfortunately, this reduced the participant population for analysis by approximately half. However, even after outlier removal, our analysis contained a robust number of approximately 1500 participants.

Third, while Tanner scores were included in the provided dataset, exploration indicated a high number of missing data points and a severely limited number of participants with repeated measures of the metric. Attempts at longitudinal NLME model development using Tanner scores failed. Of note, Marceau et al.,[15] which utilized the Tanner metric for NLME modeling, had access to annual Tanner scores across childhood. Further, while Tanner data was provided in our dataset more consistently for females (due to a precise date of menarche), no data on male spermarche was provided. Therefore, to enable sex-specific analysis of growth metrics, models in the present analysis were instead developed with the available measures of height and weight.

Fourth, PHV and aPHV were determined by cross-sectional analysis of our data outside our NLME models. For velocity metrics, we reported a PHV at aPHV of 5.5 cm/year at 14 years for boys and 4.9 cm/year at 13.3 years for girls. Abbassi[39] reported much higher PHVs of 9.5 cm/year at 13.5 years and 8.3 cm/year at 11.5 years for girls in the at-large U.S. population. While interesting, we must use caution here. Importantly, our data's PHV and aPHV metrics were cross-sectional, and visit time points were infrequent. The average age at diagnosis and enrollment was ~10 years, with the next visit at the five-year follow-up. It is plausible that the PHV was not captured in all participants, making the cross-sectional analysis of PHV and aPHV inaccurate. To overcome this limitation, a height velocity analysis was attempted using NLME

methodology, but while models could converge, model-fit was inaccurate and unable to find the required peak.

Finally, a limitation of this study is the lack of direct comparison to child populations without T1DM. As discussed, our models cannot compare directly to clinical CDC growth charts as the charts were developed using cross-sectional and not longitudinal data. However, we propose that our model can be utilized as longitudinal data becomes available from studies such as the Environmental Influences on Child Health Outcomes (ECHO) study.[40]

CONCLUSION

Clinical awareness of stunting and wasting rates in children with T1DM is important. However, despite higher blood glucose levels than current ADA recommendations, NLME modeling suggests that FAHs are similar to, or taller, than U.S. children without T1DM. Modeling also suggested that the age at pubertal takeoff was earlier in children with T1DM than reports of those without, suggesting that the disease may impact pubertal growth patterns. Exploration of covariate models for blood glucose control as measured by the HbA1c predicted minor decreases in FAH but no impacts on *timing* and *tempo* of height growth. Disease duration as a covariate also showed no impact on the *timing* and *tempo* of height growth. However, disease duration covariate models predicted reductions in FAH, which may be clinically relevant.

TABLES

Table 2.2A

Table 2.2A. Mean characteristics of boys aged 2 to 10 years old in one year increments.

Age (year)	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
No. participants (n)	1	26	41	68	73	100	119	131	140
					Mean and (SD)				
duration of disease (years)	.	0.71 (0.50)	0.94 (0.71)	1.23 (0.85)	1.49 (1.16)	1.53 (1.12)	2.48 (2.00)	2.43 (2.14)	2.83 (2.28)
height (cm)	.	100.32 (5.42)	108.79 (6.50)	114.54 (5.24)	121.40 (5.45)	127.23 (5.18)	132.89 (6.10)	139.42 (6.32)	144.40 (6.33)
height velocity (cm/year)	.	.	6.72 (3.02)	6.62 (1.92)	6.29 (1.45)	5.87 (1.48)	6.07 (1.64)	5.88 (1.12)	5.39 (0.95)
height z-score	.	0.09 (1.20)	0.53 (1.27)	0.32 (1.00)	0.40 (0.98)	0.36 (0.87)	0.25 (0.96)	0.45 (0.94)	0.45 (0.88)
height z percentile	.	50.90 (32.58)	61.72 (32.36)	59.02 (28.59)	61.07 (28.00)	61.41 (26.22)	57.01 (28.41)	63.31 (27.68)	62.95 (26.36)
weight (kg)	.	16.49 (2.22)	19.24 (2.79)	21.74 (3.28)	24.31 (4.17)	26.96 (3.87)	30.93 (5.89)	35.41 (6.94)	40.21 (8.45)
BMI z-score	.	0.41 (0.92)	0.46 (0.92)	0.59 (1.05)	0.44 (0.85)	0.39 (0.88)	0.47 (0.89)	0.52 (0.89)	0.61 (0.90)
BMI z percentile	.	64.23 (27.25)	63.52 (27.13)	67.19 (28.26)	63.44 (25.41)	62.59 (25.77)	63.87 (25.71)	65.95 (25.01)	67.60 (26.04)
HbA1c (%)	.	7.67 (0.87)	7.84 (1.13)	7.86 (1.10)	7.88 (1.17)	7.88 (1.36)	7.87 (1.18)	7.77 (1.19)	8.00 (1.50)
					n and (%)				
Stunting (HAZ)									
Above Normal Height (HAZ>0)	.	13 (50.0%)	28 (68.3%)	43 (63.2%)	49 (67.1%)	67 (67.0%)	65 (54.6%)	90 (68.7%)	93 (66.4%)
Normal Height (-1<HAZ<0)	.	8 (30.8%)	7 (17.1%)	18 (26.5%)	15 (20.5%)	26 (26.0%)	46 (38.7%)	32 (24.4%)	40 (28.6%)
Marginally Stunted (-2<HAZ<-1)	.	4 (15.4%)	6 (14.6%)	7 (10.3%)	9 (12.3%)	7 (7.0%)	7 (5.9%)	9 (6.9%)	7 (5.0%)
Moderately Stunted (-3<HAZ<-2)	.	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
Severely Stunted (HAZ<-3)	.	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total Stunted (HAZ<-1)	**.**	**5 (19.2%)**	**6 (14.6%)**	**7 (10.3%)**	**9 (12.3%)**	**7 (7.0%)**	**8 (6.7%)**	**9 (6.9%)**	**7 (5.0%)**
Wasting (WHZ)									
Above Normal Weight (HAZ>0)	.	18 (69.2%)	29 (70.7%)	52 (76.5%)	54 (74.0%)	71 (71.0%)	87 (73.1%)	100 (76.3%)	102 (72.9%)
Normal Weight (-1<WHZ<0)	.	6 (23.1%)	8 (19.5%)	8 (11.8%)	14 (19.2%)	21 (21.0%)	25 (21.0%)	24 (18.3%)	30 (21.4%)
Marginally Wasted (-2<WHZ<-1)	.	1 (3.8%)	4 (9.8%)	7 (10.3%)	5 (6.8%)	7 (7.0%)	7 (5.9%)	6 (4.6%)	8 (5.7%)
Moderately Wasted (-3<WHZ<-2)	.	1 (3.8%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Severely Wasted (WHZ<-3)	.	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total Wasted (WHZ<-1)	**.**	**2 (7.7%)**	**4 (9.8%)**	**8 (11.8%)**	**5 (6.8%)**	**8 (8.0%)**	**7 (5.9%)**	**7 (5.3%)**	**8 (5.7%)**

HAZ, height-for-age z-score. WHZ, weight-for-height z-score

Table 2.2B

Table 2.2B. Mean characteristics of boys aged 10 to 20 years old in one year increments.

Age (year)	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
No. participants (n)	177	146	189	167	176	147	140	119	113
					Mean and (SD)				
duration of disease (years)	3.33 (2.66)	3.45 (2.83)	4.26 (3.20)	4.24 (3.18)	5.10 (3.30)	5.48 (3.38)	6.52 (3.47)	7.11 (3.34)	8.23 (3.75)
height (cm)	150.34 (7.00)	157.03 (7.73)	164.04 (7.51)	169.07 (6.38)	172.83 (6.32)	176.24 (6.79)	176.09 (6.38)	177.55 (6.35)	176.14 (6.42)
height velocity (cm/year)	5.75 (1.31)	6.44 (2.16)	6.34 (1.47)	6.38 (1.60)	5.18 (1.73)	3.74 (1.91)	2.81 (1.83)	1.70 (1.48)	1.09 (1.22)
height z-score	0.54 (0.94)	0.56 (0.99)	0.49 (0.90)	0.24 (0.79)	0.14 (0.82)	0.24 (0.94)	0.05 (0.89)	0.16 (0.89)	-0.08 (0.90)
height z percentile	64.80 (27.37)	65.23 (27.90)	64.17 (26.50)	57.41 (24.82)	54.15 (26.14)	56.83 (28.25)	51.32 (27.58)	54.03 (27.30)	46.61 (27.50)
weight (kg)	43.97 (8.91)	49.30 (9.93)	55.90 (10.47)	60.97 (9.70)	67.37 (11.76)	71.93 (11.65)	73.59 (12.47)	73.97 (10.97)	75.71 (11.98)
BMI z-score	0.47 (0.90)	0.39 (0.98)	0.44 (0.88)	0.44 (0.80)	0.52 (0.90)	0.50 (0.91)	0.44 (1.03)	0.22 (0.93)	0.29 (1.04)
BMI z percentile	64.52 (26.30)	62.31 (27.69)	63.75 (25.69)	63.97 (24.73)	65.42 (26.55)	65.62 (26.05)	62.94 (28.69)	56.50 (28.51)	59.45 (28.22)
HbA1c (%)	8.16 (1.24)	8.03 (1.58)	8.30 (1.51)	8.62 (2.09)	8.56 (1.87)	8.51 (1.54)	8.97 (2.17)	8.97 (2.02)	9.00 (1.84)
					n and (%)				
Stunting (HAZ)									
Above Normal Height (HAZ>0)	118 (66.7%)	109 (74.7%)	130 (68.8%)	110 (65.9%)	91 (51.7%)	85 (57.8%)	74 (52.9%)	64 (53.8%)	50 (44.2%)
Normal Height (-1<HAZ<0)	54 (30.5%)	27 (18.5%)	49 (25.9%)	46 (27.5%)	71 (40.3%)	46 (31.3%)	48 (34.3%)	44 (37.0%)	43 (38.1%)
Marginally Stunted (-2<HAZ<-1)	5 (2.8%)	10 (6.8%)	10 (5.3%)	11 (6.6%)	14 (8.0%)	15 (10.2%)	18 (12.9%)	11 (9.2%)	20 (17.7%)
Moderately Stunted (-3<HAZ<-2)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severely Stunted (HAZ<-3)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total Stunted (HAZ<-1)	**5 (2.8%)**	**10 (6.8%)**	**10 (7.6%)**	**11 (6.5%)**	**14 (8.0%)**	**16 (10.9%)**	**18 (12.9%)**	**11 (9.2%)**	**20 17.7%)**
Wasting (WHZ)									
Above Normal Weight (HAZ>0)	127 (71.8%)	101 (69.2%)	135 (71.4%)	116 (69.5%)	127 (72.2%)	108 (73.5%)	98 (70.0%)	73 (61.3%)	75 (66.4%)
Normal Weight (-1<WHZ<0)	38 (21.5%)	35 (24.0%)	45 (23.8%)	41 (24.6%)	39 (22.2%)	30 (20.4%)	31 (22.1%)	33 (27.7%)	29 (25.7%)
Marginally Wasted (-2<WHZ<-1)	11 (6.2%)	7 (4.8%)	7 (3.7%)	9 (5.4%)	9 (5.1%)	7 (4.8%)	8 (5.7%)	13 (10.9%)	6 (5.3%)
Moderately Wasted (-3<WHZ<-2)	0 (0.0%)	2 (1.4%)	2 (1.1%)	1 (0.6%)	1 (0.6%)	2 (1.4%)	2 (1.4%)	0 (0.0%)	1 (0.9%)
Severely Wasted (WHZ<-3)	1 (0.6%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	2 (1.8%)
Total Wasted (WHZ<-1)	**12 (6.8%)**	**10 (6.8%)**	**9 (4.8%)**	**10 (6.0%)**	**10 (5.7%)**	**9 (6.1%)**	**11 (7.9%)**	**13 (10.9%)**	**9 (8.0%)**

HAZ, height-for-age z-score. WHZ, weight-for-height z-score

Table 2.3A

Table 2.3A. Mean characteristics of girls aged 2 to 10 years old in one year increments.

Age (year)	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
No. participants (n)		27	54	87	98	121	115	150	178
					Mean and (SD)				
duration of disease (years)	.	0.87 (0.54)	0.81 (0.66)	1.17 (0.86)	1.34 (0.93)	1.75 (1.29)	2.06 (1.74)	2.58 (2.09)	2.87 (2.44)
height (cm)	.	99.58 (4.79)	106.71 (5.30)	113.39 (4.55)	119.84 (5.48)	125.86 (5.34)	132.56 (5.89)	138.61 (6.57)	145.36 (7.03)
height velocity (cm/year)	.	. (.)	7.03 (1.09)	6.85 (1.09)	6.16 (1.43)	5.87 (1.56)	6.20 (2.65)	6.09 (1.12)	6.24 (1.49)
height z-score	.	0.40 (0.93)	0.49 (0.89)	0.38 (0.81)	0.24 (1.01)	0.17 (0.89)	0.31 (0.85)	0.42 (0.94)	0.54 (0.94)
height z percentile	.	59.70 (24.26)	63.31 (24.91)	61.40 (24.81)	57.98 (29.67)	55.37 (27.38)	58.85 (25.05)	61.94 (27.57)	65.31 (26.38)
weight (kg)	.	17.13 (5.44)	19.09 (4.59)	21.98 (4.57)	23.82 (3.78)	27.08 (5.43)	30.60 (5.47)	35.83 (7.43)	41.07 (9.11)
BMI z-score	.	0.69 (1.19)	0.60 (1.07)	0.75 (1.03)	0.48 (0.94)	0.44 (0.91)	0.39 (0.88)	0.55 (0.82)	0.50 (0.93)
BMI z percentile	.	67.87 (27.30)	66.48 (29.17)	69.37 (27.04)	65.08 (25.52)	62.23 (26.88)	62.09 (26.26)	66.80 (23.65)	64.85 (26.90)
HbA1c (%)	.	7.81 (1.02)	8.04 (1.18)	7.86 (1.12)	7.84 (1.06)	7.76 (1.14)	7.85 (1.27)	8.07 (1.38)	8.01 (1.32)
					n and (%)				
Stunting (HAZ)									
Above Normal Height (HAZ>0)	.	17 (63.0%)	37 (68.5%)	61 (70.1%)	61 (62.2%)	67 (55.4%)	72 (62.6%)	99 (66.0%)	127 (71.3%)
Normal Height (-1<HAZ<0)	.	10 (37.0%)	16 (29.6%)	24 (27.6%)	24 (24.5%)	41 (33.9%)	37 (32.2%)	41 (27.3%)	38 (21.3%)
Marginally Stunted (-2<HAZ<-1)	.	0 (0.0%)	1 (1.9%)	2 (2.3%)	12 (12.2%)	13 (10.7%)	6 (5.2%)	10 (6.7%)	13 (7.3%)
Moderately Stunted (-3<HAZ<-2)	.	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severely Stunted (HAZ<-3)	.	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total Stunted (HAZ<-1)	**.**	**0 (0.00%)**	**1 (1.9%)**	**2 (2.3%)**	**13 (13.2%)**	**13 (10.7%)**	**6 (5.2%)**	**10 (6.7%)**	**13 (7.3%)**
Wasting (WHZ)									
Above Normal Weight (HAZ>0)	.	19 (70.4%)	39 (72.2%)	65 (74.7%)	70 (71.4%)	78 (64.5%)	79 (68.7%)	110 (73.3%)	131 (73.6%)
Normal Weight (-1<WHZ<0)	.	6 (22.2%)	11 (20.4%)	18 (20.7%)	23 (23.5%)	37 (30.6%)	30 (26.1%)	35 (23.3%)	36 (20.2%)
Marginally Wasted (-2<WHZ<-1)	.	2 (7.4%)	4 (7.4%)	4 (4.6%)	2 (2.0%)	6 (5.0%)	5 (4.3%)	4 (2.7%)	10 (5.6%)
Moderately Wasted (-3<WHZ<-2)	.	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.1%)	0 (0.0%)	1 (0.9%)	1 (0.7%)	1 (0.6%)
Severely Wasted (WHZ<-3)	.	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total Wasted (WHZ<-1)	**.**	**2 (7.4%)**	**4 (7.4%)**	**4 (4.6%)**	**5 (5.1%)**	**6 (5.0%)**	**6 (5.2%)**	**5 (3.3%)**	**11 (6.2%)**

HAZ, height-for-age z-score. WHZ, weight-for-height z-score

Table 2.3B

Table 2.3B. Mean characteristics of girls aged 10 to 20 years old in one year increments.

Age (year)	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
No. participants (n)	226	231	199	181	157	165	161	131	138
	Mean and (SD)								
duration of disease (years)	3.40 (2.66)	3.47 (2.89)	4.37 (3.26)	5.12 (3.25)	5.68 (3.05)	6.23 (3.35)	7.31 (3.38)	8.08 (3.32)	8.73 (3.29)
height (cm)	150.91 (7.40)	156.99 (6.71)	160.21 (5.99)	162.32 (6.60)	164.36 (5.79)	164.00 (6.43)	165.16 (6.03)	163.87 (6.70)	165.50 (6.54)
height velocity (cm/year)	6.16 (1.55)	6.13 (1.63)	4.68 (1.86)	3.96 (1.93)	2.73 (1.60)	1.78 (1.44)	1.00 (0.92)	0.67 (0.95)	0.50 (0.74)
height z-score	0.43 (0.96)	0.35 (0.93)	0.16 (0.89)	0.16 (1.00)	0.32 (0.90)	0.19 (0.99)	0.33 (0.93)	0.11 (1.03)	0.34 (1.01)
height z percentile	62.40 (28.56)	60.23 (27.30)	54.28 (26.67)	54.19 (29.11)	59.50 (26.32)	55.48 (28.13)	59.20 (27.43)	52.27 (29.53)	59.29 (28.46)
weight (kg)	45.29 (10.22)	49.96 (9.50)	58.61 (10.96)	61.28 (10.87)	65.93 (10.90)	67.14 (10.08)	68.89 (11.89)	67.99 (12.62)	70.85 (12.51)
BMI z-score	0.42 (0.93)	0.37 (0.97)	0.81 (0.85)	0.77 (0.79)	0.89 (0.72)	0.90 (0.70)	0.81 (0.79)	0.72 (0.82)	0.79 (0.78)
BMI z percentile	62.77 (27.15)	62.19 (27.02)	73.46 (24.44)	73.25 (22.74)	76.84 (20.29)	77.12 (19.50)	75.25 (20.72)	72.31 (23.74)	74.47 (22.40)
HbA1c (%)	8.35 (1.60)	8.31 (1.75)	8.41 (1.83)	8.75 (1.90)	8.88 (1.62)	9.03 (2.12)	9.13 (1.97)	9.22 (2.28)	9.65 (2.30)
	n and (%)								
Stunting (HAZ)									
Above Normal Height (HAZ>0)	156 (69.0%)	154 (66.7%)	112 (56.3%)	102 (56.4%)	94 (59.9%)	97 (58.8%)	100 (62.1%)	70 (53.4%)	84 (60.9%)
Normal Height (-1<HAZ<0)	51 (22.6%)	56 (24.2%)	69 (34.7%)	52 (28.7%)	53 (33.8%)	50 (30.3%)	50 (31.1%)	42 (32.1%)	40 (29.0%)
Marginally Stunted (-2<HAZ<-1)	19 (8.4%)	21 (9.1%)	18 (9.0%)	25 (13.8%)	9 (5.7%)	16 (9.7%)	11 (6.8%)	17 (13.0%)	12 (8.7%)
Moderately Stunted (-3<HAZ<-2)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.1%)	1 (0.6%)	2 (1.2%)	0 (0.0%)	2 (1.5%)	2 (1.4%)
Severely Stunted (HAZ<-3)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total Stunted (HAZ<-1)	**19 (8.4%)**	**21 (9.1%)**	**18 (9.0%)**	**27 (14.9%)**	**10 (6.3%)**	**18 (10.9%)**	**11 (6.8%)**	**19 (14.5%)**	**14 (10.1%)**
Wasting (WHZ)									
Above Normal Weight (HAZ>0)	159 (70.4%)	155 (67.1%)	162 (81.4%)	156 (86.2%)	143 (91.1%)	147 (89.1%)	141 (87.6%)	107 (81.7%)	117 (84.8%)
Normal Weight (-1<WHZ<0)	51 (22.6%)	56 (24.2%)	30 (15.1%)	19 (10.5%)	11 (7.0%)	16 (9.7%)	18 (11.2%)	20 (15.3%)	18 (13.0%)
Marginally Wasted (-2<WHZ<-1)	14 (6.2%)	18 (7.8%)	7 (3.5%)	6 (3.3%)	3 (1.9%)	2 (1.2%)	0 (0.0%)	4 (3.1%)	2 (1.4%)
Moderately Wasted (-3<WHZ<-2)	2 (0.9%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.2%)	0 (0.0%)	1 (0.7%)
Severely Wasted (WHZ<-3)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total Wasted (WHZ<-1)	**16 (7.1%)**	**20 (8.7%)**	**7 (3.5%)**	**6 (3.3%)**	**3 (1.9%)**	**2 (1.2%)**	**2 (1.2%)**	**4 (3.1%)**	**3 (2.2%)**

HAZ, height-for-age z-score. WHZ, weight-for-height z-score

Table 2.4

Table 2.4. Non-linear mixed effects modeling of height and weight in children (n=710 boys, n=806 girls).
Model comparison significance was determined by likelihood ratio test with a $p<0.05$ considered significant.

	Basic Fixed Effect (BFE) Model				**Basic Random Effects (BRE) Model**				**Selected Random Effects (SRE) Model**			
	Boys		Girls		Boys		Girls		Boys		Girls	
	Height	**Weight**	**Height**	**Weight**	**Height***	**Weight***	**Height***	**Weight***	**Height***	**Weight***	**Height***	**Weight***
α (alpha)	0.309	0.360	0.408	0.424	0.318	0.375	0.424	0.433	0.331	0.416	0.460	0.495
β0 (beta0)	91.961	16.254	94.200	17.126	96.581	18.851	97.350	17.343	95.883	17.825	98.665	17.561
β1 (beta1)	182.969	81.210	166.783	72.332	182.540	81.096	166.199	72.261	182.131	79.019	165.910	71.360
λ (lambda)	9.283	12.150	8.222	11.258	9.597	12.460	8.376	11.281	9.580	12.177	8.566	11.266
AIC	13698	15213	15734	17842	12577	14205	14163	16566	12519	13568	13927	15917
Model Fit Prob > χ2					**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**
	SRE + HbA1c Covariate Model				**SRE + HbA1c Covariate Model**				**SRE + HbA1c Covariate Model**			
	upper asymptote (β1)				tempo (α)				timing (λ)			
	Boys		Girls		Boys		Girls		Boys		Girls	
	Height*	**Weight***	**Height***	**Weight***	**Height**	**Weight***	**Height***	**Weight**	**Height**	**Weight***	**Height**	**Weight***
α (alpha)	0.335	0.411	0.456	0.483	0.341	0.498	0.390	0.421	0.334	0.426	0.461	0.502
β0 (beta0)	96.983	17.773	98.507	17.302	96.295	18.045	97.500	17.477	96.313	17.991	98.679	17.586
β1 (beta1)	185.030	93.462	167.914	82.567	182.156	79.245	165.868	71.205	182.148	79.360	165.915	71.448
λ (lambda)	9.703	12.383	8.587	11.412	9.614	12.212	8.465	11.247	9.391	11.058	8.482	10.585
AIC	12514	13476	13922	15835	12521	13562	13918	15923	12519	13531	13929	15909
Coefficient	*-0.339*	*-1.496*	*-0.209*	*-1.146*	*-0.001*	*-0.010*	*0.008*	*0.009*	*0.029*	*0.144*	*0.011*	*0.085*
Coefficient Sig P>|z|	**0.000**	**0.000**	**0.000**	**0.000**	0.509	**0.001**	**0.000**	**0.032**	0.074	**0.000**	0.451	**0.000**
Model Fit Prob > χ2 (SRE vs. CM)	**0.009**	**0.000**	**0.009**	**0.000**	0.770	**0.004**	**0.001**	1.000	0.167	**0.000**	1.000	**0.002**
	SRE + Duration Covariate Model				**SRE + Duration Covariate Model**				**SRE + Duration Covariate Model**			
	upper asymptote (β1)				tempo (α)				timing (λ)			
	Boys		Girls		Boys		Girls		Boys		Girls	
	Height*	**Weight***	**Height***	**Weight***	**Height**	**Weight**	**Height**	**Weight***	**Height**	**Weight**	**Height**	**Weight**
α (alpha)	0.343	0.399	0.419	0.454	0.289	0.358	NC	0.407	0.356	0.448	0.490	0.523
β0 (beta0)	99.487	17.312	97.954	16.698	87.063	16.171	NC	15.727	97.537	17.978	99.708	17.549
β1 (beta1)	187.795	89.154	173.083	82.402	182.709	77.360	NC	70.197	182.184	79.847	165.965	71.719
λ (lambda)	10.239	12.690	9.023	11.833	8.902	11.890	NC	11.011	9.591	11.938	8.573	11.081
AIC	12657	13548	13806	15903	12532	13573	NC	15899	12518	13582	13934	15945
Coefficient	*-0.666*	*-1.006*	*-0.773*	*-1.111*	*0.002*	*0.014*	*NC*	*0.021*	*0.070*	*0.093*	*0.063*	*0.072*
Coefficient Sig P>|z|	**0.000**	**0.000**	**0.000**	**0.000**	**0.016**	**0.000**	NA	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**
Model Fit Prob > χ2 (SRE vs. CM)	**0.000**	**0.000**	**0.000**	**0.000**	1.000	1.000	-	**0.000**	0.074	1.000	1.000	1.000

CM, covariate model. AIC, Akaike information criterion. *, denotes BOTH significance of coefficient AND model improvement by likelihood ratio test (LRT).

FIGURES

Figure 2.1

Figure 2.1: Graphical depiction of the NLME modeling and explanation of coefficients.

$$\text{HEIGHT or WEIGHT} = \beta_0 + (\beta_1 - \beta_0)\left\{\frac{1}{1+\exp[-\alpha_i(AGE_{ti}-\lambda_i)]}\right\} + r_{ti}$$

α (alpha) = slope at λ = "tempo" (cm/year) or (kg/year) = slope at take-off
β_0 (beta0) = lower asymptote = initial height (cm) or initial weight (kg)
β_1 (beta1) = upper asymptote = final adult height (cm) or asymptotic weight (kg)
λ (lambda) = age of reaching 50% of height or weight growth = "timing" (years) = age at take-off

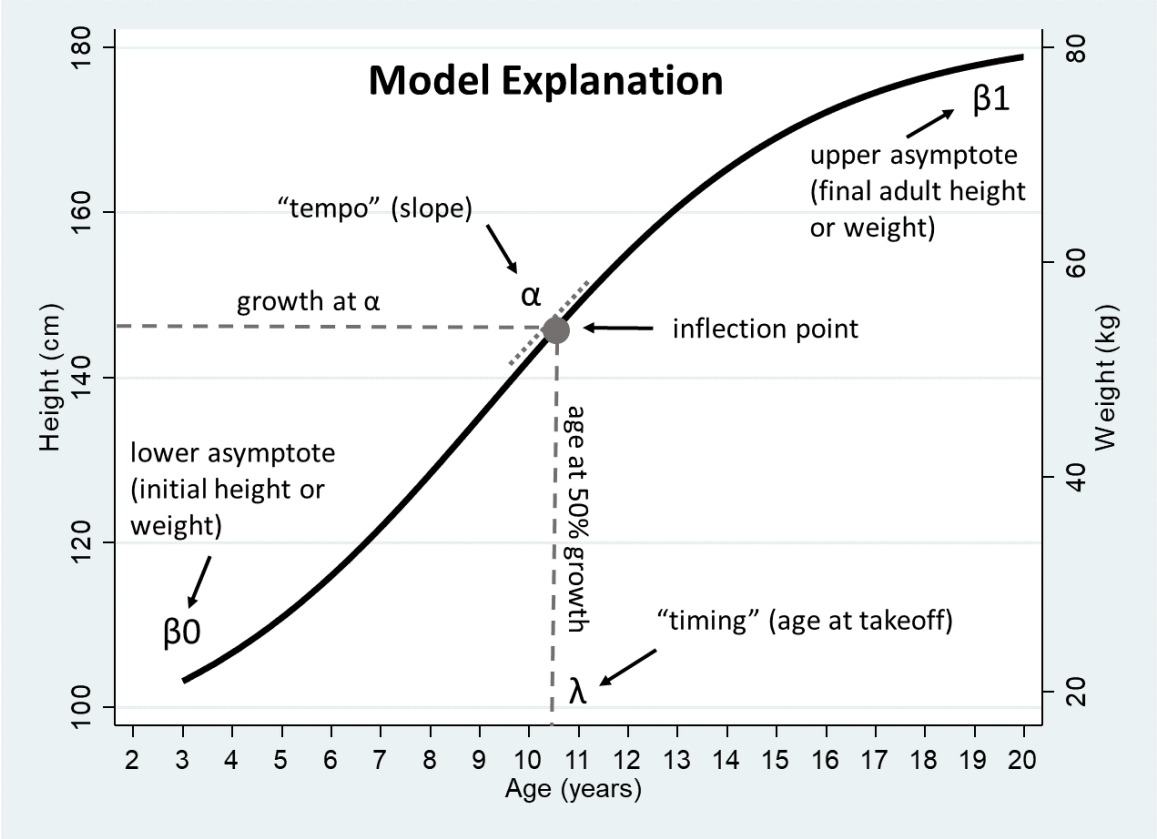


Figure 2.2

Figure 2.2: Sex specific cross-sectional annual mean stunting (HAZ<-1) and wasting (WHZ<-1) rates in children with T1DM aged 2 to 20 years. Stunting and wasting represented as solid and dashed lines, respectively, in boys (black) and girls (grey). Graphed as the percentage (%) of children stunted or wasted at each one-year age increment. Tables 2.2 and 2.3 provide *No. of participants (n)* for each sex and age.

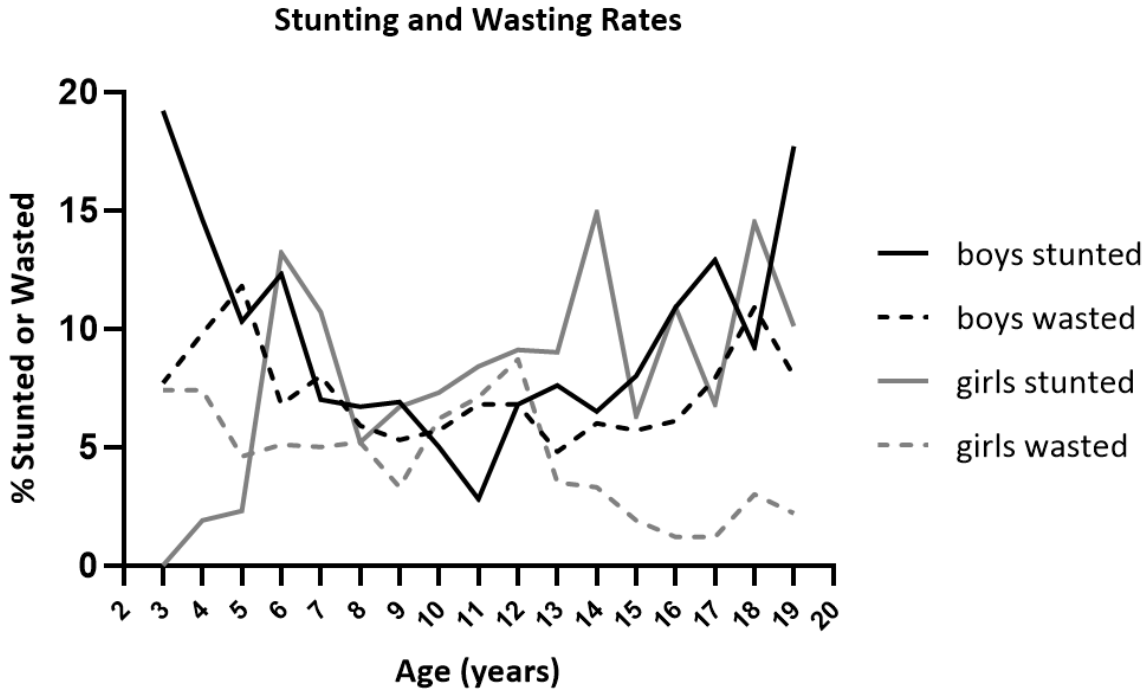


Figure 2.3

Figure 2.3: Modeling of height trajectories of boys and girls with T1DM across ages 2 to 20 years old using the selected random effects (SRE) model. The gray lines represent individual trajectories, and the solid black line represents the NLME model predicted mean height trajectory.

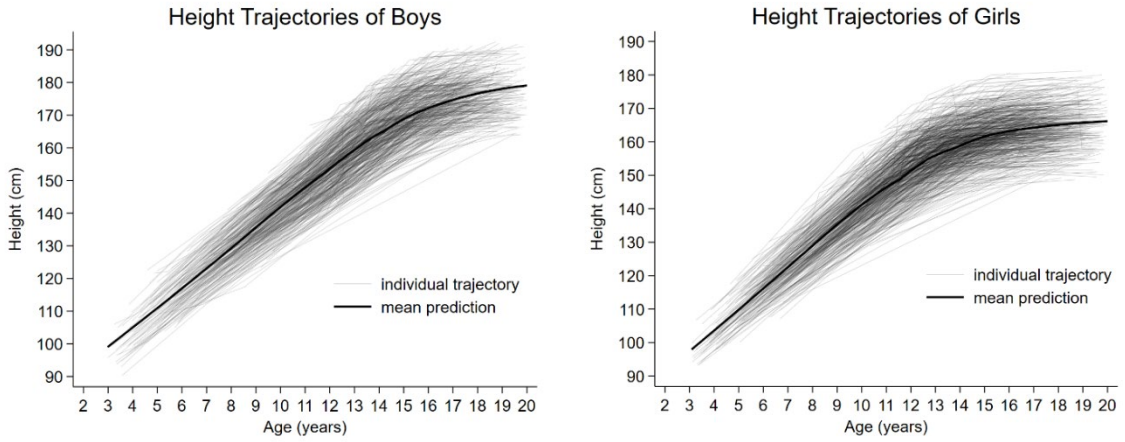


Figure 2.4

Figure 2.4: Modeling of weight trajectories of boys and girls with T1DM across ages 2 to 20 years old using the selected random effects (SRE) model. The gray lines represent individual trajectories, and the black line represents the NLME model predicted mean weight trajectory.

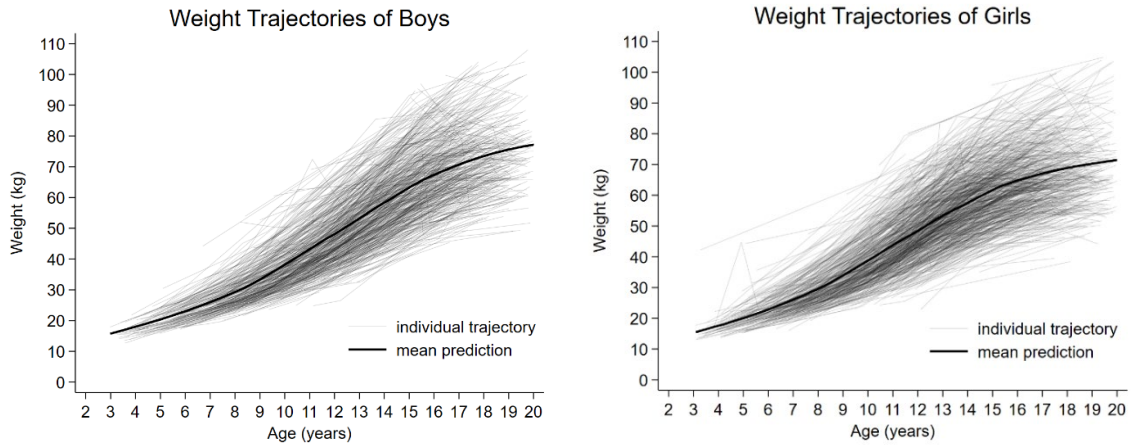


Figure 2.5

Figure 2.5: Graphical depiction of the NLME HEIGHT models for boys (black) and girls (grey) with the graph scaled to 14 years and older to focus on final adult height (β1). Overlaid are the selected random effects (SRE) model (solid lines), the SRE model including the HbA1c covariate (long dashed lines), and the SRE model including the Duration covariate (short dashed lines)

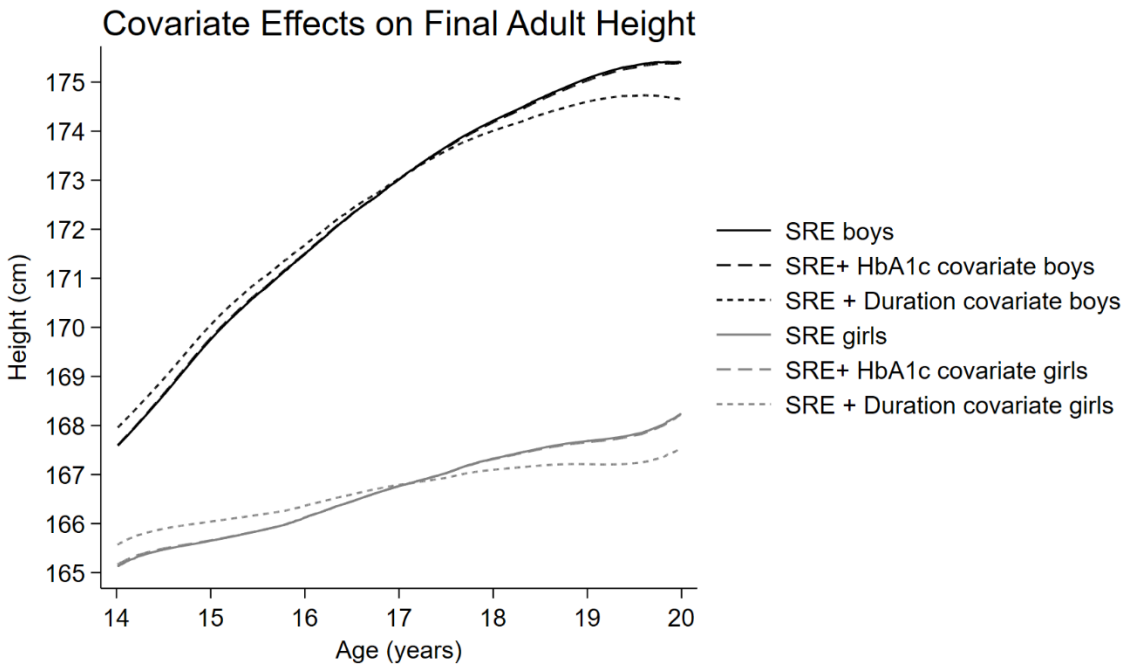
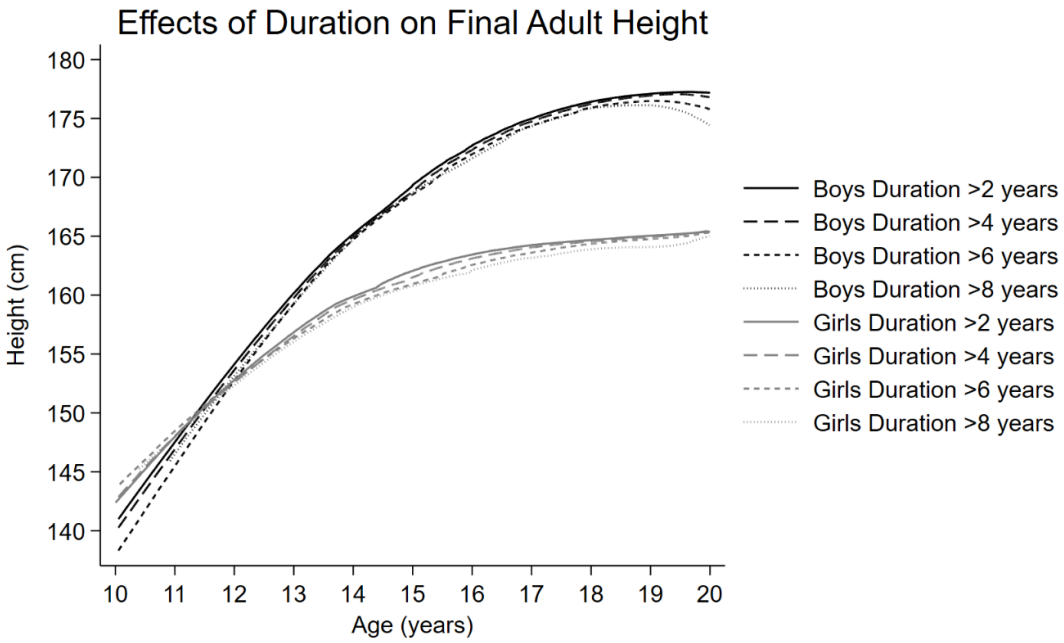


Figure 2.6

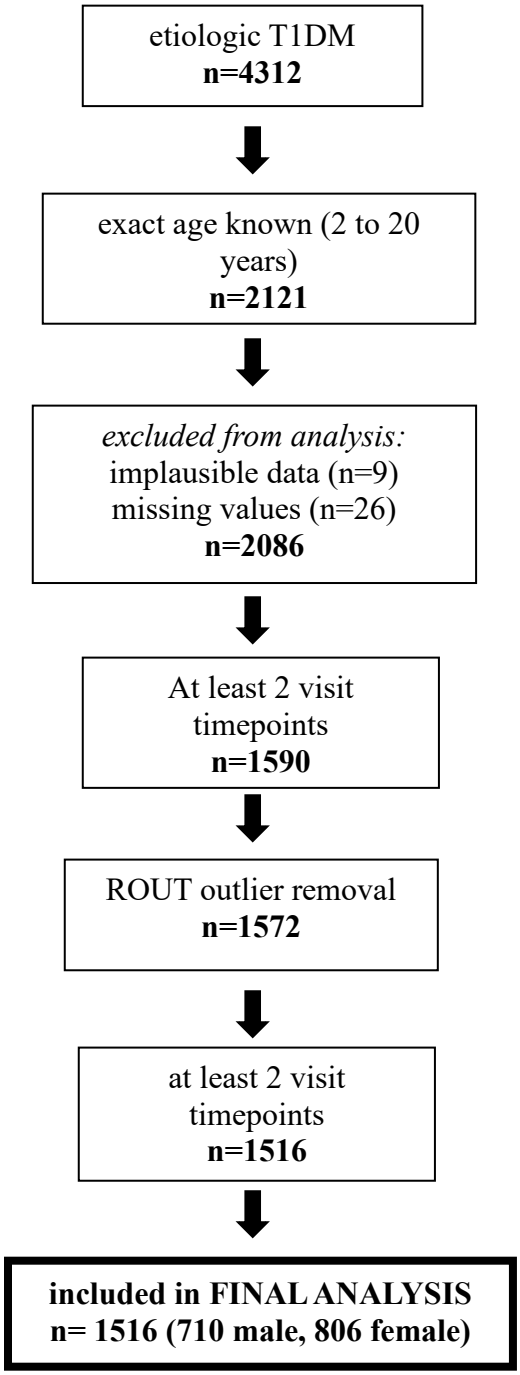
Figure 2.6: Exploration of the predicted impact of duration of disease as a covariate on final adult height (β1). Durations of 2, 4, 6, and 8 years are shown in boys (black) and girls (gray), with the graph scaled to ages 10 years and older.



SUPPLEMENTS

Supplement 2.1

Supplement 2.1: Inclusion and exclusion flowchart of participants.



Supplement 2.2

Supplement 2.2: Code for NLME models and ROUT outlier detection and removal.

```
**********************************************************************
*BASIC FIXED EFFECTS MODEL, MALES ONLY (M1m)
**********************************************************************
menl HEIGHT = {beta0:}+({beta1:}-{beta0:})*(1/(1+exp(-{alpha:}*(AGE-
{lambda:})))) if GENDERr==0, stddeviations define(beta0: {b0}) define(beta1: {b1})
define(alpha: {a2}) define(lambda: {l3}) initial (b0 80 b1 150 a2 0.3 l3 7, fixed)
estat ic
estimates store M1m
predict fitheightM1m if e(sample), yhat
**********************************************************************
*BASIC RANDOM EFFECTS MODEL, MALES ONLY (M2m)
**********************************************************************
menl HEIGHT = {beta0}+({beta1}-{beta0})*(1/(1+exp(-{alpha}*(AGE-
{lambda}))))+{U[id]} if GENDERr==0, stddeviations initial (beta0 80 beta1 150 alpha
0.3 lambda 7, fixed)
estat ic
estimates store M2m
predict fitheightM2m if e(sample), yhat
lrtest M1m M2m
**********************************************************************
*SELECTED RANDOM EFFECTS MODEL, MALES ONLY (M9m)
**********************************************************************
menl HEIGHT = {beta0:}+({beta1:}-{beta0:})*(1/(1+exp(-{alpha:}*(AGE-
{lambda:})))) if GENDERr==0, stddeviations define(beta0: {b0}+{U0[id]})
define(beta1: {b1}+{U1[id]}) define(alpha: {a2}+{U2[id]}) define(lambda:
{l3}+{U3[id]}) initial (b0 80 b1 150 a2 0.3 l3 7, fixed)
estat ic
estimates store M9m
predict fitheightM9m if e(sample), yhat
lrtest M2m M9m
**********************************************************************
*RANDOM EFFECTS COVARIATE MODEL for HbA1c, MALES ONLY
(M9mHbA1cPcnt_beta1)
*HYPOTHESIS: BG WILL DECREASE FAH (SO COVARIATE NEEDS ADDED TO
b1)
**********************************************************************
menl HEIGHT = {beta0:}+({beta1:}-{beta0:})*(1/(1+exp(-{alpha:}*(AGE-
{lambda:})))) if GENDERr==0, stddeviations define(beta0: {b0}+{U0[id]})
define(beta1: {b10}+{b11}*HbA1cPcnt+{U1[id]}) define(alpha: {a2}+{U2[id]})
define(lambda: {l3}+{U3[id]}) initial (b0 80 b10 150 a2 0.3 l3 7, fixed)
estat ic
estimates store M9mHbA1cPcnt_beta1
predict fitheightM9mHbA1cPcnt_beta1 if e(sample), yhat
lrtest M9m M9mHbA1cPcnt_beta1
```

```
*************************************************************************
*ROUT OUTLIER DETECTION AND REMOVAL (DONE BY GENDER ON FIXED EFFECTS MODELS PRIOR TO RANDOM EFFECTS MODELING)
*************************************************************************
*FIRST RUN FIXED EFFECTS HEIGHT MODEL: MALES
menl HEIGHT = {beta0:}+({beta1:}-{beta0:})*(1/(1+exp(-{alpha:}*(AGE-{lambda:})))) if GENDERr==0, stddeviations define(beta0: {b0}) define(beta1: {b1}) define(alpha: {a2}) define(lambda: {l3}) initial (b0 80 b1 150 a2 0.3 l3 7, fixed)
estimates store ROUTheightM

*calculate the residuals and graph them
predict ROUTheightM_res if e(sample), residuals
scatter ROUTheightM_res ROUTheightM
qnorm ROUTheightM_res, name(q, replace) msize(small)
pnorm ROUTheightM_res, name(p, replace) msize(small)
kdensity ROUTheightM_res, normal

*calculate the RSDR
*calculate the absolute value of the residuals
generate RSDRheightM = abs(ROUTheightM_res)
*rank them from low to high
egen RSDRheightMrank = group(RSDRheightM)
sort RSDRheightMrank
*calculate the 68.27th percentile
egen P68heightM = pctile(RSDRheightM), p(68.27)
*7.8635

*for each point now take this abs value of the residual and divide it by the RSDR (this is called the tratio)
generate tratioheightM = RSDRheightM/P68heightM
*calculate a P-value from the tratio (one-tailed)
generate pvalueheightM = ttail(10,tratioheightM)
*double it to get two-tailed p-value
replace pvalueheightM = (pvalueheightM*2)
sort pvalueheightM
egen pvalueheightMrank = group(pvalueheightM)
*graph the FDR with pvaluerank on the x-axis and p-value on the Y axis, ranked from small to large
twoway (line pvalueheightM pvalueheightMrank)

*decide on Q for FDR and calculate threshold for outliers = q-value
*Q=1%
generate qvalueheightM = 0.01*(pvalueheightM*_N)/pvalueheightMrank
sort qvalueheightM
```

```
*flag outliers 0=ok 1=outside 1%
generate outlierheightM = pvalueheightM<qvalueheightM

*drop outliers
count if outlierheightM>0
drop if outlierheightM>0
```

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Chapter 3: The Nutritional Geometry of Physical Height Growth in Children with T1DM

ABSTRACT

Background: Growth is a key indicator of overall health, influenced by both physiological and environmental factors. Altered growth patterns in children with type 1 diabetes mellitus (T1DM) have been linked to inadequate metabolic control, with poor diet and excess consumption of simple carbohydrates recognized as contributing factors. Specific dietary interventions have been shown to improve glycated hemoglobin (HbA1c). However, whether macronutrient distribution, the relationship among protein, carbohydrate, and fat, can affect height growth in children with T1DM remains unexplored.

Objective: This study aims to gain a comprehensive understanding of the macronutrient distribution as it relates to growth outcomes in children with T1DM. Nutritional geometry (NG) methods enable statistical and visual analysis of the potential influence of the macronutrient distribution on outcomes. The primary objective was to establish NG methodology within Stata software to explore the macronutrient distributions associated with physical height growth in a longitudinal study of children with T1DM.

Participants: The analysis included 1416 children with etiologic T1DM, followed from ages 2 to 20 years (71% white, 53% female) with a mean age of diagnosis of 9 years. Dietary intake data were obtained from food frequency questionnaires and analyzed for percent and absolute (gram) energy from protein, carbohydrate, and fat.

Study Design & Statistical Analysis: Nutritional geometry (NG) was employed to analyze macronutrient distribution associations with physical height growth in children

with T1DM. Mixed effects modeling, with response surface methodology using quadratic polynomials, was utilized to assess longitudinal associations.

Results: In the absence of controlling for confounders, NG analysis revealed a significant positive main effect association between fat intake and maximal height in boys, but no macronutrient associations with maximal height were detected in girls. No relationships with z-height were observed in boys or girls, suggesting that macronutrient distribution is unrelated to normal growth in this population. Further, graphical heat-map exploration across ages uncovered age-specific variations in relative percent and absolute gram macronutrient intakes associated with normal growth.

Conclusion: This analysis demonstrated the potential for NG to explore macronutrient distributions associated with longitudinal growth outcomes in children. The method may provide future utility to explore age-, sex- , and disease- specific associations toward informing precision nutrition objectives. Future analysis should consider confounding factors for a more comprehensive understanding.

BACKGROUND

Despite advancements in therapies and technologies, just one in five patients with insulin-dependent Type 1 diabetes mellitus (T1DM) can maintain glycated hemoglobin (HbA1c) within recommended levels.[1] Notably, blood glucose is more poorly controlled in children than in adults. In the T1DExchange Clinic Registry study, the average HbA1c in children was ~1-1.5% higher than in adults.[1] Concurrently, children consumed ~10% more calories from carbohydrates than adults.[2] Further, the overall macronutrient distribution of patients with T1DM across age groups differed from the U.S. population.[2]

It has been reported that the presence of T1DM can negatively impact child growth,[3] principally seen as a reduction in height velocity during puberty,[4] with alteration of the growth hormone-insulin-like growth factor 1 axis (GH/IGF-1 axis) implicated.[5,6] Elevated HbA1c has been associated with lower height z-score,[7] with many studies concluding that lack of metabolic control is the likely culprit for alteration of growth patterns.[8–10] This is further supported by the fact that with metabolic control, children with T1DM reach their genetic height potential.[4,11] Our recent analysis suggested that rates of stunting and wasting in this population may be cause for clinical concern, though final adult height models predicted the population to be taller than children without T1DM.[12]

The foundational document for advising current dietary recommendations is the Dietary Reference Intakes (DRI) developed by the Institute of Medicine (IOM). This document sets the Acceptable Macronutrient Distribution Ranges (AMDR) meant to inform the distribution of protein (PRO), fat (FAT), and carbohydrate (CHO) intakes for a healthy population. However, the AMDR in children were developed without considering optimal growth outcomes or specific disease states.[13] Towards the goal of precision nutrition, the present analysis seeks to evaluate the potential impacts of macronutrient distribution on growth outcomes in children with T1DM.

The relationship of dietary macronutrient intake with outcomes is commonly studied using simple linear regression. Linear regression assumes a linear relationship between the predictor variable(s) and the outcome of interest to determine which individual predictors primarily affect the outcome. However, macronutrients do not exist in isolation in the diet. Thus, the relationship among the macronutrients poses statistical

challenges because of this collinear nature. That is, if one macronutrient increases, the other(s) must decrease, occurring dynamically and interactively across all three of the primary macronutrients: protein (PRO), carbohydrate (CHO), and fat (FAT). Notably, the goal of studying dietary macronutrient distribution is not only to identify individual macronutrient impacts but also the impact of the distribution of the whole diet on outcomes.

A more robust method for assessing the complete macronutrient distribution could provide a more comprehensive picture. Recently, such a method, termed Nutritional geometry (NG), taken from the ecology field, has been applied and validated in human nutritional epidemiology. NG has been used extensively to explore the associations of dietary intake on growth, reproduction, and lifespan across the animal kingdom. In humans, NG methods have been applied to multiple disease states and life stages, including obesity, reproduction,[14] cardiometabolic disease,[15] aging,[16] and pubertal menarche.[17] In the menarche study, the authors compared the NG method to simple linear regression, with NG able to detect novel associations that simple linear regression could not.[17]

NG enables the quantification of the strength of associations of macronutrients on an outcome while simultaneously allowing visualization using response surface methodology.[18] The response surface method in the present analysis employs multiple linear regression with conventional p-value evaluation of coefficients but with two statistical modifications. First, including quadratic polynomial predictors embraced any potential nonlinearity between predictor (macronutrient) and outcome (growth metric). Second, the standardization of macronutrient predictors moderated any multicollinearity.

Once the relationship of the macronutrient variables has been statistically modeled using response surface analysis (RSA), visualizations can be produced using response surface mapping (RSM).

Here, we have applied NG response surface methodology to longitudinal dietary data to explore the relationship between macronutrient distribution and physical height outcomes in children with T1DM. Height and z-height were evaluated to enable quantification and visualization of relationships with macronutrient distribution. Height was evaluated to gain a clear picture of the macronutrient distribution associated with *maximal* physical height growth, while z-height provided context for comparison to a reference population in terms of *normal* physical height growth. Thus, the primary goal of the present analysis is to infer what macronutrient distribution is associated with physical growth metrics in children with T1DM.

Specifically, we address the following questions in this population: 1) What macronutrients are associated with maximal height and optimal z-height growth outcomes? 2) What is the relationship of the relative percent intake of each macronutrient with normal z-height, and how does this change with age? 3) What are the absolute gram intakes associated with normal z-height, and how does this change with age?

The central hypothesis for this study is: *"Among the macronutrients, the main effects of PRO will have the strongest positive, and CHO will have the strongest negative, association with growth outcomes in children with T1DM."*

METHODS

Data Acquisition

Data were obtained from a multicenter longitudinal study conducted from ~2000 to 2020 by the Center for Disease Control and Prevention (CDC) and the National Institute of Diabetes and Digestive Diseases (NIDDK). Study centers were located across five states, and the longitudinal study has resulted in hundreds of primary and secondary analysis publications.

The present secondary data analysis was approved by the coordinating center, and data were obtained through the Lifecourse Epidemiology of Adiposity & Diabetes (LEAD) Center at the Colorado School of Public Health of the University of Colorado (IRB#CRV018). Data were received in de-identified form and deemed exempt from oversight by South Dakota State University Institutional Review Board (#IRB-2210012-EXM). The present analysis is focused on physical child growth and dietary intake. The investigation in the present paper represents an extension of analysis from our previous publication using the same dataset exploring longitudinal physical height and weight in this population.[12]

Participant Characteristics and Data Collection

Methods for primary data collection[19] and analysis[12] have been previously described. Briefly, anthropomorphic and demographic data were collected via surveys, and clinical data were collected by medical personnel at study visits. Surveys obtained self-reported information on income, race, and education.[20–22] At initial enrollment, T1DM was confirmed via the presence of diabetes autoantibodies. Study visits consisted of physical examination and collection of height and weight. Z-height was derived from

collected height data based on the 2000 CDC growth charts, adjusting for child sex and age. Participant data was collected over time, with a maximum of six visits during childhood. Data were collected at baseline, one-year, two-year, and five-year follow-up, with two later cohorts collected at approximately five-year intervals. Food frequency questionnaire data was collected as described previously[23] using a modified Block Kid's Food Questionnaire with cultural adaptations used in the Diabetes Prevention Program.[24,25]

Inclusions and exclusions were consistent with our previous secondary analysis publication.[12] Briefly, only participants with exact known ages between 2 and 20 years were included. Outliers were detected using ROUT[26] utilizing the statistical height and weight models in our previous publication.[12] **Supplement 3.1** depicts the inclusion and exclusion flowchart which is identical to our previous publication except for one additional exclusion of participants without at least one dietary food frequency questionnaire (FFQ), resulting in a sample size of 1416 (647 boys and 769 girls). **Supplement 3.2** contains the participant baseline characteristics table.

In the context of growth, we previously reported height and z-height by age and sex in this population. Our prior nonlinear height models revealed a population that was taller in final adult height and entered puberty earlier, than their peers.[12] We also reported concerning stunting (z-height<-1) rates, particularly among children diagnosed with T1DM before ~8 years of age.[12]

Statistical Analysis

All statistical analysis was conducted in Stata/SE 18.0. For all growth outcomes and models, separate analyses were conducted for boys and girls. Models contained

independent variables related to macronutrients only, no confounding factors such as demographics or socioeconomic status were included in the models. **Supplement 3.3** contains example code for fitted RSA models and RSM graphing. Macronutrients were explored for potential associations with height and z-height. Macronutrient variables were standardized for all modeling to a mean of 0 and a standard deviation (SD) of 1. For RSA, models were evaluated for absolute gram and relative percent macronutrient intakes. All RSM was accomplished using the *twoway contour* command in Stata, using thin-plate splines and six to ten color levels. Due to the computational expense of applying thin-plate splines, a random sample of 50 individuals per sex was used for graphing of primary models. RSMs which included *age* utilized a random sample of 100 individuals per sex.

To explore whether total energy (TE) intake was associated with either height or z-height outcomes, mixed-effects modeling with repeated measures was used to test longitudinal relationships. Participant id and AGE were included as REs in the height model and participant id as an RE in the z-height model (since z-height is already age-adjusted).

Response Surface Analysis (RSA)

The relationships among the macronutrients pose special challenges for modeling and visualization because of their multicollinear nature. Multicollinearity affects the coefficients and p-values but does not influence the predictions, the precision of the predictions, or the goodness of fit statistics. However, if multicollinearity can be overcome, one can both quantify the strength of associations and perform visualization. Thus, RSA methodology was used to overcome the limitations of traditional methods

through several statistical approaches. First, quadratic polynomials were incorporated within the regression models to embrace any potential nonlinear relationships of diet variables with an outcome. Quadratic polynomials embrace the natural nonlinear "wiggliness" of the effect of diet variable(s) on the outcome.[27,28] Second, the standardization of the diet variables to a mean of 0 and an SD of 1 facilitated the improvement of multicollinearity. However, even with these approaches, RSA modeling could not overcome the multicollinearity of more than two macronutrient variables in the models. Modeling beyond a 3-way (two predictors and one outcome) becomes difficult to interpret, particularly if interactive effects are present. Therefore, in the current analysis, two macronutrients were included in the RSA models at a time, and all permutations of variables were tested in independent two-macronutrient models to explore main, quadratic, and interaction effects (e.g., model permutations run were: PRO/FAT, PRO/CHO, and FAT/CHO). All RSA regressions were performed using linear mixed-effects models with fixed effects (FEs) and random effects (REs).

Main effects determined if there was a direct effect of the predictor variable in isolation on the outcome variable. Quadratic variables in the models enabled the evaluation of curvilinear relationships between the predictor and outcome. Interactions were explored to determine if the outcome was modified by the interaction of the predictors, which can be thought of as an added effect or adjustment to the main effect when the macronutrients are present together. If interactions were not significant and significant main effects were present, we concluded that the main effects of the variables were of primary importance. Finally, age was explored as an interaction effect in some models to investigate relationships between age and outcomes.

RSA: Height

For the height outcome variable, RSA models included random effects (RE) for individual participant (id) and participant age. Using these REs acknowledges that individuals may have unique growth patterns over time and allows for participant-specific deviations from the average growth trajectory. This design enabled the identification of which macronutrient patterns are associated with maximal height within each participant's unique growth trajectory. Thus, height was undertaken as an outcome to explore how the different macronutrient distributions were associated with variations in "maximal" physical height growth.

RSA: Z-Height

Z-height is a sex-adjusted clinical metric of child stature-for-age relative to a cross-sectional reference population portrayed as SD from the mean. Here, a negative value indicates an individual is shorter in stature than the mean height of the reference population, while a positive value implies an individual is taller than the average height of the reference population.

For the z-height outcome variable, RSA models also included the participant (id) as an RE, but age was used as an FE instead of an RE. With age as an FE, the model provided a more general view of how age is associated with growth and is not tailored to individual-participant age variations. Z-height as a population-standardized metric, does not have an upward trajectory signature as height does with increasing child age. Thus, the z-height was explored to examine how growth outcomes compare to a reference population to better understand which macronutrient distribution is related to *normal* height growth.

As described in our previous work, child z-height in this population exhibited high rates of stunting, with unique patterns across ages in males versus females.[12] Therefore, for z-height analysis, girls and boys were still modeled and graphed separately, despite z-height being age and sex-adjusted. However, the utility of the metric being depicted in SDs allows direct comparison between males and females.

RSA: Intakes Associated with Normal Z-Height by Age

Including age as an FE in the z-height models allowed expanded exploration of macronutrient relationships with age. Using gram variables had the added advantage of assessing the specific absolute gram amounts of each macronutrient associated with a given z-height at specific ages. Similarly, relative percent intake associations with normal growth by age were explored. For age exploration models, RSAs were run with AGE and AGE^2 included in each model permutation. Subsequent RSM of these relationships enabled a visual depiction of the level of each macronutrient, in terms of absolute gram or relative percent intakes, for a normal (0) z-height across childhood by age. Importantly, these RSMs provided valuable sex-specific, clinically actionable intakes associated with normal growth in this population. RSMs depict a random sample of 100 individuals per sex.

Response Surface Analysis (RSA) Coefficient Interpretation

Due to the standardization of the predictor variables to avoid multicollinearity, the coefficient values from the RSA represent the change in the outcome variable associated with a one-SD change in the predictor variable. In this way, the coefficients are readily and equally interpretable across all macronutrient predictor variables. However, the coefficient values are not directly interpretable in units of the outcome variable. A

coefficient of +0.3 for a given macronutrient does not indicate an increase in the absolute amount of that macronutrient but rather a positive relationship in units of SD. For example, a macronutrient coefficient value of +0.3 would suggest that a one-SD increase in the macronutrient would result in an outcome variable value of +0.3 SD higher than its mean, holding all other variables constant.

Response Surface Mapping (RSM) Interpretation

Notably, while RSA can quantify and detect significant associations, the primary purpose of NG modeling is visualization through RSM. Importantly, even if coefficient values do not indicate significance, the associations between variables can still be visualized, aiding in interpretation, particularly if complex interactions are involved. Accordingly, the effects of the coefficients are interpreted visually using a graphing method in which two axes (predictors) represent two variables of interest on the x and y-axes, and a colored heatmap represents the third (outcome) z-axis. Conveniently, the graphs can be represented in the original absolute units of the variable (rather than the SD units reported for the coefficients), allowing valuable contextual interpretation. The heatmap coloring allows the z-axis outcome to be visualized as the change in the outcome value, with red and blue colors representing higher and lower values, respectively. The presence of quadratic polynomials in the models facilitates the curvature of the contour lines, indicating the nonlinear effects of the predictor variables on the outcomes. A basic RSM depicts macronutrient A on the x-axis, macronutrient B on the y-axis, and the growth outcome on the z-axis. RSMs incorporate all variables included in the RSA model, including those that involve main, quadratic, and interactive effects.

Additional RSMs can also be produced from the same RSA, given that the variables of interest were included as FEs in the model. For example, in our analysis, we further explored RSMs depicting age (x-axis), z-height (y-axis), and macronutrient (z-axis).

When interpreting RSMs, the main effects are visually distinguished from interactive effects by looking at the response surface. The main effects often manifest as more organized, structured patterns, while interaction effects tend to introduce complexity and irregularities in the response surface. The main effects of a specific macronutrient as one moves along the axis manifest as a simple linear or curved trend along that variable's axis and can be interpreted as an independent influence of that variable on the outcome. However, interaction effects typically result in more complex shapes, such as curvature or nonlinearity in the response surface. Observation of a nonlinear or curved pattern not explained by a single variable's main effect suggests an interaction effect. Interaction effects change the direction, steepness, or curvature of the surface as one moves across both axes. These axis changes indicate that the combined influence of the variables is more than just an additive effect. Main effects commonly appear with a "rainbow" pattern, while interactive effects have complicated patterns. Irregular patterns can indicate a more complex 3-way interactive, or the absence of any, effect.

RESULTS

Descriptive Assessments

Baseline characteristics of the population can be found in **Supplement 3.2**. In boys and girls, the cross-sectional mean macronutrient distribution across ages was 16%PRO/37%FAT/47%CHO and 16%PRO/36%FAT/48%CHO, respectively.

Our prior analysis revealed that this population may be taller than their peers. Accordingly, the mean z-height across ages was 0.316 and 0.302 for boys and girls, respectively in the present analysis. Despite these above-normal mean z-heights, we reported concerning stunting rates in our previous analysis.[12]

Total energy (TE) was explored for associations with longitudinal height and z-height outcomes. For height, there was a significant positive association of TE with height (coeff= +0.0011, p=0.001) in boys, however, the minimal coefficient magnitude indicates a modest effect size and lack of any clinically meaningful impacts. No association of TE with height was detected in girls (coeff= +0.0002, p=0.539). Further, there was no association of TE with z-height in boys (coeff= 0.0000, p=0.436) or girls (coeff= 0.0000, p=0.809). **Taken together, these results indicate that height and z-height are not associated with TE intake in this population.**

Question 1: What macronutrients are associated with maximal height and normal z-height growth outcomes in children with T1DM?

Findings in Boys-Maximal Height

RSA of height in boys (**Table 3.1**) supported significant associations between FAT intake and maximal height. There were significant positive main effects of FAT in both model permutations containing FAT (PRO/FAT and FAT/CHO) across both variable formats (relative percent and absolute gram). This result was further reinforced by a lack of quadratic or interaction effects of FAT. These results highlight the primary importance of FAT for the maximal height of boys in this population. Evaluation of RSMs (**Figure 3.1, Columns A** and **C**) supports this conclusion of a positive relationship of FAT with maximal height.

PRO as a relative percent variable uncovered negative associations with height in both PRO-containing models (e.g., PRO/FAT and PRO/CHO) with (coef= -0.637, p=0.05 and coef= -1.043, p=0.01). However, the significance of this PRO association disappears in the context of absolute gram intakes (coef= -0.857, p=0.33 and coef= +0.852, p=0.09). RSMs for PRO can be found in **Figure 3.1, Columns A and B**.

The two CHO-containing model permutations (e.g., PRO/CHO and FAT/CHO) showed significant main effects of relative percent of CHO, but in opposing directions (coef= -1.218, p=0.00 and coef= +1.912, p=0.05), preventing a conclusion. Further, there were no statistical associations of CHO when considering absolute gram intakes. Visualization of RSMs in **Figure 3.1, Columns B and C** support these conclusions.

Findings in Boys-Normal Z-Height

RSA exploring z-height in boys (**Table 3.1**) detected a significant 2-way interaction of PROxCHO in both the relative percent (coeff= +0.082, p=0.05) and absolute gram (coeff= 0.001, p=0.03) models. However, despite their significance, note that the coefficients themselves are near zero, suggesting no actual impact. Visualization of the RSM also supports a lack of any meaningful relationship (**Figure 3.2, Panels B1 and B2**). Similarly, a significant interaction effect of FATxCHO in the context of absolute gram intake was detected (coeff= -0.034, p=0.04), but again the coefficient is near zero (**Figure 3.2 Panel C2**). Further, there was no relationship detected for FATxCHO in the relative percent model (coeff= 0.131, p=0.33). However, note the interesting pattern of this relationship despite a lack of detection of statistical significance (**Figure 3.2, Panel C1**) using quadratic polynomial models.

Taken together, these data suggest a strong main effect of FAT for maximal height in boys. However, for normal z-height, the results suggest no clear relationship of any macronutrient.

Findings in Girls-Maximal Height

For girls, there were no statistically significant relationships between dietary intake and maximal height growth. There were no main, quadratic, or interactive associations (**Table 3.2**), of any macronutrient variable for relative percent or absolute gram variable formats on height, suggesting that neither macronutrient distribution nor absolute gram intakes of macronutrients play major roles in maximal height growth in girls. However, despite a lack of significant associations, RSMs (**Figure 3.3**) still reveal interesting patterns for maximal height in girls. The lack of statistical association despite clear visible relationships is likely the result of a minimal scale impact; that is, the overall influence of dietary intake on maximal height in girls spans a smaller centimeter range than in boys. The non-significance may also result from more complex (**Figure 3.3, Panel A)** relationships that are statistically undetectable in quadratic polynomial models.

Findings in Girls-Normal Z-Height

RSAs (**Table 3.2**) and RSMs (**Figure 3.4**) in girls revealed a lack of association of any macronutrient with normal z-height. RSAs reported all small near-zero, and nonsignificant, coefficients. Importantly, all RSMs depict a z-height>0 suggesting that all macronutrient distributions among female participants in the dataset as associated with above-normal z-heights. **Thus, there were no associations of macronutrients with maximal height or normal z-height in girls.**

Question 2: What is the relationship of the relative percent intake of each macronutrient with normal z-height, and how does this change with age?

An important strength of RSM is the visualization of relationships of macronutrients with outcomes in an interpretable and potentially clinically relevant context. Thus, RSMs were utilized to answer questions about specific intake quantities associated with normal z-height growth. These questions, in part, can be explored by examining **Figures 3.2 and 3.4** for boys and girls, respectfully. However, additional RSMs were created (**Figures 3.5 and 3.6**) using age-containing RSA models to explore these relationships according to child age.

Finding in Boys

RSMs depicting relative percent macronutrient intake relationships across ages in boys were explored to uncover whether specific macronutrient patterns are associated with variations in z-height across childhood. RSMs provided a visual assessment of the impact of the percentage of each macronutrient on z-height across different ages in boys (**Figure 3.5, Row 1.**) Unlike previous RSMs, the colors here represent the percent (%) intake rather than the outcome variable, with z-height instead depicted on the y-axis. This facilitated clear visual estimation of specific percent intakes by age.

In boys, there is a pattern of higher intakes of FAT and PRO, and concomitant lower intakes of CHO, associated with normal z-height until after puberty, when more moderate intakes of all three macronutrients are associated with normal z-height (**Figure 3.5, Panel A1**). Recall that there were strong main effect associations of FAT intake with maximal height in boys, but this effect was absent for z-height. Exploration of the RSM in the context of age and z-height provides evidence that the effect of %FAT on z-height

is age-dependent in boys. **Taken together, these results suggest an age-dependent relationship of percent macronutrient intake with z-height in boys.**

Findings in Girls

We concluded that macronutrients are unlikely to be associated with z-height in girls. Examining interactions between the relative percent intake of macronutrients and age could help to confirm or further describe if macronutrients play a role in z-height by age. RSMs exploring the percent intake of each percent macronutrient across ages in girls on z-height can be found in **Figure 3.6, Row 1.** As in boys, the colors represent energy intakes rather than the outcome variable, with z-height depicted on the y-axis.

Percentage intake relationships with z-height across ages in girls suggest a more complex picture than in boys. Notably, all the RSMs produced for z-height in girls were absent of a below-zero-value on the z-axis, indicating that the entire population of females with T1DM, across all percent macronutrient distributions (**Figure 3.4, Row 1**) and gram intakes (**Figure 3.4, Row 2**), are above normal for z-height. This pattern persists in **Figure 3.6, Row 1,** in which the y-axis>0.1, suggesting that a wide range of percent macronutrient intakes across ages are associated with normal and slightly above normal z-heights in girls. Further, RSMs suggest that above normal z-heights (z-height>0.4) may be supported by higher FAT and lower CHO intakes, until the onset of puberty when lower FAT and higher CHO intakes are associated. These RSMs highlight the utility of NG to detect important patterns associated with growth. **Taken together, these results suggest that while girls had more complicated patterns of percent intakes across ages than boys for above-normal z-heights, normal z-heights were supported by a wide range of macronutrient patterns.**

Question 3: What are the absolute gram intakes associated with normal z-height, and how does this change with age?

To next explore the absolute gram intakes of each macronutrient associated with z-height across ages, RSAs were run with age included as an FE. Resulting RSMs can be found in **Figure 3.5, Row 2** for boys, and **Figure 3.6, Row 2** for girls. The colors represent the absolute gram intakes rather than the outcome variable, with z-height depicted on the y-axis. The example code for such models can be found in **Supplement 3.3.**

Findings in Boys

RSMs exploring the age-related relationships of absolute gram intakes of macronutrients reveal that remarkably low gram intakes of each macronutrient were associated with normal z-heights (**Figure 3.5, Row 2**) in boys. FAT intakes of ~0-50g, PRO intakes of ~20-40g, and CHO intakes of ~50-100g are associated with normal z-height in boys to ~age 17.

Findings in Girls

Associations of absolute gram intake of each macronutrient with normal z-height in girls contrasted with boys (**Figure 3.6, Row 2**) and exhibit more complicated patterns for above normal z-height. However, as with percent intakes, gram intakes represented on graphs depicted no below-normal z-heights. Based on relationships with above-normal z-heights, the RSMs suggest that above-normal z-heights are supported across a wide range of gram intakes of each macronutrient. **Together, these results further support that girls grow normally across ages regardless of relative percent or absolute gram intakes of macronutrients.**

DISCUSSION

Applying NG to human populations holds exciting possibilities for more comprehensive dietary intake assessments on outcomes. Indeed, in our recent review,[13] no studies could be found that reported all three macronutrient coefficient associations with height outcomes in children. In the present analysis, we first explored if TE was associated with height or z-height, finding no relationship. We then used NG to detect and visualize associations between macronutrients and physical height outcomes in children with T1DM. Exploration of these relationships expands our understanding of dietary impacts on growth towards the goal of precision nutrition. Through NG, we assessed two important growth metrics in children, enabling the evaluation of both *maximal* and *normal* height growth metrics. The analysis was further extended to explore the relationship of macronutrients with z-height by age. Additional age analysis for relative percent and absolute gram intakes associated with normal growth provided an important clinically relevant context. The utility of NG highlights that relationships can be visualized and explored, even without statistically significant associations, as patterns of the response surface can still yield relevant information.

Importantly, our analysis showed that children in this population grew normally across a wide range of macronutrient patterns and intakes. This was supported both statistically through RSA and graphically through RSM. These results reinforce the commonly held tenet that hormones[29–32] and genetics[33,34] are the primary drivers of growth in children. It is crucial to know that despite the presence of disease, this population has normal growth regardless of macronutrient distribution in the diet.

However, our analysis revealed unexpected associations in boys in the context of maximal growth. Here, we will discuss several potential explanations for our findings.

The requirement for dietary PRO for human height growth is widely accepted.[35–37] PRO is uniquely essential for growth since it cannot be stored and is the only macronutrient that can be converted into body tissue protein.[13] In a study of 45 nations, while genetics and socioeconomic factors correlated with final adult height, the strongest correlates with final adult height were PRO quantity and PRO quality.[38,39] Although FAT is known to play an important role in nervous tissue development, any impacts on height are commonly assumed to be due to total energy contribution[40], indirectly rather than directly driving growth. Similarly, CHO is primarily considered a source of energy, with no known association across studies as a driver of height growth.[13] Thus, we hypothesized that PRO would have a strong main effect association with height growth in the present analysis. Further, given the presence of T1DM, we hypothesized that CHO may be negatively associated with height growth.

Interestingly, in the context of maximal height growth, our results were contrary to our hypothesis. First, girls showed no associations of any macronutrient with maximal height. However, our results showed that a diet higher in relative percent and absolute gram intakes of FAT was associated with increased maximal height in boys. Also contrary to our hypothesis, the relative percent of PRO had negative associations with maximal height in boys, though based on the RSMs may only impact higher PRO intakes >20% (**Figure 3.1, Panel B1**). Further, the main effects of relative percent CHO presented conflicting information in two different model permutations, preventing a conclusion. We propose that the unexpected finding of FAT's role in maximal height is

specific to this population due to the presence of T1DM, though mechanisms need exploration. Further, given the important role of the growth hormone/insulin-like growth factor-1 (IGF-1/GH) axis in driving child growth,[6] the need for exogenous insulin in this population may also play a role.

While child growth is a sensitive metric of overall health, there is little evidence that taller stature has any physiologic benefit. Thus, we reasoned that understanding how macronutrients are related to *normal* growth may be more clinically relevant and actionable. To gain a complete picture of the macronutrient distribution associated with normal rather than maximal height, we next explored z-height. Nevertheless, girls and boys displayed no association of any macronutrient on z-height. Importantly, RSMs suggest that the entire population of girls in this analysis exhibited above-normal z-height, supported by a wide range of macronutrient intakes.

Together, these results highlight sex differences of the impacts of macronutrients on maximal height, but not z-height growth in this population. Maximal height in boys may be primarily affected by FAT in the diet. While is girls, there is little evidence that any specific macronutrient or macronutrient distribution plays roles in height or z-height.

Despite the lack of any associations of macronutrients with z-height, we wondered if age could be resulting in hidden relationships. We were left with clinical questions about what intakes at specific ages were associated with normal growth. Thus, we next employed expanded models with the effects of age included as interaction effects. When age was used as an RE for height models, it considered that the influence of age on height varies randomly across individuals. In other words, individuals have different growth trajectories. This approach accommodated individual variability in

growth patterns and thus was appropriate for exploring maximal heights. However, models for standardized z-height included age as an FE to facilitate the investigation of age as a systematic predictor of z-height for the entire population. That is, age was considered to have a consistent and structured effect on z-height across all individuals in the sample. This provided the added benefit of being able to include age as an axis in the RSMs. The produced RSMs provided a rich picture of these relationships, enabling age-specific insight. Notably, a clearer picture was revealed by age in boys than in girls, suggesting that normal z-height in boys was supported with higher FAT and PRO as a percent of intake in the diet through childhood. Thus, the RSMs that include age are important because they tell a more complete story across child growth.

Finally, evaluating absolute gram intake across ages painted a different picture in girls versus boys. In boys, low levels of gram intake of each macronutrient were associated with normal z-height across childhood through age ~17. However, in girls, a higher gram intake of each macronutrient was associated with above-normal z-height, suggesting that girls have different minimum intake requirements than boys. Regardless, the utility of RSMs to inform potential intake recommendations holds great clinical promise.

There are important limitations of the present analysis that must be discussed. The average age of onset of T1DM among the study participants was ~10 years of age, with most participants enrolled within one year of diagnosis. As described our data is longitudinal; however, it was collected at inconsistent intervals across childhood. Thus, this type of data lent itself well to the mixed effects modeling we employed. However, since children were not enrolled until after diagnosis, this means there was limited

availability of FFQ and height data before age 10. Therefore, the assessment of relationships between child growth and dietary intake before age 10 may be less statistically robust. Further, our previous publication describing the growth trajectories of this population predicted the age of takeoff for height growth to be ~10 years old in boys and girls.[12] Both the onset of diabetes and the takeoff of puberty occurring simultaneously certainly complicates our understanding of the relationships between diet and growth. FFQ collected after age 10 may be missing important relationships of how diet may have already affected the trajectory of growth prior to diagnosis.

As mentioned, some RSMs showed complex relationships that may not be detectable with quadratic polynomial models. As such, future consideration of other modeling methods such as generalized additive models (GAM) and software that supports graphing of three macronutrients and an outcome concurrently, are proposed.[17]

The richness of NG analysis presents exciting potential to explore other outcomes in this population. Of future interest are diabetes-specific acute outcomes, such as HbA1c and insulin requirement, as well as chronic outcomes such as retinopathy and nephropathy.

Importantly, the results reported in the present analysis cannot be extrapolated to children without T1DM. Further, we acknowledge that confounding variables were not included in our NG analysis, presenting a severe limitation to our conclusion. As such, future use of the NG method must include control for birthweight, demographics and socioeconomic factors. Despite this, the illustrated methods provide exciting potential for application to other populations of children with and without disease. The fact that the DRI and AMDR are not informed based on optimal growth outcomes must be addressed.

The use of NG to explore normal growth outcomes has potential utility for informing future dietary recommendations.

CONCLUSION

Whether a child is growing properly is a sensitive metric of overall health. The relationship of dietary intake with growth is especially important in children with T1DM due to challenges of blood glucose control. The evaluation of macronutrient distribution using NG enabled both statistical and graphical assessment of the potential impacts of the whole diet on physical height growth. Our results suggest that children with T1DM grow normally across a wide range of macronutrient distributions. However, boys and not girls, are sensitive to the intake of FAT in the diet in the context of maximal growth and this relationship is age-dependent. Additional NG graphing also supplied clinical context informing potential future intake recommendations toward the goal of precision nutrition in this population.

TABLES

Table 3.1

Table 3.1: Response surface analysis (RSA) of height and z-height in boys. RSA models exploring the association of macronutrients with physical height metrics in boys. Due to mutlicollinearity, two macronutrient combinations were modeled at a time. Coefficient significance represented as P>|z|. P<0.05 are designated with red squares.

Boys	height				z-height			
	PERCENT		GRAM		PERCENT		GRAM	
	Coeff	*P*>|z|	Coeff	*P*>|z|	Coeff	*P*>|z|	Coeff	*P*>|z|
Model: PRO, FAT								
PRO	-0.637	0.05	-0.857	0.33	-0.020	0.44	0.026	0.72
FAT	0.965	0.00	2.007	0.02	0.009	0.74	0.018	0.81
PRO^2	-0.010	0.97	1.158	0.35	0.002	0.93	0.170	0.09
FAT^2	0.050	0.83	0.947	0.41	0.034	0.07	0.164	0.08
PRO x FAT	-0.134	0.73	-2.275	0.33	-0.036	0.23	-0.342	0.07
AGE	-	-	-	-	0.042	0.48	0.047	0.43
AGE^2	-	-	-	-	-0.003	0.09	-0.004	0.07
Model: PRO, CHO								
PRO	-1.043	0.01	0.852	0.09	-0.024	0.48	0.018	0.66
CHO	-1.218	0.00	0.348	0.48	-0.011	0.74	0.052	0.18
PRO^2	0.056	0.89	0.090	0.67	0.023	0.45	-0.001	0.98
CHO^2	0.080	0.83	0.070	0.80	0.055	0.07	-0.014	0.51
PRO x CHO	0.223	0.74	-0.418	0.35	0.082	0.05	0.001	0.03
AGE	-	-	-	-	0.042	0.48	0.052	0.38
AGE^2	-	-	-	-	-0.003	0.09	-0.004	0.06
Model: FAT, CHO								
FAT	2.480	0.01	1.347	0.01	0.057	0.48	0.017	0.67
CHO	1.912	0.05	-0.003	0.99	0.060	0.44	0.050	0.19
FAT^2	0.315	0.89	0.105	0.56	0.129	0.45	0.013	0.45
CHO^2	-0.086	0.97	0.264	0.38	0.014	0.93	0.005	0.84
FAT x CHO	0.266	0.95	-0.673	0.13	0.131	0.33	-0.034	0.04
AGE	-	-	-	-	0.042	0.48	0.051	0.39
AGE^2	-	-	-	-	-0.003	0.09	-0.004	0.06

PERCENT - Macronutrients are represented as a percentage of total energy intake to explore impacts of the relative distribution of macronutrients. GRAM - Models contain no adjustment for total energy intake to explore the direct impact of absolute grams of each macronutrient.

Table 3.2

Table 3.2: Response surface analysis (RSA) of height and z-height in girls. RSA models exploring the association of macronutrients with physical height metrics in girls. Due to multicollinearity, two macronutrient combinations were modeled at a time. Coefficient significance represented as P>|z|. P<0.05 are designated with red squares.

Girls	height				z-height			
	PERCENT		GRAM		PERCENT		GRAM	
	Coeff	*P*>|z|	Coeff	*P*>|z|	Coeff	*P*>|z|	Coeff	*P*>|z|
Model: PRO, FAT								
PRO	-0.339	0.17	-0.137	0.85	0.010	0.66	0.085	0.19
FAT	-0.054	0.82	0.249	0.73	-0.026	0.23	-0.084	0.20
PRO^2	0.104	0.54	0.857	0.49	0.014	0.39	0.084	0.46
FAT^2	0.037	0.82	0.609	0.62	0.009	0.54	0.050	0.65
PRO x FAT	-0.193	0.43	-1.580	0.51	-0.005	0.84	-0.138	0.53
AGE	-	-	-	-	-0.197	0.00	-0.191	0.00
AGE^2	-	-	-	-	0.006	0.00	0.005	0.00
Model: PRO, CHO								
PRO	-0.316	0.30	-0.386	0.33	0.021	0.46	-0.022	0.57
CHO	0.068	0.82	0.650	0.09	0.033	0.23	0.037	0.30
PRO^2	0.192	0.44	0.106	0.73	0.017	0.47	0.032	0.26
CHO^2	0.058	0.82	-0.118	0.49	0.014	0.54	-0.008	0.66
PRO x CHO	0.283	0.51	-0.145	0.75	0.015	0.70	-0.040	0.34
AGE	-	-	-	-	-0.197	0.00	-0.191	0.00
AGE^2	-	-	-	-	0.006	0.00	0.005	0.00
Model: FAT, CHO								
FAT	0.752	0.30	-0.244	0.53	-0.049	0.46	-0.042	0.24
CHO	1.017	0.17	0.538	0.13	-0.029	0.66	0.051	0.13
FAT^2	1.087	0.44	0.134	0.61	0.096	0.47	0.033	0.17
CHO^2	0.941	0.54	-0.048	0.76	0.123	0.39	-0.005	0.73
FAT x CHO	2.071	0.47	-0.300	0.44	0.208	0.45	-0.049	0.17
AGE	-	-	-	-	-0.197	0.00	-0.192	0.00
AGE^2	-	-	-	-	0.006	0.00	0.005	0.00

PERCENT - Macronutrients are represented as a percentage of total energy intake to explore impacts of the relative distribution of macronutrients. GRAM - Models contain no adjustment for total energy intake to explore the direct impact of absolute grams of each macronutrient.

FIGURES

Figure 3.1

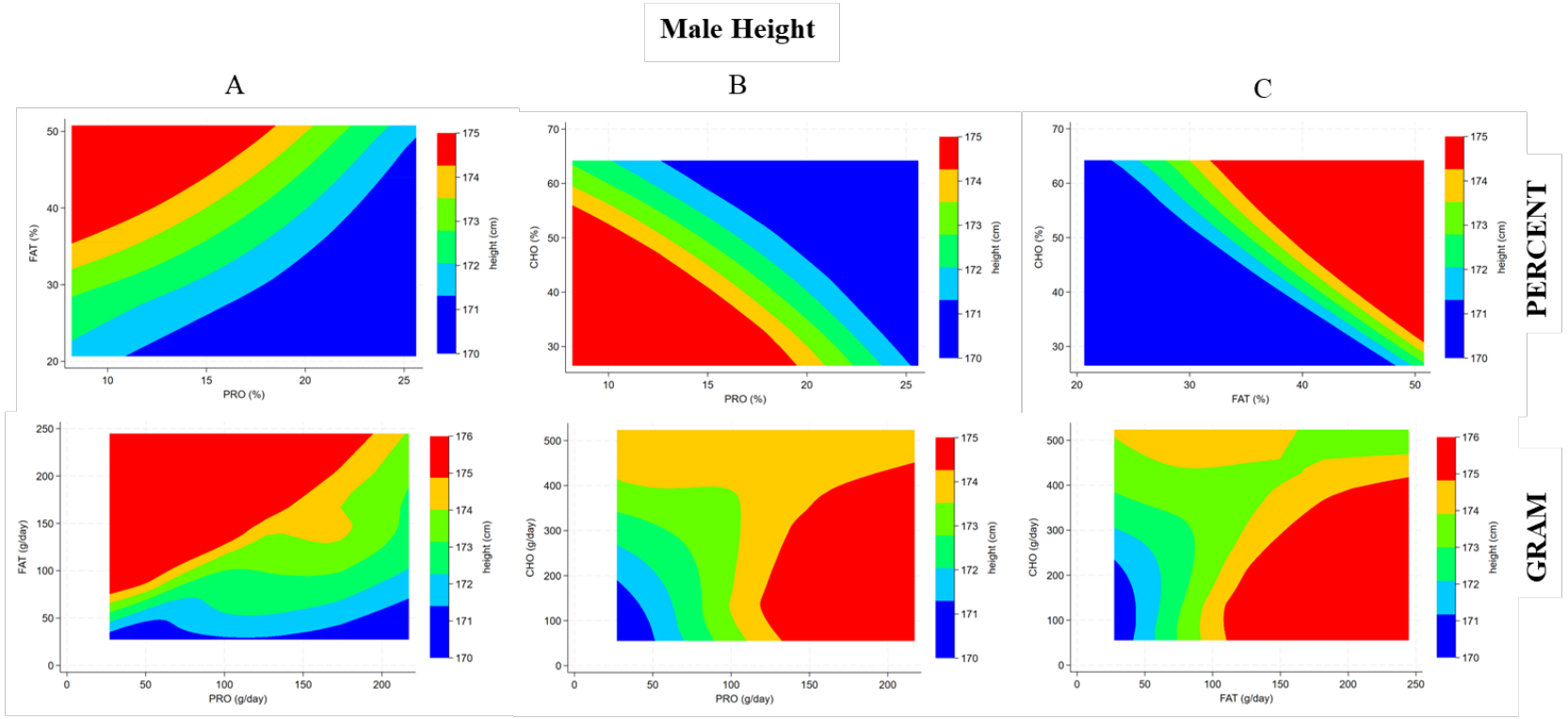


Figure 3.1: Response surface maps (RSM) of height in boys. Response surface analysis (RSA) models were used to create RSM to visualize relationships of maximal height with macronutrient distribution. RSA model coefficient results and significance can be found in Table 3.1. **Row 1:** Relative percent variable analysis. **Row 2:** Absolute gram variable analysis. Protein (PRO), carbohydrate (CHO), and fat (FAT).

Figure 3.2

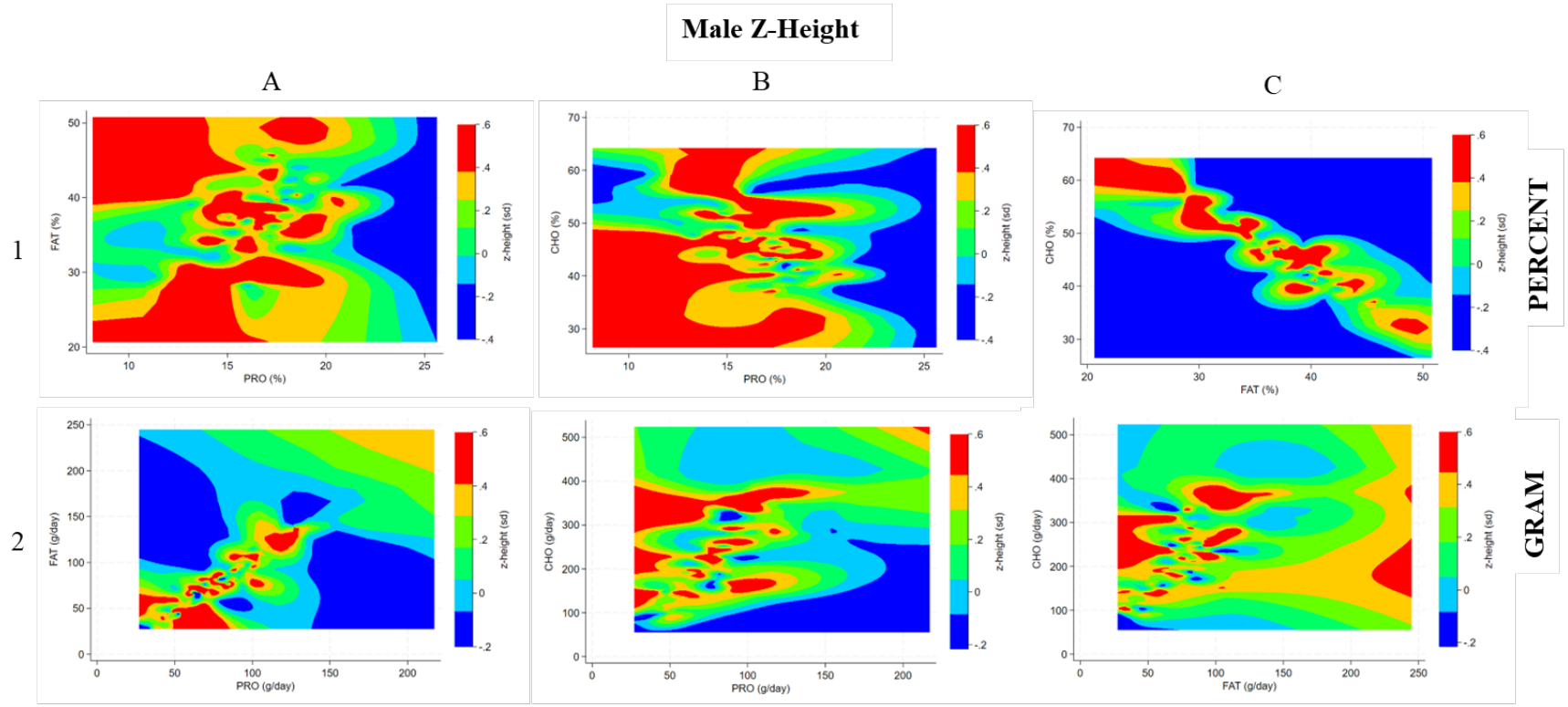


Figure 3.2: Response surface maps (RSM) of z-height in boys. Response surface analysis (RSA) models were used to create RSM to visualize relationships of normal z-height with macronutrient distribution. RSA model coefficient results and significance can be found in Table 3.1. **Row 1:** Relative percent variable analysis. **Row 2:** Absolute gram variable analysis. Protein (PRO), carbohydrate (CHO), and fat (FAT).

Figure 3.3

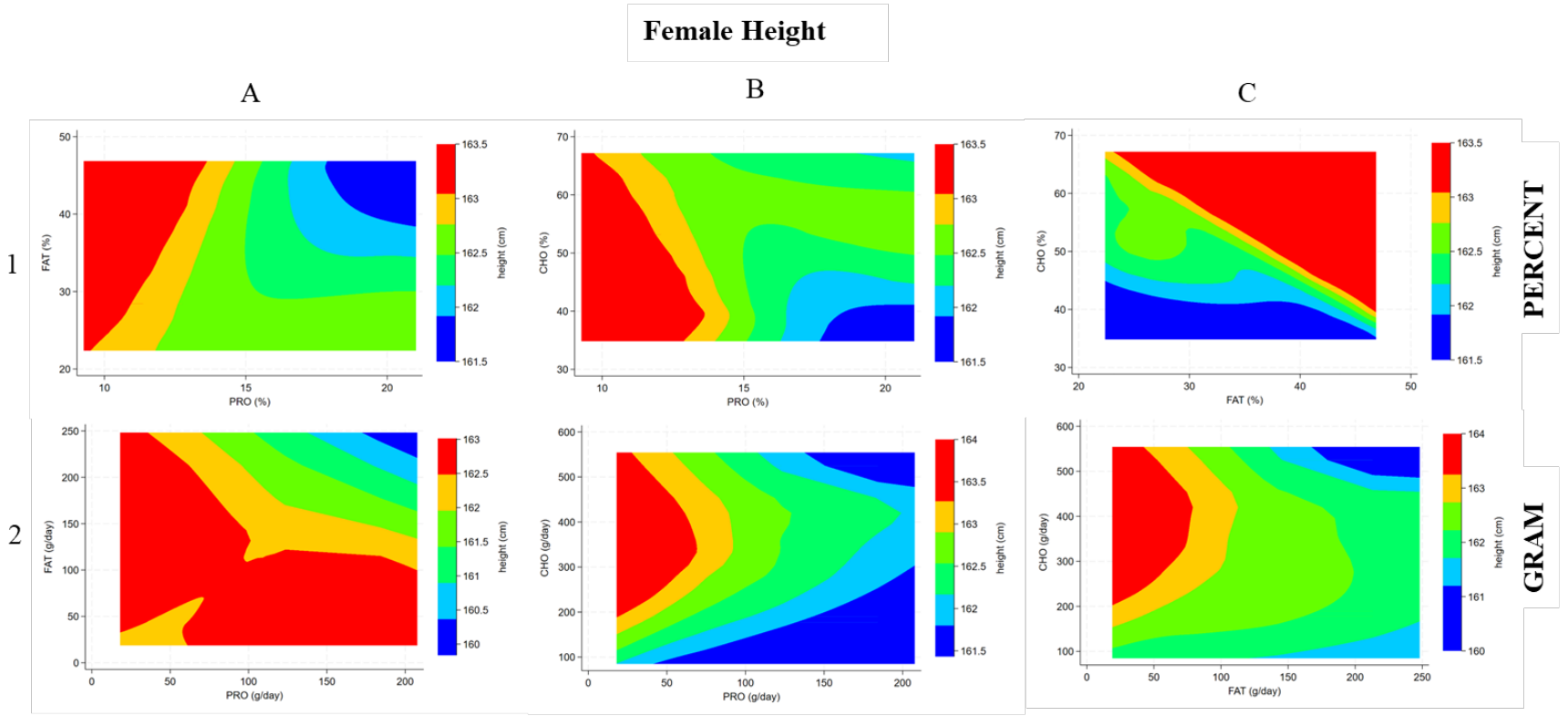


Figure 3.3: Response surface maps (RSM) of height in girls. Response surface analysis (RSA) models were used to create RSM to visualize relationships of maximal height with macronutrient distribution. RSA model coefficient results and significance can be found in Table 3.2. **Row 1:** Relative percent variable analysis. **Row 2:** Absolute gram variable analysis. Protein (PRO), carbohydrate (CHO), and fat (FAT).

Figure 3.4

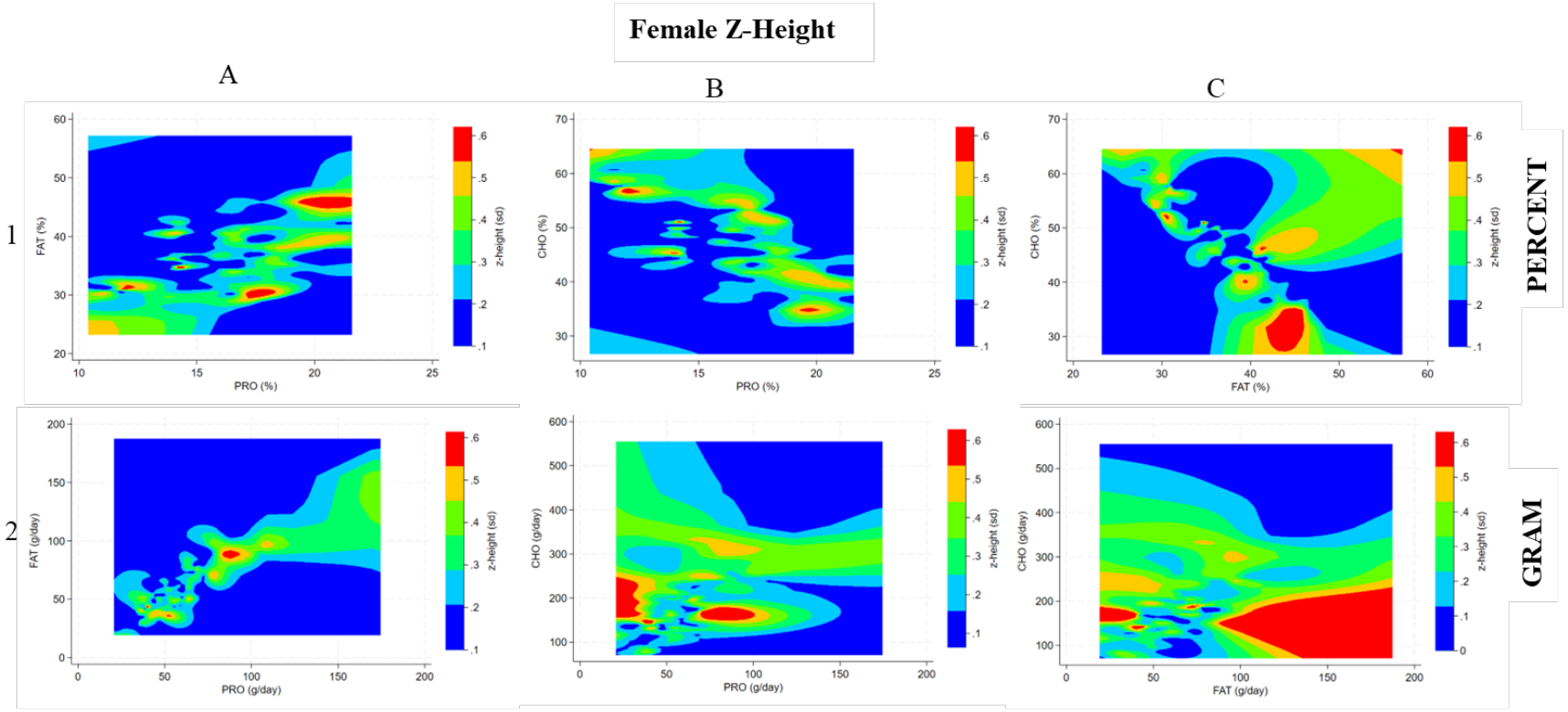


Figure 3.4: Response surface maps (RSM) of z-height in girls. Response surface analysis (RSA) models were used to create RSM to visualize relationships of normal z-height with macronutrient distribution. RSA model coefficient results and significance can be found in Table 3.2. **Row 1:** Relative percent variable analysis. **Row 2:** Absolute gram variable analysis. Protein (PRO), carbohydrate (CHO), and fat (FAT).

Figure 3.5

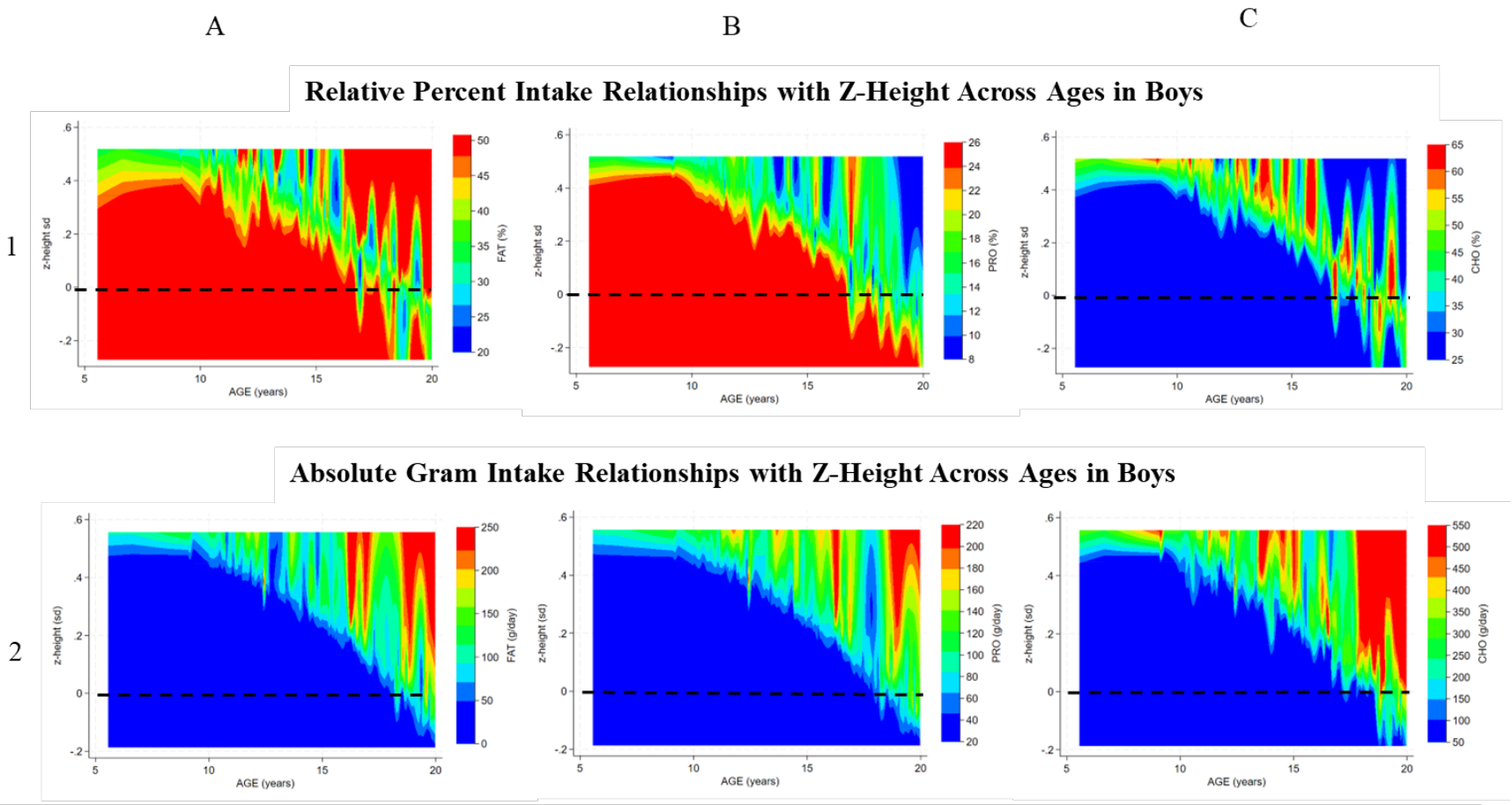


Figure 3.5: Response surface maps (RSM) of z-height relationships in boys. Row 1: Relative percent macronutrient relationships across ages. **Row 2:** Absolute gram macronutrient relationships across ages. The dashed line defines normal (0) z-height.

Figure 3.6

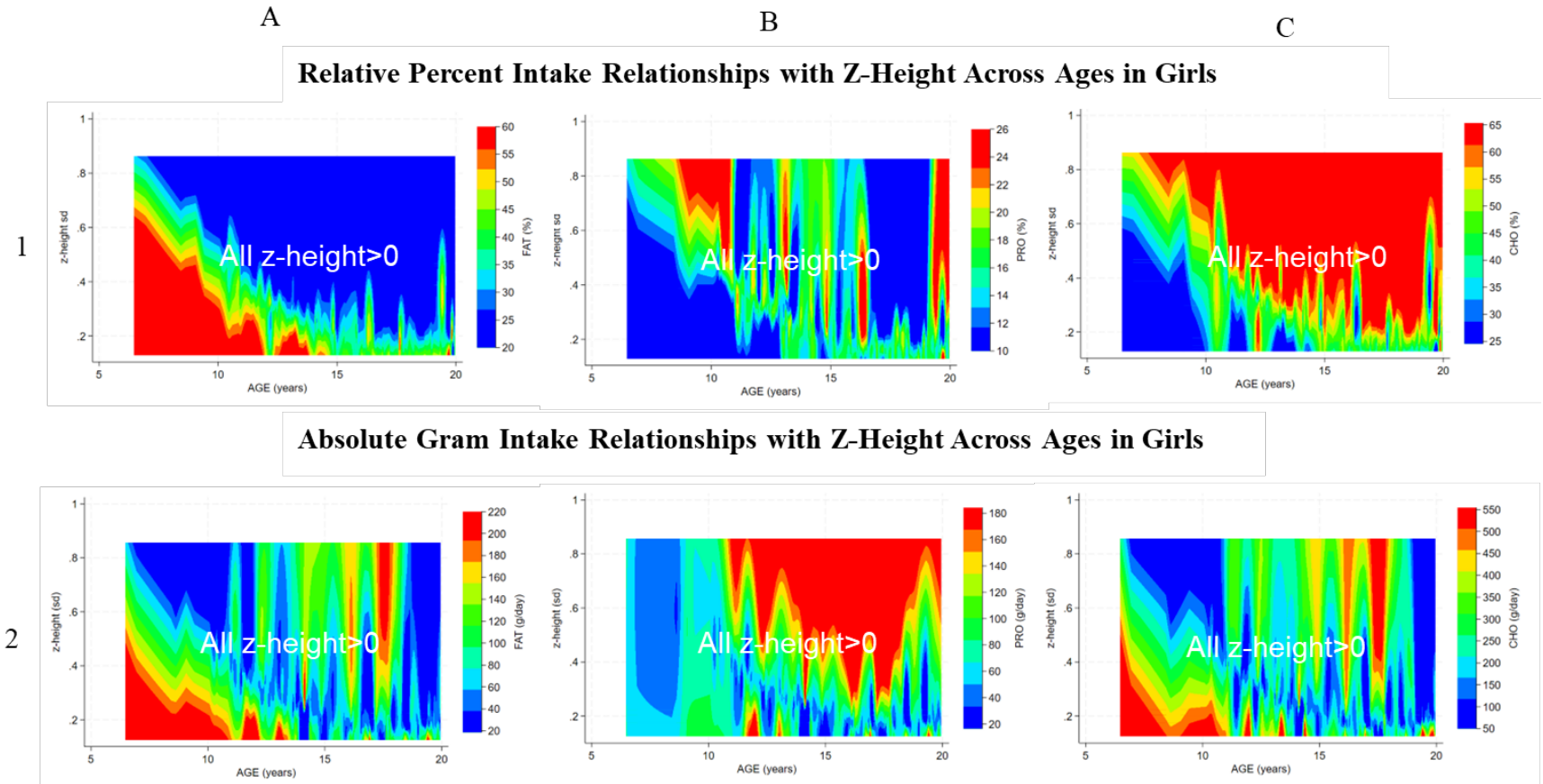
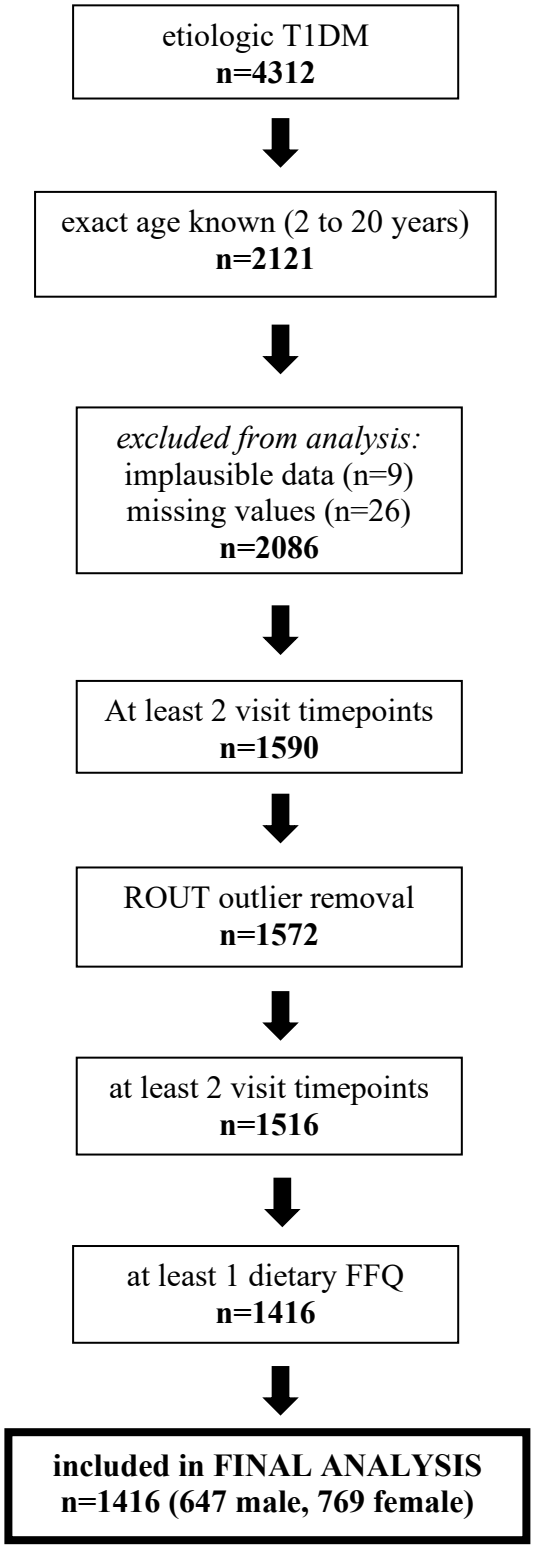


Figure 3.6: Response surface maps (RSM) of z-height relationships in girls. Row 1: Relative percent macronutrient relationships across ages. **Row 2:** Absolute gram macronutrient relationships across ages. The dashed line defines normal (0) z-height.

SUPPLEMENTS

Supplement 3.1

Supplement 3.1: Inclusion and exclusion flowchart of participants.



Supplement 3.2

Supplement 3.2. Participant baseline characteristics.

	Males	Females	Total
		Mean and (SD)	
No. participants	589	704	1293
Age (years)	10.32 (3.51)	9.71 (3.34)	9.99 (3.43)
Age at diagnosis (years)	9.54 (3.50)	8.91 (3.37)	9.19 (3.45)
Birthweight (grams)	3451.33 (602.58)	3329.64 (570.91)	3384.29 (588.18)
HbA1c (%)	7.57 (1.45)	7.64 (1.38)	7.61 (1.41)
		n and (%)	
Income (USD)			
=<$25K	80 (14.7%)	87 (13.4%)	167 (14.0%)
$25-49K	111 (20.3%)	142 (21.9%)	253 (21.2%)
$50-75K	119 (21.8%)	136 (21.0%)	255 (21.4%)
$75K+	236 (43.2%)	282 (43.6%)	518 (43.4%)
Race			
White	432 (73.3%)	489 (69.5%)	921 (71.2%)
Hispanic	89 (15.1%)	105 (14.9%)	194 (15.0%)
Black	40 (6.8%)	63 (8.9%)	103 (8.0%)
Other	28 (4.8%)	47 (6.7%)	75 (5.8%)
Parent Education			
Less than high school	22 (3.8%)	19 (2.7%)	41 (3.2%)
High school degree	87 (14.9%)	99 (14.2%)	186 (14.5%)
Some college to Associates	170 (29.2%)	220 (31.6%)	390 (30.5%)
Bachelors or more	303 (52.1%)	359 (51.5%)	662 (51.8%)

USD, United States Dollar.

Supplement 3.3

Supplement 3.3: Example code for MIXED effects quadratic polynomial response surface analysis (RSA) models and associated response surface maps (RSM)

```
**********************************************************************
*-twoway contour- takes too long to run, so must use subsample for graphing of RSMs
*all RSAs still run on FULL dataset
*50
set seed 12345
randomselect if GENDERr==0 & PROper!=., gen(selected_males) select(id) n(50)
set seed 12345
randomselect if GENDERr==1 & PROper!=., gen(selected_females) select(id) n(50)

**********************************************************************
*HEIGHT PERCENT MODEL, id:AGE as REs
**********************************************************************
*RSA: HEIGHT, PERCENT, PRO/FAT, BOYS
mixed HEIGHT PROper_std FATper_std PROper_quad FATper_quad PROperxFATper
if GENDERr==0 || id:AGE , covariance(unstructured)
estat ic
estimates store HEIGHTm_PFper_MIXED
predict HEIGHTm_PFper_MIXED if e(sample)
*RSM: HEIGHT(z), FATper(y), PROper(x)
twoway contour HEIGHTm_PFper_MIXED FATper PROper if selected_males==1,
interp(thinplatespline) level(6) ztitle(height (cm) ) ytitle(FAT (%)) xtitle(PRO (%))
zlabel(#6)

**********************************************************************
*HEIGHT GRAM MODEL, id:AGE as REs
**********************************************************************
*RSA: HEIGHT, GRAM, PRO/FAT, BOYS
mixed HEIGHT PROgrm_std FATgrm_std PROgrm_quad FATgrm_quad
PROgrmxFATgrm if GENDERr==0 || id:AGE , covariance(unstructured)
estat ic
estimates store HEIGHTm_TPFgrm_MIXED
predict HEIGHTm_TPFgrm_MIXED if e(sample)
*RSM: HEIGHT(z), FATgrm(y), PROgrm(x)
twoway contour HEIGHTm_PFgrm_MIXED FATgrm PROgrm if selected_males==1,
interp(thinplatespline) level(6) ztitle(height (cm) ) ytitle(FAT (g/day)) xtitle(PRO
(g/day)) zlabel(#6)

**********************************************************************
* Z-HEIGHT + AGE, PERCENT, id as RE, AGE as FE
**********************************************************************
*RSA: Z-HEIGHT, PERCENT, PRO/FAT, BOYS
mixed heightz PROper_std FATper_std PROper_quad FATper_quad PROperxFATper
AGE AGE_quad if GENDERr==0 || id: , covariance(unstructured)
```

```
estimates store zHEIGHTm_PFper_MIXED
predict zHEIGHTm_PFper_MIXED if e(sample)
*RSM: HEIGHT(z), FATper(y), PROper(x)
twoway contour zHEIGHTm_PFper_MIXED FATper PROper if selected_males==1,
interp(thinplatespline) level(6) ztitle(z-height (sd) ) ytitle(FAT (%)) xtitle(PRO (%))
zlabel(#6)

*AGE PERCENT RSM:
*RSM: FATper(z), z-height(y), AGE(x)
twoway contour FATper zHEIGHTm_PFper_MIXED AGE if selected_males100==1,
interp(thinplatespline) level(10) ztitle(FAT (%) ) ytitle(z-height sd) xtitle(AGE (years))
zlabel(#10)
*RSM: PROper(z), z-height(y), AGE(x)
twoway contour PROper zHEIGHTm_PFper_MIXED AGE if selected_males100==1,
interp(thinplatespline) level(10) ztitle(PRO (%) ) ytitle(z-height sd) xtitle(AGE (years))
zlabel(#10)

**********************************************************************
* Z-HEIGHT + AGE, GRAMS, id as RE, AGE as FE
**********************************************************************
*RSA: Z-HEIGHT, GRAMS, PRO/FAT, BOYS
mixed heightz PROgrm_std FATgrm_std PROgrm_quad FATgrm_quad
PROgrmxFATgrm AGE AGE_quad if GENDERr==0 || id: , covariance(unstructured)
estimates store zHEIGHTm_PFgrm_MIXED
predict zHEIGHTm_PFgrm_MIXED if e(sample)
*RSM: HEIGHT(z), FATgrm(y), PROgrm(x)
twoway contour zHEIGHTm_PFgrm_MIXED FATgrm PROgrm if selected_males==1,
interp(thinplatespline) level(6) ztitle(z-height (sd) ) ytitle(FAT (g/day)) xtitle(PRO
(g/day)) zlabel(#6)

*AGE GRAM RSM:
*RSM: FATgrm(z), z-height(y), AGE(x)
twoway contour FATgrm zHEIGHTm_PFgrm_MIXED AGE if selected_males100==1,
interp(thinplatespline) level(10) ztitle(FAT (%) ) ytitle(z-height sd) xtitle(AGE (years))
zlabel(#10)
*RSM: PROgrm(z), z-height(y), AGE(x)
twoway contour PROgrm zHEIGHTm_PFper_MIXED AGE if selected_males100==1,
interp(thinplatespline) level(10) ztitle(PRO (%) ) ytitle(z-height sd) xtitle(AGE (years))
zlabel(#10)
```

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