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Editorial Board

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Editorial

Developmental Origins of Pediatric Obesity

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Obesity is a global pandemic, with rates increasing in both the developed and developing world. Childhood obesity is a significant concern as it has negative consequences for other childhood morbidities and is often associated with adult obesity, diabetes, and cardiovascular disease.

There is an increasing body of evidence to suggest that obesity can develop in relation to early life events. This special issue focuses on new research into the developmental origins of childhood obesity. The early determinants of obesity are elegantly described in a paper in this special issue by K. E. Rhee and colleagues. They describe that genes, epigenetics, and the *in utero* environment can affect whether or not a child develops obesity. In general, obese parents are more likely to have obese children, and genetic makeup plays a role. The tremendous increase in obesity prevalence in the past decades, however, cannot be explained by genetic change alone. The change in prevalence over time has simply been too fast. The environment has changed and it is likely that a combination of genetic susceptibility to obesity with an obesogenic environment explains a large part of the rise in pediatric obesity. This gene-environment interaction may also explain individual variations in obesity development, that is, why one sedentary child eating a high-fat diet becomes obese and another child who eats similarly does not. The developmental origins hypothesis, which proposes that suboptimal conditions in early life can alter gene expression and lead to lifelong changes in the body's organs and tissues, could help to explain such enigmas. A paper by J. G. Eriksson and colleagues, in this special issue, describes an example of such a gene-environment interaction. In the Helsinki birth cohort study, they found that placental size and shape were associated with obesity, but that the associations depended on genetic makeup. A large placenta was associated with overweight status and high percent body fat in a subset of men and women whose mothers were tall and who carried the Pro12Pro genotype of the PPARγ 2 gene. This suggests that there is interplay between nutritional factors and genes at the placental level that affects later risk for obesity.

Two papers in this special issue describe modifiable maternal factors associated with offspring risk for obesity. Using data on over 40 thousand mother-child pairs from the Danish National Birth Cohort, the study by C. S. Andersen et al. describes how maternal exercise during pregnancy relates to offspring BMI at age 7 years. Maternal recreational exercise during early and late pregnancy was related to offspring BMI and obesity risk when they were 7 years old. While recreational exercise during pregnancy was inversely related to offspring BMI, the associations were largely explained by lifestyle factors such as smoking, socioeconomic status, and maternal prepregnancy BMI. Additionally, exercise intensity or changes in exercise habits during pregnancy were not related to the children's BMI or obesity risk. The other paper that addresses the association between modifiable factors during pregnancy and offspring's obesity underscores the impact of smoking. Using analyses of the NHANES data, S. E. Messiah et al. showed that smoking during pregnancy was associated with higher risk of obesity in the offspring. Additionally, breastfeeding was protective against early childhood obesity. These 2 papers add additional evidence supporting the importance of ongoing maternal exercise, refraining from

smoking and breastfeeding as strategies to reduce risk for offspring obesity.

Also included are 2 papers assessing the risk of higher weight gain over the first 3 months of life on later health outcomes. From a population-based cohort of healthy newborns in the Netherlands, A. M. V. Evelein et al. found that increased weight for length gain during the first 3 months was associated with higher BMI and subcutaneous abdominal fat 5 years later. Their finding was independent of birth weight and therefore of fetal weight gain. This suggests that accretion of fat over the first months of life is associated with body fat later in childhood. Also assessing the role of weight gain over the first 3 months of life, K. Khuc et al. found an association with signs of the metabolic syndrome at 16 years in a longitudinal cohort from Santiago, Chile. They found that early infancy weight gain was significantly associated with a higher metabolic syndrome risk score in adolescence. On the other hand, exclusive breastfeeding for 90 days or more was protective for signs of the metabolic syndrome. While the contexts of these 2 studies are markedly different, both find that more rapid weight gain in the first months of life is associated with risk for potentially adverse outcomes, years later.

D. E. Kang Sim and colleagues assessed determinants of infant growth. In a cohort of low- to middle-income Chilean infants, they assessed the relationship of psychosocial factors to infant length and weight gain, finding that higher SES was directly related to length growth over the first year, consistent with the well-known association between social status and height. Higher SES was also related to weight gain but indirectly through family factors including family composition, the physical environment, and maternal warmth. All of the factors associated with more rapid weight gain were markers of good nurturing. Failure to thrive (undernutrition) was nonexistent in this cohort. In an era of overnutrition, it is sobering to grasp that good parenting may create risk for the development of obesity and related cardiovascular and metabolic risk.

Nutritional status outside of infancy can also create risk for obesity. The paper by A. F. M. van Abeelen et al. on the role of exposure to various degrees of undernutrition during the Dutch Hunger Winter demonstrates that a limited period of severe childhood undernutrition, followed by adequate nutrition was associated with higher BMI and waist circumference, measured approximately 50 years later, in exposed women compared to those who were relatively unexposed. Furthermore, the risk for overweight or obesity was significantly increased in women who had been severely exposed to famine between birth and 9 years compared to women in the same age cohort who were relatively unexposed.

The evidence presented in this issue supports the notion that obesity prevention should start *before conception and extend at least through the first 1 to 2 years of life*. Acting early can change lifetime predisposition for obesity not only effectively but also cost effectively. Research on the developmental origins should now move beyond the descriptive stage to a more proactive stage; addressing the controlled evaluation of preventive strategies based on recent findings such as those reported in this special issue of the International Journal of Pediatrics. We are faced with pressing questions related to bringing evidence from epidemiological and clinical studies to clinical and community-based interventions. On the one hand, how do we translate these findings to actual recommendations for health professionals, especially obstetricians and pediatric practitioners? And, on the other, how do we effectively implement evidence-based recommendations on a sufficiently large-scale to have a measurable impact? We must start from a firm base of normative data on normal growth in utero and after birth. These standards should be based on longitudinal follow-up of large cohorts, with defined normative entry criteria, living in environments that promote and support normal growth. The soon-to-be released international fetal growth curves from the intergrowth study will provide normative longitudinal data for *in utero* fetal growth for the first time [1]. The multicentre growth reference study (WHO growth standards) for infants and children up to age 5 years of age, based on infants predominantly breast fed for the first 6 months of life, are the best available growth standards for now [2]. Eventually optimal growth should be defined related to long-term health outcomes.

It is crucial to develop and test new clinical models. We must convey the need to prepare for pregnancy as a first vital step for the critical stages of implantation and placentation, which support normal embryonic development. This major change in clinical care requires the establishment of a standard preconceptional reproductive health visit. This visit would allow clinicians to focus on normalizing prepregnancy weight and ensuring micronutrient sufficiency as a first step to optimal preconceptual health. Prior to pregnancy, it is important to insure that women have nutritious diets that prevent excess adiposity and supply appropriate doses of folate, iron, and zinc. At the current time, we do not know the best nutritional strategies for pregnancy in overweight and obese women. Recent Institute of Medicine (IOM) recommendations for weight gain during pregnancy (tailored to prepregnancy weight status) provide the basis for developing clinical guidelines to achieve these goals [3]. Furthermore, in developing countries, guidelines for nutrition in pregnancy should consider maternal height as it signals the mother's past nutritional status. It is important to be mindful of the risk of excess nutrition especially in those who experienced inadequate nutrition in early life.

In most settings, clinical practices are left for each practitioner to decide. For example, we lack good evidence for nutritional guidance during the transitional feeding period for infants from 6 to 12 months. In addition, there is also almost no information on how to achieve physical activity recommendations during pregnancy and infancy, and even less, on how to effectively transmit these messages to best promote and support behavior changes at the population level. Health professionals are faced with the challenge of providing diet and physical activity recommendations based on their own experience and criteria. Normative growth monitoring and recommended actions to be taken when deviations from the norm occur are seldom standardized. Appropriate responses to questions such as, "When is weight

gain during pregnancy a matter of concern?" or "When should complementary foods or formula supplementation be provided for an infant who is failing to grow?" remain unspecified in most primary health settings worldwide. More importantly, current decision-making algorithms are almost nonexistent.

If we want to maximize the results of obesity preventive actions, we urgently need clinic-, community- and health system-based intervention trials to address these issues. Formative research is also required to improve delivery of strategies with known effectiveness. Therein lies the greatest opportunity for moving from efficacy to effectiveness and public health impact. Most countries have maternal and infant nutrition health and welfare programs in place, providing unique opportunities for testing and evaluating these recommended actions. Effective interventions could then be implemented at scale; thus expanding the impact to the health of entire populations. Early life should now be presented not only as a very attractive window for effective prevention of undernutrition [4] but also for obesity preventive actions. In fact, we should focus on the time from before conception to 2 years postnatal life as critical to the prevention of malnutrition in all its forms [5] and the promotion of "healthy growth." We can begin with recent guidance regarding growth monitoring during pregnancy (IOM recommendations) and infancy (WHO standards), and continue to promote breastfeeding as the best feeding mode for the first 6 months of life.

While the latest systematic Cochrane review finds limited effectiveness from controlled interventions on prevention of childhood obesity [6], there is reason for optimism. The Healthy Beginnings Trial from Australia, a recent large randomized-controlled trial of a home-based early life intervention delivered by trained community nurses, resulted in improvements in TV viewing and feeding/eating behaviors and a significant reduction in mean BMI at 2 years [7]. The goal for new clinical practices is to promote appropriate adiposity for life-long health. In order to do this, we need new clinical approaches as outlined but this will not be sufficient. All of these efforts will be futile if we fail to build environments that facilitate and sustain changes aimed at healthy nutrition and physically active lifestyles [8]. The combination of promoting optimal weight gain from the time of conception continuing into childhood with healthy environments will ensure improved long-term health for our children and generations to come.

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Research Article

Adolescent Metabolic Syndrome Risk Is Increased with Higher Infancy Weight Gain and Decreased with Longer Breast Feeding

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Background. Prevalence of the metabolic syndrome is increasing in pediatric age groups worldwide. Meeting the criteria for the metabolic syndrome puts children at risk for later cardiovascular and metabolic disease. *Methods*. Using linear regression, we examined the association between infant weight gain from birth to 3 months and risk for the metabolic syndrome among 16- to 17-year-old Chilean adolescents ($n = 357$), accounting for the extent of breastfeeding in infancy and known covariates including gender, birth weight, and socioeconomic status. *Results*. Participants were approximately half male (51%), born at 40 weeks of gestation weighing 3.5 kg, and 48% were exclusively breastfed for ≥ 90 days. Factors independently associated with increased risk of metabolic syndrome in adolescence were faster weight gain in the first 3 months of life ($B = 0.16$, $P < 0.05$) and male gender ($B = 0.24$, $P < 0.05$). Breastfeeding as the sole source of milk for ≥ 90 days was associated with significantly decreased risk of metabolic syndrome ($B = -0.16$). *Conclusion*. This study adds to current knowledge about early infant growth and breastfeeding and their long-term health effects.

1. Introduction

As the prevalence of obesity in children and adolescents has escalated worldwide, signs of the metabolic syndrome (MetS) are increasingly observed in the pediatric age range [1]. MetS refers to a cluster of abnormal physical examination and laboratory findings, including high waist circumference, serum triglyceride, serum glucose, and blood pressure, and low-serum HDL-cholesterol. These findings synergistically relate to risk for developing type 2 diabetes and cardiovascular diseases (CVDs), including coronary artery disease and stroke [2–4]. In a study of a representative sample of US 12- to 19-year-old, 8.6% met criteria for MetS; Hispanic youth had a higher prevalence (11.2%) than white (8.9%) or black adolescents (4.0%) [2]. Children who meet the criteria are at increased risk for CVD in adulthood [5]. Focusing on the MetS during the pediatric period is expected to lead to early-prevention strategies for diabetes and CVD [5].

A large body of evidence suggests that metabolic programming can occur early in life [6–8]. Early-life risk factors include low birth weight and rapid postnatal weight gain. Breastfeeding including duration and dose appears to offer protection for obesity, type 2 diabetes, the MetS, and CVD [9–12]. In fact, the time immediately before and after birth may be a sensitive period related to metabolic and cardiovascular risk [13]. Rapid post-natal weight gain is associated with increased risk for obesity, type 2 diabetes and hypertension in young adulthood [13–18]. Infant weight gain, especially in the first 3 months, may be more important than birth weight as a predictor of later health outcomes [13]. Adolescent MetS has previously been found to be associated with infancy growth in the setting of a developed country [19].

Much of the work on fetal origins of disease has been done in developed countries beginning with Barker's work in England [7]. Research in low- to middle-income countries is needed to further delineate the roles of biology and environment related to early-life risk for cardiovascular disease and related conditions. Our cohort of low- to middle-income Chilean adolescents, studied since infancy, provides a special opportunity to address these research questions, especially because the participants were born during a period of rapid nutritional and economic transition in Chile. This transition was characterized by economic progress that led to increased consumption of calories, fat, animal protein, and processed foods, and increased mortality from non-communicable chronic diseases [20]. The aims of this study were to examine the association between infant weight gain from birth to 3 months and risk for the MetS in mid-adolescence, accounting for the extent of exclusive breast-feeding in infancy and covariates known to be associated with infant growth and the MetS, gender, birth weight, and socioeconomic status (SES).

2. Methods

2.1. Cohort. This is an observational cohort study involving adolescents who were enrolled as infants in a randomized controlled trial of iron supplementation to prevent iron deficiency anemia. Infants were enrolled from 1991–1996 in Santiago, Chile; 1657 infants completed the preventive trial at 1 year. The inclusion criteria for the preventive trial were infant birth weight of 3 kg or more, with no birth complications, major congenital abnormalities, or prior iron therapy. Due to a highly successful national breastfeeding campaign, all but 8 infants in the cohort were initially breastfed. Infants were randomly assigned to low or high iron supplementation, or usual nutrition (no added iron). A more detailed description of randomization techniques, sampling, and entrance and exclusion criteria is published elsewhere [21]. The participants have been involved in follow-up studies at 5, 10, and 16 years. At 16 years, the participants from the longitudinal cohort were invited to enroll in a study of adolescent obesity and cardiovascular risk. We report on the first 384 studied from a randomly selected sample of the original cohort evaluated at 16 years between May 2009 and January 2011. Complete data from the infancy and adolescent waves were available for 357 of the 384 adolescents. Infancy variables (birth weight, weight at 3 months, and gestational age) did not differ between the 357 studied and the original 1657 infant participants. Our analytic sample was more likely to receive bottle supplementation before 90 days, compared to the larger cohort (52% versus 45%, $P < 0.05$). The longitudinal study has been approved by the institutional review boards of the University of Michigan, Ann Arbor USA; Institute of Nutrition and Food Technology, University of Chile, Santiago, Chile for each wave of study; by the University of California, San Diego, for the 16-year study of obesity and cardiovascular risk.

2.2. Infancy Data. We included the following infancy measures: gender, weight measured at birth and at 3 months, and date of the first supplemental bottle. Maternal education was used as a proxy for SES. Mother's prepregnancy BMI was calculated from measured height and self-report of prepregnancy weight. Data on pre-pregnancy weight was not collected for the infancy study. During the 10-year wave of data collection, mothers reported their pre-pregnancy weight; it was highly correlated with their actual weight 10 years later.

2.3. Adolescent Data. Adolescents were assessed between 16 and 17 years during the fourth wave of the longitudinal research study (infancy, 5 years, 10 years, and 16-17 years). Height (cm), weight (kg), waist and hip circumference (cm), and blood pressure (mm Hg) were measured by a physician-investigator at the nutrition research center. Standardized procedures [22] were used to measure weight to the closest 0.1 kg, using a SECA scale, and height to the closest 0.1 cm, using a Holtain stadiometer. Measurements were taken twice, with a third measurement if the difference between the first two exceeded 0.3 kg for weight and 0.5 cm for height. Fasting serum triglyceride, cholesterol, and glucose levels were performed. Serum glucose concentration (mg/dL), triglycerides (mg/dL), and cholesterol (mg/dL) levels were determined using an enzymatic-colorimetric test (QCA S.A., Amposta, Spain). Using a standardized questionnaire, parents reported family history of type 2 diabetes, hypertension, dyslipidemia, and heart attack before the age of 60, in first-degree relatives.

2.4. Statistical Analysis. Infant weight gain in the first 3 months was calculated as weight gain velocity over the first 3 months (91.3 days): (weight [kg] at 3-month birth weight [kg])/(age at 3-month measurement $*$ 91.3 days). Extent of breastfeeding was assessed as a dichotomous variable representing breastfeeding without bottle supplementation for less than 90 days, compared to 90 days or more. Data was not available on introduction of complementary foods. Maternal education was assessed as a continuous measure (median for sample = 10 years). We constructed a metabolic syndrome risk z-score according to the work of Brage and colleagues [23]. The following variables were converted to z-scores: the reciprocal of the HDL value, the mean of the systolic and diastolic blood pressure measurements, waist circumference, fasting serum triglyceride, and glucose. We obtained a continuous, normally distributed metabolic risk z-score by averaging these 5 values.

For descriptive statistics, continuous variables were expressed as median and interquartile ranges and categorical variables as frequencies. We evaluated cardio/metabolic risk factors and overall prevalence of the MetS according to International Diabetes Federation definition [24]: waist circumference $\geq$94 cm for boys and $\geq$80 cm for girls, plus any two of the following four factors: triglycerides $\geq$1.7 mmol/L, HDL-cholesterol <40 mg/dL in males and <50 mg/dL in females, systolic BP $\geq$130 or diastolic BP $\geq$85 mm Hg, fasting plasma glucose $\geq$100 mg/dL. BMI percentile was described according to CDC standards.

We used SPSS for Windows version 18.0 (Chicago, IL, USA), a P value of <0.05 denoted statistical significance. Multiple linear regression models were used to determine the relationship between change in weight (kg) in the first 3 months and metabolic syndrome risk z-score, adjusting for extent of breastfeeding and the following covariates: birth weight, gender, SES, age, mother's age at birth of infant, mother's pre-pregnancy BMI, and family history of type 2 diabetes, dyslipidemia, and heart attack. We tested the full model and then, using backward elimination, removed each variable that was not significantly related to the outcome in the model based on a significant P value of <0.05. As the sample came from an iron-deficient anemia prevention trial, we tested whether iron-deficient anemia during the first year of life or iron supplementation were significant covariates in our models. Neither variable showed significant relationship in the models and were thus removed from the final models.

3. Results

Participants were assessed at a mean age of 16.6 years. Males and females represented about 51% and 49% of the sample, respectively. Participants had been born at 40 weeks of gestation weighing 3.5 kg, on average, and 48% were exclusively breastfed for ≥90 days. The median BMI percentile was 68.7 with 15.2% in the obese range and 10.4% met criteria for MetS. Table 1 describes infant and family background characteristics by gender of the 357 participants in infancy and adolescence. Cardio/metabolic risk factors are also described. Males had higher birth length, weight at three months, and higher weight gain between birth and 3 months compared to females. Males also had significantly lower HDL cholesterol and higher blood pressure values (systolic and diastolic), glucose and MetS risk z-scores than females. There were no significant differences between males and females in gestational age, birth weight, maternal education, exclusive breastfeeding for ≥90 days, and prevalence of the MetS.

The multiple variable linear regression models (full and final) are shown in Table 2. The final model revealed that weight gain over the first three months was associated with an increased MetS risk score at 16-17 years, taking into account extent of breastfeeding and gender ($B = 0.16$, 95% CI = 0.04, 0.27, $P < 0.05$). Introduction of the first bottle at 90 days or after was related to a lower MetS risk score in adolescence ($B = -0.16$, 95% CI = -0.29, -0.04, $P < 0.05$), taking into account other covariates. Additionally, being male was associated with an increased MetS risk score in the model ($B = 0.24$, 95% CI = 0.11, 0.37, $P < 0.05$). The final model explained 9% of the variance in MetS risk.

4. Discussion

We examined weight gain in the first 3 months of life and timing of bottle supplementation related to MetS risk at 16 years. In both sexes, adolescents who had more rapid weight gain during the first 3 months of infancy had higher adolescent MetS risk scores compared to those who gained less weight in early infancy. The association of weight gain with MetS risk is consistent with findings from a study addressing the same question, in a Scandinavian country [19]. Infancy weight gain has previously been associated with later obesity in childhood and adulthood [15, 18, 25, 26]. In addition, especially for low-birth-weight infants, more rapid early weight gain, sometimes called catch-up growth, has been related to higher risk of developing type 2 diabetes and/or cardiovascular disease [10]. Contrary to our findings, a Finnish study found that infants who had low weight gain in the first 6 months had higher risk for development of glucose intolerance, an effect that was greater for those with low birth weight [27]. Since our cohort excluded infants with birth weights below 3 kg, it is clear that the association we find between infant weight gain and adolescent MetS risk is independent of low birth weight. Furthermore, this association did not depend on family history of conditions related to the MetS such as type 2 diabetes, dyslipidemia, or myocardial infarction.

There is accumulating evidence that breastfeeding offers some protection related to the development of obesity, and that the effect may be "dose-dependent" [28, 29]. Because breastfed infants gain weight more slowly over the first year compared to formula-fed infants [30, 31], infant weight gain may pertain to the mechanism that decreases obesity risk in those who were breastfed. Having been breastfed has also been associated with lower risk for hypercholesterolemia, hypertension, diabetes, glucose intolerance, and insulin resistance [9–12]. To our knowledge, no other study has shown an association between breastfeeding and MetS risk in adolescence. Importantly, the significant effects of weight gain and breastfeeding were independent, suggesting that the effect of breastfeeding on MetS risk was not mediated by early infancy weight gain.

We do not know why males had higher MetS risk scores compared to females, but they had marginally significant higher birth weights and gained more weight in the first 3 months. Nonetheless, the effect of gender on MetS was independent of birth weight and infancy weight gain. This finding is consistent with higher prevalence rates of MetS in men compared to women in Chile [32]. In US adolescents, males are also more likely to have clustering of metabolic syndrome risk factors compared to girls [2]. However, in the Scandinavian study of infant weight gain and the MetS, male gender was not related to higher MetS risk [19], even though boys were similarly heavier at birth and gained more in infancy than girls. This suggests that the effect of gender is related to context rather than biology.

Our study has several limitations. The cohort was enrolled from a low- to middle-income community in Santiago, Chile, during a period of economic and nutritional transition. The setting and the fact that children with birth weights under 3 kg were not included limits generalizability. The study also has many strengths. The context of economic growth, high rates of breastfeeding, and nutritional support for infants allowed us to assess a sample where malnutrition was not a confounding factor. The longitudinal study took place at a nutrition research center allowing for detailed anthropometric measurement during infancy and the adolescent wave of data collection. Other strengths of the

Table 1: Background characteristics of study participants by gender.[†]

	Males ($n = 181$)	Females ($n = 176$)	P value*
Infancy characteristics			
Gestational age (weeks)	40 (38–40)	40 (39-40)	0.22
Birth weight (kg)	3.50 (3.28–3.78)	3.44 (3.22–3.72)	0.05
Birth length (cm)	51.0 (50.0–52.0)	50.0 (49.0–51.5)	<0.01
Weight at 3 months (kg)	6.43 (6.00–6.99)	6.00 (5.61–6.40)	<0.01
Weight gain 0–3 months (kg)	2.85 (2.43–3.28)	2.42 (2.15–2.75)	<0.01
Total years of maternal education	10 (8–12)	10 (8–12)	0.52
Exclusively breastfed ≥90 days	45.9	50.6	0.37
Adolescent characteristics and metabolic risk factors[‡]			
Age (years)	16.6 (16.6–16.9)	16.7 (16.6–16.9)	0.15
BMI percentile	64.0 (38.6–88.2)	74.9 (46.0–89.9)	0.10
Waist circumference (cm)	78.2 (73.3–87.9)	79.7 (72.2–88.1)	0.83
Elevated percentage	16.0	49.0	<0.01
Triglycerides (mg/dL)	71.6 (55.8–99.2)	73.0 (57.2–104.4)	0.77
Elevated percentage	7.2	8.0	0.78
HDL cholesterol (mg/dL)	34.1 (28.5–40.5)	40.0 (32.5–48.3)	<0.01
Low HDL (%)	28.2	24.0	0.29
Systolic blood pressure (mm Hg)	115 (107–125)	107 (102–114)	<0.01
Elevated percentage	8.3	4.4	0.09
Diastolic blood pressure (mm Hg)	70 (67–76)	68 (61–71)	<0.01
Elevated percentage	3.9	0.6	0.03
Glucose (mg/dL)	90 (84–96)	86 (80–92)	<0.01
Elevated percentage	11.6	9.1	0.44
MetS risk z-score	0.01 (−0.23–0.40)	−0.26 (−0.53–0.02)	<0.01
MetS prevalence	11.6	9.1	0.45
Family factors			
Family history of type 2 diabetes	15.3	14.4	0.82
Family history of hypertension	42.3	40.6	0.76
Family history of dyslipidemia	33.6	45.5	0.04
Family history of heart attack	8.3	5.1	0.29

[†] Values are in median (interquartile range) or percentage. *Statistical tests are either Mann-Whitney U or Chi-square.
[‡] According to the International Diabetes Federation definition [24].

Table 2: Linear regression models to determine adjusted associations with adolescent MetS risk ($n = 357$).

	Initial model		Final model	
	β	95% CI	β	95% CI
Change in weight 0–3 months (kg)	0.15	−0.01, 0.31	0.16	0.04, 0.27
Exclusively breastfed ≥90 days	−0.19	−0.36, −0.03	−0.16	−0.29, −0.04
Male	0.23	0.05, 0.01	0.24	0.11, 0.37
Birth weight (kg)	0.09	−0.14, 0.04		
Maternal education	0.01	−0.01, 0.01		
Mother's age	0.00	−0.01, 0.01		
Maternal pre-pregnancy BMI	0.02	−0.01, 0.05		
Family history of type 2 diabetes	0.10	−0.10, 0.27		
Family history of dyslipidemia	0.00	−0.17, 0.18		
Family history of heart attack	−0.06	−0.23, 0.10		
Ever iron deficiency in infancy	−0.09	−0.35, 0.16		
Iron supplemented in infancy	0.02	−0.16, 0.20		

study include prospective data collection including monthly anthropometry in infancy and breastfeeding data collected from 4 to 12 months. In addition, the adolescent data collection included family history of diabetes, hypertension, elevated cholesterol, and heart attack.

5. Conclusion

In conclusion, this study adds to the current knowledge about early infant growth and breastfeeding and their long-term health effects. Higher infant weight gain was associated with increased MetS risk, whereas longer duration of exclusive breastfeeding was protective in healthy adolescents living in a rapidly developing country. Considering the increasing prevalence of the MetS in younger age groups and associations between the MetS and later disease, the replication and validation of these findings in different contexts is warranted.

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Review Article

Early Determinants of Obesity: Genetic, Epigenetic, and In Utero Influences

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There is an emerging body of work indicating that genes, epigenetics, and the in utero environment can impact whether or not a child is obese. While certain genes have been identified that increase one's risk for becoming obese, other factors such as excess gestational weight gain, gestational diabetes mellitus, and smoking can also influence this risk. Understanding these influences can help to inform which behaviors and exposures should be targeted if we are to decrease the prevalence of obesity. By helping parents and young children change certain behaviors and exposures during critical time periods, we may be able to alter or modify one's genetic predisposition. However, further research is needed to determine which efforts are effective at decreasing the incidence of obesity and to develop new methods of prevention. In this paper, we will discuss how genes, epigenetics, and in utero influences affect the development of obesity. We will then discuss current efforts to alter these influences and suggest future directions for this work.

1. Introduction

Childhood obesity is a worldwide public health concern with several etiologic influences. The intergenerational relationship between parent and child obesity has been welldescribed [1], and twin studies have estimated that genes are responsible for 40–75% of the phenotypic variance of obesity [2–4]. However, evolutionary changes in the genome cannot explain the tremendous increase in obesity prevalence over the past 30 years. Most likely, the genetic susceptibility to obesity has always existed, but is now becoming more evident due to the influence of the obesogenic environment. This gene-environment interaction likely drives the obesity epidemic and helps to explain individual variations in obesity development, that is, why one sedentary child eating a high-fat diet becomes obese and another child who eats similarly does not. In addition to this interaction, animal studies have suggested that epigenetic influences, like nutritional exposure in utero, can alter one's gene expression and further impact the risk for obesity. Understanding how certain factors can modify gene expression during fetal development and early childhood can help to explain the rapid rise of obesity during a time when minimal to no populationwide genomic changes have occurred. This knowledge may ultimately help us prevent the development of obesity in a significant number of children. In this paper, our goal is to outline the influence of genetic, epigenetic, and in utero factors on the development of childhood obesity. With this information, we can lay the groundwork for future obesity prevention efforts.

2. Genetics

Over the past several years, many discoveries have been made regarding the genetic variation that influences complex diseases like cardiovascular disease and obesity [5]. These new discoveries have largely resulted from genomewide association studies where the application of high-throughput genotyping of millions of genetic markers enables researchers to examine genetic associations on a genomewide basis. Recent reports indicate that at least 32 genes contribute to common forms of obesity [6–11]. A number of these have also been confirmed as contributors to pediatric obesity [10, 12]. Many

of these genes are thought to be related to the development of obesity through the dysregulation of leptin or other metabolic hormones in the body. However, a majority of the newly discovered genes are expressed in the brain, emphasizing the role of the central nervous system in obesity risk [8].

The obesity-associated variant in the *FTO* gene has garnered particular interest in pediatrics because of its association with increased weight and ponderal index at 2 weeks of age [13]. FTO is located on the long arm of chromosome 16 and is expressed in the brain, specifically the hypothalamic nuclei. Those who are homozygous for the at-risk allele have been found to be up to 3 kg heavier than those who do not have the allele [10]. This weight gain is likely due to the gene's involvement in the regulation of energy intake. According to recent studies, individuals carrying the at-risk allele prefer energy dense food [14], have reduced feelings of satiety [15], display loss of control over eating [16], consume more fat and calories (even after adjusting for BMI) [17], and display a greater tendency towards consuming palatable foods after eating a meal [18]. Thus, *FTO* seems to predispose individuals to greater caloric intake and reduced feelings of satiety. On the other hand, *FTO* does not seem to be related to energy expenditure. A meta-analysis of 45 studies found that adults who were physically active could attenuate the odds of obesity associated with *FTO* by almost 30% [19]. Thus carrying a gene for obesity does not necessarily predestine one to become obese [20] but, rather, increases one's risk in the face of an obesogenic environment. Unfortunately, this attenuation of obesity risk via physical activity was not seen in children [19]. Nevertheless, taken together, these results suggest that interventions targeting food availability or physical activity may mitigate the increased genetic risk found in those with the *FTO* gene.

In addition to common forms of obesity, several rare, monogenic forms of obesity have been described including Prader-Willi syndrome and Bardet-Biedl syndrome. One of the most common forms of monogenic obesity, representing up to 5% of severe childhood obesity, is linked to melanocortin-4 receptor (*MC4R)* gene mutations [21, 22]. The *MC4R* gene is located on the long arm of chromosome 18 and encodes a G-protein-linked receptor [23] that is primarily expressed in the brain, more specifically in the paraventricular nucleus of the hypothalamus. The receptor is typically stimulated by insulin and leptin release which signals proopiomelanocortin (POMC) neurons to synthesize and release alpha-melanocyte stimulating hormone (α-MSH). When α-MSH binds to *MC4R*, individuals begin to feel satiated and increase energy expenditure through thermogenesis. Mutations in the *MC4R* gene can decrease this response and lead to rare familial forms of severe obesity [21, 24]. Mutations lead to excess intake of energy, and individuals with this mutation have displayed a preference for foods high in total and saturated fats [25]. Unlike *FTO* however, it is also associated with decreased energy expenditure [26]. Thus mutations in *MC4R* seem to impact both sides of the energy equation, that is, by increasing consumption and decreasing expenditure. While the gene has an autosomal dominant mode of transmission, it also has incomplete penetrance, thereby making clinical diagnosis difficult. Its incomplete penetrance however suggests that other factors, possibly epigenetic or environmental, may be impacting phenotypic expression. Given the different mechanism of action associated with this gene, it is important not to lose sight of the rare but often severe forms of monogenic obesity as we consider which environmental manipulations to pursue.

3. Epigenetics

While several genes have been linked to excess weight gain, the existence of these genes cannot explain the rapidly growing prevalence of obesity. Epigenetics is the study of how early environmental influences affect gene expression and ultimately growth, development, and risk for disease without changing the underlying DNA sequence. Epigenetic mechanisms involve chemical processes such as DNA methylation, covalent modifications to histones that bind to DNA, and chromatin folding that can change gene expression and chromatin structure without changing the nucleotide sequence. Epigenetic changes can sometimes promote the expression of a gene that has typically been silent or silence a gene that is usually active. Examples of this phenomenon are widely evident as stem cells differentiate into specific somatic cells, like heart tissue or brain tissue, and genes are hypo- or hypermethylated to become cancerous.

Influences that may alter gene expression include inflammation, aging, oxidative stress, and hypoxia [27]. Scientists are also examining whether other environmental factors like maternal obesity and nutritional quality before or during pregnancy can cause epigenetic changes in the fetal genome and subsequently increase the risk of a child becoming overweight. Nutritional components that may influence the methylation of epigenetically susceptible loci include folic acid, vitamin B6 and 12, selenium, choline and betaine, methionine, soy genistein, bisphenol A, tocopherols, diallyl disulfide in garlic, and tea polyphenols [28].

4. Animal Studies

For many years, scientists have been using animal models to manipulate the genome and demonstrate how environmental exposures can alter the expression of genes so that certain characteristics, such as risk for obesity, can be suppressed or expressed. The agouti mouse, which was genetically altered to have yellow fur, has been used in many of these studies. For example, scientists have demonstrated that supplementing the mouse diet with methyl donors (like dietary folates, vitamin B_{12}, methionine, and choline) can alter the expression of their genome and revert their coat color back to black [29]. While these epigenetic changes may or may not be passed down to the next generation, it does appear that it can be re-established in subsequent generations with continued dietary supplementation [30].

Interestingly, the yellow agouti mouse is also heavier and has a higher risk for hyperinsulinemia, diabetes, and tumors. The tendency for offspring of the yellow agouti mouse to be overweight is exacerbated if dams (mothers) are overweight. Supplementing the dam's diet with methyl donors, which

has previously been shown to revert the offspring's coat color back to black, also prevented the future transmission of obesity to the offspring [31]. Thus changes in diet may be epigentically altering their genome so that these mice are phenotypically black and lean again. In addition to folate and vitamin B_{12}, genistein, the major phytoestrogen in soy, has been shown to reduce the risk of obesity in the agouti mouse [32]. Whether or not genistein has similar effects on fat mass in humans is unknown. However, it is postulated that its methylating activity may explain the difference in cancer rates between Asians and Westerners. While studies that supplement human diets with methyl donors would be difficult to conduct, these animal studies suggest that the diet of pregnant mothers may be altering gene expression via epigenetic mechanisms and would therefore play an important role in influencing the health of future offspring.

The energy density of the food consumed during gestation may also be an important factor in determining one's phenotypic expression. Offspring of rats that are genetically susceptible to diet-induced obesity (DIO) are known to be heavier than offspring of rats who are diet resistant (DR). DIO dams who consume a high-energy diet or chow (normal energy diet) during gestation generally have offspring who are heavier than those from DR mothers exposed to either diet [33]. However, the exposure to high calorie diets during the gestational period exacerbated the risk of obesity in the DIO offspring such that those who were exposed to high-energy diets had the highest birth weight (compared to DIO offspring of dams on chow diets and DR offspring of dams on high calorie or chow diets) and demonstrated the greatest weight gain during the subsequent weeks despite being on similar diets as the DR offspring.

Another rat study, controlling for genetic influence, amount of gestational weight gain in the dams, and any postnatal effects from the mother via lactation, also found that the energy density of the dam's diet affected the offspring's weight trajectory, particularly if the offspring was exposed to a high-energy diet [34]. When examining the gene expression of adipose tissue and hypothalamus, it appeared that exposure to high-energy diets in utero caused an upregulation of certain gene products in the offspring which resulted in more efficient storage of the excess energy they consumed postnatally [35]. Other studies similarly suggest that maternal food intake that leads to excess gestational weight gain and associated metabolic changes in the in utero environment are affecting hypothalamic expression of genes involved in energy regulation [36, 37]. These studies demonstrate that an obesogenic in utero environment not only affects weight status at birth, but can increase the risk for obesity by priming the offspring's body to respond in a certain way to subsequent environmental or nutritional exposures. These results suggest that efforts to reduce one's exposure to high calorie diets, in utero and after the child is born, may be quite important to reduce one's risk for obesity.

Animal studies have also examined the influence of environmental exposures like nicotine and alcohol on offspring development. Findings suggest that nicotine exposure in utero increases postnatal weight gain [38] and may affect the development of hypothalamic function and subsequent appetite control through the upregulation of certain gene products [39, 40]. When exposed to alcohol in utero, rats appear to have increased gluconeogenesis and insulin resistance, making them more at risk for Type 2 diabetes [41–43]. These studies highlight the importance of other environmental exposures in explaining the rise in obesity and its associated comorbidities.

It is important to note that epigenetic changes can also occur postnatally. Since some tissues/organs and regulatory mechanisms are not fully developed at birth, there is still time to alter the expression of these genes once the offspring are born. In animal studies, cross-fostering, or suckling offspring with nonbiological mothers, changes the nutritional exposure of the offspring and can impact the development of obesity. For example, when DR offspring (who have no genetic risk for obesity) were fostered by obese DIO dams, they gained more weight than their counterparts who were fostered by DR dams. They also developed higher levels of insulin and leptin and had higher oral glucose tolerance test results [44]. Conversely, when DIO offspring were fostered by DR dams, they gained less weight compared to those suckled by DIO dams. They also had lower basal glucose levels [44]. Cross-fostering not only affected the offspring's weight and hormone levels, but changed mRNA expression of neuropeptides, insulin, and leptin receptors in the hypothalamus. The authors postulate that elements in the breast milk (such as higher insulin levels and lower polyunsaturated and monounsaturated fatty acid content in the milk of obese DIO dams) may have played a role in influencing these outcomes.

Additional studies have examined the impact of consuming high carbohydrate (HC) milk formula on the development of rats [45]. In these studies, the nutritional quality of milk was altered from its usual fat-rich state to a high-carbohydrate state without altering the total calorie content. After exposure to this milk in the immediate postnatal period, these pups developed chronic hyperinsulinemia and adult-onset obesity. At a molecular level, these pups had greater expression of mRNA related to pancreatic islet cell function and peptides of the brain (Neuropeptide Y, Agouti-related peptide, POMC, and MC4R). They were also able to transfer these traits (or risk profile) to their offspring without any further manipulations to the offspring's diet. These studies demonstrate the power of postnatal factors in modifying one's genetic predisposition and may further explain how environmental exposures are affecting the increasing prevalence of obesity.

5. Human Studies

Replicating these studies in humans is particularly challenging because of the great variety of epigenetic mechanisms that can influence gene expression as well as a lack of understanding as to where in the human genome and when during development these changes need to occur. Furthermore, studies in humans are complicated by the myriad of interpersonal and environmental factors that influence growth and development throughout life. Finally, there are many ethical considerations when conducting randomized controlled

trials that manipulate exposures in utero and alter epigenetic expression. Conducting tests to confirm that epigenetic changes were made can also be difficult in humans, thereby limiting our ability to define clear relationships between exposures and outcomes. Given these limitations, animal studies will often be needed to infer underlying mechanisms.

However, there are some human studies that suggest epigenetic changes are occurring. One such line of research is with bariatric surgery patients. In an earlier study, Marceau et al. [46] compared the results of pregnancies in a group of women (mean BMI = 47.1 ± 8.3) *before* they had biliopancreatic diversion surgery (a form of bariatric surgery) and in another group of women *after* they had surgery (mean BMI = 30.9 ± 6.4). Of the 166 infants born in the postsurgery group, only 7.7% had fetal macrosomia (excessive weight at birth) compared to 34.8% of the infants born to mothers in the presurgery group (n = 1245 infants). In further analyses, a set of mothers who had been pregnant before and after weight loss surgery were found to have gained 50% less weight during their postsurgery pregnancy. The frequency of macrosomia was 88% lower in the postsurgery offspring and the proportion of children who were severely obese decreased by 70% [47]. These children were also noted to have lower blood glucose, insulin, and triglyceride levels. After surgery, mothers had significant reductions in BMI, blood glucose, insulin, lipid, and adipokine levels. These maternal metabolic changes likely reflect changes in the in utero environment for the fetus, suggesting that the differences in the metabolic environment aftersurgery influenced child weight outcomes. While the authors could not control for other environmental exposures and the influence of genetics, studies in animals where the mother's metabolic profile has been altered while controlling for genetic and environmental influences found similar changes in the offspring's weight as seen in this human study [34].

Several studies have also shown that excessive gestational weight gain and its associated alterations in the intrauterine environment can contribute not only to overly rapid fetal and infant growth but to the future risk of childhood overweight [48, 49]. In the Growing Up Today Study cohort, Oken and colleagues [50] were able to confirm that greater weight gain during pregnancy, controlling for maternal prepregnancy BMI, was associated with increased risk of obesity in adolescents (OR = 1.42, 95% CI 1.19–1.70). There were also greater odds of having a large-for-gestational-age (LGA) infant if the mothers gained 45 lbs or more compared to those mothers who gained 20–24 lbs (OR = 4.14, 95% CI 3.33–5.15). This study was unable to tease apart the effect of shared maternal-child dietary environments and shared genetics. However, controlling for maternal BMI helped to demonstrate that excessive weight gain itself can also affect child weight status. Other studies have shown that excess weight gain and hyperglycemia in mothers can result in fetal hyperinsulinemia, which has been associated with high birth weight and impaired glucose tolerance in adolescence [51].

In addition to weight gain, recent research has found that maternal dietary intake (specifically low carbohydrate intake) during early pregnancy was associated with gene methylation linked with higher offspring weight [52]. Other studies have also found independent associations between maternal dietary intake during pregnancy and offspring weight [53], adolescent blood pressure [54], and dietary patterns [55]. These data, in conjunction with animal data showing changes in hypothalamic gene expression when rats are exposed to certain foods in utero [36, 37], suggest that epigenetic changes may be partially mediating the effects of excess gestational weight gain and increased obesity risk in children.

In addition to gestational weight gain, gestational diabetes (GDM), which is marked by new onset hyperglycemia and insulinemia during pregnancy, has been considered another phenomenon that has the potential to alter the in utero environment and subsequent phenotypic expression of genes. In a cohort of large-for-gestational-age (LGA) and appropriate-for-gestational-age (AGA) children born to mothers with and without GDM, children who were LGA and born to mothers with GDM had the greatest risk of developing metabolic syndrome [56]. Another study showed that children born to mothers with GDM had increased odds of being overweight in adolescence (controlling for maternal SES, breast feeding history, smoking, and child diet and physical activity) [57]. However, this relationship was attenuated after taking into account birth weight and maternal weight. This study suggests that the metabolic changes that occur to the in utero environment when the mother develops gestational diabetes affects the child's birth weight, which then influences the child's risk for developing obesity. However, the fact that maternal weight attenuated the relationship calls into question whether there are other genetic factors that are passed on from mother to child that predispose both mother and child to increased weight and/or diabetes-like characteristics. These common genetic factors may ultimately make them more at risk when exposed to toxic nutritional environments postnatally.

Outside of maternal weight gain and metabolic disorders, maternal smoking is an environmental factor that seems to affect child weight status. An observational study in Australia using a cohort of 3253 children demonstrated that mothers who smoked during pregnancy compared to nonsmokers had higher odds of having overweight (OR = 1.30, 95% CI 1.05–1.60) or obese (OR = 1.40, 95% CI 1.01–1.94) children at 14 years of age, controlling for maternal education, income, breast feeding history, and child's diet and physical activity [58]. Their study suggests that smoking specifically during the gestational period may have an impact on the development of the child. Infants born of smoking mothers appear to be smaller for gestational age or have lower birth weight than those of nonsmoking mothers [59–61], yet have a greater percentage of body fat and lower percentage of lean mass [62]. A recent study, however, found that providing folic acid supplements to mothers who smoked reduced their risk of having children with low birth weight [63]. Folic acid is a major methyl donor known to epigenetically alter the expression of genes. Thus, while smoking appears to impact one's risk for obesity, other nutritional factors like folic acid may be able to counteract these effects, demonstrating the plasticity of the human genome during the prenatal period.

Finally, greater weight gain velocity during the first year of life is associated with up to a fivefold increased risk of obesity later in life [64–66]. While the relationship between absolute birth weight and later risk for obesity is less clear [67], the relationship between accelerated catch-up growth and obesity risk is particularly salient among children who are born small for gestational age [68]. In industrialized nations, children who gain weight quickly during the first year of life seem to be particularly prone to later obesity, insulin resistance, and cardiovascular disease [69–71]. These findings have caused many providers to question the optimal rate of catch-up growth. However, the same genetic factors that make one child more likely to have excess catch-up growth may also affect their risk for obesity. Thus early catch-up growth may simply be a manifestation of one's genetic potential to store excess energy as fat and become overweight.

6. Discussion

While we are unable to alter which genes we are born with, findings from animal and human studies suggest that we may be able to affect the expression of these genes and therefore our risk for future disease states. It is still unclear whether or not interventions can help curb the genetic influence of obesity. However, there are several potential lines for future investigation.

One area worth exploring is how to reduce excess gestational weight gain. It appears that excess weight gain in pregnancy has deleterious effects on child weight and increases risk for delivering heavy infants [72–74]. However, it is still unclear how best to limit excess gestational weight gain and what the impact of such interventions is on offspring growth and development. In 2009, the IOM updated their recommendations to limit weight gain during pregnancy to 15–25 lbs. for overweight women and 11–20 lbs. for obese women [75]. However, reports suggest that 50% to 60% of overweight women gain more than recommended [74, 76].

At this time, few studies have evaluated interventions during pregnancy to promote weight gain within these recommendations [77]. Outside of bariatric surgery, weight control studies for pregnant women suggest that lifestyle changes that include behavioral counseling, monitoring weight gain, limiting caloric intake, and increasing physical activity may curb excessive gestational weight gain [78]. In one study of women with gestational diabetes, dietary and physical activity modifications were related to lower infant birth weight and lower risk for-large-for-gestational-age newborns, despite minimal changes in GDM risk [79]. Unfortunately, most research to date has not been randomized and contains sample sizes too small to examine the impact of interventions on offspring weight trajectories. Nevertheless, available research suggests that limiting gestational weight gain has not been associated with increased adverse outcomes for the infant in the neonatal period [72–74]. Ongoing research by the LIFE-MOMS NIH consortium of studies will help inform whether reducing gestational weight gain in obese women can reduce the risk of offspring obesity. More work is needed in order to understand how best to limit excess gestational weight gain or GDM in women, increase the effectiveness of lifestyle interventions, and understand how these interventions influence offspring obesity risk.

Maternal nutritional exposure and dietary composition during pregnancy is another area that requires attention. As seen in animal studies, exposure to certain methylating agents and the quality/quantity of maternal dietary intake during pregnancy can influence the expression of certain hormones and neuropeptides in the infant and the subsequent development of obesity. Similar methyl donor studies in humans would be difficult to conduct because of ethical considerations and the difficulty in controlling for the myriad of other influences that affect a child's risk for obesity. However, randomized trials could test the influence of maternal dietary prescriptions during pregnancy (e.g., low glycemic diet, low-fat diet, low-energy-dense diet) on maternal/fetal outcomes. Such research should include repeat assessments of maternal diet during pregnancy and infant intake postpartum. At the same time, additional animal studies will need to be conducted to more precisely determine the effect of specific nutritional elements and diets on hormone levels, gene expression, and obesity risk in the offspring, as well as determine the timing of these exposures during pregnancy.

With regards to postnatal influences, breastfeeding has been associated with a decreased risk of obesity in children [80]. However, it is unclear whether children born to overweight mothers or mothers with excessive weight gain during pregnancy can reduce their child's risk of obesity through breastfeeding. While some observational studies suggest that breastfeeding in this situation may be protective for future child overweight and the development of type 2 diabetes [81], other studies do not [82]. Unfortunately, a randomized control trial around breastfeeding similar to the animal studies that involve cross-fostering would be difficult to propose in humans. Therefore, prospective studies that follow the growth trajectory of children over time and take into account the overweight mother's prepregnancy weight, gestational weight gain, metabolic parameters, detailed feeding history during the first year of life as well as the child's subsequent diet and physical activity history may help to better clarify the impact of breast feeding on human risk for obesity among those born to mothers who are overweight, had excess gestational weight gain or diabetes during pregnancy. Given the animal studies on HC milk, a comparison between formula and breast milk consumption in infants born to overweight mothers would also be of interest.

While we know that epigenetic changes can occur in the postnatal period, it is uncertain how long after birth changes in hormone and neuropeptide expression can be altered. To date, few studies have been conducted that address the impact of feeding behaviors and nutritional quality (outside of breast feeding) in infancy and early childhood. Currently, several studies are being conducted (in the United States and Australia) that are exploring the efficacy of maternal education around nutrition and feeding behaviors during infancy on later child dietary habits, physical activity, sedentary activity, and weight gain [83–85]. While the results of these studies are pending, another study conducted in Turku,

Finland (the STRIP Baby project) intervened on fat intake among infants starting at 7 months of age. They showed that children in the intervention group had decreased cholesterol and saturated fat consumption [86], as well as lower serum cholesterol levels, LDL levels, enhanced endothelial function, and lower blood pressure as they entered adolescence [87–89]. Unfortunately, their study did not focus on overall calorie restriction and its impact on obesity status was only significant among girls [90]. We also do not know whether these dietary changes had an effect on gene expression. Nevertheless, more studies like these are needed to determine the quality and quantity of nutritional intake in the postnatal period as well as the intensity of the interventions that are needed to curb the risk for obesity. Similar studies in SGA and LGA infants would be particularly useful since these children manifest a greater risk for obesity in later life and their optimal rate of growth in the neonatal period is still in question. However, animal studies will still be needed in order to examine the metabolic and molecular impact of these interventions and determine how long after birth epigenetic changes can occur.

The ultimate goal will be to develop systems-wide environmental or policy changes (like the recent IOM recommendations for gestational weight gain) that take advantage of the mounting epigenetic evidence around obesity risk. At this time, most of the studies in this area are laboratory-based animal studies where exposures can be controlled and testing for epigenetic evidence of change is more feasible. Translating the results of these studies to humans may involve designing community-based intervention studies comparing the effects of different approaches (e.g., nutritional interventions in healthcare settings) on offspring obesity risk. Other nonrandomized studies could involve comparisons among clearly defined closed cohorts where, for example, access to certain nutritional additives is currently limited, religious or cultural practices prescribe limits on the intake of certain foods (like animal fat or protein) or during natural events that result in nutritional deprivation. Because of the inability to control for all influences and examine biological or molecular mechanisms on a populationwide level, we will frequently have to rely on animal studies to clarify the possible mechanisms of action. As greater evidence develops, policy wide changes regarding nutritional additives to food products (like Vitamin D in milk and iron in cereals), dietary recommendations during pregnancy, the composition of formula, the optimal timing of the introduction of solids, and the optimal rate of growth may help to decrease the risk for obesity in certain populations.

Genes can greatly affect one's risk of obesity. However, there are several epigenetic influences that can alter the expression of our genes and ultimately our risk of becoming obese. These factors, in conjunction with the obesogenic environment, result in a complex web of influence that can be difficult to change. At this point, we are beginning to understand the importance of maternal gestational weight and nutritional factors on offspring obesity risk. We also know that epigenetic changes can occur prenatally, postnatally and sometimes can be carried over to the next generation without any additional manipulations. The overarching influence of these epigenetic changes help to explain the growing prevalence of obesity around the world in a time when genomic changes have not occurred. However, more work needs to be done to determine if there are critical periods for these effects, the impact of other nutritional elements and dietary compositions during pregnancy and the postnatal period, and the impact of other environmental toxins on epigenetic expression. Given the limitations of human studies, laboratory-based animal studies will provide insight regarding the underlying mechanisms of action. Once mechanisms and timing of action are determined, additional studies will be needed to develop novel interventions that effect behavior change and, ultimately, study the impact of policy changes on obesity rates. Because of the developments in the field of epigenetics, we now have new insight into the plausible mechanisms that explain the rise in obesity worldwide. With this information, we will be able to develop novel interventions for potential critical periods (i.e., pregnancy and early childhood) to reduce the lifetime risk of obesity.

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Clinical Study

Perinatal Factors Associated with Cardiovascular Disease Risk among Preschool-Age Children in the United States: An Analysis of 1999–2008 NHANES Data

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We examined the relationships between selected perinatal and early infancy factors (maternal smoking during pregnancy, infant low birthweight, breastfeeding, and early introduction of solid foods [<6 months of age] and increased BMI [≥85th, ≥95th percentiles for age, sex]), waist circumference (WC), C-reactive protein (CRP), triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, non-high-density lipoprotein (HDL) cholesterol, and decreased HDL cholesterol during early childhood. The population-based sample included 3,644 3-to-6-year-old Non-Hispanic White (NHW), Hispanic, and Non-Hispanic Black (NHB) children who participated in the 1999–2008 National Health and Nutrition Examination Surveys. Analysis showed that breastfeeding was significantly protective against early childhood obesity (OR 0.43, 95% CI, 0.27–0.69) and the highest quintile for WC (OR 0.58, 95% CI, 0.37–0.32) among NHW, and against the highest quintile of non-HDL cholesterol among NHB (OR 0.56, 95% CI, 0.32–0.98). Additionally, NHW children were significantly more likely to be obese (OR 2.22, 95% CI 1.30–3.78) and have higher CRP levels (OR 1.63, 95% CI, 1.05–2.51) if their mothers smoked during pregnancy. These results support the observation that breastfeeding may be protective against early childhood obesity while maternal smoking during pregnancy is a risk factor for obesity and increased CRP levels among NHW young children.

1. Introduction

The theory that events in the perinatal period have latent effects throughout the life course has become increasingly accepted [1]. The literature on the fetal-origins hypothesis strongly suggests that while maternal malnutrition and poor maternal health might not cause major malformations in childhood, such exposures can nevertheless have enduring, or latent, effects such as restricted growth, hypertension, cardiovascular events, and altered renal function in adulthood. [1, 2] These potential maternal environments can be physiological (e.g., maternal metabolic regulation), psychobehavioral (e.g., stress, smoking), and/or ecological (e.g., poverty, unstable food supply).

The literature is emerging on how these environments affect the long-term growth and health of children as they develop into adulthood. [3–5] A recently published review of 135 studies to evaluate factors in early childhood (≤5 years of age) that are the most significant predictors of the development of obesity in adulthood reported that possible early markers of obesity included maternal smoking and maternal weight gain during pregnancy [6]. Probable early

markers of obesity included maternal body mass index, childhood growth patterns (early rapid growth and early adiposity rebound), childhood obesity, and father's employment (a proxy measure for socioeconomic status [SES] in many studies). Other recent studies have examined the relationship between prenatal exposures such as smoking during pregnancy and early feeding practices (e.g., breastfeeding, early introduction of solid foods) and adverse cardiovascular health outcomes in preschool age children [7, 8]. Results of these studies showed that maternal smoking during pregnancy was associated with a higher body mass index (BMI) at four years of age in children with a normal birth weight and in those who were small for gestational age at birth [7] and that shorter breastfeeding duration and exclusivity (no formula or solid food) during the first 6 months tended to be associated with increased growth rates for length, weight and BMI between the age of 3 and 6 months but not with the risks of overweight and obesity until the age of 3 years [8].

Early childhood is an important stage of growth to examine given that one in four US children under age 5 is either overweight (≥85th to <95th age- and sex-adjusted percentiles for BMI) or obese (≥95th age- and sex-adjusted percentiles for BMI) [9, 10]. Overweight preschool-age children are five times more likely to be overweight during adolescence and more than four times as likely to become obese as adults than are their normal-weight counterparts [11]. Recent studies have shown that obesity in this age range is associated with cardiovascular disease risk factors and varies by ethnic group [12]. The concern is that childhood overweight will contribute to the earlier onset of overall morbidity and mortality in adulthood, making early intervention crucially important [4, 5].

Preschool children are at an ideal age to examine these relationships because there are fewer exposures to environmental confounders and interactions compared to older children and adults when it might be much more challenging to distinguish the contribution of the environment versus physiology. The relationship between overweight/obesity, cardiovascular disease (CVD) risk factors and birthweight, mother's smoking status during pregnancy, breastfeeding, and early introduction of solids and how these relationships vary by ethnic group specifically is largely unknown. Therefore, we assessed these relationships in a population-based multiethnic sample of 3-to-6-year-olds to determine the influence of breastfeeding, early introduction of solid foods, smoking during pregnancy, and low birth weight on the prevalence of CVD risk factors.

2. Methods

2.1. Study Population. The periodic National Health and Nutrition Examination Survey (NHANES) uses a stratified, multistage probability design to capture a representative sample of the civilian, noninstitutionalized US population [13]. This design allows survey results from two or more periods to be combined to increase the sample size and analytic options. Each 2-year period, and any combination of 2-year periods, is a nationally representative sample. To produce estimates with greater statistical reliability for demographic subgroups and rare events, combining two or more 2-year periods of the survey results is strongly recommended [13]. Therefore, for this study, NHANES data files for 1999-2000, 2001-2002, 2003-2004, 2005-2006, and 2007-2008 were combined to form a single analytic file.

2.2. Eligibility Criteria. From the above-cited NHANES 1999–2008 data file all Non-Hispanic White (NHW), Hispanic (Mexican American, other Hispanic groups combined), and Non-Hispanic Black (NHB) boys and girls aged 3 to 6 years and their mothers were included. The following measurements were available for analysis in this age group: age, sex, ethnicity, height and weight (for BMI), WC, C-reactive protein (CRP), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol, and triglycerides (available in the morning-only randomized subsample).

Using data on response rates found on the CDC website [14], we estimated the total number of 3-to-6-year-old children who were screened in the surveys from 1999–2008 to be 4,627. Of the children screened, 4,091 (88%) participated in the interview and 3,876 (84%) participated in the examination. We eliminated 225 children who were in the "other" ethnic group category (not Hispanic, NHW or NHB) and another 7 children who were diabetic or on metabolic altering drugs; therefore, our analytic sample included 3,644 children (79% of children screened). With a sample size of more than 1000 in each ethnic group (Table 2), it is possible to detect a small effect size of 0.20 at the two-tailed 0.05 level with 80% power [15].

2.3. Measures and Data Collection. Persons selected to participate in the NHANES survey were invited to be interviewed in their homes. Household interview data were collected with computer-assisted personal interviewing procedures and included demographic, socioeconomic, dietary, and health-related information. Because the children were so young (less than 7 years old), the mothers answered all questions on their behalf. Mothers were asked questions about their pregnancy with the index child included in this analysis. Specifically included were the responses regarding self-reported smoking status during pregnancy, infant birthweight, whether the infant was breastfed, and if solid foods were introduced in the infant's diet before six months of age. After the interview, each child received a standardized physical examination at a local Medical Examination Center.

Laboratory and anthropometric measurement methods used at the Medical Examination Centers are described in *The NHANES Laboratory/Medical Technologists Procedures Manual.* [16] Briefly, anthropometric measures taken during the standardized examination consisted of barefoot standing height (with a stadiometer), weight with minimal clothing (on a digital, electronic scale) [1], and waist circumference (in the horizontal plane at a point marked just above the right

Table 1: Values defining cardiovascular disease risk factors for 3-to-6-year-old children in the 1999–2008 NHANES data, by sex and ethnicity.

	Body mass index* kg/m^2			Waist circumference, cm		C-reactive protein, mg/dL		Total cholesterol, mg/dL		HDL cholesterol, mg/dL		Non-HDL cholesterol, mg/dL		LDL cholesterol, mg/dL		Triglycerides, mg/dL	
Group	n	85th %†	95th %‡	n	Highest quintile	n	Highest quintile	n	Highest quintile	n	Lowest quintile	n	Highest quintile	n	Highest quintile	n	Highest quintile
Overall	3555	26.5	13.8	3456	57.2	2521	0.13	1754	182	1752	42	1751	128	625	109	626	103
Girls																	
Non-Hispanic Black	516	23.4	13.0	506	55.6	365	0.10	268	182	268	44	268	127	100	112	100	87
Hispanic	694	33.9	14.6	670	57.9	502	0.20	346	181	344	41	344	127	113	102	113	110
Non-Hispanic White	530	24.0	10.8	513	57.0	341	0.11	238	188	238	40	238	135	90	103	90	105
Boys																	
Non-Hispanic Black	555	18.0	12.4	538	55.5	391	0.08	272	183	272	46	272	123	120	108	120	85
Hispanic	684	18.9	19.0	660	59.0	516	0.16	368	179	369	42	368	124	119	105	120	112
Non-Hispanic White	576	18.9	11.8	569	57.2	406	0.10	262	181	261	41	261	130	83	112	83	118

* Centers for Disease Control and Prevention standardized cut-point values for age and sex
† Cut-point for defining overweight
‡ Cut-point for defining obesity

ileum on the midaxillary line, at minimal respiration after normal expiration) [16, 17].

Triglycerides and low-density lipoprotein (LDL) cholesterol were measured via blood on a nonfasting subsample (those who were examined in the morning session only) of all children ages 3 to 11 ($N = 626$). All serum blood samples were collected, processed, stored at −20°C, and shipped to the Lipid Laboratory, Johns Hopkins University, Baltimore, MD (lipids) for the1999–2006 surveys and to the University of Minnesota, Minneapolis, MN, for the 2007-2008 survey for analysis [18].

High-density lipoprotein (HDL) cholesterol was measured in supernatants after precipitation of apo B-containing lipoproteins with heparin-manganese chloride and removal of excess manganese by precipitation with sodium bicarbonate. Triglycerides were analyzed enzymatically with the use of commercial reagents and was measured in EDTA plasma after hydrolysis by lipoprotein lipase to glycerol and fatty acids. Glycerol is enzymatically phosphorylated and then oxidized to release hydrogen peroxide, which is peroxidized to form a quinine-imine chromophore that can then be read at 490 to 550 nm in a spectrophotometer [18]. Low-density lipoprotein cholesterol (LDL) was derived using the Friedewald calculation (LDL = total cholesterol-HDL cholesterol-triglyceride/5) [19].

CRP was quantified by latex-enhanced nephelometry (CRP present in the test sample forms an antigen antibody complex with the latex particles). Serum blood specimens were processed, stored and shipped to University of Washington, Seattle, WA [18]. Particle-enhanced assays were based on the reaction between a soluble analyte and the corresponding antigen or antibody bound to polystyrene particles. A dilute solution of test sample was mixed with latex particles coated with mouse monoclonal anti-CRP antibodies. Non-HDL cholesterol is defined as total cholesterol minus HDL cholesterol.

2.4. Statistical Methods. The highest quintile for CRP, total cholesterol, LDL cholesterol, non-HDL cholesterol and triglycerides and the lowest quintile for HDL cholesterol, for the entire study population were used as cut-points for analysis (Table 1). These cut-points are consistent with the percentages used for abnormal values in studies of older children [20, 21]. Logistic regression analysis was used to explore the relationships between each of the selected perinatal and infant conditions and anthropometric measurements and CVD risk factors for each ethnic group. Child's age and sex, the family's poverty/income ratio, the year of the survey (to account for possible trend over the 10 years of data), and mother's age at the child's birth were included in each model to control for potential confounding effects. Separate analyses were run for the three race/ethnicity categories. Analyses were performed with SAS SURVEY procedures (SAS version 9.2, SAS Institute, Cary, NC) to accommodate the complex sample survey design of the NHANES data. Alpha was set at 0.05 and all tests were two tailed, without correction for multiple comparisons.

Table 2: Demographic characteristics of 3,644 3-to-6-year-olds in the National Health and Nutrition Examination Survey, 1999–2008.

	N	Weighted *N*	Percent	95% CI
Gender				
Boys	1,865	7,399,751	50.9	48.6–53.2
Girls	1,779	7,135,318	49.1	46.8–51.4
Age (years)				
3	922	3,493,552	24.0	22.1–26.0
4	976	3,701,859	25.5	23.5–27.4
5	887	3,581,816	24.6	22.7–26.6
6	859	3,757,841	25.9	23.9–27.8
Ethnicity				
Non-Hispanic White	1,138	9,000,820	61.9	58.2–65.7
Hispanic	1,416	3,285,391	22.6	19.5–25.7
Non-Hispanic Black	1,090	2,248,857	15.5	13.0–17.9
Total	3,644	14,535,068		

3. Results

We analyzed data from 3,644 (weighted sample size, 14,535,068) children and their mothers (Tables 2 and 3). Overall, 13.8% of children had a BMI ≥95th percentile and 26.5% had a BMI ≥ 85th percentile for age and sex (Table 1). Approximately 65% of mothers reported breastfeeding while 42% reported introducing solids before 6 months. Almost 10% of the infants were low birth weight (<2500 grams) and 17% of the mothers reported smoking while being pregnant (Table 3).

Table 4 shows that breastfeeding was significantly protective against obesity (BMI ≥ 95th percentile ile for age and sex) (OR 0.43, 95% CI, 0.27–0.69), overweight (OR 0.61, 95% CI, 0.42–0.87), and being in the highest quintile for waist circumference (OR 0.58, 95% CI, 0.37–0.92) among the NHW group and against highest quintile for non-HDL cholesterol among NHB (OR 0.56, 95% CI, 0.32–0.98). Conversely, introducing solid foods before 6 months was not shown to be a risk factor for any CVD risk factors among all ethnic groups.

Smoking during pregnancy was a significant risk factor for obesity (OR 2.22, 95% CI, 1.13–2.83), overweight (OR 1.79, 95% CI 1.13–2.83), and highest quintile of CRP (OR 1.63, 95% CI, 1.05–2.51) among NHW (Table 5).

Table 6 shows that in general low birth weight was not a risk factor for becoming overweight or obese or having elevated CVD risk factors in this age group was associated with a diminished risk among NHW for being overweight (OR 0.33, 95% CI 0.14–0.76) and having the highest quintile of waist circumference (OR 0.34, 95% CI 0.16–0.74).

4. Discussion

The results reported here show that CVD risk in young children is associated with perinatal and infancy factors among NHW. Specifically, our analysis shows that breastfeeding is

Table 3: Sample, estimated national characteristics, and range of values for measurements in 3,644 3-to-6-year-olds in the National Health and Nutrition Examination Survey, 1999–2008.

	N	Weighted *N*	Mean	95% CI
Total sample	3,644	14,535,068	4.52	4.48–4.57
Anthropometrics				
BMI (kg/m^2)	3,555	14,165,622	16.30	16.20–16.39
Waist Circumference (cm)	3,456	13,795,833	53.86	53.56–54.17
CVD risk factor				
C-reactive protein (mg/dL)	2,521	9,679,388	0.16	0.13–0.19
Total cholesterol (mg/dL)	1,754	6,895,867	161.88	160.07–163.68
HDL cholesterol (mg/dL)	1,752	6,885,787	51.95	51.18–52.72
Non-HDL cholesterol (mg/dL)	1,751	6,884,098	20.8	17.9–23.6
LDL cholesterol (mg/dL)	625	5,807,247	92.75	90.58–94.92
Triglycerides (mg/dL)	626	5,811,466	84.87	78.37–91.37
Prenatal, infant, and social risk factor	*N*	Weighted *N*	Percent	95% CI
Breastfed	3,628	14,485,571	64.8	61.7–67.9
Solid food <6 months	3,594	14,340,199	42.0	39.4–44.5
Smoking while pregnant	3,626	14,459,865	17.4	14.9–19.8
Low birth weight	3,343	13,299,081	9.7	8.1–11.3
Poverty income ratio <1	3,378	13,649,782	25.3	23.0–27.6
Poverty income ratio <2	3,378	13,649,782	51.6	48.2–55.0
CVD risk factor	*N*	Weighted *N*	Percent	95% CI
BMI ≥85 %ile for age, sex	3,555	14,165,622	24.5	22.6–26.3
BMI ≥95 %ile for age, sex	3,555	14,165,622	12.7	11.3–14.1
Waist circumference[1]	3,456	13,795,833	20.7	18.8–22.6
C-reactive protein[1]	2,521	9,679,388	21.0	18.9–23.0
Total cholesterol[1]	1,754	6,895,867	21.0	18.6–23.5
HDL cholesterol[2]	1,752	6,885,787	18.3	15.7–20.8
LDL cholesterol[1]	625	5,807,247	23.3	19.2–27.4
Triglyceride[1]	626	5,811,466	21.8	16.9–26.8

[1] Highest quintile
[2] Lowest quintile

protective against obesity and smoking during pregnancy is a risk factor for obesity in NHW. Low birth weight was not a risk factor for CVD risk factors, particularly among NHW women. With the exception of breastfeeding being protective against the highest quintile of non-HDL cholesterol in NHB, early introduction of solid foods, smoking during pregnancy, and low birth weight were not found to be related to CVD risk factors in early childhood.

Previous NHANES analyses have shown mixed results when analyzing whether or not breastfeeding is protective against children becoming overweight and that there is a dose-dependent effect based on duration. One analysis of infant feeding and child overweight status among 3-to-5-year olds from the NHANES III showed that after adjusting for potential confounders, there was a reduced risk of being overweight for ever-breastfed children compared with those never breastfed [22]. However, there was no reduced risk of being overweight (obese). Furthermore, there was no demonstrable threshold effect or clear dose-dependent effect of the duration of full breastfeeding on being at risk of overweight or overweight (now termed overweight and obese).

Other large population-based studies have also examined whether increasing duration of breastfeeding is associated with a lower risk of overweight in a low-income population of 4-year olds in the United States. Analysis from the Pediatric Nutrition Surveillance System [23] of children up to 60 months of age found that the duration of breastfeeding showed a dose-response, protective relationship with the risk of overweight only among NHW; no significant association was found among NHB or Hispanics, very similar to our results reported here.

Others have examined a broad range of factors that may simultaneously contribute to childhood overweight in a population-based cohort of children followed from birth to 4.5 years, to determine which factors exert the most influence in early life [24]. The Quebec Longitudinal Study of Child Development 1998–2002 (QLSCD) followed a representative sample ($n = 2103$) of children born in 1998 in the Canadian province of Quebec. Measured height and weight were

Table 4: Elevated cardiovascular disease risk factors among US 3-to-6-year-olds by ethnicity and infant nutrition practices, National Health and Nutrition Examination Survey, 1999–2008.

	Hispanic		Non-Hispanic Black		Non-Hispanic White	
Perinatal factor	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P* value
Breastfed (Y/N)						
BMI ≥ 85th %ile for age, sex	1.14 (0.82–1.57)	0.43	0.84 (0.58–1.22)	0.37	0.61 (0.42–0.87)	**0.01**
BMI ≥ 95th %ile for age, sex	0.96 (0.65–1.41)	0.83	0.82 (0.53–1.28)	0.39	0.43 (0.27–0.69)	<**0.001**
Waist circumference[1]	1.33 (0.91–1.93)	0.14	0.71 (0.44–1.14)	0.16	0.58 (0.37–0.92)	**0.02**
C-reactive protein[1]	0.78 (0.53–1.16)	0.22	1.24 (0.84–1.82)	0.28	0.76 (0.52–1.13)	0.18
Total cholesterol[1]	1.45 (0.83–2.55)	0.19	0.62 (0.33–1.15)	0.13	0.92 (0.49–1.70)	0.78
HDL cholesterol[2]	0.98 (0.63–1.52)	0.93	0.87 (0.41–1.85)	0.73	0.48 (0.23–1.04)	0.06
Non-HDL cholesterol[1]	1.23 (0.70–2.14)	0.48	0.56 (0.32–0.98)	**0.04**	1.10 (0.60–2.02)	0.76
LDL cholesterol[1]	1.90 (1.01–3.55)	**0.05**	0.74 (0.30–1.86)	0.53	1.89 (0.52–6.83)	0.33
Triglycerides[1]	2.01 (0.71–5.71)	0.19	1.24 (0.56–2.74)	0.59	1.40 (0.47–4.19)	0.54
Solids < 6 months (Y/N)						
BMI ≥ 85th %ile for age, sex	1.06 (0.77–1.46)	0.72	1.13 (0.81–1.56)	0.47	1.17 (0.82–1.68)	0.38
BMI ≥ 95th %ile for age, sex	0.85 (0.61–1.20)	0.36	1.03 (0.68–1.56)	0.90	1.28 (0.82–1.99)	0.28
Waist circumference[1]	0.90 (0.60–1.35)	0.61	1.05 (0.75–1.45)	0.79	1.38 (0.96–1.98)	0.09
C-reactive protein[1]	0.79 (0.50–1.23)	0.29	0.80 (0.57–1.12)	0.20	1.50 (0.99–2.26)	0.06
Total cholesterol[1]	1.08 (0.59–1.98)	0.80	1.07 (0.58–1.99)	0.83	1.39 (0.76–2.54)	0.29
HDL cholesterol[2]	0.79 (0.45–1.37)	0.41	0.93 (0.52–1.69)	0.82	0.67 (0.38–1.16)	0.15
Non-HDL cholesterol[1]	0.85 (0.48–1.50)	0.57	1.60 (0.91–2.81)	0.10	1.34 (0.80–2.23)	0.27
LDL cholesterol[1]	0.33 (0.12–0.94)	**0.04**	1.47 (0.74–2.90)	0.27	0.87 (0.36–2.08)	0.75
Triglycerides[1]	0.71 (0.26–1.92)	0.50	0.80 (0.30–2.09)	0.64	0.90 (0.30–2.69)	0.85

[1] Highest quintile
[2] Lowest quintile

Table 5: Elevated cardiovascular disease risk factors among US 3-to-6-year-olds by ethnic group and maternal smoking during pregnancy, National Health and Nutrition Examination Survey, 1999–2008.

	Hispanic		Non-Hispanic Black		Non-Hispanic White	
Perinatal Factor	Odds Ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Maternal Smoking (Y/N)						
BMI ≥ 85th %ile for age, sex	1.49 (0.82–2.73)	0.19	0.99 (0.53–1.85)	0.98	1.79 (1.13–2.83)	**0.01**
BMI ≥ 95th %ile for age, sex	1.29 (0.62–2.68)	0.49	1.35 (0.58–3.14)	0.48	2.22 (1.30–3.78)	<**0.01**
Waist circumference[1]	1.06 (0.56–1.98)	0.87	1.18 (0.65–2.12)	0.59	1.40 (0.83–2.36)	0.20
C-reactive protein[1]	0.85 (0.38–1.90)	0.69	1.23 (0.56–2.75)	0.61	1.63 (1.05–2.51)	**0.03**
Total cholesterol[1]	0.61 (0.18–2.02)	0.42	0.62 (0.19–2.06)	0.43	0.73 (0.39–1.40)	0.35
HDL cholesterol[2]	0.61 (0.19–1.93)	0.40	1.11 (0.56–2.18)	0.77	1.29 (0.58–2.86)	0.53
Non-HDL cholesterol[1]	0.58 (0.18–1.82)	0.35	0.67 (0.19–2.41)	0.54	0.79 (0.46–1.36)	0.40
LDL cholesterol[1]	0.71 (0.16–3.26)	0.66	0.65 (0.14–2.99)	0.58	0.24 (0.06–0.90)	**0.03**
Triglycerides[1]	0.71 (0.15–3.31)	0.66	0.58 (0.15–2.25)	0.43	1.39 (0.34–5.69)	0.64

[1] Highest Quintile
[2] Lowest Quintile

available for 1550 children aged 4.5 years. Results showed that being in the highest quintiles of weight gain between birth and 5 months, as well as maternal smoking during pregnancy, almost doubles the odds of being overweight at 4.5 years.

The Viva La Familia Study was designed to identify genetic and environmental factors affecting obesity and its comorbidities in 1030 Hispanic children from 319 families [25]. Salient independent risk factors for childhood obesity in this cohort of Hispanic children were age, birth weight,

Table 6: Elevated cardiovascular disease risk factors among US 3-to-6-year-olds if low birth weight, by ethnic group, National Health and Nutrition Examination Survey, 1999–2008.

Perinatal Factor	Hispanic		Non-Hispanic Black		Non-Hispanic White	
	Odds Ratio (95% CI)	*P*-value	Odds Ratio (95% CI)	*P*-value	Odds Ratio (95% CI)	*P*-value
Low birth weight (Y/N)						
BMI ≥ 85th %ile for age, sex	0.82 (0.47–1.44)	0.49	0.88 (0.44–1.37)	0.38	0.33 (0.14–0.76)	**0.01**
BMI ≥ 95th %ile for age, sex	0.99 (0.54–1.83)	0.97	1.01 (0.46–2.23)	0.98	0.37 (0.11–1.22)	0.10
Waist circumference[1]	0.89 (0.43–1.86)	0.89	1.03 (0.56–1.88)	0.93	0.34 (0.16–0.74)	**<0.01**
C-reactive protein[1]	1.74 (0.94–3.22)	0.08	1.37 (0.81–2.29)	0.24	0.51 (0.17–1.50)	0.22
Total cholesterol[1]	1.58 (0.66–3.83)	0.31	0.64 (0.28–1.44)	0.28	1.51 (0.54–4.21)	0.43
HDL cholesterol[2]	1.37 (0.53–3.54)	0.52	1.14 (0.53–2.47)	0.74	1.28 (0.32–5.08)	0.72
Non-HDL cholesterol[1]	1.88 (0.75–4.68)	0.18	0.55 (0.25–1.25)	0.16	0.81 (0.26–2.53)	0.72
LDL cholesterol[1]	1.58 (0.40–6.23)	0.51	0.87 (0.19–3.96)	0.85	0.39 (0.02–6.71)	0.52
Triglycerides[1]	0.98 (0.20–4.71)	0.98	0.99 (0.40–2.43)	0.99	1.37 (0.22–8.49)	0.74

[1] Highest quintile
[2] Lowest quintile

maternal obesity, paternal obesity, number of children in the family, and the percentage of awake time spent in sedentary activity. They also reported that breastfeeding might have a small protective effect against childhood obesity, although the authors concluded that residual confounding might exist. The authors reported no significant effect of early introduction of solid foods on childhood obesity, consistent with our findings here. Conversely, a prospective nationally representative cohort study conducted in England, Wales, Scotland, and Northern Ireland [26] included 13,188 singleton children aged 3 years in the Millennium Cohort Study, born between 2000 and 2002, who had complete height/weight data. The main outcome measure was childhood overweight (including obesity) defined by the International Obesity Task Force cut-offs for body mass index. In the fully adjusted model, primarily individual- and family-level factors were associated with early childhood overweight: birthweight z-score, black ethnicity (compared with white), introduction to solid foods <4 months, and smoking during pregnancy. However, in agreement with both the findings here and in the Viva La Familia Study, breastfeeding ≥4 months (compared with none) was associated with a decreased risk of early childhood overweight.

Other population-based studies have shown an association between maternal smoking during pregnancy and childhood obesity. Specifically, a total of 11,653 preschool children participating in the UK Millennium Cohort Study had their weight gain z-scores calculated from 3 to 5 years [27]. In a mutually adjusted model, children were more likely to gain weight rapidly if their mothers smoked during pregnancy. Due to the cross-sectional nature of the current dataset, we were unable to explore longitudinal growth but the concept of catch-up growth has gained recent and increased attention in the literature [28–30].

Because our findings are among very young children, they may have implications throughout childhood. Our group has reported previously that risk factors for cardiometabolic disease can be detected as early as the preschool years (12) and 8 years old [31]. Other studies have noted that several CVD risk factors persist strongly and consistently through childhood into adulthood [32, 33]. The Cardiovascular Risk in Young Finns Study was one of the first groups to explore childhood predictors of the metabolic syndrome (MS), a constellation of abnormal waist circumference, insulin resistance, dyslipidemia, and hypertension [32]. In this study, fasting insulin at baseline was related to development of the syndrome after a 6-year follow-up of 1,865 children and adolescents 6-to-18-years-old. Reported results showed that baseline insulin concentration was higher in children who subsequently developed the MS, lending support to the theory that insulin resistance precedes the development of the condition in childhood.

5. Study Limitations

In a cross-sectional study, causality cannot be inferred. Blood pressure, insulin and glucose measures, which are important components of metabolic syndrome and risk factors for adult-onset CVD and diabetes, were not collected in this age group and thus were not available for analysis. Because triglycerides and LDL were measured on a subsample of the surveyed children, analyses for these variables may not have sufficient statistical power to detect significant differences. Dietary and physical activity level data were not included because the children in this analysis were so young and their eating and exercise patterns tend to be inconsistent as a result. Smoking status during pregnancy and infant feeding behaviors were self-reported and therefore subject to systematic biases. Finally, genetic influences were not examined.

6. Conclusions

This study indicates that behavioral and social factors exert critical influences on the onset of childhood overweight in preschool years among NHW families in particular. Regardless of ethnic background, all women should be advised not

to smoke, especially while being pregnant, and should be encouraged to breastfeed, unless contraindicated, as a means of providing optimal nutrition. This may in turn prove to be protective against chronic obesity and later life onset of CVD.

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Research Article

Postnatal Growth Patterns in a Chilean Cohort: The Role of SES and Family Environment

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Objective. This study examined how family environmental characteristics served as mediators in the relationship between socioeconomic conditions and infant growth in a cohort of Chilean infants. *Methods*. We studied 999 infants, born between 1991 and 1996, from a longitudinal cohort which began as an iron deficiency anemia preventive trial. SES (Graffar Index), the Life Experiences Survey, and the Home Observation for Measurement of the Environment (HOME) were assessed in infancy. Using path analysis, we assessed the relationships between the social factors, home environment, and infant growth. *Results*. During the first year, weight and length gain averaged 540 grams/month and 6.5 cm/month, respectively. In the path analysis model for weight gain, higher SES and a better physical environment were positively related to higher maternal warmth, which in turn was associated with higher average weight gain. Higher SES was directly related to higher average length gain. *Conclusions*. In our cohort, a direct relationship between SES and length gain developed during infancy. Higher SES was indirectly related to infant weight gain through the home environment and maternal warmth. As the fastest growing infants are at risk for later obesity, new strategies are needed to encourage optimal rather than maximal growth.

1. Introduction

Infant growth can have important long-term health and developmental consequences. In the case of poor weight gain, cognitive development can be impaired [1, 2]. When infancy weight gain is rapid, risk for obesity and related conditions increases [3–8]. Whether or not infant weight gain relates to socioeconomic status depends on context. Infants gain less weight in resource poor settings in underdeveloped countries [9, 10]. In developed countries, lower socioeconomic status (SES) can relate to risk for poor infant growth through several possible mechanisms including higher rates of postpartum depression or family size [11–14]. On the other hand, a recent study in a developed country showed higher infant weight gain in lower SES individuals, largely explained by lower breast feeding rates [15]. Lastly, in some settings SES has not been found to influence infant ponderal growth [16]. Thus, it is important to understand the relationship of SES to infancy weight gain in a variety of contexts and identify factors that might mediate this relationship.

When the availability of breast milk or formula and weaning foods is adequate, the relationship between SES and infant weight gain might be explained by stressful circumstances and characteristics of the home environment and the parent-infant relationship. Low-SES families are more likely to experience uncontrollable life events and may have less healthy home environments for children [17], including lower quality stimulation available in the home for children [18]. Previous research has shown that negative circumstances associated with poverty and distress among parents can compromise parents' abilities to provide sensitive, involved, and consistent parenting [19–21]. Parenting style and infant

growth have been most often explored in the context of failure to thrive, with harsh and neglectful parenting associated with poor infant growth [22].

Understanding linear growth as it relates to SES is also important, as height can be a marker of health risk. At the population level, adult height is socially determined [23, 24]. Height reflects prenatal and postnatal environments superimposed on genetic potential [25]. In addition, adult height shows an inverse association with cardiovascular [26, 27] and cardiorespiratory [27] disease, some cancers [28], and type 2 diabetes [29]. Socioeconomic gradients in height are also present in childhood and have been noted at the time of birth in representative samples [30]. A recent study in the UK that found differences in birth length based on SES did not show further differences in growth during infancy [30]. In contexts where infant nutrition is adequate, questions remain about whether or not social factors relate to linear growth during the first year.

In order to answer the question of whether or not postnatal growth was related to SES and how family environment might mediate these relationships, we used data on birth weight and length and 12-month weight, length, SES and variables from the Home Observation for Measurement of the Environment (HOME) [31] from a large, longitudinal cohort of Chilean infants. This allowed us to establish direct and indirect associations between SES, family factors and infant growth.

2. Methods

This study is a secondary data analysis to identify the relationship of socioeconomic status (SES) with ponderal (weight) and linear (length) growth and to identify family factors that mediate this relationship, in a cohort of Chilean infants during the first year of life. The infants were enrolled in a randomized controlled trial of iron to prevent iron deficiency anemia. The parent study is described first, followed by methods for the secondary data analysis.

3. Original Study

From 1991 through 1996, we recruited healthy low- to middle-income, urban Chilean infants with birth weights of ≥3 kg for a double-blind, randomized, controlled trial of iron supplementation between 6 and 12 months of age [32]. At the time in Chile, infant health was generally excellent. In fact, parasitic infections and generalized undernutrition were virtually absent. However, dietary iron deficiency was common, and iron supplementation during infancy was not routine. In the trial, infants were randomized to iron supplementation or usual nutrition at 6 months. All but 8 of the cohort were initially breast fed, but approximately one third were supplemented in the first 6 weeks with formula made from powdered full fat cow's milk. The cohort continues to be followed with waves of data collection at 5 y, 10 y, and 16 y. The protocols for the original infant study and follow-up studies have been approved annually by the Institutional Review Boards of the Universities of Michigan and Chile, and the University of California, San Diego.

4. Secondary Analysis of the Influence of SES on Growth and Mediating Factors

Of the 1657 infants who completed the preventive trial, 999 had complete data on all variables for this analysis. Those without complete data did not differ significantly from those included in this analysis by birth weight or length, sex, SES, or family factors.

4.1. Outcome Variable. Unclothed infant weight, using an electronic scale (to the nearest 0.01 kg), and length, on a recumbent length board (to the nearest 0.1 cm), were measured monthly in the first year by trained nurses [33]. Infant weight gain over the first year (grams per month) was calculat-ed as: (weight (kg) at 1 year − birth weight (kg))/(age (days) ∗30.44 days/month). Infant length over the first year (grams per month) was calculated as (length (cm) at 1 year − birth length (cm))/(age (days) ∗30.44 days/month).

4.2. Variable of Interest. SES was measured using a modified Graffar index, which included 10 items concerning family size and structure, father presence, educational level of head of household, home ownership, and ownership of appliances [34]. For this analysis, the scale was dichotomized based on the median score of 27 (range of 16 to 47), with "0" referring to low SES and "1" referring to middle SES.

4.3. Social Factors. Mothers provided the following information at the 1-year assessment. Life stress was assessed using the Life Experiences Survey [35, 36] which included 22 items such as unstable employment of the head of household, serious family conflict, and serious illness of a relative, for a possible score of 0–22 (Cronbach alpha = 0.67). Maternal depression risk was assessed using the Center for Epidemiological Studies Depression Scale (CES-D) [37] scale; a score of 16 or greater indicates risk for depression. Adult-to-child ratio [14] served as a marker of family composition. This ratio was computed as the number of income-earning adults/number of children under age 15. This variable was trichotomized, with "0" referring to one adult to one child (ratio of 1), "1" referring to more adults than children (ratio greater than 1), and "−1" referring to more children than adults (ratio less than 1).

4.4. Other Mediating Factors. Mediating factors included variables representing the infant's family and home environments. The Home Observation for Measurement of the Environment scale (HOME), measured by direct observation, was used to evaluate the quality of the home environment for nurturing (Cronbach alpha = 0.80) [38]. In the US, 6 HOME subscales are used. In this Chilean sample, we identified 5 factors using exploratory factor analysis: "maternal warmth and emotional support," "sibling participation," "physical environment," "father-infant interaction," and "cognitive stimulation." Table 1 displays Eigen values and items, with

Table 1: Exploratory factor structures and item statistics: maternal warmth, sibling participation, and physical environment[a].

Item content	Correlations		
	Maternal warmth	Sibling participation	Physical environment
Mother's voice conveys positive feelings toward child	45		
Mother caresses or kisses child at least once	45		
Mother spontaneously praises child at least twice	42		
Child's play environment is safe			74
When the child gets close to the mother, she welcomes, looks at, listens to, and is affectionate towards him/her	49		
The child is spontaneously taken up in the arms of his/her older siblings		76	
The child is spontaneously caressed, kissed, or tickled by older siblings at least 5 minutes of everyday		93	
The child is spontaneously conversed to in a directed and appropriate manner by older siblings		89	
The child is spontaneously incorporated into family activities by older siblings		84	
There are other people who are consistently important in the encouragement and care of the child		39	
The interior of the house has sufficient light and ventilation			46
The bedroom in the house is reasonably clean and orderly			55
With respect to the spare available space, there is sufficient room for the child to explore and crawl without danger			74
Eigen values	2.58	3.26	2.38

[a] Values are multiplied by 100 and rounded to the nearest integer. Only the factor items with correlations ≥ 35 are displayed.

factor-item correlations of 0.35 or higher. "Father-infant interaction" and "cognitive stimulation" were not significantly associated with infant weight gain and were excluded from the final analysis in favor of a more parsimonious model. We tested additional covariates that might partially explain the relationship between SES and growth in weight and length. As the cohort was part of an IDA preventive trial, we tested whether IDA at one-year or random assignment to iron influenced the relationship between SES and growth in the first year. We tested the effect of gestational age and number of children on weight and length gain. Gestational age (in weeks) was assessed by the date of the last menstrual period; number of children was self-reported by the mother. Lastly, we tested whether 2 separate measures of breastfeeding were related to infancy weight and length gain: bottle supplementation at 6 weeks and still breastfeeding at 6 months. Both measures were self-reported by mothers during the infancy data collection period.

5. Statistical Analysis

Statistical analyses were conducted using SAS (9.2; Cary, NC) and SPSS (17; Chicago, IL). Descriptive statistics included means and frequencies (Table 2). We compared our sample (sample with complete data) to those excluded due to missing data, with t-test and chi-square analyses. We developed a path analysis model to assess the relationships between SES and correlated variables, adult-to-child ratio, and life stress, and infant weight gain and length gain, mediated by the family and home environment (sibling participation in child care, the physical home environment related to nurturing, and maternal warmth). Path analyses were performed using SAS PROC CALIS. Standardized regression coefficients and t-statistics were used to describe the final model; t-values > 1.96 were statistically significant. Model fit was tested using the chi-square statistic (χ^2; $P > 0.05$). Goodness-of-fit indices included the root mean square error of approximation (RMSEA < 0.06), comparative fit index (CFI > 0.95), and standardized root mean square residual (SRMR < 0.03).

6. Results

Descriptive statistics are shown in Table 2. Infants were 53% male, averaged 3.5 kg and 50.6 cm at birth, gained on average 539 grams/month in the first year, and were at the 49th percentile for weight-for-age at 1 year. Infants' mean linear growth in the first year was 6.5 cm/month, and mean length-for-age percentile at 1 year was 48th percentile. Only 3 percent of the 1 year-olds had heights less than the 5th percentile. Most infants (59%) lived in households containing more children than adults. The life stress scores ranged from 0 to 14 and averaged 4.8 (2.7). Table 3 shows additional descriptive information on the social variables, stratified by SES. Participants in the middle SES group, compared to those with low SES, had better optimal nurturing environment with higher maternal warmth and

Table 2: Descriptive statistics of Chilean infants ($n = 999$)[1].

Birth weight (kg)[2]	3.5 (0.4)
Birth length (cm)[2]	50.6 (1.7)
Gestational age	39.4 (1.0)
Age at infancy evaluation	11.5 (0.4)
Weight-for-age percentile at 1 year[2]	48.7 (27.1)
Average weight gain (grams/month)	539.2 (84.2)
Length-for-age percentile at 1 year[2]	47.8 (25.8)
Average length gain (cm/month)	6.5 (0.3)
Bottle supplementation at 6 weeks	25.0
Still breastfeeding at 6 months	49.3
Number of siblings	2.1 (1.1)
Iron deficiency anemia in infancy	15.2
Iron supplemented	78.5
Maternal risk for depression	45.7
Life stress	4.8 (2.7)
Physical environment[3]	2.8 (1.3)
Maternal warmth[3]	3.4 (0.8)
Sibling participation[3]	3.9 (1.7)
Gender[2]	
Male	52.6
Female	47.4
SES	
Middle SES	52.7
Low SES	47.3
Adult-to-child ratio	
One-to-one ratio	26.4
More adults	15.1
More children	58.5

[1]Values are mean (SD) or %.
[2]Variable not included in the final model.
[3]Derived from HOME.

Table 3: Social factors by SES category.

	Middle SES	Low SES
Maternal warmth*	3.6 (0.8)	3.4 (0.8)
Sibling participation*	3.7 (1.7)	4.0 (1.6)
Physical environment*	3.2 (1.1)	2.4 (1.4)
More adults compared to children*	19.0%	10.8%
Stressful events*	4.5 (2.6)	5.0 (2.6)

*$P < 0.05$.

physical home environment, lower sibling participation in infant care, and fewer stressful events.

Figure 1 shows the standardized path coefficients and respective t-values for the tested model. All paths shown are statistically significant associations. Fit indices indicated a good model fit (RMSEA = 0.03, CFI = 0.97, and SRMR = 0.02). SES was significantly correlated with adult-to-child ratio and life stress. Adult-to-child ratio was negatively associated with sibling participation ($B = -0.45$, $P < 0.05$), which negatively related to weight gain ($B = -0.14$, $P < 0.05$). SES ($B = 0.28$, $P < 0.05$) and adult-to-child ratio ($B = 0.10$, $P < 0.05$) were related to a more positive physical environment for nurturing, and higher life stress was related to a less positive physical environment ($B = -0.10$, $P < 0.05$). The physical environment indirectly related to weight gain through greater maternal warmth ($B = 0.07$, $P < 0.05$). SES was indirectly related to infant weight gain through a more positive physical environment ($B = 0.28$, $P < 0.05$) and greater maternal warmth ($B = 0.08$, $P < 0.05$).

We now examine the strength of the associations. Of the social factors, the strongest relationships were those between adult-to-child ratio and lower sibling participation in childcare and between SES and the physical environment for nurturing. The relationships between life stress and physical environment and adult-to-child ratio and physical environment were less robust, but significant. No direct associations between SES, adult-to-child ratio, and life stress and infant growth were found. We also tested potential covariates, including iron deficiency anemia, iron assignment, depression, gestational age, number of children, and bottle supplementation of breast feeding at 6 weeks and continued breast feeding at 6 months. With the exception of number of children, which had a direct inverse relationship with weight gain ($B = -0.08$, $P < 0.05$), these factors did not significantly contribute to the model and were omitted for parsimony. Sibling participation, maternal warmth, and number of children accounted for 3% of the variance in infant weight gain.

In examining infancy length gain (Figure 2), we found pathways identical to those associated with weight gain, with the exception that there was no relationship between maternal warmth and length gain. Additionally, SES was directly related to infancy length gain, rather than indirectly as was found for weight gain ($B = 0.06$, $P = 0.05$). This relationship was marginally significant, and the strength of the association was modest. As in the weight gain model, iron deficiency anemia, iron assignment, depression, gestational age, and bottle supplementation of breast feeding at 6 weeks and continued breast feeding at 6 month did not significantly contribute to the model and were omitted for parsimony. Number of children was directly and inversely related to infancy length gain ($B = -0.07$, $P < 0.05$). Sibling participation, number of children, and SES accounted for 1% of the variance in infant length gain.

7. Discussion

This study examined the relationship between SES and family factors and postnatal growth. Results showed that infant linear growth was directly related to SES, while ponderal growth was indirectly related to SES, mediated by the physical environment for nurturing and maternal warmth. In fact, the physical environment was a pivotal-mediating factor that linked the social variables to infant weight gain. This finding suggests that less strained financial circumstances provided a more supportive home environment. This, in turn, related to higher infant weight gain indirectly through maternal warmth.

Prior research has shown direct relationships between SES and birth length as well as SES and adult height

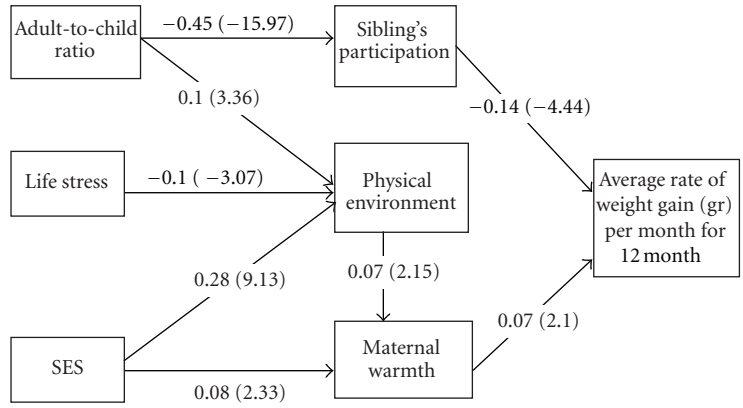

Figure 1: Standardized path coefficients (t-values) for a path model between SES and infant weight gain, mediated by home environment in 1-year-old Chilean infants (CFI = 0.97, SRMR = 0.02, RMSEA = 0.03). All paths are statistically significant ($P < 0.05$). SES significantly correlated with adult-to-child ratio and life stress. Model adjusted for direct relationship between number of children and average weight gain ($P < 0.05$).

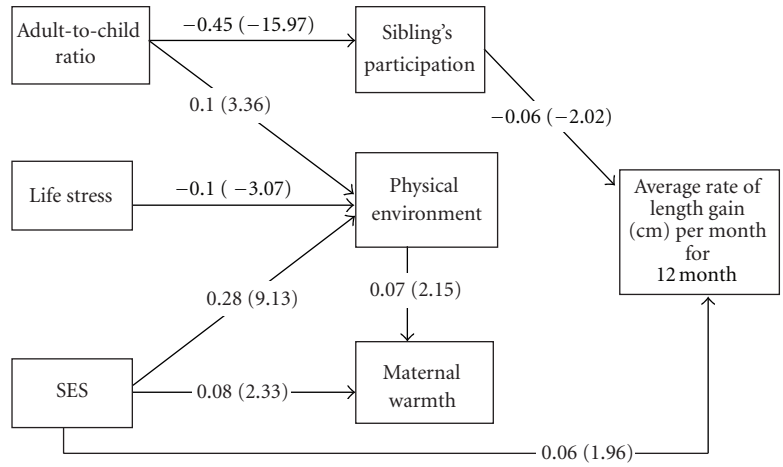

Figure 2: Standardized path coefficients (t-values) for a path model between SES and infant length gain, mediated by home environment in 1-year-old Chilean infants (CFI = 0.98, SRMR = 0.02, RMSEA = 0.03). All paths are statistically significant ($P < 0.05$). SES significantly correlated with adult-to-child ratio and life stress.

[23, 24, 30]. However, in previous work, the infant SES-length relationship has been largely explained by the association already existing at birth [39]. This was not the case in our study, perhaps because infants weighing less than 3 kg at birth were excluded, resulting in less variation in birth length than would be found in a representative cohort. The relationship between SES and postnatal length gain was independent of birth length in our sample. This gradient was not mediated by the family or nutritional factors examined, suggesting that other unmeasured characteristics related to SES were responsible. It is highly unlikely that macronutrient factors were responsible for this finding, as none of the infants exhibited poor growth, almost all were initially breast fed, and supplemental milk was freely available from the Chilean National Health Service. Other potential explanations include micronutrient deficiencies or stressful circumstances affecting the hypothalamic-pituitary-adrenal axis.

In the context of this study of low- to middle-income, urban Chilean families, SES was related to infant weight gain. It is important to note that substantial public health programs in Chile led to a decline in infant mortality from 136.2/1000 live births in 1950 to 8.9/1000 live births in 2000. During this period, infant malnutrition was virtually eradicated through a supplemental milk program and a national breast feeding campaign that was highly successful [40]. In our study, the relationship between SES and infant growth was explained by family factors including family composition, the physical environment, and maternal warmth. All of the factors associated with more rapid weight gain are related to good nurturing. We also tested the role of breast feeding exclusivity and duration on these associations and found no effect. We suspect that the homogeneity of our sample in terms of high breast feeding rates minimized the effect of nutritional factors in our study. Another nutritional factor that could play a role is the timing of introduction of

complementary foods, but we do not have data on this feeding practice. A recent study of infant growth in a multiethnic cohort in Amsterdam found higher growth rates in ethnic minority families that could not be entirely explained by different feeding practices [41]. Our study adds to the existing literature by supporting the role of psychosocial factors in infant growth. While there is a large literature relating psychosocial factors to failure to thrive [22, 42], these characteristics are not always considered in infant growth research when failure to thrive is not the focus.

Our findings lead to a difficult question, how can optimal infancy growth be promoted in an era when failure to thrive is rare and risk for obesity is high. Historically, malnutrition presented serious risk for infants in Chile and had only recently been eradicated at the time our cohort participants were infants [40]. Currently in Chile, less than 2.9% of children under 6 years old are malnourished, and only 0.3% have moderate to severe malnutrition [40]. On the other hand, 16–20 years ago when our cohort participants were infants, the obesity epidemic was beginning in Chile but was not known or evident to families or even to health providers. In 2005, preschool age Chilean children had high obesity rates: 6% of 2-year olds, 11% of 3-year olds, and 14% of 4-year olds were obese. By young adulthood (17–24 years), the overweight and obesity prevalence was 24% in men and 28% in women [43]. In our study, the families with the most resources had infants with more rapid length and weight gain. We now know that rapid weight gain in infancy creates risk for later obesity [44, 45], which creates a conundrum for all involved. It appears that what would be considered optimal care is associated with increased risk for later obesity. Therefore, the fattest baby can no longer be viewed as the healthiest baby. While significant progress has been made in promoting breast feeding and encouraging families to delay supplemental bottles and complementary foods in Chile [40] and in many other settings [46, 47], it will be important to change perceptions of families about what a healthy baby looks like and what constitutes optimal growth. As these perceptions are highly linked with cultural norms, this will take a concerted effort on many fronts.

Some of this study's particular strengths are worth noting. This large cohort of infants was assessed at a university nutrition research center where the infants had detailed anthropometric measurement every month in the first year of life. In addition, data on SES, family factors and infant feeding were prospectively collected. Furthermore, most studies of SES and infant growth have been carried out in developed countries and may not relate to infants in other settings. Our study also has important limitations. The cross-sectional path analysis model cannot establish temporal precedence nor infer causality. It therefore must be considered to be hypothesis generating. Furthermore, findings about the SES infant-growth relationship from one context may not apply in other settings. Therefore, it may not be possible to generalize these findings to other cultures, rural settings, higher SES groups, or to other countries. Regarding generalizing to Chile in more recent years, however, it is important to note that infant growth rates in a more contemporary Chilean census, born between 2002 and 2004, are similar to those of our study for infants who weighted 3 kg or greater at birth [48].

8. Conclusion

In this developing country setting of rapid economic and nutritional transition, better circumstances related to higher infant growth. Prior to the onset of the global obesity epidemic, higher infant growth would have always been a sign of good parenting and prosperity and would have portended a survival advantage for the infant. In the current era, infants who are growing the fastest are at risk for developing obesity [45]. These findings emphasize the need for better understanding of explanatory factors related to infant growth. Future research should include longitudinal studies in a variety of settings that could identify possible causal elements including biological factors, such as genetics and the effects of the intrauterine environment, and environmental factors such as nutrition and the psychosocial environment.

Conflict of Interests

The authors declare that there is no conflict of interests.

Acknowledgments

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Clinical Study

Excess Early Postnatal Weight Gain Leads to Increased Abdominal Fat in Young Children

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Background. Increased childhood weight gain has been associated with later adiposity. Whether excess early postnatal weight gain plays a role in childhood abdominal fat is unknown. *Design*. In the ongoing Wheezing Illnesses Study Leidsche Rijn (WHISTLER), birth cohort weight and length from birth to age 3 months were obtained. In the first 316 five-year-olds, intra-abdominal and subcutaneous fat were measured ultrasonographically. Individual weight and length gain rates were assessed in each child. Internal *Z*-scores of weight for length gain (WLG) were calculated. Multiple imputation was used to deal with missing covariates. *Results*. Per-1-unit increase in *Z*-score WLG from birth to 3 months, BMI, waist circumference, and subcutaneous fat were significantly higher; 0.51 kg/m^2, 0.84 cm, and 0.50 mm, respectively. After multiple imputation, a trend towards significance was observed for intra-abdominal fat as well (0.51 mm/SD). In the associations with 5-year adiposity, no interaction between postnatal *Z*-score WLG and birth size was found. *Conclusion*. Excess early postnatal weight gain is associated with increased general and central adiposity, characterized by more subcutaneous and likely more intra-abdominal fat at 5 years of age.

1. Introduction

Obesity is one of the major cardiovascular disease (CVD) risk factors and is a common health problem both in adults and in children [1]. Not only do obese children have a higher risk of becoming obese adults [2], childhood BMI is independently associated with later coronary heart disease as well [3]. Visceral fat in particular is related to an adverse metabolic profile [4] and increased CVD risk [5] through the production and secretion of metabolic active compounds like adipokines and cytokines, with effects on insulin sensitivity, lipid metabolism, and inflammation among others [6]. From a CVD prevention point of view, early prevention of intra-abdominal fat accumulation might help reducing the prevalence of type 2 diabetes mellitus and CVD. Identification of early life determinants of abdominal fat distribution is therefore important.

Growth patterns in early life have been suggested to be important for later fat distribution. Several studies determined an association between weight gain in the first 2-3 years of life and central adiposity, mostly assessed by larger waist circumference, in both adulthood [7] and early childhood [8–13]. Imaging techniques such as magnetic resonance imaging [7], ultrasonography [10, 11], or computed tomography have seldom or never been used to assess the association between postnatal growth and later central adiposity. While in these studies weight gain in the first years of life was studied, the importance of particularly the first 3 months of life in the development of central adiposity was addressed in other studies in children [14] and adults [15–17]. Weight gain in the first 3 postnatal months is thought to comprise predominantly fat mass accumulation; fat mass as percentage of body weight increases until 3–6 months of age, followed by a gradual decline [18]. Most of the previous studies did not

account for length gain in infancy, while weight gain relative to length gain might reflect adiposity better than weight gain alone [19, 20]. Whether particularly rapid weight gain for length gain in the first 3 postnatal months, so excess weight gain relative to length gain, is related to differences in intra-abdominal fat, measured ultrasonographically, in childhood remains unknown.

We set out to measure intra-abdominal and subcutaneous fat ultrasonographically in healthy 5-year-old children, to study whether differences in growth in the first 3 postnatal months, in particular increased weight gain accounting for length gain, are associated with increased central adiposity in early childhood.

2. Methods

2.1. Design and Study Population. The present study is part of the Wheezing Illnesses Study LEidsche Rijn (WHISTLER) study, an ongoing population-based birth cohort on determinants of wheezing illnesses, initiated in 2001 [21]. Healthy newborns in Leidsche Rijn, a new residential area near Utrecht city, were enrolled. Exclusion criteria were gestational age < 36 weeks, major congenital abnormalities, and neonatal respiratory disease. Currently, over 2500 infants have been included. In 2007 the study was extended for cardiovascular research questions (WHISTLER-Cardio). All five-year-olds ($n = 1124$ on April 26th, 2011) were invited according to the last-known telephone number and address, for follow-up measurements. 215/1124 (19%) subjects were lost to follow-up, due to incorrect telephone numbers and addresses, and 54/1124 (5%) were not yet contacted. Of the remaining 855 subjects, 285 (33%) declined to take part and 570 (67%) were willing to participate of whom 517 were measured before April 26th 2011. Abdominal ultrasonography was performed and intra-abdominal fat and subcutaneous fat were measured successfully in 434/517 (84%) and 463/517 (90%) subjects, respectively. In the remaining participants the focus was solely on respiratory measures. Complete data on postnatal weight gain relative to length gain and abdominal fat distribution were available for 360/517 children (70%), and in addition on birth size for 316/517 (61%). An overview of the study population is presented in Figure 1.

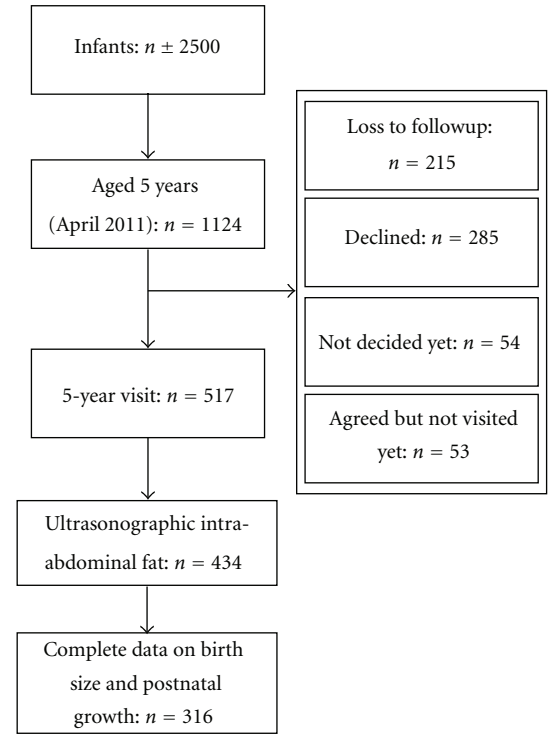

Figure 1: Overview of the study population.

WHISTLER-Cardio was approved by the paediatric Medical Ethical Committee of the University Medical Center Utrecht. Written informed parental consent was obtained.

2.2. Neonatal Visit and Follow-Up in Infancy. Parents visited the clinic when their offspring was approximately four weeks of age for lung function measurements, not further described here [22]. Birth weight in 359/360 (99.7%) children and birth length in 317/360 (88%) children were measured standardized in the hospital or by midwifes using a standard electronic scale and an infant stadiometer. Parents were asked to report these measures in a questionnaire. This questionnaire inquired for maternal age at childbirth and gestational age among others as well. In the Netherlands infants regularly visit Child Health Care Centers for standardized weight and length measurements. We asked parents to report these measurements in monthly questionnaires for a period of 12 months. The type of infant feeding was reported monthly as well [23]. Parents were instructed to answer "exclusively breastfed" if the only milk their infant had received during the month of interest was breast milk. Data on parental characteristics, like parental BMI, ethnicity and level of education among others, were obtained from the linked database of the Utrecht-Health-Project (UHP), a large health monitoring study in Leidsche Rijn [24].

2.3. Follow-Up Measurements. Methods of the follow-up measurements have been described previously [25]. Children were reinvited to visit the outpatient clinic at 5 years of age. Weight, height, and waist circumference were measured with the participants wearing indoor clothes without shoes. Standing with the feet slightly spread waist circumference was measured in duplicate at the level midway the lowest rib border and the iliac crest and hip circumference at the widest level over the major trochanter to the nearest mm. Body mass index (BMI, kg/m^2) was calculated. In addition, intra-abdominal and subcutaneous fat were measured using ultrasound according to a previously described procedure [26, 27] with a Picus Pro system (Esaote, Italy), using a CA 421 convex transducer. For intra-abdominal fat, the distances between the posterior edge of the abdominal muscles and the lumbar spine were measured using electronic callipers. Distances were measured from 3 different angles: medial, left, and right lateral, with the transducer placed longitudinally on a straight line drawn between the left and right midpoint of the lower rib and iliac crest. Measurements were performed

at the end of a quiet expiration. The average distance was calculated from the three angles. Placing the probe transversely at the level of the umbilicus subcutaneous fat was measured with electronic callipers, from the external face of the rectus abdominis mucle (linea alba) to just below the skin. The measurement was repeated three times and the average was used for analysis. For all measurements, minimal pressure was applied to eliminate manual compression of tissue. All measurements were performed by two of the investigators and a trained research nurse all blinded to infancy weight and length gain. Intraclass correlation coefficients (ICC) based on measurements by one observer in 10 and, respectively, 11 subjects on 2 different occasions for intra-abdominal and subcutaneous fat were 0.67 and 0.96, respectively. ICCs for subcutaneous fat on the three measurements per child on the same occasion were 0.94, 0.94, and 0.97 for the three observers.

In addition, information on child and parental characteristics, like smoking habits among others, with respect to the previous years was collected by questionnaires.

2.4. Infancy Growth. We used weight gain rate, length gain rate, and particularly weight gain rate adjusted for length gain rate as measures of growth in the first 3 postnatal months. These measures were studied separately, as length gain might reflect lean mass accumulation, while weight gain, and particularly weight gain accounting for length gain, might reflect fat mass accumulation.

For each child with at least two anthropometric measurements available in the first 3 postnatal months, weight gain and length gain rates were estimated using the monthly anthropometrics, to reduce an effect of measurement error and individual variation over time (regression to the mean). Since the number of weight and length measurements (median count: 3) and the age at which these were measured differed per child, the association between age, and both weight and length was assessed using linear mixed modelling, allowing for individual variation in birth weight or height and growth rate. Subsequently, to obtain weight gain rates for each child individually, linear regression modelling on the predicted weight and length values of the linear mixed model was performed stratified by child. The same steps were taken to assess individual length gain rates. Because of the small time window, weight and length gain rate were assumed constant in the first 3 postnatal months. WLG was assessed by deriving Z-scores internal to our study population for weight gain, conditioned on length gain, by using the standardized residuals from the linear regression model with weight gain as the dependent variable and length gain as the independent variable. A Z-score of +1 SD WLG indicates that the weight gain of a certain child is one standard deviation larger than the mean weight gain in the population based on the length gain of that child. Furthermore, size at birth was assessed by calculating internal Z-scores for birth weight, adjusted for birth length, gestational, age and gender.

2.5. Data Analysis. Means and dispersion measures of parent and child characteristics were calculated by tertiles of Z-score WLG. Differences by tertiles of Z-score WLG were tested using analysis of variance, or Kruskal Wallis test in case of skewed data, for continuous variables and Chi-squared tests or Fisher's exact tests for frequencies (Table 1).

For analyzing the associations between postnatal growth and fat distribution we used generalized linear modelling. BMI, waist circumference, intra-abdominal fat, and subcutaneous fat were used as dependent variables in separate models. Weight gain rate, length gain rate, and Z-score WLG were used as independent variables in separate models. After univariable analysis, adjustments for age at follow-up and gender were made. In the analyses of intra-abdominal and subcutaneous fat we additionally adjusted for observer to reduce the possibility for observer bias. Moreover, adjustments for current height were made, as achieved height can be considered as confounder when studying the association between early weight gain and WLG and fat distribution. Parental characteristics, like smoking and BMI, and infant nutrition, were not considered as confounders, as to our view these factors might explain the associations between growth and later fat distribution and might therefore be in the causal pathway.

Since an association between postnatal growth and fat distribution might be modified by fetal growth as well, we analyzed whether interaction on an additive scale was present between birth size, as proxy for fetal growth, and early postnatal growth on fat distribution.

Data on birth size was missing in 44 children due to missing birth length. We therefore imputed birth length using multiple imputation technique in SPSS version 17.0 for Windows and repeated the analyses on the 10 imputed datasets as sensitivity analysis.

All results are expressed as linear regression coefficients with 95% confidence intervals (95%-CI) and corresponding P values. Statistical significance was considered reached at $P_{2\text{-sided}} < 0.05$. All analyses were performed with SPSS version 17.0 for Windows.

3. Results

Median BMI, waist circumference, subcutaneous fat, and mean intra-abdominal fat were 15.1 kg/m^2 (interquartile range (IQR): 14.3–16.1), 52.5 mm (IQR: 50.5–54.8), 6.3 mm (IQR: 5.0–7.9), and 36.4 ± 6.5 mm, respectively. Children with higher postnatal WLG were relatively thin at birth. No differences in infant feeding type and parental characteristics were determined across growth tertiles, except for parental smoking habits and maternal gestational diabetes: parents of children with lower WLG smoked more often in the 5 years after birth and all three infants of the mothers who have had gestational diabetes belonged to the highest Z-score WLG tertile. Postnatal WLG was positively associated with weight and height of the children at the follow-up visit at 5 years of age (Table 1).

In Table 2 the associations between early postnatal growth and body fat distribution at the age of 5 years are shown. After correcting for confounders, size at birth was positively associated with BMI and waist circumference, but not with intra-abdominal and subcutaneous fat. With respect to postnatal growth, both weight gain and Z-score WLG were significantly positively associated with BMI, waist

Table 1: Associations between child and parental characteristics and tertiles of Z-score weight gain for length gain rate in the first 3 postnatal months.

	Tertiles of weight gain rate for length gain rate in the first 3 months after birth			
	1st Z-score WLG tertile (mean : −1.1)	2nd Z-score WLG tertile (mean : −0.049)	3rd Z-score WLG tertile (mean : 1.1)	
	$N = 105$	$N = 106$	$N = 105$	P value
Child characteristics				
Infancy				
Gender (% boys)	53	45	48	0.49[a]
Gestational age (days)[#]	282 (275–288)	279 (271–286)	281 (274–286)	0.07[c]
Birth weight (grams)	3564 ± 46	3430 ± 46	3642 ± 46	0.005[b]
Birth length (cm)	50.7 ± 0.22	50.7 ± 0.22	51.9 ± 0.22	<0.001[b]
Z-score birth size (SD)	0.18 ± 0.097	−0.14 ± 0.096	−0.044 ± 0.097	0.056[b]
Mean weight gain (g/day)	24.6 ± 0.26	28.0 ± 0.26	32.1 ± 0.26	<0.001[b]
Mean length gain (mm/day)	1.1 ± 0.005	1.1 ± 0.005	1.1 ± 0.005	0.95[b]
Breastfeeding (% ever)	79	79	80	0.98[a]
Exclusive breastfeeding (days)[#*]	66 (26–127)	72 (28–136)	79 (40–145)	0.26[c]
Childhood				
Age at 5 years visit (years)[#]	5.4 (5.2–5.5)	5.3 (5.2–5.4)	5.3 (5.2–5.4)	0.16[c]
Weight (kg)	19.4 ± 0.26	19.8 ± 0.26	21.6 ± 0.26	<0.001[b]
Height (cm)	114.2 ± 0.45	114.3 ± 0.45	116.7 ± 0.45	<0.001[b]
BMI (kg/m^2)[#]	14.8 (14.0–15.4)	14.9 (14.0–16.1)	15.6 (14.8–16.6)	<0.001[c]
Waist circumference (mm)[#]	52.2 (50.2–53.9)	52.0 (49.9–54.1)	54.0 (51.5–56.3)	<0.001[c]
Systolic blood pressure (mmHg)	105 ± 0.75	105 ± 0.76	106 ± 0.76	0.46[b]
Diastolic blood pressure (mmHg)	55 ± 0.68	56 ± 0.68	55 ± 0.68	0.60[b]
Parental characteristics				
Maternal age at childbirth (years)	32.5 ± 0.34	32.4 ± 0.34	32.1 ± 0.34	0.70[b]
Maternal BMI (kg/m^2)	25.4 ± 0.44	24.8 ± 0.44	24.9 ± 0.43	0.58[b]
Paternal BMI (kg/m^2)	25.6 ± 0.34	25.6 ± 0.32	25.6 ± 0.34	0.99[b]
Maternal gestational diabetes (%)	0	0	3	0.11[d]
Maternal smoking-prenatal (%)	6	6	1	0.13[a]
Parental smoking-postnatal (%)				0.039[a]
Neither one of the parents	62	70	79	
One parent	31	20	19	
Both parents	7	10	2	
Socio economic status (% high educated)	79	76	69	0.26[a]
Maternal ethnicity (% western)	93	91	92	0.85[a]

Values are means with standard errors in case of continuous variables and percentages in case of frequencies. In case of skewed data ([#]), medians with interquartile range were presented.
[#]Not normally distributed.
*Within those ever breastfed.
[a]Chi-square test.
[b]ANOVA.
[c]Kruskall Wallis test.
[d]Fisher's exact test.

circumference, and subcutaneous fat at the age of 5 years. No significant associations between both weight gain and WLG with intra-abdominal fat were observed. Length gain was associated with none of the measures of body fat distribution. Size at birth did not modify the associations between postnatal growth and body fat distribution.

After multiple imputation of birth length, to have complete data on size at birth for all 360 children in which an ultrasound was successfully performed and growth data was available, the associations between postnatal WLG and BMI, waist circumference, and subcutaneous fat strengthened. Regarding intra-abdominal fat, a trend towards significance

Table 2: Associations between both size at birth and early infancy growth parameters and fat distribution indices at 5 years.

	Body mass index (kg/m^2)		Waist circumference (cm)		Intra-abdominal fat (mm)		Subcutaneous fat (mm)	
	Linear regression coefficient (95%-CI) $N = 316$	P value	Linear regression coefficient (95%-CI) $N = 314$	P value	Linear regression coefficient (95%-CI) $N = 316$	P value	Linear regression coefficient (95%-CI) $N = 315$	P value
Z-score birth size*								
Crude	0.24 (0.080–0.39)	0.003	0.42 (0.007–0.83)	0.046	0.081 (−0.64–0.81)	0.83	0.15 (−0.21–0.51)	0.42
Model 1	0.24 (0.084–0.40)	0.003	0.45 (0.040–0.85)	0.031	0.048 (−0.67–0.77)	0.90	0.16 (−0.20–0.51)	0.38
Model 2			0.40 (0.029–0.77)	0.034	0.050 (−0.67–0.77)	0.89	0.13 (−0.21–0.48)	0.45
Model 3					0.12 (−0.54–0.78)	0.72	0.14 (−0.20–0.49)	0.42
Weight gain (gr/day)								
Crude	0.13 (0.089–0.16)	<0.001	0.34 (0.24–0.43)	<0.001	0.16 (−0.018–0.34)	0.078	0.096 (0.009–0.18)	0.031
Model 1	0.13 (0.087–0.16)	<0.001	0.33 (0.23–0.43)	<0.001	0.11 (−0.075–0.30)	0.24	0.16 (0.071–0.25)	<0.001
Model 2			0.21 (0.11–0.31)	<0.010	0.14 (−0.062–0.34)	0.18	0.10 (0.004–0.20)	0.040
Model 3					0.12 (−0.067–0.30)	0.21	0.10 (0.004–0.19)	0.041
Length gain (mm/day)								
Crude	0.79 (−2.6–4.2)	0.65	8.8 (0.005–17.6)	0.050	3.0 (−12.3–18.3)	0.70	−1.3 (−8.9–6.2)	0.73
Model 1	0.48 (−2.9–3.8)	0.78	7.7 (−1.0–16.4)	0.083	2.1 (−13.2–17.3)	0.79	−0.50 (−8.0–7.0)	0.90
Model 2								
Model 3					1.5 (−12.5–15.5)	0.84	−0.55 (−8.0–6.9)	0.89
Z-score weight for length gain**								
Crude	0.51 (0.37–0.66)	<0.001	1.2 (0.82–1.6)	<0.001	0.43 (−0.29–1.1)	0.25	0.68 (0.33–1.0)	<0.001
Model 1	0.51 (0.37–0.66)	<0.001	1.2 (0.83–1.6)	<0.001	0.42 (−0.29–1.1)	0.25	0.68 (0.34–1.0)	<0.001
Model 2			0.84 (0.46–1.2)	<0.001	0.49 (−0.26–1.2)	0.20	0.50 (0.15–0.85)	0.006
Model 3					0.44 (−0.24–1.1)	0.21	0.50 (0.15–0.85)	0.005

A Z-score of +1 SD WLG indicates that the weight gain of a certain child is one standard deviation larger than the mean weight gain in the population based on the length gain of that child.

*Birth weight adjusted for birth length, gestational age and gender.

**Weight gain rate adjusted for length gain rate and gender.

All results are linear regression coefficients with 95%-confidence intervals.

Model 1: adjusted for age and gender.

Model 2: adjusted for age, gender and current height (the analyses with rate of length gain are not adjusted for current height).

Model 3: adjusted for age, gender, current height and observer (for intra-abdominal fat and subcutaneous fat).

was observed: per 1 unit increase in Z-score WLG, intra-abdominal fat was 0.51 mm higher (95%-CI: −0.14, 1.2, P value: 0.12). Again, no interaction between size at birth and postnatal growth on body fat distribution was present.

4. Discussion

The present study contributes to current knowledge in showing that excess weight gain relative to length gain in the first 3 months after birth is associated with central adiposity. Strong associations with BMI, waist circumference, and abdominal subcutaneous fat were observed. In addition, these results suggest an increase in intra-abdominal fat as well.

Some remarks have to be made. WHISTLER is a population-based cohort and families with a healthier lifestyle might be more willing to participate. Moreover, children with follow-up measurements tended to have a higher birth weight and were larger at birth (data not shown) compared to those lost to follow-up. Since data on birth size was not available for all children, birth length was imputed using multiple imputation. Missing birth length was associated with lower gestational age and the imputed birth lengths were smaller than those nonimputed. Multiple imputation strengthened the observed associations between postnatal growth and adiposity measures in young childhood, indicating an effect of selection on the results from the complete case analyses. We consider our study population to be representative of a healthy pediatric population, as the mean weights and lengths in infancy are in line with the WHO growth charts [28]. We derived internal Z-scores for weight gain rate conditioned on length gain rate, as references values for comparable Z-scores are not available. Since data on fetal growth have not been collected as part of the present study, birth size was used as proxy. Birth weight is determined by gestational age, growth potential, and intrauterine environment. Therefore, birth weight adjusted for birth length and gestational age might be a better indicator of intrauterine exposures. Besides age, gender, current height, and sonographer, we did not consider other factors, like parental BMI, infant feeding, tobacco smoke exposure among others as confounders, as these factors might precede the studied association and might therefore be in the causal pathway. Whether or not to adjust for achieved height is topic of discussion [29, 30]. However, when comparing absolute fatness of individuals of different heights, adjustment for height is indicated [19, 20]. Since the ultrasonography was performed blinded to infancy characteristics, the probability of information bias to have occurred is negligible. Additionally, we adjusted for sonographer, to further rule out the possibility of observer bias. Although CT is currently the most accurate method to measure intra-abdominal fat [31], ultrasonography is a good, child friendly, and practical alternative in population studies, which has been shown to correlate well with results from CT and MRI [26]. When the data collection of the present study started, we chose to use ultrasonographically measured intra-abdominal depth to assess visceral fat [26, 27]. More recently, validation studies of this method in children provided conflicting results [32, 33] and another ultrasonographic method for measuring intra-abdominal fat has been described [34, 35] and validated in infants [36]. Although we previously found an association between intra-abdominal depth and vascular characteristics in the 5-year-olds of our study population as well [25], it should be kept in mind that consensus regarding the best, feasible method for measuring intra-abdominal fat in children, has not yet been reached.

Previously, associations between weight gain in the first 2 years of life and childhood BMI [8, 9], waist circumference [8, 12, 13], intra-abdominal fat [11], and both subcutaneous and preperitoneal fat [10] have been described. In the present study, we focused on excess weight gain relative to length gain the first 3 postnatal months, as the importance of particularly this period in the development of increased waist circumference in adulthood [15–17] and childhood [14] was addressed in previous studies. Associations between excess early postnatal weight gain and BMI, waist circumference, and abdominal subcutaneous fat were indeed observed in this study, and some evidence for an association with intra-abdominal fat was found as well. The difference in precision of the ultrasonographic fat measurements might explain why the association with intra-abdominal fat was less pronounced than the association with subcutaneous fat.

The observed differences in adiposity associated with excess weight gain in early infancy might be explained by increased accumulation of fat mass in the early postnatal period. Weight gain for length gain in the first months after birth primarily reflects accumulation of fat mass, since fat mass increases from approximately 13% of total body weight to 31% between 0.5 and 3–6 months of age [18]. According to the "developmental origins of human health and disease" hypothesis [37, 38] increased postnatal weight gain for length gain might be a reflection of metabolic programming following a period of relative growth impairment. However, in the present study no interaction between postnatal weight gain for length gain and size at birth was observed in the associations with adiposity at 5 years of age. This indicates that the association between increased weight gain for length gain and fat distribution is not only present for those infants who were growth restricted in pregnancy, but also for infants with normal fetal growth.

We found some evidence for an association between excess early postnatal weight gain and intra-abdominal fat. Besides these differences in quantity of intra-abdominal fat, the previously observed adverse metabolic consequences later in life associated with increased postnatal growth [15], might be further explained by differences in adipose tissue function. Adipose tissue dysfunction might be even more important than quantity alone in the development of CVD [6]. Further research is needed to study whether excess weight gain in early infancy leads to changes in adipose tissue functioning in early childhood.

While the observed differences in fat distribution are relatively small from an individual perspective, they are relevant from a population perspective. However, we should be careful in extrapolating these finding to growth interventions, as rapid postnatal growth might have benefits as well [39–41]. Moreover, to date it remains unknown how to modify infant growth in a way that avoids adverse outcomes. Based on current knowledge, prevention of known causes of

impaired fetal growth and rapid postnatal growth, such as maternal smoking during pregnancy [42], is indicated.

In conclusion, variations in postnatal growth are associated with abdominal fat in early childhood. Over the whole range of birth size, excess early postnatal weight gain relative to length gain is associated with increased general and central adiposity, characterized by higher BMI, larger waist circumference, more abdominal subcutaneous fat, and likely more intra-abdominal fat at 5 years of age.

Conflict of Interests

None of the authors have financial relationships relevant to this paper to disclose.

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Research Article

Postnatal Acute Famine and Risk of Overweight: The Dutch Hungerwinter Study

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Objective. To examine the association between undernutrition during postnatal periods of development and the risk of overweight in adulthood. *Methods*. We studied 8,091 women from Prospect-EPIC, exposed to the Dutch famine at ages between 0 and 21 years, recruited at ages between 49 and 70 years. We used linear and logistic regression models to explore the effect of famine on BMI, waist circumference, and the risk of overweight. *Results*. Overall, postnatal famine exposure was associated with increased BMI and waist circumference in a dose-dependent manner (P for trend < 0.01). Furthermore, risk of overweight was increased following famine exposure (P for trend $= 0.01$), with those severely exposed at ages 0–9 years having 25% (95% CI 1.05 to 1.50) higher risk compared to unexposed women. *Conclusions*. This study is the first to directly show a positive association between short and transient undernutrition during postnatal development and BMI, waist circumference, and overweight in adulthood.

1. Introduction

Obesity is an increasing problem worldwide; it is the fifth leading risk for death globally. Furthermore, overweight and obesity are major risk factors for chronic diseases, including cardiovascular disease, type 2 diabetes, and cancer [1]. Global estimates of the World Health Organization (WHO) indicate that more than one in ten of the world's adult population was obese in 2008 [1]. Once, obesity was considered a nutritional disease and only a problem in developed countries. However, to date the number of people suffering from overweight and obesity is dramatically increasing in developing countries as well [1]. Worldwide, a total of 43 million children under five were overweight in 2010; more than 80% of these children live in developing countries [1]. Since childhood overweight is an important precursor of overweight and obesity in adulthood [2], these numbers predict increasing fractions of overweight and obese people in the future in both developed and developing countries.

The developmental origins of chronic disease hypothesis propose that undernutrition during important periods of growth and development, including fetal life, infancy, and childhood, results in early adaptations in the structure and function of the body [3]. These adaptations may be beneficial for survival in the short term. However, in the long term, these adaptations may result in an increased risk of chronic diseases, including obesity, coronary heart disease, and type 2 diabetes.

The association between low birth weight, as a marker of intrauterine growth retardation, postnatal catch-up growth, and later body composition and chronic disease risk has been extensively researched. Humans who suffered from fetal growth retardation and subsequently showed catch-up growth were demonstrated to have higher susceptibility

to obesity, type 2 diabetes, and cardiovascular disease in later life [4–9]. Such catch-up growth was also found to be associated with a disproportionate increase in abdominal fat mass [9, 10].

Direct evidence for the early origins of obesity was provided by studies of people who were conceived during the Dutch famine. These studies demonstrated that externally imposed undernutrition during gestation, followed by adequate food supply later on, was associated with an increased risk of obesity [11–13]. Furthermore, the Dutch Famine Birth Cohort Study demonstrated associations between undernutrition during gestation and obesity-related phenotypes in adult life, including an atherogenic lipid profile [14], coronary heart disease [15], and a reduced glucose tolerance [16, 17]. Women exposed to famine in early gestation also had an increased risk of cardiovascular mortality [18].

Overall, this evidence suggests that undernutrition during fetal life, which is an important period of growth and development, is critical with respect to later life health outcomes. Next to the fetal period, childhood and adolescence are also important periods of growth and development. Little if anything is known about the later life effects of exclusive postnatal stunting of growth. Studies of these effects would require registry of exposures in distinct phases of postnatal childhood as well as registry of outcome data in individuals that were born healthy. In the Prospect-EPIC cohort study we have data with individual information on exposure to the 1944-1945 Dutch famine during childhood, adolescence, and young adulthood. In this way, we were able to examine the association between moderate or severe undernutrition during postnatal periods of development—including childhood, adolescence, and young adulthood—and BMI, waist circumference, and the risk of overweight in adult life.

2. Subjects and Methods

2.1. The Prospect-EPIC Cohort. This study included women participating in Prospect-EPIC, one of the two Dutch contributions to the European Prospective Investigation into Cancer and nutrition (EPIC). The rationale and design of both EPIC and Prospect-EPIC have been described in detail elsewhere [19, 20]. In brief, the Prospect-EPIC study includes 17,357 women living in Utrecht and vicinity, aged 49–70 years at enrolment between 1993 and 1997. All women signed informed consent before study inclusion. The study complies with the Declaration of Helsinki and was approved by the Institutional Review Board of the University Medical Center Utrecht. At baseline, the women filled in a general questionnaire on demographic and lifestyle factors, and past and current morbidity and a food frequency questionnaire, and underwent a brief standardized physical examination. In addition, a nonfasting blood sample was taken.

2.2. Famine Exposure

2.2.1. The Dutch Famine. The Dutch famine was a six-month period of severe undernutrition during the last winter of World War II. The famine struck the occupied and densely populated Western parts of The Netherlands. The average daily rations per capita dropped from about 1,400 kilocalories in October 1944 to below 1,000 kilocalories in late November 1944. At the height of the famine from December 1944 to April 1945, the official daily rations varied between 400 and 800 kilocalories, less than a quarter of the prefamine rations [21]. The relative amounts of fats, carbohydrates, and proteins remained essentially unchanged during this period [22]. In early May 1945, The Netherlands was liberated and food supplies became abundant due to Allied intervention, ending the famine abruptly.

2.2.2. Famine Exposure Assessment. The self-administered general questionnaire, which was filled in at time of enrolment by all study participants, contained questions about the 1944-1945 Dutch famine. Women were asked about their place of residence during the 1944-1945 Dutch famine and about their experiences of hunger and weight loss. Women could respond to these last two questions using one of three answer categories: "hardly," "little," or "very much." The women who had answered "not applicable" or "I do not know" to one or both famine questions were excluded from the analysis. We combined the answers into a three-point subjective famine exposure score: women who reported having been "very much exposed" to both hunger and weight loss were categorized as "severely exposed," women who reported having been "hardly exposed" to either hunger and weight loss were categorized as "unexposed," and all others as "moderately exposed."

2.2.3. Exposure Age Categories. Age at famine exposure was assessed taking October 1, 1944 as the start of the famine as reference. Exposure age was classified into three catego-ries; childhood (0 to 9 years of age at famine exposure), adolescence (10 to 17 years of age at famine exposure), and young adulthood (18 years or older at famine exposure). We defined these three general growth periods according to the seven stages in the postnatal human life cycle as defined by Bogin [23]. We defined preadolescent childhood, a period of rapid growth with many developmental milestones in physiology, behavior, and cognition, as the period between 0 and 9 years, just before the growth spurt in women [23, 24]. From the start of the growth spurt, at around 10 years, through to age 17 is called adolescence [23, 24]. This period is characterized by the growth spurt including sexual development [23, 24]. From 18 years of age, we considered persons as young adults gradually reaching homeostasis in physiology.

2.3. Subject Selection. The Prospect-EPIC cohort consists of 17,357 women. For the present study, we excluded women who were born after the famine (n = 2,559) and women who resided outside occupied Netherlands during the famine (n = 1,732). Women for whom no hunger score could be calculated were also excluded (n = 4,975), leaving 8,091 women for our analyses. In the models where we adjusted for total energy intake, we also excluded women who were

likely to have misreported their energy intake (n = 2,451); the definition of energy misreporters is described below.

2.4. Outcome Assessment. The baseline physical examination, assessed in light indoor clothing without shoes, was carried out by trained study staff. Body height was measured to the nearest 0.5 cm with a wall mounted stadiometer (Lameris, Utrecht, the Netherlands), body weight was measured to the nearest 0.5 kg with a floor scale (Seca, Atlanta, GA, USA), and waist and hip circumference were measured as the minimal circumference of the middle, respectively, the hip/buttocks, to the nearest 0.5 cm with a nonstretchable measuring tape. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). Waist to hip ratio (WHR) was calculated by dividing waist circumference in centimeters by hip circumference in centimeters.

2.5. Covariates. At baseline, participants completed a general questionnaire containing questions on demographic characteristics, presence of chronic diseases, and risk factors for chronic diseases, such as smoking habits and level of education. Smoking was defined according to the number of pack years. We categorized level of education into low (primary and lower vocational education), intermediate (advanced elementary, intermediate vocational, and higher general secondary education from 3rd year with success or completed), or high (higher vocational education, university to bachelor examination, and university completed) and used it as a proxy for socioeconomic status.

Daily dietary intake was obtained from a food frequency questionnaire containing questions on the usual frequency of consumption of 79 main food items during the year preceding enrolment. This questionnaire allows the estimation of the mean daily consumption of 178 foods. It has been validated against 12 24 h dietary recalls [25]. The 1996 Dutch food consumption table was used to calculate energy and nutrient intakes. Basal metabolic rate (BMR) was estimated using the Schofield equations [26]. Participants with a total energy intake to BMR ratio of <1.14 or >2.40 were defined as energy misreporters, according to the Goldberg et al. cut-offs [27].

2.6. Data Analysis. Prospect participant characteristics at enrolment, including demographics, energy and macronutrient intake, and lifestyle, were first tabulated against timing and severity of famine exposure, in order to evaluate potential for confounding. We used linear regression analysis to explore the effects of famine exposure on BMI and waist circumference separately. To analyze the effect of famine exposure on the risk of overweight we performed logistic regression analyses. We defined a person to be overweight if their BMI was ≥25 kg/m^2.

To study the effects of famine exposure, we used the three-point individual famine exposure score (unexposed, moderately, and severely exposed). Trend tests were used to explore dose-response relations by introducing the famine exposure score as a continuous variable (1 for "unexposed," 2 for "moderately exposed," and 3 for "severely exposed"). To assess sensitive growth periods, we analyzed the effects of famine exposure on BMI, waist circumference, and overweight within each of the exposure age categories (0–9, 10–17, and ≥18 years) and tested for interaction by introducing the cross-product of the famine exposure score and age at start of the famine to the various models.

First we analyzed the crude association between famine exposure and BMI, waist circumference, and overweight in each of the exposure age categories. In a second model, we adjusted for potential confounders including age at start of the famine (years), smoking (pack years), alcohol intake (g/day), and level of education (low/intermediate/high; socioeconomic status proxy). In a subsequent model, we additionally included average total energy intake in the year prior to enrolment as a possible intermediate variable linking childhood undernutrition to later overweight. In the model with total energy intake included, we excluded women who were likely to have misreported their energy intake. Within the women with reliable energy intake, we compared the confounder adjusted model with such model with energy intake added.

Continuous variables were introduced as such in the different models; for categorical variables we created indicator variables. We evaluated the linear regression model assumptions with a normal probability plot of the standardized residuals (normality assumption) and a scatterplot with standardized residuals versus standardized predicted values (constant variance assumption and linearity assumption). These assumptions were found to be justified. Introducing nonlinear terms to the models did not improve the fit of the data. Results of the linear regression analyses are reported as mean differences with 95% confidence intervals (CIs) between those who were moderately or severely famine exposed compared to those who were unexposed to famine. Results of the logistic regression analyses are reported as odds ratios (ORs) with 95% CI between those who were unexposed to famine compared to those who were moderately or severely famine exposed.

We performed all statistical analyses with SPSS Statistics version 17.0 (SPSS, Chicago, IL, USA). P values were based on two-sided tests with a cut-off level for statistical significance of 0.05.

3. Results

Table 1 shows the baseline characteristics of the study group. Of the total of 8,091 women, 4,425 (55%) women had experienced the famine between ages 0 to 9 years, 3,179 (39%) women at ages between 10 and 17 years, while 487 (6%) women were 18 years or over when they experienced the famine. In total, 3,675 (45%) women reported having been unexposed to famine; 3,078 (38%) had been moderately exposed and 1,338 (17%) severely exposed to famine. Women who were older at the start of the famine reported more often to be exposed to famine. Overall, severely famine exposed women had lower total energy intake and smoked more than unexposed women.

Table 1: Baseline characteristics of the study population according to age at famine (0–9 years, 10–17 years, or ≥18 years) and level of famine exposure (none, moderate, or severe).

	Age at famine								
	0–9 years			10–17 years			≥18 years		
	Level of famine exposure			Level of famine exposure			Level of famine exposure		
	None	Moderate	Severe	None	Moderate	Severe	None	Moderate	Severe
Number (%)	2148 (49)	1612 (36)	665 (15)	1345 (42)	1247 (39)	587 (19)	182 (37)	219 (45)	86 (18)
General characteristics									
Age at start of the famine (years)[a]	4.2 (0–10)	4.6 (0–10)	5.5 (0–10)	13.8 (10–18)	14.1 (10–18)	13.6 (10–18)	18.8 (18–21)	19.1 (18–21)	19.2 (18–21)
Age at recruitment (years)[a]	54.9 (49–63)	55.2 (49–63)	56.2 (49–63)	64.6 (59–70)	64.8 (59–70)	64.0 (59–70)	68.9 (67–70)	69.0 (67–70)	69.1 (67–70)
Body size									
Height (cm)[b]	165.4 (5.9)	165.1 (5.8)	164.9 (6.1)	163.4 (5.7)	163.0 (5.9)	163.1 (6.0)	161.9 (6.2)	162.7 (5.9)	161.3 (6.4)
Dietary intake									
Total energy intake (kcal)[b]	1829 (436)	1817 (428)	1811 (450)	1740 (423)	1750 (405)	1677 (417)	1703 (435)	1663 (400)	1659 (524)
Total protein intake (g)[b]	73.7 (18.4)	72.6 (17.5)	72.9 (18.4)	70.4 (17.0)	70.0 (17.2)	67.5 (16.8)	69.0 (17.1)	68.9 (18.1)	67.6 (22.2)
Total fat intake (g)[b]	72.9 (22.9)	72.3 (22.6)	72.4 (24.1)	68.3 (22.0)	69.6 (21.8)	65.8 (21.9)	67.3 (23.9)	65.1 (20.5)	64.4 (25.1)
Total carbohydrate intake (g)[b]	201.6 (53.5)	201.3 (52.0)	200.5 (53.4)	199.0 (52.7)	198.4 (51.1)	191.8 (52.2)	194.2 (50.3)	190.1 (48.7)	193.5 (65.8)
Lifestyle									
Education in 3 categories[c]									
Low	934 (43)	639 (40)	311 (47)	788 (59)	645 (52)	306 (52)	123 (68)	114 (52)	52 (60)
Intermediate	832 (39)	659 (41)	256 (38)	450 (33)	456 (37)	228 (39)	50 (27)	79 (36)	23 (27)
High	377 (18)	313 (19)	98 (15)	104 (8)	145 (12)	53 (9)	9 (5)	26 (12)	11 (13)
Smoking (pack years)[b]	6.0 (9.2)	6.6 (9.4)	8.1 (10.5)	5.4 (9.4)	6.7 (10.9)	8.0 (11.7)	3.1 (6.1)	6.2 (9.6)	6.2 (10.3)
Alcohol intake (g/day)[b]	10.1 (1.3)	10.1 (1.3)	9.3 (1.3)	6.7 (1.0)	7.1 (1.0)	6.7 (1.2)	6.3 (1.0)	5.9 (9.3)	5.0 (7.0)

[a]Median (min-max), [b]Mean (SD), [c]Number (%).

Table 2: *BMI*: means, (un)adjusted differences, and 95% confidence intervals (CIs) for women of all ages combined and within each of the three exposure age categories: 0–9 years, 10–17 years, and ≥18 years who reported to be moderately or severely exposed to famine compared to those who reported to be unexposed to famine.

	Number of subjects	Mean (SD)	Crude model		Multivariable model 1		Multivariable model 2	
			Mean difference†	95% CI	Mean difference†	95% CI	Mean difference†	95% CI
All ages								
Unexposed	3.672	26.0 (4.0)	reference	—	reference	—	reference	—
Moderately exposed	3.074	26.3 (4.0)	0.28	0.09 to 0.48	0.29	0.10 to 0.48	0.34	0.14 to 0.55
Severely exposed	1.335	26.3 (4.2)	0.32	0.07 to 0.57	0.21	−0.05 to 0.46	0.25	−0.02 to 0.52
P for trend			0.002		0.02		0.009	
Age at famine categories								
0 to 9 years								
Unexposed	2.147	25.6 (3.9)	reference	—	reference	—	reference	—
Moderately exposed	1.609	25.9 (4.0)	0.25	−0.00 to 0.51	0.33	0.07 to 0.59	0.37	0.10 to 0.64
Severely exposed	664	26.2 (4.3)	0.60	0.25 to 0.95	0.48	0.13 to 0.83	0.44	0.07 to 0.82
P for trend			<0.001		0.002		0.004	
10 to 17 years								
Unexposed	1.343	26.5 (4.0)	reference	—	reference	—	reference	—
Moderately exposed	1.246	26.7 (4.0)	0.18	−0.13 to 0.49	0.23	−0.08 to 0.54	0.31	−0.02 to 0.64
Severely exposed	585	26.4 (4.0)	−0.18	−0.57 to 0.20	−0.12	−0.51 to 0.27	−0.02	−0.44 to 0.40
P for trend			0.63		0.91		0.64	
≥18 years								
Unexposed	182	26.9 (4.3)	reference	—	reference	—	reference	—
Moderately exposed	219	27.1 (4.5)	0.18	−0.67 to 1.03	0.49	−0.38 to 1.36	0.41	−0.52 to 1.34
Severely exposed	86	27.1 (3.8)	0.25	−0.86 to 1.35	0.44	−0.67 to 1.56	0.75	−0.42 to 1.93
P for trend			0.63		0.34		0.19	

† Mean difference as compared to those who reported to be unexposed to famine.

P for interaction age at famine * famine exposure: 0.02.

Multivariable model 1: adjusted for age at start of the famine (October 1, 1944), smoking (pack years), alcohol intake (g/day), and level of education (3 categories: low, intermediate, and high).

Multivariable model 2: adjusted for age at start of the famine (October 1, 1944), smoking (pack years), alcohol intake (g/day), level of education (3 categories: low, intermediate, and high), and total energy intake (kcal), among the subgroup of women with reliable energy intake according to Goldberg's equation.

3.1. BMI and Waist Circumference. Tables 2 and 3 show the mean differences in BMI and waist circumference for all ages combined and within each of the three exposure age categories (0–9 years, 10–17 years, and ≥18 years) for those who were moderately or severely famine exposed compared to those unexposed to famine. In the three exposure age categories combined, we observed a significantly higher BMI and waist circumference among famine exposed women in a dose-dependent manner (*P* for trend for BMI: 0.002; *P* for trend for waist circumference: <0.001). After adjustment for the potential confounders age at start of the famine, smoking, alcohol intake, and level of education (socioeconomic status proxy), mean differences in BMI were 0.29 kg/m^2 (95% CI: 0.10 to 0.48) and 0.21 kg/m^2 (95% CI: −0.05 to 0.46), and mean differences in waist circumference were 0.75 cm (95% CI: 0.28 to 1.23) and 0.65 cm (95% CI: 0.02 to 1.27), for moderate and severe famine exposure, respectively, compared to no famine exposure.

Additionally including total energy intake did not change the associations between famine exposure and both BMI and waist circumference. We found a statistically significant interaction between the effects of age at start of the famine and famine exposure on BMI (*P* for interaction for BMI: 0.02; *P* for interaction for waist circumference: 0.07).

Within women in the 0-to-9 year exposure age category, we found a significant dose-dependent increase in BMI and waist circumference among famine-exposed women compared to unexposed women (*P* for trend BMI and waist circumference: <0.001). After adjustment for the potential confounders age at start of the famine, smoking, alcohol intake, and level of education (socioeconomic status proxy), mean differences in BMI were 0.33 kg/m^2 (95% CI: 0.07

Table 3: *Waist circumference:* means, (un)adjusted differences, and 95% confidence intervals (CIs) for women of all ages combined and within each of the three exposure age categories: 0–9 years, 10–17 years, and ≥18 years who reported to be moderately or severely exposed to famine compared to those who reported to be unexposed to famine.

	Number of subjects	Mean (SD)	Crude model		Multivariable model 1		Multivariable model 2	
			Mean difference†	95% CI	Mean difference†	95% CI	Mean difference†	95% CI
All ages								
Unexposed	3.670	83.8 (9.9)	reference	—	reference	—	reference	—
Moderately exposed	3.072	84.7 (10.0)	0.91	0.43 to 1.39	0.75	0.28 to 1.23	1.08	0.57 to 1.60
Severely exposed	1.334	84.9 (10.4)	1.19	0.56 to 1.82	0.65	0.02 to 1.27	0.72	0.03 to 1.41
P for trend			<0.001		0.007		0.002	
Age at famine categories								
0 to 9 years								
Unexposed	2.145	82.3 (9.6)	reference	—	reference	—	reference	—
Moderately exposed	1.609	83.0 (9.8)	0.74	0.11 to 1.38	0.84	0.21 to 1.48	1.09	0.40 to 1.77
Severely exposed	664	83.8 (10.5)	1.56	0.71 to 2.41	1.02	0.17 to 1.88	0.86	−0.09 to 1.81
P for trend			<0.001		0.004		0.008	
10 to 17 years								
Unexposed	1.343	85.7 (9.9)	reference	—	reference	—	reference	—
Moderately exposed	1.244	86.4 (9.9)	0.69	−0.08 to 1.46	0.72	−0.05 to 1.50	1.22	0.37 to 2.06
Severely exposed	584	85.8 (10.2)	0.15	−0.82 to 1.12	0.23	−0.75 to 1.20	0.44	−0.64 to 1.52
P for trend			0.45		0.37		0.13	
≥18 years								
Unexposed	182	87.0 (9.6)	reference	—	reference	—	reference	—
Moderately exposed	219	87.2 (9.9)	0.14	−1.79 to 2.07	0.72	−1.26 to 2.71	0.64	−1.64 to 2.91
Severely exposed	86	87.5 (9.9)	0.46	−2.06 to 2.98	0.73	−1.82 to 3.28	1.84	−1.02 to 4.70
P for trend			0.73		0.51		0.22	

† Mean difference as compared to those who reported to be unexposed to famine.

P for interaction age at famine * famine exposure: 0.07.

Multivariable model 1: adjusted for age at start of the famine (October 1, 1944), smoking (pack years), alcohol intake (g/day), and level of education (3 categories: low, intermediate, and high).

Multivariable model 2: adjusted for age at start of the famine (October 1, 1944), smoking (pack years), alcohol intake (g/day), level of education (3 categories: low, intermediate, and high), and total energy intake (kcal), among the subgroup of women with reliable energy intake according to Goldberg's equation.

to 0.59) and 0.48 kg/m^2 (95% CI: 0.13 to 0.83), and mean differences in waist circumference were 0.84 cm (95% CI: 0.21 to 1.48) and 1.02 cm (95% CI: 0.17 to 1.88), for moderate and severe famine exposure respectively compared to no famine exposure. Further inclusion of total energy intake in the multivariable model did not change the results.

We could not demonstrate a significant association between famine exposure and BMI and waist circumference among women in the 10-to-17 year and ≥18-year exposure age categories. Adjustment for the potential confounders age at start of the famine, smoking, alcohol intake, and level of education did not change the results, as did the additional adjustment for total energy intake.

3.2. Overweight. In the three exposure age categories combined, we observed a significantly increased risk of overweight among famine-exposed women in a dose-dependent manner (*P* for trend: 0.001). After adjustment for the potential confounders age at start of the famine, smoking, alcohol intake, and level of education, odds ratios were 1.10 (95% CI: 1.00 to 1.22) and 1.15 (95% CI: 1.01 to 1.31), for moderate and severe famine exposure, respectively, compared to no famine exposure. Additionally including total energy intake did not change these results. The *P* for interaction for the effect of age at start of the famine on the association between famine exposure and the risk of overweight was 0.10.

Within women aged 0 to 9 years at start of the famine, those moderately famine exposed had no increased risk compared to unexposed women, whereas those severely famine exposed had a significantly increased risk of overweight (*P* for trend: 0.002) (Figure 1). After adjustment for the potential confounders age at start of the famine, smoking, alcohol intake, and level of education, those moderately famine exposed had nonsignificant 10% higher odds (95%

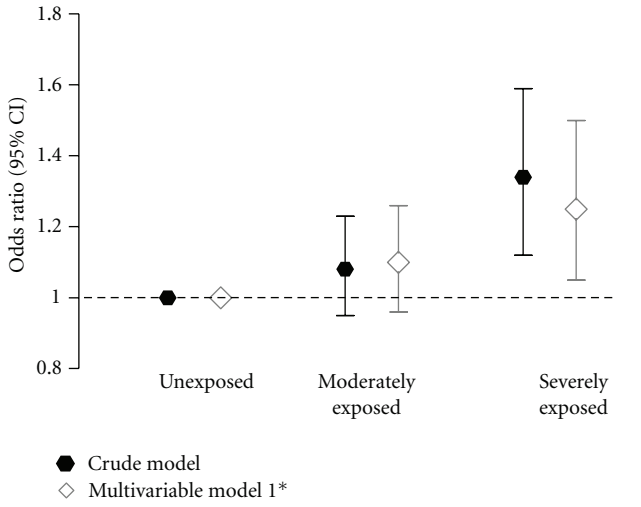

Figure 1: Odds ratios (ORs) and 95% confidence intervals (CI) for the risk of overweight (BMI $\geq$ 25 kg/m^2) for women within the 0-to-9-year exposure age category who reported to be moderately or severely exposed to famine compared to those who reported to be unexposed to famine.

CI: 0.96 to 1.26) of overweight, whereas those severely famine exposed had a significant 25% higher odds (95% CI: 1.05 to 1.50) of overweight compared to unexposed women (Figure 1). Further inclusion of total energy intake did not change the risk estimates.

We could not demonstrate a significant association between famine exposure and the risk of overweight among women in the 10-to-17 year and $\geq$18-year exposure age categories. After adjustment for the potential confounders age at start of the famine, smoking, alcohol intake, and level of education, odds ratios among women in the 10-to-17-year exposure age category were 1.13 (95% CI: 0.96 to 1.33) for moderate and 1.01 (95% CI: 0.82 to 1.25) for severe famine exposure compared to no famine exposure. Among women in the $\geq$18-year exposure age category, the adjusted odds ratios were 1.15 (95% CI: 0.75 to 1.78) for moderate and 1.60 (95% CI: 0.89 to 2.87) for severe famine exposure compared to no famine exposure.

4. Discussion

This study demonstrates for the first time by using individual famine exposure data that a relatively short period of moderate or severe undernutrition during childhood is associated with an increase in BMI and waist circumference in adult life, in a dose-dependent manner. Women exposed to famine during their childhood also had an increased risk of being overweight in adult life compared to those who were unexposed.

Before further discussion, some aspects of our study require consideration. The Dutch famine of 1944-1945 is a "natural experiment" in history, which gave us the unique possibility to study the long-term effects of acute undernutrition during childhood and young adulthood in otherwise well-nourished girls and women. In this study, we used individual data on famine exposure instead of classifying populations according to place of residence or time [28, 29], which we believe to have led to more precise exposure assessment. The drawback of individual data may be their subjective nature, which may have resulted in misclassification. However, misclassification due to recall would most likely have underestimated the observed effects, because we consider it unlikely that recall of famine exposure is related to the risk of overweight. Furthermore, the questionnaires about famine exposure were filled in before height and weight measurements were performed. Our exposure classification data agree with rationing practices at that time. Throughout World War II, the allocated individual amount of calories was based on age. Young children were relatively protected from the famine; children between 1 and 3 years of age received about 50% of the distributed amount of calories at the start of the famine, whereas those aged over 18 years received about 25% [21]. Furthermore, children were relatively protected within families and by special committees such as the Interchurch Organization [21, 30]. These historical facts are reflected in our data; the older the women were at the start of the famine, the higher the proportion that reported to have been exposed to famine. This supports the quality of our exposure data.

We found a significant dose-dependent increase in BMI and waist circumference in adult life among women exposed to famine during their childhood compared to unexposed women. In agreement with the increase in BMI and waist circumference among these women, we also demonstrated a dose-dependent increased risk of overweight, although the risk of overweight was not significantly increased among moderately famine-exposed women. Adjustment for the potential confounders age at start of the famine, smoking, alcohol intake, and education yielded slightly higher risk estimates for those who reported to be moderately exposed and slightly lower risk estimates for those who reported to be severely exposed. Including total energy intake as a possible intermediate variable into the models, linking childhood undernutrition to later overweight, did not change the results. Thus, the increased BMI, waist circumference, and risk of overweight among famine-exposed women seemed not to be mediated by an increased total energy intake.

Not only the amount of body fat, which is represented by BMI as a general adiposity measure, but also its distribution is important in evaluating chronic disease risk [31]. Increased abdominal adiposity (visceral fat) has been associated with an adverse metabolic profile and subsequently an increased risk of cardiovascular disease [32]. The results of our study suggest that disturbing important developmental periods during postnatal life are not only associated with general adiposity, but also specifically with abdominal adiposity. These results agree with those of other studies. Rapid infant weight gain after a period of growth restriction has been associated with later abdominal adiposity [33–35]. Among women with anorexia nervosa,

weight normalization has been associated with body fat redistribution towards visceral adiposity [36].

Recently, fetal-infant exposure to the Biafran famine has been associated with an increased risk of hypertension, diabetes, and overweight as compared to people born after the famine [37]. However, an association between famine exposure during childhood and the risk of overweight in adult life could not be demonstrated [37]. These results may not seem fully in agreement with ours, but the essentially different circumstances during both famines hamper a direct comparison. The Dutch famine lasted only six months, whereas the Biafran famine lasted for more than two years. Furthermore, the Biafran famine was preceded and followed by periods of relative food shortage instead of adequate nutrition in The Netherlands. The Nigerian standard of living remained rather poor after the Nigerian civil war, whereas the Dutch population grew up in a period of increasing affluence.

Two ecological studies also studied the association between severe undernutrition during childhood and BMI in adult life [28, 29]. Men and women living in Hong Kong who experienced caloric restriction for a continuous period of at least one year during their childhood (around 10 years of age) had a higher BMI in adult life [29]. The other study investigating this association demonstrated that women, but not men, who were exposed to the Great Chinese Famine between 1 and 3 years of age had a significantly increased body weight and BMI and a significantly higher prevalence of overweight and obesity as compared to women who were born after the famine [28]. Since these studies did not assess waist circumference, it is not clear whether the increases in body weight were due to increased abdominal fat mass. In these previous studies, famine exposure was defined by classifying populations according to place of residence. In contrast, our study relied on an individual famine exposure score to define the severity of famine exposure, which we believe to have led to more precise exposure assessment.

4.1. Relevance. Our findings support the notion that disturbed growth during postnatal development, particularly in childhood, can have important implications for adult health. The contemporary relevance of our finding is that famine and undernutrition are still a major problem worldwide; never before have there been so many hungry people worldwide [38]. The first Millennium Development Goal is to eradicate extreme hunger. Since childhood overnutrition is also an important precursor for overweight and obesity in adulthood [2], fighting under- and overnutrition of young children may be a powerful strategy to prevent a significant number of deaths due to overweight and obesity at adult age.

4.2. Conclusion. This study provides the first direct evidence, using individual famine exposure data, that a short period of moderate or severe undernutrition, especially during early childhood, increases the risk of overweight in adult life.

Conflict of Interests

The authors declare no conflict of interests.

Acknowledgments

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Clinical Study

Long-Term Effects of Placental Growth on Overweight and Body Composition

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Obesity is programmed in utero and small babies generally have small placentas. In some circumstances, an undernourished fetus can expand its placental surface to extract more nutrients. We hypothesize that this results in an imbalanced nutrient supply to the fetus leading to obesity. To determine whether placental size determines overweight and body composition, we studied 2003 subjects in adult life. Associations between placental surface area and indices of overweight were restricted to people who carried the Pro12Pro genotype of the *PPARγ2* gene. For every 1 SD increase in placental surface area, the odds ratio for overweight was 1.37 (95% CI 1.10 to 1.71; $P = 0.005$). Expansion of the placental surface in compensation for fetal undernutrition increases the risk of overweight and a higher body fat percentage in people carrying the Pro12Pro genotype. We suggest that similar underlying multifactorial mechanisms affect the development of obesity in general.

1. Introduction

There is a body of evidence suggesting that type 2 diabetes is programmed in utero [1, 2]. Fetal programming is the process through which fetal malnutrition leads to lifelong changes in the body organs and systems in ways that might cause disease in later life [3]. There is some evidence that obesity, a major risk factor for type 2 diabetes, is also programmed in utero. Maternal hyperglycemia is associated with obesity in the next generation [4, 5]. Women who were in utero during the Dutch famine tended to be overweight as adults as a consequence of early programming [6]. Interestingly, animal experiments show that prenatal undernutrition upregulates appetite [7].

Fetal nutrition depends on the placenta ability to transport nutrients to the fetus from its mother [8]. This ability is reflected in its size [9]. Small babies generally have small placentas, but, in some circumstances, an undernourished fetus can expand its placental surface to extract more nutrients from the mother [10]. This phenomenon is well known to sheep farmers who induce placental expansion by undernourishing ewes in midgestation. When the ewes are

returned to good pasture the expanded placenta results in a larger fatter lamb than they otherwise would be. There are findings suggesting that placental expansion occurs in humans through extension of the placental surface along its minor axis [11]. This is associated with long-term costs that include hypertension. Interestingly, in sheep placental expansion can only occur if the ewe was well nourished up to the time of mating [12].

Maternal body size, especially height, can be used as a marker of her life time nutrition. Short maternal stature is a product of poor fetal and childhood nutrition, or recurrent exposure to infections, and genetic factors [13]. The peroxisome-proliferator-activated receptor *γ2* (*PPARγ2)* gene encodes a nuclear hormone receptor that mediates adipocyte differentiation and regulates glucose and lipid metabolism [14–17]. Variants of the *PPARγ2* have repeatedly been linked to overweight, insulin resistance, and type 2 diabetes. Furthermore, PPAR*γ* is known to play an important role in controlling placental vascular proliferation, trophoblast differentiation, and invasion [18, 19].

We have previously shown that the association between expansion of the placental surface with later hypertension is dependent upon maternal height [11]. We now speculate that the long-term costs could also include overweight and obesity in later life. We therefore examined the long-term effects of placental expansions on overweight and body composition taking maternal height and genetic factors, the *PPARγ2* gene, into account. We examined this in the Helsinki Birth Cohort Study (HBCS), which comprises people born in 1934–44 for whom the size of the placental surface was measured at birth.

2. Patients and Methods

The study cohort consists of 8760 men and women who were born between 1934 and 1944 in Helsinki University Central Hospital and who visited child welfare clinics in the city. Details of the birth records and child welfare clinic records have been described [20, 21]. The birth records included the mother's height. The weight and length of the baby at birth were recorded, and we calculated the ponderal index (birth weight/length^3). The records also included the weight of the placenta, together with the maximal so-called "diameter" of the surface and a lesser "diameter" bisecting it at right angles. The diameters were measured because it was recognized that the placental surface is more oval than circular and the two diameters were used to describe this. Assuming an elliptical surface, we estimated the surface area of the placenta as maximal $\times$ lesser diameter $\times\pi/4$.

We used random number tables to select a sample of people within the cohort who were still living in Finland. In order to achieve a sample size in excess of 2000 people we selected 2902 subjects and invited them to a clinic, 2003 visited the clinic. The procedures used at the clinic have been described [21]. Written informed consent was obtained from each subject before any procedures were carried out. The Ethics Committee at the National Public Health Institute, Finland, approved the study. At the clinic height and weight were measured in light indoor clothing and without shoes on. Body mass index (BMI) was calculated as weight (kg) divided by height^2 (m^2). Estimates of total lean and fat mass were measured by bioelectrical impedance analysis using the InBody 3.0 eight-polar tactile electrode system, Biospace Co., Ltd, Seoul, Republic of Korea, as described [22]. Details of the genotyping procedure have been described previously [23].

2.1. Statistical Methods. We analysed overweight using multiple logistic regression and percent body fat and lean body mass using multiple linear regression. We always adjusted for age and gender in these regressions. The measurements of body and placental size were analysed as continuous variables. Tests for interaction used the product of the variables being studied.

3. Results

Table 1 shows the measurements of birth and placental size and current body size, together with the frequency of the Pro12Pro genotype. Table 2 shows the odds ratios and regression coefficients for three outcomes, overweight (BMI $\geq$ 25 kg/m^2), body fat percentage, and lean body mass, according to birth weight, ponderal index (birth weight/length^3), and placental size. The odds ratios and regression coefficients represent the change in each outcome that is associated with a 1 SD increase in birth size or placental size. Lean body mass was predicted by each measurement of body and placental size. Overweight was predicted by high birth weight and high ponderal index, while percent body fat was predicted by high ponderal index. Neither overweight nor percent body fat was predicted by measurements of placental size.

As in previous analyses we divided the subjects around the mother's median height (160 cm) (Table 3). In both maternal height groups lean body mass was predicted by all measurements of body and placental size. Among people whose mothers were tall a long lesser placental diameter predicted both overweight and percent body fat. There was a statistically significant interaction between the effects of mother's height and the lesser diameter on percent body fat (P for interaction = 0.02). Among people whose mothers were short, no measurements of placental size predicted overweight or percent body fat. Table 4 is therefore confined to people whose mothers' were tall. The subjects are divided according to their *PPARγ2* genotype. Among carriers of the Ala allele overweight was predicted by a large maximal diameter but there were no other associations between placental size and either overweight or percent body fat. Among people with the Pro12Pro genotype large placental area and a long lesser diameter predicted both overweight and percent body fat (Table 4). There were statistically significant interactions between the genotypes and the effects of placental area and the lesser diameter on overweight and percent body fat (P for interaction = 0.004 and 0.05 for area and 0.03 and 0.09 for the lesser diameter, resp.). In people with the Pro12Pro genotype a long maximal diameter predicted overweight but not percent body fat. In a simultaneous regression with the lesser diameter the maximal diameter no longer predicted

Table 1: Measurements of size at birth and in adult life, and frequency of PPARγ2 genotype according to gender.

	Males ($n = 927$)		Females ($n = 1075$)	
	Mean	St deviation	Mean	St deviation
Measurements at birth				
Birth weight (g)	3476	500	3353	465
Placental weight (g)	655	124	643	120
Maximal placental diameter (cm)	19.5	2.3	19.3	2.2
Lesser placental diameter (cm)	17.0	2.2	16.8	2.2
Placental surface area (cm^2)	262	58	257	58
Measurements in adult life				
Age (years)	61.5	2.8	61.5	3.0
Height (cm)	176.8	6.0	163.2	5.7
Weight (kg)	86.2	14.3	73.8	13.8
Body mass index (BMI, kg/m^2)	27.5	4.2	27.7	5.0
Body fat percentage (%)	23.8	6.0	33.9	6.9
Lean body mass (kg)	65.0	7.9	47.8	5.7
Overweight (BMI $\geq 25\,kg/m^2$, %)	74.0		67.7	
PPARγ2 genotype				
Pro/Pro (%)	68.5		67.9	

Table 2: Odds ratios (95% confidence interval) for overweight and regression coefficients for percent body fat and lean body mass in relation to birth weight and placental size.

	Overweight*	Body fat (%)+	Lean body mass (kg)+
Birth weight (z)	1.13 (1.03 to 1.25)	0.03 (−0.26 to 0.32)	1.66 (1.36 to 1.95)
P for trend	0.01	0.8	<0.001
Ponderal index (z)	1.12 (1.01 to 1.23)	0.28 (−0.01 to 0.57)	0.40 (0.10 to 0.71)
P for trend	0.03	0.05	0.008
Placental weight (z)	1.07 (0.97 to 1.18)	0.02 (−0.28 to 0.31)	0.99 (0.69 to 1.29)
P for trend	0.2	0.9	<0.001
Max placental diam (z)	1.04 (0.94 to 1.14)	0.00 (−0.30 to 0.29)	0.64 (0.34 to 0.95)
p for trend	0.5	1.0	<0.001
Lesser placental diam (z)	1.07 (0.97 to 1.18)	0.09 (−0.20 to 0.39)	0.69 (0.39 to 1.00)
P for trend	0.2	0.5	<0.001
Placental area (z)	1.05 (0.95 to 1.15)	0.05 (−0.24 to 0.34)	0.69 (0.39 to 0.99)
P for trend	0.4	0.7	<0.001

*Odds ratios from multiple logistic regressions, including age and gender, with overweight as outcome.
+Coefficients from multiple linear regressions, including age and gender, with body fat percent or lean body mass as outcome.

overweight. The results in Table 4 were similar in men and women.

4. Discussion

In the whole study sample placental size was not associated with either overweight or a high percent of body fat. We found, however, that an expanded placental surface and a long lesser diameter predicted overweight and high percent of body fat in a subset of men and women whose mothers were tall and who carried the Pro12Pro genotype of the PPARγ2 gene. Higher birth weight was associated with an increased risk of having a BMI greater than $25\,kg/m^2$ and with a greater lean body mass. This has been shown before and suggests that birth weight influences adult body mass index through its effect on lean body mass [22, 24]. Our findings suggest that lean body mass is related to the volume of placental tissue, reflected in its weight, while fat mass is related to placental surface area.

We have previously shown that an enlarged placental surface is associated with later hypertension, but this association was confined to people whose mothers were tall [11]. We interpreted this as evidence that compensatory placental expansion in humans is similar to compensatory expansion in sheep, in that it can only occur in women who were well nourished before they conceived. We have shown that people who had an enlarged placental surface and later hypertension had above-average birthweight [11]. This is consistent with sheep farming practices in which placental expansion is induced by undernourishing ewes [10, 12]. This leads to

Table 3: Odds ratios (95% confidence interval) for overweight and regression coefficients for percent body fat and lean body mass in relation to birthweight and placental size, according to mother's height. People whose mothers were >160 cm are included in the table.

	Overweight*	Body fat (%)+	Lean body mass (kg)+
Birth weight (z)	1.18 (1.02 to 1.35)	0.02 (−0.39 to 0.43)	1.54 (1.15 to 1.93)
P for trend	0.02	0.9	<0.001
Ponderal index (z)	1.15 (1.00 to 1.32)	0.28 (−0.14 to 0.69)	0.41 (0.01 to 0.82)
P for trend	0.05	0.2	0.04
Placental weight (z)	1.06 (0.93 to 1.22)	0.15 (−0.26 to 0.56)	0.90 (0.51 to 1.29)
P for trend	0.4	0.5	<0.001
Max placental diam (z)	1.02 (0.89 to 1.16)	−0.02 (−0.43 to 0.38)	0.45 (0.06 to 0.84)
P for trend	0.8	0.9	0.02
Lesser placental diam (z)	0.99 (0.86 to 1.13)	−0.21 (−0.61 to 0.20)	0.48 (0.09 to 0.88)
P for trend	0.9	0.3	0.02
Placental area (z)	0.98 (0.86 to 1.13)	−0.14 (−0.55 to 0.27)	0.47 (0.08 to 0.87)
P for trend	0.8	0.5	0.02
Tall mothers (HEIGHT > 160 cm)			
Birth weight (z)	1.11 (0.94 to 1.31)	0.21 (−0.29 to 0.71)	1.46 (0.95 to 1.97)
P for trend	0.2	0.4	<0.001
Ponderal index (z)	1.12 (0.96 to 1.32)	0.44 (−0.01 to 0.90)	0.47 (0.00 to 0.95)
P for trend	0.2	0.06	0.05
Placental weight (z)	1.06 (0.90 to 1.24)	0.01 (−0.47 to 0.49)	0.83 (0.33 to 1.32)
P for trend	0.5	1.0	0.001
Max placental diam (z)	1.06 (0.89 to 1.25)	0.12 (−0.39 to 0.62)	0.75 (0.23 to 1.28)
P for trend	0.5	0.6	0.005
Lesser placental diam (z)	1.18 (1.00 to 1.38)	0.58 (0.10 to 1.07)	0.65 (0.14 to 1.15)
P for trend	0.05	0.02	0.01
Placental area (z)	1.12 (0.95 to 1.32)	0.40 (−0.10 to 0.89)	0.71 (0.21 to 1.23)
P for trend	0.2	0.1	0.006

* Odds ratios from multiple logistic regressions, including age and gender, with overweight as outcome.
+ Coefficients from multiple linear regressions, including age and gender, with body fat percent or lean body mass as outcome.

larger fatter lambs than would otherwise be. The association between a large placental surface and later hypertension depended on a large lesser diameter rather than a large maximal diameter [11]. Our findings for overweight and percentage body fat are similar in that they are only predicted by large lesser diameter. This is a further evidence that tissue along the minor axis of the placental surface is qualitatively different to tissue along the major axis [25]. Tissue along the minor axis may be more nutritionally sensitive.

We suggest that placental expansion increases the nutrient supply to the fetus, but this supply is unbalanced. We have previously proposed that compensatory placental expansion increases glucose transfer to the fetus, but this may not be matched by transfer of other nutrients, including proteins [26, 27]. Glucose crosses the placenta by diffusion whereas protein is actively transported. Placental enlargement could affect the fetus in the same way as high circulating maternal glucose concentrations, initiating biochemical changes that ultimately lead to obesity [4]. Our findings suggest that this only occurs in people who are homozygotes for the Pro12 allele of the PPARγ2 gene. This allele is known to be linked with insulin resistance [14–17].

4.1. Limitations of the Study. We have previously discussed limitations of the Helsinki Birth Cohort Study [20, 21]. The data are restricted to subjects who were born in Helsinki University Central Hospital and attended voluntary child welfare clinics, did not emigrate, and were still alive and willing to participate in the year 2003. However, we believe that our results, based on internal comparisons within the cohort, are unlikely to differ between those who attended and those who did not. We have no information about what aspect of maternal malnutrition stimulated compensatory placental growth. In Finland, as in other northern European countries, the long winters brought shortages of fruit and vegetables. In addition, there were widespread food shortages around the time of the Second World War, when our cohort was born [28].

5. Conclusions

We have found that a large placental surface area is associated with a high body fat percentage and an increased risk of being overweight in adult life. We suggest that the enlarged surface is the result of expansion of the placental surface to compensate for fetal malnutrition in midgestation. The association between the placental surface area and adiposity was only found in people with the Pro12Pro genotype of the *PPARγ2* gene. We suggest that there is an interplay between nutritional factors and genes at the placental level, which is affecting the later risk for obesity.

Table 4: Odds ratios (95% confidence interval) for overweight and regression coefficients for percent body fat and lean body mass in relation to birthweight and placental size, in the offspring of tall mothers (height >160 cm) who were carriers of the Pro12Pro genotype.

	Overweight*	Body fat (%)+	Lean body mass (kg)+
Birth weight (z)	1.20 (0.98 to 1.47)	0.41 (−0.19 to 1.01)	1.48 (0.87 to 2.09)
P for trend	0.08	0.2	<0.001
Ponderal index (z)	1.18 (0.97 to 1.43)	0.32 (−0.28 to 0.91)	0.61 (0.00 to 1.21)
P for trend	0.1	0.3	0.05
Placental weight (z)	1.18 (0.97 to 1.44)	0.28 (−0.31 to 0.87)	0.99 (0.39 to 1.60)
P for trend	0.1	0.4	0.001
Max placental diam (z)	1.28 (1.03 to 1.59)	0.51 (−0.14 to 1.16)	0.97 (0.30 to 1.64)
P for trend	0.02	0.1	0.005
Lesser placental diam (z)	1.34 (1.10 to 1.64)	0.85 (0.24 to 1.46)	1.03 (0.40 to 1.66)
P for trend	0.004	0.006	0.001
Placental area (z)	1.37 (1.10 to 1.71)	0.77 (0.12 to 1.42)	1.09 (0.42 to 1.75)
P for trend	0.005	0.02	0.001
Pro12Ala & Ala12Ala			
Birth weight (z)	0.93 (0.68 to 1.28)	−0.22 (−1.11 to 0.66)	1.41 (0.48 to 2.35)
P for trend	0.7	0.6	0.003
Ponderal index (z)	1.06 (0.81 to 1.40)	0.89 (0.18 to 1.61)	0.31 (−0.48 to 1.09)
P for trend	0.7	0.01	0.4
Placental weight (z)	0.85 (0.64 to 1.12)	−0.56 (−1.37 to 0.24)	0.50 (−0.37 to 1.37)
P for trend	0.3	0.2	0.3
Max placental diam (z)	0.75 (0.56 to 0.99)	−0.58 (−1.37 to 0.20)	0.41 (−0.44 to 1.26)
p for trend	0.04	0.1	0.3
Lesser placental diam (z)	0.88 (0.66 to 1.16)	−0.05 (−0.84 to 0.73)	−0.15 (−1.00 to 0.69)
P for trend	0.4	0.9	0.7
Placental area (z)	0.80 (0.61 to 1.04)	−0.27 (−1.02 to 0.49)	0.12 (−0.69 to 0.93)
P for trend	0.1	0.5	0.8

* Odds ratios from multiple logistic regressions, including age and gender, with overweight as outcome.
+ Coefficients from multiple linear regressions, including age and gender, with body fat percent or lean body mass as outcome.

Conflict of Interests

The authors declare no conflict of interests.

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Research Article

Maternal Recreational Exercise during Pregnancy in relation to Children's BMI at 7 Years of Age

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Exposures during fetal life may have long-term health consequences including risk of childhood overweight. We investigated the associations between maternal recreational exercise during early and late pregnancy and the children's body mass index (BMI) and risk of overweight at 7 years. Data on 40,280 mother-child pairs from the Danish National Birth Cohort was used. Self-reported information about exercise was obtained from telephone interviews around gestational weeks 16 and 30. Children's weight and height were reported in a 7-year follow-up and used to calculate BMI and overweight status. Data was analyzed using multiple linear and logistic regression models. Recreational exercise across pregnancy was inversely related to children's BMI and risk of overweight, but all associations were mainly explained by smoking habits, socioeconomic status, and maternal pre-pregnancy BMI. Additionally, we did not find exercise intensity or changes in exercise habits in pregnancy related to the children's BMI or risk of overweight.

1. Introduction

Keeping the high prevalence of childhood overweight in mind [1], it is imperative to look for all possible causes for this serious public health issue. It is well established that some intrauterine factors may influence later body size independent of birth weight [2–5]. Many maternal factors during pregnancy are potentially modifiable and therefore obvious targets for specific recommendations of beneficial behaviours during pregnancy to prevent childhood overweight.

Physical exercise in early pregnancy is related to maternal hormonal changes and placental modifications [6–10], leading to for example, altered substrate availability to the fetus [6, 8, 11–13] and lower levels of IGF-I and IGF-II concentrations in cord blood [14]. Hence, changes in the intrauterine environment due to maternal exercise may induce structural or epigenetic changes in the fetal brain or metabolic organs involved in body weight regulation later in life.

Maternal exercise during pregnancy has been associated with lower birth weight and lower risk of both small for gestational age (SGA) and large for gestational age (LGA) in the offspring [8, 16–21]. High birth weight and LGA have consistently been found as risk factors for overweight in childhood [22, 23], and SGA may be related to later visceral obesity and the metabolic syndrome [5, 24]. If maternal exercise has a normalizing effect on birth weight, it may also be associated with a normalization of BMI and a lower risk of overweight in the child beyond what is mediated through birth weight.

Only few studies have investigated the association between intrauterine exposure to maternal exercise and the child's later body size [25]. In a small cohort, there was no differences in weight or body fat at 1 year of age in children of exercising women and non-exercising women [26]. In

contrast, an earlier case-control study on pregnant women suggested an inverse association between maternal exercise and weight and fat mass in the child at 5 years of age [27].

We used data from a large birth cohort to investigate the associations between different measures of maternal recreational exercise during early and late pregnancy and the children's BMI and risk of overweight at 7 years of age, while accounting for several potential confounding factors.

2. Materials and Methods

The study was based on data from the Danish National Birth Cohort (DNBC) in which 100,418 pregnancies among a total of 92,274 women were enrolled during the years 1996 to 2002. The cohort is described in detail elsewhere (http://www.dnbc.dk/) [28, 29]. Briefly, the women were recruited from all over Denmark in the beginning of pregnancy by their general practitioner. The women were telephone-interviewed twice during pregnancy at approximately week 16 and week 30 (Interview 1 and Interview 2) and twice after pregnancy at approximately 6 months and 18 months postpartum (Interview 3 and Interview 4).

A follow-up study of the children has been conducted. During the month that the child turned 7 years of age, the parents were asked to fill in either a mailed or web-based questionnaire about the child's health and well-being, including the latest height and weight measures. Some parents reported old measurements and some responded several years after having received the questionnaire, which gave an age span of 4.0–9.1 years of the children. In the beginning of 2011, 53,854 parents had responded to the 7-year follow-up.

In this study, live-born singletons born at 37–43 weeks of gestation ($n = 50,387$), with information on childhood weight and height at follow-up ($n = 48,312$), measured within the age span 5–8.5 y ($n = 48,218$) were included. Exclusion criteria were as follows: no maternal participation in Interview 1 ($n = 1,952$); maternal type I diabetes, gestational diabetes or preeclampsia ($n = 1,402$); missing data on exercise from interview 1 ($n = 178$); or more than 30 days between children's weight and height measurements ($n = 2,218$). Furthermore, some women ($n = 2,188$) participated with more than one pregnancy in the cohort and only the first enrolled child was included in the analyses to avoid dependent observations. These exclusions led to a sample of 40,280 individuals for analysis.

2.1. Exposure Measures. The main exposure variables included amount of recreational exercise performed in early and late pregnancy as reported in Interview 1 and 2 in the DNBC. The time point of the interviews varied, with a median value (5 and 95 percentiles) of gestational week 16 (11, 25) for Interview 1 and gestational week 31 (27, 37) for Interview 2.

In both interviews, the women were asked: (1) "Now that you are pregnant, do you engage in any kind of exercise?" When the answer was yes, the following questions were posed: (2) "What kind of exercise do you engage in?"; (3) "How many times a week do you engage in.....(answer in question 2)?"; (4) "How many minutes at a time do you engage in..... (answer in question 2)?"; (5) "Do you engage in other types of exercise?" In case of a positive answer to question 5, all the above questions were asked again, until a negative response was given. The questions asked referred to exercise as structured and planned activities. In case of uncertainty about whether an activity should be defined as exercise, it was included if the woman confirmed that it made her sweaty or short of breath. If the woman answered "no" to question 1, no further questions were asked about other possible forms of physical activity, for example, occupational or commuting activity.

The total number of minutes per week spent on recreational exercise was calculated from the duration of each exercise type and categorized into hours per week (h/wk): 0 h/wk, >0–≤1 h/wk, >1–≤2 h/wk, >2–≤3 h/wk, >3–≤5 h/wk, >5 h/wk. This information was further used to group the women according to whether they were non-exercising (0 h/wk) or exercising (>0 h/wk) in their leisure time.

Thirteen predefined types of exercise were categorized into seven groups of preferred activities defined as the type of exercise performed more than 50% of the time: Low-impact activities (aerobics/gymnastics for pregnant women, dance, walking/hiking, yoga) were activities where one foot always had to be on the ground while for high-impact activities (jogging, ball games, racket sports), both feet could leave the ground simultaneously. Other categories included swimming, workout/fitness training, bicycling, horseback riding, and a non-classifiable category for the women who did not have a preferred type of exercise. No questions during the two pregnancy interviews were specifically concerned about if, for example, cycling or walking was a transportation form or part of a more structured exercise plan, neither were the women asked about exercise practices prior to pregnancy.

From Interview 1, we also obtained information about the mother's self-reported pre-pregnancy weight, height, age at conception, parity, smoking during pregnancy, and socioeconomic status. Height and pre-pregnancy weight were used to calculate pre-pregnancy BMI (kg/m^2); parity was categorized as primiparous or multiparous and smoking during pregnancy as non-smokers, 1–10 cigarettes/day, 11+ cigarettes/day. Socio-economic status was based on education and occupation and categorized as low, middle, or high. Information about total gestational weight gain and duration of exclusive breastfeeding (0–13 wk, 14–21 wk, or ≥22 wk) was obtained from Interview 3. In Interview 4, the mothers reported weight and length of the children at 5 months and 12 months of age, measured by the general practitioner or the public health nurse. Gestational age at birth and birth weight was obtained from the National Birth Register.

2.2. Outcome Measures. The outcome variable was the children's BMI at 7 years of age (median age: 7.1 (5 and 95 percentiles: 6.5 and 7.4, resp.)), calculated from the parent-reported weight and height measures at follow-up. The weight and height was based on measurements made by the school doctor, public health nurse, general practitioner, or

by another person (i.e., the parent). It was used both as a continuous and a dichotomized variable (normal weight or overweight), according to international standards with age- and sex-specific cut-off points [30]. These cut-off scores correspond to percentile levels equal to an adult BMI of $\geq 25\,\text{kg/m}^2$. Ten percent of the children in this cohort were overweight and only one percent were obese. Therefore, overweight and obese children were analysed together and referred to as overweight children.

2.3. Statistical Analysis. The student's t-test and χ^2-test were used to examine any group differences between non-exercising and exercising mothers. Multiple linear regression analyses were used to study the association between hours of recreational exercise per week and the child's BMI at 7 years of age, as well as the association between type of exercise and the child's BMI. After log transformation due to a non-normal distribution, BMI was standardized into age- and sex-specific z-scores by subtracting the individuals value (X_i) with the population mean value (X_p) and dividing this by the standard deviation obtained from the cohort (SD):

$$Z = \frac{X_i - X_p}{SD}. \tag{1}$$

This approach was chosen because BMI changes considerably during childhood due to growth, and there was a relatively broad age span between the youngest and the oldest child in this cohort. The age-specific reference values were calculated for intervals of half a year.

Restricted cubic spline models were fitted to examine trends in data, but no significant deviations from linearity were observed (all values for $P > 0.1$).

In crude analyses, we included the child's age at measurements. The following covariates were chosen *a priori* and further included in the adjusted models: maternal age; parity; pre-pregnancy BMI; smoking during pregnancy; socio-economic status. In additional analyses, we also included total gestational weight gain, birth weight, gestational age at birth, duration of breastfeeding, and weight at 5 and 12 months to examine if there was any mediating effect of these variables on the associations between maternal exercise and the child's BMI. The same covariates were used in supplementary multiple linear regression analyses, comparing the non-exercising and exercising women for both early and late pregnancy.

We investigated whether the association between exercise in one period of pregnancy (early or late) and childhood BMI depended on the amount of exercise in the other period of pregnancy (late or early, resp.). We also analysed possible effect modification by sex, maternal smoking, pre-pregnancy BMI, and total gestational weight gain.

We repeated the analyses on a subpopulation restricted to women who completed Interview 1 in weeks 12–20 and Interview 2 in weeks 25–32 ($n = 19,461$). These cut-points were chosen as a compromise between having a reasonable time distance between the two interviews (a minimum of 4 weeks) and at the same time including as many children as possible.

To investigate if any influence of maternal exercise was present specifically at the high end of the BMI distribution, we performed multiple logistic regression analyses with overweight at 7 years (yes/no) as outcome, using the previously-mentioned adjustment strategy.

All statistical analyses were performed using Intercooled STATA 9.2 (StataCorp, TX).

3. Results

Women who did not engage in any kind of recreational exercise in early pregnancy were generally older, had a higher pre-pregnancy BMI, and put on more weight during pregnancy than women who engaged in exercise (Table 1). Furthermore, the non-exercising women were more often multiparous, from a lower social class, smokers, and they breastfed their children for a shorter period of time. Similar patterns were seen for women who did not engage in exercise late in pregnancy. Twenty percent of the women engaged in exercise in both early and late pregnancy, whereas almost half of the women were non-exercising in both periods; 19% of the women reported exercise engagement in early, but not in late pregnancy, and 12% the other way around.

Maternal smoking, pre-pregnancy BMI, total gestational weight gain, or the child's sex did not modify the association between maternal exercise and the child's BMI, nor did exercise in one period modify the association between exercise in the other period and the child's BMI (data not shown).

In crude analyses, the amount of recreational exercise in both early and late pregnancy was overall inversely related to the children's BMI (Table 2). However, all associations were weakened after adjustment and became statistically non-significant. As an example, a 7-year-old girl with an average BMI ($15.7\,\text{kg/m}^2$) for this population would have a 0.02 unit lower BMI, if her mother performed >3 to ≤5 hours of exercise per week in early pregnancy compared with a peer, whose mother was non-exercising. The attenuation of the estimates was mainly explained by adjustment for smoking habits during pregnancy, followed by socio-economic status, and maternal pre-pregnancy BMI. In additionally adjusted analyses, we included total gestational weight gain, birth weight, gestational age at birth, duration of breastfeeding, and the child's weight at 5 and 12 months, but no noteworthy changes on the estimates were observed. There were no consistent trends indicating that exercise in one of the time periods during pregnancy was more strongly associated with children's BMI (Table 2).

In adjusted analyses, no associations between preferred type of exercise and children's BMI were found. Also, results from the analyses, where all exercising mothers were grouped together and compared to non-exercising mothers, were almost identical to the results from the main analyses (data not shown).

The analyses of childhood overweight as an outcome yielded the same picture as for childhood BMI. Thus, the risk of overweight was significantly higher among the children of non-exercising mothers in crude analyses, but

Table 1: Characteristics of mothers according to recreational exercise in early pregnancy[a], Danish National Birth Cohort, 1996–2002.

	All mothers ($n = 40,280$)		Non-exercising mothers ($n = 24,492$)		Exercising mothers ($n = 15,788$)	
	Mean	SD	Mean	SD	Mean	SD
Maternal age (years)	30.6	4.2	30.8	4.2	30.4	4.1***
Pre-pregnancy body mass index (kg/m^2)	23.3	3.9	23.4	4.0	23.2	3.8***
Gestational weight gain (kg)	15.3	5.3	15.4	5.5	15.1	5.0***
Children's birth weight (g)	3,649	490	3,655	493	3,640	486**
Children's gestational age (days)	281.6	8.8	281.5	8.8	281.7	8.8*
Children's age at follow-up	7.1	0.3	7.1	0.3	7.1	0.3
Body mass index at 7 years (kg/m^2)	15.7	1.7	15.7	1.7	15.6	1.6***
	No.	%	No.	%	No.	%
Parity						
Primiparous	19,436	48%	10,186	42%	9,206	58%
Multiparous	20,889	52%	14,288	58%	6,571	42%
P-value for trend						0.01
Socio-economic status						
High	22,593	56%	12,761	52%	9,797	62%
Middle	14,565	36%	9,478	39%	5,053	32%
Low	3,077	8%	2,169	9%	905	6%
P-value for trend						0.01
Smoking						
Non-smokers	30,892	77%	18,074	74%	12,756	81%
0–9 cigarettes/day	7,402	18%	4,858	20%	2,532	16%
≥ 10 cigarettes/day	2,061	5%	1,560	6%	497	3%
P-value for trend						0.01
Breastfeeding						
None or <14 weeks	9,058	28%	5,869	29%	3,173	25%
14–21 weeks	14,368	44%	8,586	43%	5,762	45%
≥ 21 weeks	9,436	28%	5,627	28%	3,786	30%
P-value for trend						0.01

Data are presented as mean values ± standard deviation or number of individuals (%).
P value using student's *t*-test or χ^2-test, $^*P$-value < 0.05, ** < 0.005, *** < 0.001 (*P* value are 2-sided).
Abbreviations: SD, standard deviation.
[a]Missing data on pre-pregnancy BMI ($n = 624$), gestational weight gain (n =8,050), birth weight ($n = 223$), parity ($n = 30$), socio-economic status ($n = 120$), and breastfeeding (n =7,493).

after adjustment for the chosen covariates, all odds ratios were attenuated and became statistically insignificant (data not shown).

4. Discussion

In this study, we observed associations between different measures of maternal recreational exercise during early and late pregnancy and children's BMI and risk of overweight at 7 years of age. Adjustments revealed, however, that these associations were explained by maternal lifestyle factors, mainly smoking habits during pregnancy followed by socio-economic status and maternal pre-pregnancy BMI. This indicates that childhood overweight does not have its ground in the aspect of maternal activity level during pregnancy, and therefore this study provided no basis for recommending changes in exercise habits during pregnancy with the aim of reducing the risk of overweight in the child.

Previous studies of exercise and offspring outcomes have various methodological problems, such as small sample sizes, inadequate control for putative confounders, or insufficient classifications of physical activity performance [19, 20, 25, 31, 32], which our study aimed at coping with. Our cohort included a large number of participants, we used different measures of exercise (amount and type) in both early and late pregnancy, and due to the detailed information on a large number of covariates, we could control for important confounders and also study possible mediating effects of

Table 2: Associations between maternal recreational exercise during pregnancy and the children's, body mass index at 7 years of age (z-scores of log-body mass index and differences in body mass index units), Danish National Birth Cohort, 1996–2002.

		Log-body mass index z-scores				Differences in body mass index units[c]	
Exercise (hours/week) Early pregnancy	No.	Crude[a]	Adjusted[b]	95% CI	P-value for trend		
0	24,492	0	0	0		0	0
>0 to ≤1	5,707	−0.038*	−0.004	−0.032, 0.024		−0.02	−0.06, 0.05
>1 to ≤2	4,432	−0.065**	−0.021	−0.052, 0.010		−0.03	−0.09, 0.02
>2 to ≤3	2,377	−0.034	0.012	−0.029, 0.053		0.02	−0.05, 0.09
>3 to ≤5	2,152	−0.081**	−0.009	−0.051, 0.034		−0.02	−0.08, 0.06
>5	1,120	0.030	0.036	−0.022, 0.094	0.54	0.06	−0.03, 0.16
Exercise (hours/week) Late pregnancy							
0	26,149	0	0	0		0	0
>0 to ≤1	5,942	−0.059**	−0.013	−0.040, 0.0l5		−0.02	−0.06, 0.03
>1 to ≤2	3,288	−0.038*	0.020	−0.015, 0.056		0.03	−0.03, 0.09
>2 to ≤3	1,386	−0.101**	−0.030	−0.082, 0.023		−0.05	−0.14, 0.03
>3 to ≤5	1,128	−0.056	0.018	−0.041,0.076		0.03	−0.06, 0.13
>5	598	−0.114**	−0.047	−0.126, 0.032	0.36	−0.08	−0.22, 0.06

CI: confidence interval.
*$P < 0.05$, **$P < 0.01$ (P values are 2-sided).
[a]Crude models adjusted for children's age at follow-up.
[b]Additionally adjusted for maternal age, parity, pre-pregnancy body mass index, smoking and socio-economic status.
[c]A djusted changes in body mass index units in a 7-year old girl with mean body mass index of 15.67 if the mother changes exercise habits from inactive to one of the repective active groups.

relevant lifestyle-related variables. Our study has, however, also some limitations as discussed in the following.

We aimed to examine recreational exercise in early and late pregnancy, but the timespan of reported exercise was broad. Some women categorized as inactive at Interview 1 could have performed high intensity exercise in very early pregnancy or the opposite. Nevertheless, in subanalyses of women who participated in the interviews close to their scheduled time, we found similar trends as in the main analyses. More precise information about timing of exercise is needed to resolve this problem, but we assume that any misclassification of exercise is non-differential due to the prospective nature of the cohort. Most of our information was self-reported including data on maternal exercise, which may imply differential misclassification or simply imprecise information. However, a recent study on 112 pregnant women, carried out within the Norwegian Mother and Child Cohort Study (MoBa), found that questions on maternal gestational exercise correlated well with measurements from motion sensors [33]. The questions in DNBC are similar to those used in the MoBa study. An earlier comparison between the self-reported maternal pre-pregnancy BMI in the DNBC and measurements performed by their own general practitioner at the first antenatal care visit were in good agreement [34]. In addition, we performed a validation study of the parent-reported weight and height of the children in a sub-sample of the cohort ($n = 1,122$) and found no systematic bias (details can be provided on request).

The present investigation did not include occupational or other physical activity than structured exercise and hence the study could not assess the influence of total daily activity load. This is a limitation of the study, since women who are physically active at work may exclude exercise in their leisure time. Thus, non-exercising women in this cohort could actually be more overall active than the women classified as active which may introduce some misclassification. However, in the MoBa, physical activity at work, defined as being short of breath/sweating at work at least once a week, was strongly positive associated with regular recreational exercise [35]. Since our cohort is very similar to the Norwegian cohort, we believe this association to be present in our cohort as well so that the exercise reported in our study also reflects the general activity level.

Few other studies have investigated the association between maternal exercise in pregnancy and later body size in childhood. In agreement with our results, Clapp III et al. [26] found similar weight and amount of body fat in 1-year-old children of exercising and intermittently active mothers. On the other hand, a case-control study, conducted by Clapp III et al. [27], did not agree with our results. It included 40 physically active women, where half of the

women voluntarily stopped all activity during pregnancy. It showed that weight-bearing gestational exercise for ≥3 times/week for >30 minutes/session at a moderate intensity, compared to inactivity, was associated with lower weight and amount of fat in 5-year-old children. Although the study, being relatively small, obviously needs replication, there may be other reasons for the different results. It has been suggested that any influence from maternal exercise during pregnancy on the offspring may depend on the volume of the activity [25]. In the case-control study, only weight-bearing exercise was included, whereas a mixture of non-weight-bearing and weight-bearing exercise was undertaken by the women in our study. However, in our analyses on preferred kind of exercise, the weight-bearing activities (all types except swimming, bicycling, and horse-back riding) were not significantly associated with the children's BMI or risk of overweight. Another reason for the disagreement could be that the case-control study included women who were physically active before pregnancy, which may modify the association between maternal gestational exercise and the offspring's birth weight [14, 36]. Thus, athletes continuing their sports activity in pregnancy had babies with smaller birth weight than sedentary women initiating weight-bearing exercise in pregnancy [17]. We did not have information about the women's activity level before pregnancy and were therefore not able to assess its possible association with children's BMI.

It could be hypothesized that physical activity before pregnancy may modify the maternal pre-pregnancy BMI and thereby could play a role for later body size of the child. However, contrary to expectations, studies so far have not shown evidence of physical activity being a determinant of subsequent changes in BMI, neither in children nor adults [37]. Also, women who quit smoking due to their pregnancy may be more prone to weight gain [38], which could affect both exercise habits and the children's BMI. However, including gestational weight gain, in our analyses, had no noteworthy effect on the estimates. Our result may reflect that recreational exercise during pregnancy is part of an overall healthy lifestyle that includes less smoking, higher socio-economic status, and lower pre-pregnancy BMI, which all are strongly related to the children's BMI [4, 39, 40]. Thus, the crude associations in this study probably mirrored that exercising mothers in general were healthier and more active also in the postnatal period compared to non-exercising mothers.

Maternal and fetoplacental adaptations in relation to exercise of the mother have been suggested to be dependent upon the gestational period in which the exercise is performed [13]. Thus, timing of exercise in pregnancy may be important for body size in the child [12, 27, 41–44]. When compared to non-active mothers, children of mothers engaging in high intensity activity in the beginning of pregnancy and low intensity in late pregnancy were heavier at birth, whereas children of mothers who had the opposite pattern of activity were lighter [12]. In the present study, the timing or intensity of exercise during pregnancy was not associated with childhood BMI. If any biological explanation exists for the observed inverse association between gestational exercise and birth weight, the influence may only be immediate on the birth outcome and do not appear to exert any long-term effect detectable in childhood.

Women in the DNBC are likely to be healthier in general than the background pregnant population [29]. Furthermore, children in the present study had mothers who were older, of higher socio-economic status, higher parity, lower pre-pregnancy BMI, and less likely to smoke compared with excluded children. However, we did not find that pre-pregnancy BMI, total gestational weight gain, or maternal smoking modified the associations between gestational exercise and childhood BMI. We therefore assume that any relation between gestational exercise and the children's body size is the same for both included and excluded individuals and also applies to other children of mothers having similar lifestyle behaviours living in affluent countries.

In conclusion, we found an inverse association between maternal recreational exercise during pregnancy and childhood BMI or risk of overweight that could be explained by other lifestyle factors that differed between exercising and non-exercising mothers.

Conflict of Interest

There was no conflict of interest.

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