LIST OF PAPERS

1. Wibaek R[1,2], Girma T[3,4], Admassu B[4,5], Abera M[4,6], Abdissa A[4,7], Vistisen D[2], Jørgensen ME[2,10], Geto Z[8], Wells JCK[9], Kæstel P[1], Michaelsen KF[1], Friis H[1], Andersen GS[2]. Higher Weight and Weight Gain after 4 Years of Age Rather than Weight at Birth Are Associated with Adiposity, Markers of Glucose Metabolism, and Blood Pressure in 5-Year-Old Ethiopian Children. The Journal of Nutrition. 2019. doi: 10.1093/jn/nxz121. *(Published online)* *

2. Wibaek R, Vistisen D, Girma T, Admassu B, Abera M, Abdissa A, Mudie K[8], Kæstel P, Jørgensen ME, Wells JCK, Michaelsen KF, Friis H, Andersen GS. Body mass index trajectories in early childhood in relation to cardiometabolic risk profile and body composition at 5 years of age. The American Journal of Clinical Nutrition. 2019. doi: 10.1093/ajcn/nqz170. *(Published online)*

3. Wibaek R, Vistisen D, Girma T, Admassu B, Abera M, Abdissa A, Jørgensen ME, Kæstel P, Michaelsen KF, Friis H, Wells JCK, Andersen GS. Associations of fat mass and fat-free mass accretion in infancy with body composition and cardiometabolic risk markers at 5 years: The Ethiopian iABC birth cohort study. PLOS Medicine. 2019. doi: 10.1371/journal.pmed.1002888. *(Published online)*

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* *As part of all manuscript submissions, studies were reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline. For Paper 1 and 2, the STROBE guidelines were not a part of the publication, but for Paper 3 the STROBE guideline will be a part of the publication's supplementary material.*

RELATED PUBLICATIONS

During my PhD fellowship, I have co-authored the following work:

1. Wells JCK, Sawaya AL, Wibaek R, Mwangome M, Poullas MS, Yajnik R, Demaio A. The double burden of malnutrition: etiological pathways and consequences for health. Invited Lancet Series. Lancet. 2019. (Accepted)

2. Wells JCK, Wibaek R, Poullas M. Global epidemiology of use of and disparities in caesarean sections. Lancet. 2019; 394: 24-25. doi: 10.1016/s0140-6736(19)30715-9.

3. Abera M, Tesfaye M, Hanlon C, Admassu B, Girma T, Wells JC, et al. Body Composition during Early Infancy and Mental Health Outcomes at 5 Years of Age: A Prospective Cohort Study of Ethiopian Children. J Pediatr. 2018; 200: 225-231. doi: 10.1016/j.jpeds.2018.04.055.

4. Wells JCK, Wibaek R, Poullas M. The Dual Burden of Malnutrition Increases the Risk of Cesarean Delivery: Evidence From India. Frontiers in Public Health. 2018; 6. doi: 10.3389/fpubh.2018.00292.

5. Admassu B, Wells JCK, Girma T, Belachew T, Ritz C, Owino V, et al. Body composition during early infancy and its relation with body composition at 4 years of age in Jimma, an Ethiopian prospective cohort study. Nutr Diabetes. 2018; 8: 1-9. doi: 10.1038/s41387-018-0056-7.

6. Abera M, Tesfaye M, Admassu B, Hanlon C, Ritz C, Wibaek R, et al. Body composition during early infancy and developmental progression from 1 to 5 years of age: the Infant Anthropometry and Body Composition (iABC) cohort study among Ethiopian children. Br J Nutr. 2018; 119: 1263-1273. doi: 10.1017/S000711451800082X.

7. Admassu B, Ritz C, Wells JCK, Girma T, Andersen GS, Belachew T, et al. Accretion of Fat-Free Mass Rather Than Fat Mass in Infancy Is Positively Associated with Linear Growth in Childhood. J Nutr. 2018; 148: 607-615. doi: 10.1093/jn/nxy003.

8. Andersen GS, Wibaek R, Kaestel P, Girma T, Admassu B, Abera M, et al. Body Composition Growth Patterns in Early Infancy: A Latent Class Trajectory Analysis of the Ethiopian iABC Birth Cohort. Obesity (Silver Spring). 2018; 26: 1225-1233. doi: 10.1002/oby.22197.

9. Admassu B, Wells JCK, Girma T, Andersen GS, Owino V, Belachew T, et al. Body composition at birth and height at 2 years: a prospective cohort study among children in Jimma, Ethiopia. Pediatr Res. 2017; 82: 209-214. doi: 10.1038/pr.2017.59.

10. Abera M, Tesfaye M, Girma T, Hanlon C, Andersen GS, Wells JC, et al. Relation between body composition at birth and child development at 2 years of age: a prospective cohort study among Ethiopian children. Eur J Clin Nutr. 2017; 71: 1411-1417. doi: 10.1038/ejcn.2017.129.

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ENGLISH SUMMARY

Background

Suboptimal nutritional status and growth during critical windows of developmental plasticity in fetal life and early childhood are key drivers of premature mortality and disability across the life-course, and the burden of undernutrition, obesity and associated cardiometabolic diseases falls disproportionately on low- and middle-income populations. Evidence from middle- and high-income countries suggests that detrimental cardiometabolic adaptations associated with growth in early life may occur already in childhood, but evidence from low-income countries is lacking. Thus, to improve our understanding of the developmental aetiology of cardiometabolic disease risk in low-income populations and to identify potential early-life targets amenable to timely interventions that promotes healthy growth, I aimed to examine the associations of growth in early life with body composition and markers of cardiometabolic risk at 60 months of age.

Methods

In a prospective birth cohort study of healthy urban preschool children from Jimma, Ethiopia, followed from birth to 60 months of age, I estimated weight velocities in the age periods 0-3, 3-6, 6-24, 24-48 and 48-60 months in 375 children using linear-spline mixed-effects (LSME) modelling (Paper 1), four distinct body mass index (BMI) trajectories from 0-60 months in 453 children using latent class trajectory modelling (Paper 2), and fat mass (FM) and fat-free mass (FFM) growth velocities in the age periods 0-3 and 3-6 months in 507 children using LSME modelling (Paper 3). FM and FFM from 0-6 months and at 60 months were assessed using air displacement plethysmography. In all three papers, I analysed associations of the derived growth exposures with height, waist-circumference, FM, FFM and markers of cardiometabolic risk at 60 months of age using multiple linear regression analyses in different adjustment models.

Findings

In this contemporary Ethiopian birth cohort, children were on average shorter at birth with deficits in weight, FM and FFM compared to international reference data. At 60 months of age, the children had increased their deficits in weight, height and in particular FFM, but had markedly higher FM which appeared to be associated with increased FM accretion in early infancy. Children who showed a higher FM and weight accretion, and accelerated BMI growth in early infancy had higher FM, greater waist circumference and higher concentrations of cardiometabolic markers related to lipid metabolism at 60 months of age. Children who showed a higher FFM and weight accretion, as well as accelerated BMI growth in early infancy were taller and had more FFM at 60 months of age. Furthermore, children who had higher weight at 60 months and higher weight accretion from 48-60 months were taller, had greater waist circumference, higher FM, higher FFM, higher blood

pressure, and higher concentrations of cardiometabolic markers related to insulin metabolism at 60 months of age. Finally, children with a slow BMI accretion through infancy and childhood were shorter, had smaller waist circumference, lower FM and FFM, and lower concentrations of cardiometabolic markers related to lipid metabolism.

Conclusion

In this thesis, I present the first comprehensive assessment from a low-income country on how variability in weight, BMI, FM and FFM accretion in important windows of development in early life associate with size, body composition and cardiometabolic risk markers in preschool children aged 60 months. Overall, the periods from 0-3 and 3-6 months of age appeared to be important windows for the programming of body composition in childhood. I found that higher FM accretion in infancy was strongly associated with higher FM at 60 months of age, and the same was true for FFM accretion in infancy and FFM at 60 months of age. Growth in early life was not consistently associated with the studied cardiometabolic markers. However, higher weight and FM accretion in infancy, weight accretion from 48-60 months and weight at 60 months as well as accelerated BMI growth in infancy were associated with higher concentrations of a number of cardiometabolic markers at 60 months of age. Future follow-up of this cohort is needed to examine if these relationships persist or become stronger later in childhood and adolescence.

DANSK SAMMENDRAG (DANISH SUMMARY)

Baggrund

Suboptimale vækstmønstre i fosterlivet og i den tidlige barndom er associeret med for tidlig død, øget morbiditet og nedsat livskvalitet gennem hele livsforløbet. En kombination af en høj forekomst af underernæring og overvægt som følge af en accelereret transition i ernæringsmønstre, velstand og befolkningssammensætning har været medvirkende til at langt størstedelen af denne morbiditet og mortalitet tilfalder lav- og mellemindkomstlande. Studier fra mellem- og højindkomstlande har fundet, at potentielt skadelige kardiometaboliske forandringer, som følge af suboptimal vækst i fosterlivet og de første leveår, allerede opstår i barndommen. Disse sammenhænge er imidlertid ikke blevet undersøgt i lavindkomstlande. For at bidrage til fornyet viden om årsagerne bag udviklingen af kardiometabolisk risiko i lavindkomstlande samt identificere særligt vigtige vækstperioder, som kan danne basis for potentielle interventioner, der har til formål at fremme sund vækst, ønskede jeg i nærværende afhandling at undersøge sammenhængene mellem vækst tidligt i livet og kropsammensætning samt markører for kardiometabolisk risiko ved 60 månedsalderen.

Metoder

I et kohortestudie fulgte vi raske børn fra Jimma i Etiopien fra fødslen og indtil 60 månedsalderen. I den første artikel beregnede jeg hastigheder for tilvækst i vægt i aldersperioderne fra 0-3, 3-6, 6-24, 24-48 og 48-60 måneder efter fødslen blandt 375 børn ved hjælp af en metode kaldet 'linear-spline mixed-effects (LSME)' modellering. I den anden artikel beregnede jeg blandt 453 børn fire unikke forløb af legemsmasseindeks (BMI) fra 0-60 månedsalderen ved hjælp af en metode kaldet 'Latent class trajectory modelling'. I den tredje artikel beregnede jeg hastigheder for tilvækst i fedtmasse (FM) og fedtfrimasse (FFM) i aldersperioderne 0-3 og 3-6 måneder efter fødslen blandt 507 børn ved hjælp af LSME-modellering. FM og FFM blev bestemt ved hjælp af luftplethysmografi. For alle tre artikler analyserede jeg efterfølgende sammenhængene mellem de beregnede vækstforløb og højde, talje-omkreds, FM, FFM og kardiometaboliske risikomarkører målt ved 60 månedsalderen i forskellige justeringsmodeller ved hjælp af multipel lineær regressionsanalyse.

Resultater

Børnene i denne etiopiske fødselskohorte havde i gennemsnit lavere vægt og højde, samt mindre FM og FFM ved fødslen sammenlignet med internationale referencedata for normalvækst. Ved 60 månedsalderen havde børnene øget underskud i vægt, højde og især FFM, men havde markant højere FM, hvilket syntes at være associeret med forøget tilvækst i FM i den tidlige barndom. En øget tilvækst i FM og vægt samt en accelereret BMI-øgning i tidlig barndom var associeret med højere FM, større talje-omkreds og højere niveauer af en række kardiometaboliske markører relateret til lipidmetabolisme ved 60 månedsalderen. En øget tilvækst i

FFM og vægt samt en accelereret BMI-stigning i den tidlige barndom var associeret med forøget højde og FFM ved 60 månedsalderen. Endvidere var en højere vægt ved 60 månedsalderen og en øget tilvækst i vægt fra 48-60 månedsalderen associeret med en større højde, talje-omkreds, FM, FFM, højere blodtryk og højere niveauer af en række kardiometaboliske markører relateret til insulinmetabolisme ved 60 månedsalderen. Endelig var en langsom BMI-stigning i barndommen associeret med lavere højde, mindre talje-omkreds, FM, FFM og lavere niveauer af kardiometaboliske markører relateret til lipidmetabolisme.

Konklusion

I denne afhandling præsenterer jeg den første omfattende analyse af, hvordan ændringer i vægt, BMI, FM og FFM i det tidlige liv er associeret med kropssammensætning og en række markører for kardiometabolisk risiko hos 60 måneder gamle børn fra et lavindkomstland. Samlet set syntes perioderne 0-3 og 3-6 måneder efter fødslen at have betydning for udviklingen af et barns senere kropssammensætning. Jeg fandt, at en højere tilvækst i FM i barndommen var stærkt associeret med en højere FM ved 60 månedsalderen, og det samme var tilfældet for tilvækst i FFM i tidlig barndom og FFM ved 60 månedsalderen. Væksten tidligt i barndommen var imidlertid ikke entydigt forbundet med de undersøgte kardiometaboliske markører. Jeg fandt dog, at en øget tilvækst i FM, BMI og vægt i tidlig barndom samt øget tilvækst i vægt fra 48-60 månedsalderen og en højere vægt ved 60 månedsalderen var associeret med højere niveauer af en række kardiometaboliske markører ved 60 månedsalderen. Opfølgning af denne kohorte i fremtiden er nødvendig for at undersøge, om disse forhold vedbliver eller forværres senere i barndommen og det tidlige voksenliv.

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 straight forward. 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.

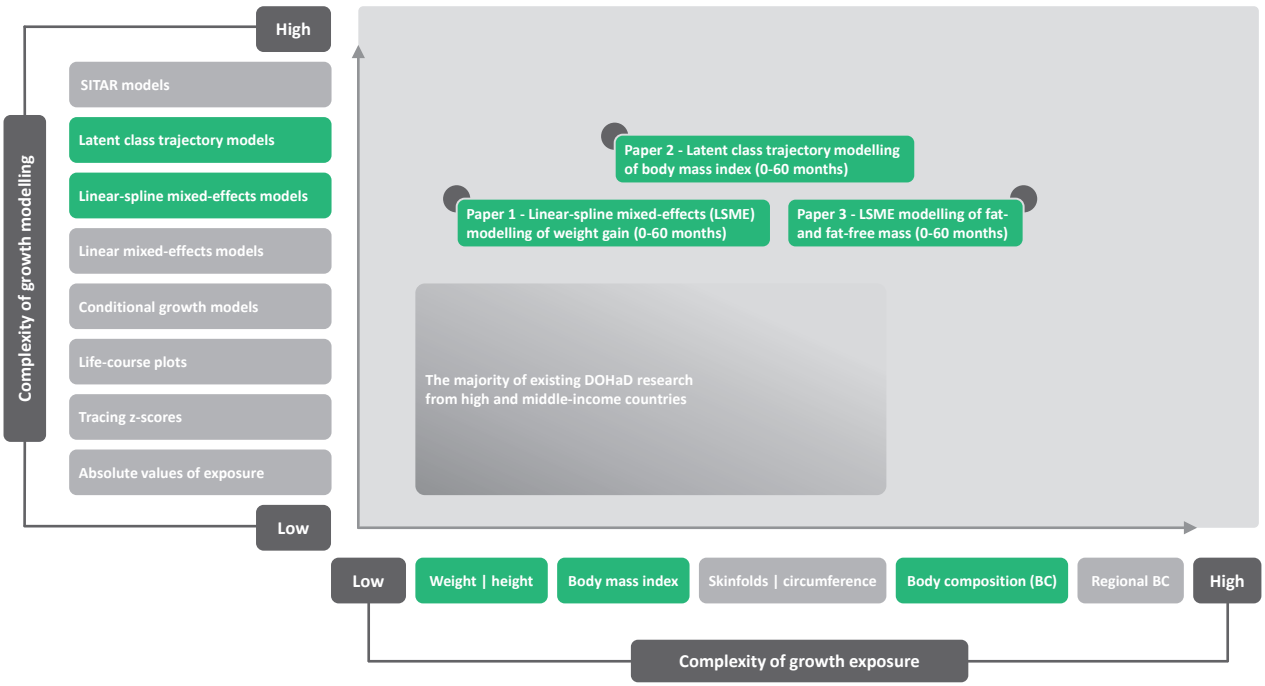

Figure 1 Schematic overview of the growth modelling methods and growth exposures applied in this thesis compared with other commonly used modelling methods and exposures. The shown list of modelling methods is not exhaustive. [1] These modelling methods in the top may be argued to have a similar level of complexity.