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Overweight/obesity, body composition and bone mass in late adolescence: the relation with birth weight, childhood body mass index and growth.

The Tromsø Study: Fit Futures, a longitudinal cohort study

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Elin Kristin Evensen

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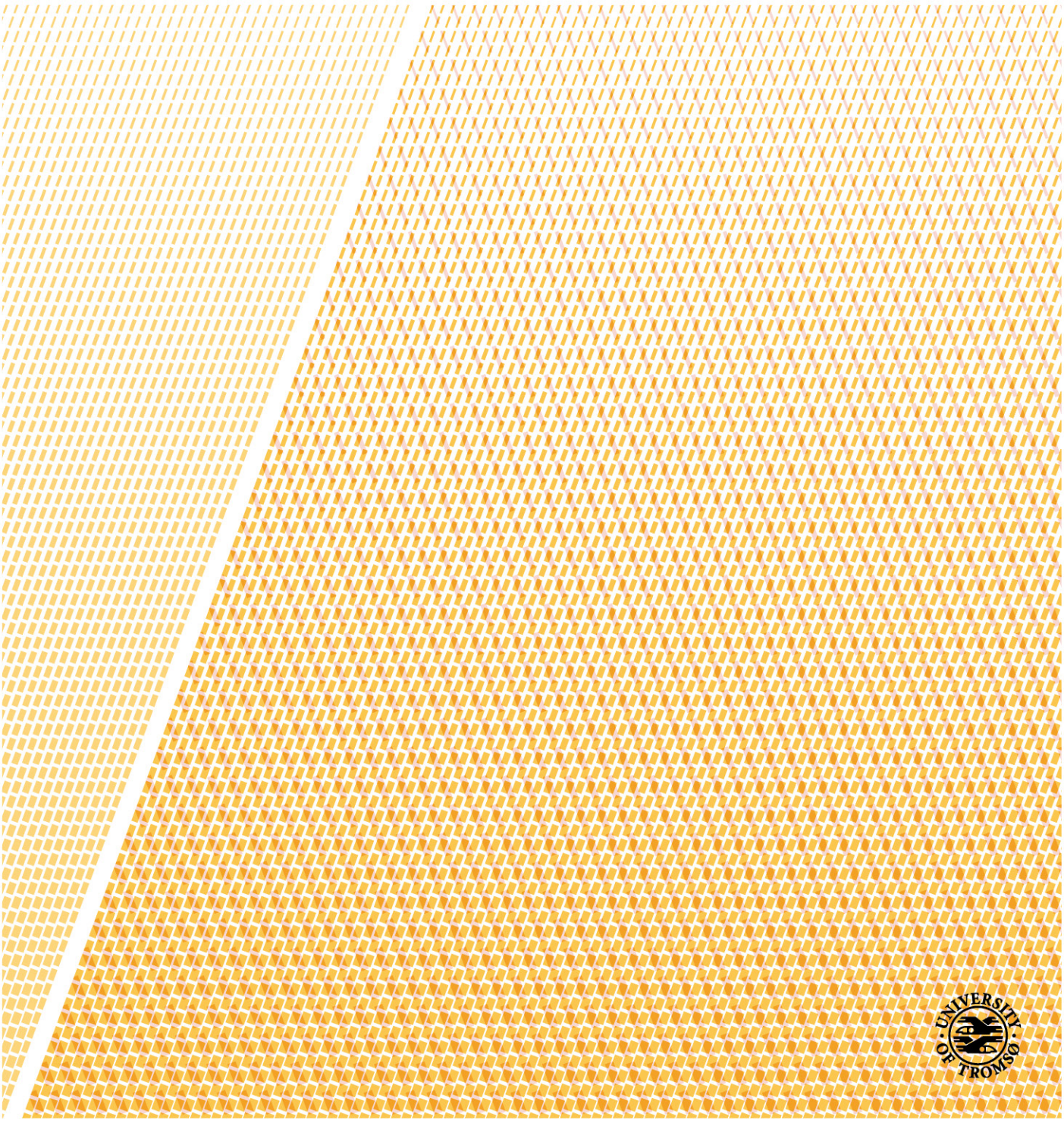

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The Tromsø Study: Fit Futures, a longitudinal cohort study

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"Knowing is not enough, we must apply. Willing is not enough, we must do."

W. H. Murray in The Scottish Himalaya Expedition, 1951.
Most frequently attributed to Johann Wolfgang von Goethe
http://www.goethesociety.org/pages/quotescom.html

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Elin Kristin Evensen

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Abstract

Background and aim: High prevalence of childhood overweight/obesity is a major health concern due to related immediate and long-term health problems. Early identification of children at risk is of interest, as preventing or delaying the onset of obesity may influence future health. The aim of this thesis was to study how early life factors such as birth weight, childhood body mass index (BMI, kg/m^2) and growth are related to overweight/obesity, body composition and bone health in adolescence.

Methods: The Tromsø Study, Fit Futures (TFF) is a population-based cohort study with participants from Tromsø and neighbouring municipalities. Two waves were conducted in 2010-2011 (TFF1) and 2012-2013 (TFF2). Data from a representative sample of 961 adolescents (48% girls) from TFF1, of which 659 had follow-up data from TFF2, formed the basis for this thesis. Longitudinal anthropometric data were retrospectively obtained from the Medical Birth Registry of Norway and childhood health records at 2-4 and 5-7 years. Body composition (fat mass and fat-free mass) and bone mass and bone density were measured by dual-energy X-ray absorptiometry at 15-17 and 18-20 years of age. In addition, height, weight and waist circumference was obtained. Participants were classified into BMI categories: underweight, normal weight, overweight and obese, according to the International Obesity Task Force age- and sex-specific cut-off values for children 2-18 years of age.

Results: The prevalence of overweight including obesity increased with age and 21% of girls and 28% of boys were overweight/obese at 18-20 years of age. There was a modest association between birth weight and overweight/obesity at 15-20 years of age, and birth weight was significantly associated with higher fat-free mass as well as bone mass in adolescence. The degree of tracking of BMI from 2-4 and 5-7 years of age up to 15-20 years of age was moderate, with stronger associations observed for more severe overweight and obesity. Overweight/obesity at 6.0 and 16.5 years of age as well as greater BMI gain between 6.0 and 16.5 years of age, were strong predictors of higher fat mass index (kg/m^2) and central overweight/obesity as well as higher fat-free mass index (kg/m^2) at 15-20 years of age. Compared to normal weight, overweight/obesity at 6.0 and 16.5 years of age revealed significantly higher levels of bone mass and bone density at total hip and total body, but underweight was consistently associated with lower bone mass and bone density at 15-20 years of age.

Conclusion: We found a modest positive association between birth weight and body composition and bone mass at 15-20 years of age. Compared to birth weight, a high childhood BMI as well as childhood growth rate had a stronger influence on bone mass and bone density in adolescence. Greater BMI gain between 6.0 and 16.5 years of age were most strongly linked to adiposity and central overweight/obesity in adolescence. Early identification of children at risk of adverse levels of adiposity is possible and preventive efforts should focus on a healthy weight development. Both childhood and adolescence are important ages for preventive efforts.

Norsk sammenfatning

Bakgrunn og mål: Den høye forekomsten av overvekt og fedme blant barn og unge i dag er bekymringsfull grunnet den økte risikoen for relaterte helseproblemer og økt risiko for utvikling av framtidig sykdom. Tidlig identifikasjon av barn under risiko er av interesse siden å forebygge eller utsette utviklingen av fedme kan påvirke framtidig helse. Målet med denne avhandlingen var å studere hvordan faktorer tidlig i livet, slik som fødselsvekt, kroppsmasseindeks (KMI, kg/m^2) og vekst i barneår påvirker forekomsten av overvekt og fedme, kroppssammensetning og beinhelse i ungdomsår.

Metode: Fit Futures er Tromsøundersøkelsens ungdomskohort (TFF), en populasjonsbasert studie blant ungdommer fra Tromsø og nærliggende kommuner som ble gjennomført i skoleårene 2010-2011 (TFF1) og 2012-2013 (TFF2). Data fra i alt 961 ungdommer (48% jenter) som deltok i TFF1, hvorav 659 også hadde oppfølgingsdata fra TFF2, danner basisen for studiene i avhandlingen. For å skaffe longitudinelle antropometriske data, ble data fra Medisinsk fødselsregister samt høyde- og vektdata fra helsestasjonsjournal ved to tidspunkt i barndommen, 2-4 og 5-7 års alder, retrospektivt samlet inn. Fra TFF ble høyde, vekt, midjemål, samt kroppssammensetning (fettmasse og fettfri masse), beinmasse og beintetthet målt ved hjelp av DXA-skanning ved 15-17 og 18-20 års alder benyttet. Alders- og kjønnsspesifikke grenseverdier, basert på KMI, for barn 2-18 år fra International Obesity Task Force ble benyttet for å kategorisere deltakerne som undervektig, normalvektig, overvektig eller med fedme.

Resultat: Forekomsten av overvekt inkludert fedme økte med økende alder og 21% av jentene og 28% av guttene hadde overvekt/fedme ved 18-20 års alder. Vi fant en signifikant, men beskjeden sammenheng mellom høyere fødselsvekt og overvekt/fedme ved 15-20 års alder, og fødselsvekt var assosiert med høyere fettfri masse og beinmasse ved 15-20 år hos begge kjønn. Overvekt og fedme var i moderat grad vedvarende over tid fra 2-4 og 5-7 års alder og opp til 15-20 års alder. Mer alvorlig overvekt og fedme var i sterkere grad assosiert med fortsatt overvekt og fedme i ungdomsalder. Dette resultatet ble bekreftet med spesifikke mål på kroppssammensetning. Overvekt/fedme ved 6.0 og 16.5 års alder, så vel som større enn forventet økning i KMI mellom 6.0 og 16.5 års alder var i sterk grad assosiert med høyere fettmasse indeks (kg/m^2) og abdominal fedme, men også en høyere fettfri masse indeks (kg/m^2) ved 15-20 år. Sammenlignet med normal vekt, var overvekt/fedme ved 6.0 og 16.5 års alder assosiert med signifikant høyere beinmasse og beintetthet i hofte og helkropp,

mens å være undervektig i barne- og ungdomsår var assosiert med lavere beinmasse og beintetthet ved 15-20 år.

Konklusjon: Vi fant at fødselsvekt var positivt assosiert med kroppssammensetning og beinmasse ved 15-20 år, men i beskjeden grad. Sammenlignet med fødselsvekt hadde senere vekst og en høy KMI betydelig større innvirkning på beinmasse og beintetthet ved 15-20 års alder. En sterk økning i KMI mellom 6 og 16.5 år var sterkest assosiert med overvekt/fedme samt abdominal fedme i ungdomsårene. Det er mulig å identifisere barn med stor risiko for vedvarende overvekt og fedme allerede i førskolealderen og forebyggende tiltak med fokus på en sunn vekt bør settes inn i småbarnsalder og førskolealder. Men, forebyggende arbeid rettet mot ungdommer synes like viktig.

List of papers

The thesis is based on the following papers, referred to in the text as paper I, II and III:

I. Evensen E, Emaus N, Kokkvoll A, Wilsgaard T, Furberg A-S, Skeie G. The relation between birthweight, childhood body mass index, and overweight and obesity in late adolescence: a longitudinal cohort study from Norway, The Tromsø Study, Fit Futures. *BMJ Open.* 2017;7(6):e015576. doi: 10.1136/bmjopen-2016-015576.

II. Evensen E, Emaus N, Furberg A-S, Kokkvoll A, Wells J, Wilsgaard T, Winther A, Skeie G. Adolescent body composition, and associations with body size and growth from birth to late adolescence. The Tromsø Study: Fit Futures – a Norwegian longitudinal cohort study. Accepted for publication in Pediatric Obesity 30. September 2018.

III. Evensen, E., Skeie, G., Wilsgaard, T., Christoffersen, T., Dennison, E., Furberg, A., Grimnes, G., Winther, A. and Emaus, N. How is adolescent bone mass and density influenced by early life body size and growth? The Tromsø Study: Fit Futures - a longitudinal cohort study from Norway. *JBMR Plus*, 2018;2(5):268-280. e.pub: 30. March 2018. doi: 10.1002/jbm4.10049

Abbreviations

aBMD	areal bone mineral density
ANOVA	analyses of variance
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
CI	confidence interval
CV	coefficient of variation
CVD	cardiovascular disease
CT	Computed tomography
DXA	dual-energy X-ray absorptiometry
FFMI	fat-free mass index
FMI	fat mass index
FMR	fat mass ratio
GA	gestational age
GEE	Generalized estimating equations
IOTF	International Obesity Task Force
LGA	large for gestational age
MBRN	Medical Birth Registry of Norway
NIPH	Norwegian Institute of Public Health
OR	odds ratio
p	probability p./pp. page/pages
pQCT	peripheral quantitative computed tomography
PDS	pubertal development scale
SD	standard deviation
SDS	standard deviation scores
SGA	small for gestational age
TFF1	The Tromsø study: Fit Futures 1, 2010/2011
TFF2	The Tromsø study: Fit Futures 2, 2012/2013
UNN	University Hospital of North Norway
WC	waist circumference
WHO	World Health Organization
WHtR	waist-to-height ratio
4-C	four-component model

1 Introduction

The Tromsø Study, Fit Futures 1 and 2 (TFF1 and TFF2) is a population-based cohort study among Norwegian adolescents. The Fit Futures study is an expansion of The Tromsø Study, and two repeated health surveys have been performed thus far in 2010/2011 and 2012/2013. The overall aim of the Fit Futures study is to study adolescents' health and health behaviour from a broad perspective [1].

Overweight and obesity among children and adolescents, as well as osteoporosis and osteoporotic fractures in the adult and elderly population, are important public health challenges today both worldwide and in Norway [2, 3]. Both topics and the relationship between them constitute the background for this thesis, which focuses on how early life factors influence body composition and bone health in adolescence. The promotion of health and prevention of illness are key elements in nursing (my profession) and my primary professional interest.

I had the opportunity to study the prevalence of overweight and obesity among children and adolescents based on data from TFF1 in conjunction with my Master's thesis in the Master's degree programme in Public Health at UiT The Arctic University of Norway. Thereafter, based on the initiative of professor Nina Emaus, a well-established researcher within the osteoporosis field, we developed the protocol for the present Ph.D. project in close collaboration with public health nutritionist and researcher, professor Guri Skeie. Although overweight and obesity have been comprehensively studied in recent years, there are few larger longitudinal studies with data from recent birth cohorts. We appreciated the unique opportunity to study the influence of early life conditions on body composition and bone strength in a young Norwegian population with a reported high prevalence of overweight/obesity. In this thesis we use the term early life in accordance with a WHO definition of early child development period from birth up to eight years of age [4]. Early life is characterized by a phase of physical-, socio-emotional-, cognitive-, and motor development and represents a window of opportunity to improve health [2, 4]. Measured anthropometric data from early life with repeated body composition measures in adolescence are scarce and are a strength of this study. Our goal was that this project could add to the knowledge of factors that may affect public health and contribute to knowledge-based preventive strategies.

1.1 Overweight and obesity

1.1.1 Definition and classification

The World Health Organization (WHO) defines overweight and obesity as abnormal or excessive fat accumulation that may impair health [5]. Body mass index (BMI) is defined as body weight in kg divided by the square of height in metres (kg/m^2), and it is the most commonly used measure of underweight, overweight and obesity [6]. In adults, BMI is divided into categories according to recommendations by the WHO [7] (Table 1).

Table 1. BMI categories - adult cut-off values	
Underweight	BMI <18.5 kg/m^2
Normal weight	BMI ≥18.5 – 24.9 kg/m^2
Overweight	BMI ≥25.0 – 29.9 kg/m^2
Obesity	BMI ≥30.0 kg/m^2

For children and adolescents younger than 18 years of age, there are several different classification systems in use [8, 9]. Among these systems, the weight for height or BMI for age according to population specific growth charts or according to the WHO growth standard for children aged 2-5 and 5-19 years are used [10, 11]. Different ways of classifying childhood overweight and obesity and the use of different growth references made it difficult to compare prevalence rates between populations. The International Obesity Task Force (IOTF) recommended developing new reference values to provide internationally comparable prevalence rates of overweight and obesity. In 2000, Cole et al. published such reference values for BMI based on childhood growth data from six countries [12]; since then, the IOTF classification system has been widely used [13]. These age- and sex-specific cut-off values for children 2-18 years of age [12] correspond to the BMI cut-offs for adults [7], which are presented above. In 2012 extended cut-off values were published, including cut-off values for underweight, in addition to cut-offs corresponding to BMIs of 27 and 35 kg/m^2 [13]. A copy of the IOTF cut-off values for girls and boys aged 2-18 years is attached in Appendices 1 and 2. Norwegian childhood reference data for length/height, weight, and BMI based on the same method have also been published [14].

Other important measures of overweight and obesity include waist circumference (WC), waist-hip ratio, and waist-to-height ratio (WHtR), which are all simple measures of central (abdominal) overweight and obesity [15]. A WC ≥80 and ≥88 cm for women and ≥94 cm and

≥102 cm for men (adult criteria for Europids) are commonly used to define central overweight and obesity, respectively, also in adolescents >16 years of age [15, 16].

1.1.2 Prevalence of overweight and obesity among children and adolescents

An increasing prevalence of overweight/obesity among children and adolescents worldwide has been observed during recent decades [2]. According to the WHO, more than 340 million children and adolescents aged 5-19 years were overweight or obese in 2016 [5]. More recent data indicate that this rising trend in BMI has plateaued, at least in some high-income countries, including Norway [17, 18]. However, the relatively high level of overweight and obesity is still a major health concern due to several related immediate and long-term health problems [2]. Geographical differences in prevalence rates and a north–south gradient have been observed both between countries and regions [2, 19], as well as between regions and urban-rural areas within Norway [18, 20-22]. Compared to, e.g., the USA and Southern European countries, the prevalence of overweight and obesity among Norwegian children is lower [19, 23]. In a national representative study among eight-year-old schoolchildren performed in 2008, 2010 and 2012, 16.2 % of girls and boys were overweight/obese (Figure 1).

Figure 1. Prevalence of overweight/obesity among eight-year-old children in Norway 2008-2012, by health region

*Percentage (%) overweight including obesity among third graders by health region, adjusted for sex and year of measurement. The green line marks the overall prevalence of overweight/obesity at a national level (16.2% *) p-value <0.05.* [20] Norwegian Institute of Public Health (NIPH), reprinted with permission.

Several studies have shown a higher prevalence of overweight and obesity among children and adolescents in the northernmost health region than in other health regions in Norway [18, 20, 22, 24, 25]. (Figures 1 and 2) It was, therefore, of particular interest to study overweight and obesity among children and adolescents in northern Norway.

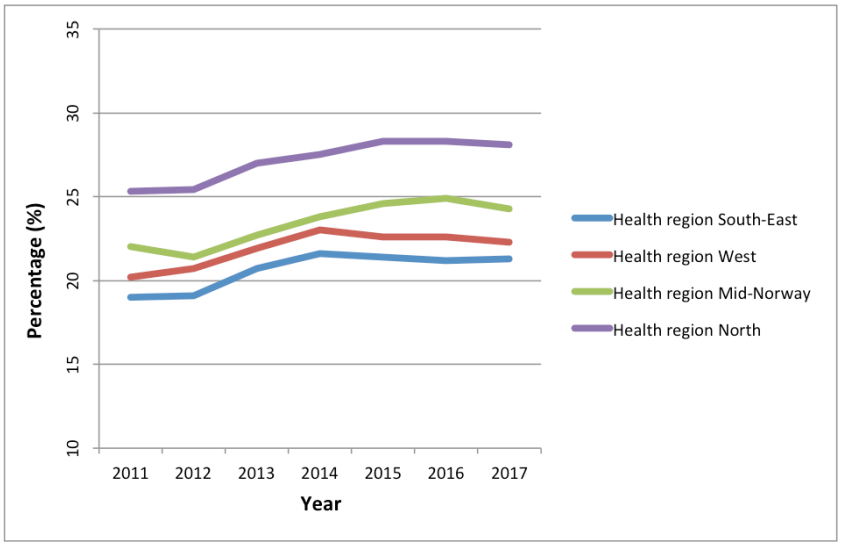

Figure 2. Percentage of overweight and obesity among 17-year-old Norwegians, by health region

Percentage (%) of overweight including obesity among Norwegian 17-year-olds (both sexes) by health region, in 2011-2017. Based on self-reported height and weight from Session 1. Source: Vernepliktsverket (Military Service) [26].

1.1.3 Overweight/obesity and health consequences

In the report "Norway: State of the Nation's Health. Findings from the Global Burden of Diseases" 2013 [27], high BMI was ranked the third highest risk factor for early death among ages 15 to 49 and as the fourth highest risk factor for early death among ages 50 to 69. Although acknowledged mainly as a health risk among adults, childhood and adolescent overweight, especially obesity, are associated with both immediate and long-term health problems [28-31]. Several studies have shown an increased risk of adult morbidity especially cardiovascular disease (CVD), type 2 diabetes, cancer, musculoskeletal problems, and other diseases as well as premature mortality [6, 32-40].

Among the short-term health consequences are elevated blood pressure, adverse blood lipid levels, and other CVD risk factors linked to obesity in childhood and adolescence [2, 29-31,

41]. Psychological health consequences and impaired quality of life have also been reported [2, 31, 42].

Overall, a moderate degree of tracking of overweight and obesity from childhood and into adulthood has been reported [6, 43]. A moderate degree of tracking from childhood to adolescence was also seen in a subgroup of the Fit Futures cohort [44]. In epidemiological studies, tracking is commonly defined as the maintenance of certain risk factors over time [45]. Studies have shown that a prolonged duration of obesity is a strong predictor of CVD and diabetes [46, 47].

1.1.4 Causes and risk factors for overweight and obesity

In principle, overweight/obesity in individuals is a result of an imbalance between energy intake and energy expenditure, which results in the storage of excess energy as fat and increased weight over time [5]. However, this is a simplistic way of understanding the pathway to overweight and obesity. Extensive research during recent decades has shown that there is not a single or simple cause for overweight and obesity, and the causes are still not fully understood [2, 28, 48]. Multiple factors, including genetic, biological, metabolic, behavioural, and environmental factors, all play roles in the development of overweight and obesity [2, 5, 49, 50].

In twin and adoption studies, the heritability of BMI is found to be high. Genetic factors are reported to explain from 40% up to 80% of BMI variation in childhood and adolescence [51, 52]. The influential roles of genetic and environmental factors vary with age. The influence of shared environmental factors decreases in adolescence, while the influence of genetic and unique environmental factors increases with age [51, 52]. An increasing understanding of a gene-environment interaction has also emerged in recent years [49]. Epigenetics refers to heritable changes that affect gene function without changing the DNA sequence, and epigenetic mechanisms are associated with obesity [53]. These mechanisms are associated with an increased susceptibility for obesity, if exposed to the so-called "obesogenic" environment [49, 53]. The WHO defines an obesogenic environment as: *"an environment that promotes high energy intake and sedentary behaviour. This includes the foods that are available, affordable, accessible and promoted; physical activity opportunities; and the social norms in relation to food and physical activity"* [54, p. V].

Reduced physical activity levels and changes in dietary habits are the most important individual-level behavioural factors highlighted [2, 5, 18]. The availability and consumption of more energy-dense food, which is high in fat and sugar, and sugar-sweetened beverages has increased over the years. Low socio-economic status and other environmental changes in society, such as changes in labour, family structures, and mode of transport, are influential factors that contribute to the overweight epidemic [2, 5].

Other factors that are suggested to play roles in the development of overweight and obesity are prenatal maternal factors such as maternal smoking, excess weight gain or diabetes during pregnancy, parental BMI, and food habits. Other early life factors are infant feeding practices, such as formula vs. breastfeeding, the introduction of solid and complementary food, and the development of taste and flavour preferences. Inflammatory markers and psychological factors such as stress in both the mother and child have also been suggested [2, 30, 55]. In the recent years, the gut microbiota has been highlighted, and assumed to play a role in the development of obesity [56].

In studies from Norway, several factors have been shown to be associated with overweight and obesity. Socio-economic status, low maternal education level, rural residency, and divorced parents are all factors associated with increased overweight/obesity in Norwegian children [21, 22, 57]. A strong positive association between parents' and their adolescent offspring's BMI has also been reported [58].

To avoid the stigmatization of individuals, it is essential to be aware of this complex system when discussing challenges and possible solutions related to the obesity epidemic [59].

1.2 Body composition

Although BMI is the most commonly used measure of overweight and obesity, it is an indirect measure of adiposity [6]. BMI has demonstrated high specificity and low sensitivity in predicting excess body fat in children and adolescents [6, 60-62], with some studies reporting that BMI fails to identify over 25% of children with excess body fat [62]. However, it has been well demonstrated that individuals with the same BMI may have very different fat mass and fat-free mass distribution [63].

1.2.1 Body composition measurements

Body composition measurements, e.g., by dual-energy X-ray absorptiometry (DXA), provide supplementary information regarding fat mass, lean mass, bone mineral content (BMC) and fat distribution [64]. DXA-derived truncal-, android and gynoid fat mass are considered valid and clinically relevant measures of central adiposity [64-66].

DXA is a three-component model that assesses fat mass, lean mass, and bone mineral in the total body and specific parts of the body [6, 67]. The four-component (4-C) model is acknowledged as the gold standard reference model for body composition [6, 64]. The model includes the assessment of water, protein, and mineral in fat-free tissue. This multicomponent model combines several measures: BMC from DXA, total body water by deuterium dilution and body volume by air-displacement plethysmography measurements [6, 64].

Other more simpler techniques that are frequently used in research include measures of WC, WHtR, skinfold thicknesses, and bioelectric impedance analysis [6, 68]. More advanced techniques, such as computed tomography (CT), magnetic resonance imaging or ultrasound are used for clinical purposes, but are also more frequently used in research. All techniques have their advantages and disadvantages. [6, 68]. Although the 4-C model is highly accurate, the disadvantages are is its low availability, and it is time consuming and expensive [6, 64]. DXA is a more frequently used non-invasive measure of body composition that is considered to be more available and less expensive with low acceptable ionizing radiation exposure for the patient as well as good precision and accuracy [6, 64, 67, 68].

WC as well as other more advanced measures of central obesity, fat mass and lean mass are regarded as better measures of cardio-metabolic risk than BMI [15, 16, 66, 69, 70]. Several body composition indices such as skinfold thickness, WC, WHtR, BMI, and lean mass have also been linked to clustered CVD risk factors in a large study of European adolescents [71].

1.2.2 Gender differences in the development of body composition

The human body composition changes throughout life and differs between males and females. Human muscle development begins in the first trimester of pregnancy, while adipose cells develop and fat deposition occurs throughout the last trimester and into infancy [72, 63]. Muscle mass and strength increase during childhood, peak in early adulthood and gradually decrease thereafter [72]. Small sex differences in body composition are evident

already at birth, although these differences are modest in childhood [73, 74]. However, endocrine changes during puberty lead to the characteristic sexual differences in body composition [73]. Pubertal maturation generally leads to higher fat-free mass in boys and higher fat mass in girls. Total fat-free mass is generally reported to be stable by 15-16 years of age in girls and by 17-19 years of age in boys. In adulthood, fat mass constitutes, on average, 13% of body weight in males and 25% in females [73]. In addition, females generally develop a gynoid body fat distribution with fat centred at the hip and thighs, and males develop an android fat distribution, with more fat in the abdominal area [73, 74]. Sex-steroids, growth hormone, and insulin-like growth factor 1 (IGF-1) are the main endocrine factors involved in pubertal growth; however, in addition to endocrine status, ethnicity, genetic, nutritional, and environmental factors all play roles in the development of adult body composition [63, 73, 74].

1.2.3 Body composition reference data

An ethnic difference in body composition is recognized, and population specific reference data for children and adolescents has been called for [74]. Reference data for children and adolescents from some populations have been published the recent years [64, 75-77]. From Norway, anthropometric growth reference data including skinfold thickness from the Bergen growth study have been published [14, 78, 79]. However, to the best of our knowledge, no DXA-derived body composition reference data for Norwegian adolescents are available.

1.3 Bone health

In addition to overweight/obesity and body composition, we wanted to study bone health in adolescence in relation to birth weight as well as childhood BMI and growth. Bone health may be defined as: *"a public health issue with an emphasis on prevention and early intervention to promote strong bones and prevent fractures and their consequences"* [80] .

1.3.1 Epidemiology of osteoporosis and osteoporotic fractures

Osteoporosis is defined as *"a systemic skeletal disease characterized by low bone density and the micro-architectural deterioration of bone tissue leading to bone fragility and a susceptibility to fracture"* [81]. In the elderly, the incidence of osteoporotic fractures in Norway is among the highest reported in the world [82], despite recent reports of a decline in hip-fracture incidence rates [83]. No specific explanation for this high level of osteoporotic

fracture rate and country differences has been found [83]. In addition to individual health consequences, loss of function and increased mortality, osteoporotic fractures constitute a major economic burden on the society [3]. Low bone density was ranked as one of the leading risk factors attributable to early death in Norway in 2013, according to findings from the Global Burden of Diseases [27].

To date, preventive strategies have, to a large degree, focused on reducing the age-related bone loss and prevention of fractures among the elderly. However, attention has shifted to the optimization of peak bone mass [84-86] (Figure 3). Peak bone mass is one of several determinants of adult bone strength, and both peak bone mass and subsequent bone loss during ageing are important determinants for the risk of osteoporotic fractures [84, 87, 85, 88].

1.3.2 Peak bone mass

The amount of bone mass naturally increases during growth and reaches a plateau in young adulthood at 20-30 years of age, depending on gender, pubertal maturation and skeletal site [89, 86] (Figure 3). Measured by DXA, areal bone mineral density (aBMD) peaks prior to 20 years of age at the proximal femoral sites, while total body bone mass peaks 6-10 years later [89]. Peak bone mass may be defined as the amount of bone mass present at the end of height growth and the end of skeletal maturation [84, 85]. Peak bone mass might also be seen as a broader concept characterized by bone density, microarchitecture and geometric properties related to bone strength [85]. Approximately 60% to 80% of the variability in peak bone mass and osteoporosis risk is determined by genetic factors [84, 85].

Several studies have shown that bone density tend to track from childhood through adolescence, which indicates that bone status in adolescence may have a long-term effect on bone health [85, 86]. However, there is a broad consensus that a combination of genetic, endocrine, environmental, and lifestyle factors influences skeletal development and that lifestyle factors might have both a positive and negative impact on the achievement of peak bone mass [84, 85, 87, 86].

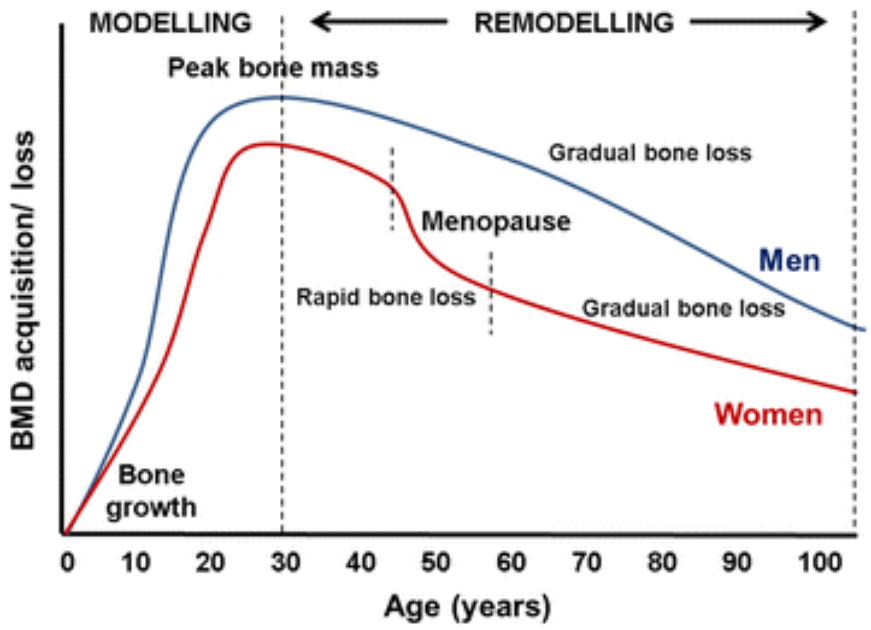

Figure 3. Peak bone mass.

Illustration (Figure 3): The general pattern of bone development and loss over time in men and women. Reprinted with permission from PMC [90 Fig.2.].

1.3.3 Skeletal development and gender differences

The foundation of bone strength is laid in utero, with subsequent growth during infancy, childhood, and adolescence as important periods for the acquisition of adult peak bone mass [87]. In utero, the pattern of the skeleton is developed during the first trimester of pregnancy, while the majority of foetal bone mass is gained during the last trimester [87]. After birth, bone mass, bone size and density increase during growth in infancy and childhood through bone modelling processes (Figure 3), and both height and weight are strong predictors [84, 87]. The amount of bone mass acquired follows a distinct age- and sex-specific pattern (Figure 3), and a gender difference in BMC and areal bone mineral density (aBMD) is present already in childhood, with boys having higher values than girls; however, when these gender differences occur are uncertain [85]. Boys also have greater bone area than girls [84, 85]. However, it is the onset of puberty that starts the growth spurt in both girls and boys, generally leading to higher mean stature in boys than in girls of the same ethnicity. The linear growth spurt starts earlier in girls than boys. Girls reach peak height velocity (maximum linear growth rate) at approximately 12.5 years of age, whereas boys reach peak height velocity approximately two years later [73, 91]. Linear growth rate peaks earlier than BMC accretion. In girls, linear growth and BMC accretion ends 2-4 years after menarche, whereas,

in boys, BMC accretion continues for a longer period [73, 84]. Other changes affecting bone strength occur during puberty, including; changes in structure, such as size and, shape, as well as changes in composition, such as the amount of cartilage, cortical and trabecular bone.

1.3.4 Measuring bone mass and density

DXA is the most common method of measuring bone mass and density in children and adolescents since it is safe, rapid, widely available and precise [85, 92]. DXA is a two-dimensional imaging technique measuring BMC and bone area. BMC divided by scanned bone area, the areal bone mineral density (aBMD: g/cm^2), is regarded as a good proxy measure of bone strength that is estimated to predict 66-74% of its variation in bone strength [93]. Bone has two principal constituents, cortical bone, a compact bone that acts as an outer shell, and trabecular bone, the sponge-like inner structure that adds strength to the bone while allowing it to be lightweight [85]. This constitution of bone makes measuring bone strength more challenging. New and more sophisticated methods such as quantitative computed tomography (QCT), high resolution peripheral QCT (HR-pQCT), and magnetic resonance imaging can provide measures of both cortical and trabecular bone, volumetric bone BMD, bone geometry, and microarchitecture [85]. Despite the capability of acquiring more detailed, high quality structural images with these new three-dimensional (3D) techniques, they are not widely used due to the need for limited specialist equipment and high costs . Therefore, DXA remains the gold standard for determination of osteoporosis as a diagnosis [3].

1.3.5 Determinants of peak bone mass

To reach the full genetic potential of peak bone mass and bone strength, sufficient nutrition and optimal mechanical loading are required. The main determinants of peak bone mass are regular weight-bearing physical activity and nutrition, especially calcium, protein, and vitamin D. In addition, several studies have indicated that other lifestyle factors such as smoking, alcohol consumption, hormonal contraceptives, and other medication as well as a sedentary lifestyle have an impact on bone accretion [86, 84, 85]. Some of these lifestyle factors, especially physical activity, were found to affect bone accretion in the Fit Future cohort. In boys, sedentary behaviour and smoking were negatively associated with BMD, whereas moderate alcohol consumption was positively associated BMD levels [94, 95].

Lean mass is found to be strongly correlated with bone mass and density, but the effect of fat

mass on peak bone mass is more controversial [85]. A recent review concluded that overweight and obese children have a significantly higher areal bone mineral density (aBMD) than normal-weight children, possibly due to increased mechanical loading, but the long-term impact is not clear [96]. By contrast, other studies have reported reduced bone mass and bone area and an increased risk of fracture among overweight and obese children [97-100]. The impact of overweight and obesity on skeletal development during growth is still uncertain, and more longitudinal studies have been requested [96, 98, 101-103]. Since lifestyle factors may contribute to 20-40% of the variance in adult peak bone mass [85], focusing on early life factors that are modifiable seems relevant. More knowledge of this relationship is warranted to support recommendations regarding bone-promoting lifestyle factors [85, 86].

1.4 Birth weight

Birth weight is commonly used as a proxy for intrauterine and maternal nutrition and may indicate maternal and environmental factors affecting foetal growth. The intrauterine programming hypothesis suggests that prenatal conditions have long-term effects on health, with a previous focus particularly emphasizing the adverse effects of low birth weight [63, 72, 104].

In a review by Brisbois et al. published in 2012, birth weight did not emerge as an early marker for adult overweight/obesity [105]. However, a recent review showed consistent associations between high birth weight and overweight later in childhood [106]. High birth weight is consistently positively associated with subsequent lean mass [63, 107-111], but associations with subsequent fat mass and central obesity are conflicting and less clear [63, 72, 107, 108, 112-114] Furthermore, low birth weight and preterm birth have been linked to central obesity [63, 72, 107, 112]. Several studies have shown a positive relationship between birth weight and bone mass in children [101] and adults [115, 116], while associations between birth weight and bone measures in adolescence have varied [101, 117]. Recent data from Norway has revealed strong associations between birth weight and overweight/obesity at 7-8 years of age [118, 119]. However, the question remains whether birth weight is a significant predictor of adiposity at a later age.

Our study population was born in 1992-1994, which represents a period with high mean birth weight in Norway (Figure 4).

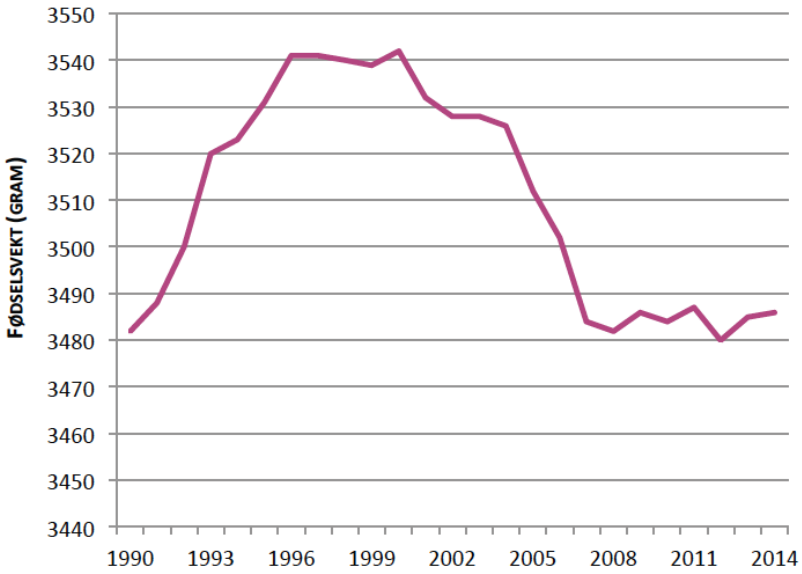

Figure 4. Mean birth weight in Norway from 1990 through 2014.

Figure 4 is from the report: "*Children's Health and the Environment – Risk and Health Promoting Factors, 2016"* by NIPH [18]. Reprinted with permission.

Mean birth weight is now back to at the same levels seen in 1980-1990. Maternal health, life-style and smoking habits might be part of the explanation for this higher mean birth weight in 1990-2005 [18, 120].

1.5 Childhood growth trajectories

In addition to birth weight and overweight/obesity reports, different patterns of growth during infancy and childhood have been reported to be a risk of later overweight and obesity [105]. Rapid weight gain in infancy or early childhood as well as the adiposity rebound (a natural occurring second increase in body mass index between the ages of 3 and 7 years) have been suggested as critical factors in the development of overweight and obesity later in life [106, 121-124]. Others have suggested that upward weight or BMI centile crossing at any age is a more precise indicator for predicting adiposity [121, 125].

Early growth in infancy compared to childhood growth may influence body composition at later stages in life differently. In some studies, weight gain later in childhood has been more strongly linked to adiposity measures [108, 109, 125-127], whereas rapid weight gain in infancy/early childhood has been more strongly linked to not only lean-/fat-free mass but also adiposity measures [63, 108-110, 113, 114, 125, 127-129]. Previous findings are not consistent, and few larger studies have investigated associations of childhood growth with

sophisticated measures of body composition in adolescence or adulthood [108, 127] The growth rate in childhood has also been linked to hip fracture risk in adulthood [130].

In this study, we had the unique opportunity to study if childhood growth was linked to DXA-measured body composition and bone mass in addition to changes in body composition during important years in late adolescence, on the cusp of adulthood. Previous studies on growth during childhood [108, 113, 116, 130, 131] might not be fully representative of the growth of children today due to the rapidly increasing prevalence of childhood overweight and obesity [17].

1.5.1 Underweight

In light of the higher prevalence of overweight and obesity among children today, the main focus of this project was to explore how overweight/obesity in childhood and adolescence influenced outcomes measured in late adolescence. However, for bone health, previous studies have reported associations between underweight and low growth rate in childhood and later osteoporotic fractures [130, 132]. Although underweight is no longer a major health concern in Norway today, it is of interest to study if previous findings from earlier birth cohorts could be confirmed in relation to body composition and bone measurements.

1.6 Hypotheses

In the classic paper from 1977, Forsdahl [133] was one of the first to introduce the hypothesis that early life conditions during infancy, childhood and adolescence could provide an explanation for CVD disease and increased mortality later in life. He based the hypothesis on the observed associations between high infant mortality rate as an index of poor living conditions, and high CVD mortality [133]. Others, especially D. Barker, have further developed the foetal origins of adult disease hypothesis, suggesting that foetal undernutrition programs body tissue and metabolism and cause later CVD or other diseases [104, 134]. The term intrauterine programming is also used [87]. The foetal origins of adult disease hypothesis was later extended to the developmental origins of health and disease hypothesis [134, 135]. This hypothesis suggests that both undernutrition in utero, which emerges as growth retardation or low birth weight, and later growth patterns through infancy, and childhood are considered casual pathways underlying CVD, hypertension and type 2 diabetes in adult life [136].

Currently, concerns about health of children and adolescents are mostly focused on whether a high birth weight or overweight/obesity in childhood is a key factor that will contribute to disease later in life.

Since 1997, the term life-course epidemiology has been used to describe studies on early life factors as determinants of later health or disease [135, 136]. Life-course epidemiology may be defined as: *"the study of long-term biological, behavioural and psychosocial processes that link adult health and disease risk to physical or social exposures acting during gestation, childhood, adolescence, adult life or across generations*" [135].

The WHO Ad hoc Working Group on Science and Evidence for Ending Childhood Obesity, uses the term life-course model to illustrate causal pathways and potential opportunities for intervention on obesity in their latest report on overweight and obesity among children (Figure 5) [2].

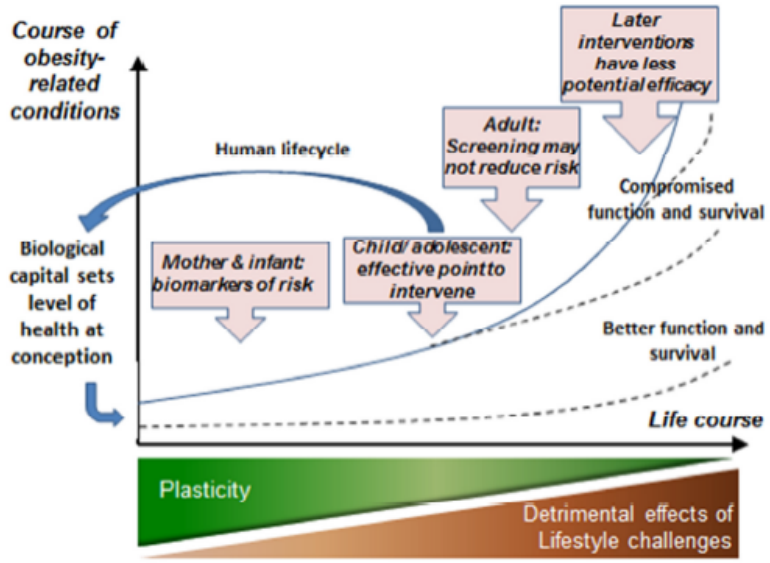

Figure 5. Life-course model of obesity and other non-communicable disease risk.

Source: WHO Meeting Report: Nurturing human capital along the life course: investing in early child development. 2013 [2] Reprinted with permission from WHO.

The intrauterine programming hypothesis, the developmental origin of health and disease hypothesis and life-course epidemiology serve as the theoretical background for our study. We hypothesized that high birth weight and higher BMI in childhood and adolescence would be positively associated with overweight/obesity, fat mass and bone strength measures in adolescence, however, with a possible threshold between high BMI and bone mass.

1.7 Rationale and aims

The overall objective of the present Ph.D. project was to study weight-related issues in the context of a population born during a period with a high mean birth weight and a relatively high prevalence of overweight and obesity among Norwegian children and adolescents.

Predictions indicate that lifestyle-related chronic illnesses will increase in the future, and may place a large demand on the health care system [137]. A concern is whether factors during birth, childhood and adolescence may imply a risk of adverse health effects later in life. Updated information on these issues is therefore important for health authorities and health care workers, who are planning preventive interventions to halt the overweight epidemic. In the White Paper: "Good health – a common responsibility" (Stortingsmelding 34, 2012–2013) [137], the need for more research on public health issues in Norway was emphasized, and data providing a regional and local overview of the health status of the population were requested. In chapter 6, it is stated that: *"the specialist health service also has a responsibility to develop knowledge and competence in collaboration with local authorities and other partners"* [137]. The Act relating to public health (Lov om folkehelsearbeid 01.01.2012) [138] imposes local and regional authorities to provide information on population health and factors that affect public health in their area of responsibility. As a researcher at the University Hospital of North Norway (UNN), it is a goal that this study, conducted in close collaboration with UiT The Arctic University of Norway and local health authorities, should contribute to knowledge that may be helpful to local health authorities and health care workers.

Effective treatment for obesity is challenging. Current treatment results for obesity in adolescents are moderate, especially for those with severe obesity [2, 31, 139] The early identification of children at risk is therefore important, as preventing or delaying the onset of obesity may influence future health [47, 46, 16]. However, the appropriate age at which to initiate preventive efforts has been a matter of discussion [140]. How early we can identify children at risk and if there is a critical age that is more influential on later body size, is therefore two questions of interest.

The overall aim was to study how early life factors were related to overweight/obesity, body composition, and bone health in the important years of transition between childhood and adulthood. More specifically, the aims of this thesis were to explore the following:

1) if overweight and obesity tracks from birth and childhood to adolescence.
2) the associations between birth weight and adolescent overweight/obesity, body composition, central overweight/obesity, bone mass, and bone density.
3) the associations between childhood growth and adolescent body composition, central overweight/obesity, bone mass, and bone density.
4) the associations between BMI categories in childhood and adolescent overweight/obesity, body composition, central overweight/obesity, bone mass, and bone density.
5) if there are any gender differences in the associations between exposures and outcomes.

The aims related to tracking (1), birth weight (2), and childhood BMI categories (4) as exposures and adolescent overweight/obesity as outcome are addressed in paper I.

The aims related to birth weight (2), childhood growth (3), and childhood BMI (4) categories as exposures and adolescent body composition and central overweight/obesity as outcomes are addressed in paper II.

The aims related to birth weight (2), childhood growth (3), and childhood BMI categories (4) as exposures and adolescent bone mass and density as outcomes are addressed in paper III.

Gender differences (5) are explored in all three papers.

2 Material and methods

2.1 Study design and study population

The present thesis utilizes data from both surveys in the population-based Fit Futures cohort, TFF1 and TFF2. In this observational study, we retrospectively collected supplementary data from the Medical Birth Registry of Norway (MBRN) and childhood health records to obtain longitudinal data at five time points from birth until 18-20 years of age (Figure 6).

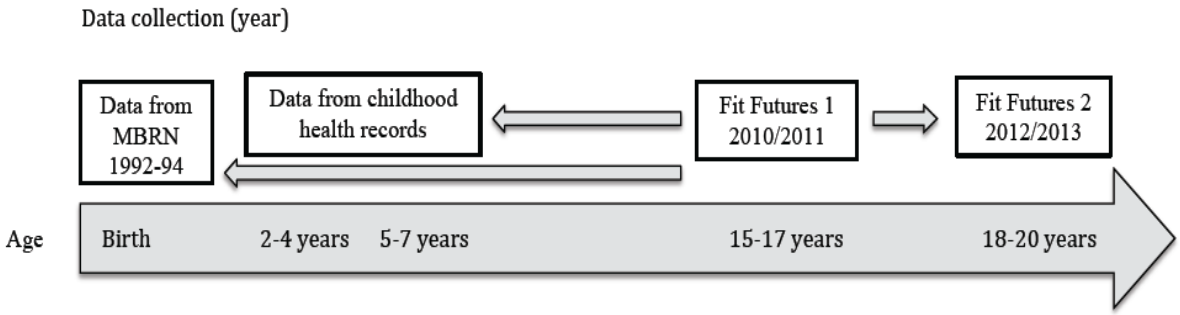

Figure 6 Timeline of data collection in the Fit Future cohort and the present study

The Tromsø Study is a population-based cohort study with seven repeated health surveys from 1974, with the latest survey performed in 2015/2016. The participants in the Tromsø Study were invited from specific age groups in the adult population of Tromsø municipality. At the start, the primary aim of the Tromsø Study was to determine the reasons for the high mortality of cardiovascular disease, which was particularly high in North Norway, and to develop ways of preventing heart attacks and strokes. The study has gradually expanded and currently covers a broad range of diseases and purposes [141]. The Fit Futures study is the youth cohort of The Tromsø Study, and the first data collection took place in 2010/2011, with a follow-up in 2012/2013 [1]. UiT The Arctic University of Norway, is responsible for the Tromsø Study, and the Fit Futures study was organized in collaboration with UNN and NIPH.

All first-year students in Tromsø and neighbouring municipalities attending the eight upper-secondary schools in Tromsø and Balsfjord in 2010/2011 were invited to TFF1. A total of 1117 students were invited, and 1038 participated in TFF1, yielding a participation rate of 92.9%. A thorough presentation of the TFF1 cohort has previously been published [94]. The follow-up study, TFF2, invited all third-year students from the same schools. All participants from TFF1 were re-invited. In TFF2, 820 individuals participated, of which 132 were new participants with data only from TFF2.

In this thesis, we used data from 961 participants in TFF1, of which 51% were boys. Participants 18 years or older in TFF1 (n=77) were excluded since they were not considered to be in the core age group of this study. Of the 961 participants, 659 had repeated measurements of height and weight, and 655 had repeated DXA-scans in TFF2. A total of 913 participants had birth weight recorded in MBRN, and 736 and 678 had height and weight measures at 5-7 and 2-4 years of age, respectively, recorded in childhood health records. A flowchart (Figure 7) shows the selection of the Fit Future cohort and the study population used in this thesis. Due to different missing patterns of main exposure and outcome variables as well as different strategies used to handle missing data, the number of subjects used in the analyses in the three papers, differs somewhat. For a detailed description of the missing data and multiple imputations to handle missing data, see section 2.5.1. A detailed description of the numbers used in the analyses is also given in each paper.

2.1.1 Age terms used

Participants in our study population were born in 1992-1994, with the majority born in 1994. The median age at the time of measurement in TFF1 was 16.6 years, with a range: of 15.7 to 17.9 years, and in TFF2 was 18.6 years, with a range of 17.8 to 20.1 years. The term adolescents and adolescence are used interchangeably throughout this thesis, describing both ages. Adolescence is defined by the WHO as ages between 10 and 19 years [142], whereas children and adolescents are defined by Statistics Norway as ages under 18 years [18]. For clarity and to separate the age groups, the age for the outcome measures in TFF1 and TFF2 is denoted 15-17 and 18-20 years of age, respectively, or 15-20 years combined. In addition, the age in TFF1 is also denoted 16.5 years in papers II and III.

The exact age at the time of the recorded measurements in the childhood health records varied; one median age was 2.5 years, ranging from 1.9 to 4.5 years, and the other median age was 6.0 years, ranging from 5.0 to 7.6 years.; therefore, for clarity and to separate the age groups, ages are denoted 2-4 or 2.5 years of age and 5-7 or 6.0 years of age, respectively.

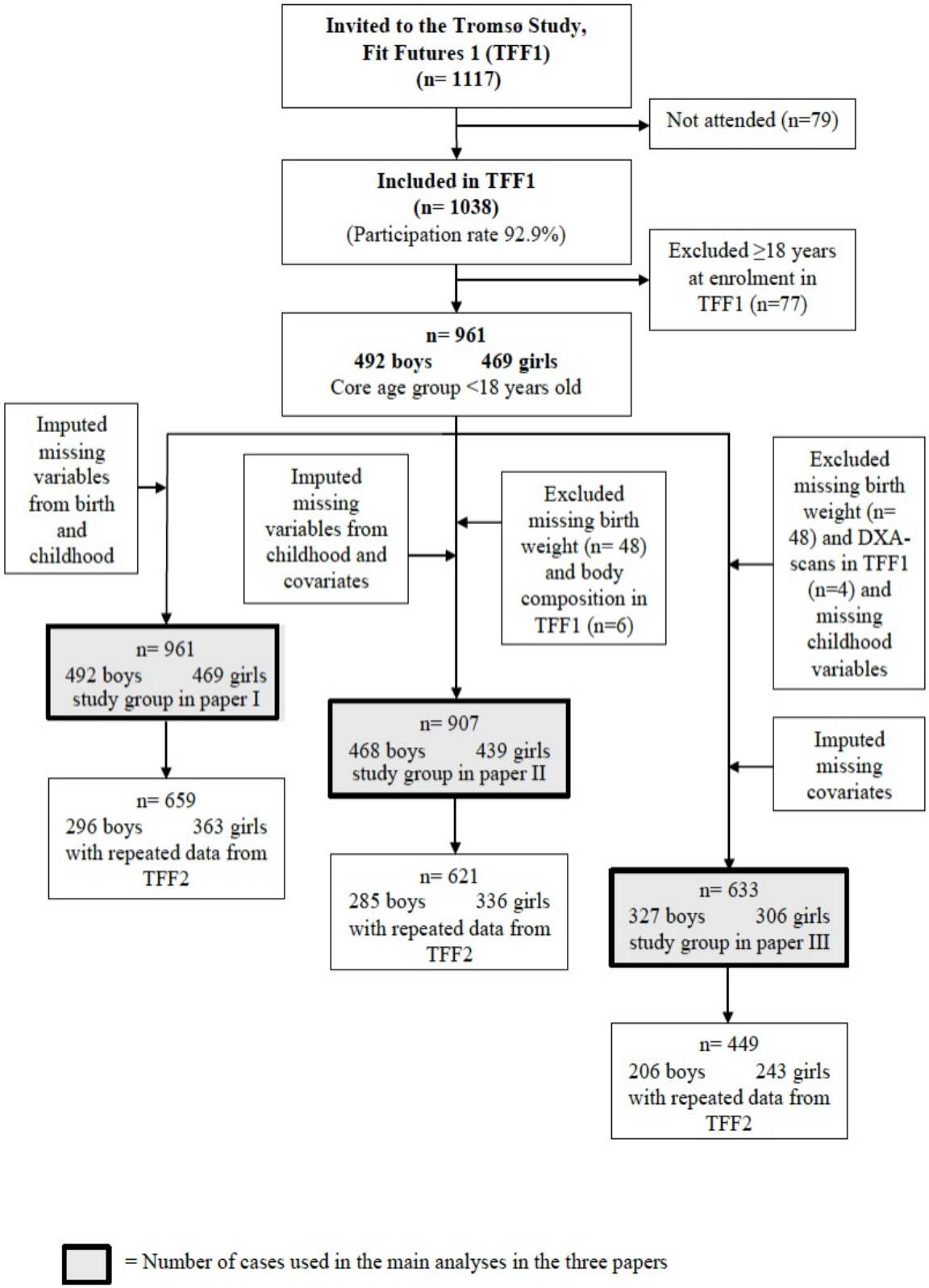

Figure 7. Flowchart of the Fit Futures cohort and selected study populations

2.2 Ethics

The present study, TFF1 and TFF2, was performed in accordance with the principles of the Declaration of Helsinki [143] and the Health Research Act [144]. The Regional Committee for Medical and Health Research Ethics, North Norway (REC North) approved TFF1 (2009/1282), TFF2 (2011/1702), as well as the present study (2014/1397) (Appendix 3). The Norwegian Data Inspectorate approved TFF1 27.07.2010 (Ref. 07/00886-7/CGN) and TFF2 31.10.2012 (Ref. 07/00886-15/EOL).

Broad consent was obtained in TFF1 and TFF2, according to the approval by REC North and the Health Research Act. Information regarding additional data collection from childhood health records and linkage to MBRN was included in the information leaflet used in both surveys (Appendices 4 and 5). All students received written and oral information and signed the consent form prior to any study-related procedures. For students younger than 16 years of age in TFF1, additional consent was obtained from their parents/guardians. The participants were compensated for their travel expenses with a gift voucher of 200 NOK.

2.2.1 Data management

Height, weight and other health data are sensitive data, and adequate and secure data handling are of the utmost importance to maintain the participants' confidence in participation in research [145]. Therefore, no separate data will be presented at the municipality level to avoid re-identification. All data have been handled and stored de-identified with a unique study code per subject and according to the procedures for secure archiving of research data at UNN. Long-term storage of data is handled through the approved data bank for the Tromsø Study. More information of data management during data collection in the present study is provided in section 2.3.1 and 2.3.3.

2.3 Supplementary data collection

2.3.1 Data from the Medical Birth Registry of Norway (MBRN)

The MBRN, managed by NIPH, is a national health registry containing information about all births in Norway [146]. Data in MBRN is collected from all maternity units by a standardized form [147] (Appendix 6). For the present study, we applied for and obtained access to data from MBRN (Appendix 7). The unique personal identification number of each person in

Norway was used to link data from MBRN with data from TFF1. A de-identified data file was created and handed out by MBRN and the data administrator of the Tromsø Study.

Information on birth weight (g), length (cm), and gestational age (GA) (weeks), as well as some supplementary data on birth (caesarean section, twin births) and mothers (age, disease, diabetes), were obtained from MBRN. For the most part, birth weight, length and GA were used in the analyses in papers I-III.

Data on BMI and smoking habits of mothers were not collected by MBRN in the relevant years for this study [147]. A total of 48 participants in TFF1 were missing birth weight from MBRN. We do not know the exact reason for this missing data. A plausible reason could be that the participants with missing data were born outside Norway and were adopted, or had moved to the Tromsø region later in childhood.

2.3.2 Calculation of exposure variables based on data from MBRN

Birth weight was divided by its standard deviation (SD) and was used as an exposure variable. Birth weight was divided into low (<2500 g), normal (≥2500-<4500 g) and high birth weight groups (≥4500 g) according to the WHO definition [120] which is presented in paper I. The ponderal index was calculated as birth weight (kg) divided by the cube of birth length (m) (kg/m^3) and was divided into tertiles. BMI at birth was calculated as birth weight (kg) divided by the square of birth length (m) (kg/m^2).

Sex-specific birth weight and BMI standard deviation scores (SDS) were calculated using LMS-coefficients (L: skewness (Box-Cox power), M: median, S: coefficient of variation) corresponding to the Norwegian growth reference [14] and used in papers I and II. Sex-specific birth weight and birth length SDS were also calculated according to GA and the British 1990 growth reference [148] and used as exposure variables in paper III.

Growth status at birth was categorized as small for gestational age (SGA; $<10^{th}$ percentile), appropriate for gestational age and large for gestational age (LGA; $>90^{th}$ percentile) based on birth weight and GA and according to a sex-specific national reference standard of births during 1987-1998 [149].

A detailed description of the specific exposure variables from birth that were used in each paper is provided in section 2.5.3.

2.3.3 Data from childhood health records

A question regarding residency at the start of school (6 years of age) was included in the TFF1 questionnaire. This question enabled data collection from childhood health records in Tromsø and the four neighbouring municipalities; Balsfjord, Storfjord, Lyngen and Karlsøy. For practical reasons, data for the participants who grew up in other municipalities or abroad were not recorded (n=193 of 1038).

The data collection was organized in cooperation with the administratively responsible public health nurses in each municipality. Since the data in childhood health records from this period mainly were recorded in paper format, the data were manually recorded and stored de-identified in a study database. A separate list with names and personal identification numbers was used to secure data collection from the correct health record. Appropriate quality assurance measures were applied to avoid error during data collection from childhood health records.

Measured height (cm), weight (kg), age (years, months), and date of measurements were retrospectively collected from childhood health records. According to guidelines, height and weight were measured in light clothing and without shoes. From 2 years of age, standing height is generally measured [150].

Regular health controls by public health nurses are offered to all children from birth through school age in accordance with national preventive health programme guidelines [150]. The health controls are voluntary, free and are generally known to have a high attendance rate [24, 25]. Length/height and weight measurements are included in the controls at some ages. In the relevant years, most children in these five municipalities had their height and weight measured at 2 and 6 years of age; therefore, data from these two target ages were collected. If data were missing for the exact age, or if a child had several measurements during the periods of approximately 2-4 years or 5-7 years, the measurement closest to the 2-year or 6-year birthday, respectively, was recorded.

The reasons for missing data from childhood health records were measurements outside our pre-defined age limits (<2.0 and >8.0 years of age), change in residency during childhood and other unknown reasons. Since height and weight data were primarily collected for clinical purposes, not research, many children were measured closely before two years of age. Along with the other reasons for missing data, this resulted in a relatively high

percentage of missing BMI category from this time point (29%), since the IOTF reference starts at 2.0 years of age [13].

2.3.4 Calculation of exposure variables based on data from childhood

Based on the height and weight at each age, BMI was calculated as weight (kg) divided by the square of height (m) (kg/m^2). BMI divided by its SD was used as a continuous exposure variable in paper I.

Age and sex-specific BMI SDS were calculated at 2-4 and 5-7 years of age, using LMS-coefficients corresponding to the Norwegian growth reference [14]. These variables were used in the analyses in paper I. Based on BMI, the participants were categorized into BMI categories. The details are shown in section 2.4.2.

A detailed description of the specific exposure variables from childhood that were used in each paper is provided in section 2.5.3.

2.4 Data from TFF1 and TFF2

Trained study nurses at the Clinical Research Unit, UNN, collected data in both TFF1 and TFF2. The data collection in TFF1 and TFF2 consisted of the following: anthropometric measurements, clinical examination, self-reported data from electronic questionnaires and clinical interviews. All measurements were performed following standardized procedures. For this thesis, we applied and obtained access to demographic variables such as sex, age (years/months), and ethnicity as well as, anthropometric measures, data from DXA-scans and some supplementary variables from questionnaires and interviews. The following variables were used in the analyses presented in this thesis.

2.4.1 Anthropometric measures from TFF1 and TFF2

Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, on an automatic electronic stadiometer/scale (Jenix DS 102, Dong Sahn Jenix, Seoul, Korea). Participants wore light clothing and no footwear or metallic objects. Based on the height and weight at each age, BMI was calculated (kg/m^2).

Waist circumference (WC) was measured to the nearest cm with a measuring tape placed horizontally at the umbilical level and at the end of a normal expiration. Subjects stood with

their arms relaxed at their sides and with their weight evenly distributed across their feet. WC was measured twice, and the mean value was used in the analyses. A WC ≥80 cm for girls and ≥94 cm for boys was used to define central overweight/obesity in this thesis [16].

2.4.2 BMI categories

The participants were categorized into the following BMI categories: underweight, normal weight, overweight and obesity as described in Table 1 and section 1.1.1. BMI reference values for every half-year and the IOTF age- and sex-specific cut-off values were used for children 2-18 years of age [13] (Appendices 1 and 2). The WHO index for adults was used at age >18 years [7]. Due to a relatively small proportion of obesity, especially in childhood, the overweight and obese category was merged in some analyses, or an alternative categorization was used: underweight, normal weight, light overweight (corresponding to adult BMI ≥25 to <27 kg/m^2) and severe overweight/obesity (corresponding to adult BMI ≥27 kg/m^2).

For comparison, BMI categories according to the WHO Child Growth Standards [10] and Growth reference 5-19 years [11] are presented in paper II, supplemental table S2. In paper I, the BMI categories are denoted as the weight class. A detailed description of the specific BMI categories that were used in each paper is provided in section 2.5.3.

2.4.3 Body composition and bone mass measured by DXA

Body composition, bone mass and bone density were measured by DXA (GE Lunar Prodigy, Lunar Corporation, Madison, Wisconsin, USA), using the appropriate mode for body size and performing the analysis with enCORE paediatric software version 13.4. Quality controls were performed on a daily basis according to the manufacturer's procedure. DXA-scans were reviewed and re-analysed if necessary. Repeated measurements in TFF1 and TFF2 were performed on the same DXA instrument with the same protocol, and all measurements from the same wave were analysed by a single, trained investigator. A final quality control evaluation excluded 10 scans from the total cohort in TFF1 due to artefacts (metal objects, etc.). DXA-scans were not performed if a possible pregnancy could not be excluded by a clinical interview and a pregnancy test.

In this thesis, we used total body lean mass and fat mass, truncal, android, and gynoid fat mass, which were all measured in grams and converted to kg where appropriate. In addition, we used BMC (g) and aBMD (g/cm^2) measured in the total body and the total hip. The left-

sided values of the total hip were used by default; however, in the case of missing data/errors, the right-sided values from both TFF1 and TFF2 were used.

2.4.4 Calculation of outcome variables based on DXA data

From the total body DXA scans, several outcome measures were derived. Fat-free mass was calculated as body weight (kg) minus fat mass (kg). The fat mass index (FMI; fat mass in kg/ height in m^2) and the fat-free mass index (FFMI; fat-free mass in kg/ height in m^2) were calculated [64]. FMI and FFMI are recommended over the frequently used percent fat mass, as they more correctly adjust for differences in height and lean mass [151]. The android:gynoid fat mass ratio (android fat mass (g) divided by gynoid fat mass (g)), which is a measure of abdominal fat, was also derived [108].

Sex- and age-specific FMI and FFMI standard deviation scores (SDS) were calculated according to a UK reference standard [64]. The change in FMI SDS and FFMI SDS between TFF1 (ages 15-17 years) and TFF2 (ages 18-20 years) was calculated as the individual FMI SDS/FFMI SDS at the latter measurement minus FMI SDS/FFMI SDS at the former measurement. These variables were used as outcome measures in paper II.

The BMC and aBMD measures were converted to sex- and age-standardized internal z-scores based on the distribution of the study sample and used as outcome measures in paper III.

2.4.5 Self-reported data from questionnaires in TFF1

Information regarding pubertal maturation and physical activity was taken from self-administered electronic questionnaires completed during TFF1 (Appendix 8).

Pubertal maturation in girls was determined based on a question of age at menarche (years, months) and classified into three levels: early (menarche age <12.5 years), intermediate (menarche age 12.5-13.9 years) and late (menarche age ≥14.0 years) matured. Three girls had not started menstruating at the time of the survey; they were classified as late matured.

Pubertal maturation in boys was based on the mean score of the pubertal development scale (PDS), which is a validated self-reported measure [152]. The boys rated four secondary sexual characteristics (height growth, facial and body/pubic hair growth, and deepening of the voice) on a scale ranging from 1 (not yet started) to 4 (complete), and the PDS-score was calculated as the total mean score of the four items. Pubertal maturation was classified as

barely started (PDS: 2.0-2.9), underway (PDS: 3.0-3.9), and completed (PDS: 4.0). None had a score <2.0 in total mean score. The PDS questions were introduced after the start of the TFF1 study. Thus, (102) 21 % of the boys had missing PDS scores.

Several instruments were used to measure physical activity in TFF1. We selected physical activity frequency measured through components of the validated WHO Health Behaviour in School-aged Children (HBSC) questionnaire [153, 154], which included the question: "If you are actively doing sports or physical activity outside school, how many days a week are you active?" Answers were given in six pre-defined categories: "never" (1), "less than once a week" (2), "1 day a week" (3), "2 to 3 days a week" (4), "4 to 6 days a week" (5), and "almost every day" (6). The answers were recoded into three categories of physical activity: "low" (1-2), "moderate" (3-4), and "high" (5-6).

Pubertal maturation and physical activity were used as covariates in adjusted analyses.

2.5 Statistical methods

Statistical analyses, multiple imputations, and linear spline multilevel models were all carried out using Stata/MP 14.1 and 15.1 for Mac (Stata Corp, College Station, TX, USA). The level of statistical significance was set to two-sided p-values <0.05.

2.5.1 Missing data and multiple imputation

As explained previously, we experienced missing data from MBRN and childhood health records. In addition, 302-306 out of 961 (31-32%) participants were either lost to follow-up in TFF2 or were missing the outcome variables of interest (Figure 7). Significantly more boys (39.8%) than girls (22.6%), p <0.001, were lost to follow-up in TFF2.

Of the 961 participants, six were missing outcome variables from TFF1, 48 (5%) were missing birth weight, 283 (29%) were missing height/weight at 2-4 years of age, and 225 (23%) were missing height/weight at 5-7 years of age, leaving 47% of the study population with five complete measurements. There were also missing data in the covariates: 88 (9%) were missing birth length, 138 (14%) were missing GA, 102 (21%) boys were missing PDS, six (1%) girls were missing menarche age, and 11 (1%) were missing data on physical activity. Some participants had missing data in more than one variable. Due to the different selection of the study population eligible for analysis in each paper, the number and percentage of missing data which is described in each paper varies somewhat.

To avoid bias and maintain power, we chose to handle missing data by multiple imputation. In papers I and II, we imputed missing covariates and exposure variables from childhood, and, in paper I, missing birth weight was also imputed. In paper III, only missing covariates were imputed.

Under the assumption of missing at random,, multiple imputations were performed using chained equations, generating twenty duplicate datasets [155]. A separate imputation model was set up for analyses in each paper, including the relevant outcome variables and all variables from the final analytic models. To increase the predictive power of the imputation models, auxiliary variables from all time points were included. Separate imputations were performed for boys and girls. Variables were imputed using linear regression for continuous variables and predictive mean matching (using 100 nearest neighbours) for variables that had a restricted range, e.g., the PDS. Pooled estimates from analyses of the 20 datasets are reported [155, 156].

2.5.2 Estimating growth trajectories using a linear spline multilevel model

In papers II and III, we wanted to explore how growth between birth and age 2.5 years, as well as between consecutive ages was related to outcome measures at 15-20 years of age. Since the exact age at the recorded childhood measurements varied and we experienced missing data, we used a linear spline multilevel model fitted by the mixed command in Stata to estimate individual growth trajectories [157]. The regression model, also referred to as "the broken stick model", uses a sequence of linear splines connected at "knot points" (connection points) at target ages to model the growth trajectory across time. This allows different linear slopes in different age intervals and different slopes between individuals [118, 157]. The model uses data from individuals and from the whole study sample to estimate person-specific length/height (cm) and weight (kg) at the following target ages: 2.5, 6.0 and 16.5 years, as well as individual growth trajectories (splines) between birth and age 2.5, and between consecutive ages. In our study, each participant had only one collected height/weight measurement at or around the target ages, and knot points were therefore placed at the median ages. In this case, the model estimated the most likely birth length as well as height and weight at 2.5 and/or 6.0 years of age when values were missing. Individual-level random effects for intercept and slopes are estimated as each person's deviation from the average

trajectory [157]. Sex and an interaction term with sex and splines were included in the model to account for sex differences in growth trajectories across time.

In a two-step process, model estimates of length/height and weight at target ages were used for further calculation of exposure variables: BMI, BMI SDS, BMI categories and growth rates. These exposure variables were further used in the statistical models to assess the relationship with the outcome measures in papers II and III.

Length/height and weight growth rates were calculated as the change in cm/kg per year between two consecutive target ages, e.g., the predicted height at 16.5 years of age minus the predicted height at 6.0 years of age divided by 10.5 years. These variables were used in the growth models in paper III, comparing growth patterns in different age intervals up to the end of the growth period, conditioned on earlier size, and assess associations with the outcomes [157, 158].

2.5.3 Statistical analyses

Descriptive characteristics of the study population are presented as the mean and SD for continuous variables and numbers and percentages for categorical variables for boys and girls separately. Since both body composition and bone acquisition differ between boys and girls, especially in adolescence, statistical analyses were stratified by sex. In paper I, combined results are also presented for the main analysis. Statistical differences between groups were tested by an independent samples t-test for continuous variables and by the X^2 test for categorical variables. Since some of the body composition measures were slightly right skewed, correlations between continuous variables were assessed by Spearman's rank correlation coefficient. ANOVA with Bonferroni correction for multiple comparisons was used to assess differences in the means between several categories.

The normality of variables was checked by a visual inspection of histograms. Scatterplots were used to check for outliers and linearity between exposures and outcome variables. We controlled for homogeneity of variance, and model residuals were checked by visual inspections of histograms and plots. No assumptions were considered violated for the models presented in the thesis. Cross-product terms with sex and exposure variables were included in the models to formally test for potential sex interactions.

Paper I

In paper I, the degree of tracking of birth weight and childhood BMI into adolescence was estimated as odds ratios (ORs) for being overweight/obese at 15-20 years of age. The outcomes were BMI categories at 15-17 and 18-20 years of age dichotomized as underweight/normal weight or overweight/obesity.

Generalized estimating equations (GEE) were used to model our longitudinal data when the outcome was dichotomized [159, pp. 128-140]. Longitudinal data are correlated within the subject and in GEE analysis the dependency of the observations is accounted for by choosing an appropriate "working correlation structure" for the repeated measurements. The model produce a population averaged estimate [159, pp. 57-68, 128-140]. GEE with a logit link function and an unstructured correlation matrix were used to estimate ORs with 95% confidence intervals (CI). Exposure variables were analysed both as continuous and categorical variables: birth weight (per 1-SD increase), birth weight SDS, ponderal index in tertiles, BMI (per 1-SD increase), BMI SDS and BMI divided into four categories at 2-4 and 5-7 years of age. In addition, due to the small proportion of obesity in childhood, an alternative approach with three BMI categories was tested: light overweight and severe overweight/obesity compared to underweight/normal weight.

Potential confounders from MBRN and TFF1 were tested, and both crude and adjusted models are presented.

Paper II

The main outcomes in paper II were body composition measures at 15-20 years of age: FMI SDS, FFMI SDS, and android:gynoid FMR. In addition, WC was dichotomized as central overweight/obesity or not, FMI was dichotomized as $<$ or $\geq$1.0 SDS and used as outcomes. Exposure variables in the main analyses were birth weight and ponderal index per 1-SD increase, growth status at birth: being born small, or appropriate or large for GA. In addition, BMI categories at 2.5, 6.0 years of age were dichotomized as underweight/normal weight and overweight/obesity. BMI at 16.5 years of age were divided in four categories: underweight, normal weight, light overweight and severe overweight/obesity. In the analyses of childhood growth in this paper, the BMI gains between birth and age 2.5, and between consecutive ages were used as the exposure variables.

Linear mixed models [159] were used to assess associations between exposure variables and repeated measures of body composition as continuous outcomes at 15-17 and 18-20 years of age. Our data have a two-level structure were repeated observations are clustered within subjects. To account for the clustering of the observations, we used linear mixed models with only a random intercept on the subject level. In the model, correction for the clustering are carried out by estimating the variance of the intercepts and adding this to the longitudinal regression model. However, only the fixed effects are reported [159, pp. 69-85]. GEE were used in the analysis of binary outcome variables (see 2.5.3 paper I).

A conditional growth model [158, 160] was used to assess the impact of BMI gain in different age intervals related to the outcomes. In a conditional growth model, growth measures are adjusted for prior body size. Accordingly, standardized residuals were obtained by multiple linear regression analyses of BMI SDS at all target ages regressed on prior BMI SDS. These residuals were used simultaneously in linear mixed models with FMI SDS, FFMI SDS and android:gynoid FMR as outcomes. Standardized beta coefficients are reported for FMI SDS and FFMI SDS. This index of growth is statistically independent of body size at the start of each growth period and adjusts for both catch-up growth and regression to the mean [160]. This approach asks a prospective question: for each child, is he/she growing more than expected, given his or her body size at the start of the growth period, and how is this growth associated with the outcome measure? [158]

Models were adjusted for potential confounding factors; birth weight was adjusted for GA, associations between BMI at age 2.5 and 6.0 were adjusted for height at the same ages, and BMI at age 16.5 was additionally adjusted for height, pubertal maturation and physical activity levels. All conditional growth models were adjusted for GA, pubertal maturation and physical activity levels.

In a subgroup analysis of those with body composition measures from both TFF1 and TFF2 (n=621), we used a conditional growth model to explore the relationship between BMI gain and changes in FMI SDS and FFMI SDS between 15-17 and 18-20 years of age.

Paper III

The main outcomes in paper III were bone measures: total hip and total body standardized BMC and aBMD scores (z-scores) at 15-20 years of age. Exposure variables were birth weight SDS and BMI categories: underweight, normal weight and overweight/obesity at 2.5,

6.0 and 16.5 years of age. In analyses of childhood growth in this paper, the height (cm/year) and weight (kg/year) growth rate between birth and 2.5, 2.5 to 6.0, and 6.0-16.5 years of age based on the linear spline multilevel model were used as the exposure variables.

Linear mixed models with a random intercept on the subject level (see 2.5.3 paper II) were used to evaluate the relationship between exposure variables and repeated BMC and aBMD z-scores as continuous outcomes. Both crude models and models adjusted for potential confounding factors are presented. Details of covariates used in the separate models, are described in the paper's method section as well as in the tables in paper II.

In the analyses of growth and in accordance with others [161, 162], the rate of length/height growth was conditioned on earlier body size, and weight gain was conditioned on earlier body size as well as concurrent height growth. Hence, this model asks the same prospective question as the standard conditional growth model used in paper II [158].

Analysis of growth can be challenging, and several models can be used [157, 158, 160]. See section 4.1.9 for a discussion of the choice of growth models.

3 Results

3.1 Summary of paper I

The association between birth weight and later overweight/obesity has not been established. The aim of this study was to investigate the relation between both birth weight and childhood BMI and adolescent overweight/obesity in a sample of 961 adolescents with repeated height and weight measurements at 15-17 and 18-20 years of age.

The prevalence of overweight including obesity increased with age and was 14.0% and 18.5% in girls and 8.8% and 10.9% in boys at 2-4 and 5-7 years of age, respectively. At 15-17 and 18-20 years of age, 20.6% and 20.9% of girls and 23.4% and 28.0% of boys were overweight/obese, respectively. The prevalence of obesity was <1.5% at 2-4 years and increased to 6.6% in girls and 8.1% in boys at 18-20 years of age.

We found a statistically significant but modest association between birth weight and overweight/obesity at 15-20 years of age. In the adjusted analyses, a 1-SD (586 g) higher birth weight was associated with a 1.25-fold higher odds of overweight/obesity at 15-20 years of age (95% CI: 1.06 to 1.48). Being born small for gestational age was associated with lower odds of overweight/obesity at 15-20 years of age compared to those appropriate for gestational age, with an OR: of 0.40 (95% CI: 0.22 to 0.72).

Childhood BMI was also associated with overweight/obesity at 15-20 years of age. A 1-SD (1.35 kg/m^2) increase in BMI at age 2-4 years rendered an OR of 1.66 (95% CI: 1.40 to 1.96), and a 1-SD (1.83 kg/m^2) increase in BMI at age 5-7 years rendered an OR of 3.23 (95% CI: 2.56 to 4.07) for overweight/obesity at 15-20 years of age. Children with more severe overweight/obesity (corresponding to an adult BMI ≥27 kg/m^2) had considerably higher odds of later overweight/obesity compared to those with light overweight or their normal weight peers, with an OR of 3.01 (95% CI: 1.47 to 6.18) and an OR of 11.51 (95% CI: 6.63 to 19.99) at ages 2-4 and 5-7, respectively.

In conclusion, the association between birth weight and overweight/obesity at 15-20 years of age was modest. The degree of tracking of BMI from 2-4 and 5-7 years to adolescence was moderate to strong. Severe overweight/obesity at 2-4 and 5-7 years of age was a strong predictor of later overweight/obesity.

3.2 Summary of paper II

Fat mass, fat-free mass as well as fat distribution are related to cardio-metabolic risk. This study aimed to explore how birth weight, childhood BMI and BMI gain were related to adolescent body composition and central overweight/obesity. A dataset with 907 subjects was used in the main analyses, and a subset of 621 subjects was used in the analyses of change in FMI and FFMI between 15-17 and 18-20 years of age.

We found a weak but statistically significant association between birth weight and FFMI SDS at 15-20 years of age in both sexes and with FMI SDS only in girls. We did not find any indications that being born small for gestational age was associated with adverse levels of fat mass or central overweight/obesity.

Greater BMI gain in each age interval from birth and up to 16.5 years of age, conditioned on prior body size, was associated with higher FMI, FFMI and central overweight/obesity. The strongest associations were seen in the age period 6-16.5 years; β coefficients of FMI SDS: 0.67 (95% CI: 0.63 to 0.71) and FFMI SDS: 0.46 (95% CI: 0.39 to 0.52) in girls, and FMI SDS: 0.80 (95% CI: 0.75 to 0.86) and FFMI SDS: 0.49 (95% CI: 0.43 to 0.55) in boys were obtained. While greater BMI gain in early childhood, before 6.0 years of age, was more equally associated with both higher FFMI SDS and FMI SDS, greater BMI gain later in childhood was more strongly related to higher FMI SDS.

In both sexes, overweight/obesity at 6.0 years of age was associated with significantly ($p<0.001$) higher odds of central overweight/obesity; an OR of 4.78 (95% CI: 3.05 to 7.48) in girls, and an OR of 5.56 (95% CI: 3.24 to 9.54) in boys, compared to being underweight/normal weight, were obtained. Both light and severe overweight/obesity at age 16.5 years revealed considerably higher ORs for an FMI SDS ≥1.0 at 15-20 years of age.

In addition, we present descriptive age- and sex-specific DXA-derived body composition measures for Norwegian girls and boys at age 15-20 years in this paper.

In conclusion, compared to birth and early childhood, overweight/obesity at later ages, as well as greater BMI gain between 6.0 and 16.5 years of age are strong predictors of higher fat mass and central overweight/obesity at 15-20 years of age.

3.3 Summary of paper III

The effect of birth weight and childhood BMI on adolescents' bone parameters has not been established. The aim of this longitudinal, population-based study was to investigate the association of birth weight, childhood BMI, and growth with adolescent bone mass and bone density. A study sample with 633 adolescents with measurements from birth, childhood and adolescence was used in the analyses.

In the crude analysis in both sexes, a statistically significant positive association with total body BMC was observed per 1-SDS increase in birth weight; β coefficients of 0.31 (95% CI: 0.20. to 0.41, $p<0.001$) in girls and 0.13 (95% CI: 0.02 to 0.23, $p=0.017$) in boys were obtained. A higher rate of length growth, conditioned on earlier size, from birth up to 2.5 years of age and a higher rate of weight gain from 6.0 to 16.5 years of age, conditioned on earlier size and concurrent height growth, revealed stronger associations with bone accretion at age 15-20 compared to other ages.

Compared to being normal weight, overweight/obesity at 16.5 years of age was associated with higher aBMD z-scores: β coefficients of 0.78 (95% CI: 0.53 to 1.03) and 1.08 (95% CI: 0.85 to 1.31) in girls and 0.63 (95% CI: 0.42 to 0.85) and 0.74 (95% CI: 0.54 to 0.95) in boys at total hip and total body, respectively, were obtained. Similar associations were seen for BMC. Overall, stronger associations were seen for total body than for total hip and with BMC than with aBMD.

In conclusion, birth weight influences adolescent bone mass, but to a lesser degree than later growth and BMI in childhood and adolescence. Our findings did not indicate that overweight/obesity in childhood negatively affected bone mass accretion at total hip and total body, but underweight was consistently associated with lower bone mass and bone density.

4 Discussion

The overall aim of this thesis was to study how early life factors were related to overweight/obesity, body composition, and bone mass accretion in adolescence and whether any associations that may imply a future health risk were observed. Caution is required when interpreting results from a single observational study, and the validity of the study must be considered. Before we can draw conclusions, some important limitations and strengths of the study population, the design and methods as well as the results must be discussed. The question is whether chance, bias or confounding have distorted the associations that were observed?

4.1 Methodological considerations

The internal validity of a study refers to whether results and inferences drawn from the study are true for the study population. Validity may also be expressed as the opposite of bias [136, 163, p. 128]. Bias may be defined as:

> *"systematic deviation of results or inferences of truth. Processes leading to such deviation. An error in the conception and design of a study – or in the collection, analysis, interpretation, reporting, publication, or review of data – leading to results or conclusions that are systematically (as opposed to randomly) different from the truth"* [136, p. 21].

In epidemiological studies of humans and health, errors are inevitable, but must be recognized and reflected on [164, pp. 83-86]. However, random error is not necessarily a problem in studies with large sample sizes and may be handled by proper use of statistical analysis. Systematic error, in contrast, may lead to bias.

Potential threats to internal validity in epidemiological studies are often classified as selection bias, information bias and confounding [164, p. 85]. Potential threats to internal validity in the current study and how this has been handled will be discussed in the following sections.

4.1.1 The study design

A strength of this study is its longitudinal design, which utilizes a mixture of prospective and retrospective data from birth until 18-20 years of age based on the Fit Futures cohort. Longitudinal cohort studies are limited since they are costly and time consuming. In prospective cohort studies, it may take several years to collect enough outcome data on

relatively rare conditions [163,pp. 108-109]. Retrospective data collection is therefore a convenient approach to shorten the time from collection of exposure data until outcome measurements and hence provide more up-to-date data on health conditions that may vary over time. However, lack of recorded information and missing data may hamper such a study compared to prospective data collection [163, p. 96]. Data collection from health registries and the reported high attendance rate at public health clinics minimized the risk of information bias. Hence, recall bias, which may be a problem in studies with retrospective data collection [163, p. 112] was not a problem in our study. Missing data from birth and childhood were not related to the outcome. The sensitivity analyses showed no significant differences in body composition measures in TFF1 between participants with missing birth weight and/or childhood BMI and those with no missing (paper II, supplemental table. S6). This cohort study is also prospective in the sense that the exposure variables (birth weight/ BMI in childhood) were measured before the outcome and hence allowed us to study associations between exposure and later overweight/obesity, body composition and bone measures in adolescence . The most important feature with the longitudinal study designs is the opportunity it provides to study the natural, individual development of disease or health status over time, e.g., tracking [159, pp. 6-7, 164, p. 15]. Longitudinal studies including children are also warranted since they allow the study of relationships between growth and later outcomes [6, 63, 85].

Although the design is longitudinal, some of the performed analyses might be considered cross-sectional, since both the exposure and the major part of the outcome were measured at the same time point. The cross-sectional design provides the opportunity to measure the prevalence of diseases or other factors [164, p. 15], as in this case, the prevalence of overweight and obesity at different ages. The main limitation with cross-sectional analysis is that the time order of cause and effect cannot necessarily be determined [136, p. 64]. However, since we included both outcome measures at TFF1 and TFF2 in the mixed model and GEE analyses, a longitudinal relationship was assured. Overall, the retrospective data collection and the longitudinal design with data from birth until 18-20 years of age are therefore considered a strength of this study.

4.1.2 Missing data and risk of selection bias

The high attendance rate in TFF1 and the population-based design minimized the risk of selection bias. More than 90% of the population in the age group 16-18 years of age in this

region attend upper-secondary school [165], which was also the case in the relevant years for this thesis; this is an entitlement in Norway. However, since 31% of the participants were lost to follow-up in TFF2, in addition to the missing data from MBRN and childhood health records, the risk of selection bias was introduced. Selection bias may result in distortion of the estimated associations between exposure and outcome as a result of systematic bias in the selection of the study population or in systematic differences in characteristics of participants and non-participants in a study [136, p. 258, 163, pp. 134-135].

Due to the retrospective collection of exposure variables from birth and childhood, missing data were not dependent on the outcome. The results of the analyses of missing pattern and the sensitivity analyses between those with missing data from birth/childhood and those without missing data are presented in the supplementary files related to the papers I (table S3) and II (table S6). Drop-out analysis showed that significantly more boys than girls were lost to follow-up in TFF2. Girls who were lost to follow-up in TFF2 had slightly higher BMI in TFF1 and significantly ($p<0.05$) higher FMI, WC and android:gynoid FMR. Boys who were lost to follow-up inTFF2 had significantly ($p<0.01$) higher android:gynoid FMR in TFF1 compared to those who participated in TFF2. No other significant differences in main outcomes in TFF1 were observed.

We consider the risk of selection bias as limited; however, the risk should not be ruled out. In addition, we have handled missing data by the multiple imputation approach.

4.1.3 Handling missing data

Missing data is a frequent problem in cohort studies with several waves of data collection [166], which also occurred in our study. There has been no consensus on the best way to handle missing data. The most frequently used method, is complete case analysis [166, 167]. In two out of three papers, we chose to use multiple imputation to impute the missing childhood exposure variables. The main reasons for this approach were to avoid bias due to missing data, and to retain the sample size to increase precision and power. We assume that data are missing at random (MAR), but there is no method to test to be absolutely sure that data are missing at random based in terms of the observed data [155, 167]. We performed sensitivity analyses and repeated all main analyses in datasets with complete cases. In these analyses, similar results were obtained, which may serve as verification that the results from datasets with imputed data are valid. Since sensitivity analyses showed that bone measures

did not differ between those with and without missing data from birth and childhood, we chose to use a complete case dataset in paper III and only imputed missing covariates. There is no such thing as a perfect imputation model. However, complete case analyses may also be biased and may result in substantial loss of precision and power [155, 166, 167]. The multiple imputation approach is now a recommended and available statistical method for handling missing data [167]. We only imputed missing data in exposures and covariates, not missing outcome variables from TFF2, since missing not at random (MNAR) [167] cannot be ruled out. Imputed missing predictors are less prone to be biased if the reasons for the missing data are unrelated to the outcome [155, 167], as was the case in our study.

We consider the risk of selection bias as limited and our efforts to handle missing data as appropriate and sufficient to judge that our estimates are not severely biased. As imputed values tend to have somewhat lower mean values, the reported prevalence of overweight and obesity from childhood might be underestimated and hence weaken the associations with outcome measures.

4.1.4 Information bias and misclassification

Information bias refers to systematic errors in the reporting or recording of data, measurement errors, or errors in the analysis and interpretation of data [136, pp. 149, 180, 164, p. 88]. Data collection in both TFF1 and TFF2 was performed over a limited time (<1 year) by a limited number of trained study nurses, following standardized study procedures for all measurements and calibration procedures for instruments to reduce intra-and inter-observer variability and ensure valid, high quality data. This approach minimized the risk of measurement errors in data from TFF1 and TFF2 and hence reduced the risk of dependent misclassification of the outcome measures in our study. Misclassification refers to an erroneous classification of an individual or a value into a wrong category [136, p. 186], e.g., misclassification as overweight instead of normal weight.

The validity of data from MBRN is reported to be very good, at least for the main variables used in our study: birth weight and GA [168]. GA from MBRN was determined by ultrasound examination, or the last menstrual period if ultrasound was missing. Still, errors in GA reporting are not unusual [149], and three implausible values of GA were set as missing and later imputed.

Measurement error might be a bigger problem in the retrospectively collected clinical data since we do not know if they were measured under the same strict procedures and quality controls as those in the study. In addition, various instruments have been used. In our study, the childhood height and weight measurements were obtained from different health clinics using various scales and stadiometers. A simulation study of height and weight measurements in children by NIPH showed that the estimated prevalence of overweight and obesity increased systematically with increasing instrument error. This study concluded that failure to calibrate measuring instruments may lead to an overestimation of overweight/obesity and in the referenced study this corresponded to 0.5% higher prevalence of overweight/obesity [169]. However, the study also showed that instrument error might lead to either an overestimation or underestimation of actual weight or height [169], and potential misclassification bias in our study is assumed to be non-differential, affecting all children equally.

Misclassification can be differential, depending on actual values of other variables and hence affecting subgroups unequally, or non-differential, which is classified as random with as many misclassifications in one direction or group as the other [163, pp. 138-145, 164, pp. 103-108]. Non-differential misclassification in exposure variables may still be a problem and generally weakens the associations between exposure and outcome [164].

Measured height and weight from MBRN, childhood health records and TFF1 and TFF2 are a strengths of this study, compared to studies that must rely on self-reported values, which are known to be error-prone. When data are retrospectively collected, self-reported values may be affected by recall bias [163, p. 112]. This problem was avoided by the use of registry data.

The accuracy, precision and reliability of measurements must also be considered under the heading of information bias and measurement errors. Accuracy may be defined as: *"the degree to which a measurement or an estimate represents the true value of the attribute that is being measured"* [136, p. 3] and may be used as a synonym to validity. Precision may be defined as: *"relative lack of random error"* [136, p. 222]. A measurement can be accurate but not precise or vice-versa. Reliability may be understood as a quality that is sound and dependable. Reliability also refers to the degree to which the results obtained by a measurement procedure can be replicated, if performed under identical conditions [136, p. 246]. In the following sections, these terms will be discussed in relation to body composition

measures obtained by DXA-scans and the accuracy of BMI and WC as measures of adiposity.

4.1.5 Accuracy and reliability of DXA-scans

Several efforts were made to ensure valid and reliable body composition and bone measurements obtained from DXA-scans in TFF1 and TFF2. Repeated DXA measurements were performed using the same instrument with documented high precision [170-172]. The coefficient of variation (CV %; SD/mean x100) is a measure of precision/repeatability. In vivo, the densitometer CV for the DXA instrument in use has been estimated to be1.17% for total hip [170] which is an outcome used in our study. The precision (CV) of lean mass and fat mass estimates of the Lunar Prodigy instrument have been reported by others to be <2.0% for total body and somewhat higher for regional estimates, up to 3.2% for truncal fat mass [171, 172]. Trained personnel performed the scans and quality controls; phantom calibrations were performed according to the manufacturer's procedures, and all measurements from the same wave were analysed by a single, trained investigator.

DXA-derived body composition measures have shown very good agreement (correlation coefficients 0.94-0.98 for fat mass SDS and fat-free mass SDS) with the 4-C model, which is regarded as the gold standard for measuring body composition [6, 64, 173]. Good agreement has also been found between DXA and CT measures of visceral adipose tissue [174]. Imperfect positioning of subjects on the scanning bed, technical artefacts such as metal objects, heterogeneity in soft tissue and variation in hydration status of fat-free tissue may affect the accuracy of DXA measurements [67, 92]. DXA is regarded to be more reliable in healthy adults with constant tissue hydration but is less accurate in leaner individuals with low fat mass [6, 173]. However, scanning performed by trained personnel and overall young, healthy study subjects should minimize the effect of such measurement errors.

Measures of BMC and aBMD with DXA are proxy measures of bone strength [85]. There has been no clear consensus regarding whether BMC or aBMD should be the outcome of interest in studies of bone accretion in children and adolescents [85, 92]; hence, we have presented both measures. DXA is a two-dimensional technique that does not capture the depth of the bone and has known limitations to measure true volumetric bone density [85]. This size-related artefact might overestimate true bone density in larger bones and underestimate bone density in smaller bones [91, 92, 175]. This limitation was unfortunately

erroneously expressed in one sentence in paper III (page 11). Different size adjustments have been recommended, e.g., calculation of bone mineral apparent density (BMAD) or adjustment for bone area [85, 175, 176]. Nevertheless, we chose to use aBMD as an outcome since it was measured in late adolescence, and, in particular, it is frequently used. Moreover, aBMD eases comparisons with other previous studies of adolescents, in addition to comparisons of future studies. Despite its limitations, aBMD is the measure used to diagnose osteoporosis and is related to fracture risk [81] which is the clinical outcome of interest; therefore, it is of special interest.

To handle these limitations, measurements were analysed using paediatric software. All analyses of body composition and bone outcomes were stratified by sex to eliminate size-related artefacts that are dependent on sex. Sensitivity analyses excluding non-white participants did not affect bone parameters [94]. In addition, all analyses were adjusted for height, and statistical models at 16.5 years were additionally adjusted for pubertal maturation to minimize the effect of possible measurement errors. In summary, we judged the DXA body composition and bone measures to be valid, and they are feasible and safe solutions to use in adolescents.

4.1.6 BMI, WC and FMI SDS as measures of adiposity

Several studies have shown that BMI has high specificity and low sensitivity in predicting excess body fat in children and adolescents [6, 60-62, 177]. Nevertheless, BMI is the most frequent and convenient measure of overweight and obesity used in epidemiological studies [6, 65]. In paper I, we used BMI both as the exposure and outcome measure; however, in paper II, we utilized the DXA-derived measures of fat mass and fat-free mass as outcomes and could therefore evaluate the accuracy of BMI as a measure of adiposity.

In both sexes, there were strong and significant associations between overweight and obesity at 16.5 years of age and higher FMI and android:gynoid FMR at 15-20 years of age (paper II, Table 2). Those with light overweight and especially those with more severe overweight/obesity had significantly and considerably higher odds of central overweight/obesity measured by WC and an FMI SDS ≥1.0 compared to those with normal weight. (paper II, Table 3). However, in individuals with the same BMI, the levels of FMI and FFMI varied, as shown in Figure 8.

Figure 8. Levels of FMI and FFMI by dichotomized BMI categories

Figure 8 shows the levels of FMI (kg/m^2) and FFMI (kg/m^2) within underweight (thin)/normal weight and overweight/obese girls and boys at 15-17 years of age. Red points indicate variation in FMI and FFMI in two individual girls and boys with the same BMI (kg/m^2). The Tromsø study: Fit Futures (n=907)

The diagnostic accuracy of the BMI classification used in this thesis [13] was evaluated by the calculation of sensitivity and specificity in our study population (n=907/625). The dichotomized BMI categories, the underweight/normal weight and overweight/obesity at age 15-17 and 18-20 years, were used as test criteria, and fat mass index SDS ≥ or <1.0 at the same ages were used as the outcome (here, used as the true/definitive test). The results are shown in Table 2.

Table 2. Sensitivity and specificity of BMI categories to predict fat mass index SDS ≥ or < 1.0 at 15-17 and 18-20 years of age for girls and boys

		15-17 years of age			18-20 years of age		
		Fat mass index SDS [b]					
GIRLS	BMI category [a]	≥1.0	<1.0	Total (n)	≥1.0	<1.0	Total (n)
	Overweight/obesity	76	16	92	63	10	73
	Under-/normal weight	7	340	347	10	257	267
	Total (n)	83	356	439	73	267	340
	Sensitivity [c]	76/(76+7) = 0.92			63/(63+10) = 0.86		
	Specificity [d]	340/(340+16) = 0.96			257/(257+10) = 0.96		
		15-17 years of age			**18-20 years of age**		
		Fat mass index SDS [b]					
BOYS	BMI category [a]	≥1.0	<1.0	Total (n)	≥1.0	<1.0	Total (n)
	Overweight/obesity	95	14	109	60	20	80
	Under-/normal weight	24	335	359	11	194	205
	Total (n)	119	349	468	71	214	285
	Sensitivity [c]	95/(95+24) = 0.80			60/(60+11) = 0.85		
	Specificity [d]	335/(335+14) = 0.96			194/(194+20) = 0.91		

[a] BMI categories according to IOTF age-and sex-specific cut-off values for children 2-18 years of age. Overweight/obesity corresponding to adult BMI ≥25.0, normal weight corresponding to adult BMI <25.0 [13]
[b] Fat mass index standard deviation score (SDS) according to UK reference data [64]
[c] Sensitivity = a/(a+c)
[d] Specificity = d/(b+d)

Both the sensitivity and specificity of the BMI categories were high. In girls, the sensitivity was 0.92 and 0.86 at ages 15-17 and 18-20 years, respectively, and the specificity was 0.96. The corresponding values for boys were; as follows: sensitivity was 0.80 and 0.85 and specificity was 0.96 and 0.91 at ages 15-17 and 18-20 years, respectively.

This finding indicates that the dichotomized BMI categories correctly identifies most adolescents who have excess fat mass (few false negatives) and also correctly identifies most adolescents who do not have excess fat mass (few false positives). However, it can of course be questioned whether an FMI SDS ≥1.0 is the correct cut-off to define excess fat mass or whether it is arbitrary or too low. The values over 1.0 SD are, however, also used as the definition of overweight also in a comparable study [78]. Furthermore, a clinically verified cut-off value to define adverse levels of adiposity in adolescents is yet to be established [69, 151, 178]. Comparisons of body composition measures should be made with normative data

developed from age- and gender-matched, genetically comparable populations obtained with comparable methods [74, 151]. Due to the lack of a DXA-derived body composition reference standard for Norwegian adolescents, the use of the British reference standard was a convenient option [64]. As shown in Table 1 in paper II, our study population was quite similar to the British reference population, with a mean FMI SDS of 0.23 and 0.06 at 15-17 years of age, and 0.22 and 0.02 at 18-20 years of age for girls and boys, respectively. However, some imprecision in the calculation of body composition SDS, and some misclassification in the dichotomized variable might have occurred.

Our judgement, in line with that of others [60, 61, 65, 177], is that BMI is a good proxy measure of adiposity at the group level. However, in an assessment of individuals, BMI alone should be used with caution. Individual levels of fat mass and fat-free mass may vary significantly within the BMI categories, as others have also shown [151, 179].

WC was measured twice, in according to standardized procedures, to minimize intra-observer variability. As reported in paper II, we found significant positive correlations between different measures of central overweight/obesity. WC was positively correlated with DXA-measured truncal fat mass with correlation coefficients ranging from of 0.77–0.83 in girls and 0.85–0.88 in boys. Equal correlation coefficients were seen for WC and android fat mass (data not shown), and were somewhat lower for android:gynoid FMR and truncal fat mass. A gender difference in central overweight/obesity was observed with more than twice as many girls as boys classified with central overweight/obesity. This may, at least partly, be related to accuracy of the reference [16] and this should be further studied. In another study, WC showed both high sensitivity and high specificity in measuring truncal fat mass in adolescents [180]. Unfortunately, the analyses from our Lunar Prodigy instrument did not provide separate data for visceral and subcutaneous fat mass, which is a newer and more sophisticated feature. Newer studies have shown a stronger link between visceral fat and metabolic and CVD risk than traditional methods [174, 181]. However, WC and DXA-measured android fat mass have shown fair agreement with DXA-measured visceral fat mass [181].

4.1.7 Potential misclassification based on BMI

The estimated prevalence of overweight and obesity may differ depending on the reference in use, especially in childhood [8, 19]. We consistently used the IOTF reference throughout this thesis, mainly due to its recommended and frequent use in studies [13]. This method allowed

us to compare the prevalence rates in our study with those in other studies from Norway and other countries [8, 19, 20, 22, 24-26, 118, 119, 182, 58]. For comparison, prevalence rates were calculated according to both the IOTF reference and the WHO Child Growth Standards and Growth reference for 5-19 years of age [10, 11, 13], which was presented in paper II, see supplemental Table S2. As shown in Table S2, the estimated prevalence of overweight/obesity at 6.0 and 16.5 years of age was somewhat lower according to the IOTF reference than to the WHO reference. At 2.5 years of age, the overweight/obesity prevalence estimates based on the IOTF reference were considerable higher than those based on the WHO reference. Girls: 9.1% vs. 2.5%, boys: 6.4% vs 3.2% according to IOTF and WHO references, respectively. These are all well-known differences between the references, both due to difference in construction and the use of different source populations [12, 19, 20, 108].

The predicted BMI values at the exact ages of 2.5, 6.0 and 16.5 years used in papers II and III were slightly but significantly (all, $p<0.05$) lower than the observed values, as shown in supplementary Table S4 in paper II and supplementary Table 1 in paper III. This result also affected the reported BMI categories and prevalence rates to some extent. Hence, the percentage of overweight/obesity varies slightly with the subgroups and methods used in the three different papers.

The use of a reference with high specificity, such as the IOTF reference, might underestimate the true prevalence of overweight/obesity from 6.0 years of age but also achieves few false positives [8]. There is always a balance between high sensitivity (risk of more false positives) and high specificity (risk of more false negatives), and some misclassification errors are inevitable [164, pp. 178-184]. Non-differential misclassification in dichotomous variables will generally attenuate the estimated associations [164, pp. 105-107, 163, p. 143]. Hence, the result of misclassification errors in this study is most likely that the associations between overweight/obesity at 6.0 and 16.5 years of age reported in this thesis are somewhat weaker and that associations between overweight/obesity at 2.5 years of age are somewhat stronger than those we would have observed if we had used another reference or if no misclassification errors were present.

Regardless of which reference is used to categorize participants into BMI categories, participants with the highest BMI will be in the highest BMI category, and participants with the lowest BMI will be classified as underweight [13, 19]. Where it was suitable, we used the BMI category of severe overweight/obesity (corresponding to an adult BMI ≥ 27 kg/m^2) to

compare those in the highest BMI category least prone to potential misclassification with those of normal weight and less severe overweight. In paper I, we also found that BMI used as a continuous variable showed the same pattern as analyses with BMI categories. In addition, analyses of growth in papers II and III supported the associations obtained with BMI categories. Overall, this approach justifies the interpretation of the results from analyses with BMI categories based on the IOTF reference.

4.1.8 Validity of covariates

Of the covariates measured in TFF1 used in this study, pubertal maturation and physical activity levels were based on self-reported data using an electronic questionnaire. Self-reported data are, in general, regarded as less accurate than measured data, but are often a practical choice in larger epidemiological studies. For sensitive information such as questions regarding pubertal status, an electronic questionnaire has advantages compared interviews or examinations since they are more anonymous [163, 183].

The Tanner stages of puberty assessed by health professionals, are regarded as the gold standard for pubertal assessment [184, 185], but not available for the fit Futures cohort. In girls, pubertal maturation was based on questions regarding menarche age, which is a validated question with acceptable accuracy [186]. In boys, pubertal maturation was based on the PDS, which has been shown to be fairly reliable although is a somewhat approximate estimate [152, 184]. In our study, pubertal maturation was used as a covariate, and, in line with others, we consider these self-reported data to be sufficiently accurate for this purpose [185, 187].

We used the questions of physical activity frequency measured through the HBSC questionnaire [154]. Both reliability and validity of the HBSC questionnaire has been tested [188], also in Norwegian adolescents [153]. The authors concluded that the instrument had acceptable reliability and validity [153, 188]. Although the possibility of misclassification errors cannot be ruled out, we consider the physical activity frequency categories to be an acceptable measure as a covariate.

4.1.9 Confounding and interaction

Confounding might be defined as confuse or mix together and refers to a distortion of the estimated association between an exposure and an outcome due to the presence of another

factor (or factors), which explains all or part of the observed association. Confounding factors are associated with both the exposure and outcome (a common cause) [136, p. 55, 164, pp. 93-96]. Unfortunately, neither the information on potential confounding factors known from other studies [2, 21, 57, 105, 106], such as the; mothers' BMI and weight gain during pregnancy, smoking habits, parents' education level and socio-economic status, nor the participants' physical activity levels, nutrition and other lifestyle factors in childhood were available from MBRN or the childhood health records. By an omission, birth order was not collected from MBRN. Hence, only a limited number of confounding factors were tested and included in the models. The inclusion of other potential confounding factors from birth and childhood might have improved our statistical models and most likely reduced the estimated associations to some extent.

There are two ways of handling potential confounding in statistical analyses: stratification or adjustment. Age, sex and height were considered the most likely confounding factors available in our study; hence, all analyses were stratified by sex. Birth weight was adjusted for GA. In paper I, age was included in the multivariable analyses. In papers II and III, we used the predicted values of the exposure at exact ages so that measurement age did not differ between the subjects (another method to adjust for values measured at different ages). In addition, birth length and height were tested in the models in different ways. From TFF1, more covariates were available. Based on relevant literature and findings from other Fit Futures studies [94], height, pubertal maturation, and physical activity were considered the most important confounding factors and were therefore included in the analyses of exposures at age 15-17 years to adjust for potential confounding. There is a balance between the comprehensive adjustment for several covariates and the risk of overadjustment bias with loss of power [189]. Thus, only covariates considered necessary have been included, but whether the models are too simplistic as a result of this choice is a point of discussion.

Interaction or effect modification may be defined as: *differences in the effect measure for one factor at different levels of another factor* [136, pp. 90 and 152]. This refers to both the underlying biological factors as well as a statistical interaction [136]. Potential interactions between sex and exposure variables were tested by including product terms in the main statistical models used in all papers in addition to presenting results stratified by sex. Due to the unmeasured physical activity data from childhood, it was not possible to test the potential

interaction between BMI and levels of physical activity. Testing this potential effect modifier would have elaborated our results.

4.1.10 Statistical modelling

There were several challenges in choosing the appropriate statistical models to analyse our longitudinal data. Analytical problems are recognized and debated in the field of life-course epidemiology [190].

First, missing data were handled with multiple imputation to minimize bias and retain an adequate sample size for each research question to keep precision at an acceptable level.

Second, adjustments for potential mediators were considered. Adjusting for potential mediators such as current or intermediate body size, e.g., BMI in childhood or adolescence, is controversial and is now, generally, not considered correct when analysing the foetal origin of the adult disease hypothesis [160, 189, 191, 192]. A mediator may be defined as:

> *"a variable that occurs in a causal pathway from a causal (independent) variable to an outcome (dependent) variable. It causes variation in the outcome variable and itself is caused to vary by the original causal variable. Such a variable will be associated with both the causal and the outcome variable"* [136, p. 152].

Adjusting for later body size when studying the effect of earlier body size might be seen as a measure of change in body size between the timepoints and an alternative hypothesis, that later growth is equally or more influential on the outcome, must be considered [191]. Adjusting for mediators, treating them as confounders, are considered an overadjustment and generally will bias results towards the null or even reverse the estimated effect [189, 192]. Directed acyclic graphs (DAGs) were used as a practical and visual aid in the discussion of choosing variables that should be included in the statistical models [163, pp. 186-209, 189]. In addition, unmeasured potential confounding and mediating factors discussed in section 4.1.9, e.g., physical activity levels in childhood, constituted an extra challenge. Alternative, more sophisticated statistical approaches to analyse direct and indirect effects of birth weight and later body size on outcome measures was therefore not an option [192]. Therefore, generally, no adjustment was made for mediators in the models since an unbiased estimate could not be assumed [189]. As an alternative approach, we modelled growth to assess the impact of later body size on the outcome of interest in papers II and III.

Modelling of growth is challenging since there are several different statistical models in use [118, 157, 158, 160, 190, 193]. We have used both a linear spline multilevel model in paper III and in addition, the more commonly used conditional growth model in paper II. Linear spline multilevel modelling [157] was used to predict length/height and weight at exact ages in childhood and estimate individual growth trajectories. This is a simplification of the actual growth trajectories. However, this is a particularly useful method to address challenges such as irregular measurement schedule, data from different sources, measurement errors, and missing values [157, 158]. The model estimates of growth rates in different age intervals can be used directly to explore associations between childhood growth and later outcomes [157], and this was done in paper III. In addition, a conditional growth model, which is a regression model with unexplained residuals, was used as a second step in the analysis of growth in paper II [160]. An advantage of this model is the use of a single model and this index of growth is statistically independent of body size at the start of each growth period and adjusts for both catch-up growth and regression to the mean [193]. The use of different growth models in this thesis might seem confusing. However, the two models are similar, and, in practice, they produced approximately identical estimated coefficients (results not shown). The interpretation of the results are the same in our study [158] and explores the influence of growing more than expected in different age intervals, given previous body size, upon the outcome [157, 158, 160]. The reasons for using two different models in papers II and III were mainly due to different traditions in the different disciplines, and hence different advice from co-authors and reviewers.

GEE and/or linear mixed models were used in the main statistical analyses in all three papers. These models are the preferred choice in analysing longitudinal data, as they take into account that the repeated measures are correlated. These models are assumed to be robust to missing data, as all available data are used in the analyses, and cases are not excluded due to missing data [159, pp. 214-221]. In addition, GEE analyses provide a population-averaged estimate, which generally obtains lower and valid estimates when the outcome is dichotomous [159, pp. 137-138].

Overall, we consider the choice of statistical approaches to have given valid and reliable estimated associations, not solely due to chance or bias.

4.1.11 Summary of internal validity

The longitudinal population-based design and overall high response rate indicates that the results obtained in this study are generalizable to the majority in the source population, although the risk of selection bias due to missing childhood data and drop-out at follow-up cannot be completely ruled out. High quality data from the Fit Future study combined with measured data from birth and childhood minimize the risk of information bias. However, the estimated prevalence rates of overweight and obesity in childhood might be somewhat imprecise. Although the statistical models could have been more comprehensive, we consider the associations reported to be valid and reliable estimates, and, overall, we regard this study to be valid.

4.2 External validity

External validity refers to what extent the results obtained in a study can be generalized to be valid in other populations or groups that did not participate in the study [136, p. 288].

Overall, we consider the results from this study to be fairly valid for the Norwegian adolescent population and for populations at the same age and with similar characteristics. As shown in paper II, the body composition measures in our study population were similar to those in the British reference population. However, some reservations must be made.

Some uncertainty is related to the estimated prevalence of overweight and obesity, especially at 18-20 years of age due to the lower participation rate in TFF2 than that in TFF1. Compared to other regions of Norway, the prevalence of overweight and obesity in our study population is somewhat higher at 15-17 and 18-20 years of age and might not be representative of the entire Norwegian adolescent population [22, 26, 182]. Compared to data from the Bergen Growth Study [79, 182], the mean BMI and WC in both girls and boys were considerably higher in our study cohort; however, compared to data from the Young-HUNT study, the mean BMI and WC were similar [58]. Hence, the age and sex-specific body composition reference data presented in paper II may not be representative of the entire Norwegian adolescent population. To the best of our knowledge, this is the first study to present DXA-measured body composition reference data for Norwegian adolescents, and these data should be further compared with other Norwegian youth populations before extrapolation.

Furthermore, the participants in the Fit Futures cohort were born in a period during which a higher average birth weight was observed in Norway and a birth cohort effect cannot be excluded [164, pp. 314-319]. The prevalence rates of overweight/obesity reported in our study are lower compared to data from the USA and southern European countries [19, 23]. Since our study population was mainly of white ethnicity, the data may not be representative of populations of other ethnicities.

4.3 Discussion of results

Epidemiology is commonly defined as the study of the distribution and determinants of health-related events, states, or disease frequency in specified human populations as well as the application of this knowledge to control the relevant health problems [136, p. 95, 163, p. 32, 164, p. 3]. There is an ongoing debate regarding to what extent causal inferences can be drawn from epidemiological studies [163, pp. 5-31]. Disease variation can be described and causes may be explored, although difficult due to the complex natural history of most health problems and diseases. Furthermore, analysis of health problems and disease variation might generate hypotheses on causes and environmental risk factors and knowledge from epidemiological studies are important for planning prevention efforts and resources needed [164, pp. 16-17 and 157-160]. The results presented in this thesis are mainly observed patterns of associations, and no conclusions on causality can be drawn.

The common exposures, birth weight, childhood BMI, and growth, are key links among the three papers presented in this thesis. The discussion will therefore focus on the observed associations of these exposures with the outcomes in adolescence and are organized according to the aims presented in section 1.7. The aim related to gender differences will be discussed under each of the other four aims.

4.3.1 Tracking overweight and obesity

In paper I, we studied the tracking of high birth weight and BMI in childhood until adolescence. We found a significant but modest association between birth weight and overweight/obesity at 15-20 years of age. In a review by Brisbois et al. [105], birth weight was reported to be extensively studied (n=55). Both low and high birth weight showed mixed results with no clear conclusion that birth weight was an early marker of adult (18-50 years of age) obesity. Two other reviews found consistent associations between higher birth weight and overweight later in childhood (6 months–18 years of age) [106], (2–16 years of age)

[123]. In two studies from Norway that included children born mainly in the years 2003-2004, a stronger degree of tracking of body size was observed from birth until 7-8 years of age [118, 119]. Since tracking coefficients are influenced by time between measurements [45], the lower tracking coefficients over longer timespans, as was observed in our study, could be an explanation for the differences observed. However, a birth cohort effect cannot be ruled out. A recent published large cohort study showed that the majority of children with high birth weight tended to revert to normal weight in infancy and maintained a normal weight until eight years of age [194].

Among those classified as overweight/obese at 15-17 years of age, the mean birth weight and mean BMI were higher during childhood compared to those of normal weight at 15-17 years of age (paper I, Table 3). The tracking of BMI and overweight from childhood to adolescence was moderate. This finding is in line with the results reported in previous reviews, which also concluded that the tracking of childhood weight status into adolescence or adulthood overall was moderate [6, 43].

The modest degree of tracking of overweight/obesity from birth and 2.5 years of age is positive. The highest tracking coefficients were seen at 5-7 years of age. Furthermore, children with obesity or more severe overweight/obesity, at 2-4 and 5-7 years of age had considerably higher odds of later overweight/obesity compared to those with light overweight or their normal weight peers. This finding is in line with a previous review [105] and a large simulation study that predicted a higher relative risk of adult obesity with increasing BMI and age in childhood [195]. Hence, there are clear indications that the tracking of obesity is consistent from childhood until adolescence [23, 105].

Furthermore, we observed that the prevalence of overweight/obesity steadily increased with age, with the highest prevalence rates observed at 18-20 years of age. An increase in the prevalence of overweight/obesity with age has been seen in other cohorts as well [23, 196, 197], including other Norwegian cohorts [198, 199]. This finding is of concern since tracking, especially of obesity, from adolescence into adulthood has been reported to be more substantial [6, 43]. The main concern for future health is related to the consistently reported increased risk of adult disease for those with a stable and high BMI from childhood to adulthood [34, 37, 39, 46, 47, 200].

4.3.2 Associations with birth weight

The mean birth weight and the proportion with high birth weight were somewhat higher (4.5%) in our study population than those in national data from 1992-1994 birth records (3.7-4.2%) [120].

Although birth weight was a modest indicator of later overweight/obesity, it was significantly, however modestly, linked to higher FFMI in both sexes, and equally linked to higher FMI only in girls (paper II). The association between birth weight and fat-free mass later in life is consistent with findings from several other studies [63, 107-111, 113, 114, 201]. In addition, in both sexes, a modest, but significantly positive association was seen between birth weight and total body BMC at 15-20 years of age (paper III). This result is in line with consistent findings of a link between higher birth weight and higher bone mass in adults [101, 115, 116], supporting the intrauterine programming of the skeletal [87]. However, no clear association was seen with aBMD. Also this finding in line with others [101, 115, 117].

A 1-SD (590 g) increase in birth weight was associated with somewhat higher odds of central overweight/obesity defined by WC and an FMI ≥1.0 at 15-20 years of age (paper II). Also this most clearly observed in girls. Similar estimated ORs were seen for birth weight and overweight/obesity defined by BMI in paper I. Analyses with the ponderal index as exposure confirmed the findings (papers I and II). Although birth weight has been consistently associated with overweight/obesity at different ages later in childhood [106, 123], associations between higher birth weight and fat mass later in life have been less consistent, and most studies have reported weak or no significant relationship [63, 72, 108, 110, 111, 113, 114, 201].

The gender difference observed in this thesis might be by chance. No statistically significant interaction between sex and birth weight was observed when a cross-product term was included in the statistical models. Stronger associations between birth weight and adiposity measures in girls have also been found by others [107, 109], while the opposite was seen in a Swedish study [114]. Overall, we did not find strong indications that a higher birth weight was related to adiposity in adolescence. Especially in boys, the observed associations might, to a larger degree, reflect a larger body size and both higher fat-free and fat mass but not necessarily adiposity.

Furthermore, low birth weight and being born small for GA have been linked to later obesity, especially central obesity [63, 72, 112, 202, 203]. However, we did not find any indications that low birth weight was associated with adverse levels of fat mass or central overweight/obesity. Being born small for GA was associated with lower odds of overweight/obesity at 15-20 years of age (paper I) and lower odds of central overweight/obesity and an FMI ≥1.0 (paper II) compared to those born appropriate for GA. Hence, we could not confirm previous findings of a higher risk of central obesity related to low birth weight. This was a somewhat surprising finding, and our results should be interpreted with caution. The proportion born small for GA was low, 9.8-10.8% and 11.1-12.6% in boys and girls, respectively, depending on the study population used in each paper. However, others have claimed that earlier findings of a relation between small for GA births and later adiposity may be due to overadjustment for causal mediators such as current body size and reported similar results to ours [192]. Others have also shown that postnatal weight gain was more influential than low birth weight on later total body and abdominal fat mass [110]. We did not study catch-up growth among those born small for GA specifically, as this was outside the scope of this thesis, hence we cannot elaborate this finding. A large Nordic cohort study with children born from 1924–1976 has linked both low birth weight and increased BMI at age 7 years to later CVD risk in adulthood. No increased CVD risk was found for children with a birth weight above 4.0 kg [204]. This study support the hypothesis of low birth weight as an independent risk factor for adult CVD but also shows that later growth and body size in childhood is influential on later CVD [104, 133, 134].

Our findings, in line with several others, support consistent evidence for a link between foetal growth and fat-free mass later in life, but evidence for fat mass and central obesity was weaker. In addition, a link between birth weight and later bone mass was confirmed. Since body composition as well as bone mass, to a large extent, are explained by genetic factors, this may not be surprising [51, 52, 84, 87]. In a review of twin studies, the heritability of BMI was found to be high, from 60-80% across ages, while the influence of varying environmental factors increased with age, up to 40% [52]. In addition, the relatively high mean birth weight in this cohort generally supports sufficient nutrition in utero to optimize growth and development. To test if later growth and body size was more influential than birth weight, we analysed childhood growth.

4.3.3 Associations with childhood growth

In paper II, we found that childhood BMI gain in each age interval from birth and up to 16.5 years of age, conditioned on earlier body size, was significantly associated with higher FMI SDS, FFMI SDS as well as higher android:gynoid FMR at 15-20 years of age. The magnitude of the associations increased with age and greater BMI gain between ages 6.0-16.5 years of age was most strongly related to higher fat mass in adolescence.

This finding indicates that centile crossing is more "obesogenic" at later ages, which is a finding that is supported by several other studies [108, 109, 121, 125-127, 195]. We observed strong associations between greater BMI gain between 6.0 and 16.5 years of age and higher android:gynoid FMR at 15-20 years of age. This is in concordance with findings from a Swedish study [126], which showed that the amount of subcutaneous and, especially, the visceral adipose tissue in young adult men was associated with increasing BMI during adolescence. In contrast, a rapid weight gain in early infancy and up to 2 years of age has consistently been linked to overweight/obesity later in childhood or adolescence [105, 106, 123, 124]. However, fewer studies have linked childhood growth to measures of body composition later in life. In our study, greater BMI gain in early childhood, especially from birth to 2.5 years of age, was positively associated with both higher FMI and FFMI at 15-20 years of age and the magnitude of the associations were similar. This is in line with others that have observed similar or stronger associations of infant growth with later lean mass than with fat mass [63, 109, 110, 125, 129].

A question of interest was if there was a critical age interval that was more influential on later body size than others. Our growth models are independent of previous growth and body size at the start of each period and the standardized coefficients of FMI and FFMI SDS may be compared [158, 193]. We observed that associations with fat mass and central obesity measures at 15-20 years became stronger for each age interval, so a clear critical age was not observed. However, a higher BMI gain than expected between 6.0-16.5 years, given the body size at 6.0 years of age was most predictive of a higher FMI and central obesity. Others have found that BMI changes between 2 and 6 years of age were most strongly associated with fat mass at age 15 [127] or overweight in young adulthood [205]. Based on large cohort studies, greater BMI gain later in childhood, in different age intervals from 2 years of age and onwards, as well as in adolescence, has been linked to an increased risk of CVD [131, 206, 207] and type 2 diabetes [34] in adulthood. Early identification of children at risk, especially

those with a rapid increase in BMI before the age of 5-7, may therefore be possible and of importance. However, later childhood and adolescence emerge as an age period where adiposity develops and is therefore of equal importance.

A more novel finding in our study was that greater BMI gain in childhood and adolescence neither indicated a continued increase in FMI between ages 15-17 and 18-20 years, nor did we see a continued increase in FFMI between the same ages. This finding might indicate that body composition measures are stabilizing in the transition to young adulthood in our study population. However, these analyses were performed in a subgroup of the study population with complete measurements from both TFF1 and TFF2, and we cannot rule out the possibility of selection bias. Thus, this finding needs to be confirmed in further studies.

In paper III, we observed that higher rates of length/height growth from birth up to 6.0 years of age were positively associated with bone mass accretion at 15-20 years of age, with a high length growth rate from birth to 2.5 years of age, showing the strongest associations with both total hip and total body BMC. Weight gain in each age interval was positively associated with all bone measures at 15-20 years of age. The magnitude of the standardized coefficients increased with age and a high rate of weight gain from 6.0 to 16.5 years of age showed the strongest positive associations with both bone mass and bone density at age 15-20 years. In contrast, a high rate of height growth from 6.0 to 16.5 years of age displayed weaker or no associations with bone mass and negative associations with bone density at age 15-20 years. Similar findings were seen for both sexes. The same pattern was seen by Kuh et al., who have studied bone strength in males and females at 60-64 years of age. Height velocity in early childhood showed stronger associations with aBMD than height velocity between 7-15 years, and the impact of weight velocity increased with age [208].

These findings correspond well with our findings that early childhood growth was more strongly related to fat-free mass in adolescence. Notice that fat-free mass is constituted of mostly lean mass but also of bone mass. Furthermore, a greater BMI as well as greater weight gain between the ages 6.0-16.5 years was positively linked to both fat-free mass, fat mass and bone mass. We know from other studies that both lean and fat mass are of importance for bone accretion, with lean mass being the most important contributor [102, 209], also shown in another study of the Fit Future cohort [210].

How these different growth trajectories may affect final achievement of peak bone mass is

not yet clear. There are gender differences in the timing of skeletal growth which can be explained by pubertal development status, and probably not all, especially the boys in our study population, have reached final height. However, we know from another study of the Fit Futures cohort that there is a high degree of tracking of BMC, aBMD and height between TFF1 and TFF2 and that bone acquisition is levelling off. In particular, the girls may have reached an aBMD plateau at femoral sites [211]. In a population of young Swedes, Alwis et al. showed that peak hip BMC and aBMD was reached by 18 years of age in both sexes [76]. In addition, others have shown that there is a high degree of tracking of bone mass levels during childhood and adolescence, increasing with age [85, 212, 213]. This indicates that our findings to some degree may reflect adult bone levels [211]. The finding that a higher rate of height growth from 6.0 to 16.5 years of age revealed somewhat higher levels of BMC, but negative aBMD is not unexpected since height gain, especially during pubertal maturation, both influences BMC and bone size (bone area) and may, as a consequence, give lower aBMD if BMC does not increase proportionally more than bone area [84]. It is well known that linear growth peaks earlier than bone mass acquisition; however, this phase of bone remodeling and reduced bone strength is known to be transitory [73, 84, 214].

Compared to birth weight, height and weight gain in childhood showed stronger associations with both bone mass and bone density in adolescence. Others have also concluded that postnatal growth and weight gain are the main determinants of bone mass in childhood [215], as well as bone density in young adulthood [117].

How different patterns of childhood growth will affect future fracture risk, which is the clinical outcome of interest, remains unknown. Mikkola et al., who studied hip fractures in old age that were associated with growth in individuals born between 1934-44, found increased hip fracture risk in men, but not in women, related to increased height growth at 2-7 years of age and BMI gain between 7-11 years of age [216]. We did not observe a negative effect on BMC and aBMD in adolescence related to growth in these age groups in our study population. One can therefore speculate if this might be related to different nutritional and environmental conditions in early life between different birth cohorts.

The use of different metrics of growth and adiposity outcomes and the study of different age intervals make comparisons across studies somewhat challenging [193]. Overall, our findings coincide with the findings of others. Compared to birth weight, growth in early life were indeed influential of later body composition and bone mass and density in adolescence. Since

we have limited data from the childhood period it is not possible for us to elaborate how different early life nutritional factors, physical activity levels and other environmental factors known to affect childhood growth [2, 4, 85], contributes to our findings.

4.3.4 Associations with BMI categories in childhood

To complement the picture, we also explored how overweight/obesity as well as underweight was related to body composition and bone measures in adolescence. Our results in papers II and III related to BMI categories were largely in agreement with those found by analyses of growth. Compared to normal weight, overweight/obesity at each age were consistently associated with higher FMI and FFMI, central overweight/obesity as well as bone mass at 15-20 years of age. In girls, the magnitude of the association between overweight/obesity at 2.5 years of age and fat-free mass and fat mass was equal. In boys, overweight/obesity at 2.5 years of age was more strongly related to higher fat-free mass than fat mass. At later ages, overweight/obesity was more strongly related to higher fat mass than fat-free mass.

Similar to centile crossing, overweight/obesity seems to be more "obesogenic" at later ages. This outcome corresponds well with our finding of a larger degree of tracking of overweight/obesity from 5-7 years of age than earlier ages, and is in line with findings by others [195, 217]. In addition, more severe overweight and obesity (corresponding to an adult BMI ≥27) were more strongly associated with higher FMI in adolescence than light overweight and normal weight. Hence, a BMI close to the cut-off values for overweight, require caution, especially in younger children, since the level of FMI and FFMI may vary within the same BMI. See also the discussion in section 4.1.6 about the accuracy of BMI. This finding is of clinical relevance for health care professionals working with children and adolescents. To rely on BMI alone to identify young children at risk for overweight/obesity might therefore not be suitable. Considering that several factors including dietary and physical activity habits as well as genetic and parental factors play a role in the development of overweight/obesity [2, 21, 22, 49, 57, 58, 106, 217], these factors should be taken into account in addition to BMI. Supplemental measures of overweight/obesity may also be considered, such as WC measurements. Although children at risk may be identified in early childhood, later childhood and adolescence emerge as an important period for development of overweight/obesity. Our data suggest that these periods are of equal importance as target ages for preventive efforts. As several studies have linked overweight/obesity in childhood with later adult disease risk, preventive efforts seems justified [29, 31-33, 37-39, 204]. As

Bjerregaard et al. concluded, overweight at 7 years of age was associated with an increased risk of type 2 diabetes only if it persisted until puberty or later ages [34]. As Figure 5 [2] illustrates, the plasticity for introducing effective interventions are largest in childhood and adolescence.

We also observed that overweight/obesity was associated with higher BMC and aBMD in adolescence. Compared to normal weight, overweight/obesity at 6.0 and 16.5 years of age revealed between 0.5-1.1 higher z-scores for total hip BMC and aBMD at 15-20 years of age. The corresponding coefficients for total body were somewhat stronger. This seems to be a positive finding, since a 10% increase in peak aBMD is estimated to delay the development of osteoporosis in women by 13 years [218]. We could therefore not conclude that overweight/obesity in childhood was negative for bone mass accretion. However, we found indications of a non-linear relationship. The effect of increasing BMI at 16.5 years of age on both total hip and total body BMC and aBMD was levelling off when BMI exceeded 30 kg/m^2 (paper III, Supplemental Figures 1 and 2). The few obese adolescents in our study population limit our ability to draw firm conclusions.

The relationship between overweight/obesity and bone mass and bone density are not settled, with both positive [96, 102, 219] and negative reports [97, 98]. In a recent review reporting consistent evidence for higher bone mineral density in overweight and obese children, longitudinal studies on the long-term impact were requested [96]. Our longitudinal study contributes to increased understanding of this topic. Some have shown an increased risk of fracture among overweight children [103, 100]. Others have pointed to the effect of a higher weight loading that might be site specific, with a larger effect in weight bearing sites such as the hip and spine, as this supports the notion of adaptation to mechanical loading [96, 98, 102, 220]. Although our findings revealed somewhat larger effects on total body, than on total hip, this seems plausible. Higher total body bone density levels in overweight/obese children are also reported by several others [96]. We did not evaluate aBMD in the distal radius, which would have been relevant since overweight/obesity is linked to increased risk of forearm fractures [98, 100]. However, other factors might contribute to the increased fracture risk, such as greater forces involved in falls due to heavier weight [98].

Compared to normal weight, underweight in childhood and adolescence was consistently associated with lower levels of BMC and aBMD as well as lower fat-free mass at 15-20 years of age (data on body composition from childhood not shown). In a study of Finnish

children and adolescents 7-19 years of age, both high and low levels of fat mass were associated with lower levels of bone strength measured by pQCT and DXA [221]. The low levels of bone mass and bone density observed in underweight children and adolescents, combined with the reported high degree of tracking of bone mass [211], this is a problem of clinical importance. In Norway and Western societies, under nutrition is rare and a concern belonging to the past; however, malnutrition could still be a problem which needs attention [2]. From a global perspective, there are still more children who are moderate to severe underweight than obese [17]. In our study population, the prevalence of underweight was less than 9% in adolescence, somewhat higher in childhood, and higher in boys than girls, according to the IOTF reference. Lean mass is consistently reported to be of high importance for bone mass accrual but also fat mass plays a role [98, 102, 209, 220, 221]. The reason for concern is that previous studies have shown an association between underweight in childhood and increased risk of hip fracture later in life [130, 132]. In addition, both high body fat and low fat-free mass have been shown to be independent predictors of all-cause mortality in adults [222]. Our findings support that early life factors, such as BMI, are of importance to achieve a high peak bone mass. Hence, maintenance of a healthy weight and adequate levels of physical activity to build and maintain muscle mass must be considered a well-documented advice to promote bone health in young people [84, 85].

As previously discussed in section 4.1.5, a limitation with the DXA technique is the possibility of overestimating aBMD in larger bones and hence underestimating aBMD in smaller bones [92, 91, 175]. Part of the effect might also be related to maturity. Overweight/obese children tend to enter puberty earlier than normal weight and underweight children, and peak bone mass accrual may occur earlier [98, 103]. Hence, part of the observed larger aBMD values related to growth and overweight/obesity can be explained by these factors. However, analyses were adjusted for concurrent height and pubertal maturation, and it seems unlikely that the observed strong and significant associations solely are related to size artefacts and earlier maturation. A consistent pattern with higher levels of BMC supports the findings for aBMD. Thus, we consider the patterns observed as valid and reliable.

5 Conclusions

In summary, our studies demonstrated a modest positive association between birth weight and overweight/obesity at 15-20 years. In both sexes, birth weight was most clearly linked to fat-free mass; an association with bone mass was also confirmed. However, compared to birth weight, a high childhood BMI and childhood growth rates were more influential on all outcome measures in adolescence.

The tracking of BMI from 2-4 and 5-7 years until adolescence was moderate, with stronger associations observed at the latter age and for more severe overweight and obesity. This result was confirmed in the study of body composition.

Greater BMI gain between 6.0 and 16.5 years of age were the strongest predictor of a high fat mass index and central overweight/obesity in adolescence. Hence, greater BMI gain was more "obesogenic" at later ages.

Our findings did not indicate that overweight/obesity in childhood negatively affected bone mass accretion at total hip and total body; however, underweight was consistently associated with lower bone mass and bone density.

The observed associations therefore confirmed our initial hypothesis, that early life factors are associated with later health-related outcomes.

The early identification of children at risk of adverse levels of adiposity is therefore possible. However, all children at risk were not identified before 5-7 years of age, and, since later childhood and adolescence emerge as an important period for development of overweight/obesity, we conclude that these ages are of equal importance as target ages for preventive efforts.

Preventive efforts should focus on a healthy weight development and promote physical activity both to prevent overweight/obesity and for an optimal bone accretion.

6 Further perspectives

This thesis focused on weight-related issues in early life and the relation with health outcomes in adolescence: overweight/obesity, body composition and bone health. This, fairly large, population-based study contribute updated knowledge on public health issues that are relevant also in Norway. It is our hope that this knowledge may be of help for health authorities and health care workers who are planning preventive interventions for the future.

6.1 Possible implications for public health

Childhood and adolescence represent a window of opportunity for lifestyle interventions to change the path, as shown in Figure 5 [2]. The findings from our study support that both early life and later childhood and adolescence, are of importance for later development of overweight/obesity as well as bone health and hence are important phases for intervention and prevention efforts. This is in line with the latest recommendations from WHO [2] and some preventive initiatives addressing these age groups are described in the White Papers related to public health, from the Norwegian government [137, 223].

The modest degree of tracking of overweight/obesity from birth and 2.5 years of age is positive. A "wait and see" approach, as suggested also by others [129, 194], seems sensible for overweight infants and toddlers. Later childhood and adolescence emerge as important age periods and preventive efforts should focus to a larger degree on these age groups.

Not all children at risk of later overweight/obesity may be identified in early childhood or by BMI alone. Considering that several parental and environmental factors play a role in the development of overweight/obesity, a family approach in targeted prevention efforts is recommended. Preventive efforts should also focus on all children and environmental factors in the society so that not only individual-based life-style choices are considered but also the environment that such choices are made in. This approach is especially important to avoid "Victim-blaming" of young people in the best of intentions [224].

Both overweight and underweight may have adverse health effects. Sufficient maternal nutrition, maintenance of a healthy weight and physical activity levels through childhood and adolescence are important for maximizing the peak bone mass [84, 85].

It is of importance to highlight another part of the picture; the majority of the adolescents in this study population had a birth weight within the normal range and were of normal weight

in childhood and maintained a normal weight during adolescence. This contributes to an overall positive perspective for future health.

6.2 Further perspectives for research

The findings presented in this thesis may provide a basis for further studies.

Whether our observations of childhood growth patterns associated with adverse body composition measures in adolescence will lead to a disease remains to be seen. Longitudinal studies on growth, body composition and adult disease risk are currently sparse, and follow-up studies are warranted [6, 16, 32, 33, 63].

The ideal body composition for young adults related to low disease risk, is not quite clear. The ideal balance between fat mass and muscle mass is yet to be established [69, 151, 178]. For instance, sarcopenic obesity is a concern in the elderly, but there is no consensus for young people [178]. The descriptive age-and sex-specific body composition data published in our study should be further compared with other Norwegian youth populations.

Follow-up surveys of the Fit Future cohort are highly recommended, and a wave three is under planning. It would be of interest to see if our findings reported in this thesis could be confirmed over a longer timespan into adulthood. Further follow-up studies will provide opportunities to investigate how anthropometric and lifestyle factors in early life and adolescence may affect peak bone mass, body composition and disease risk in adult life. Firm knowledge of associations with “hard endpoints” may support preventive strategies which also includes promotion of a healthier environment.

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Paper I

BMJ Open

The relation between birthweight, childhood body mass index, and overweight and obesity in late adolescence: a longitudinal cohort study from Norway, The Tromsø Study, Fit Futures

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ABSTRACT

Objectives Childhood overweight/obesity is associated with later overweight/obesity. However, the association between birth weight and later overweight/obesity has not been established. The aim of this study was to investigate the relation between both birth weight and childhood body mass index (BMI), and adolescent overweight/obesity in a Norwegian population.

Methods The Tromsø Study – Fit Futures is a population-based cohort study conducted in 2010–2011 and 2012–2013 in Tromsø, Norway. A representative sample of 961 adolescents participated. Longitudinal anthropometric data were obtained from the Medical Birth Registry of Norway, childhood health records at 2–4 and 5–7 years of age, and repeated measurements at 15–18 and 18–20 years of age. Outcome was defined as normal weight (adult BMI <25 kg/m^2) or overweight/obese (adult BMI ≥25 kg/m^2) at 15–20 years of age according to international age- and sex-specific cut-off values for children. Associations were investigated using generalised estimating equations.

Results In adjusted analyses, a 1-SD (586 g) higher birth weight was associated with a higher OR for overweight/obesity at 15–20 years of age (OR 1.25, 95% CI 1.06 to 1.48). Childhood BMI was also associated with overweight/obesity at 15–20 years of age: a 1-SD (1.35 kg/m^2) increase in BMI at age 2–4 years rendered an OR of 1.66 (95% CI 1.40 to 1.96); a 1-SD (1.83 kg/m^2) increase in BMI at age 5–7 years rendered an OR of 3.23 (95% CI 2.56 to 4.07). When compared with normal-weight children, those with severe overweight/obesity in childhood (adult BMI ≥27 kg/m^2) showed stronger associations with overweight/obesity at 15–20 years of age: OR 3.01 (95% CI 1.47 to 6.18) and OR 11.51 (95% CI 6.63 to 19.99) at ages 2–4 and 5–7, respectively.

Conclusion Associations between birth weight and overweight/obesity at 15–20 years of age were modest, whereas the influence of BMI at 2–4 and 5–7 years on overweight/obesity at 15–20 years was moderate to strong.

Strengths and limitations of this study

- The main strengths of this study are its population-based design and access to longitudinal data from birth (1992–1994 cohort) to 18–20 years of age.
- The high attendance rate and representative sample from a Norwegian adolescent population minimise selection bias.
- Data from the national Medical Birth Registry of Norway and objectively measured height and weight were used to calculate body mass index at all ages, reducing the risk of information bias.
- Missing data from childhood measurements were handled with a multiple imputation technique.
- A limitation of this study is the lack of information on potential confounding factors such as parental and lifestyle factors at birth and childhood.

INTRODUCTION

The increasing prevalence of overweight/obesity among children worldwide is a major health concern due to several related immediate and long-term health problems.[1–7] A moderate degree of tracking (maintenance of certain risk factors over time) has been reported from childhood to adolescence and into adulthood, indicating that individuals experience only small changes in weight class positions throughout their life.[6 8 9] However, the question remains whether birth weight is a predictor of later overweight/obesity. In a review by Brisbois et al[10], birth weight did not emerge as an early marker for adult overweight/obesity, but a recent review reported consistent associations between high birth weight and overweight later in childhood.[11] Data from Norway also revealed strong associations between birth

weight and overweight/ obesity at 7–8 years of age.[12 13] From a health perspective, it is of interest to investigate whether high birth weight also tracks into adolescence/ early adulthood.

Lately, the focus of this investigation has shifted to early-life factors, especially genetic factors that influence obesity and later health problems.[14–16] Information on the degree of tracking of high birth weight and body mass index (BMI) during early childhood is important for health authorities and healthcare workers who are planning preventive interventions to halt the overweight epidemic. Effective treatment of childhood obesity has proven to be very challenging[17]; therefore preventive efforts are of major importance. However, the appropriate age at which to initiate such efforts is still a matter of discussion.[1 14]

To answer these questions, we aimed to explore the associations between both birth weight and childhood BMI and overweight/ obesity in adolescence in a population-based cohort of Norwegian adolescents born in 1992–1994, a period with high mean birth weight in Norway.[18]

METHODS

Fit Futures is an expansion of The Tromsø Study, a population-based study from Northern Norway with repeated health surveys among adults. All first-year students in all upper-secondary schools in the municipalities of Tromsø and Balsfjord in 2010–2011 (n=1117) were invited to Fit Futures 1 (FF1). Of these invited students 1038 (92.9%) attended. Detailed information on FF1 and its youth cohort has already been presented.[19 20] A follow-up study, Fit Futures 2 (FF2), was conducted 2 years later during 2012–2013, and re-invited all participants from FF1. The present study consists of the 961 participants (492 boys and 469 girls) in FF1 who were aged <18 years at FF1 (born 1992–1994). Among these, 659 had anthropometric measurements available at 18–20 years of age in FF2.

Longitudinal anthropometric data were obtained through linkage to the Medical Birth Registry of Norway (MBRN) and childhood health records. Each student's unique personal identification number was used to link to the MBRN, from which information on birth weight and length, gestational age, and other variables related to birth were obtained. Height, weight, age, and date of measurements at two time points were collected from childhood health records. In Norway, regular health controls by public health nurses, including measurement of height and weight, are offered for all children in accordance with national preventive health programme guidelines. Most of our participants had their height and weight measured at 2 and 6 years of age. If data were missing for those exact ages or there were supplementary measurements, the measurement closest to the 2- and 6-year birthday was recorded. The exact age of the participants at the time measurements were taken varied slightly; therefore the age groups are reported as 2–4 (mean age 2.6 years) and 5–7 years of age (mean age 6.0 years).

A total of 411 included participants (43%) had one or more variables missing from the MBRN and/ or childhood health records (5% missing birth weight, 29% and 23% missing height/ weight at 2–4 and 5–7 years of age, respectively). Reasons for missing the childhood measurements were change of residency and measurements outside the age limits. Three hundred and two (31%) participants had missing data at FF2. A flow chart shows the study population and exclusions/ missing information (figure 1).

The Regional Committee for Medical and Health Research Ethics, North Norway (REK nord) approved FF1, FF2 and the present study (Reference number: 2014/ 1397/ REK nord). All students and parents/ guardians of students <16 years of age gave written informed consent.

Data/measurements

Trained study nurses performed anthropometric measurements in FF1 and FF2, following standardised procedures. Participants wore light clothing and no footwear. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, on an automatic electronic scale/ stadiometer (Jenix DS 102 stadiometer, Dong Sahn Jenix, Seoul, Korea) at FF1 (15–17 years of age; mean age 16.6 years) and FF2 (18–20 years of age; mean age 18.6 years).

Height and weight were used to calculate BMI (weight/ height^2; kg/ m^2) at 2–4, 5–7, 15–17 and 18–20 years of age and participants were classified into weight classes: underweight (adult BMI <18.5 kg/ m^2), normal weight (adult BMI ≥18.5 to <25 kg/ m^2), overweight (adult BMI ≥25 to <30 kg/ m^2), and obese (adult BMI ≥30 kg/ m^2). BMI reference values for every half-year and the International Obesity Taskforce (IOTF) age- and sex-specific cut-off values were used for children 2–18 years of age.[21] The WHO index for adults was used at age >18 years.[22] Due to the small proportion of obesity at 2–4 and 5–7 years of age participants were also classified into the following weight classes: normal weight, light overweight (adult BMI ≥25 to <27 kg/ m^2), and severe overweight/ obesity (adult BMI ≥27 kg/ m^2). The childhood BMI variables were used as predictors in the analyses.

When used as an outcome, weight classes at 15–17 and 18–20 years of age were dichotomised as normal weight (adult BMI <25 kg/ m^2) or overweight/ obesity (adult BMI ≥25 kg/ m^2).

Birth weight was divided into low (<2500 g), normal (≥2500 to <4500 g) and high birth weight (≥4500 g) according to the WHO definition.[18] The ponderal index (PI)—birth weight (kg) divided by the cube of birth length (m) (kg/ m^3)—was divided into tertiles. Age- and sex-specific weight and BMI SD scores (SDS) were calculated using LMS coefficients corresponding to the Norwegian growth reference.[23] Growth status at birth was categorised as small for gestational age (<10th

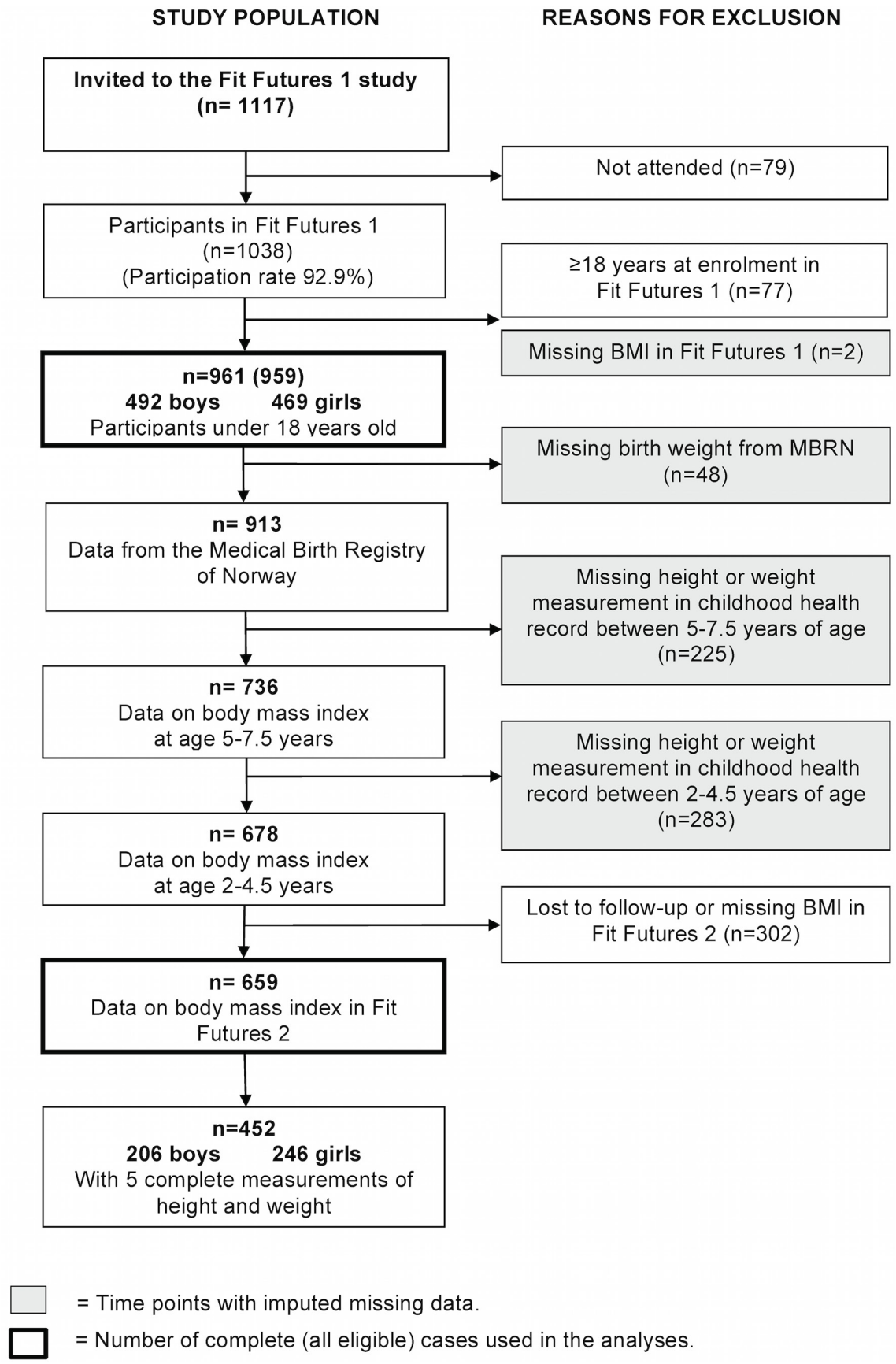

Figure 1 Flow chart of the study population, The Tromsø Study, Fit Futures 2010–2011 and 2012–2013. BMI, body mass index; MBRN, Medical Birth Registry of Norway.

percentile), appropriate for gestational age, and large for gestational age (>90th percentile) based on birth weight and gestational age and according to a national reference standard of births in 1987–1998.[24]

Girls were categorised into three stages of pubertal maturation: early (<12.5 years), intermediate (12.5–13.9 years), and late (≥14.0 years), based on age at menarche specified in self-administered questionnaires. Pubertal maturation in boys was classified as barely started, underway, and completed based on a validated self-reported measure.[25]

Statistics

Characteristics of the study population are presented as means and SD or numbers and percentages, by sex and weight class at 15–17 years of age. Differences between groups were assessed by t-test for continuous variables and by the χ^2 test for categorical variables. Associations between BMI at different ages were assessed with Spearman's rank correlations.

Tracking of birth weight or childhood BMI and weight class into adolescence was estimated as odds ratios (ORs) for being overweight/ obese in adolescence (15–17 and 18–20 years of age, as a combined endpoint). Generalised estimating equations (GEE) were used with a logit link function and an unstructured correlation matrix in crude and multivariable models. Predictors were birth weight (per 1-SD increase), birth weight SDS, PI in tertiles, BMI (per 1-SD increase), BMI SDS and weight class at 2–4 and 5–7 years of age. Covariates included in the multivariable models were gestational age/ age, maternal age, and sex. All models were run in the total cohort and by sex. Covariates tested but not included in the final models were: multiple births, caesarean section, maternal disease or diabetes, time between measurements, and participation in FF2. Potential interaction between sex and birth weight or childhood BMI was assessed by including cross-product terms in the models. Pubertal maturation was tested as a potential mediator. However, as it did not affect the coefficients and interaction terms were not significant, pubertal maturation was not included in the final models. Linearity was assessed by visual inspections of scatterplots, with birth weight and BMI as continuous variables (see online supplementary figures 1-3). No sign of a non-linear relationship was observed, but we analysed the predictors both as continuous and categorical variables.

Due to the relatively large number of missing explanatory variables, we performed multiple imputations on data that were missing at birth, 2–4 years and 5–7 years of age using chained equations generating 20 duplicate datasets.[26 27] (see online supplementary document). The estimates from the 20 imputed datasets were combined into an overall estimate with corresponding SE using Rubin's rule.[26 27]

Multiple imputations and statistical analyses were carried out using Stata/ MP 14.1 for Mac (Stata Corp, College Station, TX, USA). The level of statistical significance was set to two-sided p values <0.05.

RESULTS

Overall mean birth weight was 3530 g and the proportion of participants with high birth weight (≥4500 g) was 4.5%. Characteristics of the study population at birth and at mean ages 2.6, 6.0, 16.6 and 18.6 years are presented by sex (table 1). The prevalence of overweight/ obesity was 14.0% and 18.5% in girls, 8.8% and 10.9% in boys at 2–4 and 5–7 years of age, respectively. At 15–17 and 18–20 years of age, 20.6% and 20.9% of girls, and 23.4% and 28.0% of boys, were overweight/ obese. The prevalence of obesity was <1.5% at 2–4 years and increased to 6.6% in girls and 8.1% in boys at 18–20 years of age (table 2).

Of the study population, 47.0% (452) had five complete measurements. The imputed dataset and the observed-cases dataset were similar with respect to main characteristics and prevalence rates of overweight/ obesity. Comparisons between the datasets are presented in (see online supplementary tables 1-2). The distribution of missing childhood data between sexes and weight classes at 15–17 or 18–20 years of age is presented in (see online supplementary table 3).

We explored sex-specific differences in anthropometric measurements from birth throughout childhood between participants classified as normal weight and overweight/ obese at 15–17 years of age (table 3). Girls classified as overweight/ obese at 15–17 years of age had higher mean birth weight (158 g, p<0.05) than their normal weight female counterparts. Differences in mean BMI and mean weight also increased with age both among girls and boys classified as overweight/ obese at 15–17 compared with their normal weight counterparts. Mean differences in BMI were 0.84 and 2.28 kg/ m^2 among girls and 0.48 and 1.61 kg/ m^2 among boys at 2–4 and 5–7 years of age, respectively (p<0.05). Mean differences in weight were 1.0 and 3.8 kg among girls at 2–4 years and 5–7 years of age, respectively, and 0.3 and 2.7 kg among boys at 2–4 years and 5–7 years of age, respectively (only significant for boys at age 5–7) (table 3).

PI at birth and BMI in childhood were positively (p<0.001) correlated with BMI in adolescence. Spearman's Rho between PI at birth and BMI at 15–17 and 18–20 years of age were 0.13 and 0.12, respectively. Corresponding values for BMI at age 2–4 were 0.32 and 0.26, and for BMI at age 5–7 they were 0.57 and 0.51. BMI at 15–17 years of age was highly correlated with BMI at 18–20 years of age (Spearman's Rho 0.85; p<0.001).

Tracking analysis

In multivariable GEE analyses, a 1-SD (586 g) increase in birth weight was associated with higher odds of overweight/ obesity at 15–20 years of age (OR 1.25, 95% CI 1.06 to 1.48). Infants in the highest tertile of birth weight had significantly higher odds of later overweight/ obesity compared with those in the lowest tertile, but not compared with the mid tertile (adjusted OR for highest vs lowest tertile of PI 1.56, 95% CI 1.08 to 2.24) (table 4). Repeating the analysis with growth categories as a predictor gave results similar to those obtained with

Table 1 Characteristics for girls and boys of the Fit Futures cohort at birth and four ages up to 18–20 years, The Tromsø Study, Fit Futures, observed cases*

Characteristics	Girls			Boys			
	n	Mean/%	(SD)	n	Mean/%	(SD)	p Value†
Birth							
Birth weight (g)	443	3455.0	(576.7)	470	3601.0	(590.0)	<0.001
Birth length (cm)	419	49.4	(2.3)	454	50.2	(2.3)	<0.001
Gestational age (weeks)	393	39.7	(1.8)	430	39.6	(2.1)	0.176
Preterm birth (before GA week 37)	15	3.8%		23	5.4%		0.292
Ponderal index (kg/m^3)	419	28.73	(2.81)	454	28.45	(2.75)	0.141
Body mass index (kg/m^2)	419	14.19	(1.49)	454	14.28	(1.52)	0.338
Birth weight SDS‡	443	−0.58	(1.74)	470	−0.24	(1.32)	0.001
Body mass index SDS‡	419	0.06	(1.05)	454	−0.02	(1.04)	0.265
Birth weight group:	443			470			0.015
Low birth weight (<2500 g)	20	4.5%		17	3.6%		
Normal birth weight (2500–4500 g)	412	93.0%		423	90.0%		
High birth weight (≥4500 g)	11	2.5%		30	6.4%		
Size for gestational age:	443			470			0.554
Small for gestational age	49	11.1%		46	9.8%		
Appropriate for gestational age	356	80.4%		375	79.8%		
Large for gestational age	38	8.6%		49	10.4%		
Maternal age at birth	443	28.4	(5.3)	441	28.1	(5.3)	0.995
2–4 years of age							
Age (years)	328	2.6	(0.4)	350	2.6	(0.4)	0.952
Height (cm)	328	91.2	(4.6)	350	92.7	(4.7)	<0.001
Weight (kg)	328	13.5	(1.7)	350	14.1	(1.8)	<0.001
Body mass index (kg/m^2)	328	16.17	(1.39)	350	16.37	(1.30)	0.053
Weight SDS‡	328	−0.12	(1.11)	350	0.16	(1.16)	0.001
Body mass index SDS‡	328	−0.04	(1.17)	350	−0.07	(1.07)	0.217
5–7 years of age							
Age (years)	354	6.0	(0.4)	384	6.1	(0.4)	0.253
Height (cm)	354	116.7	(5.3)	384	118.3	(5.3)	<0.001
Weight (kg)	352	21.8	(3.8)	384	22.2	(3.5)	0.143
Body mass index (kg/m^2)	352	15.96	(2.04)	384	15.82	(1.74)	0.304
Weight SDS‡	352	0.0004	(1.10)	384	0.11	(1.02)	0.162
Body mass index SDS‡	352	−0.06	(1.10)	384	−0.03	(0.98)	0.616
15–17 years of age							
Age (years)	469	16.6	(0.4)	492	16.6	(0.4)	0.325
Height (cm)	467	164.9	(6.5)	492	176.9	(6.7)	<0.001
Weight (kg)	467	60.9	(11.5)	492	70.2	(14.4)	<0.001
Body mass index (kg/m^2)	467	22.39	(3.96)	492	22.38	(4.17)	0.952
Pubertal maturation, §girls:	464			–	–	–	
Early (<12.5 years)	147	31.7%					
Intermediate (12.5–13.9 years)	212	45.7%					
Late (≥14.0 years)	105	22.6%					
Pubertal maturation, §boys:	–	–	–	387			
Barely started (PDS 2.0–2.9)				69	17.8%		

Continued

Table 1 Continued

Characteristics	Girls			Boys			
	n	Mean/%	(SD)	n	Mean/%	(SD)	p Value†
Underway (PDS 3.0–3.9)				285	73.6%		
Completed (PDS 4.0)				33	8.5%		
18–20 years of age							
Age (years)	363	18.6	(0.4)	296	18.7	(0.3)	0.105
Height (cm)	363	165.7	(6.5)	296	179.1	(6.5)	<0.001
Weight (kg)	363	63.2	(12.0)	296	75.2	(14.6)	<0.001
Body mass index (kg/m^2)	363	23.02	(4.22)	296	23.42	(4.18)	0.228

*In observed data n is varying from 659 to 961.
†p Value for sex difference was obtained by t-test or χ^2 test.
‡SDS, SD scores according to Norwegian reference data.[23]
§Pubertal maturation is based on age of menarche in girls and according to Pubertal Development Scale (PDS) in boys; total score of four items of secondary sexual characteristics on a scale from 1 to 4 (sum of total score divided by 4). None had a score <2.0 in total score.[25]
GA, gestational age.

PI in tertiles. In adjusted analyses, being small for gestational age was associated with lower odds of overweight/obesity at 15–20 years of age compared with those appropriate for gestational age (OR 0.40, 95% CI 0.22 to 0.72). Infants large for gestational age did not have significantly higher odds of overweight/obesity compared with those appropriate for gestational age (adjusted OR for large vs. appropriate for gestational age 1.31, 95% CI 0.84 to 2.05) (data not shown).

Childhood BMI was associated with overweight/obesity in adolescence (OR per 1-SD increase in BMI at age 2–4: 1.66, 95% CI 1.40 to 1.96; OR per 1-SD increase in BMI at age 5–7: 3.23, 95% CI 2.56 to 4.07). Children who were obese at 2–4 years of age had fivefold increased odds of becoming overweight/obese in adolescence (OR 5.35, 95% CI 1.42 to 20.09) compared with their normal weight peers, while at 5–7 years of age the estimated OR was 15.59 (95% CI 6.60 to 36.85), compared with those of normal weight. Cross-product terms between sex and birth weight/BMI were tested and no significant interaction was found (table 4).

Due to the small number of obese children, CIs were wide for these groups. Therefore additional analyses were performed with weight class in three groups as predictor. At 2–4 years of age, those with light overweight (adult BMI ≥25 to <27 kg/m^2 (n=52)) had an OR of 1.88 (95% CI 1.08 to 3.29) and those with severe overweight/obesity (adult BMI ≥27 kg/m^2 (n=25)) had an OR of 3.01 (95% CI 1.47 to 6.18) for overweight/obesity at 15–20 years of age, compared with those of normal weight. At 5–7 years of age the corresponding ORs were 4.96 (95% CI 2.82 to 8.73) for light overweight (n=48) and 11.51 (95% CI 6.63 to 19.99) for severe overweight/obesity (n=59) when compared with those of normal weight (data not shown).

Table 2 Weight classes* at four ages, The Tromsø Study, Fit Futures observed cases†

	Age	2–4 years		5–7 years		15–17 years		18–20 years	
		n	%	n	%	n	%	n	%
Girls	Underweight	48	14.6	37	10.5	24	5.1	16	4.4
	Normal weight	234	71.3	250	71.0	347	74.3	271	74.7
	Overweight	41	12.5	49	13.9	70	15.0	52	14.3
	Obesity	5	1.5	16	4.6	26	5.6	24	6.6
	Total	328	100.0	352	100.0	467	100.0	363	100.0
Boys	Underweight	43	12.3	28	7.3	38	7.7	24	8.1
	Normal weight	276	78.9	314	81.8	339	68.9	189	63.9
	Overweight	27	7.7	27	7.0	79	16.1	59	19.9
	Obesity	4	1.1	15	3.9	36	7.3	24	8.1
	Total	350	100.0	384	100.0	492	100.0	296	100.0

*Weight classes according to the International Obesity Taskforce (IOTF) age- and sex-specific cut-off values for children 2–18 years of age and the WHO index for adults from age 18–20.[21 22]
†In observed cases n is varying at different ages from 659 to 959.

Table 3 Sex-specific anthropometric characteristics from birth up to 15–17 years of age for normal weight and overweight/obese 15–17-year-olds in the Tromsø Study, Fit Futures (n=961)

	Girls				Boys			
	Normal weight		Overweight/obese		Normal weight		Overweight/obese	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Birth weight (g)	3418.0	(3358.1 to 3478.2)	3576.0	(3462.0 to 3689.5)	3597.0	(3535.5 to 3659.0)	3622.0	(3522.2 to 3721.4)
Birth weight SDS	−0.67	(−0.86 to −0.49)	−0.24	(−0.52 to −0.04)	−0.25	(−0.39 to −0.11)	−0.19	(−0.41 to 0.03)
Birth length (cm)	49.2	(48.9 to 49.4)	49.7	(49.2 to 50.1)	50.1	(49.9 to 50.4)	50.1	(49.7 to 50.6)
Ponderal index (kg/m^3)	28.55	(28.24 to 28.85)	29.03	(28.44 to 29.62)	28.34	(28.04 to 28.64)	28.61	(28.14 to 29.08)
Weight 2–4 years (kg)	13.2	(13.0 to 13.4)	14.2	(13.8 to 14.6)	14.0	(13.8 to 14.2)	14.3	(13.9 to 14.7)
Weight SDS† 2–4 years	−0.23	(−0.36 to −0.09)	0.23	(−0.02 to 0.48)	0.09	(−0.04 to 0.22)	0.42	(0.14 to 0.69)
Height 2–4 years (cm)	90.8	(90.3 to 91.2)	91.8	(90.8 to 92.9)	92.6	(92.4 to 93.3)	92.3	(91.4 to 93.2)
BMI 2–4 years (kg/m^2)	16.00	(15.84 to 16.16)	16.84	(16.53 to 17.15)	16.25	(16.10 to 16.40)	16.73	(16.43 to 17.04)
Weight 5–7 years (kg)	20.8	(20.5 to 21.1)	24.6	(23.6 to 25.5)	21.5	(21.2 to 21.8)	24.2	(23.4 to 25.1)
Weight SDS† 5–7 years	−0.27	(−0.37 to −0.17)	0.80	(0.57 to 1.02)	−0.09	(−0.19 to 0.001)	0.75	(0.54 to 0.97)
Height 5–7 years (cm)	116.2	(115.6 to 116.7)	117.5	(116.3 to 118.7)	117.9	(117.4 to 118.5)	118.9	(117.9 to 119.9)
BMI 5–7 years (kg/m^2)	15.41	(15.25 to 15.57)	17.69	(17.16 to 18.22)	15.44	(15.30 to 15.58)	17.05	(16.59 to 17.51)
Weight 15–17 years (kg)	56.8	(56.2 to 57.5)	76.8	(74.3 to 79.4)	64.4	(63.6 to 65.3)	88.9	(86.2 to 91.6)
Height 15–17 years (cm)	165.0	(164.4 to 165.7)	164.3	(162.9 to 165.6)	176.9	(176.2 to 177.5)	177.0	(175.8 to 178.3)
BMI 15–17 years (kg/m^2)	20.84	(20.65 to 21.03)	28.42	(27.59 to 29.25)	20.57	(20.36 to 20.78)	28.30	(27.59 to 29.01)

*Analysed in the dataset with 20 imputations (multiple imputation), n=961 (469 girls and 492 boys).
†SDS, SD scores according to Norwegian reference data.[23]
BMI, body mass index.
Numbers in italic type are significant.

Table 4 Odds ratios for overweight including obesity* in adolescence (15–20 years of age) overall and by sex. The Tromsø Study, Fit Futures 2010–11 and 2012–13†

	Overweight/obesity at 15–20 years of age												
	All				Girls				Boys				
	Crude		Adjusted‡§		Crude		Adjusted¶		Crude		Adjusted[5]		
Birth	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	p Value[14]
Birth weight per SD	1.22	(1.06 to 1.41)	1.25	(1.06 to 1.48)	1.39	(1.10 to 1.74)	1.37	(1.05 to 1.77)	1.08	(0.90 to 1.29)	1.15	(0.93 to 1.43)	0.090
Birth weight SDS	1.15	(1.04 to 1.27)	1.18	(1.05 to 1.33)	1.22	(1.03 to 1.44)	1.20	(0.99 to 1.46)	1.06	(0.92 to 1.22)	1.12	(0.95 to 1.33)	
Ponderal index in tertiles:													0.020/0.016[15]
Low	1.00	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.	
Medium	1.30	(0.90 to 1.89)	1.34	(0.91 to 1.96)	1.67	(0.94 to 2.97)	1.65	(0.92 to 2.95)	1.08	(0.67 to 1.75)	1.13	(0.69 to 1.87)	
High	1.53	(1.07 to 2.18)	1.56	(1.08 to 2.24)	1.75	(1.02 to 3.00)	1.67	(0.96 to 2.90)	1.44	(0.89 to 2.32)	1.47	(0.90 to 2.39)	
2–4 years of age													
BMI per SD	1.66	(1.41 to 1.95)	1.66	(1.40 to 1.96)	1.96	(1.55 to 2.47)	2.03	(1.60 to 2.58)	1.42	(1.12 to 1.80)	1.39	(1.08 to 1.77)	0.062
BMI SDS	1.55	(1.32 to 1.83)	1.55	(1.31 to 1.82)	1.94	(1.51 to 2.49)	1.93	(1.51 to 2.48)	1.33	(1.05 to 1.67)	1.32	(1.05 to1.67)	
Weight class at 2–4 years:													
Underweight	0.42	(0.24 to 0.73)	0.42	(0.24 to 0.73)	–	–	–	–	–	–	–	–	
Normal weight	1.0	Ref.	1.0	Ref.	–	–	–	–	–	–	–	–	
Overweight	1.75	(1.09 to 2.84)	1.74	(1.07 to 2.82)	–	–	–	–	–	–	–	–	
Obese	5.49	(1.44 to 20.98)	5.35	(1.42 to 20.09)	–	–	–	–	–	–	–	–	
5–7 years of age													
BMI per SD	3.10	(2.47 to 3.88)	3.23	(2.56 to 4.07)	3.72	(2.57 to 5.37)	3.72	(2.59 to 5.34)	2.73	(2.02 to 3.70)	2.88	(2.10 to 3.95)	0.215
BMI SDS	3.11	(2.53 to 3.82)	3.11	(2.53 to 3.81)	3.95	(2.80 to 5.57)	3.95	(2.82 to 5.53)	2.63	(2.00 to 3.44)	2.62	(1.99 to3.44)	
Weight class at 5–7 years:													
Underweight	0.23	(0.08 to 0.61)	0.22	(0.08 to 0.61)	–	–	–	–	–	–	–	–	
Normal weight	1.0	Ref.	1.0	Ref.	–	–	–	–	–	–	–	–	
Overweight	5.25	(3.34 to 8.25)	5.35	(3.37 to 8.48)	–	–	–	–	–	–	–	–	
Obese	15.68	(6.54 to 37.62)	15.59	(6.60 to 36.85)	–	–	–	–	–	–	–	–	

*Weight classes according to the International Obesity Taskforce (IOTF) age- and sex-specific cut-off values for children 2–18 years of age and the WHO index for adults from age 18–20.[21 22]
†Analysed in the dataset with 20 imputations (multiple imputation), n=961 (469 girls and 492 boys).
‡Variables at birth are adjusted for gestational age, maternal age and sex, except sex-specific SDS, which is adjusted for gestational age and maternal age.
§Variables at 2–4 and 5–7 years of age are adjusted for age, maternal age and sex, except age- and sex-specific weight class and SDS, which is adjusted only for maternal age.
¶Variables in sex specific analysis are adjusted for gestational age/age and maternal age, except age- and sex-specific SDS which is adjusted only for maternal age.
**p Value for sex difference (interaction term) in crude analysis.
††p for trend in all cases: 0.020 in crude analysis, 0.016 in adjusted analysis.
BMI, body mass index (kg/m^2); GEE, generalised estimating equations; Ref, reference group; SDS, SD scores according to Norwegian reference data.
Numbers in italic type are significant (p<0.05).

DISCUSSION

In this population-based longitudinal study of Norwegian adolescents born in 1992–1994, we found a statistically significant, but modest, association between birth weight and overweight/ obesity at 15–20 years of age. Tracking of BMI and overweight from childhood to adolescence was moderate. Children with more severe overweight/ obesity had considerably higher odds of later overweight/ obesity compared with those with light overweight or their normal weight peers. The prevalence of overweight/ obesity increased with age. More girls than boys were overweight/ obese at 2–4 and 5–7 years of age, but at 15–20 years this shifted so that more boys than girls were overweight/ obese. Tracking of overweight/ obesity from birth and childhood into adolescence was generally stronger in girls than in boys; however, no significant interaction with sex was found.

Mean birth weight and the proportion with high birth weight (4.5%) were somewhat higher than national data from 1992 to 1994 birth records (3.7–4.2%).[18] High mean birth weight and high prevalence rates of overweight/ obesity in children have been reported from the northernmost region of Norway.[18 28] The prevalence of overweight/ obesity in childhood we observed was comparable with findings from other studies from Norway that included similar age groups[13 29]; however, the prevalence of overweight/ obesity in adolescence was higher than figures from comparable Norwegian studies.[29 30] The prevalence of overweight/ obesity is generally lower in the Nordic countries compared with the USA and southern European countries, which was reflected in our study.[31–33]

Birth weight as a risk factor for overweight/ obesity at later ages has been extensively studied with varying results.[10 11 34] In the review by Brisbois et al 25 of 43 studies found an association between birth weight and adult BMI or overweight/ obesity, but with no clear conclusion that birth weight was an early marker for adult overweight/ obesity.[10] Six of seven studies in a review by Weng et al found significant and strong associations between high birth weight and childhood overweight.[34] In two recent studies from Norway, increased BMI SDS at birth was associated with overweight including obesity at 8 years of age (OR per 1-SDS increase in BMI at birth 1.8, 95% CI 1.6 to 2.0).[12] A moderate degree of tracking of body size from birth to 7 years of age was found in the Norwegian Mother and Child Cohort Study.[13] Our finding of a statistically significant association between birth weight and overweight/ obesity in adolescence is in line with these studies. However, birth weight was only a modest predictor of later overweight/ obesity in our study, probably due to the longer timespan. Stronger tracking of overweight/ obesity over a shorter timespan has been reported.[12 13 34] In contrast to our findings, two newer population-based studies from Sweden, which were comparable to our study, did not find high birth weight to be associated with high BMI or obesity at 15 or 20 years of age.[35 36] Since tracking coefficients are influenced by time, comparisons between studies are challenging.[8 37]

The participants in our study were born in a period during which there was a higher mean birth weight in the Norwegian population. The percentage of infants with a birth weight over 4500 g increased in Norway from 1990 to 2000, before declining to the same level as in 1990.[18] If birth weight emerged as a strong predictor of later overweight/ obesity, one would expect to see a high degree of tracking in our study compared with studies of children with a lower mean birth weight, but the estimated tracking coefficients were only moderate. However, since the prevalence of overweight/ obesity in adolescence is relatively high in our study population, a birth cohort effect cannot be ruled out.

Among those classified as overweight/ obese at 15–17 years of age, mean weight was generally higher at birth and BMI was significantly higher at 2–4 years of age. The estimated tracking coefficients from 2–4 and 5–7 years of age were moderate among our overweight participants and stronger among those classified with severe overweight/ obesity. Our findings are in line with previous results from this cohort, as well as other studies and reviews.[6 7 9 35 38 39] Birth weight or BMI/ overweight at 2–4 years of age were not strong predictors of later overweight/ obesity; BMI/ weight class at 5–7 years of age were stronger predictors. Others have also observed a stronger degree of tracking from 5 to 6 years of age, especially among subjects classified as obese.[32 35 36 39]

Weight status can fluctuate throughout childhood,[32] and we observed this in our study population.[38] The proportion of those with a high birth weight (>4500 g) that were overweight/ obese at later ages varied between 17–34%; it was lowest at 5–7 years of age and highest in adolescence. The proportion of infants with a normal birth weight that were classified as overweight/ obese at later ages were 10–24%; this proportion was lowest at 2–4 years of age and highest in adolescence (data not shown).

The IOTF reference for BMI classification has low sensitivity but high specificity compared with other references.[21 33] Hence, the estimated prevalence of overweight/ obesity based on the IOTF reference may be too low and could influence the predictive ability of the classification. On the other hand, a Swedish study comparing different references concluded that the IOTF reference would identify the fewest false positive cases.[33] We also calculated weight and BMI SDS based on the Norwegian reference population.[23] Mean weight SDS at 2–4 and 5–7 years of age was higher; however, mean BMI SDS was comparable to the reference population.[23] GEE analyses give a population-averaged estimate, which generally gives lower and valid estimates when the outcome is dichotomous.[40] We therefore consider the estimated tracking coefficients in our study to be representative of Norwegian children.

The strengths of this study are the population-based design of the Fit Future study and a high attendance rate, which minimise selection bias. In this region more than 90% of the population in the age group 16–19

years attend upper-secondary school (an entitlement in Norway). Birth variables from the MBRN and measured height and weight data at all ages assures good compliance and good quality data, which limits the risk of information bias. We have longitudinal data over a relatively long time-span from birth in the 1990s up to 18–20 years of age. This study brings updated data on tracking of overweight and obesity from a representative sample of Norwegian children and adolescents. The prevalence of overweight/ obesity at 15–20 years of age may not be a representative estimate for the entire Norwegian adolescent population or populations of different ethnicities. However, the associations found in the tracking analysis are considered to be comparable to other populations with similar characteristics.

The main limitation of this study was the missing data. The percentage of missing main variables from childhood did not differ between sexes or weight classes in adolescence (see online supplementary table 3). More boys than girls were missing at FF2 and we cannot rule out that they were not missing at random.[26] This leads to some uncertainty in the estimated prevalence of overweight/ obesity in childhood and at 18–20 years of age. However, analysis of the imputed dataset, the observed-cases dataset and only complete-cases dataset, all gave similar results. A recognised method was used to impute the missing childhood values.[27] Mean values were generally lower after imputation, compared with observed cases, but differences were small (see online supplementary table 1 and table 2). Childhood height and weight data are obtained from different health clinics and an overestimation of overweight/ obesity due to instrument error might occur.[41] However, potential misclassification bias is assumed to be non-differential. Factors known to affect overweight/ obesity, such as maternal BMI, smoking habits, and socioeconomic status, were not registered in the MBRN for these children.[10] Nor did we have access to information on lifestyle factors from childhood, and the effect of these potential confounding factors cannot be excluded. BMI is a simple measure of obesity and does not separate between fat and muscle mass, although it is widely used in clinical practice and research. BMI in children varies with growth and results need to be interpreted with some caution.[6] More sophisticated measures of body composition would give better measures of adiposity, which is more strongly linked to disease risk in adulthood. Unfortunately, such data were not available for the present study.

Several researchers have recommended early intervention and prevention efforts, some starting even before conception.[1 10 11 14] 'The first 1000 days' are suggested as a critical early-life period.[11] Treatment of obesity among children/ adolescents is challenging, which is why establishing healthy habits early in life is of the utmost importance.[1 14 17] We aimed to shed light on the most appropriate age to start risk-based preventive efforts. Our findings do not indicate that most children at risk can be identified already at birth or at 2–4 years of age. However, children with more severe overweight/ obesity and a high risk of later overweight/ obesity could be identified before 5–7 years of age. Development of overweight/ obesity is complex; it involves genetic and multiple environmental factors and is still not fully understood.[1 15 16] Since genetic factors can explain 40–75% of BMI variation in childhood and adolescence,[16] some degree of tracking is probably inevitable. Strong positive associations have been seen between parents and their adolescent offspring's BMI.[42] Identifying children at risk of later overweight/ obesity requires a family approach. The influential role of genetic factors varies with age,[16] and may be prevented by behavioural changes.[15] Prevention of overweight/ obesity therefore requires efforts tailored at addressing parents and children at different ages. More research is needed into preventive and treatment programmes for families and children at different ages.

SUMMARY AND CONCLUSION

Birth weight did not have a strong influence on overweight/ obesity at 15–20 years of age. Tracking of BMI from early childhood to late adolescence was moderate. Severe overweight/ obesity at 2–4 and 5–7 years of age was a strong predictor of later overweight/ obesity. However, the prevalence of overweight/ obesity increased with age. Prevention efforts should therefore address children of all ages.

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Contributors ASF, NE and AK contributed to the conception, study design and data acquisition of the Fit Futures study. ASF is the principal investigator of the Fit Futures study. EE, NE and GS contributed to the conception, design, data collection, analyses and interpretation of data, as well as drafting the manuscript in the present study. EE performed the statistical analyses. TW gave advice on statistical analysis and especially revised the manuscripts method and result sections. All authors have contributed substantially in interpretation of data and critically revising the manuscript. All authors have read and approved the final submitted manuscript.

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Competing interests None declared.

Patient consent Participants' consent: obtained.

Ethics approval The Tromsø Study, Fit Futures was approved by the Norwegian Data Protection Authority (reference number 2009/1282) and the Regional Committee for Medical and Health Research Ethics, North Norway (REK nord) approved Fit Futures 1 and 2 and the present study (Reference number: 2014/1397/REK nord).

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Data sharing statement No additional data are available.

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SUPPLEMENTARY DOCUMENT – DESCRIPTION OF THE MISSINGNESS PATTERN AND THE IMPUTATION MODEL USED FOR THE PAPER:

The relation between birthweight, childhood body mass index, and overweight and obesity in late adolescence: a longitudinal cohort study from Norway, The Tromsø Study, Fit Futures.

A total of 43% participants (411) were missing one or more of the height/length and weight variables from the birth registry (5% were missing birthweight) and/or childhood measurements (29% missing height/weight at 2-4 years of age, 23% missing height/weight at 5-7 years of age). In 31% (302) of participants data were missing from follow-up at Fit Futures 2, leaving 47.0% (452) of the core study population with five complete measurements.

Due to the relatively large number of missing explanatory variables, we performed multiple imputations to handle missing data. The missingness pattern was checked and found to be arbitrary, thus data was assumed to be missing at random (MAR). Multiple imputations were performed for nine variables from birth and childhood: birthweight, length, gestational age, exact age, and height and weight at 2-4 and 5-7 years of age. In addition, body mass index (BMI) for two girls at 15-17 years of age was imputed. Multiple imputations were performed by chained equations, generating twenty duplicate datasets. The missing values were replaced by imputed values based on the observed information from all five ages. The imputation model included all variables from the final generalised estimating equations analysis, and it included BMI at 15-17 and 18-20 years of age as outcome variables. Calculated variables based on imputed values, such as weight class, were registered as passive variables. To account for a

significant interaction term between sex and BMI at 2-4 years of age, separate imputations were performed for boys and girls. To increase the predictive power of the imputation model, we included auxiliary variables: height, weight, waist circumference and exact age at Fit Futures 1, a dichotomous variable of missing or not at Fit Futures 2, and variables from the birth registry (maternal age at birth, caesarean section, multiple births, maternal disease or diabetes). Variables were imputed using linear regression for continuous variables and predictive mean matching (using 100 nearest neighbours) for variables that had a restricted range or were slightly skewed (the age variables, gestational age, weight, and BMI variables).

Participants with missing BMI at follow-up did not have a significantly higher BMI at Fit Futures 1 vs. those attending Fit Futures 2 (girls: 23.0 vs. 22.2 kg/m^2; p= 0.06, boys: 22.7 vs. 22.2 kg/m^2; p=0.20). Significantly more boys (39.8%) than girls (22.6%) were missing at Fit Futures 2. We chose not to use imputed missing BMI for those lost to follow-up in Fit Futures 2, since imputation of outcome variables are questionable and we cannot rule out the possibility of missingness that is not random (MNAR). Therefore all analyses performed on the imputed dataset include 961 subjects at 15-17 years of age and complete-case data for 659 subjects at 18-20 years of age.

Supplementary Table S.1. Comparison of the dataset with observed data and the dataset with imputed values (20 multiple imputations) for selected variables for girls and boys of the Fit Futures cohort at birth and four ages up to 18-20 years, The Tromsø Study, Fit Futures

Characteristics	Girls				Boys			
	Observed data [1]		Imputed data [2]		Observed data [1]		Imputed data [2]	
	Mean/n	(SD)/%	Mean/n	(SD)/%	Mean/n	(SD)/%	Mean/n	(SD)/%
Birth								
Birthweight (grams)	3454.8	(576.7)	3450.5	(574.8)	3601.0	(590.0)	3603.0	(586.7)
Birth length (cm)	49.4	(2.3)	49.3	(2.4)	50.2	(2.3)	50.1	(2.3)
Gestational age (weeks)	39.7	(1.8)	39.8	(1.8)	39.6	(2.1)	39.6	(2.1)
Ponderal index (kg/m^3)	28.73	(2.81)	28.65	(2.88)	28.45	(2.75)	28.40	(2.78)
Body mass index (kg/m^2)	14.19	(1.49)	14.12	(1.55)	14.28	(1.52)	14.24	(1.54)
Birthweight SDS [3]	-0.58	(1.74)	-0.58	(1.73)	-0.24	(1.32)	-0.24	(1.31)
Body mass index SDS [3]	0.06	(1.05)	0.01	(1.12)	-0.02	(1.04)	-0.46	(1.06)
Birthweight group:								
Low birthweight (<2500 g)	20	4.5 %	22	5.0 %	17	3.6 %	17	4.0 %
Normal birthweight (2500-4500 g)	412	93 %	436	93.0 %	423	90.0 %	444	90.0 %
High birthweight (≥4500 g)	11	2.5 %	11.5	2.0 %	30	6.4 %	31	6.0 %
Small for gestational age	49	11.1%	64	13.5 %	46	9.8%	53	10.8 %
Appropriate for gestational age	356	80.4%	361	77.1 %	375	79.8%	385	78.3 %
Large for gestational age	38	8.6%	44	9.4 %	49	10.4%	54	10.9 %
Maternal age at birth	28.4	(5.3)	28.4	(5.3)	28.1	(5.3)	28.1	(5.3)
2-4 years of age								
Age (years)	2.6	(0.4)	2.5	(0.3)	2.6	(0.4)	2.6	(0.3)
Height (cm)	91.2	(4.6)	91.0	(4.4)	92.7	(4.7)	92.7	(4.4)
Weight (kg)	13.5	(1.7)	13.4	(1.6)	14.1	(1.8)	14.1	(1.7)
Body mass index (kg/m^2)	16.17	(1.39)	16.17	(1.38)	16.37	(1.30)	16.36	(1.31)
Weight SDS [1]	-0.12	(1.11)	-0.13	(1.12)	0.16	(1.16)	0.17	(1.15)
Body mass index SDS [3]	0.04	(1.17)	0.03	(1.17)	-0.07	(1.07)	-0.08	(1.09)
5-7 years of age								
Age (years)	6.0	(0.4)	6.0	(0.4)	6.1	(0.4)	6.1	(0.4)
Height (cm)	116.7	(5.3)	116.4	(5.1)	118.3	(5.3)	118.2	(5.2)
Weight (kg)	21.8	(3.8)	21.6	(3.5)	22.2	(3.5)	22.1	(3.3)
Body mass index (kg/m^2)	15.96	(2.04)	15.88	(1.94)	15.82	(1.74)	15.81	(1.72)
Weight SDS [1]	0.0004	(1.10)	-0.05	(1.05)	0.11	(1.02)	0.11	(0.99)
Body mass index SDS [3]	-0.06	(1.10)	-0,10	(1.09)	-0.03	(0.98)	-0.03	(1.00)
15-17 years of age								
Age (years)	16.6	(0.4)	-	-	16.6	(0.4)	-	-
Height (cm)	164.9	(6.5)	164.9	(6.5)	176.9	(6.7)	-	-
Weight (kg)	60.9	(11.5)	60.9	(11.4)	70.2	(14.4)	-	-
Body mass index (kg/m^2)	22.39	(3.96)	22,39	(3.95)	22.38	(4.17)	-	-
18-20 years of age	No imputed values							
Age (years)	18.6	(0.4)	-	-	18.7	(0.3)	-	-
Height (cm)	165.7	(6.5)	-	-	179.1	(6.5)	-	-
Weight (kg)	63.2	(12.0)	-	-	75.2	(14.6)	-	-
Body mass index (kg/m^2)	23.02	(4.22)	-	-	23.42	(4.18)	-	-

[1] In observed data n is varying from 659-961 (328-469 girls and 296-492 boys)
[2] Dataset with 20 imputations n= 961(469 girls and 492 boys) in each imputations.
[3] SDS= Standard deviation scores according to Norwegian reference data.[23]
SD = Standard deviation
- = No imputed values, mean and SD are equal to the observed data.

Supplementary Table S.2. Weight classes [1]at four ages, The Tromsø Study, Fit Futures - Comparison of observed cases [2] and imputed datasets [3]

	Age	2- 4 years		5-7 years		15-17 years		18-20 years
		Observed cases	Imputed data	Observed cases	Imputed data	Observed cases	Imputed data	Observed cases [4]
		n= 678	n= 961	n= 736	n= 961	n= 959	n= 961	n= 659
Girls	Underweight	14.6	14.8	10.5	10.7	5.1	5.1	4.4
	Normal weight	71.3	72.5	71.0	72.4	74.3	74.4	74.7
	Overweight	12.5	11.3	13.9	13.1	15.0	14.9	14.3
	Obesity	1.5	1.3	4.6	3.9	5.6	5.5	6.6
	Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Boys	Underweight	12.3	13.6	7.3	8.4	7.7	7.7	8.1
	Normal weight	78.9	77.4	81.8	80.5	68.9	68.9	63.9
	Overweight	7.7	7.9	7.0	7.6	16.1	16.1	19.9
	Obesity	1.1	1.0	3.9	3.5	7.3	7.3	8.1
	Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0

[1] Weight classes according to the International Obesity Taskforce (IOTF) age- and sex-specific cut-off values for children 2-18 years of age and the WHO index for adults from age 18 -20.[21 ,22]

[2] In observed cases n is varying at different ages from 659-959.

[3] N=961

[4] No imputed values, mean and SD are equal to the observed data.

Supplementary table S.3. Distribution of missing data (%) total, by gender and weight classes in two categories at Fit Futures 1 and 2. The Tromsø Study, Fit Futures

		Weight class in two categories							
	Total [1]	**Girls**[2]				**Boys** [2]			
Main variables with missing		**15-17 years**		**18-20 years**		**15-17 years**		**18-20 years**	
		Normal weight	Overweight Obesity	Normal weight	Overweight Obesity	Normal weight	Overweight Obesity	Normal weight	Overweight Obesity
Birthweight	5.0	5.9	4.2	5.9	4.0	4.5	4.4	3.8	3.6
Length at birth	9.2	*12.4* [3]	*4.2* [3]	12.2 [4]	6.6 [4]	7.7	7.8	5.2 [5]	10.8 [5]
Gestational age	14.4	16.4	15.6	16.0	14.5	12.2	13.9	12.7	10.8
BMI 2-4 year	29.5	30.7	27.1	28.6	26.3	28.9	28.7	25.8	27.7
BMI 5-7 year	23.4	26.4	18.8	23.3	17.1	20.7	26.1	18.3	20.5

[1] % total missing among 961 cases.

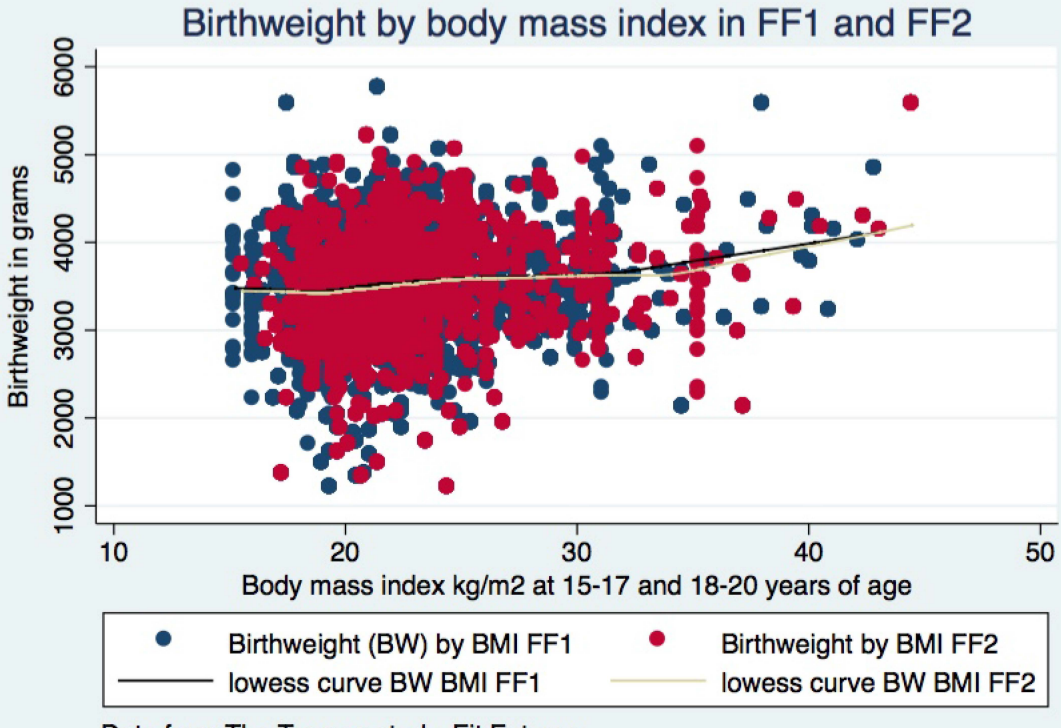
[2] No significant difference between girls and boys in distribution of total missing for each of the five variables. Birthweight: girls:, 5.5 % boys, 4.5 %; Length at birth: girls, 10.7% boys, 7.7%; Gestational age: girls, 16.2% boys 12.6%; BMI 2-4 years: girls, 30.1 boys, 28.9; BMI 5-7 years: girls 25.0% boys 22.0%.

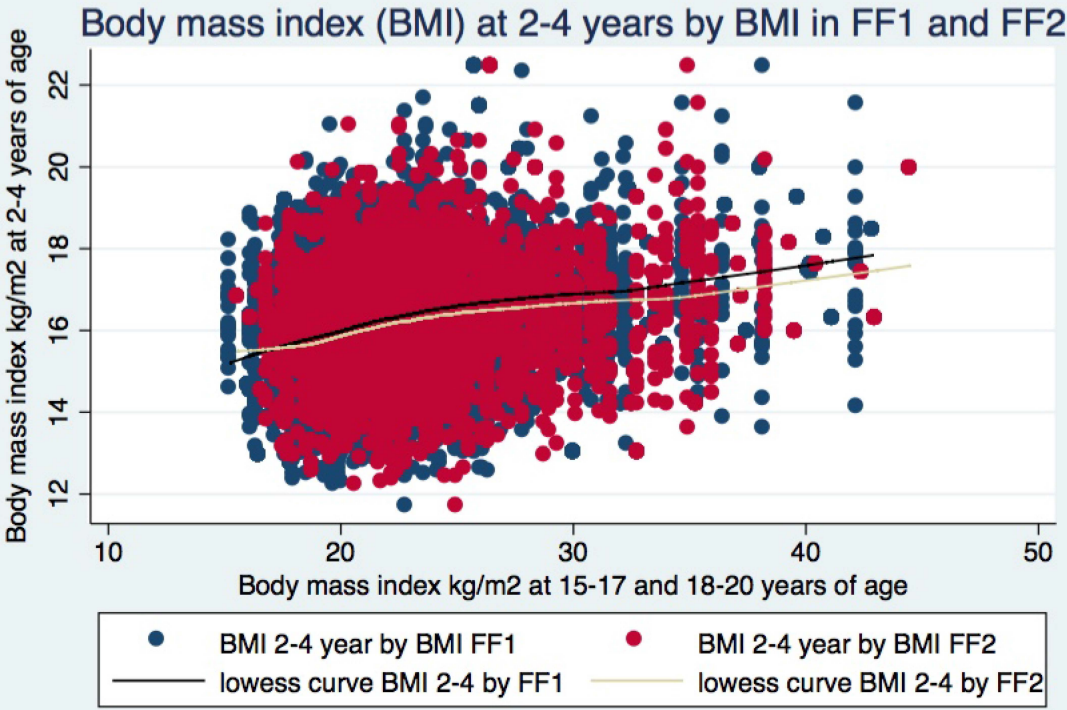
[3] Chi-square test, p=0.02 Significant differences between weightclasses in *Italic*.

[4] Chi-square test, p=0.16

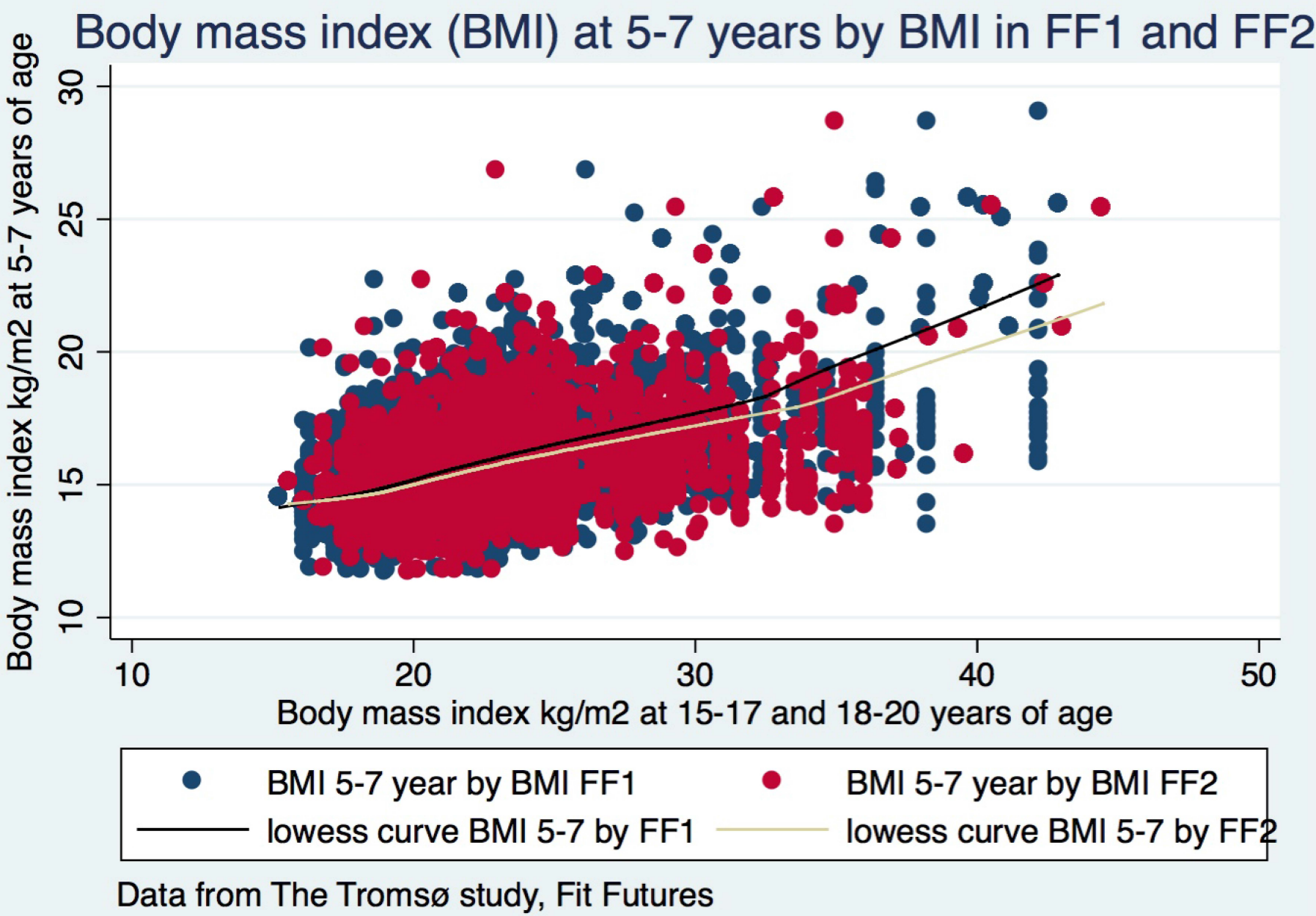
[5] Chi-square test, p=0.08

BMI, Body mass index kg/m^2


Birthweight by body mass index in FF1 and FF2
Birthweight in grams
1000
2000
3000
4000
5000
6000
10
20
30
40
50
Body mass index kg/m2 at 15-17 and 18-20 years of age
Birthweight (BW) by BMI FF1
Birthweight by BMI FF2
lowess curve BW BMI FF1
lowess curve BW BMI FF2
Data from The Tromsø study, Fit Futures



Data from The Tromsø study, Fit Futures


Body mass index (BMI) at 5-7 years by BMI in FF1 and FF2
Body mass index kg/m2 at 5-7 years of age
10
15
20
25
30
10
20
30
40
50
Body mass index kg/m2 at 15-17 and 18-20 years of age
BMI 5-7 year by BMI FF1
BMI 5-7 year by BMI FF2
lowess curve BMI 5-7 by FF1
lowess curve BMI 5-7 by FF2
Data from The Tromsø study, Fit Futures

Paper II

Adolescent body composition, and associations with body size and growth from birth to late adolescence. The Tromsø Study: Fit Futures – a Norwegian longitudinal cohort study.

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Running head: Childhood growth and adolescent body composition

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ABSTRACT

Background: Fat- and fat-free masses and fat distribution are related to cardio-metabolic risk.

Objectives: To explore how birth weight, childhood body mass index (BMI) and BMI gain were related to adolescent body composition and central obesity.

Methods: In a population-based longitudinal study, body composition was measured by dual-energy X-ray absorptiometry in 907 Norwegian adolescents (48% girls). Associations between birth weight, BMI-categories, and BMI gain were evaluated by fitting linear mixed models, and conditional growth models with fat mass index (FMI, kg/m^2), fat-free mass index (FFMI, kg/m^2) standard deviation scores (SDS), central obesity at 15-20 years, and change in FMI SDS and FFMI SDS between ages 15-17 and 18-20 as outcomes.

Results: Birth weight was associated with FFMI in adolescence. Greater BMI gain in childhood, conditioned on prior body size, was associated with higher FMI, FFMI and central overweight/obesity with the strongest associations seen at age 6-16.5 years: FMI SDS: β=0.67 (95% confidence interval: 0.63, 0.71), FFMI SDS: 0.46 (0.39, 0.52), in girls, FMI SDS: 0.80 (0.75, 0.86), FFMI SDS: 0.49 (0.43, 0.55), in boys.

Conclusions: Compared to birth and early childhood, high BMI and greater BMI gain at later ages, are strong predictors of higher fat mass and central overweight/obesity at 15-20 years of age.

ABBREVIATIONS:

BMI, body mass index; FMI, fat mass index; FFMI, fat-free mass index; SDS, standard deviation scores; CVD, cardiovascular disease; DXA, dual-energy X-ray absorptiometry; TFF1, The Tromsø Study, Fit Futures 1; TFF2, The Tromsø Study, Fit Futures 2; GA, gestational age; SGA, small for gestational age; LGA, large for gestational age; MBRN, the Medical Birth Registry of Norway; WC, waist circumference; FM, fat mass; FFM, fat-free mass; FMR, fat mass ratio; IOTF, the International Obesity Task Force; PDS, pubertal development scale; WHO, World Health Organization; SD, standard deviation; GEE, generalized estimating equations; OR, odds ratio; CI, confidence interval; r_s, Spearman's rank correlation coefficient; 4C, 4-component model.

INTRODUCTION

Childhood and adolescent obesity is associated with increased risk of adult morbidity, especially cardiovascular disease (CVD) and diabetes type 2 (1-4). Prolonged duration of obesity is also a strong predictor of CVD and diabetes (5, 6). A moderate degree of tracking (maintenance of certain risk factors over time) of overweight and obesity from childhood to adolescence and adulthood has been reported (3, 7). Body mass index (BMI, kg/m^2) is a common measure of overweight and obesity (3). However, childhood BMI might not accurately predict adverse levels of adiposity (3, 8), and children with the same BMI may have very different fat- and fat-free mass distribution (9).

Body composition measurements e.g. by dual-energy X-ray absorptiometry (DXA), provide supplementary information regarding fat-, lean-, fat-free mass, and fat distribution (10). Such body composition indices, as well as waist circumference and other measures of central obesity, are regarded as better measures of cardio-metabolic risk than BMI (11-13), and have been linked to clustered CVD risk factors in European adolescents (14).

Birth weight is used as a proxy for intra-uterine and maternal nutrition, and may indicate maternal, and environmental factors affecting foetal growth. Birth weight is consistently positively associated with subsequent lean mass (9, 15-19), but associations with subsequent fat mass, and central obesity are less clear (9, 15, 16, 20-22). Early postnatal growth, compared to childhood growth, may influence body composition later in life differently; weight or BMI gain later in childhood has been more strongly linked to adiposity measures (9, 16-18, 21-25). However, previous findings are not consistent, and few larger studies have investigated associations between childhood growth and DXA measures of body composition in adolescence or adulthood (16, 25). The International Diabetes Federation has requested

more research into early growth, body composition and fat distribution among children and adolescents (13).

Current treatment results for obesity in adolescents are moderate, especially for those with severe obesity (26). Early identification of children at risk is important, as preventing or delaying onset of obesity may influence future health (5, 6, 13). To identify if there are critical periods of growth during childhood and adolescence, we need more research into the relation between birth weight, childhood BMI gain, and body composition later in life (13, 27).

In this study, we present population-based body composition measures obtained by DXA in Norwegian boys and girls at 15-17 and 18-20 years of age. The aim of the study was to explore: i) how birth weight, childhood BMI and BMI gain were related to body composition measures and central obesity in late adolescence, and ii) if childhood BMI gain was related to changes in body composition in the transition to young adulthood.

METHODS

Study sample

The Tromsø Study: Fit Futures, a population-based prospective cohort study has been described previously (28). The cohort consists of adolescents from the Tromsø region, Northern Norway. Fit Futures 1 (TFF1) was conducted in 2010-2011 and 961 (92.9%) participants were in the core age group of 15-17 years (born 1992-1994). A follow-up study, Fit Futures 2 (TFF2), was conducted in 2012-2013 and re-invited all participants from TFF1. Trained study nurses at the Clinical Research Unit, University Hospital of North Norway, performed data collection, following standardized procedures. For this study, anthropometric

data from birth and childhood was retrospectively collected. Each participant's unique personal identification number was used to link to the Medical Birth Registry of Norway (MBRN) and childhood health records. A sample of 907 girls and boys were eligible for analysis in the present study (Figure 1).

The Regional Committee for Medical and Health Research Ethics, North Norway approved TFF1, TFF2 and the present study (Reference number: 2014/1397). All students, and parents/guardians of students younger than 16 years of age, gave written informed consent.

Anthropometric data

Information on birth weight (g), length (cm), gestational age (GA; weeks) was obtained from MBRN. GA was determined by ultrasound examination, or last menstrual period if ultrasound was missing. We calculated ponderal index (birth weight/birth length^3; kg/m^3). Growth status at birth was categorised as small for gestational age (SGA; <10th percentile), appropriate for gestational age and large for gestational age (LGA; >90th percentile) based on birth weight and GA, according to a national reference standard of births in 1987-1998 (29).

Anthropometric measurements are part of regular health controls by public health nurses in accordance with national preventive health programme guidelines. We retrospectively collected height (cm), weight (kg), age (years, months), and date of measurements at target ages; 2 and 6 years, from childhood health records for children living in Tromsø and the neighbouring municipalities during childhood. The exact age of the participants at the time measurements were taken varied slightly; median ages: 2.5 (range: 1.9-4.5) and 6.0 years (range: 5.0-7.7).

In TFF1 and TFF2, height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, on an automatic electronic scale/stadiometer (Jenix DS 102 stadiometer, Dong Sahn Jenix, Seoul, Korea). Participants wore light clothing and no footwear. Waist circumference (WC) was measured to the nearest cm with a measuring tape placed horizontally at umbilical level and at the end of a normal expiration. Subjects were standing with arms relaxed at sides and weight evenly distributed across feet. WC was measured twice and the mean value was used in the analyses. A WC ≥80 cm for girls and ≥94 cm for boys was used to define central overweight/obesity (13). Age at outcome measures in TFF1 and TFF2 are denoted 15-17 (median age: 16.6 range: 15.7-17.9 years), and 18-20 (median age: 18.6 range: 17.8-20.1 years) years of age, respectively or combined as 15-20 years of age.

Total body DXA scans were performed in TFF1 and TFF2 with the same DXA instrument, a GE Lunar prodigy (Lunar Corporation, Madison, Wisconsin, USA). Reported precision (Coefficient of variation) of the Lunar Prodigy instrument was <2.0% for total body measures (30). Lean mass, fat mass (FM), and bone mineral content were assessed and analysed with enCORE paediatric software version 13.4. Fat-free mass (20) was calculated as body weight minus FM. Fat mass index (FMI; FM in kg/ height in m^2), and fat-free mass index (FFMI; FFM in kg/ height in m^2) were calculated (10). Android:gynoid fat mass ratio (FMR; android FM (g) divided by gynoid FM (g)), a measure of abdominal fat, was also derived (16). Sex and age specific FMI and FFMI standard deviation scores (SDS) were calculated according to a UK reference standard (10). Change in FMI SDS and FFMI SDS between age 15-17 and 18-20 years was calculated as the individual FMI SDS/FFMI SDS at the latter age minus FMI SDS/FFMI SDS at the first age.

Height and weight were used to calculate BMI (weight/height^2; kg/m^2) at each age. BMI SDS was calculated according to the Norwegian reference standard (31). Participants were classified into BMI categories using the International Obesity Task Force (IOTF) age- and sex-specific cut-off values for children 2-18 years of age (32). Due to a relatively small proportion of participants with obesity, it was not possible to analyse obesity alone. Therefore, in the main analysis BMI was dichotomised as normal weight (adult BMI <25 kg/m^2) and overweight/obesity (adult BMI ≥25 kg/m^2). In addition, we used the following four categories; underweight (corresponding to adult BMI <18.5 kg/m^2), normal-weight (adult BMI ≥18.5-<25kg/m^2), light overweight (adult BMI ≥25-<27 kg/m^2) and severe overweight/obesity (adult BMI ≥27 kg/m^2). For comparison, prevalence rates according to the WHO Child Growth Standards and Growth reference 5-19 years are presented (33, 34).

Covariates from TFF1

Girls were categorised into three stages of pubertal maturation: early (<12.5 years), intermediate (12.5-13.9 years) and late (≥14.0 years), based on age at menarche reported in self-administered questionnaires. Pubertal maturation in boys was classified as barely started (PDS: 2.0-2.9), underway (PDS: 3.0-3.9), and completed (PDS: 4.0), based on the pubertal development scale (PDS), a validated self-reported measure. The boys rated four secondary sexual characteristics on a scale ranging from 1 (not yet started) to 4 (complete) and the PDS-score was calculated as a total mean score of the four items (28, 35). None had a score <2.0 in total score.

Physical activity frequency was measured through the validated WHO Health Behaviour in Schoolchildren questionnaire (36), which included the question: “If you are actively doing sports or physical activity outside school, how many days a week are you active?” Answers

were given in six predefined categories; “never” (1), “less than once a week” (2), “1 day a week” (3), “2 to 3 days a week” (4), “4 to 6 days a week” (5), and “almost every day” (6). The answers were recoded into three categories of physical activity: “low” (1-2), “moderate” (3-4), and “high” (5-6).

Statistical analyses

Sex specific characteristics of the study population are presented as means and standard deviations (SD) for continuous variables and numbers and percentages for categorical variables. Correlations between body composition and anthropometric measurements were explored by Spearman’s rank correlation coefficient (r_s).

Since age at childhood measurements varied, we used linear spline multilevel models fitted by Stata’s mixed command to estimate individual growth trajectories (37). “The broken stick model” (37, 38) uses data from individuals and from the whole study population to estimate person-specific length/height (cm) and weight (kg) with knots at target (median) ages: 2.5, 6.0 and 16.5 years, and individual growth trajectories between birth and age 2.5, and consecutive ages. Individual-level random effects for intercept and slopes are estimated as each person’s deviation from the average trajectory (37). Sex and an interaction term with sex and splines were included in the model to account for sex-differences in growth trajectories over time. In a two-step process, birth length, birth weight, height and weight at target ages were estimated by the model and used to calculate BMI variables.

The main outcomes in the present study were FMI SDS, FFMI SDS, android:gynoid FMR, and changes in FMI SDS/FFMI SDS between 15-17 and 18-20 years of age. In addition, FMI SDS and WC dichotomized, using the thresholds described above, were used as outcomes.

Exposure variables in the main analyses were birth weight per 1 SD, growth status at birth; being born small, appropriate or large for GA, in addition to BMI category at 2.5, 6.0 and 16.5 years of age. We used linear mixed models with a random intercept on the subject level to explore associations between exposure variables and repeated measures of FMI SDS, FFMI SDS, and android:gynoid FMR at 15-17 and 18-20 years of age, as continuous outcomes. In addition, generalized estimating equations (GEE) with a logit link function and an unstructured correlation matrix were used in the analysis of binary outcome variables. We explored the odds (ORs) of having central overweight/obesity (WC dichotomized), or a FMI SDS $\geq$ 1.0 (vs. not) at 15-20 years of age related to the exposure variables.

We used conditional growth modelling (39) to assess BMI gain between birth and age 2.5, and consecutive ages. In conditional growth models, growth measures are adjusted for prior body size. Accordingly, standardized residuals were obtained by multiple linear regression analyses of BMI SDS at all target ages regressed on prior BMI SDS (39). These residuals were used simultaneously in a linear mixed model with the outcomes. This index of growth is statistically independent of body size at the start of each growth period, and adjusts for both catch-up growth, and regression to the mean. This approach asks a prospective question; for each child, is he/she growing more than expected, given his or her size at the start of the growth period and how is this growth associated with the outcome measure.

In a subgroup analysis of those with body composition measures both from TFF1 and TFF2, we used conditional growth modelling to explore the relationship with change in FMI SDS and FFMI SDS.

Since body composition differs between girls and boys and according to pubertal maturation (40), all analyses were stratified by sex. Cross-product terms with sex and exposure variables were used to test for potential sex interactions. Models were adjusted for potential confounding factors; birth weight was adjusted for GA, associations between BMI at age 2.5 and 6.0 were adjusted for height at the same ages, BMI at age 16.5 was additionally adjusted for height, pubertal maturation and physical activity levels. Conditional growth models were adjusted for GA, pubertal maturation and physical activity levels.

Normality and linearity of exposures and outcome variables and residuals were checked by visual inspections of histograms and plots. No assumptions were considered violated for the final models applied.

We experienced missing data; height and weight from childhood health records, covariates from MBRN or from questionnaires in TFF1. The percentages (numbers) of missing values were; 10% (91) for GA, 4% (40) for birth length, 27% (244), and 22% (196) for height and weight at 2.5 and 6.0 years, respectively. In TFF1, 1% (11) was missing data on physical activity. Of the boys 22% (102) were missing PDS, of the girls 1% (6) were missing menarche age (Figure 1). To minimize selection bias, missing values were estimated/imputed under the assumption of missing at random. Linear spline multilevel models were used to estimate missing birth length, height and weight at age 2.5 and 6.0. Multiple imputation was used to impute missing GA and covariates from TFF1 based on exposure and outcome variables. We used chained equations, generating 20 imputations and we report pooled estimates (41). Separate imputations were performed for boys and girls. In sensitivity analyses, the main analyses were repeated in a complete cases dataset (n=633). Differences

between participants with and without missing data were explored by t-test for continuous variables and by the χ^2 test for categorical variables.

All procedures were performed in Stata/MP 15.1 for Mac (Stata Corp, College Station, TX, USA). Statistical significance level was set to a two-sided p-value of 5%.

RESULTS

We analysed data from 439 girls and 468 boys, 94% of the core age group <18 years of age in TFF1. Of these, 68.5% (336 girls and 285 boys) had body composition measures from both TFF1 and TFF2 (Figure 1), and were used in the subgroup analysis.

Body composition and overweight/obesity

Characteristics of the study population from birth up to 18-20 years of age are presented in Table 1. The vast majority (99%) was of white ethnicity. Additional detailed descriptive body composition measures per sex and age are provided in Table S1.

According to the IOTF definition, the prevalence of overweight including obesity was 9.1% and 15.0% in girls, 6.4% and 8.6% in boys at 2.5 and 6.0 years of age, respectively. At 15-17 and 18-20 years of age, 20.8% and 21.4% of girls, and 23.4% and 28.0% of boys were overweight/obese (**Table 1**). Comparisons with the WHO definitions are presented in Table S2.

The proportion with a FMI SDS ≥1.0 was 19% and 17% in girls, 25% and 15% in boys at 15-17 and 18-20 years of age, respectively. The proportion classified with central overweight/obesity was 32.0% among girls, 13.5% among boys at 15-17 years of age (Table

1). There were significant positive correlations between WC and DXA measured truncal FM, girls: (r_s= 0.830, n=439, r_s= 0.770, n=336), boys: (r_s= 0.854, n=468, r_s= 0.879, n=285) at 15-17 and 18-20 years of age, respectively. Positive correlations were also seen between android:gynoid FMR and truncal FM, girls: (r_s= 0.804, n=439, r_s=0.792, n=336), boys: (r_s=0.718, n=468, r_s=0.689, n=285) at 15-17 and 18-20 years of age, respectively. All correlation coefficients p <0.001.

Birth weight, body composition and central overweight/obesity

In both sexes, birth weight was positively associated (p<0.01) with FFMI SDS at 15-20 years of age (Table 2). The estimates are equivalent to 1.9 kg FFM in girls and 2.2 kg FFM in boys at age 15-20 per 1 SD (590 g) increase in birth weight. Birth weight was significantly associated with higher FMI SDS at age 15-20 only in girls: 0.19 SDS (95% CI, 0.08 to 0.31, p<0.01). To remove a possible effect of length at birth, we analysed ponderal index and the estimated coefficients were similar as for birth weight (Table 2). There was no statistically significant association between birth weight and android:gynoid FMR (Table 2). Birth weight was significantly associated with height at 15-20 years of age in both sexes (girls: 2.5 cm, boys: 2.2 cm, p<0.001) per 1 SD higher birth weight (data not shown). Being born SGA was associated with lower FMI SDS and FFMI SDS, however only significant in girls (p<0.05) (Table 2). In girls, 1 SD higher birth weight was associated with a significantly increased odds of central overweight/obesity (OR 1.32, 95% CI 1.06 to 1.64) and a FMI SDS ≥1.0 (OR 1.38, 95% CI 1.05 to 1.81) whereas being born SGA revealed significantly reduced odds of central overweight/obesity (OR 0.50, 95% CI 0.26 to 0.99). In boys, being born SGA was associated with significantly reduced odds of a FMI SDS ≥1.0 (OR 0.44, 95% CI 0.21 to 0.92) (Table 3).

BMI gain and body composition

Associations of individually modelled growth (i.e. conditional changes in BMI SDS between birth, age 2.5 years and consecutive ages) with body composition measures at 15-20 years of age are shown in Figure 2 (Table S3). Childhood BMI gain was significantly positively associated with FMI SDS, FFMI SDS and android:gynoid FMR at 15-20 years of age ($p<0.001$). The magnitude of the associations increased with age. The observed effect of increasing BMI from birth to 2.5 years of age was similar for FMI- and FFMI SDS. Greater BMI gain at later ages had a stronger impact on FMI SDS than on FFMI SDS with the highest estimates for growth between ages 6.0-16.5 years (Figure 2).

BMI gain and changes in FMI and FFMI SDS

On average, in both boys and girls, a small positive increase in FMI SDS was seen between TFF1 and TFF2 (Table 4). There was a significant positive correlation between FMI SDS at the two time points; girls: ($r_s = 0.796$ n= 336 $p<0.001$), boys: ($r_s = 0.845$ n= 285 $p<0.001$). Greater BMI gain in early childhood was not a significant predictor of increase in FMI-, or FFMI SDS between 15-17 and 18-20 years of age (Table 4). In both girls and boys, greater BMI gain between ages 6.0-16.5 years was associated with a weak, but significant decrease in FMI SDS but no significant change in FFMI SDS (Table 4). These findings were confirmed if change in absolute values of FMI and FFMI were used as outcome instead of the SDS (data not shown).

BMI categories, body composition and central overweight/obesity

In girls, overweight/obesity at 2.5 or at 6.0 years of age was associated with a significantly higher FMI SDS and FFMI SDS, compared to being under-/normal weight at the same ages (Table 2). The magnitude of the associations was similar. In boys, overweight/obesity at 2.5

years of age was significantly positively associated with FFMI SDS at 15-20 years of age. Overweight/obesity at 6.0 years of age was associated with significantly higher FMI SDS and FFMI SDS compared to being under-/normal weight, and the indices were estimated to give similar effects. At age 16.5 years, stronger associations were seen with FMI SDS than FFMI SDS for those with overweight/obesity, compared to those of normal weight. Stronger estimated effects were seen with higher BMI, in both sexes. Compared to normal weight, severe overweight/obesity at age 16.5 corresponded to an average of 21.3 kg increased FM in girls, and 22.3 kg increased FM in boys. Furthermore, in both sexes, overweight/obesity both at 6.0 and 16.5 years of age was significantly associated with an increased android:gynoid FMR at 15-20 years of age (Table 2). No such association was seen with overweight/obesity at 2.5 years of age. Underweight was consistently associated with significantly lower FMI SDS and FFMI SDS at all ages (data shown only for 16.5 years). In addition, overweight/obesity at 6.0 and 16.5 years of age was associated with significantly increased odds of central overweight/obesity and a FMI SDS ≥1.0 compared to those of normal weight, in both girls and boys (Table 3).

Sensitivity and dropout analyses

Sensitivity analyses showed no significant differences in body composition measures compared to cases with missing birth weight and/or childhood measurements. Sensitivity analyses produced results similar to those presented, except that birth weight in girls no longer was significantly associated with FMI SDS (data not shown). Dropout analyses (n=907) showed that significantly more boys (39.1%) than girls (23.5%) were either lost to follow-up or were missing body composition measures in TFF2 ($p<0.001$). No significant difference in birth weight or childhood BMI was seen between those with body composition measures from TFF2 and those with missing values. However, girls who were missing in

TFF2 had significantly higher FMI, FMI SDS, mean waist and android:gynoid FMR in TFF1 than those with data also from TFF2 ($p<0.05$). Boys who were missing in TFF2 did not differ from those with complete data except for significantly ($p<0.01$) higher android:gynoid FMR in TFF1 (data not shown). Additional information on observed and estimated/imputed values and sensitivity analyses are provided in Table S4, S5 and S6.

DISCUSSION

In this longitudinal population-based study with repeated DXA derived body composition measures in adolescence, we found a weak significant association between birth weight and FFMI SDS at 15-20 years of age in both sexes, and with FMI SDS only in girls. We did not find any indications that low birth weight was associated with adverse levels of FM or central obesity. BMI gain in each age interval from birth and up to 16.5 years of age was associated with higher FMI-, FFMI SDS, and android:gynoid FMR, with the strongest associations seen for the age period 6-16.5 years. While increasing BMI in early childhood was more equally associated with both FFMI- and FMI SDS, increasing BMI later in childhood was more strongly related to FMI SDS. However, a greater BMI gain in childhood was not associated with a continued rise in FMI between 15-17 and 18-20 years of age. In both sexes, overweight/obesity at 6.0 and 16.5 years of age was associated with significantly higher odds of both central overweight/obesity and a FMI SDS $\geq$1.0, compared to being under-/normal weight.

We compared our DXA derived body composition data with British reference data (collected 2001-2010) (10) due to lack of such reference data for Norwegian adolescents. DXA reference data for FFMI and FMI were derived from the British database, which correlate strongly ($r >0.93$ in both sexes) with equivalent FFMI and FMI SDS obtained from the gold

standard 4-component (4C) model in the same sample (10). Overall, our study population was similar to the British reference population (10), as shown in table 1. Compared to Swedish normative data, (42) our adolescents had higher weight, BMI and FM at all ages between 15-19 years. The Swedish data (42) were collected 10-20 years before our study. This may explain some of the differences, as the prevalence of overweight/obesity has increased in recent decades (43). Variation between DXA scanners may also influence the measures (30, 42). Our cohort represents a Norwegian adolescent population, however with a restriction since the prevalence of overweight/obesity, and BMI SDS at 16.5 years of age was somewhat higher than reported from other regions of Norway (31, 44), and since the participants were of mainly white ethnicity.

Birth weight, body composition and central overweight/obesity

In accordance with others (9, 15-19, 21, 22), we found an association between higher birth weight and FFMI later in life. Associations between higher birth weight and FMI have been less consistent (9), and we observed a positive association with FMI only in girls. However, no statistically significant interaction with sex was seen. In girls, birth weight was also associated with increased odds of a WC ≥80 cm, but there was no relation with android:gynoid FMR. Also Sachdev et al., found associations between birth weight and adiposity only in girls (17). In both sexes, there was a positive association between birth weight and height at 15-20 years of age. Previous findings of significant associations between birth weight and overweight/obesity measured by BMI (7, 27), might therefore reflect a larger body size, not necessarily adiposity. Associations between birth weight and later body composition are partly explained by genetic factors. In a review of twin studies, heritability of BMI was found to be high, from 60-80% across ages while the influence of environmental factors increased with age, up to 40% (45). Low birth weight, or preterm birth has been linked

to central obesity (9, 15, 20). We could not confirm an association between low birth weight and later adverse levels of FMI or central obesity, results in line with findings from a Dutch study of preterm infants (18).

BMI gain and body composition

Conditional BMI gain between ages 2.5-6.0, and 6.0-16.5 years, was strongly associated with both higher FMI SDS and FFMI SDS at 15-20 years of age, with the highest estimates seen for FMI SDS in the latter age interval. Overweight/obesity at the ages 6.0 and 16.5 years reflected similar patterns. BMI gain in early childhood, before 2.5 years of age, indicated a stronger association with FFMI, or a more equal association with FMI and FFMI, in line with another study (46). Greater BMI gain after age 6.0 years, was more strongly associated with higher FM in adolescence. This suggests that centile crossing is more "obesogenic" at later ages, also observed by others (16, 17, 23, 24). Others have found that BMI changes between 2-6 years of age were most strongly associated with FM at age 15 (25), or adult overweight (47). Barker et al. (48), linked rapid BMI gain between 2 and 11 years with CVD risk. A recently published study showed that upward BMI centile crossing between 7 years of age and early adulthood was associated with an increased risk of type 2 diabetes. However, overweight at 7 years of age was associated with an increased risk of type 2 diabetes only if it persisted until puberty or later ages (4). Early identification of children at risk, especially those with a rapid increase in BMI around the age of six, may therefore be possible and of importance. However, later childhood and adolescence emerge as an important period for development of overweight or obesity (47), and are therefore of equal importance as target for preventive efforts. Different influential factors may be of importance in different age groups. As reported by Nan et al. (45), the influence of unique environmental factors on BMI increased with age.

BMI gain and changes in FMI SDS

We found no indication that greater BMI gain in childhood was associated with a continued rise in adiposity between 15-17 and 18-20 years of age. A weak decline in FMI SDS was observed, which may indicate that body composition measures are stabilising in the transition to young adulthood. It should be noted that these analyses were performed in a subgroup of the study population and the possibility of selection bias cannot be ruled out.

Central overweight/obesity

A concern is related to the relatively large proportion (32.0%) of girls with a WC ≥80 cm at 15-17 years of age, since there is a link between central obesity and disease risk (6, 13). A WC threshold of 80.9 cm in girls and 83.5 cm in boys was moderate to highly accurately associated with an unhealthier clustered CVD risk in European adolescents (14). In line with findings from the GOOD study from Sweden (23), we observed a strong association between greater BMI gain between 6.0 and 16.5 years of age and central overweight/obesity measures at 15-20 years of age. The observed gender difference in central overweight/obesity may, at least partly, be related to accuracy of the reference (13). Stronger correlation between WC and truncal fat mass was observed among boys. More boys than girls were classified as overweight/obese based on BMI both according to the IOTF and the WHO reference. However, considerably higher prevalence of central obesity in girls has recently been reported from another Norwegian youth cohort (49). This should be a subject of further investigation.

Strengths and limitations

The main strengths of this study are its large, population-based design and access to longitudinal data from birth to 18-20 years of age. The high attendance rate in TFF1 and the

population-based design reduce the risk of selection bias. Body composition was measured with DXA, which has shown very good agreement with 4C models (10), and CT measures of visceral adipose tissue (50). Data from MBRN and objectively measured height and weight data from childhood and from the Fit Futures study reduce the risk of information bias. Longitudinal data from birth and childhood with repeated body composition measures, at the end of height growth, on the cusp of adulthood, is rare and a strength of this study. The main limitation is missing data. Despite >90% participation rate in TFF1 this introduces a risk of selection bias. However, sensitivity analyses showed that missing data from birth and/or childhood were not related to the outcome. While more boys than girls did not attend TFF2, dropout analyses showed higher levels of FMI and central obesity measures in girls who did not attend TFF2. We used linear spline multilevel modelling (37), and multiple imputation (41), to handle missing data. These are recommended methods to deal with challenges as we experienced; when data are not measured at the same point in time, data are from different sources or with missing data. The predicted height and weight values led to somewhat lower proportions of overweight/obesity at age 2.5 and 6.0, than those observed. The estimated associations between BMI categories in childhood and body composition in adolescence might therefore be somewhat underestimated. Sensitivity analyses of complete cases did not indicate that missing data highly influenced of our estimates. Unfortunately, information on potential confounding factors, such as parental, nutritional, physical activity levels, and other lifestyle factors were not available from MBRN and childhood health records. Such factors might influence body composition, and would likely have improved our statistical models. Whether our observation of patterns of BMI gain linked to adverse body composition in adolescence will lead to disease, remains to be seen. Longitudinal cohort data on growth, body composition and adult disease risk are currently sparse, and follow-up studies warranted (1-3, 9, 13).

Conclusion

Overweight/obesity at 6.0 and 16.5 years of age as well as greater BMI gain in this age period are strong predictors of higher FMI, FFMI as well as central obesity measures at 15-20 years of age. Early identification of children at risk of adverse levels of adiposity is possible and preventive efforts should focus both on childhood and adolescence.

Conflict of interest:

The authors declare that they have no conflict of interest.

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Author's contributions:

ASF and NE designed and conducted TFF1 and TFF2. NE, and EE were responsible for supplementary data collection from childhood health records. JW calculated SDS according to the UK reference. EE carried out the statistical analysis and drafted the initial manuscript. TW gave statistical counselling. EE takes responsibility for the integrity of the data analysis. EE, GS, AK, ASF, JW, TW,

AW and NE made substantial contributions to the interpretation of data, critically revised the manuscript and gave their approval of the final version of the manuscript.

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Table 1. Sex specific characteristics of the study population at birth and four ages up to 18-20 years of age. The Tromsø Study: Fit Futures (n=907)

	Girls			Boys		
Characteristics	n	mean/%	SD	n	mean/%	SD
Birth						
Birth weight (g)	439	3453.9	579.3	468	3601.1	591.3
Birth length (cm) [a]	439	49.4	1.7	468	50.2	1.7
Gestational age (weeks)	389	39.7	1.8	427	39.6	2.1
Body mass index (kg/m^2) [a]	439	14.08	1.71	468	14.21	1.67
BMI SDS [a b]	439	-0.04	1.31	468	-0.07	1.15
Size for gestational age [c]:	389			427		
SGA	49	12.6%		46	10.8%	
AGA	302	77.6%		332	77.7%	
LGA	38	9.8%		49	11.5%	
2.5 years of age						
Weight [a]	439	13.5	1.4	468	14.2	1.4
Height (cm) [a]	439	91.6	3.3	468	93.2	3.2
Body mass index (kg/m^2) [a]	439	16.10	1.27	468	16.31	1.18
BMI SDS [a b]	439	-0.13	1.13	468	-0.23	0.98
BMI category [a d]:	439			468		
Underweight	61	13.9%		52	11.1%	
Normal weight	338	77.0%		386	82.5%	
Light overweight	29	6.6%		17	3.6%	
Severe overweight/obesity	11	2.5%		13	2.8%	
6.0 years of age						
Weight [a]	439	21.5	3.4	468	21.6	2.9
Height (cm) [a]	439	116.9	4.3	468	118.1	4.3
Body mass index (kg/m^2) [a]	439	15.70	1.96	468	15.47	1.62
BMI SDS [a b]	439	-0.23	1.17	468	-0.25	1.06
BMI category [a d]:	439			468		
Underweight	53	12.1%		66	14.1%	
Normal weight	320	72.9%		362	77.4%	
Light overweight	37	8.4%		21	4.5%	
Severe overweight/obesity	29	6.6%		19	4.1%	
16.5 years of age						
Weight [a]	439	61.5	11.9	468	70.4	14.6
Height (cm) [a]	439	165.6	6.3	468	177.7	6.5
Body mass index (kg/m^2) [a]	439	22.40	4.07	468	22.24	4.19
BMI SDS [a b]	439	0.46	1.20	468	0.35	1.15
BMI category [a d]:	439			468		
Underweight	27	6.2%		40	8.6%	
Normal weight	321	73.1%		318	68.0%	
Light overweight	38	8.7%		41	8.7%	
Severe overweight/obesity	53	12.1%		69	14.7%	
Waist circumference (cm)	439	77.5	10.3	468	81.9	11.2
Central overweight/obesity [i]	141	32.1%		63	13.5%	
Fat mass	439	20.6	9.0	468	14.7	10.8
Fat mass trunk	439	9.9	4.8	468	7.4	5.7
Fat-free mass	439	40.7	4.7	468	55.5	6.9
Fat mass index (kg/m^2)	439	7.55	3.28	468	4.67	3.39
Fat-free mass index (kg/m^2)	439	14.91	1.34	468	17.67	1.66

Fat mass index SDS [e]	439	0.23	0.95	468	0.06	1.15
Fat-free mass index SDS [e]	439	0.01	0.96	468	-0.09	0.95
Android:gynoid fat mass ratio	439	0.33	0.09	468	0.38	0.11
Pubertal maturation, girls [f]:	436			-	-	-
Early (<12.5 y.)	130	29.8%		-	-	-
Intermediate (12.5-13.9 y.)	204	46.8%		-	-	-
Late (≥14.0 y.)	102	23.4%		-	-	-
Pubertal maturation, boys [g]:	-	-	-	366		
Barely started (PDS 2.0-2.9)	-	-	-	65	17.7%	
Underway (PDS 3.0-3.9)	-	-	-	270	73.8%	
Completed (PDS 4.0)	-	-	-	31	8.5%	
Physical activity – frequency [h]	436			460		
Low	145	33.3%		171	37.2%	
Moderate	188	43.1%		169	36.7%	
High	103	23.6%		120	26.1%	
18-20 years of age						
Age (years)	358	18.6	0.4	303	18.6	0.4
Weight	340	63.7	12.1	285	75.1	14.6
Height (cm)	340	166.0	6.4	285	179.1	6.5
Body mass index (kg/m^2)	340	23.12	4.29	285	23.36	4.15
BMI category [d]:	340			285		
Underweight	15	4.4%		24	8.4%	
Normal weight	252	74.1%		181	63.5%	
Light overweight	27	7.9%		36	12.6%	
Severe overweight/obesity	46	13.5%		44	15.4%	
Waist circumference (cm)	340	78.1	11.5	285	84.6	11.8
Central overweight/obesity [i]	107	31.5%		54	19.0%	
Fat mass	336	21.8	9.4	285	16.6	11.3
Fat mass trunk	336	10.7	5.4	285	8.9	6.4
Fat-free mass	336	41.7	4.9	285	58.4	7.2
Fat mass index (kg/m^2)	336	7.93	3.46	285	5.18	3.45
Fat-free mass index (kg/m^2)	336	15.13	1.39	285	18.18	1.78
Fat mass index SDS [e]	336	0.22	1.05	285	0.02	1.18
Fat-free mass index SDS [e]	336	0.13	0.97	285	-0.17	1.07
Android:gynoid fat mass ratio	336	0.35	0.10	285	0.43	0.11

[a] Birth length, height, weight at 2.5, 6.0 and 16.5 years of age, and BMI, BMI SDS, BMI category at birth, 2.5, 6.0 and 16.5 years of age based on estimated values by linear spline multilevel model at the exact target age.
[b] BMI SDS according to Norwegian reference data (31)
[c] Size for gestational age according to Norwegian reference data (29)
[d] BMI categories according to IOTF age-and sex-specific cut-off values for children 2-18 years of age (32); underweight (adult BMI <18.5kg/m^2), normal weight (adult BMI ≥18.5-<25kg/m^2), light overweight (adult BMI ≥25-<27 kg/m^2), severe overweight/obesity (adult BMI ≥27 kg/m^2)
[e] Standard deviation scores (SDS) for body composition measures according to UK reference data (10)
[f] Pubertal maturation is based on age of menarche in girls.
[g] Pubertal maturation is based on Pubertal Development Scale (PDS) in boys (35). None had a score <2.0 in total score.
[h] Physical activity is categorised into three groups based on Health Behaviour in School Children questionnaire (36)
[i] Central overweight/obesity is defined as a waist circumference ≥80 cm for girls and ≥94 cm for boys (13).
SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; BMI, body mass index

Table 2. Regression coefficients for associations between birth weight, BMI category at 2.5, 6.0, and 16.5 years of age and fat mass index SDS, fat-free mass index SDS and android:gynoid fat mass ratio at 15-20 years of age in girls and boys, The Tromsø Study, Fit Futures

	GIRLS (n=439)			BOYS (n=468)		
	FMI SDS	**FFMI SDS**	**Android:gynoid FMR**	**FMI SDS**	**FFMI SDS**	**Android:gynoid FMR**
Birth [b]						
Birth weight per SD	0.19 (0.08, 0.31) **	0.18 (0.07, 0.29) **	-0.00 (-0.01, 0.01)	0.09 (-0.03, 0.21)	0.15 (0.04, 0.25) **	-0.00 (-0.02, 0.01)
Ponderal index per SD	0.14 (0.05, 0.24) **	0.16 (0.06, 0.25) **	-0.00 (-0.01, 0.01)	0.09 (-0.02, 0.21)	0.12 (0.03, 0.22) *	-0.00 (-0.01, 0.01)
Size for gestational age [c]:						
SGA	-0.40 (-0.67, -0.13) **	-0.30 (-0.56, -0.04) *	-0.00 (-0.03, 0.03)	-0.34 (-0.68, 0.01)	-0.03 (-0.32, 0.26)	-0.01 (-0.04, 0.03)
AGA	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
LGA	0.20 (-0.11, 0.51)	0.30 (-0.01, 0.61)	-0.01 (-0.04, 0.02)	0.27 (-0.06, 0.60)	0.37 (0.08, 0.65) *	0.00 (-0.03, 0.03)
2.5 years of age [d]						
Under-/normal weight	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Overweight/obesity	0.50 (0.19, 0.81) **	0.50 (0.19, 0.80) **	0.01 (-0.02, 0.04)	0.34 (-0.08, 0.76)	0.61 (0.25, 0.96) **	-0.02 (-0.06, 0.02)
6.0 years of age [d]						
Under-/normal weight	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Overweight/obesity	1.18 (0.95, 1.41) ***	0.97 (0.74, 1.20) ***	0.08 (0.06, 0.10) ***	1.17 (0.82, 1.52) ***	1.07 (0.77, 1.37) ***	0.11 (0.08, 0.15) ***
16.5 years of age [e]						
Underweight	-0.90 (-1.14, -0.66) ***	-0.66 (-0.95, -0.38) ***	-0.05 (-0.08, -0.03) ***	-1.10 (-1.35, -0.85) ***	-1.23 (-1.49, -0.97) ***	-0.04 (-0.07, -0.02) **
Normal weight	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Light overweight	0.94 (0.73, 1.14) ***	0.67 (0.43, 0.92) ***	0.07 (0.05, 0.09) ***	1.30 (1.05, 1.55) ***	0.43 (0.18, 0.68) ***	0.11 (0.09, 0.14) ***
Severe overweight/obesity	1.95 (1.77, 2.13) ***	1.45 (1.24, 1.67) ***	0.15 (0.13, 0.18) ***	1.80 (1.60, 2.00) ***	0.97 (0.77, 1.17) ***	0.18 (0.16, 0.20) ***

Based on analysis with linear mixed models. Values reflect standardized β coefficients (95% CI) for FMI SDS and FFMI SDS and β coefficients (95% CI) for android:gynoid FMR.
Analysed in a dataset with 20 imputations (multiple imputation of missing co-variates at birth and at 16.5 years of age), n=907 (439 girls and 468 boys)

[a] Fat mass index and Fat-free mass index SDS according to UK Reference data (10)

[b] Birth models are adjusted for gestational age.

[c] Size for gestational age according to Norwegian Reference data (29)

[d] BMI categories according to IOTF age- and sex-specific cut-off values for children 2-18 years of age (32). Dichotomised: under-/normal weight (adult BMI <25kg/m^2), overweight/obesity (adult BMI ≥25 kg/m^2). Models at 2.5, and 6.0 years of age are adjusted for height.

[e] BMI in four categories according to IOTF (32): underweight (adult BMI <18.5kg/m^2), normal weight (adult BMI ≥18.5-<25kg/m^2), light overweight (adult BMI ≥25-<27 kg/m^2), severe overweight/obesity (adult BMI ≥27 kg/m^2). Models at 16.5 years of age are adjusted for height, pubertal maturation and physical activity frequency.

CI, Confidence interval; FMI, fat mass index (kg/m^2); FFMI, fat-free mass index (kg/m^2); FMR, fat mass ratio; SD, standard deviation; SDS, standard deviation score; Ponderal index (kg/m^3); SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age.

* p<0.05, ** p<0.01, *** p<0.001

Table 3. Odds ratios (95% CI) for central overweight/obesity[a] or a fat mass index SDS[b] ≥ 1.0 at 15-20 years of age, The Tromsø Study: Fit Futures

	Girls		Boys	
	Waist category (≥80 cm)	**FMI SDS ≥ 1.0**	**Waist category (≥94 cm)**	**FMI SDS ≥ 1.0**
Birth [c]				
Birth weight per SD	1.32 (1.06, 1.64)*	1.38 (1.05, 1.81) *	1.23 (0.96, 1.58)	1.08 (0.87, 1.34)
Size for gestational age [d]				
SGA	0.50 (0.26, 0.99)*	0.39 (0.15, 1.04)	0.47 (0.20, 1.14)	0.44 (0.21, 0.92) *
AGA	*Reference*	*Reference*	*Reference*	*Reference*
LGA	1.46 (0.84, 2.53)	1.40 (0.69, 2.83)	1.62 (0.82, 3.18)	1.02 (0.54, 1.94)
2.5 years of age [e]				
Under-/normal weight	*Reference*	*Reference*	*Reference*	*Reference*
Overweight/obesity	1.39 (0.77, 2.52)	2.00 (1.03, 3.89) *	1.32 (0.61, 2.87)	1.18 (0.57, 2.45)
6.0 years of age [e]				
Under-/normal weight	*Reference*	*Reference*	*Reference*	*Reference*
Overweight/obesity	4.78 (3.05, 7.48) ***	7.41 (4.49, 12.20) ***	5.56 (3.24, 9.54) ***	4.14 (2.41, 7.09) ***
16.5 years of age [f]				
Underweight	0.18 (0.04, 0.73) *	0.68 (0.16, 2.85)	0.48 (0.06, 3.69)	0.12 (0.02, 0.87) *
Normal weight	*Reference*	*Reference*	*Reference*	*Reference*
Light overweight	6.50 (3.92, 10.77) ***	12.49 (6.55, 23.81) ***	10.40 (4.99, 21.68) ***	12.84 (7.34, 22.45) ***
Severe overweight/obesity	18.81 (10.91, 32.42) ***	74.22 (40.22, 136.96) ***	63.89 (34.98, 116.70) ***	23.28 (14.73, 36.80) ***

[a] Central obesity were defined as a waist circumference ≥80 cm for girls, and ≥94 cm for boys at 15-20 years of age.
Data were analysed with Generalized estimating equations (GEE) and values reflect odds ratios (OR) with 95% CI.
Analysed in a dataset with 20 imputations (multiple imputation of missing co-variates at birth and at 16.5 years of age), n=907 (439 girls and 468 boys)
[b] Fat mass index and Fat-free mass index SDS according to UK reference data (10)
[c] Birth models are adjusted for gestational age.
[d] Size for gestational age according to Norwegian reference data (29)
[e] BMI categories according to IOTF age- and sex-specific cut-off values for children 2-18 years of age (32). Dichotomised: under-/normal weight (adult BMI <25kg/m^2), overweight/obesity (adult BMI ≥25 kg/m^2). Models at 2.5, and 6.0 years of age are adjusted for height.
[f] BMI in four categories according to IOTF (32): underweight (adult BMI <18.5kg/m^2), normal weight (adult BMI ≥18.5-<25kg/m^2), light overweight (adult BMI ≥25-<27 kg/m^2), severe overweight/obesity (adult BMI ≥27 kg/m^2). Models at 16.5 years of age are adjusted for height, pubertal maturation and physical activity frequency.
OR, Odds ratio; CI, Confidence interval; FMI, fat mass index (kg/m^2); SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age.
* p<0.05; *** p<0.001

Table 4 Standardized regression coefficients for associations of conditional BMI gain between birth, 2.5, 6.0, and 16.5 years of age with changes in fat mass index SDS and fat-free mass index SDS between 15-17 and 18-20 years of age in girls and boys, The Tromsø Study: Fit Futures

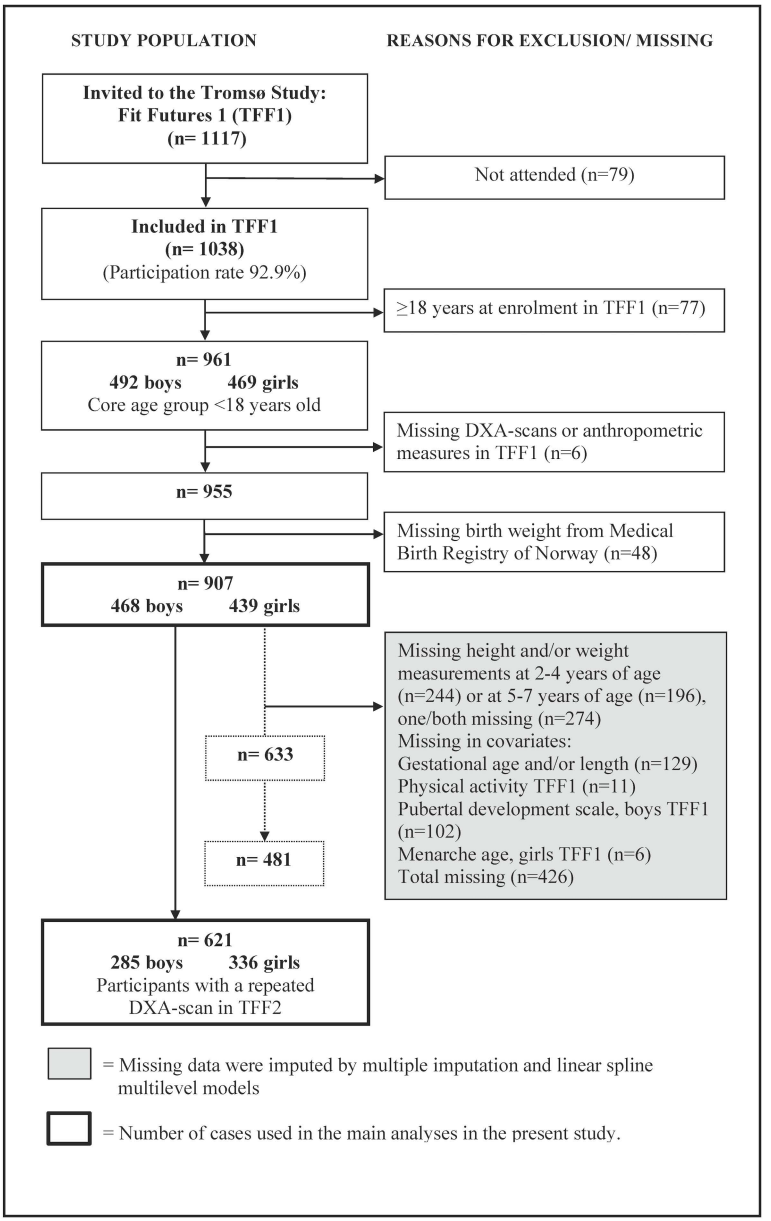
GIRLS	**Δ FMI SDS** [a]	**Δ FFMI SDS** [a]
Mean change (SD)	0.04 (0.61)	0.12 (0.49)
Birth to 2.5 years of age	-0.01 (-0.07, 0.06)	-0.02 (-0.08, 0.03)
2.5 to 6.0 years of age	0.05 (-0.01, 0.12)	0.03 (-0.02, 0.09)
6.0 to 16.5 years of age	-0.08 (-0.15, -0.02) *	-0.02 (-0.07, 0.04)
BOYS		
Mean change (SD)	0.01 (0.62)	-0.05 (0.49)
Birth to 2.5 years of age	-0.06 (-0.14, 0.01)	0.01 (-0.05, 0.07)
2.5 to 6.0 years of age	-0.04 (-0.11, 0.04)	0.02 (-0.04, 0.08)
6.0 to 16.5 years of age	-0.11 (-0.18, -0.04) **	0.01 (-0.05, 0.07)

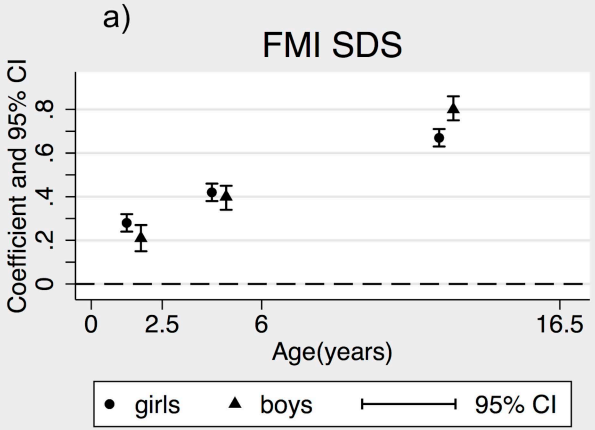
Values are based on multiple linear regression models and reflect change in standardized coefficients (95% CI) per standardized residual of conditionally modelled gain in BMI SDS. Conditional growth variables are independent of prior body size. Models are adjusted for gestational age, pubertal maturation and physical activity frequency.
Analysed in a dataset with 20 imputations (multiple imputation of missing co-variates at birth and at 16.5 years of age), n=621 (336 girls and 285 boys)
[a] Fat mass index and Fat-free mass index SDS according to UK Reference data (10)
CI, Confidence interval; FMI, fat mass index (kg/m^2); FFMI, fat-free mass index (kg/m^2); SD, standard deviation; SDS, standard deviation score
* $p<0.05$, ** $p<0.01$

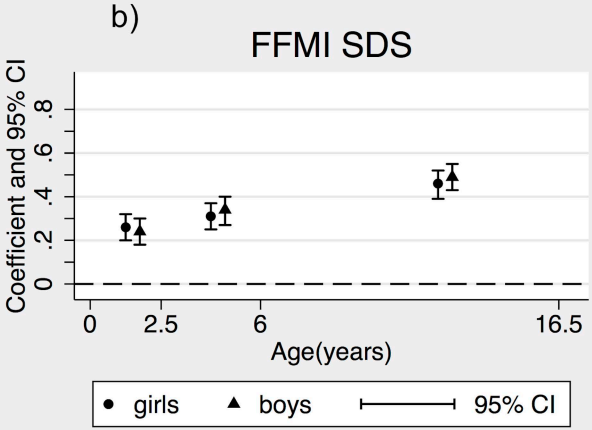
Figure legends

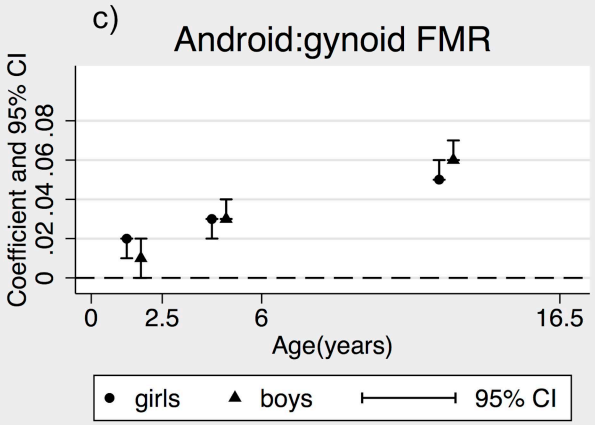
Figure 1 Flowchart of the study population, The Tromsø study: Fit Futures

Figure 2 Associations of conditional BMI gain from birth up to age 16.5 years with a) FMI SDS, b) FFMI SDS and c) android:gynoid FMR at 15-20 years of age, in girls and boys. Values are based on linear mixed models and reflect β coefficients and 95% CI per standardized residual of conditionally modelled BMI gain. Models are adjusted for gestational age, pubertal maturation and physical activity frequency measured in TFF1. (See also Table S2) Markers are placed approximately at mid-point of each growth period. The Tromsø study: Fit Futures (n=907; 439 girls and 468 boys)


STUDY POPULATION
REASONS FOR EXCLUSION/ MISSING
Invited to the Tromsø Study: Fit Futures 1 (TFF1) (n= 1117)
Not attended (n=79)
Included in TFF1 (n= 1038) (Participation rate 92.9%)
≥18 years at enrolment in TFF1 (n=77)
n= 961 492 boys 469 girls Core age group <18 years old
Missing DXA-scans or anthropometric measures in TFF1 (n=6)
n= 955
Missing birth weight from Medical Birth Registry of Norway (n=48)
n= 907 468 boys 439 girls
Missing height and/or weight measurements at 2-4 years of age (n=244) or at 5-7 years of age (n=196), one/both missing (n=274)
Missing in covariates:
Gestational age and/or length (n=129)
Physical activity TFF1 (n=11)
Pubertal development scale, boys TFF1 (n=102)
Menarche age, girls TFF1 (n=6)
Total missing (n=426)
n= 633
n= 481
n= 621 285 boys 336 girls Participants with a repeated DXA-scan in TFF2
= Missing data were imputed by multiple imputation and linear spline multilevel models
= Number of cases used in the main analyses in the present study.


a)
FMI SDS
Coefficient and 95% CI
0 .2 .4 .6 .8
0 2.5 6 16.5
Age(years)
girls boys 95% CI


b)
FFMI SDS
Coefficient and 95% CI
0 .2 .4 .6 .8
0 2.5 6 16.5
Age(years)
girls boys 95% CI


c)
Android:gynoid FMR
Coefficient and 95% CI
0 .02 .04 .06 .08
0 2.5 6 16.5
Age(years)
girls boys 95% CI

Adolescent body composition, and associations with body size and growth from birth to late adolescence. The Tromsø Study: Fit Futures – a Norwegian longitudinal cohort study
Elin Evensen*, Nina Emaus, Anne-Sofie Furberg, Ane Kokkvoll, Jonathan Wells, Tom Wilsgaard, Anne Winther, Guri Skeie

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Table S1 Age and sex specific descriptive anthropometric measures and DXA-derived body composition data at age 15-19 years of age. The Tromsø Study: Fit Futures

Girls	Age (years) 15 n=14	Age (years) 16 n=362	Age (years) 17 n=63	Age (years) 18 n=283	Age (years) 19 n=53
Weight (kg)	60.3 (8.3)	61.4 (11.9)	60.6 (10.4)	63.5 (12.0)	63.6 (12.0)
Height (cm)	164.4 (6.0)	164.9 (6.5)	165.9 (5.7)	166.1 (6.5)	165.6 (6.1)
Body mass index (kg/m^2)	22.46 (3.81)	22.55 (4.14)	21.98 (3.35)	23.03 (4.19)	23.25 (4.54)
Waist circumference (cm)	77.3 (9.8)	77.5 (10.4)	77.4 (10.4)	77.9 (10.9)	77.8 (12.7)
Fat mass (kg)	21.2 (6.6)	20.7 (9.2)	19.8 (8.2)	21.7 (9.4)	22.3 (9.7)
Fat mass trunk (kg)	10.1 (3.9)	9.9 (4.9)	9.5 (4.5)	10.7 (5.3)	11.1 (5.7)
Lean mass (kg)	37.1 (3.4)	38.7 (4.7)	38.7 (4.3)	39.4 (4.9)	38.9 (4.4)
Fat-free mass (kg)	39.2 (3.5)	40.7 (4.7)	40.8 (4.4)	41.8 (4.9)	41.3 (4.6)
Fat mass index (kg/m^2)	7.95 (2.74)	7.60 (3.36)	7.19 (2.91)	7.88 (3.42)	8.20 (3.69)
Fat-free mass index (kg/m^2)	14.52 (1.38)	14.95 (1.38)	14.80 (1.11)	15.15 (1.39)	15.05 (1.38)
Fat mass index SDS [a]	0.43 (0.96)	0.25 (0.95)	0.08 (0.95)	0.21 (1.04)	0.26 (1.13)
Fat-free mass index SDS [a]	-0.26 (1.02)	0.03 (0.98)	-0.08 (0.86)	0.14 (0.96)	0.06 (1.03)
Android:gynoid fat mass ratio	0.34 (0.09)	0.34 (0.09)	0.32 (0.09)	0.36 (0.10)	0.35 (0.10)
Boys	**Age (years) 15 n=35**	**Age (years) 16 n=374**	**Age (years) 17 n=59**	**Age (years) 18 n=226**	**Age (years) 19 n=59**
Weight (kg)	67.6 (12.5)	70.5 (14.8)	69.6 (12.86)	74.7 (14.8)	76.4 (14.2)
Height (cm)	174.8 (6.9)	177.2 (6.6)	177.4 (7.30)	179.2 (6.4)	178.8 (7.0)
Body mass index (kg/m^2)	22.13 (4.04)	22.41 (4.29)	22.02 (3.32)	23.23 (4.16)	23.87 (4.10)
Waist circumference (cm)	79.7 (9.9)	82.3 (11.6)	81.1 (9.2)	84.3 (12.0)	85.9 (10.8)
Fat mass (kg)	14.8 (10.2)	14.9 (11.2)	13.0 (8.7)	16.2 (11.5)	18.3 (10.4)
Fat mass trunk (kg)	7.5 (5.6)	7.5 (5.9)	6.7 (4.6)	8.6 (6.5)	9.9 (5.9)
Lean mass (kg)	50.6 (5.5)	53.8 (7.0)	54.8 (7.0)	56.1 (7.1)	55.6 (7.3)
Fat-free mass (kg)	52.8 (5.3)	55.6 (7.0)	56.6 (6.9)	58.5 (7.2)	58.1 (7.5)
Fat mass index (kg/m^2)	4.88 (3.50)	4.74 (3.48)	4.09 (2.63)	5.03 (3.50)	5.75 (3.22)
Fat-free mass index (kg/m^2)	17.25 (1.15)	17.67 (1.72)	17.93 (1.46)	18.20 (1.77)	18.13 (1.82)
Fat mass index SDS [a]	0.22 (1.08)	0.08 (1.17)	-0.12 (1.06)	-0.03 (1.19)	0.22 (1.10)

Fat-free mass index SDS [a]	-0.13	(0.68)	-0.09	(0.99)	-0.08	(0.88)	-0.14	(1.06)	-0.26	(1.10)
Android:gynoid fat mass ratio	0.38	(0.11)	0.38	(0.11)	0.39	(0.09)	0.42	(0.11)	0.45	(0.10)

Values are means and standard deviations (SD). Age groups: 15: 15.7-15.9; 16: 16.0-16.9; 17: 17.0-17.9; 18: 18.0-18.9; 19: 19.0-20.1

Measures at age 15-17 years are from Fit Futures 1, and at 18-19 years of age are repeated measures two years later from those who also participated in Fit Futures 2.

[a] Standard deviation scores (SDS) for body composition measures according to UK reference data [10].

DXA, dual X-ray absorptiometry; BMI, body mass index; n, number

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Table S2 BMI categories for girls and boys at 2.5, 6.0 and 16.5 years of age according to WHO and IOTF definitions. The Tromsø study: Fit Futures (n=907)

	WHO reference [a]		IOTF reference [b]	
Girls	n	%	n	%
2.5 years of age	439		439	
Underweight	4	0.9	61	13.9
Normal weight	424	96.6	338	77.0
Overweight/obesity	11	2.5	40	9.1
6.0 years of age	439		439	
Underweight	57	13.0	53	12.1
Normal weight	300	68.3	320	72.9
Overweight/obesity	82	18.7	66	15.0
16.5 years of age	439		439	
Underweight	40	9.1	27	6.2
Normal weight	301	68.6	321	73.1
Overweight/obesity	98	22.3	91	20.7
Boys				
2.5 years of age	468		468	
Underweight	4	0.9	52	11.1
Normal weight	449	95.9	386	82.5
Overweight/obesity	15	3.2	30	6.4
6.0 years of age	468		468	
Underweight	70	14.9	66	14.1
Normal weight	335	71.6	362	77.4
Overweight/obesity	63	13.5	40	8.6
16.5 years of age	468		468	
Underweight	68	14.5	40	8.6
Normal weight	282	60.3	318	67.9
Overweight/obesity	118	25.2	110	23.5

BMI categories are based on BMI (kg/m^2)calculated from predicted height/weight values at exact ages 2.5, 6.0 and 16.5 years, by the linear spline multilevel model.

[a] WHO growth standard for children 2-5 years [34] using <-2SD for underweight, >+2 SD for overweight including obesity, and WHO growth reference for ages 5-19 years [35] using <-1 SD for underweight, >+1 SD for overweight including obesity.

[b] BMI categories according to International Obesity Taskforce age-and sex-specific cut-off values for children 2-18 years of age [33]; underweight (adult BMI <18.5kg/m^2), normal weight (adult BMI ≥18.5-<25kg/m^2), overweight including obesity (adult BMI ≥25 kg/m^2)

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Table S3 Regression coefficients for associations of conditional BMI gain between birth, 2.5, 6.0, and 16.5 years of age with fat mass index SDS, fat-free mass index SDS and android:gynoid fat mass ratio at 15-20 years of age in girls and boys, The Tromsø Study: Fit Futures

GIRLS	**FMI SDS** [a]	**FFMI SDS** [a]	**Android:gynoid FMR**
Birth to 2.5 years of age	0.28 (0.24, 0.32)***	0.26 (0.20, 0.32)***	0.02 (0.01, 0.02)***
2.5 to 6.0 years of age	0.42 (0.38, 0.46)***	0.31 (0.25, 0.37)***	0.03 (0.02, 0.03)***
6.0 to 16.5 years of age	0.67 (0.63, 0.71)***	0.46 (0.39, 0.52)***	0.05 (0.05, 0.06)***
BOYS			
Birth to 2.5 years of age	0.21 (0.15, 0.27)***	0.24 (0.18, 0.30)***	0.01 (0.00, 0.02)**
2.5 to 6.0 years of age	0.40 (0.34, 0.45)***	0.34 (0.27, 0.40)***	0.03 (0.03, 0.04)***
6.0 to 16.5 years of age	0.80 (0.75, 0.86)***	0.49 (0.43, 0.55)***	0.06 (0.06, 0.07)***

Values are based on linear mixed models and reflects β coefficients (95% CI) per standardized residual of conditionally modelled gain in BMI SDS. Conditional growth variables are independent of earlier body size. Models are adjusted for gestational age, pubertal maturation and physical activity frequency.
Analysed in a dataset with 20 imputations (multiple imputation of missing co-variates at birth and at 16.5 years of age), n=907 (439 girls and 468 boys)
[a] Fat mass index and Fat-free mass index SDS according to UK Reference data [10]
CI, Confidence interval; FMI, fat mass index (kg/m^2); FFMI, fat-free mass index (kg/m^2); FMR, fat mass ratio; SDS, standard deviation score
** p<0.01, *** p<0.001

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Table S4 Differences between observed measurements and those predicted by the linear spline multilevel model, for girls and boys in The Tromsø study: Fit Futures

	n	Mean actual measurement (SD)		n	Mean predicted measurement (SD)		Mean difference
Age 2-4 years	663	2.6	(0.4)	907	2.5	-	-0.1
Age 5-7 years	713	6.0	(0.4)	907	6.0	-	0
Age 15-17 years	907	16.6	(0.4)	907	16.5	-	-0.1
Girls							
Weight (kg)							
Birth weight	439	3.45	(0.58)	439	3.45	(0.56)	-0.0002
Weight 2-4 years	320	13.49	(1.72)	439	13.50	(1.37)	0.01
Weight 5-7 years	339	21.88	(3.87)	439	21.51	(3.37)	-0.37
Weight 15-17 years	439	61.23	(11.61)	439	61.49	(11.85)	0.25
Length/height (cm)							
Length at birth	415	49.40	(2.30)	439	49.41	(1.72)	0.01
Length 2-4 years	320	91.27	(4.55)	439	91.56	(3.27)	0.29
Length 5-7 years	341	116.74	(5.24)	439	116.90	(4.28)	0.16
Length 15-17 years	439	165.06	(6.41)	439	165.61	(6.33)	0.55
Body mass index (BMI kg/m^2)							
BMI at birth	415	14.18	(1.49)	439	14.08	(1.71)	-0.1
BMI 2-4 years	320	16.16	(1.40)	439	16.10	(1.27)	-0.06
BMI 5-7 years	339	15.99	(2.05)	439	15.70	(1.96)	-0.29
BMI 15-17 years	439	22.46	(4.02)	439	22.40	(4.07)	-0.06
Boys							
Weight (kg)							
Birth weight	468	3.60	(0.59)	468	3.60	(0.57)	0.0002
Weight 2-4 years	343	14.11	(1.75)	468	14.20	(1.41)	0.09
Weight 5-7 years	372	22.16	(3.51)	468	21.62	(2.92)	-0.54
Weight 15-17 years	468	70.16	(14.42)	468	70.35	(14.58)	0.19
Length/height (cm)							
Length at birth	452	50.20	(2.30)	468	50.23	(1.72)	0.03
Length 2-4 years	343	92.74	(4.71)	468	93.24	(3.24)	0.50
Length 5-7 years	372	118.24	(5.37)	468	118.10	(4.29)	-0.14
Length 15-17 years	468	177.03	(6.72)	468	177.67	(6.50)	0.64
Body mass index (BMI kg/m^2)							
BMI at birth	452	14.28	(1.52)	468	14.21	(1.67)	-0.07
BMI 2-4 years	343	16.37	(1.30)	468	16.31	(1.18)	-0.06
BMI 5-7 years	372	15.79	(1.70)	468	15.47	(1.62)	-0.32
BMI 15-17 years	468	22.34	(4.15)	468	22.24	(4.19)	-0.10

The numbers presented are numbers, mean (SD)

[a] BMI categories according to International Obesity Taskforce age-and sex-specific cut-off values for children 2-18 years of age [33]; underweight (adult BMI <18.5kg/m^2), normal weight (adult BMI ≥18.5-<25kg/m^2), light overweight (adult BMI ≥25-<27 kg/m^2), severe overweight/obesity (adult BMI ≥27 kg/m^2)

BMI, body mass index; SD, standard deviation

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Table S5 Descriptive statistics for selected variables with missing data at birth and at 16.5 years of age, showing observed and imputed values for girls and boys, The Tromsø Study: Fit Futures

Characteristics	**Girls**						**Boys**					
	Observed			Imputed [a]			Observed			Imputed [a]		
Birth	n	Mean/%	(SD)	n	Mean/%	(SD)	n	Mean/%	(SD)	n	Mean/%	(SD)
Gestational age (weeks)	389	39.7	1.8	439	39.8	1.8	427	39.6	2.1	468	39.6	2.0
Size for gestational age [b]:	389			439			427			468		
Small for GA	49	12.6%			13.3%		46	10.8%			10.7%	
Appropriate for GA	302	77.6%			77.1%		332	77.7%			78.2%	
Large for GA	38	9.8%			9.6%		49	11.5%			11.1%	
16.5 years of age												
Menarche age	433	13.0	1.2	439	13.0	1.2	-	-	-	-	-	-
Pubertal maturation, girls [c]	436			439			-	-	-	-	-	-
Early (<12.5 years)	130	29.8%			29.9%		-	-	-	-	-	-
Intermediate (12.5-13.9 years)	204	46.8%			47.2%		-	-	-	-	-	-
Late (≥14.0 years)	102	23.4%			22.8%		-	-	-	-	-	-
Pubertal development scale (PDS)	-	-	-	-	-	-	366	3.3	0.4	468	3.3	0.4
Pubertal maturation, boys [d]	-	-	-	-	-	-	366			468		
Barely started (PDS 2.0-2.9)	-	-	-	-	-	-	65	17.7%			18.2%	
Underway (PDS 3.0-3.9)	-	-	-	-	-	-	270	73.8%			73.6%	
Completed (PDS 4.0)	-	-	-	-	-	-	31	8.5%			8.2%	
Physical activity – frequency	436			439			460			468		
Low	145	33.3%			33.2%		171	37.2%			37.3%	
Moderate	188	43.1%			43.2%		169	36.7%			36.7%	
High	103	23.6%			23.6%		120	26.1%			26.0%	

[a] Estimated values from a dataset with multiple (20) imputations, n= 439 girls and 468 boys.
[b] Size for gestational age (GA) according to Norwegian reference data [30]. Imputed values are based on observed birth weight and imputed GA
[c] Pubertal maturation is based on age of menarche in girls.
[d] Pubertal maturation is based on PDS in boys. [36]

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Table S6 Differences between complete cases and participants with missing birth weight and/or childhood BMI, girls and boys in The Tromsø study: Fit Futures

	Complete cases n=633		Missing birth weight/ childhood BMI n= 322		Mean difference	p-value [a]
Girls						
TFF1						
Missing: no/yes	306	65.8%	159	34.2%		0.762 [b]
Fat mass index (kg/m^2)	7.61	(3.45)	7.31	(2.76)	0.30	0.342
Fat-free mass index (kg/m^2)	14.87	(1.41)	14.93	(1.19)	-0.06	0.658
Fat mass index SDS	0.23	(0.99)	0.19	(0.84)	0.04	0.689
Fat-free mass index SDS	-0.03	(1.01)	0.04	(0.88)	-0.06	0.503
Waist circumferrence (cm)	77.56	(10.88)	76.62	(8.54)	0.94	0.343
Android:gynoid fat mass ratio	0.33	(0.09)	0.34	(0.08)	-0.003	0.733
TFF2						
Missing: no/yes	243	68.3%	113	31.7%		0.714 [b]
Fat mass index (kg/m^2)	7.96	(3.67)	7.69	(2.77)	0.27	0.494
Fat-free mass index (kg/m^2)	15.07	(1.44)	15.18	(1.25)	-0.11	0.491
Fat mass index SDS	0.20	(1.12)	0.20	(0.88)	-0.0003	0.998
Fat-free mass index SDS	0.08	(1.00)	0.17	(0.92)	-0.10	0.378
Waist circumferrence (cm)	77.98	(11.69)	77.59	(10.42)	0.38	0.765
Android:gynoid fat mass ratio	0.35	(0.10)	0.36	(0.09)	-0.006	0.594
Boys						
TFF1						
Missing: no/yes	327	66.7%	163	33.3%		0.762 [b]
Fat mass index (kg/m^2)	4.55	(3.43)	4.88	(3.32)	-0.33	0.313
Fat-free mass index (kg/m^2)	17.62	(1.70)	17.85	(1.59)	-0.23	0.149
Fat mass index SDS	0.01	1.16	0.16	1.14	-0.15	0.169
Fat-free mass index SDS	-0.12	(0.98)	0.02	(0.91)	-0.14	0.116
Waist circumferrence (cm)	81.69	(11.45)	82.37	(11.07	-0.67	0.537
Android:gynoid fat mass ratio	0.38	(0.11)	0.38	(0.11)	-0.006	0.557
TFF2						
Missing: no/yes	206	69.6%	90	30.4%		0.714 [b]
Fat mass index (kg/m^2)	4.94	(3.42)	5.75	(3.73)	-0.81	0.068
Fat-free mass index (kg/m^2)	18.13	(1.83)	18.46	(1.60)	-0.34	0.134
Fat mass index SDS	-0.07	(1.19)	0.20	(1.19)	-0.27	0.075
Fat-free mass index SDS	-0.20	(1.10)	0.01	(0.97)	-0.21	0.123
Waist circumferrence (cm)	84.04	(11.60)	86.11	(12.10)	-2.07	0.164
Android:gynoid fat mass ratio	0.43	(0.11)	0.43	(0.11)	-0.005	0.731

Values reported are mean (SD) or number and %
n= 955, 465 girls, 490 boys with data from TFF1, 356 girls and 296 boys with data from TFF2.
[a] p-values are obtained by two-samples t-test.
[b] Sex difference in missing between girls and boys obtained by Chi-square test.
BMI, body mass index; SDS, standard deviation scores; TFF1, The Tromsø study: Fit Futures 1; TFF2, The Tromsø study: Fit Futures 2

Paper III

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How Is Adolescent Bone Mass and Density Influenced by Early Life Body Size and Growth? The Tromsø Study: Fit Futures—A Longitudinal Cohort Study From Norway

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ABSTRACT

The effect of birth weight and childhood body mass index (BMI) on adolescents' bone parameters is not established. The aim of this longitudinal, population-based study was to investigate the association of birth weight, childhood BMI, and growth, with adolescent bone mass and bone density in a sample of 633 adolescents (48% girls) from The Tromsø Study: Fit Futures. This population-based cohort study was conducted in 2010–2011 and 2012–2013 in Tromsø, Norway. Bone mineral content (BMC) and areal BMD (aBMD) were measured at total hip (TH) and total body (TB) by dual-energy X-ray absorptiometry (DXA) and converted to internal *Z*-scores. Birth weight and childhood anthropometric measurements were retrospectively obtained from the Medical Birth Registry of Norway and childhood health records. Associations between birth weight, BMI, and growth were evaluated by fitting linear mixed models with repeated measures of BMC and aBMD at ages 15 to 17 and 18 to 20 years as the outcome. In crude analysis, a significant positive association ($p < 0.05$) with TB BMC was observed per 1 SD score increase in birth weight, observed in both sexes. Higher rate of length growth, conditioned on earlier size, from birth to age 2.5 years, and higher rate of weight gain from ages 6.0 to 16.5 years, conditioned on earlier size and concurrent height growth, revealed stronger associations with bone accrual at ages 15 to 20 years compared with other ages. Compared with being normal weight, overweight/obesity at age 16.5 years was associated with higher aBMD *Z*-scores: β coefficient (95% confidence interval [CI]) of 0.78 (0.53, 1.03) and 1.08 (0.85, 1.31) in girls, 0.63 (0.42, 0.85) and 0.74 (0.54, 0.95) in boys at TH and TB, respectively. Similar associations were found for BMC. Being underweight was consistently negatively associated with bone parameters in adolescence. In conclusion, birth weight influences adolescent bone mass but less than later growth and BMI in childhood and adolescence. © 2018 The Authors. *JBMR Plus* Published by Wiley Periodicals, Inc. on behalf of the American Society for Bone and Mineral Research

KEY WORDS: BIRTH WEIGHT; CHILDHOOD BMI; BONE MINERAL DENSITY

Introduction

Osteoporotic fractures constitute an important public health problem worldwide.[1] Peak bone mass is one of several determinants of adult bone strength.[2,3] Preventive strategies have mainly focused on reducing age-related bone loss and preventing fractures among the elderly. However, early-life factors and optimization of peak bone mass are important factors to consider.[4,5] Maximizing peak bone mass may contribute to risk reduction of later osteoporotic fracture.[4] A combination of genetic, hormonal, environmental, and lifestyle factors influence skeletal development,[2,3,6,7]

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and lifestyle factors may contribute to 20% to 40% of variance in adult peak bone mass.[6,7] The foundation of bone strength is laid in utero,[3,8] and subsequent growth in infancy, childhood, and adolescence is important for the acquisition of adult peak bone mass.[3,8] Several studies have shown a positive relationship between birth weight and bone mass in children[9] and adults,[8,10] supporting the intrauterine programming hypothesis, whereas associations between birth weight and bone strength parameters in adolescence/young adulthood have varied.[9,11] Thinness and low growth rate in childhood have been associated with an increased risk of hip fracture later in life.[12,13] Previous studies on birth weight and growth during infancy might not be representative of the growth of children today[8,12] because of the rapidly increasing prevalence of childhood overweight and obesity.[14] A recent review concluded that overweight and obese children have a significantly higher areal bone mineral density (aBMD) than normal-weight children, possibly because of increased mechanical loading, but the long-term impact is not clear.[15] By contrast, other studies have reported reduced bone mass and bone area and an increased risk of fracture among overweight and obese children.[16,17] The impact of overweight and obesity on skeletal development during growth is still uncertain, and more longitudinal studies are warranted.[9,15,17–19] Our study population was born between 1992 and 1994, a period with a high mean birth weight in Norway.[20] An increasing prevalence of overweight and obesity among Norwegian children and adolescents was also observed in the last decades.[21] The main aims of this study were therefore 1) to explore the relationship between both birth weight and childhood body mass index (BMI) and adolescent bone mass and bone density; and 2) to investigate any differences in adolescent bone mass and density related to childhood growth. We hypothesized that higher birth weight as well as high growth rate and higher childhood BMI would be positively associated with adolescent bone strength parameters, however with a possible threshold for BMI.

Materials and Methods

Study population

The Tromsø Study: Fit Futures is a population-based study with repeated health surveys among adolescents in Northern Norway. All first-year students in Tromsø and neighboring municipalities attending upper-secondary schools in 2010–2011 ($n = 1117$) were invited to Fit Futures 1 (TFF1); 1038 students (92.9%) attended. Among these students, 961 were in the core age group of 15 to 17 years (born 1992–1994). A follow-up study, Fit Futures 2 (TFF2), was conducted 2 years later (2012–2013) and reinvited all participants from TFF1. Detailed information on TFF1 and TFF2 has been presented earlier.[22,23] Data from the cohort were supplemented with retrospectively collected anthropometric data from birth and childhood. A sample of 633 participants (48% girls), with measurements from birth, childhood, and one or two dual-energy X-ray absorptiometry (DXA) measurements from ages 15 to 17 and 18 to 20 years was eligible for the analysis in the present study (a flowchart is shown in Fig. 1). This constitutes 66% of the 961 students in the core age group in TFF1. The Regional Committee for Medical and Health Research Ethics, North Norway (REK nord) approved TFF1, TFF2, and the present study (reference number: 2014/1397/REK nord).

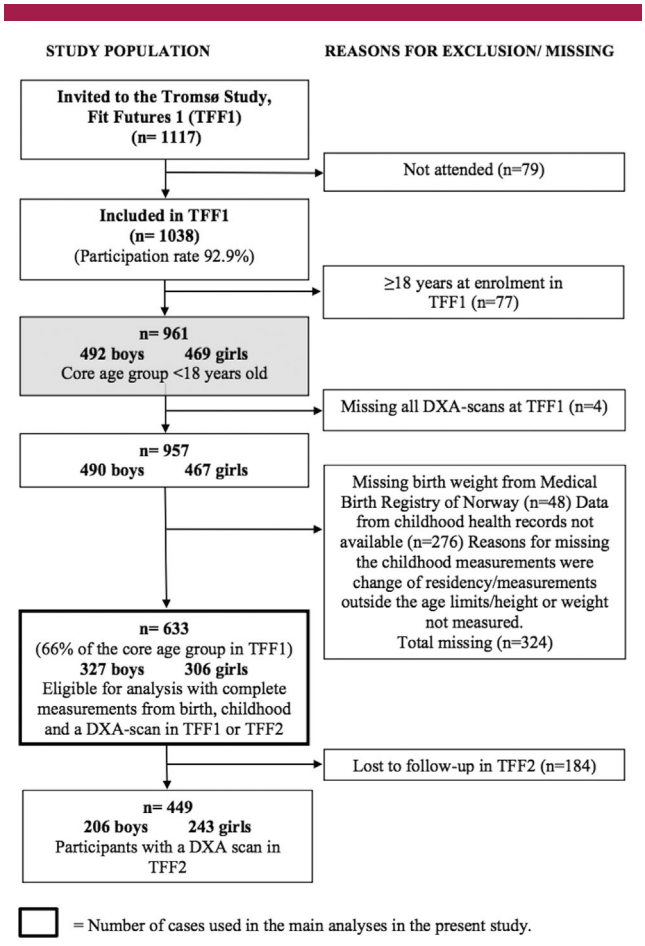

FIG. 1. Flow chart of the study population, The Tromsø Study: Fit Futures 1 and 2.

All students and parents/guardians of students age <16 years gave written informed consent.

Bone mass and bone density at ages 15 to 17 and 18 to 20 years

Bone mass and bone density in this study were measured as total hip (TH) and total body (TB) bone mineral content (BMC; g) and aBMD (g/cm^2) by DXA (GE Lunar Prodigy, Lunar Corporation, Madison, WI, USA) and analyzed with Encore pediatric software version 13.4. In vivo, the densitometer coefficient of variation for TH was estimated at 1.17%.[24] Repeated measurements were performed in TFF1 and TFF2 with the same DXA instrument, and all measurements from the same wave were analyzed by a single investigator. The left-side values were used as an outcome measure in the analyses. In case of missing data or error, the right-side values from both TFF1 and TFF2 were used. We converted the bone measures to sex- and age-standardized internal *Z*-scores based on the distribution of the study sample.

Height and weight in TFF1 and TFF2 were measured to the nearest 0.1 cm and 0.1 kg, respectively, on an automatic electronic stadiometer/scale (Jenix DS 102, Dong Sahn Jenix, Seoul, Korea). Participants wore light clothing and no footwear. Trained study nurses at the Clinical Research Unit, University Hospital of North Norway, performed DXA and all anthropometric measurements, following standardized procedures.

Measures from birth and childhood

Information on birth weight (g), length (cm), and gestational age (GA; weeks) were obtained through linkage to the Medical Birth Registry of Norway (MBRN) using participants' unique personal identification number. GA was determined by ultrasound examination or last menstrual period if ultrasound was missing. Anthropometric measurements are part of regular health examinations by public health nurses in accordance with national preventive health program guidelines. Therefore, we were able to retrospectively collect data on height (cm), weight (kg), age (years, months), and date of measurements at two time points (target ages; 2 and 6 years of age) from childhood health records. The exact age of the participants at the time measurements were taken varied slightly (median age 2.5 years, range 1.9 to 4.5 years and median age 6.0 years, range 5.0 to 7.6 years).

Estimating length/height and weight growth trajectories

Because not all participants were measured at exact same age, we used linear spline multilevel model[25] to estimate each participant's height (cm) and weight (kg) at the ages 2.5, 6.0, and 16.5 years. The model, also referred to as "the broken stick model,"[25] use data from individuals and from the whole study sample to estimate person-specific birth weight, length/height, and weight with knots at the target ages 2.5, 6.0, and 16.5 years, and length/height and weight growth trajectories between consecutive ages. In our study, each participant had only one collected height/weight measurement around the target ages and knot points were therefore placed at the median ages. Individual-level random effects for intercept and slopes are estimated as each person's deviation from the average trajectory.[25] Sex and an interaction term with sex and splines were included in the model to account for sex differences in growth trajectories over time. Five percent of participants were missing length at birth, and missing values were predicted with this model. In a two-step process, model estimates were used for further calculation of exposure variables that were used in our analysis of the outcome measures. Models were fitted using the mixed command in Stata.[25] Length/height and weight growth rate were calculated as change in cm/kg per year between two consecutive target ages, eg, predicted height at 16.5 years of age minus predicted height at 6.0 years of age divided by 10.5 years.

Exposure variables

Sex-specific birth weight and length standard deviation scores (SDS) were calculated according to GA, using the British 1990 growth reference.[26]

Based on BMI (predicted weight [kg]/predicted height [m^2]) at 2.5, 6.0, and 16.5 years, participants were categorized into the following BMI categories: underweight (corresponding to adult BMI $<18.5\,kg/m^2$), normal weight (adult BMI ≥ 18.5 to $<25\,kg/m^2$), and overweight/obesity (adult BMI $\geq 25\,kg/m^2$). Because of a relatively small proportion of obesity at these ages, we merged the overweight and obese category. Sex-specific BMI reference values at the target ages were used according to the International Obesity Taskforce age- and sex-specific cut-off values for children ages 2 to 18 years.[27]

Covariates from questionnaires in TFF1

Information regarding ethnicity, pubertal maturation, and physical activity was taken from self-administered questionnaires completed during TFF1. Girls were categorized into three stages of pubertal maturation: early ($<$12.5 years), intermediate (12.5 to 13.9 years), and late ($\geq$14.0 years), based on age at menarche. Pubertal maturation in boys was classified as barely started, underway, and completed based on the pubertal development scale (PDS). The boys rated four secondary sexual characteristics on a scale ranging from 1 (not yet started) to 4 (complete) and the PDS score was calculated as a total mean score of the four items.[22,28] Physical activity frequency was measured through the validated WHO Health Behaviour in Schoolchildren (HBSC) questionnaire,[29] which included the question: "If you are actively doing sports or physical activity outside school, how many days a week are you active?" Answers were given in six predefined categories; "never" (1), "less than once a week" (2), "1 day a week" (3), "2 to 3 days a week" (4), "4 to 6 days a week" (5), and "almost every day" (6). The answers were recoded into three categories of physical activity: "low" (1–2), "moderate" (3–4), and "high" (5–6).

Statistical analyses

Characteristics of the study population are presented as means and standard deviations (SD) or numbers and percentages for girls and boys separately. ANOVA with the Bonferroni correction for multiple comparisons was used to assess differences in mean height according to BMI category. The main outcomes in the present study were TH and TB standardized BMC and aBMD scores (*Z*-scores) at ages 15 to 17 and 18 to 20 years. In a two-step process, we used linear spline multilevel model[25] to predict each participant's height and weight at exact ages 2.5, 6.0, and 16.5 years. In the second step, linear mixed models with a random intercept on the subject level were used to evaluate the relationship between birth weight SDS, BMI category at 2.5, 6.0, and 16.5 years of age, height and weight growth rate, and repeated BMC and aBMD *Z*-scores as continuous outcomes. Associations of birth weight SDS, or BMI category, with BMC/aBMD *Z*-scores as outcomes were assessed using the following models: 1) unadjusted; 2) birth weight SDS adjusted for GA and birth length; 3) BMI category adjusted for height at 2.5 and 6.0 years of age, respectively; 4) BMI category at 16.5 years of age adjusted for height at same age, pubertal maturation, and physical activity, as potential confounding factors. In accordance with others,[30,31] associations of length/height and weight growth rate with BMC/aBMD outcomes were assessed using the following models: 1) models of length/height growth were adjusted for birth weight, length/height at the beginning of each period and preceding length/height growth rate; 2) models of weight gain were adjusted for birth weight, length/height, and weight at the beginning of each period and length/height growth rate over the same time span. The models from birth to age 2.5 years were additionally adjusted for GA. The models from ages 6.0 to 16.5 years were additionally adjusted for pubertal maturation.

Because bone growth, magnitude, and tempo of bone acquisition differ between girls and boys, especially in adolescence,[3,4] all analyses were stratified by sex. Cross-product terms with sex and exposure variables were included in the models to formally test for potential sex interactions. No statistically significant sex difference was observed. Maternal age at birth and age at outcome measurement was included as potential confounders. However, they did not affect the estimated coefficients and were not included in the final models. Normality and linearity of exposures and outcomes and residuals were checked by visual inspections of histograms and plots. There

were signs of nonlinearity between BMI at age 16.5 years and bone measurements (Supplemental Fig. S1). A formal test with a quadratic term of BMI at age 16.5 years in the final model confirmed a nonlinear relationship with TB BMC and aBMD. BMI in categories were therefore used as the exposure variable. For ease of comparison, BMI categories were used at all ages. No assumptions were considered violated for the final models.

We experienced additional missing data in covariates, and to avoid bias, we performed multiple imputations (20 imputations) of missing values using chained equations.[32] The percentage of missing covariates in the study sample were 20% in total; 9% for GA, 1% for physical activity, 11% for PDS in boys, and <1% for menarche age in girls. The values were imputed based on observed data from all 633 participants. The imputation model included all variables from the final adjusted models, BMC and aBMD outcome variables, in addition to auxiliary data from the MBRN. Sensitivity analyses were performed in the data set with no imputations ($n = 633$ only observed values) and in a complete-case data set ($n = 367$). The results were similar and the results of mixed model analyses presented here are from the imputed data sets. In a dropout analysis, we explored differences between participants with and without missing data by *t* test for continuous variables and by the chi-square test for categorical variables. Multiple imputations, linear spline multilevel models, and statistical analyses were all carried out using Stata/MP 14.2 for Mac (StataCorp., College Station, TX, USA). The level of statistical significance was set to two-sided *p* values of <0.05.

Results

Characteristics of the study population

In the present study, we used data from 327 boys and 306 girls with measurements from birth and childhood, and DXA measurements from 15 to 17 years of age. Seventy-one percent of our study sample (206 boys and 243 girls) also had DXA measures from TFF2 (Fig. 1). The dropout analysis showed no significant difference in mean values of the exposure variables or outcome variables at TFF1, between those participating at TTF2, and those lost to follow-up. Nor were significant differences observed in mean BMC/aBMD variables for participants missing childhood exposure variables. However, significantly more boys than girls were lost to follow-up (data not shown). The majority (98%) of our study sample was of white ethnicity. Characteristics for the study population from birth to 18 to 20 years of age, with predicted length/height, weight, and BMI measures from birth to 16.5 years of age, are shown in Table 1. Mean birth weight was 3480 g among girls and 3575 g among boys. The prevalence of overweight/obesity was 11.4% and 17.6% in girls, and 7.9% and 10.4% in boys at 2.5 and 6.0 years of age, respectively. At age 16.5 years, 22% of girls and boys were overweight/obese. Differences between observed and predicted length/height and weight values and calculated BMI at target ages were small and are shown in Supplemental Table S1. Characteristics for variables with missing and imputed values are shown in Supplemental Table S2. Results of ANOVA showed no significant difference in height at 15 to 17 or 18 to 20 years of age between the three BMI categories at 2.5, 6.0, or 16.5 years of age, neither in girls nor boys (data not shown).

Birth weight and bone measures

In crude analyses, 1 SD score higher birth weight was significantly associated with 0.31 (95% confidence interval [CI] 0.20 to 0.41, $p < 0.001$) higher TB BMC *Z*-scores at 15 to 20 years of age in girls, and 0.13 (95% CI 0.02 to 0.23, $p = 0.017$) higher TB BMC *Z*-scores in boys (Tables 2 and 3). In girls, significant associations were also found with TH BMC and TB aBMD *Z*-scores (Table 2). After additional adjustment for length at birth, the association attenuated, except for TB BMC in girls. However, no statistically significant interaction was found between sex and birth weight.

BMI category and bone measures

We found a pattern of increasing TH and TB BMC/aBMD *Z*-scores with higher BMI category. Stronger associations were found with advancing age (Tables 2 and 3). In both sexes, in crude analyses and analyses adjusted for height, overweight/obesity at 6.0 years of age was associated with higher TH and TB BMC at 15 to 20 years of age compared with those of normal weight. Significant associations were also found with TB aBMD in both sexes and with TH aBMD only in girls. In both sexes, crude analysis revealed a significant association between overweight/obesity at 2.5 years of age and higher TB BMC values at age 15 to 20 years. In analyses adjusted for current height, pubertal maturation, and physical activity, overweight/obesity at 16.5 years of age was associated with >1.0 *Z*-score higher TH and TB BMC among girls. Positive associations were also found for aBMD: TH aBMD *Z*-scores 0.78 (95% CI 0.53 to 1.03) and TB aBMD 1.08 (95% CI 0.85 to 1.31) in girls. Significant positive associations with BMC/aBMD *Z*-scores were also found among overweight/obese boys at age 16.5 years; TH aBMD 0.63 (95% CI 0.42 to 0.85), TB aBMD 0.74 (95% CI 0.54 to 0.95) (Tables 2 and 3). The effect of BMI leveled off at BMI >30 kg/m^2 (Supplemental Figs. S1 and S2). A formal test with a quadratic term for BMI at age 16.5 years was significant for TB BMC and aBMD for both girls and boys. In both sexes, being underweight at 2.5, 6.0, or 16.5 years of age was associated with negative BMC and aBMD *Z*-scores at 15 to 20 years of age compared with those of normal weight. The strongest negative associations were found at 16.5 years of age (Tables 2 and 3).

Length/height and weight growth trajectories and bone measures

In analyses of individually modeled length/height growth trajectories, a 1-SD higher length/height growth rate in early childhood (from birth to 2.5 years of age and from 2.5 to 6.0 years of age) showed positive associations with both TH and TB BMC and aBMD *Z*-scores at 15 to 20 years of age (Table 4). Length growth rate from birth to 2.5 years of age, conditioned on earlier size, showed the strongest associations with TH and TB BMC *Z*-scores in both sexes. A 1-SD higher height growth rate from 6.0 to 16.5 years of age, conditioned on earlier size and growth and pubertal maturation, displayed weaker, or negative, nonsignificant associations with BMC/aBMD at 15 to 20 years of age in both girls and boys (Table 4).

Individually modeled rate of weight gain, conditioned on earlier size and growth and concurrent height growth, was positively associated with bone parameters at 15 to 20 years of age. Estimated coefficients increased with age for both TH and TB and BMC and aBMD. The strongest associations between 1-SD higher rate of weight gain and bone parameters, conditioned on earlier size and growth and concurrent height growth, were found between 6.0 and 16.5 years of age (Table 4).

Table 1. Sex-Specific Characteristics of the Study Population at Birth and Four Ages Up to 18 to 20 Years (The Tromsø Study: Fit Futures)

	Girls			Boys		
Characteristics[a]	*n*	Mean/%	SD	*n*	Mean/%	SD
Birth						
Birth weight (g)	306	3480.6	554.3	327	3575.2	566.7
Birth length (cm)	306	49.5	1.6	327	50.1	1.8
Gestational age (weeks)	272	39.8	1.8	303	39.5	2.1
Birth weight SDS[b]	306	0.24	1.03	327	0.26	1.04
Birth length SDS[b]	306	−0.37	0.81	327	−0.33	0.82
2.5 years of age						
Weight (kg)	306	13.6	1.6	327	14.2	1.6
Height (cm)	306	91.6	3.2	327	93.1	3.3
Body mass index (kg/m^2)	306	16.11	1.37	327	16.32	1.30
BMI category[c]	306			327		
Underweight	49	16.0%		47	14.4%	
Normal weight	222	72.6%		254	77.7%	
Overweight/obese	35	11.4%		26	7.9%	
6.0 years of age						
Weight (kg)	306	21.6	3.8	327	21.6	3.3
Height (cm)	306	117.1	4.2	327	118.0	4.5
Body mass index (kg/m^2)	306	15.69	2.20	327	15.48	1.79
BMI category[c]	306			327		
Underweight	48	15.7%		51	15.6%	
Normal weight	204	66.7%		242	74.0%	
Overweight/obese	54	17.6%		34	10.4%	
16.5 years of age						
Weight (kg)	306	61.9	12.3	327	69.9	14.6
Height (cm)	306	166.1	6.0	327	177.7	6.6
Body mass index (kg/m^2)	306	22.44	4.32	327	22.07	4.20
BMI category[c]	306			327		
Underweight	20	6.5%		31	9.5%	
Normal weight	218	77.8%		224	68.5%	
Overweight/obese	68	22.2%		72	22.0%	
BMC total hip (g)	305	32.1	4.7	327	39.8	6.6
BMC total body (g)	306	2545.3	392.6	327	2936.7	462.4
aBMD total hip (g/cm^2)	305	1.06	0.12	327	1.11	0.15
aBMD total body (g/cm^2)	306	1.14	0.08	327	1.18	0.09
Pubertal maturation,[d] girls	303			—	—	
Early (<12.5 years)	85	28.1%		—	—	
Intermediate (12.5–13.9 years)	152	50.2%		—	—	
Late (≥14.0 years)	66	21.8%		—	—	
Pubertal maturation,[e] boys	—	—		259		
Barely started (PDS 2.0–2.9)	—	—		46	17.8%	
Underway (PDS 3.0–3.9)	—	—		196	75.7%	

Table 1. (*Continued*)

Characteristics[a]	Girls			Boys		
	n	Mean/%	SD	*n*	Mean/%	SD
Completed (PDS 4.0)	—	—		17	6.6%	
Physical activity–frequency	303			321		
Low	103	34.0%		118	36.8%	
Moderate	133	43.9%		117	36.5%	
High	67	22.1%		86	26.8%	
18–20 years of age						
Age (years)	259	18.6	0.4	211	18.7	0.4
Weight (kg)	246	63.7	12.3	206	74.4	14.4
Height (cm)	246	166.3	6.2	206	179.5	6.7
Body mass index (kg/m^2)	246	23.07	4.57	206	23.07	4.08
BMC total hip (g)	242	32.4	4.8	206	41.4	7.2
BMC total body (g)	243	2612.1	377.3	206	3190.7	473.0
aBMD Total hip (g/cm^2)	242	1.07	0.13	206	1.15	0.16
aBMD Total body (g/cm^2)	243	1.15	0.07	206	1.23	0.09

SD = standard deviation; SDS = standard deviation scores; BMI = body mass index; BMC = bone mineral content; aBMD = areal bone mineral density; PDS = pubertal development scale.

[a]Birth weight, birth length, weight, and height are predicted mean values (SD) at target ages (2.5, 6.0, and 16.5 years), using linear spline multilevel model. Birth weight and length SDS, BMI, and BMI category at the target ages are based on these predicted values. The rest of the characteristics are observed values measured between 15 to 17 and 18 to 20 years of age.

[b]SDS according to British 1990 growth charts, version UK.[26]

[c]BMI categories according to International Obesity Taskforce age- and sex-specific cut-off values for children 2–18 years of age; underweight (adult BMI $<$18.5 kg/m^2), normal weight (adult BMI $\geq$18.5–$<$25 kg/m^2), overweight obesity (adult BMI $\geq$25 kg/m^2).[27]

[d]Pubertal maturation is based on age of menarche in girls.

[e]PDS in boys; total score of four items of secondary sexual characteristics on a scale from 1 to 4 (sum of total score divided by 4 (none had a score $<$2.0 in total score).[28]

Table 2. Associations of Birth Weight and BMI Category[a] at 2.5, 6.0, and 16.5 Years of Age With Bone Mineral Content and Bone Mineral Density at 15 to 20 Years of Age in Girls (The Tromsø Study: Fit Futures)

	Total hip		Total body		Total hip		Total body	
	Crude models				Adjusted models[b]			
Girls ($n = 306$)	β (95% CI)	*p* Value	β (95% CI)	*p* Value	β (95% CI)	*p* Value	β (95% CI)	*p* Value
Bone mineral content								
Birth								
Birth weight SDS[c]	0.19 (0.08, 0.29)	0.001	0.31 (0.20, 0.41)	<0.001	0.09 (−0.06, 0.24)	0.220	0.21 (0.07, 0.35)	0.004
2.5 years of age								
Underweight	−0.27 (−0.58, 0.03)	0.079	−0.49 (−0.79, −0.20)	0.001	−0.26 (−0.55, 0.03)	0.080	−0.47 (−0.74, −0.21)	<0.001
Normal weight	Ref.		Ref.		Ref.		Ref.	
Overweight/obese	0.29 (−0.06, 0.64)	0.104	0.50 (0.16, 0.84)	0.004	0.20 (−0.14, 0.54)	0.243	0.37 (0.06, 0.68)	0.018
6.0 years of age								
Underweight	−0.28 (−0.58, 0.02)	0.064	−0.49 (−0.77, −0.20)	0.001	−0.23 (−0.52, 0.05)	0.110	−0.41 (−0.66, −0.17)	0.001
Normal weight	Ref.		Ref.		Ref.		Ref.	
Overweight/obese	0.64 (0.35, 0.93)	<0.001	0.89 (0.62, 1.16)	<0.001	0.51 (0.23, 0.78)	<0.001	0.70 (0.46, 0.93)	<0.001
16.5 years of age								
Underweight	−0.56 (−0.98, −0.15)	0.008	−0.79 (−1.16, −0.42)	<0.001	−0.47 (−0.85, −0.09)	0.016	−0.72 (−1.03, −0.41)	<0.001
Normal weight	Ref.		Ref.		Ref.		Ref.	
Overweight/obese	0.91 (0.66, 1.15)	<0.001	1.22 (1.00, 1.44)	<0.001	1.05 (0.83, 1.28)	<0.001	1.34 (1.16, 1.53)	<0.001
Areal bone mineral density								
Birth								
Birth weight SDS[c]	0.07 (−0.04, 0.18)	0.236	0.14 (0.03, 0.25)	0.014	0.07 (−0.08, 0.22)	0.353	0.10 (−0.05, 0.25)	0.181
2.5 years of age								
Underweight	−0.18 (−0.48, 0.13)	0.261	−0.39 (−0.69, −0.08)	0.012	−0.17 (−0.48, 0.13)	0.264	−0.38 (−0.67, −0.08)	0.013
Normal weight	Ref.		Ref.		Ref.		Ref.	
Overweight/obese	0.12 (−0.23, 0.47)	0.501	0.35 (−0.00, 0.69)	0.051	0.11 (−0.24, 0.47)	0.529	0.29 (−0.05, 0.63)	0.098
6.0 years of age								
Underweight	−0.34 (−0.65, −0.04)	0.027	−0.51 (−0.80, −0.22)	<0.001	−0.34 (−0.64, −0.03)	0.030	−0.48 (−0.76, −0.20)	0.001
Normal weight	Ref.		Ref.		Ref.		Ref.	
Overweight/obese	0.47 (0.18, 0.76)	0.001	0.82 (0.55, 1.10)	<0.001	0.45 (0.16, 0.75)	0.002	0.74 (0.46, 1.01)	<0.001
16.5 years of age								
Underweight	−0.47 (−0.90, −0.04)	0.031	−0.80 (−1.20, −0.41)	<0.001	−0.28 (−0.71, 0.15)	0.203	−0.56 (−0.94, −0.17)	0.005
Normal weight	Ref.		Ref.		Ref.		Ref.	
Overweight/obese	0.69 (0.44, 0.95)	<0.001	0.99 (0.76, 1.23)	<0.001	0.78 (0.53, 1.03)	<0.001	1.08 (0.85, 1.31)	<0.001

BMI = body mass index; CI = confidence interval; SDS = standard deviation scores.

Values are based on linear mixed models and reflect standardized β coefficients for bone mineral content and areal bone mineral density, 95% CI, and corresponding *p* value. Models at birth and at 16.5 years of age are based on data with multiple imputation of missing covariates.

[a]BMI category according to International Obesity Taskforce age- and sex-specific cut-off values for children 2 to 18 years of age; underweight (adult BMI <18.5 kg/m^2), normal weight (adult BMI ≥18.5–<25 kg/m^2), overweight/obesity (adult BMI ≥25 kg/m^2).[27]

[b]Birth weight standard deviation score are additionally adjusted for gestational age and birth length. Childhood models are adjusted for height at 2.5 and 6.0 years of age, respectively. Model at 16.5 years of age are adjusted for height at same age, pubertal maturation and physical activity–frequency measured in Fit Futures 1.

[c]Sex-specific birth weight standard deviation scores are adjusted for gestational age and calculated according to British 1990 growth charts, version UK.[26]

Table 3. Associations of Birth Weight and BMI Category[a] at 2.5, 6.0, and 16.5 Years of Age With Bone Mineral Content and Bone Mineral Density at 15 to 20 Years of Age in Boys (The Tromsø Study: Fit Futures)

	Total hip		Total body		Total hip		Total body	
	Crude models				Adjusted models[b]			
Boys ($n = 327$)	β (95% CI)	*p* Value	β (95% CI)	*p* Value	β (95% CI)	*p* Value	β (95% CI)	*p* Value
Bone mineral content								
Birth								
Birth weight SDS[c]	0.03 (−0.07, 0.13)	0.579	0.13 (0.02, 0.23)	0.017	−0.12 (−0.27, 0.03)	0.126	−0.08 (−0.23, 0.07)	0.291
2.5 years of age								
Underweight	−0.06 (−0.36, 0.24)	0.696	−0.16 (−0.47, 0.14)	0.289	−0.06 (−0.34, 0.22)	0.688	−0.16 (−0.42, 0.10)	0.222
Normal weight	Ref.		Ref.		Ref.		Ref.	
Overweight/obese	0.21 (−0.18, 0.61)	0.291	0.45 (0.06, 0.84)	0.025	0.04 (−0.33, 0.41)	0.826	0.21 (−0.13, 0.55)	0.233
6.0 years of age								
Underweight	−0.20 (−0.49, 0.09)	0.184	−0.31 (−0.60, −0.02)	0.036	−0.12 (−0.38, 0.15)	0.388	−0.20 (−0.43, 0.04)	0.099
Normal weight	Ref.		Ref.		Ref.		Ref.	
Overweight/obese	0.42 (0.08, 0.77)	0.017	0.68 (0.34, 1.02)	<0.001	0.33 (0.01, 0.64)	0.043	0.55 (0.27, 0.82)	<0.001
16.5 years of age								
Underweight	−0.73 (−1.07, −0.39)	<0.001	−0.90 (−1.22, −0.59)	<0.001	−0.54 (−0.82, −0.27)	<0.001	−0.80 (−1.02, −0.58)	<0.001
Normal weight	Ref.		Ref.		Ref.		Ref.	
Overweight/obese	0.67 (0.43, 0.91)	<0.001	0.97 (0.74, 1.19)	<0.001	0.67 (0.48, 0.86)	<0.001	0.94 (0.78, 1.10)	<0.001
Areal bone mineral density								
Birth								
Birth weight SDS[c]	−0.02 (−0.12, 0.09)	0.732	0.02 (−0.08, 0.13)	0.651	−0.13 (−0.28, 0.02)	0.096	−0.10 (−0.25, 0.05)	0.191
2.5 years of age								
Underweight	−0.05 (−0.35, 0.25)	0.747	−0.15 (−0.46, 0.15)	0.319	−0.05 (−0.34, 0.25)	0.748	−0.15 (−0.44, 0.14)	0.300
Normal weight	Ref.		Ref.		Ref.		Ref.	
Overweight/obese	0.09 (−0.31, 0.48)	0.668	0.20 (−0.19, 0.60)	0.307	−0.02 (−0.40, 0.37)	0.924	0.06 (−0.32, 0.43)	0.766
6.0 years of age								
Underweight	−0.15 (−0.44, 0.14)	0.302	−0.22 (−0.50, 0.07)	0.138	−0.11 (−0.39, 0.18)	0.459	−0.15 (−0.42, −0.12)	0.274
Normal weight	Ref.		Ref.		Ref.		Ref.	
Overweight/obese	0.31 (−0.03, 0.66)	0.075	0.64 (0.30, 0.99)	<0.001	0.26 (−0.08, 0.60)	0.130	0.57 (0.24, 0.89)	0.001
16.5 years of age								
Underweight	−0.60 (−0.94, −0.25)	0.001	−0.90 (−1.23, −0.58)	<0.001	−0.38 (−0.69, −0.08)	0.013	−0.74 (−1.03, −0.45)	<0.001
Normal weight	Ref.		Ref.		Ref.		Ref.	
Overweight/obese	0.61 (0.37, 0.85)	<0.001	0.74 (0.50, 0.97)	<0.001	0.63 (0.42, 0.85)	<0.001	0.74 (0.54, 0.95)	<0.001

BMI = body mass index; CI = confidence interval; SDS = standard deviation scores.

Values are based on linear mixed models and reflect standardized β coefficients for bone mineral content and areal bone mineral density, 95% CI, and corresponding *p* value. Models at birth and at 16.5 years of age are based on data with multiple imputation of missing covariates.

[a]BMI category according to International Obesity Taskforce age- and sex-specific cut-off values for children 2 to 18 years of age; underweight (adult BMI <18.5 kg/m^2), normal weight (adult BMI ≥18.5 to <25 kg/m^2), overweight/obesity (adult BMI ≥25 kg/m^2).[27]

[b]Birth weight standard deviation score are additionally adjusted for gestational age and birth length. Childhood models are adjusted for height at 2.5 and 6.0 years of age, respectively. Model at 16.5 years of age are adjusted for height at same age, pubertal maturation, and physical activity–frequency measured in Fit Futures 1.

[c]Sex-specific birth weight standard deviation score are adjusted for gestational age and calculated according to British 1990 growth charts, version UK.[26]

Table 4. Associations of Length/Height and Weight Growth Rate Between Birth 2.5, 6.0, and 16.5 Years of Age With Bone Mineral Content and Bone Mineral Density at 15 to 20 Years of Age in Girls and Boys (The Tromsø Study: Fit Futures)

		Bone mineral content				Areal bone mineral density			
		Total hip		Total body		Total hip		Total body	
Per SD increase in height or weight growth rate	Mean increase/yr	β (95% CI)	*p* Value	β (95% CI)	*p* Value	β (95% CI)	*p* Value	β (95% CI)	*p* Value
Girls ($n = 306$)									
Birth to 2.5 years of age									
Length (1.1 cm/yr)[a]	16.9	0.24 (0.12, 0.35)	<0.001	0.37 (0.26, 0.47)	<0.001	0.01 (−0.11, 0.13)	0.882	0.18 (0.06, 0.30)	0.003
Weight (0.6 kg/yr)[b]	4.0	0.20 (0.06, 0.34)	0.006	0.33 (0.20, 0.45)	<0.001	0.13 (−0.02, 0.28)	0.080	0.32 (0.17, 0.46)	<0.001
2.5 to 6.0 years of age									
Height (0.6 cm/yr)[c]	7.3	0.21 (0.10, 0.32)	<0.001	0.30 (0.20, 0.40)	<0.001	0.12 (0.00, 0.24)	0.050	0.23 (0.12, 0.34)	<0.001
Weight (0.8 kg/yr)[d]	2.3	0.21 (0.10, 0.32)	<0.001	0.29 (0.20, 0.38)	<0.001	0.24 (0.12, 0.36)	<0.001	0.35 (0.24, 0.46)	<0.001
6.0 to 16.5 years of age									
Height (0.6 cm/yr)[c,e]	4.7	0.14 (−0.05, 0.33)	0.143	0.06 (−0.11, 0.23)	0.470	−0.10 (−0.30, 0.10)	0.327	−0.19 (−0.38, 0.00)	0.053
Weight (1.2 kg/yr)[d,e]	3.8	0.46 (0.33, 0.59)	<0.001	0.57 (0.48, 0.67)	<0.001	0.35 (0.21, 0.50)	<0.001	0.42 (0.29, 0.54)	<0.001
Boys (n = 327)									
Birth to 2.5 years of age									
Length (1.1 cm/yr)[a]	17.2	0.33 (0.22, 0.43)	<0.001	0.47 (0.37, 0.56)	<0.001	0.20 (0.09, 0.30)	<0.001	0.32 (0.21, 0.42)	<0.001
Weight (0.6 kg/yr)[b]	4.2	0.11 (−0.02, 0.24)	0.098	0.17 (0.06, 0.29)	0.004	0.09 (−0.05, 0.22)	0.202	0.16 (0.02, 0.29)	0.021
2.5 to 6.0 years of age[e]									
Height (0.6 cm/yr)[c]	7.1	0.22 (0.12, 0.31)	<0.001	0.28 (0.19, 0.37)	<0.001	0.11 (0.01, 0.21)	0.039	0.17 (0.07, 0.27)	0.001
Weight (0.8 kg/yr)[d]	2.1	0.16 (0.04, 0.28)	0.011	0.24 (0.13, 0.34)	<0.001	0.14 (0.01, 0.27)	0.030	0.29 (0.17, 0.42)	<0.001
6.0 to 16.5 years of age									
Height (0.6 cm/yr)[c,e]	5.7	0.20 (0.02, 0.38)	0.027	0.23 (0.08, 0.39)	0.004	−0.01 (−0.20, 0.18)	0.912	−0.02 (−0.20, 0.17)	0.843
Weight (1.2 kg/yr)[d,e]	4.6	0.30 (0.20, 0.40)	<0.001	0.41 (0.33, 0.48)	<0.001	0.27 (0.17, 0.38)	<0.001	0.33 (0.24, 0.43)	<0.001

SD = standard deviation; CI = confidence interval.

Values are based on multiple linear mixed models and reflect standardized β coefficients for bone mineral content and areal bone mineral density, 95% CI, and corresponding *p* value. Models at birth and at 16.5 years of age are based on data with multiple imputation of missing covariates.

[a]Length growth from 0 to 2.5 years of age are adjusted for birth weight, birth length, and gestational age.

[b]Weight growth from 0 to 2.5 years of age are adjusted for birth weight, birth length, gestational age, and length growth over the same time span.

[c]Height growth models are adjusted for birth weight, height at start of the growth period, and preceding height growth.

[d]Weight growth models are adjusted for birth weight, height and weight at start of the growth period, and length growth over the same time span.

[e]Models of growth from 6.0 to 16.5 years of age are additionally adjusted for pubertal maturation.

Sensitivity analysis

Sensitivity analysis excluding children born preterm (4.4% born before GA week 37) or twins (3.8%) did not change the results or revealed patterns. Only minor changes in estimated coefficients were found in all analyses. Twins or preterm-born participants were therefore not excluded from the analyses. Sensitivity analyses run on a data set with no imputations and in a complete-case data set produced results similar to those presented.

Discussion

In this longitudinal population-based study of adolescents, we have explored associations between birth weight, childhood BMI, and growth rate with BMC and aBMD at 15 to 20 years of age. A significantly positive association was found between birth weight and TB BMC at 15 to 20 years of age, both in girls and boys. We observed significant associations between higher childhood BMI and greater adolescent bone mass. In both sexes, overweight/obesity at 6.0 or 16.5 years of age revealed from 0.5 to 1.1 higher *Z*-scores for TH BMC and aBMD at 15 to 20 years of age compared with those of normal weight. The corresponding associations with TB were somewhat stronger. Being underweight during childhood and adolescence was consistently negatively associated with bone parameters at 15 to 20 years of age. In early childhood, up to 6.0 years of age, higher rates of length/height growth and weight gain were positively associated with bone mass accrual at 15 to 20 years of age. In this period, a high rate of length/height growth was more strongly associated with adolescent bone mass accrual than a high rate of weight gain. In contrast, a high rate of weight gain, but not height growth, from 6.0 to 16.5 years of age showed strong positive associations with both bone mass and density.

Childhood and adolescence represent a critical window of opportunity for lifestyle interventions to maximize bone mass.[4] Information on how BMI and growth in childhood influence later peak bone mass is important, especially in times of increasing childhood overweight and obesity. Our study brings updated results on this relationship from a country and a population at high risk of osteoporotic fractures in the adult population.[33] The observed associations were partly supportive of our initial hypothesis of a positive association between high birth weight, higher childhood BMI, and adolescent BMC/aBMD. Higher TB BMC and aBMD values in children (2 to 18 years) with overweight/obesity, compared with normal-weight children, have been shown in other, mostly cross-sectional studies.[15] The importance of our study is its longitudinal design with data from birth up to 18 to 20 years of age. We observed that overweight/obesity at 2.5 years of age in girls and at 6.0 and 16.5 years of age in both boys and girls were associated with higher BMC/aBMD in late adolescence. This seems a positive finding because a 10% increase in peak aBMD is predicted to delay the development of osteoporosis in women by 13 years.[34] However, it could be questioned whether the higher aBMD in individuals with overweight/obesity is sufficient given the excess weight load. Other studies have shown conflicting effects of obesity and excess fat on bone strength, and reported increased risk of fracture among overweight children.[16,17] We found indications that the effect of increasing BMI at 16.5 years of age on TB BMC and aBMD was leveling off when BMI exceeded 30 kg/m^2 (Supplemental Figs. S1 and S2). However, there were few obese adolescents in our study population, limiting our ability to draw firm conclusions.

Both boys and girls with overweight/obesity at 16.5 years of age had significantly higher TH aBMD *Z*-scores compared with those of normal weight. Greater weight gain in each period from age 2.5 years was also positively associated with higher TH aBMD. This supports the notion of adaption to mechanical loading.[15,18] Another study from this same cohort showed that tracking (stability) of overweight/obesity from childhood to 15 to 20 years of age was moderate to strong,[35] so a high weight loading is likely to have persisted over time. Others have also found long-term benefits of high childhood BMI on bone mass in adulthood, in addition to physical fitness.[36] As reported by others, the effect of excess weight on bone might be site-specific[37,38] and might in part be explained by increased lean mass.[18,38] In another cross-sectional study of the TFF1 cohort,[39] both fat mass and lean mass emerged as strong predictors of bone mass at femoral neck and total hip, with lean mass being the most influential. It also showed that in adolescents, especially girls with low lean mass, fat mass was more important.[39] Clark and colleagues found positive associations between fat mass and bone mass and bone growth in prepubertal children and concluded that adipose tissue stimulates bone growth.[40] Results from a Mendelian randomized study suggested that adiposity is causally related to increased aBMD in children, especially at weight-bearing sites.[37] Others have pointed to greater lean mass in overweight children, which may account for differences.[18,41] Because we do not have information on childhood body composition, we cannot distinguish between the potential different impacts of fat and lean mass in childhood. In this picture, it is, however, important to notice the consistent trend of being underweight during childhood and at 16.5 years of age was associated with lower BMC/aBMD *Z*-scores at 15 to 20 years of age compared with those of normal weight, both in girls and boys. This is in line with findings from another study of Scandinavian children and adolescents.[42] Previous studies have also shown an association between thinness in childhood and increased risk of hip fracture later in life.[12,13]

Our results confirm earlier findings that a high rate of height and weight growth in early childhood is associated with higher bone mass at different ages later in life.[43,44] Gaining height faster than others between 6.0 and 16.5 years of age revealed lower effect estimates than faster growth in early childhood. This is in line with findings by Kuh and colleagues, who have studied bone measures in early old age.[44] They found lower effect estimates for aBMD for height gain between 7 and 15 years than for height growth in early childhood. They found that hip aBMD was negatively associated with postpubertal height gain, especially in boys, explaining the findings with redistribution of bone as a biomechanical response to longitudinal growth.[44] We found that length/height and weight gain at different age periods influenced bone measures at 15 to 20 years of age differently. How this may affect final achievement of peak bone mass and future fracture risk is not yet clear. Mikkola and colleagues who studied growth in individuals born between 1934 and 1944 found that in men, hip fracture risk in older age was driven by increase in height between 2 and 7 years of age and gain in BMI between 7 and 11 years of age. However, in women, early growth was not associated with the risk of hip fractures.[45]

In all analyses, higher effect estimates were found for BMC than for aBMD. This is not unexpected because height gain,

especially during maturation, both influence BMC and bone size (bone area) and may as a consequence give lower aBMD if BMC does not increase proportionally more than bone area.[2,4,5] This was most clearly observed for height growth between 6.0 to 16.5 years of age in boys, which resulted in significantly higher TH and TB BMC but negative aBMD. The limitations of the two-dimensional DXA technique might also overestimate bone area in larger bones and hence underestimate aBMD.[2]

Overall, higher estimated BMC/aBMD *Z*-scores were found for girls than for boys. However, no statistically significant sex difference was found when cross-product terms with sex and the exposure variables were included in the models. Stronger associations with bone mass in girls have also been observed in several other studies.[10,15,41] We know from other studies of the Fit Futures cohort that there are sex differences in the timing of skeletal growth and that especially the boys have probably not reached peak bone mass.[23] Hormonal influence and pubertal timing may partly account for that, as suggested by others.[15,41] Pubertal maturation is likely a mediator in the relationship between weight in childhood and bone acquisition, as illustrated in another study.[41]

Birth weight was associated with higher TB BMC at 15 to 20 years of age in both sexes. The estimated effect was modest, 0.13 (95% CI 0.02 to 0.23) and 0.31 (95% CI 0.20 to 0.41) *Z*-score higher TB BMC in boys and girls, respectively. This is in line with previous studies.[8,10,46] This finding supports the importance of intrauterine skeletal development, as shown by others.[3,8,10,43] Associations between birth weight and bone strength parameters later in life have been contradictory.[9–11] Youths in this cohort were born in a period with high mean birth weight in Norway,[20] generally supporting sufficient nutrition in utero, which may limit our power to study maternal nutritional effects on later bone health. Information on maternal smoking and BMI was not available from the MBRN for this birth cohort, but we know from other MBRN data that few had any diseases. Generally, maternal health is good; undernutrition and severe malnutrition is rare among the Norwegian mothers of today.[20,47] Leunissen and colleagues found no influence of birth size on TB aBMD at 18 to 24 years of age and concluded that postnatal growth and weight gain were the main determinants.[11] In our study, associations between birth weight and aBMD was only significant for TB in girls. Stronger associations were found with later height growth and weight gain, and adolescent bone mass accrual, than for birth weight and adolescent bone mass. After additional adjustment for BMI at 16.5 years of age, the effect of birth weight was no longer significant (data not shown). According to Lucas and colleagues,[48] if the associations are attenuated or removed after adjustment for later size, later size is likely to be more relevant than early size. There is consistent evidence that both intrauterine life and childhood are important periods for foundations of later bone mass.[8–11,43,44] Although the majority of variance in peak bone mass is explained by genetic factors,[6,7] environmental factors at different ages are of importance.[4] Sufficient maternal nutrition and healthy lifestyle during pregnancy and maintenance of a healthy weight through childhood all seem therefore important for the maximizing of peak bone mass. From other studies, we also know that physical activity plays an important role.[2,36] Even today, both undernutrition and malnutrition and obesity constitute a challenge related to optimal bone accrual. To promote bone health in adulthood, public health efforts should focus on these topics. This is recently highlighted by other researchers in the field of pediatric and adolescent bone health.[49]

The main strength of this study is its population-based design and access to longitudinal data from birth to 18 to 20 years of age. The high attendance rate in TFF1 and the population-based design reduce the risk of selection bias. Most studies of bone strength in children/adolescents are cross-sectional studies; thus, longitudinal studies are called for.[15,17,18] Our study is fairly large compared with others in the field.[10,15,17,18] This gave us the opportunity to stratify the analyses by sex to avoid biased estimates due to differences in bone growth between girls and boys, especially during adolescence.[3,4,18] Data from the MBRN and objectively measured height/weight in childhood minimized the risk of information bias. Repeated DXA measurements were performed using the same instrument with a documented good precision[24] to avoid systematic error in the outcome measures. Repeated measures of bone mass at 15 to 17 and 18 to 20 years of age are an advantage because BMC and aBMD increase during adolescence, which has been observed in this cohort.[23]

The main limitation in this study is the number of participants with missing data. Despite a high participation rate in TFF1 (>90%), this introduces a risk of selection bias. Because of the retrospective collection of exposure variables, missing data from birth and childhood are not dependent on the outcome. More boys than girls did not attend TFF2. However, dropout analyses did not indicate any other main differences between participants with and without missing data. Sensitivity analyses did not indicate that missing data were influential in our estimates. Linear spline multilevel modeling[25] was used to predict length/height and weight at exact ages in childhood and estimate growth trajectories. This is a particularly useful method to deal with challenges when data are not measured at the same point in time, data are from different sources, and with missing values.[25] A recognized method was used to impute missing covariates.[32] We used linear mixed models, assumed to be robust against missing data,[50] and missing data from TFF2 did not affect the number of participants included in the analyses because all available data were used. Another limitation is the lack of information on potential confounding factors, such as parental (genetic), nutritional, physical activity, and other lifestyle factors at birth and childhood that are known to affect skeletal development.[3,4] We cannot rule out the possibility of unmeasured confounders, making our models somewhat incomplete and open to residual confounding. Measures of BMC and aBMD with DXA are a proxy for bone strength,[2] and DXA measurements have some limitations versus more sophisticated measures of bone strength like bone macro- and microarchitecture.[2,5] However, aBMD is estimated to predict 66% to 74% of the variation in bone strength[51] and is the most frequently used measure in children and adolescents.[2]

In summary, we saw a positive association between high birth weight and BMC in adolescence. Length/height growth and weight gain in childhood revealed stronger associations with bone accrual at 15 to 20 years of age. We therefore conclude that birth weight has an effect on adolescent bone mass but less than later growth and BMI in childhood and at adolescence. Overall stronger associations were found for TB than for TH and stronger associations with BMC than with aBMD. Our findings did not indicate that overweight/obesity in childhood negatively affected bone mass accrual, but underweight was consistently associated with lower BMC and aBMD *Z*-scores.

Disclosures

All authors state that they have no conflicts of interest.

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Authors' roles: Study design and conduct: ASF, NE, and GG. Data collection: ASF, NE, and EE. Data analysis: EE. Statistical counseling: TW. Data interpretation: EE, GS, and NE. Drafting manuscript: EE, GS, and NE. Revising manuscript content: TC, ED, ASF, GG, TW, and AW. Approving final version of manuscript: EE, GS, TC, ED, ASF, GG, TW, AW, and NE. EE takes responsibility for the integrity of the data analysis.

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Supplemental table 1: Differences between observed measurements and those predicted by the linear spline multilevel model, for girls and boys in The Tromsø study: Fit Futures

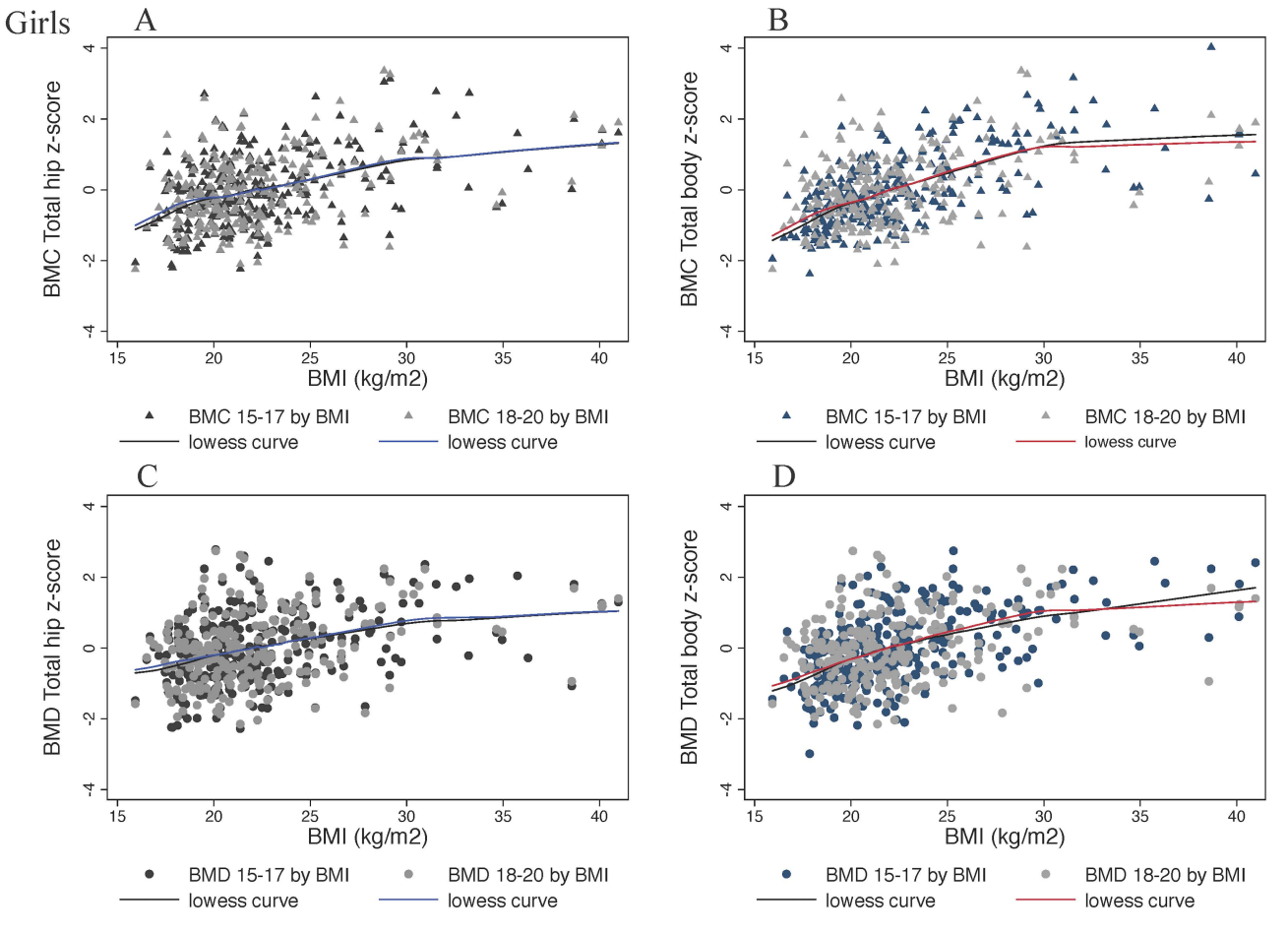
	n	Mean actual measurement (SD)		Mean predicted measurement (SD)		Mean difference (SD)	
Age 2-4 years	633	2.6	(0.4)	2.5	-	-0.1	
Age 5-7 years	633	6.0	(0.4)	6.0	-	0	
Age 15-17 years	633	16.6	(0.4)	16.5	-	-0.1	
Girls							
Weight models (kg)							
Birth weight	306	3.48	(0.58)	3.48	(0.55)	-0.0002	(0.026)
Weight 2-4 years	306	13.51	(1.69)	13.55	(1.55)	0.031	(1.09)
Weight 5-7 years	306	21.87	(3.93)	21.58	(3.80)	-0.30 **	(1.38)
Weight 15-17 years	306	61.57	(12.09)	61.91	(12.25)	0.34 ***	(1.16)
Length/height models (cm)							
Length at birth	287	49.44	(2.14)	49.47	(1.63)	0.023	(0.61)
Length 2-4 years	306	91.27	(4.39)	91.63	(3.18)	0.36	(3.72)
Length 5-7 years	306	116.75	(5.06)	117.08	(4.15)	0.32 *	(2.39)
Length 15-17 years	306	165.51	(6.09)	166.10	(6.02)	0.56 ***	(0.69)
Body mass index (BMI kg/m^2)							
BMI at birth	287	14.30	(1.49)	14.30	(1.56)	0.005	(0.27)
BMI 2-4 years	306	16.20	(1.39)	16.11	(1.37)	-0.09 ***	(0.33)
BMI 5-7 years	306	15.97	(2.10)	15.69	(2.20)	-0.29 ***	(0.47)
BMI 15-17 years	306	22.48	(4.29)	22.44	(4.32)	-0.04 *	(0.33)
Boys							
Weight models (kg)							
Birth weight	327	3.57	(0.59)	3.58	(0.57)	0.0002	(0.027)
Weight 2-4 years	327	14.11	(1.76)	14.19	(1.60)	0.074	(1.04)
Weight 5-7 years	327	22.10	(3.55)	21.63	(3.30)	-0.47 **	(1.47)
Weight 15-17 years	327	69.71	(14.42)	69.86	(14.57)	0.15	(1.45)
Length/height models (cm)							
Length at birth	317	50.03	(2.38)	50.05	(1.79)	0.021	(0.68)
Length 2-4 years	327	92.77	(4.66)	93.14	(3.33)	0.36	(3.79)
Length 5-7 years	327	117.99	(5.25)	118.00	(4.46)	0.01	(2.43)
Length 15-17 years	327	177.14	(6.74)	177.74	(6.56)	0.60 ***	(1.16)
Body mass index (BMI kg/m^2)							
BMI at birth	317	14.25	(1.52)	14.25	(1.61)	-0.002	(0.29)
BMI 2-4 years	327	16.36	(1.31)	16.32	(1.30)	-0.04 *	(0.33)
BMI 5-7 years	327	15.81	(1.75)	15.48	(1.79)	-0.33 ***	(0.48)
BMI 15-17 years	327	22.17	(4.17)	22.07	(4.20)	-0.1 ***	(0.33)

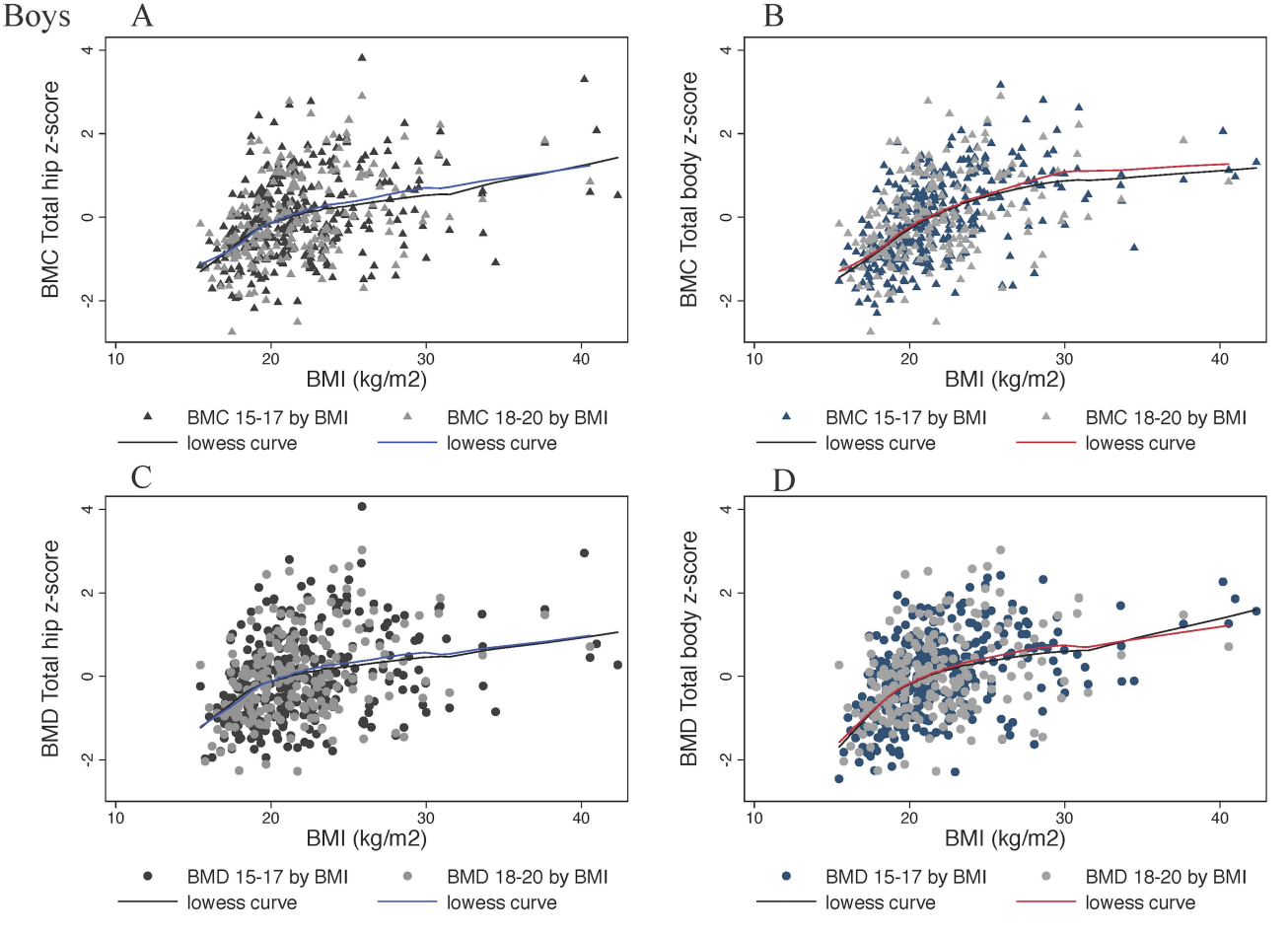
Paired samples t-test; mean difference significantly different from zero
* $p<0.05$ ** $p<0.001$ ** $p<0.0001$

Supplemental table 2. Descriptive statistics for selected variables with missing data at birth and at 15-17 years of age, showing observed and imputed values for girls and boys, The Tromsø Study: Fit Futures

Characteristics	**Girls**						**Boys**					
	Observed			Imputed [a]			Observed			Imputed [a]		
Birth	n	Mean/%	(SD)	n	Mean/%	(SD)	n	Mean/%	(SD)	n	Mean/%	(SD)
Gestational age (weeks)	272	39.8	1.8	306	39.8	1.7	303	39.5	2.1	327	39.5	2.1
15-17 years of age												
Menarche age	302	13.0	1.2	306	13.0	1.2	-	-	-	-	-	-
Pubertal maturation, girls [b]	303			306			-	-	-	-	-	-
Early (<12.5 years)	85	28.1%			28.2%		-	-	-	-	-	-
Intermediate (12.5-13.9 years)	152	50.2%			50.4%		-	-	-	-	-	-
Late (≥14.0 years)	66	21.8%			21.5%		-	-	-	-	-	-
Pubertal development scale (PDS)	-	-	-	-	-	-	259	3.29	0.43	327	3.29	0.43
Pubertal maturation, boys [c]	-	-	-	-	-	-	259			327		
Barely started (PDS 2.0-2.9)	-	-	-	-	-	-	46	17.8%			17.8%	
Underway (PDS 3.0-3.9)	-	-	-	-	-	-	196	75.7%			75.6%	
Completed (PDS 4.0)	-	-	-	-	-	-	17	6.6%			6.6%	
Physical activity – frequency	303			306			321			327		
Low	103	34.0%			34.2%		118	36.8%			36.8%	
Moderate	133	43.9%			43.8%		117	36.5%			36.4%	
High	67	22.1%			22.0%		86	26.8%			26.8%	

[a] Estimated values from a dataset with multiple (20) imputations, n= 306 girls and 327 boys.
[b] Pubertal maturation is based on age of menarche in girls.
[c] Pubertal maturation is based on PDS in boys.[(28)]


Girls
A
BMC Total hip z-score
BMI (kg/m2)
BMC 15-17 by BMI
BMC 18-20 by BMI
lowess curve
lowess curve
B
BMC Total body z-score
BMI (kg/m2)
BMC 15-17 by BMI
BMC 18-20 by BMI
lowess curve
lowess curve
C
BMD Total hip z-score
BMI (kg/m2)
BMD 15-17 by BMI
BMD 18-20 by BMI
lowess curve
lowess curve
D
BMD Total body z-score
BMI (kg/m2)
BMD 15-17 by BMI
BMD 18-20 by BMI
lowess curve
lowess curve


Boys
A
BMC Total hip z-score
BMI (kg/m2)
BMC 15-17 by BMI
BMC 18-20 by BMI
lowess curve
lowess curve
B
BMC Total body z-score
BMI (kg/m2)
BMC 15-17 by BMI
BMC 18-20 by BMI
lowess curve
lowess curve
C
BMD Total hip z-score
BMI (kg/m2)
BMD 15-17 by BMI
BMD 18-20 by BMI
lowess curve
lowess curve
D
BMD Total body z-score
BMI (kg/m2)
BMD 15-17 by BMI
BMD 18-20 by BMI
lowess curve
lowess curve

Appendices

1. IOTF extended cut-off values for boys 2012
2. IOTF extended cut-off values for girls 2012
3. Letter of approval from REC North for project no 2014/1397
4. The information leaflet and the consent form used in TFF1
5. The information leaflet and the consent form used in TFF2
6. Registration form for MBRN, 1967-1998
7. Letter of approval from MBRN
8. Extract from the questionnaire in TFF1

Boys									
BMI (kg/m²) at age 18 years									
Age (months)	Age (years)	16	17	18,5	23	25	27	30	35
24	2	13,6	14,29	15,24	17,54	18,36	19,07	19,99	21,2
25	2,08	13,58	14,26	15,2	17,49	18,31	19,03	19,95	21,16
26	2,17	13,55	14,23	15,16	17,45	18,26	18,98	19,9	21,11
27	2,25	13,52	14,2	15,13	17,41	18,22	18,93	19,85	21,07
28	2,33	13,5	14,17	15,09	17,36	18,17	18,89	19,81	21,03
29	2,42	13,47	14,14	15,06	17,32	18,13	18,85	19,77	20,99
30	2,5	13,44	14,11	15,02	17,28	18,09	18,8	19,73	20,95
31	2,58	13,42	14,08	14,99	17,24	18,05	18,76	19,68	20,91
32	2,67	13,39	14,05	14,95	17,2	18	18,72	19,64	20,88
33	2,75	13,37	14,02	14,92	17,16	17,97	18,68	19,61	20,84
34	2,83	13,34	13,99	14,89	17,12	17,93	18,64	19,57	20,81
35	2,92	13,32	13,96	14,86	17,08	17,89	18,61	19,54	20,78
36	3	13,3	13,94	14,83	17,05	17,85	18,57	19,5	20,75
37	3,08	13,27	13,91	14,8	17,01	17,82	18,54	19,47	20,72
38	3,17	13,25	13,89	14,77	16,98	17,79	18,5	19,44	20,7
39	3,25	13,23	13,86	14,74	16,95	17,75	18,47	19,41	20,67
40	3,33	13,21	13,84	14,71	16,91	17,72	18,44	19,38	20,65
41	3,42	13,19	13,81	14,68	16,88	17,69	18,41	19,36	20,63
42	3,5	13,16	13,79	14,66	16,85	17,66	18,38	19,33	20,61
43	3,58	13,14	13,76	14,63	16,83	17,63	18,36	19,31	20,6
44	3,67	13,12	13,74	14,61	16,8	17,61	18,33	19,29	20,59
45	3,75	13,1	13,72	14,58	16,77	17,58	18,31	19,27	20,57
46	3,83	13,08	13,7	14,56	16,75	17,56	18,29	19,25	20,56
47	3,92	13,06	13,67	14,53	16,72	17,54	18,27	19,24	20,56
48	4	13,04	13,65	14,51	16,7	17,52	18,25	19,23	20,56
49	4,08	13,02	13,63	14,49	16,68	17,5	18,24	19,21	20,56
50	4,17	13	13,61	14,46	16,66	17,48	18,22	19,21	20,56
51	4,25	12,98	13,59	14,44	16,64	17,46	18,21	19,2	20,56
52	4,33	12,96	13,57	14,42	16,62	17,45	18,2	19,2	20,57
53	4,42	12,94	13,55	14,4	16,61	17,44	18,19	19,2	20,59
54	4,5	12,92	13,53	14,38	16,59	17,43	18,19	19,2	20,6
55	4,58	12,9	13,51	14,36	16,58	17,42	18,18	19,2	20,63
56	4,67	12,88	13,49	14,34	16,56	17,41	18,18	19,21	20,65
57	4,75	12,86	13,47	14,32	16,55	17,4	18,18	19,22	20,68
58	4,83	12,84	13,44	14,3	16,54	17,4	18,18	19,23	20,71
59	4,92	12,82	13,42	14,28	16,53	17,39	18,19	19,25	20,75
60	5	12,8	13,4	14,26	16,52	17,39	18,19	19,27	20,79
61	5,08	12,78	13,38	14,24	16,51	17,39	18,2	19,29	20,84
62	5,17	12,75	13,36	14,22	16,51	17,4	18,21	19,32	20,89
63	5,25	12,73	13,34	14,2	16,5	17,4	18,23	19,35	20,95
64	5,33	12,71	13,32	14,18	16,5	17,41	18,24	19,38	21,01
65	5,42	12,69	13,3	14,17	16,5	17,41	18,26	19,42	21,08
66	5,5	12,66	13,27	14,15	16,5	17,42	18,28	19,46	21,15
67	5,58	12,64	13,25	14,13	16,5	17,44	18,31	19,5	21,23
68	5,67	12,62	13,23	14,11	16,5	17,45	18,33	19,55	21,31
69	5,75	12,6	13,21	14,1	16,51	17,46	18,36	19,59	21,4
70	5,83	12,58	13,19	14,08	16,51	17,48	18,39	19,65	21,49
71	5,92	12,56	13,18	14,07	16,52	17,5	18,42	19,7	21,59
72	6	12,54	13,16	14,06	16,52	17,52	18,45	19,76	21,69
73	6,08	12,52	13,14	14,04	16,53	17,54	18,49	19,82	21,79
74	6,17	12,5	13,12	14,03	16,54	17,56	18,53	19,88	21,9
75	6,25	12,48	13,11	14,02	16,56	17,59	18,57	19,94	22,01
76	6,33	12,47	13,1	14,01	16,57	17,62	18,61	20,01	22,12
77	6,42	12,45	13,08	14,01	16,58	17,64	18,65	20,08	22,24
78	6,5	12,44	13,07	14	16,6	17,67	18,7	20,15	22,35
79	6,58	12,43	13,06	14	16,62	17,7	18,74	20,22	22,47
80	6,67	12,42	13,06	13,99	16,64	17,73	18,79	20,29	22,59
81	6,75	12,41	13,05	13,99	16,66	17,77	18,84	20,36	22,71
82	6,83	12,4	13,05	13,99	16,68	17,8	18,89	20,44	22,83

83	6,92	12,39	13,04	13,99	16,7	17,84	18,94	20,51	22,96
84	7	12,39	13,04	14	16,73	17,88	18,99	20,59	23,08
85	7,08	12,39	13,04	14	16,75	17,91	19,04	20,66	23,21
86	7,17	12,39	13,04	14,01	16,78	17,95	19,09	20,74	23,33
87	7,25	12,39	13,04	14,02	16,81	17,99	19,15	20,82	23,45
88	7,33	12,39	13,05	14,02	16,84	18,04	19,2	20,9	23,58
89	7,42	12,39	13,05	14,04	16,87	18,08	19,26	20,98	23,7
90	7,5	12,39	13,06	14,05	16,9	18,12	19,32	21,06	23,83
91	7,58	12,4	13,07	14,06	16,93	18,17	19,38	21,14	23,95
92	7,67	12,4	13,07	14,07	16,97	18,21	19,43	21,22	24,08
93	7,75	12,41	13,08	14,09	17	18,26	19,5	21,3	24,21
94	7,83	12,41	13,09	14,1	17,04	18,31	19,56	21,39	24,34
95	7,92	12,42	13,1	14,12	17,08	18,36	19,62	21,47	24,47
96	8	12,43	13,11	14,13	17,12	18,41	19,68	21,56	24,6
97	8,08	12,44	13,13	14,15	17,15	18,46	19,75	21,65	24,74
98	8,17	12,44	13,14	14,17	17,19	18,51	19,81	21,74	24,88
99	8,25	12,45	13,15	14,18	17,23	18,56	19,88	21,83	25,02
100	8,33	12,46	13,16	14,2	17,27	18,62	19,95	21,92	25,16
101	8,42	12,47	13,17	14,22	17,32	18,67	20,02	22,02	25,31
102	8,5	12,48	13,19	14,24	17,36	18,73	20,09	22,11	25,45
103	8,58	12,49	13,2	14,26	17,4	18,78	20,16	22,21	25,61
104	8,67	12,5	13,21	14,28	17,44	18,84	20,23	22,31	25,76
105	8,75	12,51	13,23	14,3	17,49	18,9	20,3	22,41	25,92
106	8,83	12,52	13,24	14,32	17,53	18,95	20,37	22,51	26,07
107	8,92	12,53	13,25	14,34	17,57	19,01	20,45	22,61	26,23
108	9	12,54	13,27	14,36	17,62	19,07	20,52	22,71	26,4
109	9,08	12,55	13,28	14,38	17,67	19,13	20,6	22,82	26,56
110	9,17	12,56	13,3	14,4	17,71	19,19	20,67	22,92	26,72
111	9,25	12,58	13,31	14,42	17,76	19,25	20,75	23,03	26,89
112	9,33	12,59	13,33	14,44	17,8	19,31	20,83	23,13	27,05
113	9,42	12,6	13,35	14,47	17,85	19,37	20,9	23,24	27,22
114	9,5	12,61	13,36	14,49	17,9	19,43	20,98	23,34	27,39
115	9,58	12,63	13,38	14,51	17,94	19,49	21,06	23,45	27,55
116	9,67	12,64	13,4	14,53	17,99	19,55	21,13	23,55	27,71
117	9,75	12,65	13,41	14,56	18,04	19,61	21,21	23,66	27,88
118	9,83	12,67	13,43	14,58	18,09	19,67	21,29	23,76	28,04
119	9,92	12,68	13,45	14,61	18,13	19,74	21,36	23,86	28,2
120	10	12,7	13,47	14,63	18,18	19,8	21,44	23,96	28,35
121	10,08	12,71	13,49	14,66	18,23	19,86	21,51	24,06	28,51
122	10,17	12,73	13,51	14,68	18,28	19,92	21,59	24,16	28,65
123	10,25	12,74	13,53	14,71	18,32	19,97	21,66	24,25	28,8
124	10,33	12,76	13,55	14,73	18,37	20,04	21,73	24,35	28,94
125	10,42	12,78	13,57	14,76	18,42	20,09	21,8	24,44	29,08
126	10,5	12,8	13,59	14,79	18,47	20,15	21,88	24,54	29,22
127	10,58	12,81	13,61	14,82	18,52	20,21	21,95	24,63	29,35
128	10,67	12,83	13,63	14,84	18,56	20,27	22,02	24,72	29,48
129	10,75	12,85	13,66	14,87	18,61	20,33	22,09	24,81	29,61
130	10,83	12,87	13,68	14,9	18,66	20,39	22,16	24,9	29,73
131	10,92	12,89	13,7	14,93	18,71	20,45	22,23	24,98	29,86
132	11	12,91	13,73	14,96	18,76	20,51	22,29	25,07	29,97
133	11,08	12,94	13,75	14,99	18,81	20,56	22,36	25,15	30,09
134	11,17	12,96	13,78	15,02	18,86	20,62	22,43	25,24	30,2
135	11,25	12,98	13,8	15,05	18,91	20,68	22,5	25,32	30,31
136	11,33	13	13,83	15,08	18,95	20,74	22,56	25,4	30,42
137	11,42	13,03	13,86	15,12	19	20,79	22,63	25,48	30,52
138	11,5	13,05	13,89	15,15	19,05	20,85	22,7	25,56	30,63
139	11,58	13,08	13,92	15,18	19,1	20,91	22,76	25,64	30,73
140	11,67	13,1	13,94	15,22	19,15	20,97	22,83	25,72	30,83
141	11,75	13,13	13,97	15,25	19,2	21,03	22,89	25,79	30,93
142	11,83	13,16	14,01	15,29	19,25	21,08	22,96	25,87	31,02
143	11,92	13,19	14,04	15,32	19,31	21,14	23,02	25,94	31,12
144	12	13,21	14,07	15,36	19,36	21,2	23,09	26,02	31,21

145	12,08	13,24	14,1	15,4	19,41	21,25	23,15	26,09	31,3
146	12,17	13,28	14,13	15,44	19,46	21,31	23,22	26,17	31,39
147	12,25	13,31	14,17	15,47	19,51	21,37	23,28	26,24	31,47
148	12,33	13,34	14,2	15,51	19,56	21,43	23,34	26,31	31,56
149	12,42	13,37	14,24	15,55	19,61	21,49	23,4	26,38	31,64
150	12,5	13,4	14,27	15,59	19,67	21,54	23,47	26,45	31,73
151	12,58	13,44	14,31	15,63	19,72	21,6	23,53	26,52	31,81
152	12,67	13,47	14,34	15,67	19,77	21,66	23,6	26,59	31,89
153	12,75	13,5	14,38	15,71	19,82	21,72	23,66	26,66	31,97
154	12,83	13,54	14,42	15,75	19,88	21,78	23,72	26,73	32,04
155	12,92	13,58	14,46	15,8	19,93	21,83	23,78	26,8	32,12
156	13	13,61	14,5	15,84	19,99	21,89	23,84	26,87	32,19
157	13,08	13,65	14,54	15,88	20,04	21,95	23,91	26,94	32,27
158	13,17	13,69	14,58	15,93	20,09	22,01	23,97	27	32,33
159	13,25	13,73	14,62	15,97	20,15	22,07	24,03	27,07	32,41
160	13,33	13,76	14,66	16,02	20,2	22,13	24,1	27,14	32,48
161	13,42	13,8	14,7	16,06	20,26	22,19	24,15	27,2	32,54
162	13,5	13,84	14,74	16,11	20,31	22,24	24,22	27,26	32,6
163	13,58	13,88	14,79	16,16	20,37	22,3	24,28	27,33	32,67
164	13,67	13,93	14,83	16,2	20,43	22,36	24,34	27,39	32,74
165	13,75	13,97	14,87	16,25	20,48	22,42	24,4	27,46	32,8
166	13,83	14,01	14,92	16,3	20,54	22,48	24,46	27,52	32,86
167	13,92	14,05	14,96	16,35	20,6	22,54	24,53	27,58	32,92
168	14	14,09	15,01	16,39	20,65	22,6	24,59	27,64	32,97
169	14,08	14,14	15,05	16,44	20,71	22,66	24,65	27,7	33,03
170	14,17	14,18	15,1	16,49	20,76	22,72	24,71	27,76	33,08
171	14,25	14,22	15,14	16,54	20,82	22,77	24,76	27,82	33,14
172	14,33	14,26	15,19	16,59	20,88	22,83	24,82	27,88	33,19
173	14,42	14,31	15,23	16,64	20,93	22,89	24,88	27,94	33,25
174	14,5	14,35	15,28	16,68	20,99	22,95	24,94	28	33,3
175	14,58	14,4	15,33	16,73	21,04	23	25	28,05	33,34
176	14,67	14,44	15,37	16,78	21,1	23,06	25,06	28,11	33,39
177	14,75	14,48	15,42	16,83	21,15	23,12	25,11	28,16	33,43
178	14,83	14,53	15,46	16,88	21,21	23,17	25,17	28,22	33,47
179	14,92	14,57	15,51	16,93	21,26	23,23	25,22	28,27	33,52
180	15	14,61	15,55	16,98	21,31	23,28	25,27	28,32	33,56
181	15,08	14,66	15,6	17,02	21,37	23,33	25,33	28,37	33,6
182	15,17	14,7	15,64	17,07	21,42	23,39	25,38	28,42	33,64
183	15,25	14,74	15,69	17,12	21,47	23,44	25,43	28,47	33,67
184	15,33	14,78	15,73	17,16	21,52	23,49	25,48	28,52	33,71
185	15,42	14,83	15,78	17,21	21,57	23,54	25,53	28,56	33,74
186	15,5	14,87	15,82	17,26	21,62	23,59	25,58	28,61	33,78
187	15,58	14,91	15,87	17,3	21,67	23,64	25,63	28,66	33,81
188	15,67	14,95	15,91	17,35	21,72	23,69	25,68	28,7	33,85
189	15,75	15	15,95	17,4	21,77	23,74	25,73	28,75	33,88
190	15,83	15,04	16	17,44	21,82	23,79	25,78	28,8	33,92
191	15,92	15,08	16,04	17,49	21,87	23,84	25,83	28,84	33,95
192	16	15,12	16,08	17,53	21,92	23,89	25,88	28,89	33,98
193	16,08	15,16	16,12	17,57	21,97	23,94	25,92	28,93	34,01
194	16,17	15,2	16,17	17,62	22,01	23,99	25,97	28,97	34,05
195	16,25	15,24	16,21	17,66	22,06	24,04	26,02	29,02	34,08
196	16,33	15,28	16,25	17,71	22,11	24,08	26,07	29,06	34,12
197	16,42	15,32	16,29	17,75	22,16	24,13	26,11	29,11	34,15
198	16,5	15,36	16,33	17,79	22,2	24,18	26,16	29,15	34,19
199	16,58	15,4	16,37	17,83	22,25	24,22	26,21	29,2	34,23
200	16,67	15,44	16,41	17,88	22,29	24,27	26,25	29,24	34,26
201	16,75	15,47	16,45	17,92	22,34	24,32	26,3	29,29	34,31
202	16,83	15,51	16,49	17,96	22,39	24,37	26,35	29,34	34,35
203	16,92	15,55	16,53	18	22,43	24,41	26,4	29,38	34,39
204	17	15,59	16,57	18,04	22,48	24,46	26,44	29,43	34,43
205	17,08	15,62	16,6	18,08	22,52	24,5	26,49	29,48	34,48
206	17,17	15,66	16,64	18,12	22,57	24,55	26,54	29,52	34,52

207	17,25	15,69	16,68	18,16	22,61	24,6	26,58	29,57	34,57
208	17,33	15,73	16,72	18,2	22,66	24,64	26,63	29,62	34,61
209	17,42	15,76	16,75	18,24	22,7	24,69	26,68	29,67	34,66
210	17,5	15,8	16,79	18,28	22,74	24,73	26,72	29,71	34,7
211	17,58	15,83	16,83	18,31	22,79	24,78	26,77	29,76	34,75
212	17,67	15,87	16,86	18,35	22,83	24,82	26,81	29,81	34,8
213	17,75	15,9	16,9	18,39	22,87	24,87	26,86	29,86	34,85
214	17,83	15,93	16,93	18,43	22,91	24,91	26,91	29,9	34,9
215	17,92	15,97	16,97	18,46	22,96	24,96	26,95	29,95	34,95
216	18	16	17	18,5	23	25	27	30	35

Girls									
BMI (kg/m²) at age 18 years									
Age (months)	Age (years)	16	17	18,5	23	25	27	30	35
24	2	13,4	14,05	14,96	17,25	18,09	18,83	19,81	21,13
25	2,08	13,37	14,02	14,93	17,21	18,05	18,79	19,77	21,09
26	2,17	13,35	14	14,9	17,17	18	18,75	19,73	21,05
27	2,25	13,32	13,97	14,86	17,13	17,96	18,71	19,68	21,01
28	2,33	13,3	13,94	14,83	17,09	17,92	18,67	19,64	20,97
29	2,42	13,27	13,91	14,8	17,05	17,88	18,63	19,6	20,94
30	2,5	13,25	13,88	14,77	17,01	17,84	18,59	19,57	20,9
31	2,58	13,22	13,86	14,74	16,98	17,81	18,55	19,53	20,87
32	2,67	13,2	13,83	14,71	16,94	17,77	18,52	19,5	20,84
33	2,75	13,18	13,8	14,68	16,91	17,74	18,48	19,47	20,81
34	2,83	13,15	13,78	14,65	16,88	17,71	18,45	19,44	20,79
35	2,92	13,13	13,75	14,62	16,85	17,68	18,42	19,41	20,77
36	3	13,11	13,73	14,6	16,82	17,64	18,39	19,38	20,74
37	3,08	13,09	13,7	14,57	16,79	17,62	18,36	19,36	20,72
38	3,17	13,07	13,68	14,54	16,76	17,59	18,34	19,33	20,7
39	3,25	13,04	13,66	14,52	16,73	17,56	18,31	19,31	20,69
40	3,33	13,02	13,63	14,49	16,7	17,53	18,29	19,29	20,67
41	3,42	13	13,61	14,47	16,68	17,51	18,26	19,27	20,66
42	3,5	12,98	13,59	14,44	16,65	17,48	18,24	19,25	20,65
43	3,58	12,96	13,56	14,42	16,62	17,46	18,22	19,23	20,64
44	3,67	12,94	13,54	14,39	16,6	17,44	18,2	19,21	20,63
45	3,75	12,91	13,52	14,37	16,58	17,41	18,18	19,2	20,62
46	3,83	12,89	13,49	14,34	16,55	17,39	18,16	19,18	20,62
47	3,92	12,87	13,47	14,32	16,53	17,37	18,14	19,17	20,62
48	4	12,85	13,45	14,3	16,51	17,35	18,13	19,16	20,61
49	4,08	12,83	13,43	14,27	16,49	17,34	18,11	19,15	20,62
50	4,17	12,81	13,4	14,25	16,47	17,32	18,1	19,15	20,62
51	4,25	12,78	13,38	14,23	16,45	17,31	18,09	19,14	20,63
52	4,33	12,76	13,36	14,2	16,43	17,29	18,08	19,14	20,64
53	4,42	12,74	13,34	14,18	16,42	17,28	18,07	19,14	20,66
54	4,5	12,72	13,31	14,16	16,4	17,27	18,06	19,14	20,67
55	4,58	12,7	13,29	14,14	16,39	17,26	18,06	19,15	20,69
56	4,67	12,67	13,27	14,12	16,37	17,25	18,06	19,15	20,72
57	4,75	12,65	13,25	14,1	16,36	17,24	18,06	19,16	20,74
58	4,83	12,63	13,23	14,08	16,35	17,24	18,06	19,17	20,77
59	4,92	12,61	13,21	14,06	16,34	17,23	18,06	19,19	20,81
60	5	12,59	13,18	14,04	16,33	17,23	18,06	19,2	20,84
61	5,08	12,56	13,16	14,02	16,32	17,23	18,07	19,22	20,89
62	5,17	12,54	13,14	14	16,32	17,23	18,08	19,24	20,93
63	5,25	12,52	13,12	13,98	16,31	17,23	18,09	19,27	20,98
64	5,33	12,5	13,1	13,97	16,31	17,24	18,1	19,3	21,04
65	5,42	12,48	13,08	13,95	16,3	17,24	18,12	19,33	21,09
66	5,5	12,45	13,06	13,93	16,3	17,25	18,13	19,36	21,16
67	5,58	12,43	13,04	13,92	16,3	17,26	18,15	19,4	21,22
68	5,67	12,41	13,02	13,9	16,3	17,27	18,18	19,43	21,29
69	5,75	12,39	13	13,89	16,31	17,28	18,2	19,48	21,37
70	5,83	12,37	12,99	13,87	16,31	17,3	18,22	19,52	21,44
71	5,92	12,36	12,97	13,86	16,32	17,31	18,25	19,57	21,52
72	6	12,34	12,96	13,85	16,32	17,33	18,28	19,61	21,61
73	6,08	12,32	12,94	13,84	16,33	17,35	18,31	19,67	21,7
74	6,17	12,31	12,93	13,83	16,34	17,37	18,35	19,72	21,79
75	6,25	12,29	12,92	13,82	16,36	17,39	18,38	19,78	21,89
76	6,33	12,28	12,9	13,82	16,37	17,42	18,42	19,84	21,99
77	6,42	12,27	12,9	13,81	16,39	17,45	18,46	19,9	22,09
78	6,5	12,26	12,89	13,81	16,4	17,48	18,5	19,96	22,19
79	6,58	12,25	12,88	13,81	16,42	17,51	18,55	20,03	22,3
80	6,67	12,24	12,88	13,81	16,44	17,54	18,59	20,1	22,41
81	6,75	12,23	12,87	13,81	16,47	17,58	18,64	20,17	22,53
82	6,83	12,23	12,87	13,81	16,49	17,61	18,69	20,24	22,64

83	6,92	12,23	12,87	13,82	16,52	17,65	18,74	20,32	22,76
84	7	12,23	12,87	13,83	16,54	17,69	18,8	20,39	22,88
85	7,08	12,23	12,88	13,83	16,57	17,73	18,85	20,47	23
86	7,17	12,23	12,88	13,84	16,61	17,78	18,91	20,55	23,13
87	7,25	12,23	12,89	13,86	16,64	17,82	18,97	20,63	23,26
88	7,33	12,24	12,9	13,87	16,67	17,87	19,03	20,72	23,39
89	7,42	12,24	12,9	13,88	16,71	17,91	19,09	20,8	23,52
90	7,5	12,25	12,91	13,9	16,74	17,96	19,15	20,89	23,65
91	7,58	12,25	12,92	13,91	16,78	18,01	19,22	20,98	23,79
92	7,67	12,26	12,93	13,93	16,82	18,07	19,28	21,07	23,93
93	7,75	12,27	12,95	13,95	16,86	18,12	19,35	21,16	24,07
94	7,83	12,28	12,96	13,96	16,9	18,17	19,42	21,25	24,21
95	7,92	12,29	12,97	13,98	16,94	18,23	19,49	21,35	24,36
96	8	12,3	12,98	14	16,99	18,28	19,56	21,44	24,5
97	8,08	12,31	13	14,02	17,03	18,34	19,63	21,54	24,65
98	8,17	12,32	13,01	14,04	17,07	18,39	19,7	21,64	24,8
99	8,25	12,33	13,03	14,06	17,12	18,45	19,77	21,74	24,95
100	8,33	12,34	13,04	14,08	17,16	18,51	19,85	21,84	25,1
101	8,42	12,35	13,06	14,1	17,21	18,57	19,92	21,94	25,26
102	8,5	12,37	13,07	14,12	17,25	18,63	20	22,04	25,42
103	8,58	12,38	13,09	14,15	17,3	18,69	20,07	22,14	25,58
104	8,67	12,39	13,1	14,17	17,34	18,75	20,15	22,24	25,74
105	8,75	12,4	13,12	14,19	17,39	18,81	20,22	22,35	25,9
106	8,83	12,41	13,13	14,21	17,44	18,87	20,3	22,45	26,06
107	8,92	12,42	13,15	14,23	17,48	18,93	20,38	22,56	26,22
108	9	12,44	13,16	14,26	17,53	18,99	20,46	22,66	26,39
109	9,08	12,45	13,18	14,28	17,58	19,05	20,53	22,77	26,55
110	9,17	12,46	13,2	14,3	17,63	19,12	20,61	22,88	26,72
111	9,25	12,47	13,22	14,33	17,68	19,18	20,69	22,99	26,88
112	9,33	12,49	13,23	14,35	17,73	19,24	20,77	23,09	27,05
113	9,42	12,5	13,25	14,38	17,78	19,31	20,85	23,2	27,21
114	9,5	12,52	13,27	14,4	17,83	19,38	20,94	23,31	27,38
115	9,58	12,53	13,29	14,43	17,88	19,44	21,02	23,42	27,55
116	9,67	12,55	13,31	14,46	17,94	19,51	21,1	23,53	27,71
117	9,75	12,57	13,33	14,49	17,99	19,58	21,18	23,64	27,88
118	9,83	12,59	13,36	14,52	18,04	19,64	21,27	23,75	28,04
119	9,92	12,61	13,38	14,55	18,1	19,71	21,35	23,86	28,2
120	10	12,63	13,4	14,58	18,16	19,78	21,43	23,97	28,36
121	10,08	12,65	13,43	14,61	18,21	19,85	21,52	24,08	28,52
122	10,17	12,67	13,46	14,64	18,27	19,92	21,6	24,19	28,68
123	10,25	12,69	13,48	14,68	18,33	19,99	21,69	24,29	28,83
124	10,33	12,72	13,51	14,71	18,39	20,07	21,77	24,4	28,98
125	10,42	12,74	13,54	14,75	18,45	20,14	21,86	24,51	29,14
126	10,5	12,77	13,57	14,78	18,51	20,21	21,95	24,62	29,28
127	10,58	12,79	13,6	14,82	18,57	20,28	22,03	24,72	29,43
128	10,67	12,82	13,63	14,86	18,63	20,36	22,12	24,83	29,58
129	10,75	12,85	13,67	14,9	18,7	20,43	22,2	24,94	29,72
130	10,83	12,88	13,7	14,94	18,76	20,51	22,29	25,04	29,86
131	10,92	12,91	13,74	14,98	18,82	20,58	22,38	25,15	30
132	11	12,94	13,77	15,03	18,89	20,66	22,47	25,25	30,14
133	11,08	12,97	13,81	15,07	18,95	20,73	22,55	25,36	30,28
134	11,17	13,01	13,84	15,11	19,02	20,81	22,64	25,46	30,41
135	11,25	13,04	13,88	15,16	19,09	20,89	22,73	25,57	30,54
136	11,33	13,08	13,92	15,2	19,15	20,96	22,81	25,67	30,67
137	11,42	13,11	13,96	15,25	19,22	21,04	22,9	25,77	30,8
138	11,5	13,15	14	15,3	19,29	21,12	22,99	25,87	30,93
139	11,58	13,18	14,04	15,35	19,36	21,2	23,08	25,98	31,05
140	11,67	13,22	14,09	15,39	19,42	21,27	23,16	26,08	31,17
141	11,75	13,26	14,13	15,44	19,49	21,35	23,25	26,18	31,3
142	11,83	13,3	14,17	15,49	19,56	21,43	23,34	26,28	31,42
143	11,92	13,34	14,22	15,54	19,63	21,51	23,42	26,38	31,54
144	12	13,38	14,26	15,59	19,7	21,59	23,51	26,47	31,66

145	12,08	13,42	14,31	15,65	19,77	21,66	23,59	26,57	31,77
146	12,17	13,47	14,35	15,7	19,84	21,74	23,68	26,67	31,89
147	12,25	13,51	14,4	15,75	19,91	21,82	23,76	26,76	32
148	12,33	13,55	14,45	15,8	19,98	21,9	23,85	26,86	32,11
149	12,42	13,6	14,5	15,86	20,05	21,97	23,93	26,95	32,22
150	12,5	13,64	14,54	15,91	20,12	22,05	24,02	27,05	32,33
151	12,58	13,69	14,59	15,96	20,19	22,12	24,1	27,14	32,43
152	12,67	13,73	14,64	16,02	20,26	22,2	24,18	27,22	32,53
153	12,75	13,78	14,69	16,07	20,33	22,27	24,26	27,31	32,63
154	12,83	13,82	14,74	16,13	20,39	22,35	24,34	27,4	32,73
155	12,92	13,87	14,79	16,18	20,46	22,42	24,42	27,49	32,82
156	13	13,92	14,84	16,23	20,53	22,49	24,49	27,57	32,91
157	13,08	13,96	14,89	16,29	20,59	22,56	24,57	27,65	33
158	13,17	14,01	14,94	16,34	20,66	22,63	24,64	27,73	33,09
159	13,25	14,06	14,99	16,4	20,72	22,7	24,71	27,81	33,17
160	13,33	14,1	15,04	16,45	20,79	22,77	24,79	27,88	33,24
161	13,42	14,15	15,09	16,5	20,85	22,84	24,86	27,96	33,32
162	13,5	14,2	15,13	16,55	20,91	22,9	24,92	28,03	33,39
163	13,58	14,24	15,18	16,61	20,98	22,97	24,99	28,1	33,47
164	13,67	14,29	15,23	16,66	21,04	23,03	25,06	28,16	33,53
165	13,75	14,34	15,28	16,71	21,1	23,09	25,12	28,23	33,6
166	13,83	14,38	15,33	16,76	21,15	23,15	25,18	28,29	33,66
167	13,92	14,43	15,38	16,81	21,21	23,21	25,25	28,36	33,72
168	14	14,47	15,42	16,86	21,27	23,27	25,31	28,42	33,78
169	14,08	14,52	15,47	16,91	21,33	23,33	25,37	28,48	33,83
170	14,17	14,57	15,52	16,96	21,38	23,39	25,42	28,53	33,88
171	14,25	14,61	15,57	17,01	21,43	23,44	25,48	28,59	33,93
172	14,33	14,65	15,61	17,06	21,49	23,5	25,53	28,64	33,98
173	14,42	14,7	15,66	17,11	21,54	23,55	25,59	28,69	34,03
174	14,5	14,74	15,71	17,16	21,59	23,6	25,64	28,74	34,07
175	14,58	14,79	15,75	17,2	21,64	23,65	25,69	28,79	34,11
176	14,67	14,83	15,8	17,25	21,69	23,7	25,74	28,84	34,15
177	14,75	14,87	15,84	17,3	21,74	23,75	25,78	28,88	34,18
178	14,83	14,92	15,88	17,34	21,79	23,8	25,83	28,92	34,21
179	14,92	14,96	15,93	17,39	21,83	23,84	25,87	28,97	34,25
180	15	15	15,97	17,43	21,88	23,89	25,92	29,01	34,28
181	15,08	15,04	16,01	17,47	21,92	23,93	25,96	29,05	34,31
182	15,17	15,08	16,05	17,51	21,96	23,97	26	29,08	34,33
183	15,25	15,12	16,09	17,56	22,01	24,01	26,04	29,12	34,36
184	15,33	15,16	16,13	17,6	22,05	24,05	26,08	29,15	34,39
185	15,42	15,2	16,17	17,64	22,09	24,09	26,12	29,19	34,41
186	15,5	15,24	16,21	17,68	22,13	24,13	26,15	29,22	34,43
187	15,58	15,27	16,25	17,72	22,17	24,17	26,19	29,25	34,45
188	15,67	15,31	16,28	17,75	22,2	24,21	26,23	29,29	34,48
189	15,75	15,34	16,32	17,79	22,24	24,24	26,26	29,31	34,49
190	15,83	15,38	16,36	17,82	22,28	24,28	26,29	29,34	34,51
191	15,92	15,41	16,39	17,86	22,31	24,31	26,32	29,37	34,53
192	16	15,45	16,42	17,9	22,35	24,34	26,36	29,4	34,54
193	16,08	15,48	16,46	17,93	22,38	24,38	26,39	29,42	34,56
194	16,17	15,51	16,49	17,96	22,41	24,41	26,42	29,45	34,58
195	16,25	15,54	16,52	17,99	22,44	24,44	26,45	29,48	34,6
196	16,33	15,57	16,55	18,02	22,48	24,47	26,48	29,5	34,62
197	16,42	15,6	16,58	18,06	22,51	24,5	26,5	29,53	34,63
198	16,5	15,63	16,61	18,08	22,54	24,53	26,53	29,55	34,64
199	16,58	15,65	16,64	18,11	22,57	24,56	26,56	29,58	34,66
200	16,67	15,68	16,66	18,14	22,59	24,59	26,59	29,6	34,68
201	16,75	15,7	16,69	18,17	22,62	24,61	26,61	29,63	34,7
202	16,83	15,73	16,71	18,19	22,65	24,64	26,64	29,65	34,71
203	16,92	15,75	16,74	18,22	22,68	24,67	26,67	29,68	34,73
204	17	15,78	16,76	18,24	22,7	24,7	26,69	29,7	34,75
205	17,08	15,8	16,78	18,27	22,73	24,72	26,72	29,73	34,77
206	17,17	15,82	16,81	18,29	22,76	24,75	26,74	29,75	34,78

207	17,25	15,84	16,83	18,31	22,78	24,77	26,77	29,77	34,8
208	17,33	15,86	16,85	18,34	22,81	24,8	26,8	29,8	34,82
209	17,42	15,88	16,87	18,36	22,83	24,82	26,82	29,82	34,84
210	17,5	15,9	16,89	18,38	22,86	24,85	26,85	29,85	34,87
211	17,58	15,91	16,91	18,4	22,88	24,88	26,87	29,87	34,89
212	17,67	15,93	16,93	18,42	22,9	24,9	26,9	29,9	34,91
213	17,75	15,95	16,95	18,44	22,93	24,93	26,92	29,92	34,93
214	17,83	15,97	16,96	18,46	22,95	24,95	26,95	29,95	34,95
215	17,92	15,98	16,98	18,48	22,98	24,98	26,97	29,98	34,98
216	18	16	17	18,5	23	25	27	30	35

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord			29.09.2014	2014/1397/REK nord
			Deres dato:	Deres referanse:
			19.08.2014	

Vår referanse må oppgis ved alle henvendelser

Nina Emaus

2014/1397 Fit Futures: Fødselsvekt og vektutvikling i barndom og overvekt, kroppssammensetning og beinhelse hos unge

Forskningsansvarlig: UIT Norges Arktiske Universitet
Prosjektleder: Nina Emaus

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) i møtet 18.09.2014. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikklovens § 4.

Prosjektleders prosjektomtale
Overvekt og fedme er viktige folkehelseutfordringer i Norge og det samme er osteoporotiske brudd. Denne longitudinelle studien skal generere ny kunnskap om fødselsvekt og vektutvikling i barneår har betydning for forekomst av overvekt og fedme, kroppssammensetning og beinstyrke i ungdomsår for å få kunnskap om når forebyggende tiltak bør settes inn. Beinstyrke har stor betydning for bruddrisiko og grunnlaget legges i barne- og ungdomsår og vekt kan ha både positiv og negativ effekt på beinstyrken. Studien vil benytte innsamlede data fra Fit Futures, en befolkningsundersøkelse med kartlegging av livsstil og helse hos ungdom. 1038 ungdommer deltok i 2010/11 med oppfølging i 2012/13. Høyde og vektdata fra helsestasjonsjournaler i tillegg til innhenting av fødselsvekt fra medisinsk fødselsregister vil gi oss longitudinelle data og en mulighet til å studere vektutviklingen fra fødsel, gjennom barneår til ung voksen alder og innflytelsen dette har på vekt, kroppssammensetning og beinstyrke.

Vurdering

Studien skal gjøres på data som allerede er innhentet i forbindelse med FIT Futures, som er en del av Tromsøundersøkelsen, bare på ungdommer.

Det søkes om å få koble disse data opp mot Medisinsk fødselsregister, samt å innhente supplerende data fra journal på helsestasjonene.

Vurdering av om det avgitte samtykke fra Fit Futures er dekkende
Informasjonsskrivet inneholder informasjon om at de innsamlede data kan bli koblet opp mot Medisinsk fødselsregister, samt innhenting av supplerende data helsestasjon. Det avgitte samtykke ansees for å være dekkende i forhold til det som skal gjøres i denne studien.

Vedtak
Med hjemmel i helseforskningsloven § 2 og § 9, samt forskningsetikkloven § 4 godkjennes prosjektet.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest 01.06.2020, jf. hfl. 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Kopi til:postmottak@iho.uit.no

PERSONVERN OG SIKKERHET

Alle medarbeidere som jobber med undersøkelsen, har taushetsplikt. Opplysningene som samles inn, vil bare bli brukt til godkjente forskningsformål, som beskrevet over.

Opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver. Koden oppbevares separat ved Universitetet i Tromsø, og kun noen få autoriserte personer har tilgang. Den enkelte forsker får ikke tilgang til opplysninger som gjør det mulig å identifisere enkeltpersoner. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

I noen tilfeller kan det være aktuelt å gjøre analyser av blodprøver eller genetiske analyser ved forskningsinstitusjoner i utlandet. Hvis dette gjøres, vil våre utenlandske samarbeidspartnere ikke få opplysninger som kan knytte prøvene opp mot deg som person.

Tromsøundersøkelsen gjennomfører Fit futures i samarbeid med Universitetssykehuset Nord-Norge og Nasjonalt folkehelseinstitutt. Data som samles inn på sykehuset, overføres til Universitetet i Tromsø når datainnsamlingen er avsluttet. Ingen av opplysningene som framkommer i undersøkelsen, lagres i journalsystemet på sykehuset. Databehandlingsansvarlig er Universitetet i Tromsø. Tromsøundersøkelsen administrerer utlevering av data til forskningsprosjekter. Hvem som er ansvarlig for forskningsprosjektene, finner du her http://www.tromsoundersokelsen.no. Fit futures er godkjent av Datatilsynet og Regional komité for medisinsk og helsefaglig forskningsetikk, Nord-Norge. Deltakere er forsikret gjennom Norsk Pasientskadeerstatningsordning.

FRIVILLIG DELTAKELSE

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i undersøkelsen, og dette vil ikke få noen konsekvenser for deg. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte Tromsøundersøkelsen, Institutt for samfunnsmedisin, Universitetet i Tromsø, 9037 Tromsø, telefon 77644816, e-post: tromsous@uit.no.

RETT TIL INNSYN OG SLETTING AV PRØVER OG OPPLYSNINGER OM DEG

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har også rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

ENERGI

VIL DU DELTA?

Hvis du er fylt 16 år, gir du selv ditt samtykke til å delta. Du kan da signere vedlagte skjema (hvitt ark) og ta det med til undersøkelsen. Det er også mulig å undertegne skjemaet når du kommer til Forskningsposten.

Hvis du ikke er fylt 16 år, må du be dine foreldre/foresatte om lov til å delta. Da må både du og dine foreldre/foresatte signere vedlagte skjema (hvitt ark) som du tar med deg til undersøkelsen.

ANSVARLIGE FOR GJENNOMFØRING AV FIT FUTURES UNDERSØKELSEN

Fit futures ledes av en styringsgruppe, og følgende forskere er ansvarlige for gjennomføringen:

Anne-Sofie Furberg
prosjektleder, lege, Universitetssykehuset Nord-Norge
e-post: anne-sofie.furberg@unn.no, telefon 77 75 58 24

Christopher Sivert Nielsen
psykolog, Nasjonalt folkehelseinstitutt
e-post: Christopher.Sivert.Nielsen@fhi.no, telefon 21 07 82 77

Guri Grimnes
lege, Universitetssykehuset Nord-Norge og Universitetet i Tromsø
e-post: guri.grimnes@unn.no, telefon 77 66 94 83

SPØRSMÅL?

Dersom du/dere har spørsmål om undersøkelsen, kontakt Forskningsposten UNN på telefon 77 62 69 09 eller prosjektadministrator for Fit futures på telefon 930 03 925.

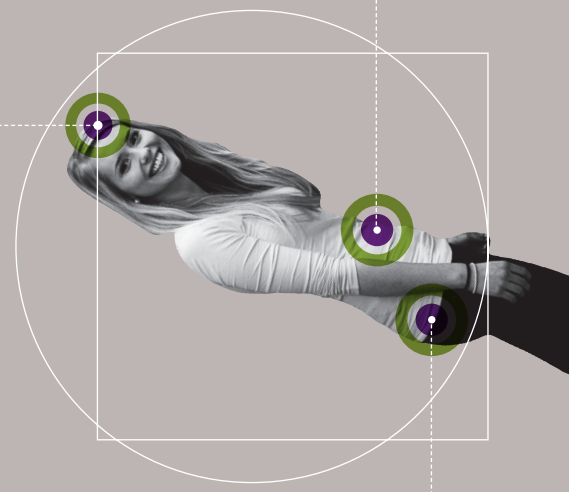
www.fitfutures.no

UNN – VI BRYR OSS – SAMMEN TAR VI ANSVAR

UNIVERSITETET I TROMSØ

folkehelseinstituttet

FAST FOOD

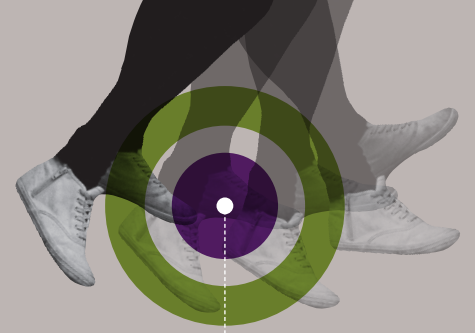


SOSIALT NETTVERK

FitFutures
EN DEL AV TROMSØUNDERSØKELSEN

DIN HELSE DIN FREMTID

INVITASJON TIL Å DELTA I HELSEUNDERSØKELSE BLANT UNGDOM



HVA ER FIT FUTURES?

Fit futures er et forskningsprosjekt der vi undersøker ungdommers fysiske helse og livsstil.

HVORFOR ER DETTE VIKTIG?

Voksnes helse undersøkes i mange studier, men man har mindre kunnskap om helse blant ungdom. Selv om få ungdommer har alvorlige sykdommer, legges mye av grunnlaget for fremtidig helse i ungdomsårene. Denne undersøkelsen kan bidra til at vi får økt kunnskap om hvordan man kan forebygge sykdom og om hvordan diagnoser kan stilles på et tidligere tidspunkt.

HVA FORSKES DET PÅ?

Hovedområdene det forskes på er:

- Eksem og kviser
- Infeksjoner
- Fysisk aktivitet og overvekt
- D-vitamin
- Jernmangel
- Genmodifisert mat
- Miljøgifter
- Smerte
- Beintetthet
- Diabetes
- Øresus
- Medisinbruk
- Frafall fra skole
- Tannhelse

Informasjonen fra undersøkelsen vil også bli brukt til forskning om de store folkehelseproblemene generelt, slik som hjerte-karsykdommer, lungesykdommer, kreft, nedsatt fruktbarhet og smerte. Det vil også bli forsket på arbeidsførhet i skole og yrke i forhold til sykdom, helse og livsstil. En del av prosjektene vil studere samspillet mellom arv, miljø og sykdom og helse; til slike prosjekter vil det bli hentet ut genetisk arvestoff fra blodprøvene. I framtiden kan data bli brukt i forskningsprosjekter som i dag ikke er planlagt. For alle slike nye prosjekter kreves det at prosjektet er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk. En oversikt over godkjente prosjekter finner du her (www.tromsoundersokelsen.no). Nettsiden holdes løpende oppdatert. Her kan du også lese om våre forskningsresultater.

HVEM KAN DELTA?

Alle ungdommer på VG1 blir invitert til å delta. Hvis du er 16 år eller mer, kan du selv bestemme om du vil delta. Er du under 16 år, må du ha samtykke fra dine foreldre eller foresatte.

AKTIVITET

SLIK FOREGÅR UNDERSØKELSEN

Undersøkelsen gjennomføres i skoletiden. Selve undersøkelsen tar 2-3 timer, og du må påregne å være borte fra skolen en halv dag. Skolen anser dette som gyldig skolefravær. Du blir undersøkt på Forskningsposten, Universitetssykehuset Nord-Norge, av erfarne forskningssykepleiere og tannleger/tannhelsesekretærer. Undersøkelsen består av følgende deler:

- *Spørreskjema* der vi spør om livsstil, trivsel, sykdommer og helseplager gjennom livet, og familieforhold.
- *Intervju* der vi spør om hvilke medisiner du bruker, om du har noen sykdom i dag og litt om sosialt nettverk. Kvinner spørres også om menstruasjon og graviditet.
- *Generell helseundersøkelse* der vi måler høyde, vekt, livvidde og hoftevidde, blodtrykk og puls, samt tar blodprøve, en hårprøve fra nakken, og en bakterieprøve fra nesebor og hals med en fuktet vattpinne.
- Måling av *smertefølsomhet* der vi måler følsomhet for trykk, kulde og varme. Smerten kommer gradvis, og du kan selv avbryte når som helst.
- *Kroppsscan* (DEXA) der vi måler beintetthet og forholdet mellom fett- og muskelvev. Dette skjer ved at du ligger rolig i ca. 10 minutter mens kroppen scannes.
- *Tannundersøkelse* som blir din årlige undersøkelse ved den offentlige tannhelsetjenesten og omfatter klinisk undersøkelse, tannrøntgen, kliniske foto og avtrykk for studiemodeller.

Etter undersøkelsen vil du få utlevert en liten *aktivitetsmåler* som er festet i et smalt strikkbelte til å ha under klærne. Denne måler hvor mye du beveger deg i løpet av dagen. Apparatet leveres på skolen etter en ukes bruk. Da vil det samtidig tas ny bakterieprøve fra nesebor og hals.

Noen deltakere vil bli forespurt om å undersøkes en gang til. Det vil da være aktuelt å gjenta noen av undersøkelsene og gjøre enkelte utvidede undersøkelser.

HVA SKJER MED DE BIOLOGISKE PRØVENE?

Med blodprøven gjøres analyser av bl.a. hormonnivåer, fettstoffer, blodsukker, vitaminer, miljøgifter og markører på betennelse og sykdommer. Det blir også hentet ut arvestoff (DNA og RNA) for genetiske analyser. Bakterieprøvene brukes til å måle forekomst av gule stafylokokker. Hårprøven analyseres for å se på nivå av kvikksølv. Prøvene lagres i Forskningsbiobanken for Tromsøundersøkelsen ved Universitetet i Tromsø. Hvis du sier ja til å delta, gir du også samtykke til at de biologiske prøvene og analyseresultatene inngår i biobanken.

INFORMASJON FRA ANDRE KILDER OG BRUK AV DATA I FRAMTIDEN

Opplysninger og prøver som du gir, blir oppbevart på ubestemt tid til bruk i forskning omkring helse og sykdom som omtalt i denne brosjyren. Det kan også hende at vi tar kontakt med deg igjen for å spørre om du vil være med på en ny undersøkelse. For spesielle forskningsprosjekter kan det være aktuelt å sammenstille informasjon fra Fit futures med nasjonale helseregistre som Reseptregisteret, Medisinsk fødselsregistrer, Kreftregisteret, Norsk pasientregister, Dødsårsaksregisteret og andre nasjonale registre over sykdommer som det forskes på i Tromsøundersøkelsen. I tillegg kan det være aktuelt å innhente helseopplysninger fra spesialist- og primærhelsetjenesten, for eksempel informasjon om beinbrudd og høyde- og vektdata fra helsestasjon, til bruk i forskning på sykdommer og helseproblemer som det forskes på i Tromsøundersøkelsen. Det kan også bli innehentet data fra registre i Statistisk sentralbyrå slik som miljø, befolkning, utdanning, inntekt, offentlige ytelser, arbeidsdeltakelse og andre forhold som kan ha betydning for helsa. For å undersøke om sykdommer går i arv, kan opplysninger om deg sammenstilles med opplysninger om dine slektninger, dersom disse har deltatt i deler av Tromsøundersøkelsen. Dette blir gjort ved å innhente opplysninger om slektskap fra Familieregisteret. Fra skolen vil vi innhente dine opplysninger om studieprogram, klasse, kjønn, antall fraværsdager, om du fullfører skoleåret og om karakterer i fagene norsk, matematikk og engelsk.

Sammenstillinger av informasjon krever noen ganger nytt samtykke og/eller annen type godkjenning slik som dispensasjon fra taushetsplikten eller godkjenning av offentlige instanser, for eksempel Regional komité for medisinsk og helsefaglig forskningsetikk, Datatilsynet eller NAV.

MULIGE ULEMPER OG FORDELER

Deltakelse innebærer at du må bruke noe tid. Deler av undersøkelsen kan også innebære ubehag. Dette gjelder særlig blodprøven. Dersom du vet at du har problemer med å ta blodprøve, kan du kontakte Forskningsposten på telefon 77 62 69 09 eller snakke med sykepleier når du kommer til undersøkelsen for å finne en løsning på dette.

Dersom resultatet av prøvene dine viser at det er nødvendig med oppfølging av tannlege, lege eller henvisning til spesialist, vil du bli orientert om det. Ved behov for henvisning til spesialist, vil vi sørge for henvisning og tilbud om oppfølging ved sykehuset.

Deltakere får et gavekort til en verdi av kr. 200 ved oppmøte som kan brukes i de fleste butikker i Tromsø.

TEKNOLOGI

SMERTE

MILJØGIFTER

RØYK OG SNUS

FitFutures
EN DEL AV TROMSØUNDERSØKELSEN

VIL DU DELTA?

Samtykke til å delta i studien Fit futures

Jeg er villig til å delta i studien

_____

(DITT FULLE NAVN I BLOKKBOKSTAVER)

Sted _____ Dato _____

_____

(DIN SIGNATUR)

VIL DU DELTA OG ER UNDER 16 ÅR?

Foreldre/foresatte sitt samtykke til deltakelse i Fit futures

Jeg samtykker herved i at mitt/vårt barn kan delta i undersøkelsen

_____

(BARNETS FULLE NAVN I BLOKKBOKSTAVER)

Sted _____ Dato _____

_____

(SIGNATUR FORELDER/FORESATT 1)

_____

(SIGNATUR FORELDER/FORESATT 2)

STØY

TANNHELSE

FRIVILLIG DELTAKELSE

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i undersøkelsen, og dette vil ikke få noen konsekvenser for deg. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte Tromsøundersøkelsen, Institutt for samfunnsmedisin, Det helsevitenskapelige fakultet, Universitetet i Tromsø, 9037 Tromsø, telefon 77 64 48 16, e-post: tromsous@uit.no.

HVA SKJER MED DE BIOLOGISKE PRØVENE?

Med blodprøven gjøres analyser av bl.a. hormoner, fettstoffer, blodsukker, vitaminer, miljøgifter og markører på betennelser og sykdommer. Det blir også hentet ut arvestoff (DNA og RNA) for genetiske analyser. Bakterieprøvene brukes til å måle forekomst av gule stafylokokker og meningokokker. Prøvene lagres i Forskningsbiobanken for Tromsøundersøkelsen ved Universitetet i Tromsø. Hvis du sier ja til å delta, gir du også samtykke til at de biologiske prøvene og analyseresultatene inngår i biobanken.

PERSONVERN OG SIKKERHET

Alle medarbeidere som jobber med undersøkelsen, har taushetsplikt. Opplysningene som samles inn, vil bare bli brukt til godkjente forskningsformål, som beskrevet over.

Når det forskes på data fra undersøkelsen, gjøres dette uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver. Koden oppbevares separat ved Universitetet i Tromsø, og kun noen få autoriserte personer har tilgang. Den enkelte forsker får ikke tilgang til opplysninger som gjør det mulig å identifisere enkeltpersoner. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

I noen tilfeller kan det være aktuelt å gjøre analyser av blodprøver eller genetiske analyser ved forskningsinstitusjoner i utlandet. Hvis dette gjøres, vil våre utenlandske samarbeidspartnere ikke få opplysninger som kan knytte prøvene opp mot deg som person.

Tromsøundersøkelsen gjennomfører Fit Futures i samarbeid med Universitetssykehuset Nord-Norge og Nasjonalt folkehelseinstitutt. Data som samles inn på sykehuset, overføres til Universitetet i Tromsø når datainnsamlingen er avsluttet. Ingen av opplysningene som framkommer i undersøkelsen, lagres i journalsystemet på sykehuset. Databehandlingsansvarlig er Universitetet i Tromsø. Tromsøundersøkelsen administrerer utlevering av data til forskningsprosjekter. Hvem som er ansvarlig for forskningsprosjektene, finner du her (www.tromsoundersokelsen.no). Fit Futures er godkjent av Datatilsynet og Regional komité for medisinsk og helsefaglig forskningsetikk, Nord-Norge. Deltakere er forsikret gjennom Norsk Pasientskadeerstatningsordning.

RETT TIL INNSYN, SLETTING AV PRØVER OG OPPLYSNINGER

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har også rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inkludert i analyser eller brukt i vitenskapelige publikasjoner.

BRUS & JUICE

VIL DU DELTA?

Hvis du vil delta, melder du deg på questback-link sendt til din epost eller tar kontakt med prosjektadministrator Annelene Moberg på 93 00 39 25 eller Siv Normann Gundersen på 93 00 39 54. Når du kommer til Forskningsposten på UNN, signerer du samtykkeskjema.

ANSVARLIGE FOR GJENNOMFØRING AV FIT FUTURES

Fit Futures ledes av en styringsgruppe, og følgende forskere er ansvarlige for gjennomføringen:

Anne-Sofie Furberg
prosjektleder, lege, Universitetssykehuset Nord-Norge og Universitetet i Tromsø
e-post: anne-sofie.furberg@uit.no, telefon 0 77 66

Christopher Sivert Nielsen
psykolog, Nasjonalt folkehelseinstitutt
e-post: Christopher.Sivert.Nielsen@fhi.no, telefon 21 07 82 77

Guri Grimnes
lege, Universitetssykehuset Nord-Norge
e-post: guri.grimnes@unn.no, telefon 0 77 66

Nina Emaus
professor i helsefag, Universitetet i Tromsø
e-post: nina.emaus@uit.no, telefon 77 66 07 62

SPØRSMÅL?

Dersom du har spørsmål om undersøkelsen, kontakt:

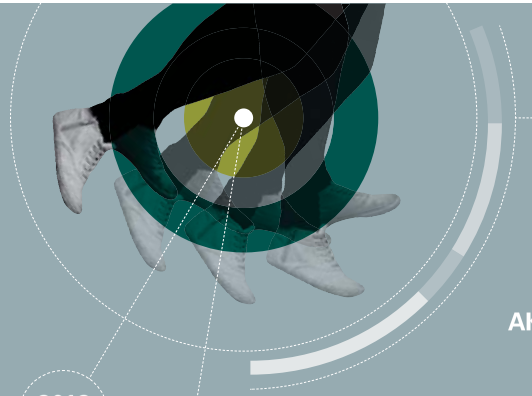
- Prosjektadministrator **Annelene Moberg** på telefon 93 00 39 25
- Prosjektadministrator **Siv Normann Gundersen** på telefon 93 00 39 54
- **Forskningsposten UNN** på telefon 77 62 69 09

WWW.FITFUTURES.NO

UNN · Sammen tar vi vare på hverandre

Universitetet i Tromsø

folkehelseinstituttet



2012
2013

AKTIVITET

ENERGI

FitFutures 2
EN DEL AV TROMSØUNDERSØKELSEN

DIN HELSE DIN FREMTID

INVITASJON TIL Å DELTA I HELSEUNDERSØKELSE BLANT UNGDOM

MILJØGIFTER

ASTMA OG ALLERGI

HVA ER FIT FUTURES?

Fit Futures er et forskningsprosjekt der vi følger helse og livsstil fra ungdom til voksen alder. Studien begynte med undersøkelser av elever på VG 1 i Tromsø og Balsfjord skoleåret 2010-2011.

HVEM KAN DELTA?

Alle ungdommer på VG3 i Tromsø og Balsfjord blir invitert til å delta. Dette gjelder også om du er i yrkespraksis. Elever som var med i første runde av Fit Futures og siden har sluttet på skolen, er også invitert.

Vi ønsker både nye og tidligere deltakere velkommen!

HVORFOR ER DETTE VIKTIG?

Voksnes helse undersøkes i mange studier, men man har mindre kunnskap om helse blant ungdom. Selv om få ungdommer har alvorlige sykdommer, legges mye av grunnlaget for fremtidig helse i ungdomsårene. Denne undersøkelsen kan bidra til at vi får økt kunnskap om hvordan man kan forebygge sykdom og om hvordan diagnoser kan stilles på et tidligere tidspunkt. Ved å gjenta undersøkelsen kan vi følge med hvordan helsen utvikler seg over tid.

HVA FORSKES DET PÅ?

Hovedområdene det forskes på er:

- Smerte
- Eksem og kviser
- Beintetthet
- Astma og allergi
- Diabetes
- Infeksjoner
- Øresus
- Fysisk aktivitet og overvekt
- Medisinbruk
- D-vitamin
- Frafall fra skole
- Jernmangel
- Genmodifisert mat
- Miljøgifter
- Personlighet og helseatferd
- Tannhelse, syreskader og medfødte skader på tennene

Informasjonen fra undersøkelsen vil også bli brukt til forskning på de store folkehelseproblemene generelt, som hjerte-karsykdommer, lungesykdommer, kreft, nedsatt fruktbarhet og smerte. Det vil også bli forsket på arbeidsforhet i skole og yrke, knyttet til sykdom, helse og livsstil. En del av prosjektene vil studere samspillet mellom arv, miljø, sykdom og helse; til slike prosjekter vil det bli hentet ut genetisk arvestoff fra blodprøvene. I framtiden kan data bli brukt i forskningsprosjekter som i dag ikke er planlagt.

For alle slike nye prosjekter kreves det godkjenning av Regional komité for medisinsk og helsefaglig forskningsetikk. En oversikt over godkjente prosjekter finner du her: **www.tromsoundersokelsen.no**. Nettsiden holdes løpende oppdatert, og her kan du lese om våre forskningsresultater.

SLIK FOREGÅR UNDERSØKELSEN

Undersøkelsen gjennomføres i skoletiden eller arbeidstiden og tar 2–3 timer. Du må regne med å være borte fra skolen eller praksis en halv dag. Skolene anser dette som gyldig fravær. Fravær fra lærebedriften må avklares med den enkelte arbeidsgiver, men erfaringen er at de fleste arbeidsgivere gir fri for å delta i denne typen undersøkelse.

Du blir undersøkt på Forskningsposten, Universitetssykehuset Nord-Norge, av erfarne forskningssykepleiere og tannpleiere. Undersøkelsen består av følgende deler:

- *Spørreskjema* der vi spør om livsstil, trivsel, sykdommer og helseplager gjennom livet, personlighet og familieforhold.
- *Intervju* der vi spør om hvilke medisiner du bruker, om du har tatt vaksine mot smitt- som hjernehinnebetennelse, om du har noen sykdom i dag og litt om ditt sosiale nettverk. Jenter spørres også om menstruasjon og graviditet.
- *Generell helseundersøkelse* der vi måler høyde, vekt, livvidde og hoftevidde, blodtrykk og puls. Vi tar også blodprøve, spyttprøve og bakterieprøver. Bakterieprøvene tas fra nese, hals og hud med en fuktet vattpinne.
- *Kroppsscan* (DEXA) der vi måler beintetthet og forholdet mellom fett- og muskelvev. Dette skjer ved at du ligger rolig i ca. 10 minutter mens kroppen scannes.
- *Tannundersøkelse* der vi tar foto av tennene dine. Dersom du deltok i første runde av Fit Futures, vil vi også undersøke bittet ditt ved at du biter sammen med en tynn, bløt plate mellom tennene. Undersøkelsen av bittet er nødvendig for å sette sammen tannmodellene fra første runde av Fit Futures. Det vil ikke bli gjort en tannundersøkelse slik som du vanligvis får hos tannlege eller tannpleier.
- *Lungefunksjonsundersøkelse* (Spirometri) der du skal puste ut så hardt du klarer gjennom et munnstykke. Mengden luft som blåses ut, er et mål på lungefunksjonen din. Etter å ha tatt undersøkelsen en gang, vil du få puste inn en dose av astmamedisinen Ventoline® som kan utvide luftveiene dine. Deretter gjentas lungefunksjonsundersøkelsen en gang til, og vi måler om lungefunksjonen din blir bedre med medisin eller ikke.

Etter undersøkelsene vil du få utlevert en liten aktivitetsmåler som er festet i et smalt strikkbelte til å ha under klærne. Denne måler hvor mye du beveger deg i løpet av døgnet. Etter en ukes bruk, leverer du aktivitetsmåleren til prosjektadministrator på skolen.

Noen deltakere vil bli spurt om å undersøkes en gang til. Det vil da være aktuelt å gjenta noen av undersøkelsene og gjøre enkelte utvidede undersøkelser.

MULIGE ULEMPER OG FORDELER

Deltakelse innebærer at du må bruke noe tid. Deler av undersøkelsen kan også innebære ubehag, dette gjelder særlig blodprøven. Dersom du vet at du har problemer med å ta blodprøve, kan du kontakte Forskningsposten på telefon 77 62 69 09 eller snakke med sykepleier når du kommer til undersøkelsen, for å finne en løsning på dette.

Dersom resultatet av prøvene dine viser at det er nødvendig med oppfølging av tannlege, lege eller henvisning til spesialist, vil du bli orientert om det. Ved behov for henvisning til spesialist, vil vi sørge for henvisning og tilbud om oppfølging ved sykehuset.

Alle deltakere får et gavekort til en verdi av kr. 200 som kan brukes i de fleste butikker i Tromsø. Transport til og fra UNN organiseres av undersøkelsen.

TIPS OG RÅD FØR UNDERSØKELSEN

Har du fjernet halsmandlene?
Dersom du vet eller tror at du har fjernet halsmandlene, spør gjerne de hjemme om dette. Hvor gammel du var og hvorfor det skjedde. Mange får fjernet halsmandlene i småbarnsalderen, og da er det vanskelig å vite dette sikkert selv.

Bruker du astmamedisiner?
Før undersøkelsen skal du ikke bruke noen astmamedisiner som utvider luftveiene.

- Dersom du bruker Singulair, slutter du med denne 3 dager (72 timer) før undersøkelsen.
- Dersom du bruker Serevent, Oxis, Onbrez, Seretide eller Symbicort, slutter du med denne 2 dager (48 timer) før undersøkelsen.
- Dersom du bruker Ventoline, Bricanyl, Airomir, Salbutamol eller Buventol, slutter du kvelden før undersøkelsen (12 timer før).
- Det er ikke nødvendig å slutte med Pulmicort, Budesonid, Flutide, Becotide, AeroBec, Beclomet, Giona, Asmanex eller Alvesco.
- Dersom du blir verre av din astma på grunn av medisinpause, kan du likevel bruke luftveisåpnende medisiner (Ventoline, Bricanyl, Airomir, Salbutamol eller Buventol).

Bruker du andre medisiner?
Skriv ned navn på medisiner du bruker fast og ta med på undersøkelsesdagen. Har du brukt antibiotika siste 3 måneder, noter ned navnet på denne også.

INFORMASJON FRA ANDRE KILDER OG BRUK AV DATA I FRAMTIDEN

Opplysninger og prøver som du gir, blir oppbevart på ubestemt tid til bruk i forskning omkring helse og sykdom som omtalt i denne brosjyren. Det kan også hende at vi tar kontakt med deg igjen for å spørre om du vil være med på en ny undersøkelse. For spesielle forskningsprosjekter kan det være aktuelt å sammenstille informasjon fra Fit Futures med nasjonale helseregistre som Reseptregisteret, Medisinsk fødselsregister, Kreftregisteret, Norsk pasientregister, Dødsårsaksregisteret og andre nasjonale registre over sykdommer som det forskes på i Tromsøundersøkelsen. I tillegg kan det være aktuelt å innhente helseopplysninger fra spesialist- og primærhelsetjenesten og Den offentlige tannhelsetjenesten, for eksempel informasjon om beinbrudd, høyde- og vektdata fra helsestasjon, og røntgenbilder av tenner, til bruk i forskning på sykdommer og helseproblemer som det forskes på i Tromsøundersøkelsen. Det kan også bli innhentet data fra registre i Statistisk sentralbyrå slik som miljø, befolkning, utdanning, inntekt, offentlige ytelser, arbeidsdeltakelse og andre forhold som kan ha betydning for helsa. For å undersøke om sykdommer går i arv, kan opplysninger om deg sammenstilles med opplysninger om dine slektninger, dersom disse har deltatt i deler av Tromsøundersøkelsen. Dette blir gjort ved å innhente opplysninger om slektskap fra Familieregisteret. Fra skolen vil vi innhente dine opplysninger om studieprogram, klasse, kjønn, antall fraværsdager, om du fullfører skoleåret og om karakterer i fagene norsk, matematikk og engelsk.

Sammenstillinger av informasjon krever noen ganger nytt samtykke og/eller annen type godkjenning slik som dispensasjon fra taushetsplikten eller godkjenning av offentlige instanser, for eksempel Regional komité for medisinsk og helsefaglig forskningsetikk, Datatilsynet eller NAV.

FitFutures 2
EN DEL AV TROMSØUNDERSØKELSEN

VIL DU DELTA?

Samtykke til å delta i studien Fit Futures 2

Jeg er villig til å delta i studien

_____

(DITT FULLE NAVN I BLOKKBOKSTAVER)

Sted _____

Dato _____

_____

(DIN SIGNATUR)

STATENS HELSETILSYN
Postboks 8128 Dep.
0032 OSLO

Medisinsk registrering av fødsel

Sendes 9. dag etter fødselen til fylkeslegen (stadsfysikus) i det fylket der moren er bosatt.

Merk: Det skal fylles ut blankett for hvert barn (foster). Dør barnet etter fødselen, skal det også fylles ut legeerklæring om dødsfall, og/eller dødsfallet meldes til skifteretten (lensmannen).

Barnet

Barnet var 1 ☐ Levende født 2 ☐ Dødfødt foster | Født dag, mnd., år | Klokkeslett | Personnr. | Skriv ikke her

1 ☐ Enkel 2 ☐ Tvilling 3 ☐ Trilling 4 ☐ Firling | Kjønn 1 ☐ Gutt 2 ☐ Pike

Etternavn, alle fornavn (bare for levendefødte)

Fødested. Navn og adresse på sykehuset/fødehjemmet | Kommune

Faren

Etternavn, alle fornavn | Født dag, mnd., år | Bostedskommune

Moren

Etternavn, alle fornavn. Pikenavn | Født dag, mnd., år

Bosted. Adresse | Kommune

Ekteskapelig status 1 ☐ Ugift 6 ☐ Samboende 2 ☐ Gift 3 ☐ Enke 4 ☐ Separert 5 ☐ Skilt | Ekteskapsår (gifte)

Antall tidligere fødte (før denne fødselen) | Levende fødte | Av disse i live | Dødfødte

Er moren i slekt med faren? 1 ☐ Nei 2 ☐ Ja. Hvilket slektskapsforhold:

Morens helse før svangerskapet

1 ☐ Normal 2 ☐ Sykdom (spesifiser):

Siste menstruasjons første blødningsdag

Morens helse under svangerskapet

1 ☐ Normal 2 ☐ Komplikasjoner (spesifiser):

Ble fødselen provosert

1 ☐ Nei 2 ☐ Ja

Inngrep under fødselen

1 ☐ Nei 2 ☐ Ja (spesifiser):

Inngrepet utført av 1 ☐ Lege 2 ☐ Jordmor

Komplikasjoner i forbindelse med fødselen

1 ☐ Nei 2 ☐ Ja (spesifiser):

Fostervann, placenta og navlesnor

1 ☐ Normalt 2 ☐ Patologisk (spesifiser):

Barnets tilstand

Bare for levende fødte. Tegn på asfyksi? 1 ☐ Nei 2 ☐ Ja | Apgarscore etter 1 min. | etter 5 min.

For levende fødte og dødfødte. Tegn på medfødt anomali, på skade eller sykdom? 1 ☐ Nei 2 ☐ Ja. Hvilke:

Lengde (i cm) | Hode-omkr. (i cm) | Vekt (i g) | For døde innen 24 timer Livet varte i | Timer | Min

For dødfødte. Døden inntrådte 1 ☐ Før fødselen 2 ☐ Under fødselen
Dødsårsak:

Seksjon? 1 ☐ Nei 2 ☐ Ja

Alvorlige arvelige lidelser i slekten

1 ☐ Nei 2 ☐ Ja Sykdommens art og hos hvilke slektninger:

Sted (sykehusets stempel) | Dato | Jordmor | Lege

50 000. 5.96. SEM GRAFISK

folkehelseinstituttet
Norwegian Institute of Public Health

Nina Emaus
Universitetet i Tromsø
Institutt for helse- og omsorgsfag
9037 Tromsø

Deres ref.:
Vår ref.: vesu/15-1789, PDB 1819, websak 15/1077
Dato: 27.11.2015

Utlevering av data fra Medisinsk fødselsregister

Det vises til søknad om tilgang til data fra Medisinsk fødselsregister, mottatt 27.04.2015. I søknaden er det oppgitt at data skal benyttes i forbindelse med prosjektet *'Fit Futures: Fødselsvekt og vektutvkling i barndom og overvekt, kroppssammensetning og beinhelse hos unge'*. Data fra Medisinsk fødselsregister ønskes koblet med data innsamlet til Tromsøundersøkelsens ungdomsundersøkelse, Fit Futures I og II.

Folkehelseinstituttet har vurdert søknaden og funnet at prosjektet ligger innenfor formålene med Medisinsk fødselsregister, jf. Medisinsk fødselsregisterforskriften § 1-3.

Nødvendige tillatelser og hjemmelsgrunnlag
Utleveringen skjer med hjemmel i Medisinsk fødselsregisterforskriften § 3-5. Det foreligger forhåndsgodkjenning fra REK, datert 29.09.2014(2014/1397/REK nord), og forskningsdeltakerne har gitt samtykke til at data om dem kan innhentes fra Medisinsk fødselsregister.

Materiale
Materialet består av uttrekk av indirekte personidentifiserbare data fra Medisinsk fødselsregisters standardiserte recordformat (2015Q2, versjon 4.60). Variablene leveres i henhold til variabelliste vedlagt søknaden. Datæne er organisert med en record per barn i mottatt koblingsnøkkel, og er identifisert med løpenummeret fra koblingsnøkkelen.

Av 1038 individer i koblingsnøkkelen var det bare 965 som fant noen match i MFR.

Dokumentasjon
Dokumentasjon av variablene finnes på våre nettsider: www.mfr.no under *Datautlevering*. Se avsnittet *Tilgjengelige data*. Pass på at variabeldokumentasjonens versjonsnummer samsvarer med den leverte recordversjonen.

Vilkår for utlevering av data

- Opplysningene skal kun brukes til det formål som er nevnt i søknaden.
- Opplysningene skal ikke overlates til andre enn prosjektmedarbeidere som er oppgitt i søknaden. Alle som mottar datasettet har taushetsplikt i henhold til helseforskningsloven § 7, jf. helseregisterloven § 17.
- Opplysningene skal oppbevares betryggende og på en slik måte at uvedkommende ikke får tilgang til dem, og ellers i samsvar med sikkerhetsbestemmelsene i personopplysningsforskriftens kapittel 2.

- Prosjektslutt er 31.12.2019. Utleverte data fra Medisinsk fødselsregister skal da slettes. Skriftlig bekreftelse på at materialet har blitt slettet skal oversendes Folkehelseinstituttet.
- Bakveisidentifisering eller forsøk på rekonstruksjon av identitet på utlevert materiale er ikke tillatt.
- Publisering og annen offentliggjøring skal gis en slik form at enkeltpersoner ikke kan identifiseres.
- I publikasjoner der det benyttes data fra Medisinsk fødselsregister skal "Medisinsk fødselsregister" (MFR) eller "Medical Birth Registry of Norway" (MBRN) nevnes i metodedelen og/eller under "acknowledgements" av hensyn til litteratur søk.

Ansvarsbegrensning
Databehandlingsansvarlig for Medisinsk fødselsregister har ikke ansvar for tolkning og rapportering på bakgrunn av det utleverte datamaterialet.

Kostnader
I medhold av Medisinsk fødselsregisterforskriften § 3-7 kan Folkehelseinstituttet kreve dekket faktiske utgifter som påløper i forbindelse med behandling og tilrettelegging av opplysninger knyttet til konkrete oppdrag. Deres oppdrag vil bli fakturert med kr. 7.000 eks. mva for 8 timer. Faktura vil bli sendt fra Folkehelseinstituttet når materialet er utlevert.

Dette er et enkeltvedtak som kan påklages etter forvaltningsloven § 28. En eventuell klage sendes Folkehelseinstituttet innen tre uker etter at De har mottatt brevet.

Vi ønsker lykke til med prosjektet!

Med vennlig hilsen

Marta Ebbing
Avdelingsdirektør

Vernar Sundvor
Rådgiver

FF - Generelt spørreskjema - Uke 1

Vi ønsker å vite mer om livsstil og helse.

Bruk den tiden du trenger til å svare så presist du kan.

Alle svarene dine blir behandlet med taushetsplikt.

Bruk "neste >>" og "<< tilbake" - knappene i skjema for å bla deg fremover og bakover.

Lykke til og tusen takk for hjelpen!

DEG OG DIN FAMILIE

1) Er du:

- ○ Jente
- ○ Gutt

6) Hva er den høyeste fullførte utdanningen til dine foreldre? (sett kryss for alle utdanningene du vet om for mor og far)

	Grunnskole	Yrkesfaglig videregående, yrkesskole	Allmennfaglig videregående skole eller gymnas	Høyskole eller universitet, mindre enn 4 år	Høyskole eller universitet, 4 år eller mer	Vet ikke
Mors utdanning	○	○	○	○	○	○
Fars utdanning	○	○	○	○	○	○

7) Hva regner du deg selv som: (kryss av for ett eller flere alternativ)

- ☐ Norsk
- ☐ Samisk
- ☐ Kvensk/Finsk
- ☐ Annet, spesifiser her

8) I hvilken kommune bodde du da du var 5-6 år (førskolealder/1.klasse)?

Velg kommune ▼

9) Er du født i Norge?

- ○ Ja
- ○ Nei, spesifiser hvilket land

10) Er din biologiske mor født i Norge?

- ○ Ja
- ○ Nei, spesifiser hvilket land

11) Er din biologiske far født i Norge?

- ○ Ja
- ○ Nei, spesifiser hvilket land

PUBERTET

Her har vi noen spørsmål om kroppslige forandringer som skjer gjennom ungdomstiden:

32) Har du fått menstruasjon?

- Ja
- Nei

Hvor gammel var du da du fikk menstruasjon første gang?

33) År

Velg...

34) Måneder

Velg...

35) Har du fått eller begynt å få kjønnshår?

- Ja
- Nei

36) Har du fått eller begynt å få bryster?

- Ja
- Nei

37) Har du fått eller begynt å få kjønnshår?

- Ja
- Nei

38) Hvor gammel var du da du begynte å få kjønnshår?

Velg...

58) Hvor mange dager i uken driver du med idrett/fysisk aktivitet utenom skoletid?

- Aldri
- Sjeldnere enn 1 dag i uka
- 1 dag i uka
- 2-3 dager i uka
- 4-6 dager i uka
- Omtrent hver dag

59) Omtrent hvor mange timer per uke bruker du til sammen på idrett/fysisk aktivitet utenom skoletid?

- Ingen
- Omtrent 1/2 time
- Omtrent 1 - 1 1/2 time
- Omtrent 2 - 3 timer
- Omtrent 4 - 6 timer
- 7 timer eller mer

60) Hvor slitsom er vanligvis idretten/aktiviteten du driver med utenom skoletid?

- Ikke anstrengende
- Litt anstrengende
- Ganske anstrengende
- Meget anstrengende
- Svært anstrengende

Utenom skoletid: Hvor mange timer per dag ser du på PC, TV, DVD og liknende?

FORHÅNDSVISNING

FF2 Generelt spørreskjema - UKE 1

PUBERTET

28) Når man er tenåring, er det perioder da man vokser raskt. Har du merket at kroppen din har vokst fort (blitt høyere)?

- Nei, den har ikke begynt å vokse
- Ja, den har såvidt begynt å vokse
- Ja, den har helt tydelig begynt å vokse
- Ja, det virker som om jeg er ferdig med å vokse raskt

<< Tilbake Neste >>

12 % completed

FORHÅNDSVISNING

FF2 Generelt spørreskjema - UKE 1

29) Og hva med hår på kroppen (under armene og i skrittet)? Vil du si at håret på kroppen din har:

- ○ Ikke begynt å vokse enda
- ○ Såvidt begynt å vokse
- ○ Helt tydelig begynt å vokse
- ○ Det virker som om håret på kroppen er utvokst

<< Tilbake Neste >>

13 % completed

FORHÅNDSVISNING

FF2 Generelt spørreskjema - UKE 1

30) Hvor gammel var du da du begynte å få hår i skrittet (kjønnshår)?

Velg ... Velg ...

<< Tilbake Neste >>

13 % completed

FORHÅNDSVISNING

FF2 Generelt spørreskjema - UKE 1

31) Har du begynt å komme i stemmeskifte?

- Nei, har ikke begynt ennå
- Ja, har såvidt begynt
- Ja, har helt tydelig begynt
- Det virker som om stemmeskifte er ferdig

32) Har du begynt å få bart eller skjegg?

- Nei, har ikke begynt ennå
- Ja, har såvidt begynt
- Ja, har helt tydelig begynt
- ja, har fått en god del skjeggvekst

<< Tilbake Neste >>

14 % completed