Young adults with childhood-onset inflammatory bowel disease - aspects on bone mineral density, body composition and physical exercise

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Abstract

Background: Our research group has previously shown that low bone mineral density (BMD) is common in children and adolescents with inflammatory bowel disease (IBD). However, there is limited knowledge on the development of BMD and body composition traits (skeletal muscle and body fat) in early adulthood in this patient group.

Objective: The main objective of this thesis was to gain additional understanding of BMD and body composition in young adults with childhood-onset IBD.

Method: We performed a follow-up in young adulthood in 74 patients with childhood-onset IBD. Bone mineral density, skeletal muscle index (SMI), and fat percentage (fat %) were measured with dual X-ray absorptiometry. Body composition profiles were defined based on SMI and fat % Z-scores: i) normal, ii) obese, iii) myopenic, iv) myopenic-obese. Bone geometry and microstructures were estimated with high-resolution peripheral quantitative computed tomography. Physical exercise during the previous year was registered. Results were compared to normative control cohorts from nearby regions.

Results: Young adults, especially men with childhood-onset IBD, are at risk for low areal BMD and those young men also show widespread deficits in bone microstructures. Young adults with childhood-onset IBD have a risk for altered body composition traits with an overrepresentation of abnormal body composition profiles (myopenic, obese, and myopenic-obese) compared to controls. Young men with Crohn's disease have an especially high risk for myopenia. Despite the detrimental effects of having childhood-onset IBD, we found that high levels of regular physical exercise in young adulthood are associated with normal BMD and body composition traits.

Conclusion: Young adult patients with childhood-onset IBD are at risk for disturbances in BMD and body composition.

Keywords: IBD, BMD, Body composition, Physical exercise, HR-pQCT

Sammanfattning på svenska

Bakgrund: Vår forskningsgrupp har tidigare rapporterat att det är vanligt med låg bentäthet hos barn och ungdomar med inflammatorisk tarmsjukdom (IBD). Det finns dock begränsad kunskap om bentäthet samt kroppssammansättning (muskel och fett) hos patientgruppen i ung vuxenålder.

Mål: Huvudmålet med denna avhandling var att öka kunskapen om bentäthet och kroppssammansättning hos unga vuxna med pediatrisk IBD.

Metoder: Vi genomförde en uppföljning av 74 unga vuxna med pediatrisk IBD. Bentäthet liksom skelettmuskel index (SMI) och fettprocent (fett %) mättes med dual X-ray absorptiometri. Utifrån SMI och fett % Z-score definierade vi fyra kroppssammansättnings profiler: i) normal, ii) obese (hög fett %), iii) myopenic (lågt SMI), iv) myopenic-obese (både lågt SMI och hög fett %). Bengeometri och benmikrostrukturer analyserades med hög-resolution peripheral quantitative computed tomography. Patienternas fysiska träningsvanor senaste året registrerades. Resultaten jämfördes med normativa kontroller från närliggande regioner.

Resultat: Unga vuxna patienter, speciellt män, med pediatrisk IBD löper risk för låg bentäthet. Vidare har dessa unga vuxna utbredda förändringar i benmikrostrukturer. Stor andel av de unga vuxna patienterna har även en störd kroppssammansättning med överrepresentation av avvikande profiler (myopenic, obese och myopenic-obese) jämfört med kontroller. Unga män med Crohns sjukdom löper störst risk för myopeni. Regelbunden fysisk träning verkar dock kompensera för den IBD-associerade risken för låg bentäthet och avvikelser i kroppssammansättning.

Slutsatser: Unga vuxna patienter med pediatrisk IBD har ökad risk för störningar i bentäthet och kroppssammansättning.

List of papers

This thesis is based on the following studies, referenced in the text by their Roman numerals.

I. **Sigurdsson GV**, Schmidt S, Mellström D, Ohlsson C, Kindblom JM, Lorentzon M, Saalman R.

Bone Mass Development from Childhood into Young Adulthood in Patients with Childhood-onset Inflammatory Bowel Disease.

Inflamm Bowel Dis. 2017 Dec;23(12):2215-2226. PMID: 29064856.

II. **Sigurdsson GV**, Schmidt S, Mellström D, Ohlsson C, Karlsson M, Lorentzon M, Saalman R.

Altered body composition profiles in young adults with childhood-onset inflammatory bowel disease.

Scand J Gastroenterol. 2020 Feb;55(2):169-177. PMID: 32008409.

III. **Sigurdsson GV,** Schmidt S, Mellström D, Ohlsson C, Karlsson M, Lorentzon M, Saalman R.

Physical exercise is associated with beneficial bone mineral density and body composition in young adults with childhood-onset inflammatory bowel disease.

Manuscript submitted.

IV. **Sigurdsson GV**, Schmidt S, Mellström D, Ohlsson C, Saalman R, Lorentzon M.

A high proportion of young adult male patients with childhood-onset IBD have compromised cortical and trabecular bone microstructures.

Manuscript.

Contents

Abbreviations

5-ASA	5-aminosalicylic acid
aBMD	Areal bone mineral density
BMD	Bone mineral density
BMI	Body mass index
CDAI	Crohn's disease activity index
DXA	Dual X-ray absorptiometry
fat %	Fat percentage
HR-pQCT	High-resolution peripheral quantitative computed tomography
IBD	Inflammatory bowel disease
IBD-U	Inflammatory bowel disease, unclassified
IQR	Interquartile range
OPG	Osteoprotegerin
PBM	Peak bone mass
PCDAI	Pediatric Crohn's disease activity index
PHV	Peak height velocity
pQCT	Peripheral quantitative computed tomography
PUCAI	Pediatric ulcerative colitis activity index
RANK	Receptor activator of nuclear factor kappa-B
RANKL	Receptor activator of nuclear factor kappa-B ligand
SD	Standard deviation
SMI	Skeletal muscle index
TNF	Tumor necrosis factor
vBMD	Volumetric bone mineral density

1 Introduction

Inflammatory bowel disease (IBD) is a group of diseases that entails chronic inflammation in different parts of the gastrointestinal tract. The prevalence of IBD in Sweden is among the highest globally, affecting about 1/150 people[1]. Almost a quarter of patients receive their diagnosis in childhood[2], making IBD one of the most common chronic childhood illnesses in the western world[3]. The prevalence of childhood-onset IBD in Sweden is elevated as well, and the incidence rises both in Sweden and globally[4, 5]. It is well known that children with IBD are at risk of disturbances of growth due to multiple factors related to the disease[6]. During this growth phase in childhood, the body composition changes and the majority of bone development occurs[7-9]. Our research group has previously shown that children with IBD run an increased risk to have low bone mineral density (BMD)[10, 11]. However, there is limited knowledge on the development of bone mineralization and body composition traits from adolescence to early adulthood in this patient group.

1.1 Inflammatory bowel disease

1.1.1 Clinical characteristics

Patients with IBD, both children and adults, suffer from chronic, relapsing inflammation in different parts of the gastrointestinal channel, depending on the disease subcategory. The main subcategories are ulcerative colitis and Crohn's disease, and a minority of patients with IBD fall into an unclassified category (IBD-U)[12]. The disease often progresses slowly for weeks to months before a diagnosis is established, but a more acute disease progression is also seen in some patients. It is challenging to differentiate between ulcerative colitis and Crohn's disease on clinical symptoms only (**Figure 1**). Diarrhea and abdominal pain are dominant symptoms in both disease subcategories. Bloody stools are more common in ulcerative colitis, whereas in Crohn's disease, low-grade fever, weight loss, and perianal disease are more frequent[12]. Delayed puberty and growth retardation are typical clinical features in pediatric patients with Crohn's disease and may be the only symptoms in some patients. The clinical picture of IBD is dependent on various factors, such as subcategory, the extension of disease, and intensity of inflammation[12].

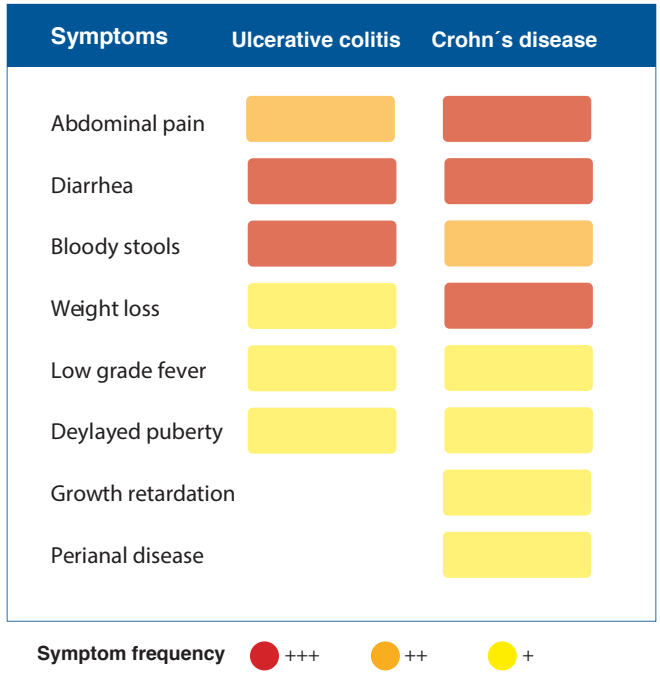

Figure 1. Clinical symptoms and signs at diagnosis in patients with childhood-onset IBD.

1.1.2 Diagnosis

Diagnosis of IBD is based on clinical, endoscopic, histological, and radiological findings and the exclusion of other differential diagnoses, mainly infectious colitis[12]. In patients with ulcerative colitis, inflammation is most intense in the rectum and can extend throughout the colon (**Figure 2**). The inflammation is continuous and confined to the gastrointestinal wall's superficial mucosal layer. In contrast, patients with Crohn's disease can have segmental inflammation in any part of the gastrointestinal tract (**Figure 2**). In Crohn's disease, all gastrointestinal wall layers can be affected, leading to strictures or fistulae in some patients[12].

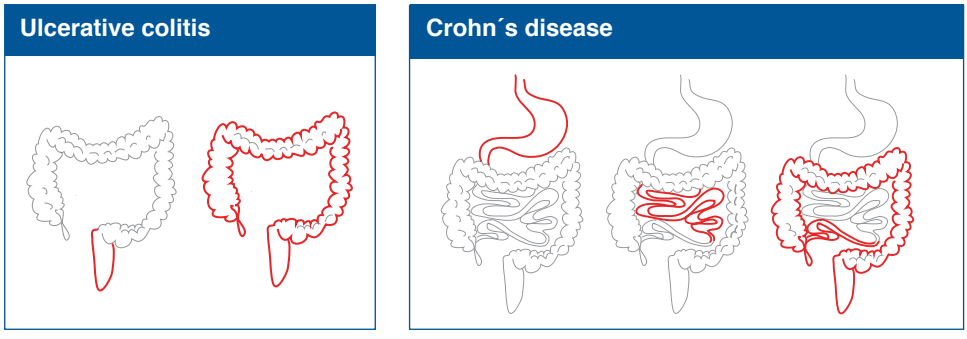

Figure 2. The extent of inflammation in patients with childhood-onset IBD.

1.1.3 Disease phenotype

In children with IBD, both ulcerative colitis and Crohn's disease are classified according to the phenotype with the Paris classification[13], including age at diagnosis, the extent of inflammation, growth restriction. Further, in Crohn's disease, the presence of perianal disease is included and the disease behavior is defined as inflammatory, stricturing, or penetrating. The Paris classification is a modified version of the Montreal classification[14] of IBD used in the adult population.

1.1.4 Epidemiology and etiology

IBD can manifest in children of all ages, however, most cases debut usually after ten years of age[15]. Sweden has one of the highest prevalence numbers of childhood-onset IBD globally; 75/100.000 children were reported to have IBD in 2010, around 1500 children in total[16]. The prevalence of ulcerative colitis and Crohn's disease in children is similar in Sweden (30/100.000 and 29/100.000 respectively), with some indication that the incidence of Crohn's disease is on the rise[5], whereas IBD-U is less common (16/100.000)[16].

The cause of IBD remains unknown, but current research on the pathogenesis focuses on four main areas: the gut and systemic immune system, environmental triggers, the microbiome, and genetics[17].

1.1.5 Treatment and disease activity

Treatment of childhood-onset IBD in Sweden is based on national guidelines[18], which in turn follow European guidelines[19].

Treatment options include nutritional, pharmaceutical, and surgical treatment. All patients should also receive lifestyle advice (i.e., smoking cessation and physical activity) and psychological support as needed (**Figure 3**). The treatment goal for each patient is to achieve remission of both subjective (symptoms) and objective (i.e., laboratory parameters and endoscopy) signs of the disease, without any severe side effects or negative impact of therapies on quality of life[18]. In pediatric patients, other important treatment goals are to achieve normal growth, pubertal development, and optimal bone health[19].

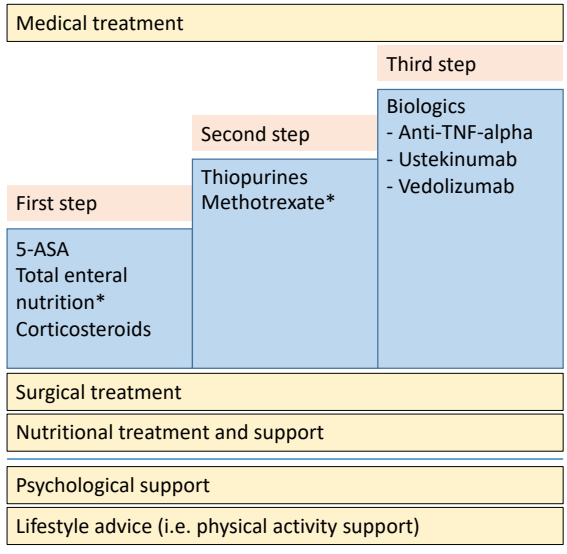

Figure 3. Treatment options in patients with childhood-onset IBD. 5-ASA, 5-aminosalicylic acid; TNF, Tumor necrosis factor. *in patients with Crohn's disease

Clinicians use validated disease activity indices to assess disease activity and the need for acute medical or surgical intervention at a certain time point. In childhood, the Pediatric Ulcerative Colitis Activity Index[20] (PUCAI) and Pediatric Crohn's Disease Activity Index[21] (PCDAI) are mainly used. In adulthood, several activity indices exist[22], i.e., the MAYO score[23] for ulcerative colitis and Crohn's Disease Activity Index (CDAI)[24]. However, estimating inflammatory activity over a long time, such as during a patient's whole disease course, is challenging[25]. To date, there is no consensus on how to estimate and describe disease course severity over time reliably.

1.1.6 Complications of IBD

Patients with IBD have both long-standing chronic local enteric inflammation and systemic inflammation. Disease-associated complications include, e.g., growth retardation in pediatric patients[26], iron deficiency, and decreased BMD[11].

Patients with IBD can also develop several extraintestinal manifestations that sometimes are unrelated to the degree of intestinal inflammation, for example, joint pain and arthritis, eye disease (uveitis), skin disease (erythema nodosum), liver diseases (primary sclerosing cholangitis, autoimmune hepatitis), inflammation in the oral cavity (orofacial granulomatosis), and skeletal inflammation (chronic recurrent multifocal osteomyelitis)[27].

1.1.7 Unique aspects of childhood-onset IBD

The manifestation of IBD at a young age results in a long disease duration with subsequent increased risk for complications and specifically in patients with ulcerative colitis, an increased risk for cancer development[18]. The extent of

inflammation at diagnosis is often greater in children with IBD than adults. Children with ulcerative colitis have more often inflammation in the entire colon and in patients with Crohn's disease, a colonic engagement is more often reported in children than adults[28, 29].

When IBD affects children during puberty, a crucial period for the growth and development of bones and body composition[7-9], there are several risk factors for BMD and body composition development disturbances. These include, i.e., lack of physical exercise, chronic inflammation, nutrition problems, and pharmaceutical side effects[30, 31]. There is, however, limited knowledge on how childhood-onset IBD *per se* may influence BMD[32] and body composition development[33] into early adulthood, a time when peak bone mass (PBM) should have been achieved.

1.2 Bone structure, physiology, and assessment of bone mineral density

1.2.1 Bone structure

The skeleton divides into the axial and appendicular skeleton. The axial part (head, vertebrae, and rib cage) defends some of the vital organs (brain, spinal cord, heart, and lungs). In contrast, the appendicular part makes up the limbs and serves as attachment sites for tendons and muscles, enabling body movement.
The skeleton comprises long bones (i.e., femur, tibia, and humerus) and flat bones (skull, ileum, and scapula). Its primary function is mechanical, but it also stores calcium and phosphate, has immunological and endocrine functions, and is home to hematopoiesis.

Bones consist of an outer layer, periosteum, a thin membrane that overlies the cortical bone, which surrounds the trabecular bone and the medullary cavity (**Figure 4**). Cortical bone is mainly found in the shaft of long bones and the surface of flat bones. The osteons in the cortical bone have a dense structure, concentrically laid down around central canals known as Haversian canals (**Figure 4**). Around the canal containing blood vessels, nerves, lymphatics, and connective tissue are concentric layers of bone matrix (lamellae). There are tiny spaces (lacunae) containing osteocytes between the lamellae layers (**Figure 4**).

Trabecular bone is less compact, lighter, and has an irregular structure. It is most abundant in flat bones and the ends of long bones. The trabecular bone has a honeycomb-like appearance (**Figure 4**) made from lamellae forming trabeculae (plates and bars) aligned to support stress from external compression. Thicker and more numerous trabeculae result in a more robust structure. The trabecular bone's resistance to compressive forces is why it is predominant in the vertebrae.

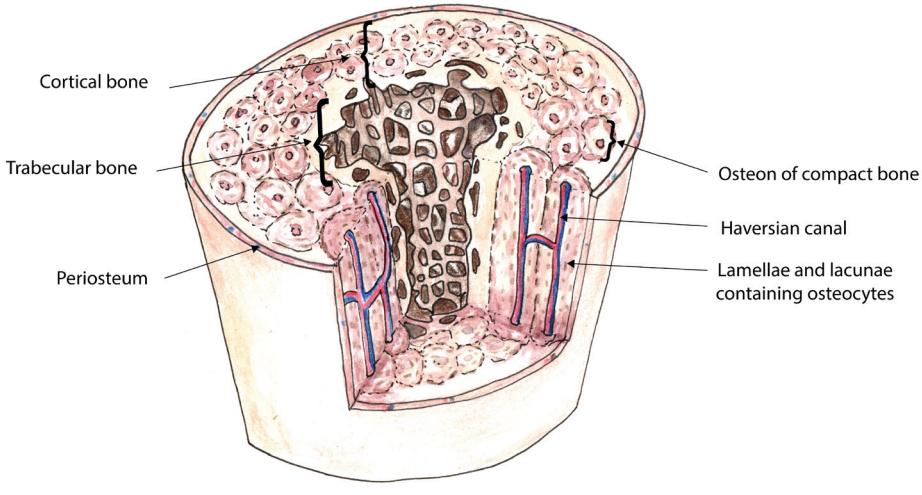

Figure 4. Cortical and trabecular bone microstructures.

1.2.2 Bone remodeling

Bone tissue undergoes constant remodeling to maintain stability and integrity[34]. Three cell types comprise the basic multicellular unit of the bone and act in a coordinated manner: i) osteoblasts (4–6% of bone cells), are responsible for new bone formation, ii) osteocytes (90–95% of bone cells), make up the majority of bone structure and bone mass, and osteoclasts (1–2% of bone cells), have a role in bone resorption[35]. The bone turnover process in adults is in equilibrium between bone formation and bone resorption. The activation of this process results in endosteal surface (outside the bone surface) absorption by osteoclasts, attracting osteoblasts that form osteocytes and osteoid that calcifies to thicken and strengthen the bone during an approximately three to six months process. The rate of bone turnover is highest in sites where trabecular bone predominates, such as the vertebrae, and lowest at sites with a high proportion of cortical bone, i.e., the hip[36].

1.2.3 Regulating factors of bone turnover

The bone turnover process is regulated by both mechanical and biochemical factors, including receptor activator of nuclear factor kappa-B ligand (RANKL), receptor activator of nuclear factor kappa-B (RANK), and osteoprotegerin (OPG)[37]. The RANKL-RANK-OPG system's discovery changed the understanding of bone homeostasis and osteoimmunity. The RANK receptor located on osteoclast precursor cells and mature osteoclasts is activated by RANKL, inducing osteoclast proliferation and bone resorption. Osteoblasts secrete RANKL to stimulate bone resorption and OPG that inhibits RANKL from binding to RANK and, by that, decreases bone resorption. The balance between RANKL and OPG regulates osteoclast activity and

is influenced by multiple factors, i.e., mechanical loading, inflammatory cytokines, and hormones[37]. By affecting this system, activated T and B cells, TNF-alpha and corticosteroids can increase osteoclast activity and bone resorption[36]. Thus, patients with IBD who suffer from local as well as systemic inflammation are especially at risk.

Bone health can be defined as a state in which the skeleton serves its purpose, i.e., provides adequate mobility, protects against injury, stores minerals, and executes hormonal as well as endocrinological functions[38]. Many factors influence the bone mass accumulation and contribute to bone health. Of those, IBD is associated with several of the modifiable factors that influence BMD directly as well as through their effects on body composition traits (skeletal muscle and body fat) (**Figure 5**). These are inflammation *per se*, physical exercise, nutrition, corticosteroids, and other/unknown factors[39-41]. Childhood-onset IBD can affect height development, which can influence BMD directly or through the body composition traits. Also, several non-modifiable factors (genetics, age, and gender[42, 43]) influence BMD directly as well as through their effect on height and body composition traits. Notably, genetic factors are reported to account for 60–80% of the variation in BMD[42, 44].

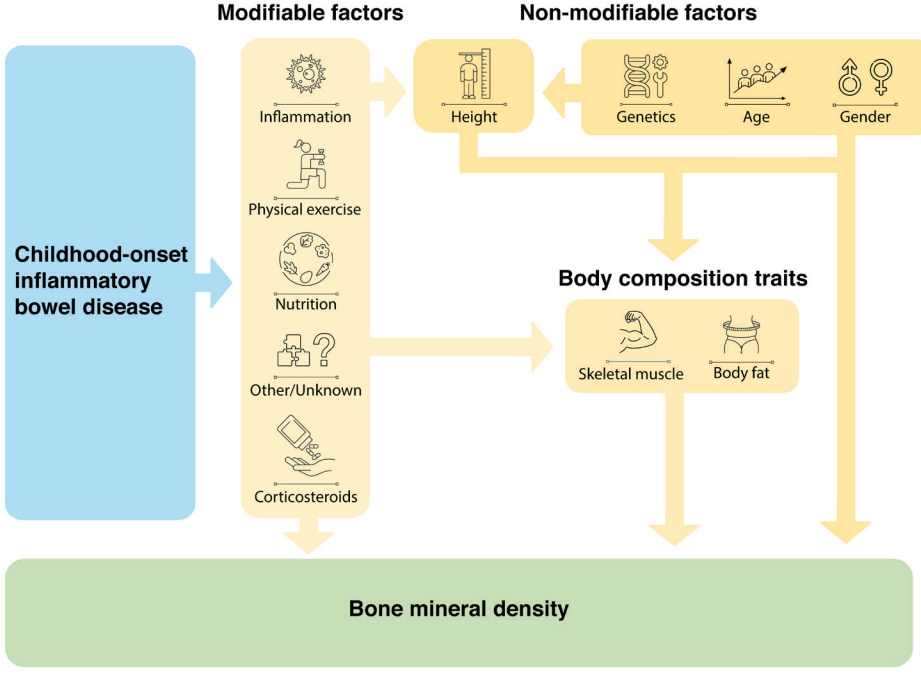

Figure 5. Inflammatory bowel disease is associated with several factors that possibly influence BMD directly as well as through their effects on height and body composition traits (skeletal muscle and body fat). Genetics, age, and gender are non-modifiable factors associated with BMD, height, and body composition traits.

1.2.4 Bone mineralization in childhood and peak bone mass

In adulthood, the bone turnover process described above maintains the bones' stability and strength. However, in childhood, bone formation dominates as the child is growing and the majority of bone mass (around 40%) accumulates during puberty[7]. Factors contributing to optimal bone mineralization such as regular physical exercise[41], adequate nutrition[45], and absence of inflammation[31] need to be present during this period. They are crucial for bone development and achievement of the genetically determined maximum PBM in young adulthood. According to Baxter-Jones et al., PBM is achieved in the lumbar spine and total hip, regardless of gender, about five years after the individual's peak height velocity (PHV) and in the total body about seven years after PHV[7, 46]. After attaining PBM in early adulthood, BMD gradually declines with age[47] (**Figure 6**). Peak bone mass is one of the most important factors influencing fracture risk later in life[48]. The age-related decline in BMD can lead to osteoporosis, especially in older women, as BMD decreases more rapidly after menopause (**Figure 6**). Osteoporosis is defined by the WHO as areal BMD (aBMD) value below -2.5 SD from the young adult mean (T-score)[49]. However, the use of T-score is limited to adults over 50 years of age. Thus in children and younger adults, aBMD measurements are often based on age- and gender-matched controls and presented as aBMD Z-score[50].

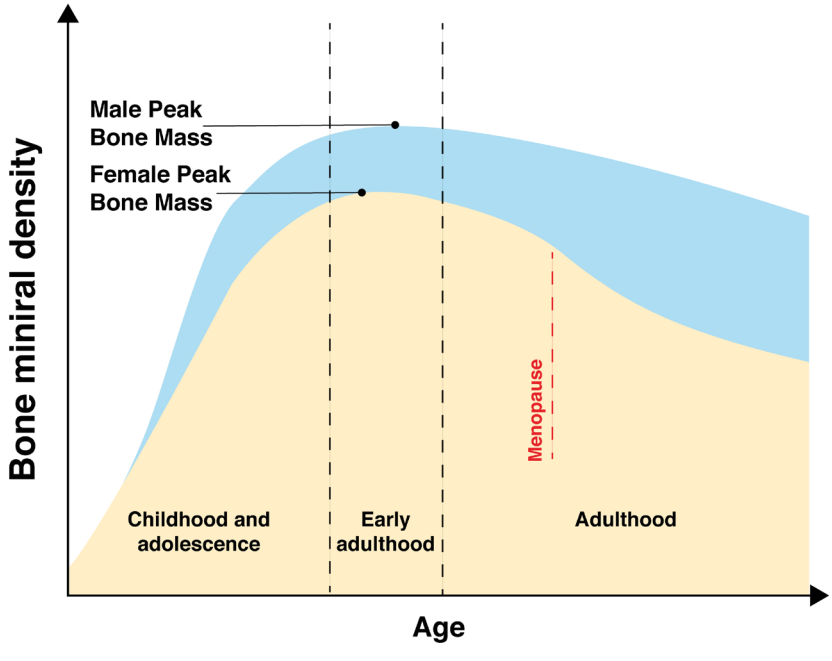

Figure 6. Development of BMD over time. The majority of BMD accumulates during childhood and adolescence and reaches PBM in young adulthood. After that, age-related loss of BMD ensues. This process accelerates in women after menopause.

1.2.5 Bone mineral density measurements

The golden standard for measuring BMD in the clinical setting is dual x-ray absorptiometry (DXA)[51]. This technique uses two x-ray beams of different energy levels to differentiate between bone and soft tissue. The low-energy beams attenuate more while passing through bone than through soft tissue, whereas the high-energy beams are equally attenuated regardless of tissue type. Based on the differences in attenuation, estimations of areal BMD (aBMD) will then be calculated in grams of bone per cm^2 for the whole body and at specific sites of the skeleton (i.e., lumbar spine, hip).

The machine software provides values for aBMD, bone mineral content, and bone area. Further, it calculates Z-scores of aBMD for children and adolescents compared to age- and gender-appropriate normative references. DXA is mainly used in clinical practice to diagnose bone fragility and estimate fracture risk in adult patients. However, research interest in BMD development during childhood and adolescence has increased, especially in patients with chronic inflammatory diseases, as low BMD and even osteoporosis in early adulthood could have severe consequences in late adulthood as bone health deteriorates with age[52].

While DXA has advantages such as widespread availability, high precision, and a low dose of radiation (5–10 μSv)[53], one important limitation of DXA is that it is only two-dimensional. Therefore, additional aspects of BMD such as three-dimensional volumetric BMD (vBMD), bone geometry, and microstructures need to be investigated with more advanced techniques. Bone geometry and vBMD can be investigated with peripheral quantitative computed tomography (pQCT). In order to assess bone microstructures and architecture, such as thickness and separation of the trabeculae, high-resolution pQCT (HR-pQCT) is used. This microstructure is the foundation of bone strength[54]. In contrast to the DXA method, these pQCT techniques are primarily used in research and not in a clinical setting yet.

1.3 Bone mineral density in patients with inflammatory bowel disease

Studies of BMD in patients with IBD are primarily conducted with DXA, resulting in aBMD measurements. Several studies in children, but none in adulthood, have been conducted using pQCT reporting vBMD measurements and bone geometry[55-59]. To our knowledge, only two studies have been published using HR-pQCT[60, 61], one in a group of adolescent and adult patients and the other in middle-aged patients.

Children and adolescents with IBD have an increased risk of low aBMD[10, 11, 62, 63]. Our research group and others have previously shown that almost 50% of children and adolescents with IBD have aBMD Z-scores lower than -1 and 25% lower than -2, without apparent gender differences[10, 11, 62, 64, 65]. Several studies have reported lower aBMD in children with Crohn's disease than those with ulcerative colitis[64, 66], whereas other studies found no difference[11, 63].

Adult patients with IBD have also an increased risk of low aBMD[67, 68]. Two recent studies found lower aBMD in middle-aged male patients compared to female patients[69, 70]. In most reports, no difference in aBMD is found between patients with Crohn's disease and those with ulcerative colitis[67, 69], but a few studies have reported lower aBMD in patients with Crohn's disease[68, 71].

Only one study has, to our knowledge, investigated the development of aBMD prospectively from childhood to adulthood[33]. In this study from Laakso et al., adults with childhood-onset IBD were reported to have low aBMD Z-scores at follow-up in early adulthood without improving aBMD Z-scores since childhood. In accordance, a retrospective study found that young adults with childhood-onset IBD who had conducted a DXA scan in young adulthood showed aBMD Z-scores lower than -1 in around 50% of cases[32]. Thus, despite limited data in young adulthood, low aBMD in childhood appears to persist into early adulthood without substantial improvements. However, Schmidt et al. from our research group reported that patients in late adolescence (17 to 19 years of age) had improved their aBMD Z-scores in the lumbar spine at first follow-up after two years[11]. Our research group concluded that there might be evidence that patients potentially could improve their BMD by the time they reached early adulthood. This finding raised the question of whether young adults with childhood-onset IBD could continue to increase their aBMD beyond the expected age for attaining PBM.

By using the three-dimensional measurement method pQCT, several studies have found trabecular vBMD as well as cortical vBMD[55, 58, 59] to be consistently low in children with IBD[55-59]. Interestingly, Werkstetter and colleagues found cortical vBMD to be high at diagnosis of IBD[56] with normalization after 12 weeks of IBD treatment and after reaching remission[57].

Further examination of the bone microstructures, utilizing HR-pQCT in adolescents and young adult patients with IBD (aged 12–33 years), some of them with childhood-onset IBD, revealed deficits in trabecular thickness and larger separation of trabeculae but no deficits in cortical thickness or density[60]. In contrast, in a group of older adults with IBD (median age 44 years), both cortical thickness and density were affected, but trabecular microstructures appeared to be intact[61].

1.4 Body composition

Body composition describes the proportions of fat mass and fat-free mass of an individual. Fat-free mass is all soft tissue except fat mass and is synonymous with lean mass. As with bone mass development, the majority of both lean mass and fat mass are acquired in adolescence[72]. The optimal analysis method of body composition depends on localization. A two-component method using DXA is widely used, measuring fat mass and lean mass. However, multicomponent models that divide body composition into fat, water, protein, and mineral are more accurate for measuring the composition of the total body[73]. The fat mass component is reliably estimated with DXA and should be adjusted for body size either for height as a fat mass index or for total body weight as percentage fat mass (fat %)[73].

Dual-X-ray absorptiometry can measure lean mass as a useful surrogate marker for skeletal muscle[74]. However, lean mass is not only skeletal muscle but also other soft tissue and water. Thus, skeletal muscle mass estimation is most reliable in the appendices where the lean mass is primarily skeletal muscle mass, tendons, and ligaments[75]. Further, for increased accuracy of skeletal muscle mass estimations with DXA, Baumgartner et al.[76] developed the appendicular skeletal muscle mass index (SMI). It is attained by dividing appendicular lean mass by height squared (lean mass in arms and legs [kg]/height [cm]^2).

In healthy individuals, body composition components and BMD measurements correlate with each other. The skeletal muscle affects bone tissue directly and there is a strong correlation between SMI and BMD[77]. In contrast, fat mass and, thus, increased weight are associated with higher BMD, although to a lesser extent than SMI[78]. Further, Baumgartner et al.[79] proposed that SMI and fat mass should be interpreted simultaneously in the elderly by defining four specific body composition profiles: normal profile, sarcopenic profile (low skeletal muscle mass), obese profile (high fat mass), and sarcopenic-obese profile (a combination of both low skeletal muscle mass and high fat mass). However, in recent years, a consensus has been reached that sarcopenia is defined by both lack of skeletal muscle mass (myopenia) and muscle function[80]. Thus, in this thesis, the term ´myopenia´ is used for lack of skeletal muscle mass when there is no data on muscle function.

1.4.1 Body composition in IBD

Body composition has been studied only to a limited extent in children with IBD. Total body lean mass deficits seem to be common[81-83], but there are conflicting reports on how fat mass is affected[81-83]. After the publication of study II in this thesis, one study reported SMI in children with IBD, highlighting deficits of skeletal muscle mass[84].

Body composition has been more widely studied in adults with IBD, although with divergent results. A recent review[85] summarized seventeen studies that reported data from adult patients with Crohn´s disease. Lean mass deficits were reported in 28% of patients and fat mass was low in 31%. Eight studies reported data from adult patients with ulcerative colitis; a reduction in lean mass was found in 13% of patients, fat mass was reduced in 13%, and increased in 12% of patients compared to controls. It appears that the male gender was more often found to be a risk factor for alterations in body composition components[85], especially in patients with Crohn's disease[86].

Two studies have focused on SMI and its association to BMD in adult patients with IBD. One focused on patients with Crohn's disease, finding a high prevalence of myopenia associated with low aBMD[87]. The other found myopenia to be prevalent (21%), regardless of disease subcategory or gender, and that low SMI predicted low aBMD. A strong association has been found in pQCT studies between variables indicating low skeletal muscle mass and deficits in trabecular and/or cortical vBMD[55-59].

Body composition reflects the balance of physiological and, in chronic diseases such as IBD, pathophysiological processes. Patients with IBD have several risk factors that can affect this balance, such as nutritional problems[88], inflammation *per se*[89, 90], lack of physical exercise[91], and corticosteroid side effects[92], and which potentially manifest as altered body composition (**Figure 5**). These risk factors resemble those known for low BMD.

In this context, it has to be noted that body mass index (BMI) as an estimation of body composition in patients with IBD has proved to be unreliable[85, 93]. Thus, more accurate methods are needed and DXA is the most widely available method.

1.5 Physical exercise in IBD

The terms 'physical exercise' and 'physical activity' are often used interchangeably. However, physical activity is considered any movement by skeletal muscles resulting in energy expenditure measured in kilocalories. It can be categorized into different activities such as sports, occupational, household, and other activities. Physical exercise is a physical activity category. It is a planned, structured, and regular activity to improve or maintain physical fitness[94].

Children with IBD are reported to be less physically active than age-matched healthy controls[95]. As regular physical exercise in childhood promotes healthy exercise habits in early adulthood, this could lead to less physical exercise in adulthood[96]. However, to the best of our knowledge, there are no data available regarding this in young adults with childhood-onset IBD.

Physical exercise habits in adults with IBD have also been studied. Tew et al. reported that less than one-fifth of adults with IBD were engaged in a high amount of regular physical exercise and one-third was more or less sedentary[97]. In comparison, a study on physical exercise habits in healthy adults from Sweden reported higher physical activity levels, where two-fifths of adults were heavily engaged in physical exercise[98].

Physical exercise plays a vital role in developing and maintaining bone health and body composition. The importance of skeletal muscle activity is well-documented in healthy individuals[99-101]. The relationships between physical exercise, BMD, lean mass, and fat mass in patients with IBD have only been studied to a limited extent; no data are available in young adults with childhood-onset IBD. Of the studies in both children and adult patients with IBD[102, 103], physical exercise appears to be positively associated with higher aBMD and lean leg mass and lower fat mass.

2 Aims

2.1 General aim

The main objective of this thesis was to gain additional understanding of bone health and body composition in young adults with childhood-onset IBD.

2.2 Specific aims

I. This study aimed to investigate whether young adults with childhood-onset IBD have compromised bone mineralization and to correlate their BMD data to anthropological measures and disease subcategories. A secondary aim was to examine whether patients with childhood-onset IBD have the potential to improve their BMD into young adulthood beyond the expected age for attaining PBM, as our previous data have indicated.

II. This study aimed to investigate body composition with the focus on SMI and fat % in young adults with childhood-onset IBD. A secondary aim was to evaluate to which extent BMD and body composition traits relate to each other.

III. This study aimed to investigate the amount of physical exercise undertaken by young adults with childhood-onset IBD and its associations to BMD, SMI, and fat %. A secondary aim was to evaluate whether there is a link, at the individual level, between physical exercise habits in adolescence and later in early adulthood.

IV. This study aimed to investigate the extent of microstructural alterations in young adult males with IBD and the association between these changes and the patient's SMI and the amount of physical exercise.

3 Patients and methods

3.1 Patients

This thesis is a part of a longitudinal study conducted by our research group. The current thesis is primarily based on the data from the second follow-up in young adulthood. A total of 166 patients were initially identified from the only two centers in the catchment area responsible for the diagnosis, treatment, and follow-up of childhood-onset IBD and were invited to participate in our longitudinal study. As a result, the recruited patient population included individuals with mild, moderate, and severe disease, representing the entire clinical spectrum of childhood-onset IBD. These two centers are The Queen Silvia Children's Hospital at Sahlgrenska University Hospital, Gothenburg, and the Department of Pediatrics at Södra Älvsborgs Hospital, Borås.

In total, 144 of the 166 initially eligible patients participated in the baseline measurement conducted between 2003 and 2005. These baseline aBMD results have previously been published by Schmidt et al.[10] Of those 144 patients, 126 participated in the first follow-up measurement two years later, between 2005 and 2007, of which the results were also previously published by Schmidt et al.[11]

In this current second follow-up, DXA measurements for BMD and the body composition of 74 young adult patients with IBD were carried out between 2012 and 2015. Thus, a total of 52 out of 126 patients at the first follow-up did not participate in the second follow-up. Patients who did not participate had relocated out of the area, declined to participate, or we failed to establish contact. These non-participants (n=52) did not differ significantly regarding clinical characteristics from the participants included in the second follow-up (**Table 1**).

Table 1. Characteristics of participants and non-participants at the first follow-up, the last common study visit

Patient characteristics	Participants (n=74)	Non-participants (n=52)	p value
Age (years)	16.7±2.9	17±3.1	0.650
Weight (kg)	60.7±15.6	59.4±16.1	0.643
Height (cm)	168±13.3	170.7±14.5	0.296
Female gender, n (%)	25 (34%)	19 (37%)	0.752
Crohn's disease, n (%)	25 (34%)	13 (25%)	0.287
Age at diagnosis (years)	11.1±3.3	11.2±3.4	0.924
Disease duration (years)	3.4±2.7	3.7±2.9	0.597
Current corticosteroid treatment	7 (10%)	5 (11%)	0.557
Any azathioprine treatment	37 (54%)	22 (46%)	0.235
Total body aBMD Z-score	0.1±1.2	0.2±1.3	0.649
Lumbar spine aBMD Z-score	-0.8±1.4	-0.7±1.5	0.658

aBMD, Areal bone mineral density. Values are displayed as mean±SD or n (%). Difference between groups tested with Student's *t* -test or Fisher's exact test.

3.2 Patient cohorts

Study I included all patients that participated in the described second follow-up. Study II included all patients that had reached 18 years of age at any study visit and not only the second follow-up. Study III included all patients that participated in the second follow-up and answered the physical exercise questionnaire. Study IV included all male patients at the second follow-up (**Table 2**).

3.3 Control cohorts

We used several control cohorts in this project regarding BMD and body composition (**Table 2**).

3.3.1 Study I - Control cohorts – Bone mineral density data

The GOOD study: This cohort included 1,068 population-based young adult men aged 18–25 years from the greater Gothenburg area, Sweden (the GOOD study[46, 104]).
LUNAR standard references: The normative healthy reference database, which uses sex, weight, ethnicity- and age-specific reference data, is provided by the DXA manufacturer LUNAR® (GE Medical Systems Lunar).
We used the current Swedish national standards for growth monitoring and evaluation as the references for height, weight, and PHV[9, 105].

3.3.2 Study II - Control cohorts – Bone mineral density and body composition data

The GOOD study: This cohort included 1,068 population-based young adult men aged 18–25 years from the greater Gothenburg area, Sweden (the GOOD study[46, 104]).
Normative data, Malmö: This cohort entailed normative data collected from 221 young adults (113 men and 108 women) in the age range of 18–30 years from the greater Malmö area, Sweden[106].

3.3.3 Study III - Control cohorts – Bone mineral density, body composition, and physical exercise data

The GOOD study: This cohort included 1,068 population-based young adult men aged 18–25 years from the greater Gothenburg area, Sweden (the GOOD study[46, 104]).
Normative data, Malmö: This cohort entailed normative data collected from 221 young adults (113 men and 108 women) in the age range of 18–30 years from the greater Malmö area, Sweden[106]. Of those, 86 had available physical exercise data and were included in study III.
Pediatric osteoporosis prevention (POP) study: This cohort consisted of 187 young adults (97 men and 90 women) aged 18–25 years from the Malmö region[107].

3.3.4 Study IV - Control cohort – HR-pQCT, body composition, and physical exercise data

The GOOD study: Each patient was matched by age and height with five controls (n=245) from the GOOD study[46, 104].

Table 2. Overview of study participants and control cohorts by study I-IV.

	Study I	Study II	Study III	Study IV
Patients	**74**	**94**	**72**	**49**
Study visit	All patients at the second follow-up	Any study visit	Second follow-up	Second follow-up
Age	17.6-27.7	≥18	≥18	≥18
Controls	GOOD study (n=1068)	GOOD study (n=1068)	GOOD study (n=1068)	GOOD study (n=245, age- and height-matched)
	Standard references LUNAR	Malmö normative data (n=221)	Malmö normative data (n=86)	
			POP study (n=187)	
Controls in total	**1068**	**1289**	**1341**	**245**

3.4 Data collection

We registered the following clinical data: age, gender, height, weight, disease subcategory, disease duration, and age at disease-onset. Furthermore, data from medical records were obtained regarding pharmacologic treatments received at or before the study visit. These included corticosteroids, 5-aminosalicylic acid (5-ASA), azathioprine, methotrexate, and biological therapy [anti-tumor necrosis factor (TNF)-alpha]. No biological therapies other than anti-TNF-alpha were used in these patients. Intestinal surgery due to IBD and fistula surgical procedures data were also registered.

Height was measured to the nearest 0.5 cm using a wall-mounted stadiometer. Weight was measured to the nearest 0.1 kg using a calibrated standard scale with the participants in light clothes. The hand's maximal grip strength (kg) was measured at the second follow-up in the majority of patients (n=70) using the Jamar hydraulic hand dynamometer (5030J1, Jackson, MI, USA) with an adjustable handgrip.

Detailed growth and weight charts from birth until 18 years of age were available for 43 patients, with age at PHV being derived from each growth curve for which there was sufficient information on all three growth phases and fitting the Infancy-Childhood-Puberty model by minimizing the sum of the squares using a modification of the Levenberg-Marquardt algorithm[108]. For PHV estimation, two or more measurements during the critical "peri-PHV" period were needed, not more than two years from PHV and not more than three years from each other. PHV is generally believed to be reached within two years of pubertal onset[105, 108]. According to Greulich and Pyle's method, bone age was estimated at baseline by a radiograph of the left wrist, as previously published by our group[10].

3.5 Bone mineral density

A total of 74 patients participated in all three study visits (baseline, first follow-up, and second follow-up), during which they underwent DXA scans for estimation of aBMD (g/cm^2), bone mineral content (g), and bone area (cm^2) in the total body, lumbar spine (L1–L4), and total hip. All DXA measurements were performed at the Sahlgrenska University Hospital in Gothenburg (Sweden). We used a Lunar densitometer (DPX-IQ version 4.7e; GE Medical Systems Lunar, Madison, WI), with Lunar software ver. 4.7, for the baseline and first follow-up measurements. The data for these measurements have previously been published[10, 11]. At the second follow-up, we used the Lunar Prodigy DXA (GE Medical Systems Lunar). The GOOD cohort controls were measured with the same Lunar Prodigy DXA apparatus[46] as the patients. The control populations from the Malmö region were measured using a Lunar DPX-L (version 1.3z; GE Medical Systems Lunar) apparatus[106]. The correlation of aBMD measurements between the DPX-IQ and Prodigy DXA machines is very strong at different measurement sites (R=0.98–0.99)[109]. The aBMD, bone mineral content, and bone area values were expressed as absolute values. Areal BMD was also expressed as age- and gender-adjusted Z-score, based on the control

population and in the first study, the DXA manufacturer standard reference. The aBMD Z-score for total hip could not be calculated at the first follow-up due to the manufacturer's lack of reference data.

3.6 HR-pQCT

The bone microstructure was measured non-invasively with HR-pQCT at the ultra-distal tibia. The leg ipsilateral to the non-dominant arm of the participant was fixated in anatomically formed carbon shells and placed in the HR-pQCT machine (XtremeCT; Scanco Medical AG, Brüttisellen, Switzerland). The operator placed a reference line at the tibia's articular plateau, which was identified with an ordinary X-ray. Images were taken at a fixed distance (22.5 mm) from the reference line. With an isotropic resolution of 82 μm, the device captured 104 parallel images and depicted a 9.02 mm 3D representation of the bone (**Figure 7**).

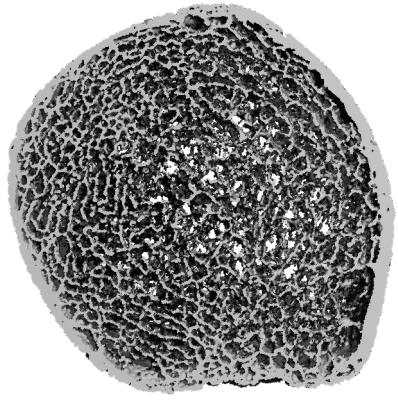

Figure 7. Representative image from our HR-pQCT scan at the tibia, showing cortical and trabecular microstructures.

Images were obtained in approximately three minutes, and the effective dose generated was 3 μSv per measurement. Measurements were repeated until quality was sufficient. A contour was automatically placed around the bone to separate the periosteal surface from the surrounding extra-osseous soft tissue. This contour could be adjusted by the operator when needed. The standard analysis was performed according to an earlier described protocol[110]. From the measurements the following parameters were obtained: volumetric density (mg/cm^3), cortical cross-sectional area (mm^2), cortical volumetric BMD (mg/cm^3), cortical thickness (mm), periosteal circumference (mm), trabecular cross-sectional area (mm^2), trabecular bone volume fraction (%), trabecular number (mm^{-1}), trabecular thickness (mm), and trabecular separation (mm). The two same operators performed all measurements and graded image quality using recommendations from the manufacturer.

3.7 Body composition

Lean soft tissue mass of the total body, arms, and legs (kg), as well as total body fat mass (kg), were measured with DXA using a Lunar densitometer (DPX-IQ version 4.7e; GE Medical Systems Lunar, Madison, WI). The GOOD cohort controls were measured with the same Lunar Prodigy DXA apparatus[46] as the patients, while the control populations from the Malmö region were measured using a Lunar DPX-L (version 1.3z; GE Medical Systems Lunar) apparatus[106]. The correlation of body composition measurements using different Lunar machines is strong (R=0.99 for lean mass and R=0.99 for fat %)[109]. Therefore, no adjustments were made to the raw measurement data. We calculated SMI as the sum of the arms and legs lean soft tissue mass divided by the height squared (kg/m^2). Skeletal muscle index is a reasonable estimate of the total body skeletal muscle mass[77]. Fat mass was calculated as the fat mass percentage (fat %) of the total body weight[73].

3.8 Body composition profiles

By taking each patient's SMI and fat % into account, we modified the theoretical model proposed by Baumgartner[79], defining four body composition profiles. In our modified model, we use the term myopenia for an SMI Z-score <-1 to define low skeletal muscle mass, which is in line with Bryant et al.[111]
The four body composition profiles were defined as follows:
i) **normal**: SMI Z-score >-1 and fat % Z-score <1;
ii) **obese**: SMI Z-score >-1 and fat % Z-score >1;
iii) **myopenic**: SMI Z-score <-1 and fat % Z-score <1;
iv) **myopenic-obese**: SMI Z-score <-1 and fat % Z-score >1.

The cut-off for SMI Z-score of <-1 in the controls corresponded to SMI of 6.1 kg/m^2 for females and 7.5 kg/m^2 for males. Obesity was defined as fat % Z-score >1, which corresponded to fat % of >39% for females and >27% for males. The cut-offs for myopenia in the present study were higher than in the original publication of Baumgartner[79], where myopenia was defined as SMI Z-score lower than -2, cut-offs were SMI of 5.5 kg/m^2 for females and 7.26 kg/m^2 for males. Cut-offs for fat % were similar to Baumgartner[79], >38% for females and >27% for males.

3.9 Physical exercise

At the second follow-up in early adulthood, we used a standardized physical exercise questionnaire to gather physical exercise habits in the last 12 months. The questionnaire also included questions regarding participation in sports during childhood and adolescence. Physical exercise was defined as regular training, whereas activities such as bicycling to work were not considered. Physical exercise was registered as the time in hours per week (h/w) spent on training. Seasonality was taken into account and the weekly amount of training was averaged for the entire year. In this thesis, we use the term "amount of physical exercise" to describe the

average amount of training over the past year in hours per week. Corresponding data on physical exercise in the control group (n=1,341) were also registered in hours per week (h/w) and averaged for the past year.

3.10 General statistics

The thesis author performed statistical analyses with SPSS ver. 26 software (IBM Corp., Armonk, NY). Continuous variables were presented as median [range or interquartile range (IQR)] or mean (SD). Categorical variables were presented as n (%). Differences between three or more groups were tested with analysis of variance (ANOVA), the Kruskal-Wallis one-way ANOVA, or Extended Fisher's exact test based on variable type and distribution. The differences between any two groups were tested with the Mann-Whitney *U*-test, student's *t*-test, or Fisher's exact test based on variable type and distribution. All tests were 2-tailed and conducted, assuming a significance level of 0.05.

3.10.1 Study I - Specific statistics

A single sample *t*-test was used to compare the patient's standard reference aBMD Z-score to the standard reference population mean Z-score of zero. The regression models were constructed with a stepwise approach with the total body aBMD and lumbar spine aBMD Z-scores as dependent variables. The following primary predictors were selected: aBMD Z-score at baseline; gender; weight at second follow-up; and the average parental aBMD Z-score (previously published by our group[44]). The following secondary predictors were used for the selection process: height Z-score at second follow-up; age at second follow-up; disease subcategory; age at diagnosis; been treated with biological agents, azathioprine, 5-ASA or corticosteroids; and the difference between bone age and chronologic age (ΔBA-CA) at baseline measurement.

The final model included all four primary predictors and three secondary predictors: age at diagnosis, previous treatment with biologics, and corticosteroids. The other secondary predictors were not significant confounders or predictors and did not improve the model.

3.10.2 Study II - Specific statistics

We used measurements in our combined control cohort for SMI, fat %, and aBMD in total body, spine, and femoral neck to calculate age- and gender-specific Z-scores. Using linear regressions in females and males separately, we calculated age-specific expected mean values for SMI, fat %, and aBMD. Using these expected values and the measured values for each study participant, we calculated an individual Z-score for SMI, fat %, and aBMD, using the following formula: the measured value of the participant, minus the expected mean value of controls for the participant's age, divided by the root mean square error of the regression model.

Differences in continuous variables between groups of body composition profiles

were tested with an analysis of variance (ANOVA), followed by a Student's *t*-test in-between groups with Bonferroni correction as a posthoc test, if the ANOVA was statistically significant. All correlations between SMI, fat %, and aBMD Z-scores were estimated with Spearman's rank correlation coefficient (r).

We used a multivariable regression model to estimate the association between aBMD Z-score (dependent variable) and diagnosis of IBD (covariate 1) and SMI Z-score (covariate 2).

3.10.3 Study III - Specific statistics

Age- and gender-specific Z-scores were calculated with the same formula as in study II. The multivariable regression models had one aBMD or body composition trait Z-score as a dependent variable (total body aBMD, spine aBMD, femoral neck aBMD, SMI, or fat %). "Diagnosis of IBD" and "physical exercise subgroup" were used as covariates. Additionally, SMI Z-score was added as a covariate for the second model with femoral neck aBMD as the dependent variable.

3.10.4 Study IV - Specific statistics

The control cohort of 245 young men was selected from 829 control subjects. We used propensity score matching for age and height with an R package plugin for SPSS. The patient to control ratio of 1:5 was used for a maximal number of controls and minimal variation of the matching variables.

Each multivariable regression model had one HR-pQCT measurement as the dependent variable. Three covariates were used as predictors: diagnosis of IBD, SMI, and physical exercise subgroup (≥4 hours per week vs. <4 hours per week).

4 Results

4.1 Study I - BMD in young adults with childhood-onset IBD

This study aimed to investigate whether young adults with childhood-onset IBD have compromised bone mineralization and to correlate their BMD data to anthropological measures and disease subcategories. A secondary aim was to examine whether patients with childhood-onset IBD have the potential to improve their BMD into young adulthood beyond the expected age for attaining PBM, as our previous data have indicated. At the second follow-up in young adulthood, 74 patients with childhood-onset IBD participated and were measured with a DXA scan.

4.1.1 Results

A high percentage of the patients with childhood-onset IBD had low aBMD Z-scores in the lumbar spine. One third of the patients, 33.8% (n=25), had an aBMD Z-score of less than -1 and 9.5% (n=7) had an aBMD Z-score of less than -2. The total body and hip aBMD Z-scores were similar to what was expected in the normal population, 15.6% and 2.2%, for -1 and -2, respectively.

There was a clear gender difference concerning aBMD Z-scores in the patient cohort. Young adult male patients had lower mean aBMD Z-score in the total body (-0.2±1 SD, p=0.150), lumbar spine (-0.8±1.1 SD, p<0.001), and total hip (-0.5±0.9 SD, p<0.001) than the LUNAR standard references. Similarly, low aBMD Z-scores were observed when male patients were compared to the controls from the GOOD study. In contrast, the young adult female patients had similar or slightly higher aBMD Z-scores in the total body (0.4±1 SD, p=0.040), lumbar spine (-0.1±1.1 SD, p=0.810), and total hip (0.2±0.9 SD, p=0.380) compared to the LUNAR standard references. A comparison between male and female patients revealed lower aBMD Z-scores in male patients at all three measurement sites (mean difference [95% CI]): total body (-0.64, [-1.13 – -0.15]), lumbar spine (-0.75, [-1.29 – -0.21]), and total hip (-0.71, [-1.16 – -0.25]).

A gender difference was also observed with regard to height. Male patients with IBD in early adulthood were shorter (mean height Z-score -0.38±0.9 SD, p=0.004) compared to national references. In contrast, female patients with IBD had a similar mean height Z-score of -0.24 (±1.2 SD, p=0.338) compared to national references.

A total of 17 patients, seven women and ten men, had per definition, reached the estimated age for PBM in the lumbar spine and total hip at the baseline study visit or the first follow-up when as at least five years had elapsed since peak height velocity. Notably, at the second follow-up, we observed significant increases in lumbar spine aBMD in this group beyond the expected age for attaining PBM.
The entire group of patients with IBD increased the aBMD Z-score in the lumbar spine between the first follow-up (-0.9±1.4 SD) and the current second follow-up (-0.6±1.2 SD, p=0.001). No such significant difference was seen for the total body aBMD Z-score.

4.1.2 Conclusion

Young adult men with childhood-onset IBD are at risk for compromised aBMD Z-scores. However, both male and female patients showed improvements in aBMD after being expected to have achieved PBM.

4.2 Study II - Body composition in young adults with childhood-onset IBD

This study aimed to investigate body composition with the focus on SMI and fat % in young adults with childhood-onset IBD. A secondary aim was to evaluate to which extent BMD and body composition traits relate to each other.

All patients who had reached the age of 18 years at any study visit (n=94, male gender n=64, ulcerative colitis n=65) were included in this analysis. Body composition can be divided into two major compartments: muscle and fat. The DXA scan measures lean mass, which is in the appendices mainly comprised of skeletal muscle. Therefore, we used SMI to represent the muscle compartment. Skeletal muscle index is the combined weight of lean mass in arms and legs divided by the participant's height squared (kg/m^2), similarly to the calculation of BMI. The DXA scan also measures the fat mass and we used the percentage of fat mass (fat %) by dividing the total fat mass with the participant's total weight to represent the fat compartment.

Furthermore, based on a theoretical model proposed by Baumgartner et al.[79], we developed a modified version. We defined four body composition profiles, described in greater detail in the chapter 3.8 in the *Patients and Methods* section. Z-scores for SMI and fat % were calculated from a large control cohort and both SMI and fat % were taken into account to define the body composition profiles.

4.2.1 Results

In total, 51% of the patients with IBD had a normal body composition profile compared to 72% of the controls (p<0.001) (**Table 3**). A larger proportion of patients (33%) had a profile including myopenia (lack of skeletal muscle mass) than the controls (17%, p<0.001) (**Table 3**). Similarly, 25% of the patients had an obese body composition profile compared to 14% of the controls (p=0.006) (**Table 3**). A profile

with a combination of myopenia and obesity was observed in 9% of the patients compared to 2% of the controls (p=0.002) (**Table 3**). Patients with myopenia as part of their profile were also found to have lower grip strength than those without myopenia.

We compared the aBMD Z-scores of patients with a normal body composition profile to patients with the other three profiles (obese, myopenic, myopenic-obesity). The mean total body aBMD Z-score of patients with the myopenic (-1.3±0.7) and myopenic-obese (-1.4±0.9) profile was lower than in patients with a normal body composition profile (-0.2±1.1), p<0.001, and p=0.004, respectively. However, the mean total body aBMD Z-score in patients with an obese profile (0±1) was similar to those with a normal profile (p=0.542).

We observed a strong positive correlation between SMI Z-score and aBMD Z-scores when combining all participants into one group. The correlation was significant for aBMD Z-scores in the total body (r=0.61, p<0.001), spine (r=0.52, p<0.001) and femoral neck (r=0.55, p<0.001). However, there were no significant correlations between the fat % Z-score and aBMD Z-scores.

Using multivariable regression analyses and adjusting for SMI Z-score, we found that a diagnosis of IBD was independently associated with a lower aBMD Z-score in the total body (B, 95% CI) (-0.33, -0.51– -0.15), lumbar spine (-0.51,-0.70 – -0.32) and femoral neck (-0.37,-0.58 – -0.16).

4.2.2 Conclusion

The body composition of young adults with childhood-onset IBD deviated from the control cohort as body composition profiles including myopenia and obesity were more common in the patient group. Despite the strong correlation of SMI Z-scores to aBMD Z-scores, the IBD diagnosis *per se* was independently associated with a reduction in aBMD Z-scores.

4.3 Study III - Physical exercise in young adults with childhood-onset IBD

This study aimed to investigate the amount of physical exercise undertaken by young adults with childhood-onset IBD and its associations to BMD, SMI, and fat %. A secondary aim was to evaluate whether there is a link, at the individual level, between physical exercise habits in adolescence and later in early adulthood. In our second follow-up in early adulthood, a total of 72 patients underwent a DXA scan and answered a questionnaire regarding physical exercise. A total of 1,341 controls combined from three different cohorts were used.

Three subgroups based on the amount of regular physical exercise over the last year were defined:

Subgroup 1: no physical exercise; patients (n=31)/controls (n=428).
Subgroup 2: less than four hours a week; patients (n=19)/controls (n=428).
Subgroup 3: four or more hours a week; patients (n=22)/controls (n=485).

4.3.1 Results

We observed in the patient cohort of young adults with childhood-onset IBD somewhat lower participation in physical exercise (around 60%) than in the controls (around 70%); however, the difference was not statistically significant (p=0.053). The patients who exercised regularly in young adulthood reported higher sports participation in late adolescence than those who were sedentary (subgroup 1).

The sedentary patients (subgroup 1) had significantly lower aBMD Z-scores in the total body, spine, and femoral neck than the controls in subgroup 1. Patients in subgroup 2, who trained less than four hours a week, had similarly low aBMD Z-scores in the total body and spine but not in the femoral neck compared to controls in subgroup 2. When comparing the patients who trained more than four hours a week (subgroup 3) to controls, we found similar aBMD Z-scores in the total body but lower Z-scores in the spine and femoral neck. However, when patients in subgroup 3 were compared to the entire control cohort consisting of the controls for all three exercise subgroups, they had similar aBMD Z-scores, close to zero, at all three measurement sites. The subgroup of patients who trained regularly tended to have higher aBMD Z-scores at the total body and femoral neck than those who were sedentary (subgroup 1). However, the difference in aBMD Z-score between the three physical exercise subgroups did not reach statistical significance for the total body, femoral neck, or spine aBMD Z-scores.

Concerning SMI Z-scores in the different physical exercise subgroups, we found that patients in subgroup 1 had a significantly lower SMI Z-score compared to subgroups 2 as well as 3. When comparing the SMI Z-score of the three patient exercise subgroups separately with that of the entire control cohort (control exercise subgroups 1, 2, and 3), only patient exercise subgroup 1 differed in median SMI Z-score to the entire subgroup of controls. A higher degree of physical exercise was associated with a higher SMI Z-score as the SMI Z-score differed significantly between patients in exercise subgroups 1, 2, and 3.

Both patient subgroups 1 and 2 had a higher fat % Z-score than the corresponding control exercise subgroups. However, patients in subgroup 3 had a fat % Z-score in the same range as the corresponding control exercise subgroup. Furthermore, the difference between each patient exercise subgroup (subgroups 1, 2, and 3) was also significant. The higher the amount of physical exercise was, the lower was the fat % Z-score.

To investigate if a diagnosis of IBD *per se* was independently associated with aBMD Z-score deficits when adjusted for the amount of physical exercise subgroup (categorized in three exercise subgroups, of which subgroup 1 constitutes the reference group), we performed several multivariable regression analyses. We found that suffering from IBD was negatively associated with Z-scores at all aBMD measurement sites, regardless of the physical exercise subgroup. Furthermore, performing regular physical exercise of four or more hours a week (subgroup 3) was independently associated with higher aBMD Z-scores at all sites. Less than

four hours of physical exercise a week (exercise subgroup 2) was also associated with higher aBMD Z-scores in the total body and femoral neck, albeit not in the spine. Furthermore, to analyze whether the association of physical exercise was mediated through the effect of skeletal muscles on bone and not the exercise *per se*, an additional regression analysis for the femoral neck was performed. This analysis showed that, when comparing subgroup 2 and 3 to subgroup 1, physical exercise was independently associated with increased aBMD Z-score in the femoral neck when adjusted for SMI Z-score and diagnosis of IBD.

4.3.2 Conclusion

Regular physical exercise participation tended to be lower in young adults with childhood-onset IBD compared to controls. Despite the negative relationship of having IBD on aBMD and body composition, patients who exercise regularly tended to have a positive association with higher aBMD and significantly more muscle mass and lower fat mass.

4.4 Study IV - Young adult male patients with childhood-onset IBD had compromised cortical and trabecular bone microstructures

This study aimed to investigate the extent of microstructural alterations in young adult males with IBD and the association between these changes and the patient's SMI and the amount of physical exercise. A total of 49 young men from the second follow-up in early adulthood were included in this analysis. Each participant was scanned with HR-pQCT to measure bone geometry and microstructures. The patients were compared to a control group of young men (n=245) selected from the GOOD study cohort by propensity score matching for age and height in a 1:5 patient to controls ratio.

4.4.1 Results

Analyzing bone geometry parameters, young men with IBD showed a reduction of the cortical area compared to controls. However, no significant differences were seen in the trabecular or total tibia area. The vBMD, cortical vBMD, and trabecular volume fraction were lower in patients than in controls.

Significant differences in microstructures were apparent, as cortical and trabecular thickness were lower, and the trabeculae were more separated in patients than in controls. Patients with Crohn's disease had cortical and trabecular bone parameters in the same range as those with ulcerative colitis.

We performed multivariable regression analyses with each measured bone parameter as a dependent variable. The following three parameters were used as covariates: SMI Z-score, physical exercise of four or more hours, and a diagnosis of IBD. We found that IBD *per se* was independently associated with all previously mentioned bone parameters, except trabecular separation. Furthermore, SMI Z-score was

independently associated with all measured bone parameters, except cortical vBMD. Physical exercise of four or more hours was not independently associated with any bone parameters.

4.4.2 Conclusion

Young adult men with childhood-onset IBD had deficits in cortical and trabecular bone geometry and microstructures compared to age- and height-matched male controls.

5 Discussion

The importance of bone health in patients with IBD has received increasing attention in the last decades. The current ECCO/ESPGHAN consensus guidelines[19] emphasize bone health as a marker of effective therapy and disease control in children with IBD and advocate BMD monitoring. They noted that failure to control inflammation with consequent compromised bone health could result in an increased risk of fractures later in life. However, there is limited data on BMD and body composition in adult patients with childhood-onset IBD.

This thesis aimed to investigate BMD development in patients with childhood-onset IBD from childhood into early adulthood. The purpose was also to evaluate body composition traits in these young adult patients. Further, we wanted to investigate the physical exercise habits in young adults with childhood-onset IBD and these habits' association to BMD and body composition traits.

In summary, we could show in our cohort of young adults with childhood-onset IBD that lumbar spine BMD deficits persisted from childhood into young adulthood. However, we could also observe some BMD improvements during late adolescence, which raises the question as to whether patients with childhood-onset IBD may have the potential to increase lumbar spine aBMD beyond the estimated time for PBM. We found that young adult male patients were especially at risk for low aBMD and had widespread bone microstructural alterations. The body composition traits in young adults with childhood-onset IBD were altered as well. A higher proportion of patients with IBD had myopenic or myopenic-obesity body composition profiles than controls. The profiles, which include low SMI, were associated with decreased BMD. Having childhood-onset IBD was independently associated with compromised BMD and body composition. However, regular physical exercise in patients with IBD was associated with higher BMD, higher SMI, and lower fat %.

5.1 Bone health in young adults with childhood-onset IBD

In study I of this thesis, we showed that young adults with childhood-onset IBD often had low aBMD in the lumbar spine at follow-up. Around one-third of the patients had lumbar spine aBMD Z-scores lower than -1. Further, one in ten patients had a very low lumbar spine aBMD Z-score below -2. To our knowledge, only two other smaller studies have reported aBMD measures in young adult patients with childhood-onset IBD. In accordance with our results, Laakso et al.[33] reported low aBMD in about a third of young adults with childhood-onset IBD. Further, Guz-Mark et al.[32] reported half of the young adults to have low aBMD, possibly overestimating the proportion due to a retrospective study design and selection bias. In contrast, studies involving middle-aged adult patients with IBD have reported a reduced prevalence of low aBMD, in around a fifth of adults with IBD[67, 68]. Our research group has previously published aBMD measurements in childhood and adolescence for this cohort[10, 11]. Around half of the children with IBD had aBMD Z-scores lower than -1 and a quarter of patients lower than -2[10]. However, our previous data indicated also that there could be a potential in these patients to increase their lumbar spine aBMD after having reached 18 years of age[11].

In this thesis, we aimed to evaluate whether young adult patients with childhood-onset IBD may have the potential to improve BMD beyond the expected age of PBM. We found that in total 17 patients in our cohort had reached the age for PBM attainment at the first follow-up, around six years before the current second follow-up. Time for PBM attainment in a healthy population was based on Baxter-Jones et al. that found PBM to be achieved in the lumbar spine and hip five years after PHV[7]. In those 17 patients, supposedly having achieved PBM according to this estimation, we observed an increase of aBMD in both the lumbar spine (both genders) and total hip (females only) at the second follow-up. To conclude, this continued increase of BMD may indicate a window for BMD development of the lumbar spine beyond what is expected in the normal population.

In the group as a whole, we observed that the patients with childhood-onset IBD improved their lumbar spine aBMD Z-scores now in early adulthood compared to the previous first follow-up. These findings contrasted with Laakso et al.[33] who reported no such improvement when patients were followed-up into early adulthood.

The most pronounced aBMD deficits in patients with IBD were found in the lumbar spine. These deficits might be explained by the fact that the lumbar spine is mainly comprised of trabecular bone[36]. Due to its high bone turnover, trabecular bone is sensitive to harmful factors, such as inflammation *per se* and corticosteroids[37], both common in patients with IBD.

Advanced bone measurement techniques, such as HR-pQCT, are able to deepen the knowledge of the nature of bone deficits in patients with IBD but DXA is still the golden standard in the clinical setting. Using an HR-pQCT scan of the tibia, we found that both the cortical and trabecular microstructures were altered in young men with childhood-onset IBD compared to controls, even after adjusting for SMI

and physical exercise. To the best of our knowledge, only two HR-pQCT studies in patients with IBD have been published. In contrast to our study IV, Pepe et al.[60] reported a deficiency only in trabecular structures in children and young adults aged between 12 and 33 years of age (average age at diagnosis 17.3 years), some of them with childhood-onset IBD. Furthermore, Haschka et al.[61] found that only cortical structure deficits were associated with IBD in older adult patients (median age 44 years).

Our findings of deficits in both trabecular and cortical bone are in line with previous reports from children with IBD utilizing an older model of pQCT. This older model measures vBMD in trabecular and cortical bone separately without the ability to assess any microstructures. In several of these studies, both cortical and trabecular vBMD were lower in children with IBD than in controls[55, 58, 59]. To conclude, young adults with childhood-onset IBD run a high risk of compromised microstructures in both trabecular and cortical bone.

5.2 Body composition in young adults with childhood-onset IBD.

The evaluation of body composition traits, SMI and fat %, was performed in male and female patients separately. However, to interpret skeletal muscle and body fat together in all patients, we modified a model initially proposed by Baumgartner et al.[79] to investigate body composition in the elderly. Such a model has, to our knowledge, not been previously used in patients with IBD. By combining SMI and fat percentage from a DXA scan, we defined four body composition profiles: i) normal, ii) myopenic, iii) obese, iv) myopenic-obese.

Our results show that a larger proportion of patients with IBD had alterations in body composition than controls. About a third of the patients had myopenia (low skeletal muscle mass) compared to around a fifth of the controls. Further, a fourth of the patients with IBD had obesity compared to less than a fifth of controls. Further, 10% of the patients exhibited a myopenic-obese profile compared to only 2% of the controls. The use of SMI to estimate skeletal muscle mass has also been used by Bryant et al.[111]. In contrast to our findings, they reported myopenia only in about a fifth of adult patients with IBD (median age of 33 years). However, our patient cohort appears to have a longer disease duration as well as disease onset during childhood, possibly explaining this discrepancy as long-standing inflammation is associated with skeletal muscle defects[89].

Our findings of a high prevalence of myopenia in early adulthood concern as an age-related decline of skeletal muscle mass occurs later in adulthood[112]. We also found that patients with myopenia had lower grip strength than patients without myopenia, indicating a possible risk for developing sarcopenia (a combination of low muscle strength and muscle mass) later in adulthood. In the elderly, sarcopenia is associated with increased risk for falls and fractures[113], lower quality of life[114],

mobility disorders[115], and mortality[116]. Thus, suffering from myopenia already in early adulthood could imply a higher risk for severe consequences later in life. Previous studies, focusing on body composition measured with DXA in patients with IBD, have reported findings of total body lean mass deficiencies in both children[82, 117] and adults[85, 86]. Even though total body lean mass does not estimate skeletal muscle mass as accurately as SMI[74], those previous studies support our findings that patients with IBD are at risk of developing skeletal muscle deficits.

About a quarter of our patients was found to have obesity as part of their body composition profile, which was significantly more frequent than in controls. Previous studies have shown divergent results reporting either high or low fat mass in adult patients with IBD[85, 117, 118]. Previous studies of body composition vary greatly in design and cohort selection. Adjustments for age, weight, and gender must be considered when assessing fat mass[85]. Studies that focus on the impact of obesity in IBD have used high BMI as a marker for obesity. Although BMI is less accurate in estimating fat mass in patients with IBD than DXA scan[81, 119], it is more readily available and widely used. High BMI (overweight and obesity) in patients with IBD has been, besides well-known risk factors of obesity[120], associated with early surgical intervention in patients with Crohn's disease[121], more perioperative complications[122], increased need for colectomy in patients with ulcerative colitis[123] and predicted the need for dose escalation with adalimumab in patients with Crohn's disease[124]. To conclude, our results indicate a high prevalence of obesity in young adults with IBD.

A myopenic-obese profile was found significantly more often in patients with IBD than controls. This profile may combine the risks of myopenia as well as obesity. Furthermore, a myopenic-obese body composition profile has been linked to an increased risk for cardiometabolic syndrome[125] and rapid loss of physical functions in late adulthood[126]. Notably, this group of patients had BMI similar to those with a normal body composition profile, thus, supporting the view that the traditional BMI to estimate body composition in patients with IBD is often inaccurate[81, 119]. This particular body composition profile had not been described in patients with IBD previously. Interestingly, Alsufyani et al. recently adopted our model in a study of Saudi Arabian children with IBD and reported, in line with our results, a high proportion of either myopenic or obese profile compared to controls[84]. However, in contrast to our findings in young adult patients, they did not report the myopenic-obese body composition profile to be more prevalent in children with IBD than in controls. Further studies are needed to determine the development of body composition profiles from childhood throughout adulthood.

Both the myopenic and myopenic-obese profiles were associated with low aBMD, thus, as expected, the SMI Z-score was found to be independently associated with lower aBMD. Similarly, Bryant et al.[111] also reported associations between low SMI and low BMD in adult patients with IBD. Such an association between myopenia and low aBMD has also been reported in healthy European men[127]. Skeletal muscle index estimates skeletal muscle mass more accurately than total body lean mass[74] and correlates more strongly to aBMD[77]. Therefore, we would suggest that SMI may

be used in future research on body composition and BMD instead of total body lean mass. However, the variation in SMI did not explain all the aBMD deficits in our group of patients with IBD as a diagnosis of IBD was independently associated with low aBMD.

In young adulthood, patients with the obese body composition profile appeared to have normal aBMD. However, fat % was not independently associated with changes in aBMD. This finding was somewhat unexpected as it is well known that increased weight is associated with denser bones in healthy adults[128] and that fat mass *per se* is associated with higher aBMD in healthy adults[78].

The patient group with myopenic-obese profile appeared to have the longest disease duration and earliest disease-onset of the profile groups. Thus, this body composition profile might result from a cumulative inflammatory burden, in line with findings in older adults, where chronic systemic inflammation has been associated with low skeletal muscle mass and high fat percentage[129]. In addition to inflammation, several other factors may influence body composition traits (**Figure 5**): Physical exercise promotes skeletal muscle gains[130] and reduces fat[131]; nutritional status can be associated with low muscle mass[88, 132] and obesity[133]; the use of corticosteroids is associated with higher fat mass[92].

5.3 Physical exercise

We examined physical exercise habits in young adults and about 60% reported some form of regular physical exercise during the last year. The patient groups' sport participation tended to be lower than that of controls (70%), although the difference did not reach statistical significance. Similar to our results, it seems that both children[95] and adults[97] with IBD tend to exercise less than controls. Regrettably, physical exercise is rarely discussed in the clinical setting[134], only in about one-third of cases. In general, training is well tolerated[135] and has been shown to increase the quality of life[136] and reduce disease flares[137]. However, during active disease flares, intensive training is cautioned[138].

The relationship between the amount of physical exercise and body composition has not been studied previously in young adult patients with childhood-onset IBD. In this thesis, all patients and controls were divided separately into three physical exercise subgroups based on their regular physical exercise: i) sedentary, ii) less than four hours of exercise per week, and iii) more than four hours of physical exercise weekly. We found increasing amounts of physical exercise to be associated with higher aBMD, higher SMI, and lower fat % in these young adult patients with IBD, especially in those with four or more hours of exercise per week. This patient group had aBMD and body composition traits in the same range as the control cohort average. These findings support the view that physical exercise could be a powerful tool to counteract alterations in aBMD and body composition[102]. Physical exercise can strengthen the bone by activating the muscle-bone unit[101] and with activities such as jumping, directly affecting the skeleton[99]. We also found a similar association with

BMD, thus, physical exercise was independently associated with higher aBMD in the femoral neck after adjusting for SMI. Further, we showed that a diagnosis of IBD was independently associated with low aBMD after adjustments for SMI and amount of physical exercise.

Interestingly, young adult patients that had regular physical exercise were more likely to have participated in sports during late adolescence than those patients that were sedentary. Suggesting that exercise habits of patients with IBD in childhood and adolescence may be associated with physical exercise engagement in adulthood. This relationship has been found in healthy individuals[107] and physical exercise in childhood and adolescence has further been associated with bone health in adulthood[139].

5.4 Gender differences

The group of young adult male patients had lower aBMD Z-scores than controls, whereas female patients did not show any differences. There are conflicting results regarding corresponding gender variation in children with IBD and most studies have not found any difference[62, 65]. However, our research group[10, 11] had previously found that male gender was possibly associated with lower aBMD in a pediatric cohort of patients with IBD. Further, Gokhale et al.[64] found pubertal and postpubertal girls with IBD in the United States to be more likely to have low aBMD than boys with IBD. Studies in adult patients with IBD have suggested that there might be an unmet need for vigilance for low BMD in male patients with IBD[69, 140]. Despite this need, low BMD and osteoporosis are important subjects for women in general, especially postmenopausal women who are at risk[141] and this also applies to women with IBD[71, 142].

The exact reason for the BMD gender difference in our cohort is unclear as many factors affect bone mineralization. However, we found no indication that age at disease-onset, disease duration, and/or received medical/surgical therapy differed between men and women in young adulthood. Body composition traits in both men and women with IBD were similar to corresponding controls, although women with IBD had a higher fat % Z-score than men. However, we observed no gender-related differences in physical exercise habits.

A possible reason why young men with childhood-onset IBD are at greater risk of developing low BMD than young women may be that most of the bone mass is achieved during adolescence[7] and/or different factors influence bone mineralization in males and females[143]. In healthy male adolescents, bone mass development is primarily dependent on the growth of the muscle-bone unit. This muscle-bone unit is susceptible to inflammation, lack of physical exercise, and nutritional deficits[143]. In contrast to males, bone mass accrual in female adolescents is less dependent on the interplay between muscle and bone but more dependent on estrogen[143]. Thus, it may be an actual gender difference as the impact of IBD possibly affects the muscle-bone unit more in males than in females during childhood.

5.5 Crohn's disease vs. ulcerative colitis

In this thesis, we found no apparent difference regarding BMD in patients with Crohn's disease compared to those with ulcerative colitis. There are conflicting results in the literature on whether there is a difference in BMD between the IBD subcategories. Several studies found aBMD to be lower in patients with Crohn's disease than patients with ulcerative colitis, both in childhood[64, 66], and adulthood[68, 71, 144], whereas others, in line with our previous and current findings[10, 11], did not find any difference[33, 67, 69].

Skeletal muscle mass did not differ between patients with Crohn's disease and ulcerative colitis (men and women combined). In line with our findings, SMI is reported to be similarly low, regardless of disease subcategory, in both children[84] and adult patients[111] with IBD. However, in the current project, male patients with Crohn's disease had a lower SMI Z-score than controls, whereas male patients with ulcerative colitis did not differ from controls. This difference might result from the disease being more active during childhood and adolescence in those with Crohn's disease, possibly affecting the muscle-bone unit to a greater extent[143]. Regrettably, other studies focusing on SMI did not stratify by gender when comparing IBD subcategories[84, 111]. The use of SMI in studies of body composition in IBD is relatively new and previous studies have instead used total body lean mass[85]. Similar to our findings that SMI is more compromised in patients with Crohn's disease, Bryant et al. published a systematic review of 19 studies on body composition in adults with IBD. A total of 28% of patients with Crohn's disease and 13% of patients with ulcerative colitis were found to have low lean mass.

Fat percentage was in the same range in young adults with Crohn's disease and those with ulcerative colitis. Interestingly, by taking both fat % and SMI into account and defining body composition profiles, we found that patients with ulcerative colitis were overrepresented in the obese body composition profile. Fourteen patients with ulcerative colitis (21%) and one patient with Crohn's disease (3%) had high fat % without skeletal muscle mass deficits. Similar to our results, Bryant et al.[85] recently reported that the prevalence of increased fat mass in adult patients with Crohn's disease was 3%. However, the corresponding figure in patients with ulcerative colitis was 12%, a lower figure than we have found.

In study III, we found that patients with Crohn's disease and those with ulcerative colitis reported that they were engaged in regular physical exercise to about the same extent. Between 50–60% of the young adults with childhood-onset IBD exercised regularly, so it is unlikely that subcategory differences in body composition are associated with physical exercise habits.

Our opinion is that our patient cohort of young adults with IBD in this second follow-up represents the whole clinical spectrum of childhood-onset IBD. The cohort was population-based at baseline[10] and participants did not differ from non-participants with regard to DXA measurements or clinical characteristics at the previous first follow-up (**Table 1**).

In summary, young adults with Crohn's disease and those with ulcerative colitis have similar aBMD. Skeletal muscle mass deficits are prominent in male patients with Crohn's disease. High fat percentage (obesity) appears to be more common in patients with ulcerative colitis than those with Crohn's disease, regardless of gender.

5.6 Clinical implications

- Young adults with childhood-onset IBD showed alterations in both BMD and body composition. There is a need for preventive and therapeutic measures for patients with IBD as these alterations are potentially associated with morbidity later in adulthood.
- It would be of clinical value if all DXA scans included interpretation of body composition measurements such as SMI and fat %, in addition to estimation of aBMD. Currently, reference data are lacking for children. For young adults, threshold values from this thesis (study II) are available.
- Physical exercise appears to be important for counteracting BMD deficits and alterations in body composition traits. In our opinion, physical exercise should be routinely addressed in the clinical setting. A physical therapist may play an essential role in the multidisciplinary IBD team.
- Normal body composition traits might be a valuable surrogate marker for effective treatment and remission. Conversely could altered body composition serve as a red flag for incomplete disease control.
- In the transition from pediatric to adult care of IBD, it may be of importance to highlight BMD deficits and lifestyle factors such as physical exercise, not least because of that the development of BMD seems to continue into young adulthood.

6 Main conclusions

- Young adults, especially men with childhood-onset IBD, are at risk for low aBMD and those young men also show widespread deficits in bone microstructures.
- Young adult female patients with childhood-onset IBD have similar aBMD compared to age- and gender-matched controls.
- Both male and female patients with childhood-onset IBD appear to improve their aBMD beyond the expected age for PBM.
- Young adults with childhood-onset IBD have a risk for altered body composition traits (myopenic, obese, and myopenic-obese profile) compared to controls.
- Young adult men with Crohn's disease have an especially high risk for myopenia.
- Regular physical exercise in young adulthood may help to counteract the detrimental effects of IBD on BMD and body composition traits

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