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The Developmental Origins of Children's Energy Balance-Related Behavior and Physical Fitness

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10. ENGLISH SUMMARY



Obesity is considered one of the biggest threats to global health of the 21st century. It is associated with a wide range of serious health complications and with an increased risk of premature onset of illnesses, including diabetes and cardiovascular disease. A large body of evidence now suggests that susceptibility for obesity and cardiovascular disease at least partly originate in early life, with increased risks associated with unbalanced maternal diet, placental insufficiency or postnatal nutritional excesses. This field is known as the Developmental Origins of Health and Disease (DOHaD). It warrants serious consideration from a public health perspective, because this may eventually lead to new public health strategies for obesity prevention and for identification of groups at risk. In search of the underlying mechanisms linking early life with later disease, a hypothesis emerged that linked suboptimal early life nutrition with unfavorable later energy balance-related behaviors, encompassing energy intake, eating behavior, physical activity (PA) and sedentary behavior (SB), and reduced physical fitness levels. This might, in turn, increase later disease risk.

To study the role of prenatal and early postnatal growth, as measured by birth weight and infant growth, respectively, in childhood energy balance-related behaviors and physical fitness, we formulated the following research questions:

1. What is the currently available evidence for the association of birth weight and infant growth with energy balance-related behavior in humans?
2. What is the association of birth weight and infant growth with childhood energy intake and eating behavior?
3. What is the association of birth weight and infant growth with childhood PA and SB?
4. What is the association of birth weight and infant growth with childhood physical fitness?
5. Does autonomic nervous system (ANS) activity mediate a potential association of birth weight and infant growth with energy balance-related behaviors in children?

An introduction to the relevance of early life influences to the current obesity pandemic and the potential underlying role of energy balance-related behaviors and physical fitness is outlined in **Chapter 1**. This chapter provides a narrative overview of the studies that led to the current state of the DOHaD paradigm, as well as the preliminary evidence for physical fitness, energy balance-related behavior and ANS activity to be parts of the pathway from early life nutrition to adult onset disease. In **Chapter 2**, the aims and outline of this thesis are presented, as well as an overview of the Amsterdam Born Children and their Development (ABCD) cohort, in which the studies of this thesis were embedded. The ABCD study is a prospective community-based cohort study initiated in 2003 by the Municipal Health Service, the Academic Medical Center and the VU University Medical

Center. One of the objectives of the ABCD study is to gain more insight into early life conditions and the extent to which these conditions explain children's health in later life. In this cohort, data was collected by questionnaires completed by mothers and their children, child health care registration and hands-on measurements. **Chapter 3** describes the rationale and design of an add-on study. This study was conducted within the framework of the ABCD study and designed and coordinated by the author of this thesis. The study was developed to examine the association of birth weight and infant growth trajectories with physical fitness, PA levels and SB in a subgroup of 194 children of the ABCD study, who were 8-9 years old at the time.

In **Chapter 4**, we present the results of a systematic review on the association of birth size or infant growth with later energy intake, eating behaviors, PA or SB in humans. We appraised the methodological quality of the studies and synthesized the extracted data through a best-evidence synthesis. Based on 41 relevant publications of overall low methodological quality, we found no evidence for an association of birth weight with later energy intake, eating behavior, PA or SB. There was moderate evidence for an association of extreme birth weights (at both ends of the spectrum) with lower PA levels at a later age. Evidence for the association of infant growth with energy balance-related behavior was generally insufficient. We concluded that there is a need of high-quality studies on this topic and of studies that appreciate infant growth as a possible determinant of later energy balance-related behaviors.

Chapter 5 focused on energy intake and eating behavior. Here, we present the independent associations of birth weight and postnatal weight and height gain with energy intake and satiety response at 5 years of age. We found that excessive infant and childhood weight gain are associated with increased energy intake and diminished satiety response. Rapid height gain seemed to be beneficial for childhood energy intake. Birth weight was neither related to energy intake nor to satiety response. We argued that the association of postnatal growth with energy intake and satiety response provides a potential mechanism linking early life influences with later obesity and cardiovascular disease.

The independent associations of birth weight and infant growth (in weight, height and body mass index (BMI)) with childhood moderate-to-vigorous PA (MVPA) and SB are described in **Chapter 6**. This study was part of the add-on study addressed in **Chapter 3**. We found that birth weight was not significantly related to MVPA or SB in these children aged 8-9 years. However, children with accelerated infant weight and/or BMI gain were more sedentary in childhood, while children with increased infant height gain engaged in

more MVPA at 8-9 years. These associations were predominantly explained by growth in the first year of life, not the second year.

In **Chapter 7**, we described the association of early growth with physical fitness in childhood in the group of children of the add-on study, and whether these associations are mediated by fat-free mass, MVPA or SB. Intriguingly, we found that children with low birth weight and subsequent accelerated infant weight gain had lower aerobic fitness at 8-9 years of age. This in contrast to children with only low birth weight (with normal infant weight gain) or only accelerated infant weight gain (after normal birth weight), who had a similar aerobic fitness level to children with normal birth weight and normal infant weight gain. This finding supports the 'mismatch concept', indicating that the combination of prenatal undernutrition with postnatal overnutrition is particularly detrimental for later health. In addition, we found a positive association of birth weight with neuromuscular fitness. This was for more than 75% mediated by differences in fat-free mass. Infant growth expressed as BMI gain (instead of weight gain), however, was associated with reduced neuromuscular fitness. This was not mediated by either fat-free mass, MVPA or SB.

In **Chapter 8**, we turned our attention to the ANS, and how autonomic function relates to early growth. Because autonomic activity has repeatedly been associated with altered behavior in childhood, including impulsivity and sensitivity to food reward, we additionally assessed whether variations in autonomic activity could explain the effects of early growth on energy-balance related behaviors. We found that children with low birth weight had increased sympathetic nervous system activity compared to normal birth weight children, which is considered unfavorable for later health. Infant height gain was associated with a more favorable, decreased sympathetic activity. Levels of sympathetic activity, however, did not mediate the associations of suboptimal perinatal growth with detrimental energy balance-related behaviors. There was no shift in parasympathetic activity associated with either birth weight or infant growth.

Chapter 9 is dedicated to a reflection on the main findings of this thesis. We discuss the broader perspective and potential clinical relevance of our results and consider the clinical and methodological limitations of our studies. We also reflect on the implications of our findings for public health policies, and propose directions for future research on the Developmental Origins of Energy Balance-Related Behavior and Physical Fitness. In short, main conclusions drawn from the findings of this thesis are:

- There is no evidence to support the hypothesis that birth weight (as a proxy for prenatal nutrition) is associated with any of the studied energy balance-related behaviors, i.e., energy intake, eating behavior, PA or SB, in the human population;

- Postnatal growth, more than prenatal growth, is associated with energy balance-related behaviors and physical fitness levels in childhood;
- The definition of postnatal growth is of crucial importance when studying the Developmental Origins of Energy Balance-Related Behaviors and Physical Fitness levels, because the associations with the different outcomes vary greatly between weight gain, BMI gain, and linear growth, and between the different periods of growth. In general, we observed detrimental associations with weight and BMI gain and beneficial associations with height gain, especially when growth was confined to the period of early infancy (i.e., the first year of life);
- Perinatal growth is associated with childhood ANS function, but the implications on later disease risk should probably be sought outside behavioral processes, as ANS activity did not mediate any of the associations of birth weight or infant growth with energy balance-related behaviors.