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QUALITY OF LIFE, PHYSICAL ACTIVITY AND BONE HEALTH IN IDIOPATHIC SCOLIOSIS

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The images on the cover illustrate a normal spine and a scoliotic spine. The images in this book have been provided by Elias Diarbakerli, Allan Abbott and Paul Gerdhem.

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Quality of life, physical activity and bone health in idiopathic scoliosis

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To my beloved parents, Jan & Maha Diarbakerli, for always believing in me

To my family for your tireless support

ABSTRACT

Idiopathic scoliosis is a deformation of the spine affecting 1-3% of children and adolescents during growth. Severe deformities may lead to pulmonary dysfunction, pain and decreased quality of life. The etiology of the disease remains unknown. However, bone health and its possible role in the development of scoliosis has been discussed the last decade.

A large cohort of individuals with idiopathic scoliosis (n=2,057), both adolescents and adults, was used to assess the impact of treatment characteristics, onset of the condition and gender on quality of life and physical activity. Furthermore, a cohort of non-scoliotic individuals (n=272) was assessed for quality of life and physical activity similarly in order to establish reference values. Another cohort of adolescents with idiopathic scoliosis (n=78) was examined and assessed regarding bone health and compared to non-scoliotic adolescents (n=52).

We found that quality of life in individuals with idiopathic scoliosis was overall similar many years after treatment and management with marginally lower values for those who had been surgically treated. Gender and onset of idiopathic scoliosis did not have an impact on quality of life. However, the quality of life did not reach the level of the non-scoliotic cohort. Physical activity was found to be similar between individuals with and without idiopathic scoliosis. Our cohort of adolescents with idiopathic scoliosis had lower values at central skeletal sites such as the spine and hip on bone scans compared to the adolescents who did not have scoliosis. Despite this finding, sustained fractures did not differ in adulthood in our cohort of adults with idiopathic scoliosis compared to non-scoliotic adults.

SUMMARY IN SWEDISH (SAMMANFATTNING PÅ SVENSKA)

Idiopatisk skolios innebär en deformering av ryggraden hos växande barn och ungdomar. Uppskattningsvis 1–3% av barn och ungdomar utvecklar tillståndet. Svåra fall av skolios kan leda till nedsatt lungfunktion, smärta och nedsatt livskvalitet. Orsaken till skolios är inte känd men under det senaste årtiondet har skeletthälsans roll som potentiell orsak till skolios diskuterats.

En stor kohort av individer med idiopatisk skolios (n=2,057), både barn och vuxna, undersöktes i syfte att kartlägga effekten av behandling, typ av skolios och kön på livskvalitet och fysisk aktivitet. Vidare undersöktes en grupp av individer utan skolios (n=272) på samma sätt gällande livskvalitet och fysisk aktivitet med syfte att samla in referensvärden. En grupp barn med idiopatisk skolios (n=78) undersöktes avseende benhälsa och jämfördes mot en grupp barn utan skolios (n=52).

Vi fann att livskvalitet hos individer med idiopatisk skolios skiljde sig marginellt många år efter behandling. Kirurgiskt behandlade individer hade något lägre värden. Kön och typ av skolios påverkade inte livskvalitet. Värdena för livskvalitet hos individer med idiopatisk skolios var klart lägre jämfört med individer utan skolios. Gruppen barn med idiopatisk skolios hade lägre benmassa i rygg och höft vid bentäthetsmätning jämfört med barnen utan skolios. Trots dessa fynd så fann vi ingen skillnad i förekomst av tidigare fraktur hos vuxna med idiopatisk skolios jämfört med vuxna utan skolios.

LIST OF SCIENTIFIC PAPERS

I. **Health-related quality of life in adulthood in untreated and treated individuals with adolescent or juvenile idiopathic scoliosis**

Elias Diarbakerli, Anna Grauers, Aina Danielsson, Paul Gerdhem

The Journal of Bone and Joint Surgery American volume. 2018;100(10):811-7.

II. **Quality of life in males and females with idiopathic scoliosis**

Elias Diarbakerli, Anna Grauers, Aina Danielsson, Allan Abbott, Paul Gerdhem

Spine. 2019;44(6):404-10.

III. **Population-based normative data for the Scoliosis Research Society 22r questionnaire in adolescents and adults, including a comparison with EQ-5D**

Elias Diarbakerli, Anna Grauers, Paul Gerdhem

European Spine Journal. 2017;26(6):1631-7.

IV. **Adults with idiopathic scoliosis diagnosed at youth experience similar physical activity and fracture rate as controls**

Elias Diarbakerli, Anna Grauers, Aina Danielsson, Paul Gerdhem

Spine. 2017;42(7):E404-E10.

V. **Bone health in adolescents with idiopathic scoliosis: a comparison with age- and sex matched controls**

Elias Diarbakerli, Panayiotis Savvides, Axel Wihlborg, Ingrid Bergström, Allan Abbott, Paul Gerdhem

Manuscript

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LIST OF ABBREVIATIONS

BC	Before Christ
BMC	Bone Mineral Content
BMD	Bone Mineral Density
CTLSO	Cervicothoracolumbosacral orthosis
DXA	Dual energy x-ray absorptiometry
EQ-5D	EuroQol-5 Dimensions
IPAQ-SF	International Physical Activity Questionnaire – Short Form
pQCT	peripheral Quantitative Computed Tomography
SAQ	Spinal Appearance Questionnaire
ScoliGeneS	Scoliosis and Genetics in Scandinavia project
SRS-22r	Scoliosis Research Society-22 revised
TBLH	Total Body Less Head
TLSO	Thoracolumbosacral orthosis

1 BACKGROUND

1.1 INTRODUCTION

The human spine, *columna vertebralis*, is a robust and central structure in the human body consisting of 33 vertebrae. The cervical spine is formed by seven vertebrae, twelve vertebrae form the thoracic spine, five lumbar, five sacral and four coccygeal vertebrae. The sacral vertebrae are fused together and form the sacrum which articulates to the last (fifth) lumbar vertebra. Motion in the spine is allowed through the intervertebral joints and the intervertebral disc. Movements of the spine can occur in the sagittal, frontal and transverse plane. The healthy spine is normally straight in the frontal plane but curved in the sagittal plane, known as lordosis (cervical and lumbar spine) and kyphosis (thoracic spine). The terms kyphosis and scoliosis were described as early as in ancient Greece by Hippocrates (460-370 BC) and nearly five centuries later, Galen of Pergamon continued describing scoliosis, kyphosis and also lordosis. The work of Hippocrates and Galen benefitted management of spinal deformities for more than 1,500 years (1).

1.2 DEFINITION AND ETIOLOGY

Idiopathic scoliosis is a condition affecting the growing spine in adolescents and children. The spine is affected in all three plane and diagnosis is confirmed on standing radiograph of the spine when the frontal curvature surpasses ≥ 10 degrees as measured according to the methods described by Cobb (2). Clinical manifestations such as trunk deformity and back asymmetry correlates with scoliosis, however discrepancies are seen in some cases (3).

The term idiopathic indicates that the deformity is of unknown origin and therefore is a diagnosis of exclusion. For this reason, other entities such as congenital malformations or neuromuscular types of scoliosis need to be excluded in order to confirm an idiopathic scoliosis. About one fifth of individuals with scoliosis have a secondary pathology causing the deformity, whilst the remaining 80% have an idiopathic origin (4). Clinical entities suggesting a secondary cause may be pain, neurological deficits and a primary left thoracic curve, usually indicating the need for further investigation with Magnetic Resonance Imaging (MRI) (5, 6). Neural axis abnormalities have however been described to be present in almost 15% of individuals with idiopathic scoliosis despite the absence of other findings. Most common findings are Chiari malformations and syringomyelia, disturbing the flow of cerebrospinal fluid (7).

Causes for idiopathic scoliosis have been proposed and discussed in the literature. Genetics, growth asymmetry, hormonal influence and anatomical factors have been proposed as contributors to the etiology of the condition (8-11). In 2016, a study by Grimes et al suggested that cilia motility in zebrafish plays an important role for spine morphogenesis (12). The authors showed that protein tyrosine kinase-7 (*Ptk7*), a gene important for proteins transducing extracellular signals across the cell membrane, mutant zebrafish had dysfunctional ependymal cilia motility which resulted in defect of the cerebrospinal flow, eventually giving rise to scoliosis. By restoring through transgenic reintroduction of *Ptk7* the cilia function at onset of scoliosis, it was seen that progression of the deformity was halted.

Other studies, mainly based on Chinese individuals with idiopathic scoliosis, have shown that bone health may play a role in the etiology and development of idiopathic scoliosis (11, 13-15). Since many theories have arisen in the literature regarding etiology, guidelines from the Society on Scoliosis Orthopaedic and Rehabilitation Treatment (SOSORT) suggest a multifactorial origin (4).

In the literature, the prevalence of idiopathic scoliosis has been approximated to 1-3% ranging from 0.47%-5.2% in studies. About one tenth of affected individuals require treatment (16-18). Girls and boys are affected equally but girls are heavily overrepresented in advanced scoliosis with a ratio 7:1 in curves surpassing 30 degrees (19, 20). Besides idiopathic scoliosis, other types of spine-related disorders can affect adolescents. Lumbar disc herniation is, for example, another condition that can be seen in children. In a previous large cohort of patients operated for lumbar disc herniation (n=10,615), 1.4% were adolescents (21).

1.3 PROGNOSTIC FACTORS

The risk of progression of scoliosis is highly dependent on maturity and factors associated to it, such as the status of menarche and skeletal maturity as estimated by hand radiographs and the ossification of the crista apophysis (Risser sign) (22-25). Other factors such as family history and Tanner staging (pubertal status) are tools used in assessing remaining growth (4).

It has been suggested that the risk of progression in the beginning of puberty is 20% in small curves (10 degrees), 60% in curves of 20 degrees and 90% in curves of 30 degrees. These numbers are greatly decreased to 2%, 20% and 30% respectively, at the end of puberty (26, 27). At skeletal maturity, the risk for further progression is low. However, in curves reaching 50 degrees, continuous progress at a rate of 1 degree per year has been shown to occur (28).

1.4 CLASSIFICATIONS

There are a number of classification systems for idiopathic scoliosis that are being used in order to determine management. The curve can be of thoracic, thoracolumbar or lumbar location which is determined by the apex (i.e. the most deviated vertebra in the coronal plane). Most commonly, a primary right thoracic convexity with a compensatory convexity to the left in the lumbar junction is observed. A three-curve pattern is also a possibility where left convex compensatory curves cranial and caudal to the primary, right thoracic curve are seen. Double major curves, meaning two curves of similar size, is another possibility not rarely observed.

Onset

Individuals are commonly categorized according to onset of the condition; infantile (0-3 years of age), juvenile (4-9 years of age) and adolescent (10-18 years of age) (29, 30). A diagnosis at age 18 years or older is classified as adult idiopathic scoliosis (4). Those having a juvenile or adolescent onset have many similarities in natural history, outcomes and treatment modalities (31) (paper I, paper IV). Those with an infantile onset have however a different prognosis and natural course not resembling the other types of onset and will therefore not be discussed furthermore in this thesis (32).

Curve size

The magnitude of the curve on a standing radiograph is an important foundation for treatment and management. Figure 1 illustrates a scoliotic spine measured according to Cobb. Curves are classified as mild (up to 20 degrees), moderate (21-35 degrees), moderate to severe (36-40) and severe (40 degrees or larger) (4). There are some cut-off points in the Cobb angle which are based upon general agreements in SOSORT guideline and other literature (4, 19, 26, 33):

- A Cobb angle on radiograph below 10 degrees should not be categorized as scoliosis.
- A curve over 30 degrees elevates risk for curve progression in adulthood and may impair quality of life.
- With a curve surpassing 50 degrees there is almost a certainty that progression in adulthood will occur with subsequent impairments in quality of life.

Fig 1. A standing radiograph of a right thoracic curve of 54 degrees measured according to Cobb where the 4th thoracic vertebra is the cranial end vertebra and the 11th thoracic vertebra is the caudal end vertebra. The 9th thoracic vertebra serves as the apex of the curve.

Curve type

The Lenke classification system is being applied mainly in the surgical setting. Curve type, a lumbar spine modifier and a sagittal thoracic modifier are used to classify the type of curve. The curves are described as structural or nonstructural. Furthermore, they are described as main thoracic, double thoracic, double major, triple major, thoracolumbar/lumbar, or thoracolumbar/lumbar-main thoracic. This way of classifying curves has shown to have an advantage when planning for surgical interventions by enhancing the selection of segments to fuse, resulting in a more accurate estimation of needed segments to fuse (34, 35). Other classification systems, also for exercise and brace prescription, have also been proposed (36-38).

1.5 TREATMENT

Individuals with idiopathic scoliosis at risk for progression in their deformity are offered treatment depending on the magnitude of the scoliosis and remaining growth. Bracing is usually the first line of choice in skeletally immature adolescents with curves between 25-45 degrees and arthrodesis surgery is considered in those having curves exceeding 45-50 degrees

in the Cobb angle, with additional considerations regarding risk for further curve progression, symptoms and age (4, 5).

History

Treatment for spinal deformities has been performed since ancient Greece. In the time of Hippocrates, manipulation treatment of the spine was already in use. However, Hippocrates himself advocated diet and extension when treating spinal deformities. He was a pioneer and the founder of devices applicating traction forces and correction for spinal deformities (1). Treatment for spinal deformities remained rather unmodified, based on Hippocrates and Galen of Pergamon's principles, until the 16th century when Ambroise Paré introduced the first supportive brace, and later in the 19th century, William Adams and Lewis Albert Sayre further developed casting in combination with gymnastic exercises (39).

In 1911, by Russell Hibbs, invasive surgery was carried out for the first time with the goal to halt progression (40). This was achieved through bony fusions of the vertebrae and required immobilization for 6 months postoperatively. Major complications, such as death and infections, were common consequences of the procedure.

Brace treatment

Brace treatment for scoliosis has been refined and developed throughout history. The Milwaukee brace, also called CTLSO (cervicothoracolumbosacral orthosis), was the first widely used brace in conservatively treated individuals with idiopathic scoliosis, described in 1958 (41). This rather uncomfortable brace was made of leather girdles, a metal superstructure and a chin rest giving rise to traction forces.

To date there are several types of braces, labelled differently but with the same task, aiming to halt progression and alter the natural course of scoliosis (4). The most widely used brace is the thoracolumbosacral orthosis (TLSO) or underarm brace, also referred to as the Boston brace. It is worn 20-23 hours per day until skeletal maturity with regular radiological and clinical follow-ups. Treatment with the TLSO brace has shown to halt rate of progression in idiopathic scoliosis (42, 43). The dose-response relation has received much attention recently and it is now generally agreed that the desired effect is better achieved with increased in-brace time (4, 43, 44).

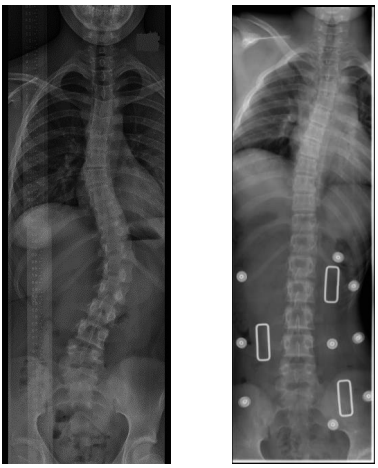


Figure 2. Standing radiograph of a patient without brace to the left and in a Boston brace to the right

Negative aspects associated with brace treatment have been reported. It is mainly issues regarding compliance and a negative impact on quality of life in patients treated with full time bracing that have been reported (45, 46). These concerns have led to an increased interest in nighttime brace treatment, where an over corrective effect is achieved during nighttime, without need for brace use at daytime. With this type of bracing, psychosocial and compliance benefits have been shown in a smaller study of 33 individuals with idiopathic scoliosis (47). Another study assessing the Providence nighttime brace retrospectively showed similar benefit to the Boston brace in progression rate of the deformity in 36 female patients (48). However, there is a need for prospective and randomized trials in order to determine potential benefits from nighttime bracing.

Another side effect of monitoring possible progression of idiopathic scoliosis is the regular follow-ups with radiographs. This exposes patients to radiation repeatedly during growth. A previous study reported higher frequency of cancer, mainly breast and endometrial types of cancer, in adults that had been managed for scoliosis at adolescence compared to individuals without scoliosis (49). This study raises questions regarding the potential need of other, radiation free, ways to monitor possible curve progression and some studies have shown that ultrasonography may be beneficial for this purpose (50, 51).

Exercise treatment

In the SOSORT guidelines for conservative treatment of idiopathic scoliosis, scoliosis-specific exercises play a major role in both mild curves as the only intervention and in more severe curves together with brace treatment. The exercise methods with largest scientific base are the

Schroth method and SEAS (Scientific Exercises Approach to Scoliosis). The Schroth method was developed in the early 1920's by Katharina Schroth, a german physiotherapist who developed treatment principles for moderate and severe curves. The methods have over time been further developed with exercise-prescription based on curve size and type; consisting of specific postural correction, breathing correction patterns and correction of postural perception which are taught to the patient (38). Studies on the Schroth method have shown promising results where the deformity seem to be positively influenced (52-54).

The SEAS approach is used both as only treatment in mild curves, as addition to bracing and also in postoperative stages in fused patients. SEAS principles are based on active self-correction movements that are individually created based on evaluation tests for each patient. Commonly, the program is performed by the patient at home with regular follow-ups with a physiotherapist. The aim of this approach is to increase patients' spinal perception and increase neuromuscular control (55). Studies on SEAS have shown mainly effect on mild curves, decreasing the risk of developing a larger curve requiring brace treatment (56-58).

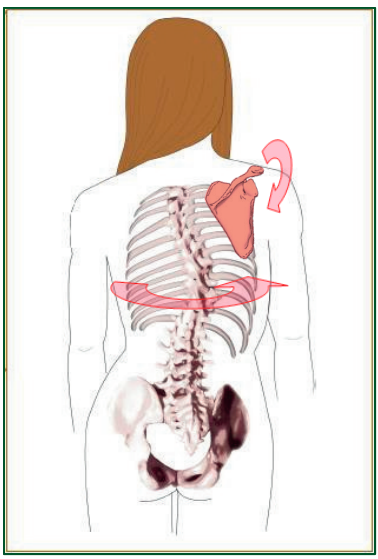


Figure 3. Example of active correction of a primary right-convex thoracic curve with compensatory left-convex lumbar curve. An active retraction of the shoulder and scapula together with ventralisation of the right lower ribs to influence a 3-dimensional neutral alignment of the deformity.

Surgery

In larger curves, surgery is advocated in order to stop further progression and restore spinal balance (4, 5, 16).

The first instrumented spinal surgery approach for spinal deformities was introduced in the 1960's and was revolutionary for the time. It was introduced by Paul Harrington who invented the famous Harrington-rod and this intervention was golden standard for many decades (59). The correction was achieved through application of a distraction force of the concave side and a compression force of the convex side of the spine. Accompanied with decortication and facetectomies, bony fusion along the spine were achieved through bone transplant from the iliac crest. To aid fusion, patients were immobilized in a cast for six months. This technique efficiently halted progression, however only minimally decreased the scoliosis and led to a stiff and, in many cases, flat back.

Since spine surgery was revolutionized by the Harrington-rods, an increasing need for correction in all three planes of the deformity has been warranted. Segmental fixation techniques were first introduced in the 1980's and included placements of anchoring devices in multiple vertebrae that were attached to metal rods in alignment with the spine (60, 61). With this technique, correction of the deformity became possible which previously was not achievable with the Harrington technique. Suk and colleagues confirmed later the safe and effective usage of pedicle screws which became widely used (62).

Today, segmental fixation with pedicle screws using a posterior approach is generally used in the surgical management of idiopathic scoliosis. Anterior approach, where the spine is reached from the side by a thoracotomy or thoracoabdominal technique, is also used but is not advantageous in longer fusions where posterior approach is more appropriate (63, 64). Furthermore, a previous review study reported on pulmonary dysfunction subsequent to anterior approach in thoracic curves, which was recommended to be used for specific types of thoracolumbar curves (Lenke 5C) or lumbar curves with fusion commonly between Th11 and L3 (65).

According to recommendations from guidelines, return to daily activities and school should be considered after 3-4 weeks and full contact activities after 6 months when treated surgically for idiopathic scoliosis (66).

Figure 4. Standing radiograph of a patient before and after surgery with pedicle screw fixation

Complications due to surgical intervention for idiopathic scoliosis, even though being rather rare, include pseudoarthrosis, instrumentation failure and infection. Furthermore, perioperatively, there is a risk for neural tissue and spinal cord damage that may lead to persistent problems (5).

1.6 QUALITY OF LIFE

The World Health Organization (WHO) defines quality of life as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment" (67).

Idiopathic scoliosis has shown to have a negative effect on quality of life compared to individuals without scoliosis. This applies particularly at a psychological level in brace treated individuals. A previous study showed that a quarter of individuals treated with brace experienced a ruined teenage period, leading to a cessation of all spare time activities because of the treatment (46). It has also been shown that individuals who have been treated surgically are satisfied to a higher extent compared to those who have been treated with brace at long term (68, 69) (paper I). Other studies have shown higher frequency of back and neck problems in those having idiopathic scoliosis compared to individuals without scoliosis, as well as an increased cosmetic concern (16, 70, 71). Nevertheless, individuals with idiopathic scoliosis

seem to function quite good both at short- and long term in terms of activity, employment and having a family (16, 72) (Paper I and Paper IV).Weinstein et al showed in their 50-year follow-up study of untreated idiopathic scoliosis patients that those having curves of 70 degrees or more were likely to have pulmonary dysfuncton and that several impairments were seen in those having curves of 100 degrees or larger (16).

The magnitude of the scoliosis, i.e. the magnitude of the Cobb angle, has shown to be associated with quality of life where a larger curve had a negative impact (73). On the contrary, other studies have shown no correlation of the curve size and quality of life (69, 74). Furthermore, onset of idiopathic scoliosis (i.e. juvenile or adolescent) does not appear to correlate with quality of life (paper I). There seems to be an inconsistency regarding the negative effect on quality of life and the distal fused level; some studies report a negative effect when the fusion is extended to the lumbar spine (75, 76) (paper I) and other studies report no effect (77, 78). Other surgical characteristics, such as number of fused vertebrae and amount of correction, do not seem to influence quality of life in adulthood (paper I).

1.7 PHYSICAL ACTIVITY

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure. Physical inactivity has been recognized to be a global burden, both economically and from a health perspective, and identified as one of the most common risk factors for developing disease (79, 80). Many chronic illnesses, such as diabetes mellitus (type 2) and cardiovascular disease, have been shown to be associated with level of physical activity (81).

Physical activity and idiopathic scoliosis

Individuals with idiopathic scoliosis have previously been shown to be restricted in adulthood in sporting activities, mainly due to functional impairment and the frequency of back pain (82). In terms of general physical activity, not limited to but including sporting activities, idiopathic scoliosis patients seem to be similarly active as non-scoliotic individuals, both during adolescence (83) and in adulthood (paper IV).

1.8 BONE HEALTH

The dense and compact part of the skeleton, *cortical bone*, is mainly found in the shafts of long bones and constitutes 80% of the skeleton. *Trabecular bone*, the inner meshwork that predominates vertebrae, the epiphyses of long bones and the iliac crest constitutes 20% of the

human skeleton. The largest depot of calcium in the human body is in the skeleton, mostly as crystalline hydroxyapatite. Together with calcium, phosphates are the main minerals of the skeleton (84, 85). Further functions of the skeleton include mechanical support and site for attachment of muscles and also as protection for vital organs.

Throughout life in humans, the skeleton undergoes a process of remodeling where resorption and formation of bone results in a completely new skeleton every ten years. On a cellular level, there are mainly three bone cells managing bone remodeling: *osteoblasts, osteoclasts* and *osteocytes*. The osteoblasts, in the beginning derived from precursor cells in the bone marrow and periosteum, form bone through secretion of collagen. Osteoclasts are derived from precursor cells of macrophage cells and have a bone-resorbing function. The osteocytes are embedded in bone and are derived from osteoblasts. Osteocyte cells form a network together with nerve fibers, sensing and responding to mechanical stimuli resulting eventually in remodeling of bone. The remodeling process in bone is regulated through the actions of several hormones, including parathyroid hormone (PTH), the vitamin D family, oestrogens, growth hormones among others. The process of remodeling is also influenced by other factors such as diet, drugs and physical activity (84, 85).

In children, growth is largely driven by growth plate chondrogenesis. Anatomically, the growth plate is a thin surface of cartilage located in most bones of the body where chondrocytes grow and secrete extracellular matrix components. The process subsequently emerges into new cartilage tissue and new bone tissue. This causes children to grow longer and taller as bone is continuously produced at the growth plate. The *modelling* of bone starts as early as in fetal life and continues during adolescence until ossification of growth plates and termination of longitudinal growth. *Remodeling* of bone is a process also initiated in fetal life that continues throughout adolescence and is characterized by renewing bone without changing the shape of it (86). Many regulatory systems processed by hormones, paracrine factors, extra- and intracellular matrix particles are necessary for normal growth. Variations in genetics however seem to play a major role in the variations of height in individuals (87, 88). It has been stated that the growth period during childhood and adolescence is the most important period for mineralization of the human skeleton and that a significant part of total body bone mass is accumulated during and by the end of adolescence (89, 90). At growth during adolescence, bone has a greater ability to adapt to mechanical stimuli than at maturity which might be a possible explanation for the larger effect of physical activity on bone among adolescents and children (91). The peak bone mass has been highlighted as a vital determinant of the lifetime risk of developing osteoporosis and is reached by the third decade (92). Maximizing the level

of bone mass during childhood and adolescence have shown to be associated with decreased risk of osteoporosis later in life and consequently, a disturbance in the bone formatting process during growth may increase risk for fractures both at adolescence and during adulthood (86, 90). Disturbances that can interfere with accumulation of bone mass are, for example, conditions such as osteogenesis imperfecta, osteomalacia, Paget disease, Ehler-Danlos syndrome, inflammatory bowel disease and malignancies among others (93). Glucocorticoids, despite being administered orally, inhaled or intraarticularly, have shown to be related to growth retardation in children, especially when the child is exposed for a long period (94-97). Glucocorticoids act on all bone cells but also on chondrocytes in the growth plates, they also reduce growth hormone and insulin-like growth factor 1 – both playing roles in growth regulation (98, 99). Further disturbances in the acquisition of bone mass during adolescence may be low rate of physical activity, dietary habits and intake of alcohol or cigarette smoke. Genetic factors do also affect the ability to maximize bone mass during growth (86).

The effect of physical activity on bone mass has been established in numerous studies. The mechanical stimuli on bone from physical activity has been shown to be important throughout life but especially during growth (100). It is mainly high-impact activities, such as running and jumping that has shown to stimulate bone growth and is recommended for children and adolescents to prevent osteoporosis and fractures later in life (101). A previous study on more than 2,000 males, previously athletes, showed that they had an overall reduced risk for sustaining fractures and in particularly frailty fractures compared to males who were not former athletes (102). The findings have been supported by other studies (103, 104).

Measuring bone

Bone density was not possible to measure in a noninvasive fashion until the 1970's when single photon absorptiometry (SPA) was introduced, making it possible to measure 2-dimensional areal bone mineral density (aBMD expressed as g/cm^2). However, this method was not optimal due to difficulties in distinguishing between osteoporotic patients and healthy individuals (105). To date, dual energy x-ray absorptiometry (DXA) is used to measure BMD and has several advantages including low radiation dose, short scan times, easy patient set-up, proven ability to assess fracture risk and provides reproducible data (106, 107). The disadvantages with DXA is that it only provides 2-dimensional measurements and cannot discriminate between cortical and trabecular bone, furthermore, DXA cannot evaluate mechanical abilities of bone (106, 107).

There is a consensus that BMD values should be interpreted using T-score or Z-score for the spine and hip in order to make an osteoporosis diagnosis. T-scores are calculated by taking the difference between the patient's BMD and the mean BMD in young and healthy adults (i.e. peak bone mass), matched for gender and ethnic group, and expressing the difference in relation to the young adult population's standard deviation (SD) (106, 108):

$$T - Score = \frac{Measured\ BMD\ -\ Young\ adult\ mean\ BMD}{Young\ adult\ population\ SD}$$

According to the World Health Organization, T-scores should be interpreted as following (109, 110):

- T-score of or over -1.0 is normal
- T-score over -2.5 but below -1.0 is defined as *ostepenia*
- T-score below -2.5 is defined as osteoporosis
- Established osteoporosis is considered when T-score is below -2.5 in conjunction with at least one frailty fracture

The Z-score is a value calculated from age- and sex matched SD scores. Recommendations from the International Society for Clinical Densitometry (ISCD) suggest the use of T-scores in menopausal women and men at age 50 years or older. For premenopausal females and males below 50 years of age, the Z-score is recommended for BMD reporting and this applies in particular to children. A Z-score of -2.0 or lower is defined as "below the expected range for age" and above the value is considered to be "within the expected range for age". An osteoporosis diagnose is therefore always preceded by a history of fractures and mainly vertebral types of fractures. Hence, an osteoporosis diagnose in children cannot be based solely on DXA scanning (111). For the pediatric population, usage of the term *osteopenia* is discouraged (111).

In order to evaluate cortical and trabecular bone separately, peripheral Quantitative Computed Tomography (pQCT) was introduced for the forearm in 1974 by Rüegsegger et al (112). Some years later, QCT for the spine was also introduced (113). In contrast to DXA, pQCT and QCT are three-dimensional multi-slice scanners that measure the true volumetric BMD in g/cm^3 of the skeleton, enabling possibility to separate cortical and trabecular bone, analyze separate compartments of bone, distinguish endosteal and periosteal circumference, as well as assess

biomechanical abilities of bone (114, 115). Despite the advantages of QCT, DXA became the gold standard monitor of BMD in the 1990's and this was due to better accuracy, lower dose of ionizing radiation, better availability, easier to operate and was associated with lower cost compared to QCT. This resulted in many studies on osteoporosis and BMD, providing DXA data on a large scale (114).

Bone health and idiopathic scoliosis

The role of bone health in idiopathic scoliosis has been studied and is considered to have a possible role in the pathogenesis of the condition. Data from China, mainly, has shown that low BMD is more frequent in idiopathic scoliosis patients compared to non-scoliotic individuals, persists throughout the growth period and is associated to curve severity (11, 13, 116-119). It has also been suggested that low BMD is a prognostic factor for the progression of the deformity (15, 120). A small study of 22 females with idiopathic scoliosis of American origin also showed low BMD that do persist throughout growth, and that this phenomenon seemed to be a trait for the condition (121). Data from Iran, based on 46 individuals with idiopathic scoliosis and 54 non-scoliotic individuals, on the same topic also confirmed that low BMD is more prevalent in those with idiopathic scoliosis (122). Despite the concurring findings of the above-mentioned studies regarding low BMD, and the persistence of it throughout growth, the rate of sustained fractures does not seem to differ between individuals with and without idiopathic scoliosis at adulthood (Paper IV).

1.9 SUMMARY OF PROBLEM AREAS

Previous research covering quality of life in individuals with idiopathic scoliosis has mainly focused on brace treated and surgically treated individuals. Furthermore, females and individuals with an adolescent onset have been most commonly targeted in studies. There is a lack of comprehensive data on males with idiopathic scoliosis, juvenile onset and untreated individuals. Furthermore, the level of physical activity and prevalence of fractures have not been elucidated in previous studies. Since bone health might play a role in the pathogenesis of the condition, based on literature mainly from China, it is important to provide data from different regions and populations.

2 AIMS

The overall aim of this thesis is to elucidate the wellbeing of individuals with idiopathic scoliosis in terms of quality of life, physical activity and bone health. The specific aims are:

- To describe quality of life in individuals with idiopathic scoliosis with regards to treatment
- To describe and compare quality of life in males and females with idiopathic scoliosis
- To establish reference, i.e. normative, values for the disease specific instrument Scoliosis Research Society (SRS) 22-revised questionnaire
- To map physical activity and self-assessed fracture rate in adulthood for individuals with idiopathic scoliosis
- To describe bone health in adolescents with idiopathic scoliosis

3 SUBJECTS AND METHODS

Details of the subjects and the inclusion process for each population can be found in the corresponding papers.

3.1 STUDY COHORTS AND DATA COLLECTION

ScoliGeneS, the Scoliosis and Genetics in Scandinavia project (Paper I, II and IV)

The project ScoliGeneS was initiated in 2004 at Skåne university hospital, Malmö, Sweden. The overall aim of the project was to study genetics, health and heredity in patients with idiopathic scoliosis. Criteria for being eligible in the project were:

Inclusion criteria

- Idiopathic scoliosis with an onset at youth
- Cobb angle equal to or larger than 10 degrees
- Untreated or treated with brace/surgery
- Standing posteroanterior radiograph of the spine before age 27 years

Exclusion criteria

- Non-idiopathic scoliosis, i.e. neuromuscular, syndromic or congenital nature
- Degenerative scoliosis
- Metabolic disorders (not including diabetes mellitus)
- Thoracic surgery at childhood
- Abnormal spine on MRI (if done)
- Mental retardation
- Juvenile rheumatoid arthritis
- Mb Scheuermann
- Abnormal neurological assessment on exam

After two years, in 2006, the study became a multi-centre study as it was extended to Sahlgrenska university hospital in Gothenburg and to Karolinska university hospital in Stockholm. The study extended further in 2009 through inclusion and collaboration with two more Swedish hospitals; the Sundsvall/Härnösand county hospital and Umeå university hospital. Finally, in 2012, a Danish site was included in the project – Denmark's Middlefart hospital. To date, the ScoliGeneS project is ongoing. Table 1 summarizes recruiting strategies for the Swedish patients in the project.

Table 1.

Strategy I	*Strategy II*	*Strategy III*
Using ICD codes to search for untreated or treated individuals with idiopathic scoliosis in outpatient and inpatient records. Contact by regular mail.	Recruitment during hospital visit of patients currently under observation or treatment.	Using the Gothenburg Scoliosis Database*. Subjects were contacted by regular mail.

* a prospectively collected sample of individuals with idiopathic scoliosis managed at the Sahlgrenska university hospital

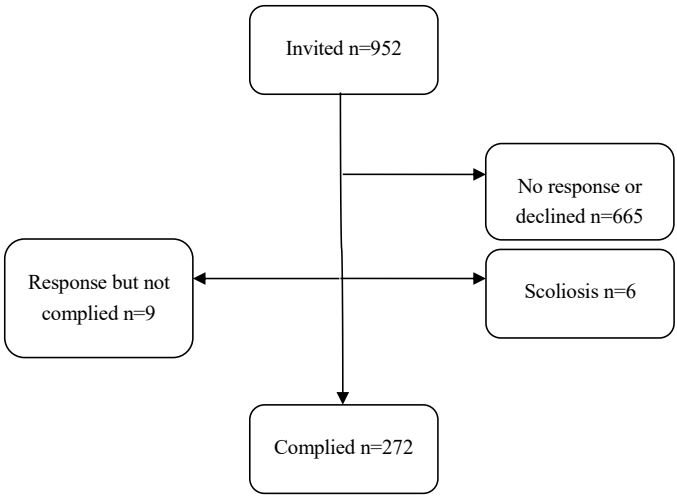
From 2004 and up to December 2013, 4,404 individuals had been invited to participate in the ScoliGeneS project and 1,885 individuals participated, including Danish patients. The Swedish participants were asked to answer a first survey on age at onset, family history of idiopathic scoliosis, back problems, smoking and occupational strain. A second survey based on the first one, but including the Spinal Appearance Questionnaire (SAQ), EQ-5D, SRS-22r and the International Physical Activity Questionnaire-short form (IPAQ-SF) were administered to the patients. Up to November 2017, 2,057 individuals had been invited to answer the second survey and this population constitute paper I, II and IV in the current thesis.

In paper IV, IPAQ-SF was answered by all individuals with and without idiopathic scoliosis.

Normative values (paper III)

Individuals aged 16 years or older were randomly invited from the Swedish population register by mail. The Stockholm county population register was used to contact individuals of ages below 16 years and their legal guardians. The controls were not clinically examined for scoliosis but had an item in the survey about the presence of scoliosis. On this basis, controls could be excluded due to scoliosis after confirmation was made by phone contact. Figure 5 illustrates the recruiting process of the controls. They all answered the disease-specific SRS-22r and the generic EQ-5D-3L.

Fig 5. Flow scheme illustrating the recruitment of controls in paper III.



Bone health in adolescents with and without idiopathic scoliosis (paper V)

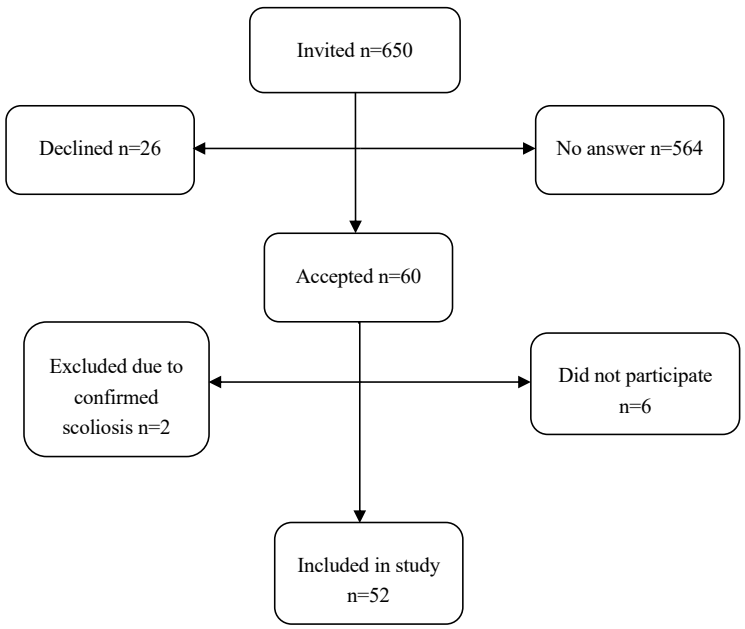
Adolescents with idiopathic scoliosis, not yet skeletal mature, observed or treated at the department of orthopaedics, Karolinska university hospital in Stockholm, Sweden, were invited to participate in the study between 2011 and 2018. Inclusion criteria were scoliosis of an idiopathic nature with a Cobb angle of or larger than 10 degrees. In all, 159 individuals with idiopathic scoliosis were invited and 78 of them participated.

Controls were invited through mail and were age- and sex matched. They were contacted and identified through the Stockholm County population register, from the outpatient clinic or local advertisement at the department of orthopaedics, Karolinska university hospital. The controls, and when aged under 15 years their legal guardian, signed an informed consent and underwent the same investigation as the individuals with idiopathic scoliosis. Figure 6 illustrates the recruiting process of the controls.

On acceptance, the individuals were scheduled to perform DXA (iDXA GE Healthcare) of the spine, hip and forearm. Bone mineral content (BMC) of total body less head (TBLH) was also obtained from DXA. Calibrations were made with a spine phantom and coefficient of variation (CV) was 1.4%. Peripheral quantitative computed tomography (pQCT) measurements were carried out using a Stratec XCT-2000 scanner (Stratec, Pforzheim, Germany) and analyzed using Stratec software version 5.5d or 5.40. Scans were made at sites that contain predominantly trabecular bone (4% sites) and cortical bone (66% and 38% sites in the radius

and tibia, respectively). The left tibia and radius were measured. The following parameters were determined at the selected bone sites: total volumetric bone mineral density (vBMD), trabecular vBMD, cortical vBMD, trabecular content, total cross-sectional area, cortical cross-sectional area, cortical thickness, endocortical circumference, and periosteal circumference. Quality assurance for pQCT was performed on a daily basis. The European Forearm Phantom (EFP) was used for calibrations and the CV was 0.27% for the phantom. Hand radiographs were performed on the left side and skeletal age was estimated according to Tanner-Whitehouse 3 (TW3) by experienced radiologists not involved in the current study.

Fig 6. Flow chart of the controls in paper V.



3.2 QUESTIONNAIRES

All individuals answered the disease specific SRS-22r and the generic EQ-5D-3L. The SRS questionnaire was initially constructed to increase insight on surgically treated patients' perception of their condition and has been modified throughout the years since it was presented. At its current form, it is labelled SRS-22r and consists of 22 items divided into 5 domains covering function, pain, self-image, mental health and satisfaction. An index score can be calculated for each domain and subsequently, a total index value is possible to calculate based on all domains. A subscore, the total score excluding the satisfaction domain, is used for untreated individuals. The domain- and index scores range from 1 (worst) to 5 (best) (123, 124).

The SRS-22r questionnaire has proven to be a valid and reliable instrument to use when studying idiopathic scoliosis patients and has been translated to other languages in several studies (125-128). Since idiopathic scoliosis patients function overall well in daily life, it can be argued for a possible ceiling effect in SRS-22r, but this has been shown not to be an issue for the questionnaire (124).

The 3-level version of EQ-5D (EQ-5D-3L) contains five dimensions covering mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For each dimension, one of three options is possible to pick and reflects how well the responder can manage each dimension (129, 130). An index value can be derived by using a tariff representing the societal perspective on health. For this thesis, both the UK (paper I-IV) and a recent Swedish (paper III) tariff have been used (130, 131).

IPAQ-SF is a questionnaire on physical activity where the responder is asked to estimate amount of activity he/she has been performing during the previous seven days at a vigorous, moderate and low intensity level. It also has an item on sedentary behavior and spare time activity level.

Items on family history, previous fractures, comorbidities, sporting activities, work strain, dietary habits and back problems were also answered by the participants.

3.3 STATISTICS AND DATA MANAGEMENT

All analyses were performed in SPSS version 22-24 (IBM Corp., Armonk, NY, USA).

In paper I, analysis of covariance was used to compare treatment groups with adjustments for age, sex, treatment and caudal extent of fusion. Stratifications on age, curve severity and

surgical characteristics were done. Visual estimations using box plot analyses were used to determine the impact of the number of fused vertebrae and caudal fusion on the SRS-22r.

In paper II, analysis of covariance was used for comparisons with adjustments for age and type of treatment. Comparisons of males and females in age groups and treatment groups were performed. Scores of the patients were compared to the reference values for males and females in Paper III.

In Paper III, stratifications for the normative cohort was done on age and gender. Analyses were performed with analysis of covariance with adjustments for age and sex. Spearman's test was used to assess correlation between EQ-5D and SRS-22r. A conversion of the SRS-22r subscore was also done to enable comparisons with data on SRS-22 subscore.

In paper IV, the primary outcome measure was if individuals achieved at least moderate activity level during the last 7 days or not. Furthermore, a logarithmical transformation of Metabolic Equivalent Task (MET) minutes/week was done to achieve normal distribution after visual estimation of skewness. Data was managed according to the IPAQ committees' guideline (132). The individuals with and without idiopathic scoliosis were also compared on self-reported fracture history and participation in current exercise or competitive sporting activities. Analysis of covariance was then used for comparisons with adjustments for age, sex and body mass index (BMI).

For the last paper, paper V, the Mann-Whitney U test was used for data that was not normally distributed and independent samples t-test for normally distributed data. This was done by visual estimation of histograms. The chi-square test was used for categorical data.

3.4 ETHICS

For all parts of this thesis, ethical approval has been obtained. Details are found in the separate papers.

4 RESULTS

4.1 PAPER I

The individuals with idiopathic scoliosis who were treated surgically had lower scores in the SRS-22r subscore, EQ-5D index and the domains function and self-image compared with the untreated and brace treated individuals (all $p \leq 0.026$, adjusted for age and sex), Table 1.

When comparing the SRS-22r satisfaction domain between brace treated and the surgically treated individuals, the latter had significantly higher scores, 3.45 vs 4.03 ($p<0.001$). Comparisons on age groups for all patients showed lower scores on SRS-22r self-image domain in those aged 46 years or older compared to their younger peers aged 26-45 years and those aged ≤ 25 years (3.76, 3.94 and 3.87 respectively, $p=0.003$ adjusted for treatment). The oldest group had on the other hand higher scores on SRS-22r mental health domain compared with those aged 26-45 years and those aged ≤ 25 years (4.02, 3.99 and 3.73 respectively, $p<0.001$ adjusted for treatment).

For the surgically treated individuals, fusion extending caudal to L2 was associated with lower scores on SRS-22r subscore (3.89 vs 4.07, $p=0.010$), SRS-22r function domain (4.21 vs 4.40, $p=0.017$), SRS-22r pain domain (3.88 vs 4.17, $p=0.006$) and EQ-5D index (0.74 vs 0.81, $p=0.020$). Number of fused vertebrae and amount of correction did not influence neither of the SRS-22r scores nor EQ-5D (all $p \geq 0.07$ with adjustments for caudal extent of fusion and preoperative Cobb angle). Age at onset, i.e. juvenile or adolescent onset did not influence SRS-22r subscore, the separate domains or EQ-5D (all $p \geq 0.35$).

Table 2. Comparisons in treatment groups concerning the SRS-22r subscore, SRS-22r domains and EQ-5D index. All analyses adjusted for age and sex. Data is presented as mean (SD).

	Untreated n=347	Brace treated n=459	Surgically treated n=381	P-value
SRS-22r, function	4.47 (0.64)	4.49 (0.61)	4.33 (0.75)	0.001
SRS-22r, pain	4.16 (0.76)	4.14 (0.78)	4.05 (0.89)	0.11
SRS-22r, self-image	3.97 (0.76)	3.83 (0.78)	3.79 (0.82)	0.002
SRS-22r, mental health	3.99 (0.71)	3.94 (0.72)	3.87 (0.76)	0.28
SRS-22r, subscore	4.15 (0.59)	4.10 (0.57)	4.01 (0.64)	0.007
EQ-5D index	0.82 (0.20)	0.82 (0.20)	0.79 (0.24)	0.026

4.2 PAPER II

The SRS-22r subscore and the SRS-22r domains function, pain, and mental health were higher in males compared with females (p=0.01, p=0.04, p=0.01, and p<0.001, respectively, adjusted for age and if treated or not). The SRS-22r self-image domain and the EQ-5D index did not differ (p=0.69 and p=0.10, respectively).

For the surgically treated individuals, males had higher scores on SRS-22r mental health domain (4.10 vs 3.85, p=0.001, adjusted for age and operation method). In the SRS-22r total score, the separate SRS-22r domains and EQ-5D index there were no differences between the surgically treated males and females (all $p \geq 0.06$). The same phenomenon was seen in brace treated individuals where males had higher scores on the SRS-22r mental health domain (4.24 vs 3.92, p=0.002, adjusted for age) compared with females while the other SRS-22r values and EQ-5D index were similar (all $p \geq 0.06$).

In the untreated group, there was a significant difference in the SRS-22r pain domain where the males had higher scores (4.27 vs 4.06, p=0.04) compared with females. In the SRS-22r subscore, the other SRS-22r domains and EQ-5D index there were no differences between the groups (all $p \geq 0.12$).

When comparing treated idiopathic scoliosis females to national norms, significantly lower scores were observed with reductions of between 0.22 and 0.71 for the SRS-22r scores. The treated male group showed similar results, with reductions of between 0.11 and 0.67 for the SRS-22r scores, except for the mental health, which was not reduced. For the untreated males and females, significant reduction of the pain and self-image scores were observed (between 0.31 and 0.56) in comparison with the national norms, resulting in significant reductions of the SRS-22r subscores. The females had a significant reduction in the function score as well.

4.3 PAPER III

There were generally small differences in the SRS-22r between sexes and age groups. The mean SRS-22r subscore was lowest in women aged 40-59 years with mean (CI 95%) 4.3 (4.1-4.5) and highest in males aged ≤ 19 years, 4.7 (4.6-4.8). Overall, males tended to have higher SRS-22r subscore than females in the youngest age group, but not in the other age groups.

For EQ-5D index, based on the UK tariff, lower scores were observed with higher age. Table 3 illustrates data for age groups and for males and females.

Spearman's correlation coefficient was 0.62 ($p < 0.001$) when assessing correlation between SRS-22r subscore and EQ-5D index (UK tariff) and 0.61 ($p < 0.001$) when assessing SRS-22r and EQ-5D index based on the Swedish tariff.

4.4 PAPER IV

No difference was seen between individuals with and without idiopathic scoliosis in terms of achieving at least moderate activity the last seven days (p=0.40). Neither was there a difference in MET-minutes/week between the groups (p=0.06). Furthermore, the level of activity in spare time and participation in current exercise or competitive sporting activities did not differ between both groups (p=0.26 and p=0.94 respectively). The individuals with idiopathic scoliosis reported more time in sedentary than the individuals without idiopathic scoliosis (360 vs 300 minutes/week, p=0.02). No differences were seen in sustained fractures (p=0.72).

Fewer surgically treated individuals achieved at least moderate activity compared to the untreated and brace treated individuals (p=0.046). They also participated to a lesser extent in exercise or competitive sporting activities (p=0.003) and performed less intense activities during spare time (p=0.036) compared to the brace treated and untreated individuals.

Physical activity parameters in this study were not different between individuals with an adolescent (n=976) or juvenile (n=169) onset (all $p \geq 0.05$).

4.5 PAPER V

Mean age was 13.7 years for the idiopathic scoliosis individuals and 13.8 years for the controls. In the scoliosis group there were 72% females and 75% were females in the control group. Significantly lower DXA values were observed in individuals with idiopathic scoliosis compared to those without: femoral neck (p=0.024), L1-L4 (p=0.014), L3-L4 (p=0.010) total hip (p=0.013) and radius at 4% (p=0.003), but not in the mid radius (p=0.20). BMC for TBLH was also similar between both groups (p=0.25).

For pQCT values it was only a significant difference in total vBMD at 4% in the radius (p=0.038) and lower trabecular value at this site (p=0.029) where the individuals with idiopathic scoliosis had lower values. No differences were seen in tibia values between the groups (all $p \geq 0.059$).

When comparing on curve severity in the idiopathic scoliosis group, those with larger curves had higher femoral neck BMD (0.98 vs 0.90 g/cm^2, p=0.027), but no differences were

observed on DXA in other sites (all $p \geq 0.08$). For the pQCT values, no differences were seen in radius and tibia (all $p \geq 0.07$).

Table 3. Mean (CI 95%) SRS-22r subscore index and EQ-5D index for all age groups, including men and women.

	Age ≤19 (n=61)	Age 20-39 (n=66)	Age 40-59 (n=84)	Age ≥60 (n=61)
SRS-22r subscore index - all	4.7 (4.6-4.8)	4.5 (4.4-4.6)	4.4 (4.2-4.5)	4.5 (4.3-4.6)
SRS-22r subscore index- women	4.6 (4.5-4.7)	4.5 (4.4-4.6)	4.3 (4.1-4.5)	4.4 (4.2-4.6)
SRS-22r subscore index - men	4.7 (4.6-4.8)	4.5 (4.3-4.6)	4.4 (4.3-4.6)	4.5 (4.3-4.6)
EQ-5D index – all – UK tariff	0.93 (0.89-0.97)	0.90 (0.86-0.93)	0.87 (0.83-0.91)	0.87 (0.84-0.91)
EQ-5D index – women – UK tariff	0.91 (0.85-0.97)	0.91 (0.87-0.94)	0.86 (0.80-0.91)	0.84 (0.78-0.90)
EQ-5D index – men – UK tariff	0.97 (0.93-1.0)	0.88 (0.81-0.96)	0.89 (0.83-0.95)	0.90 (0.86-0.94)
EQ-5D index – all – Swedish tariff	0.95 (0.93-0.96)	0.94 (0.92-0.95)	0.93 (0.91-0.94)	0.93 (0.91-0.94)
EQ-5D index – women – Swedish tariff	0.94 (0.92-0.96)	0.94 (0.93-0.96)	0.92 (0.89-0.94)	0.92 (0.89-0.94)
EQ-5D index – men – Swedish tariff	0.96 (0.94-0.97)	0.93 (0.90-0.96)	0.94 (0.92-0.96)	0.94 (0.92-0.96)

5 DISCUSSION AND CONCLUSION

5.1 QUALITY OF LIFE IN IDIOPATHIC SCOLIOSIS

Treatment

In the first study, consisting of 1187 individuals with idiopathic scoliosis, there were slightly lower values on quality of life outcomes for the surgically treated individuals compared to brace treated and untreated individuals. The differences in the SRS-22r outcomes did not reach previously established thresholds for what can be considered as clinically relevant (133, 134). Our results, based on a large cohort, are concordant with previous studies showing overall similar quality of life in treated and untreated individuals, and in brace treated and surgically treated individuals (46, 68, 135). The most prevalent difference was seen between brace treated and surgically treated individuals on satisfaction with treatment. Despite having overall lower scores on both SRS-22r and EQ-5D, the surgically treated individuals were still significantly more content with their treatment compared to the brace treated individuals. This finding is in line with previous reports (68, 136). In a previous study, it was also shown that quality of life improves at short-term for those treated surgically (137). Based on our data and previous reports, we can conclude that treatment for idiopathic scoliosis with bracing and surgery is not associated with significant impairments in quality of life.

In the surgically treated individuals, we found that a caudal extent of fusion in the lumbar spine was associated with lower values on quality of life outcomes. Previous studies have been inconsistent on this matter (75-78, 138-140). The more recent studies not reporting correlation between the distal fused level and quality of life are based on adolescents and hence only short-term outcomes (77, 78). Sanchez-Raya et al report findings similar to ours on long-term, based on a small sample (n=41) (76). Previous studies not showing correlation between distal level of fusion and quality of life in long-term are based on individuals only operated with Harrington instrumentation and did not use SRS-22r outcomes (138-140). The number of fused vertebrae was not related to quality of life outcomes in this study, which a previous study is consistent with (138).

Onset and age groups

Onset of idiopathic scoliosis, i.e. juvenile or adolescent onset, did not influence quality of life outcomes. Previous reports have shown similar results in terms of back problems and quality of life (31, 70). When comparing individuals in separate age groups, there were only small differences in some of the SRS-22r domains.

Gender

Paper II is the first large and comprehensive study comparing males and females with idiopathic scoliosis, showing slightly better values for males compared with females not reaching previously established thresholds for minimal clinical important difference (133, 134). The findings of this study are in line with previous reports on gender differences in the general population (141).

When comparing untreated, brace treated and surgically treated males to females, there are numerical differences favoring the males however not reaching statistical significance in most of the quality of life outcomes. Previous studies have also shown overall similar outcomes. One small study of 6 males and 43 females surgically treated for idiopathic scoliosis showed higher mental health outcomes in the males (142), while another study reported better preoperative self-image, less postoperative pain and better mental health in males (n=123) compared with females (n=621) but with similar benefits of surgery (143).

We compared males and females to national norms (data from paper III) and found that both treated and untreated males and females scored significantly lower than the general population. There was a significant reduction of self-image and pain outcomes, suggesting possible perceived issues also in smaller curves. Idiopathic scoliosis is however not the only type of spinal disorder resulting in negative self-image in adulthood. A previous study on adults previously treated with fusion in situ for high-grade spondylolisthesis showed markedly decreased self-image scores on SRS-22r compared to healthy controls (144).

Health related quality of life is similar between males and females with idiopathic scoliosis with slightly higher values for males. In treatment subgroups, differences are small between males and females. Compared to the general populations, reductions for both treated and untreated males and females were observed. Based on the results from this study, management of idiopathic scoliosis should not differ for males and females.

Normative values

In paper III, based on Swedish adolescents and adults, we present reference values for the SRS-22r and EQ-5D. Variations in age and sex were small. There was a moderate to good correlation between both questionnaires. We used a conversion algorithm for conversion of our SRS-22r data to SRS-22 previously published by Lai et al (145), to enhance comparisons with previous studies.

Normative data have been published previously for SRS-22 based on American adults (146) and American adolescents (147, 148). The values from the previous studies were lower compared to the values in the current paper which might be explained with discrepancies in sample size and sampling procedures. The paper by Berven et al only consisted of 34 individuals (146) whilst the other papers were performed in schools with anonymous questionnaires (147, 148). The sample in the current study consisted of adolescents and adults from different regions in Sweden, the youngest individuals were however based in Stockholm County.

Small age and sex related variations for the SRS-22r and EQ-5D were observed in this study. Those aged 40-59 years reported marginally lower scores than those in the oldest age group. Similar observations have been described for the EQ-5D, and especially for the anxiety domain which had a modest correlation to the SRS-22r mental health domain in the current study (149). This study provides, for the first time, normative data for SRS-22r based on Swedish adults and adolescents, including both males and females. Due to differences in scores compared to previous published data, there is a need for region-specific values to get valid references when comparing to scoliosis patients.

5.2 PHYSICAL ACTIVITY AND BONE HEALTH IN IDIOPATHIC SCOLIOSIS

The results in paper IV for the first time elaborates physical activity levels in idiopathic scoliosis comprehensively, many years after management and treatment. Data from this study did not show any differences in self-reported physical activity levels between adults with idiopathic scoliosis and controls. This is in line with a previous study with similar methodology, however on adolescents with idiopathic scoliosis, which did not show any difference in physical activity level between patients (n=239) and controls (n=58) (83). Another previous study by Parsch et al compared adults with idiopathic scoliosis (n=59) at a mean of 22 years after treatment with an age-adjusted control cohort (n=33) on sporting activities and found that the scoliosis patients were to a higher extent restricted in sporting activities due to impairment and back pain (82). The current study differs quite a lot from the study by Parsch et al in methodology; the sample size is much larger in the current study, comprised both sporting activities and general physical activity, used a different questionnaire and comprised untreated individuals with idiopathic scoliosis.

Self-reported fracture history did not differ between individuals with idiopathic scoliosis and controls. This can be, to some extent, unexpected due to many previous reports showing lower

bone mass in idiopathic scoliosis patients compared to non-scoliotic individuals (11, 13, 116, 150-152). An explanation might be that the median age of the current study's scoliosis cohort was 42.5 years, and since the largest part of fractures are seen after 50 years of age, this study cannot draw any valid conclusions regarding fractures in older ages (153).

Comparing scoliosis subgroups, it was observed that surgically treated individuals had a bit lower level of physical activity compared to previously brace treated and untreated individuals. A previous study on 28 non-operated and 31 operated individuals with idiopathic scoliosis did not show difference in sporting activities, at a mean of 22 years after treatment (82). Furthermore, onset of idiopathic scoliosis did not influence level of physical activity in the current study. Surgically treated individuals who had a fusion extending caudal to L2 participated less in exercise or competitive sporting activities compared to those with fusion to L2 as most caudal vertebra. This is in contrast with a previous study on 31 operated individuals where caudal extent of fusion did not influence sporting activities in adulthood (82). Others have on the other hand reported significantly decreased spinal motion when fusion is extended to the lower lumbar spine (154-156).

Physical activity does not appear to be different in adulthood between individuals with idiopathic scoliosis and controls. Surgical intervention for the trait is associated with slightly lower activity level compared with brace treated and untreated individuals. The onset of idiopathic scoliosis does not influence activity level.

In paper V, bone health in European adolescents with idiopathic scoliosis was compared with an age- and sex matched cohort of non-scoliotic adolescents. Data showed lower BMD in central skeletal sites in idiopathic scoliosis individuals compared to controls based on DXA, such as hip and spine, but similar BMD value in pQCT for tibia and radius except for ultradistal radius. Previous studies, mainly from China but also smaller cohorts from Iran and America, have shown that idiopathic scoliosis patients are more frequently suffering from low BMD than healthy controls do (11, 13, 121, 122).

The findings in DXA of the current study are in line with previously published data, but there is a discrepancy in pQCT where no differences were found between individuals with idiopathic scoliosis compared to controls, except for the ultradistal radius. There have been overall concurring findings in the previous studies mainly originating from China on pQCT data. Discrepancies, as compared to the current study, may be due to differences in nutrition or genetics, indicating a need for further research on possible ethnic variance. Low BMD has

shown to be related to curve severity and a prognostic factor for progression (15, 120, 150). Curve severity was not associated with low BMD in the current study.

The current study comprised both males and females in the scoliosis population. An interesting finding was that differences between scoliosis individuals and controls vanished when comparing only females. This might be caused by issues in power, but gender differences should be considered in future studies on bone health and idiopathic scoliosis.

We used both the lumbar spine, radius and the hip as sites for measuring BMD with DXA. Previous studies have reported that axial rotation in the lumbar spine might negatively affect DXA and may therefore not be reliable as source for BMD estimation in scoliosis patients (157, 158). A decrease up to 20% in BMD has been estimated in rotations up to 50-60 degrees. The current study did comprise mainly thoracic curves and we also verified the difference by comparing the mean of L3-L4, considered to be least rotated, in both groups which still showed significant differences. Another study showed that it is degenerative changes in the spine (osteophytes, osteochondrosis and vascular calcification), and not scoliosis, that mainly affects DXA outcomes (159). The findings of paper V suggest lower BMD in adolescents with idiopathic scoliosis compared to controls, which seemed to be most apparent at central skeletal sites.

5.3 GENERAL REMARKS AND LIMITATIONS

This thesis provides data on previously underrepresented idiopathic scoliosis subgroups such as males, juvenile idiopathic scoliosis patients and untreated individuals in terms of quality of life and physical activity. The thesis also establishes reference values for the SRS-22r based on both adolescents and adults. It provides data on bone health based on European individuals with idiopathic scoliosis, previously not studied. The outcomes were measured with instruments commonly used in previous studies internationally.

Strength and limitations paper I, II and IV

Limitations of the studies do however exist. All of the studies had a cross-sectional design, limiting possibilities to draw conclusions on causality and monitor prospective changes. The ScoliGeneS project has been ongoing with data gathered continuously. This has resulted in discrepancies in the study populations for every paper that is based on patients from ScoliGeneS, since previously missing data could be obtained at a later stage, giving variability in sample size for the different papers (paper I, II and IV). The large samples in paper I, II and IV, including subgroups not often targeted in studies, is a strength. Furthermore, usage of valid

and reliable instruments further strengthens the results of these studies. The questionnaire used in paper IV, the IPAQ-SF, has been validated in several populations and is suggested to be a good tool for surveillance of physical activity but has shown limitations in terms of easily overestimation of physical activity and lack of accounting for specific types of physical activity (160-162).

Further limitations of the studies are that age at diagnosis was mainly self-assessed and the lack of radiographs in conjunction with the survey. This makes comparisons on radiograph data limited. In paper IV, sustained fractures were self-assessed and not objectively verified. There is a probability that this underestimates the true fracture rate compared to the addition of radiological data (153).

Strength and limitations paper III

Normative data for Swedish adults and adolescents of both genders was presented for the disease-specific SRS-22r. The instrument was compared and correlated to the generic EQ-5D, showing moderate to good correlation between the instruments. Based on ours and previous findings, it is advised to use both generic and disease-specific outcomes to assess quality of life (163, 164).

The low response rate in adolescents was a major limitation in this study and might affect external validity. It has however been shown in a previous study that representativeness might not be necessary other than that the controls should not have the studied trait (165). The EQ-5D-Y, specifically and targeted for children and adolescents, was not used in this study (166). The youngest individuals answered EQ-5D to enhance comparisons to adults, as suggested by others (163). Another limitation might be the sample size, larger samples would be desirable to further delineate age and sex differences.

Strength and limitations paper V

We had an age- and sex matched control group, enhancing comparisons to our idiopathic scoliosis group. Both pQCT and DXA were used, performed and assessed by experienced personnel not involved in the current study.

The cross-sectional design of the study limits the possibility to monitor possible persistence of low BMD in our population. The participation rate in the control population was low and might affect external validity. The controls were nevertheless a non-scoliotic population, controlled with DXA which is considered a reliable method in excluding scoliosis (167).

5.4 FUTURE IMPLICATIONS

This thesis has shown that treated individuals with idiopathic scoliosis have comparable outcomes in terms of quality of life and physical activity compared with untreated individuals, with slightly lower scores for surgically treated individuals. This warrants a possible need for a comprehensive mapping and deeper analysis of the postoperative phase and function outcomes. There may also be a possible need for standardizing aftercare in general with regards to improvements in function, rehabilitation and follow-ups.

There seems to be a consistency in the literature that brace treated individuals are more dissatisfied with their treatment compared to surgically treated individuals. The brace treated individuals could therefore also benefit from closer monitoring both during brace treatment and after cessation in terms of postural retraining and perception of the own body with an empowering strategy from healthcare professionals since idiopathic scoliosis affects growing adolescents and children often during a vulnerable stage in life.

Compared with national norms, both males and females with idiopathic scoliosis in this thesis have markedly lower quality of life scores especially in terms of pain and self-image. Future investigations of the effectiveness of self-image and pain modulating interventions in patients displaying these impairments are motivated to potentially improve health related quality of life to normative levels.

Furthermore, this thesis implicates future studies on bone health with a prospective approach in idiopathic scoliosis patients from different regions to monitor changes in bone health and, ideally, have follow-ups up to adulthood with monitoring of fracture incidence.

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