# Motivation and objectives

Growth is used as an evaluation of nutritional status and is a well-established indicator of health and well-being of a child. Monitoring growth of a child may reveal aspects of under- and overnutrition. This might be seen as acute undernutrition, i.e., wasting (loss of weight), chronic undernutrition, i.e., stunting (reduced growth in length/height), or as overweight or obesity [1]. Childhood undernutrition as well as overweight and obesity have important consequences for health and well-being during childhood as well as in later adult life. In children complications related to obesity include hyperinsulinaemia, hypertension, raised levels of triglycerides and total cholesterol as well as social and psychological problems[2]. There is also evidence suggesting childhood obesity increases adult morbidity and mortality independently of adult BMI and other confounding factors [3].

BMI is one global index used to assess nutritional status, but BMI does not reveal the body composition as it reflects both body fat and lean mass. Nevertheless, BMI is considered the best available weight-height index describing the body composition. In adults it is unrelated to height and correlates to skinfold thickness and s-insulin [4]. For children the use of squared height in the denominator does not result in the index being unrelated to height[5] and another weight-height index might therefore be more appropriate than BMI to assess body fat. Still, in children a high BMI is associated with an increased risk of metabolic syndrome later in childhood [6] as well as an increased risk of coronary heart disease in adulthood [7].

One useful method for a reliable assessment of the body composition is dual-energy X-ray absorptiometry (DEXA). However, DEXA scans are difficult to obtain in small children due to the fact that they have to lay still for some time and further a DEXA scan is expensive and is hence unavailable in many settings. Simple anthropometric measurements like weight, height, waist and mid-upper arm circumference (MUAC) are easy to conduct everywhere, but their validity to assess body composition in terms of fat, lean and muscle mass is not confirmed.

Infancy is an established life-course period in general known as a potentially critical period for being predisposed for later obesity [8]. In infancy growth velocity and hence the demands on nutritional intake is high. The rate of weight gain in this period is the highest both in absolute

terms and relative to body size. Several characteristics concerning early growth patterns including higher infant weight gain and early adiposity rebound, which is represented by a nadir on the BMI curve, have been consistently associated with long term risk of obesity [8]. Similar to the later adiposity rebound infancy also involves a turning point of the BMI curve, the infant BMI peak. However, little is known about this turning point and its predictive ability for later obesity.

Childhood growth and body composition is influenced by internal as well as external factors including genetics, lifestyle and nutrition. During early infancy, the choice is between breastfeeding and formula feeding, which has been shown not only to affect the current status of growth and body composition [9] but also to have long term consequences on for instance IQ [10, 11] and risk of later obesity [12–14]. For some exposures and outcomes, like breastfeeding and IQ, it may be sufficient to establish an association and perhaps to consider the presence of a dose-response relationship. For other more crucial outcomes, like folic acid and neural tube defects [15], vitamin A and malformations [16] or long chain n-3 fatty acids and preterm deliveries [17], the specific dose-response relationship might be of particular interest due to a focus on safe dose estimation. If this relationship is nonlinear and extrapolation is of interest, choosing the right model among several candidate models is of great importance. In order to handle uncertainty introduced by model selection, model averaging may provide a useful solution, though current limitations to the estimation of corresponding standard errors also affect the safe dose estimates.

In a period of high growth velocity, like infancy, a randomized clinical trial with the purpose of investigating the effect of for instance a diet component on body composition could take this into account by comparing growth patterns over the trial period. When the outcome is a multi-outcome like body composition with several components it is often of interest to test the effect on all aspects of the outcome, i.e. on several outcome variables (fat mass, lean mass, bone mass etc.). However, with an increasing number of tests comes an increased family wise error rate and hence a need for multiplicity adjustment in longitudinal studies.

The objective of the present thesis was to contribute to these areas of research. This led to the following specific objectives for the papers included in this thesis:

Paper 1:

- To validate the ability of simple anthropometric measurements to assess body composition in children using different methods for model comparison.
- To validate BMI as an estimator of fat mass proportion. That is, to estimate the optimal power of height in the ratio of weight to height to best determine the fat mass proportion.

Paper 2:

- To estimate and describe the infant BMI peak for children in a Danish cohort using a nonlinear mixed effects model with subject-specific random effects.
- To test whether infant feeding patterns are associated with the timing of infant BMI peak
- To test whether the timing of the infant BMI peak is associated with later body composition

Paper 3:

- To propose and implement a method for quantifying uncertainty in model averaging by incorporating the correlations between parameter estimates.
- To propose and implement a method for simultaneous inference in model averaging.

Paper 4:

- To propose and implement an improved method for multiplicity adjustments in longitudinal studies with multiple outcomes, by modeling correlations between test statistics in several individually fitted linear mixed models.