INTRODUCTION

Non-communicable diseases (NCDs) such as type 2 diabetes (T2D) and cardiovascular diseases (CVD) are among the leading causes of death and disability worldwide (1, 2), and the number of years of life lost (YLLs) to in particular T2D is projected to increase markedly in the coming two decades (3). While T2D and CVD often have been described as diseases occurring mostly in high-income countries, almost 80% of the global mortality burden related to T2D and CVD are occurring in low- and middle-income countries (LMIC) (4).

Target 3.4 of the Sustainable Development Goals (SDGs) aims to reduce premature mortality from NCDs by a third between 2015 and 2030. By analysing how achieving this target would improve the longevity of populations in 183 countries, Cao et al. (5) found that low-income and lower-middle-income countries would enjoy the greatest benefits on life expectancy from meeting this target, but also warned that these countries had shown the slowest progress.

In all regions across sub-Saharan Africa, the prevalence of T2D and CVD are on the rise and at a speed that outpaces the health systems’ ability to cope with the chronic burden of these conditions (6-10). The burgeoning NCD epidemic in LMIC is primarily driven by modifiable risk factors such as obesity, high blood pressure, hyperglycaemia, and hyperlipidaemia (11), which all have been found to track from childhood to adulthood (12, 13). A high body mass index (BMI) in childhood is not only associated with obesity in adulthood (14-16), but also premature morbidity and mortality from NCDs in adulthood (17-20). While, the rise in age-standardised BMI and obesity in children and adolescents has plateaued in high-income countries, it continues to rise in LMIC (21). Hence, with a steady increase in childhood overweight and obesity in LMIC, the burden of diet-related NCDs is likely to further accelerate in the coming years (21, 22).

In many LMIC, the increasing burden of childhood obesity, coincides with persistent high levels of fetal and child undernutrition (i.e. low birth weight (LBW), wasting and stunting), which continues to impair health and development of millions of children worldwide (21, 23). This phenomenon is termed the double burden of malnutrition (DBM), and is characterised by co-existence of undernutrition and overweight/obesity or diet-related NCDs, within individuals across the life-course, and within households or populations (24). The key drivers of the DBM are rapid shifts in the population demographics, disease patterns, diet composition and rural to urban migration, which are all characteristics of most countries in sub-Saharan Africa (10, 25, 26).

When undernutrition and obesity co-occur within individuals it has substantial consequences for health, as these conditions interact in complex ways through the life-course. For instance, LBW has been found to substantially elevate the risk of overweight, T2D and CVD later in life (27-32), and it has been suggested that
these risks are substantially increased when growth restriction in fetal life and infancy is followed by rapid weight accretion in the first years of life (31, 33-38). A number of studies from middle- (39-42) and high-income countries (35, 43-52) have found that detrimental metabolic adaptations and important changes in body composition (BC) related to growth in early life may be initiated already in childhood. However, the effect of early growth on later BC seems to be pointing in different directions with weight accretion being associated with later lean mass in middle-income countries, but both fat- and lean mass in high-income countries (53). I found no evidence from low-income countries studying the relative importance of size at birth and successive periods of growth in early life on subsequent BC and markers of cardiometabolic risk in early childhood. This is surprising, as populations in these countries currently experience a rise in the DBM resulting from a rapid nutrition transition, and therefore are particularly vulnerable to the programming effect of growth in early life.

In the global health community, we want children to grow better to reduce the prevalence of undernutrition and stunting in early life, but at the same time avoid inadvertently making the children overweight or obese. To better understand the developmental aetiology of cardiometabolic risk in low-income populations undergoing nutrition transition and to identify potential early-life targets amenable for interventions promoting healthy growth, it is important to study the timing of how growth in early-life is related to markers of adiposity and cardiometabolic risk in these populations.

The majority of the existing evidence has assessed how later health outcomes are associated with for example weight at birth, a proxy indicator for intrauterine growth, or growth from only a few time points (Figure 1). Evidence that has emerged using these simple exposures such as weight at birth has been criticised for being the results of unmeasured confounding and selection bias (54), for not being able to uncover important aspects of growth in important intermediary windows of development between exposure and outcome (55), and for insufficient adjustments for current and baseline weights (56). Furthermore, it has been suggested that the proposed negative associations of weight at birth with later risk of cardiometabolic diseases are the result of postnatal growth acceleration rather than restricted growth in fetal life (36, 57, 58).

The papers presented in this thesis are based on data from a birth cohort of Ethiopian children with several repeated measures of weight, height and BC. This enabled me to study the relative importance of the dynamic changes in these variables in important windows of development in early childhood. As shown in Figure 1, a wide range of methods exists to model changes in repeated measures over time, which each have their benefits and drawbacks (59, 60).

Based on the specific data structure of repeated measures, I identified two types of sophisticated mixed-effects modelling methods to flexibly and robustly estimate the non-linear growth patterns in early life. Thus,
in Paper 1, I modelled changes in weight using linear-spline mixed-effects (LSME) modelling and aimed to examine the relative importance of weight velocity in selected age periods from 0-60 months of age with BC and markers of cardiometabolic risk at 60 months. This will broaden the current evidence base by providing the first comparable data from a low-income sub-Saharan African population. I hypothesised that weight accretion in selected periods the first 60 months of life would be positively associated with height, waist circumference, fat mass (FM) and fat-free mass (FFM) and markers of cardiometabolic risk related to lipid metabolism and glucose homeostasis at 60 months of age, and that not all periods of weight accretion would be equally important for the later outcomes.

In Paper 2, I extended my focus beyond weight to examine the influence of BMI trajectories on BC and markers of cardiometabolic risk at 60 months of age. In this paper, I used a data-driven growth modelling method, entitled latent class trajectory (LCT) modelling, to identify distinct patterns of BMI growth from birth to 60 months. I therefore did not examine the relative importance of growth in discrete age periods as in Paper 1, but rather the relative importance of distinct BMI trajectories across the whole age range. Since I applied a data-driven approach for modelling the exposure, specifying a priori hypotheses is not straightforward. However, based on previous literature applying LCT modelling in children (61-65), I hypothesised that the LCT modelling would be able to identify a number of groups of children with distinct BMI trajectories, and that diverging patterns of BMI accretion would associate differently with BC and markers of cardiometabolic risk at 60 months of age.

Finally, in Paper 3, I applied the same growth modelling approach as in Paper 1, but rather than weight accretion, I was able to examine how the differential effects of the metabolically diverse tissues of FM and FFM in early infancy were associated with subsequent BC and markers of cardiometabolic risk. I hypothesised that FM and FFM accretion in infancy would associate differently with the 60 months outcomes. More specifically, I hypothesised that FM accretion in infancy would associate positively with markers of adiposity, including FM and waist circumference, lipid metabolism and glucose homeostasis and that FFM accretion in infancy would be positively associated with height and FFM at 60 months of age.
Figure 1 Schematic overview of the growth modelling methods and growth exposures applied in this thesis compared with other commonly used modelling methods and exposures. The shown list of modelling methods is not exhaustive. These modelling methods in the top may be argued to have a similar level of complexity.