Aspects of generalised joint hypermobility on pelvic girdle pain and physical disability during and after pregnancy

KERSTIN AHLQVIST
Pelvic girdle pain is common during pregnancy, but its multifactorial mechanisms are not completely understood. Generalised joint hypermobility is associated with musculoskeletal pain due to fragile connective tissue. The increased laxity of ligaments during pregnancy may be related to pelvic girdle pain. Women with fragile connective tissue may be more prone to developing pain during pregnancy. The overall aim was to examine whether generalised joint hypermobility increases the likelihood of experiencing pelvic girdle pain and physical disability during and after pregnancy. In Study I, the inter- and intra-rater reliability of joint mobility measurements in 49 adults were investigated, evaluating 12 joints. Study II explored the association between self-reported generalised joint hypermobility and pelvic girdle pain during pregnancy involving 2,217 women. In study III, the association between clinically assessed generalised joint hypermobility and pelvic girdle pain during and after pregnancy were examined, involving 356 women. Study IV focused on the development of physical disability from early pregnancy to nine months postpartum considering pelvic girdle pain, generalised joint hypermobility and overweight, and whether the onset of pelvic girdle pain and the level of physical disability during pregnancy was associated with physical disability nine months postpartum. The findings in this thesis indicated good-to-excellent inter- and intra-rater reliability in most mobility measurements. Women who self-reported generalised joint hypermobility exhibited higher odds of experiencing pelvic-girdle pain, particularly in early pregnancy. Clinically assessed generalised joint hypermobility was associated with increased pain intensity in early pregnancy and, when combined with overweight, an increased risk of pelvic girdle pain. Physical disability increased during pregnancy irrespective of pelvic girdle pain status, but the overall prognosis was positive. Pelvic girdle pain had the strongest influence on disability, in contrast to generalized joint hypermobility and overweight. Early-onset pelvic girdle pain during pregnancy and a higher disability index during pregnancy were associated with physical disability nine months postpartum. Women experiencing pelvic girdle pain early in pregnancy may benefit from evaluation for generalised joint hypermobility, as they may experience more intense pain. It is crucial to develop methods for preventing and managing pelvic girdle pain, given its strong association with physical disability during and after pregnancy. Early-onset pelvic girdle pain and a higher disability index during pregnancy were predictors of physical disability nine months postpartum.

Keywords: Beighton score, Contompasis score, Disability Rating Index, Pelvic girdle pain, Generalised joint hypermobility, Reliability, Hospital del Mar criteria, Goniometer, Overweight, Physical Disability, Pregnancy, Range of motion

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To my Family
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


IV. Ahlqvist K., Bjelland EK., Pingel R., Schlager A., Peterson M., Olsson CB., Nilsson-Wikmar L., Kristiansson P. Development of physical disability from early pregnancy to nine months postpartum – the impact of pelvic girdle pain, generalized joint hypermobility and overweight. *In manuscript*
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As a physiotherapist in primary care for over 30 years, I have met many women seeking help for varying degrees of pregnancy-related low back- and pelvic girdle pain. These women wish to reduce their pain to be able to cope with daily activities, sleep better and enjoy their pregnancy or postpartum period. Some women also seek help for pronounced long-term problems that started during pregnancy several years prior. They have met many health care providers without satisfactory results. They are often disappointed and frustrated that they have not received appropriate help, and that their problems have not been taken seriously upon. As a healthcare provider, I have often felt the need to identify early in pregnancy those women who are at an increased risk of developing pelvic girdle pain. Additionally, it is vital for us to learn more about this condition to be able to offer more effective, evidence-based treatments.

Another patient group that I have often encountered in primary care comprises women seeking treatment for pain and functional limitations due to joint hypermobility in one or more joints. Some of these women have experienced problems during their pregnancy, while others worry that their joint hypermobility-induced pain will be exacerbated during pregnancy. This made me wonder if there might be a connection between generalised joint hypermobility and pelvic girdle pain during and after pregnancy. There is, of course, no single cause that can account for the wide range of factors associated with pregnancy-related pelvic girdle pain; rather, it is a mixture of biopsychosocial factors. Since the understanding of pain is complex, it cannot be fully addressed within a thesis. Therefore, this thesis adopts a biomedical perspective, focusing on the impact of generalised joint hypermobility on pelvic girdle pain and physical disability during and after pregnancy.
Introduction

Definition and diagnosis
There is no gold standard for the diagnosis of pelvic girdle pain, but the European Guidelines for the diagnosis and treatment of pelvic girdle pain suggested a definition for musculoskeletal pelvic pain. They added the term “girdle” to pelvic pain to differentiate it from gynaecological and/or urological issues (1).

Pelvic girdle pain generally arises in relation to pregnancy, trauma or arthritis and osteoarthritis. Pain is experienced between the posterior iliac crest and the gluteal fold, particularly in the vicinity of the sacroiliac joints. The pain may radiate in the posterior thigh and can also occur in conjunction with/or separately in the symphysis. The endurance capacity for standing, walking and sitting is diminished. The diagnosis of pelvic girdle pain can be reached after exclusion of lumbar causes. The pain or functional disturbances in relation to pelvic girdle pain must be reproducible by specific clinical tests.

It is recommended that diagnosis should be confirmed through specific clinical tests to distinguish it from low back pain (1, 2). In this thesis, pelvic girdle pain is defined as pain felt between the posterior iliac crest and the gluteal fold, particularly in the vicinity of the sacroiliac joints and/or in conjunction with the symphysis. In Studies III and IV, the diagnosis will be verified with clinical tests.

Prevalence of pregnancy-related pelvic girdle pain
Pregnancy-related pelvic girdle pain is not a modern phenomenon. Symphysis pubis dysfunction in relation to pregnancy was mentioned by Hippocrates (c.400 BC) (3). The first prevalence studies were reported in the 20th century, conducted mainly in the Scandinavian countries and the USA (3). Pelvic girdle pain was perhaps, therefore, initially suggested as a Western phenomenon, most commonly seen in Scandinavia. Today, pelvic girdle pain is considered a condition during pregnancy (4-7), with reported prevalence rates ranging from 4% to 86% (1, 5, 6, 8). This wide variability may be attributed to differences in study design, whether data was self-reported or clinically assessed, and in the latter, which specific clinical tests were used for diagnosis. The
severity of pain may also be of importance, as the prevalence decreased by approximately 20% when excluding mild complaints (9).

Although it has been established that pelvic girdle pain is a specific form of low back pain (1, 10, 11), which can occur separately or in conjunction with low back pain, many studies make no distinction between them. In general, studies that include both low back pain and pelvic girdle pain in their outcome variable tend to report higher prevalence rates compared to those that only include pelvic girdle pain. In Sweden, the prevalence of pelvic girdle pain varies between 42% and 82% when low back pain is included (4, 5, 12-20). The reported cumulative incidence for this group in Sweden was 49% (15). The European Guidelines report a point prevalence of about 20% for pelvic girdle pain during pregnancy, with similar estimates from the National Institute for Health and Care Excellence guidelines (UK) (1, 21).

The lack of a clear definition for pregnancy-related pelvic girdle pain, as well as the diverse terminology used to describe symptoms from the pelvic area, may contribute to the wide range of prevalence figures (22). Symptoms in this area have, in addition to being labelled pelvic girdle pain, also been referred to as for example, back pain (12), pelvic joint pain, pelvic girdle syndrome, symphysisiolysis, sacroiliac syndrome (23), low back pain (15), lumbar pelvic pain (16), symptom-giving pelvic girdle relaxation (24) and pelvic instability (25). In addition, differences in study design also contribute to the wide range of prevalence rates (1). Was the study retrospective, prospective or cross-sectional? At which stage of pregnancy was the pelvic girdle pain measured? These differences can jeopardise the interpretation of research results and make comparisons between studies difficult.

Anatomy and biomechanics of the pelvis

The pelvic girdle comprises the sacrum and the iliac bones, joined posteriorly by the left and right sacroiliac joints and anteriorly by the pubic symphysis (26) (Figure 1). In the female pelvis, the sacrum is wider, more uneven, less curved and more backward tilted compared to the male sacrum. The sacroiliac joints are the largest axial joints in the human body (27). These highly specialised synovial joints, based on its specific architecture with irregular surfaces and a well-developed fibrous apparatus, limit mobility to provide stability (28). The pubic symphysis consists of a fibrocartilaginous disc, sandwiched between the articular surfaces of the pubic bones, reinforced by ligaments. It withstands tensile, shearing and compressive forces, allowing only a very limited range of movement (29).

The mobility of the sacroiliac joints has been much debated. It is concluded that small movements are present, on average 2° in all three planes of the joints (28, 30), both in symptomatic and asymptomatic individuals (31). Specifically, in flexion-extension, there is about 3° of movement; axial rotation, about
1.6°; and lateral bending, about 0.9°. Overall, female sacroiliac joints exhibit greater mobility, especially under increased stresses/loads and pelvis ligament strains, compared to males (27).

Optimal pelvic stability is a function of the structural ‘self-locking mechanisms’, the form (joint anatomy) and force closure (compressive forces) of the sacroiliac joints (32), and neuromotor control (33, 34). How the passive and active musculoskeletal structures interact and cooperate is not fully understood (35). Static and dynamic stability throughout the body requires optimal functioning and cooperation of passive (bones, joint capsule, discs and ligaments), active (muscles and tendons) and the neural control subsystems (34). The sacroiliac joints play an important part in effectively transferring load between the spine and legs during weight-bearing. The function of the pelvis is vital for locomotion, childbirth and supporting the abdominal viscera. Pelvic joints are functionally interrelated with muscular, fascial and strong ligamentous interconnections to provide dynamic stability. Muscles of the abdomen, pelvis and lower extremities attach to the bony structures of the pelvic girdle (28), where back- and hip extensors (36, 37), together with abdominal muscles (38), contribute as important compressive forces (32).

Figure 1. Simplified image of the pelvic joints. Illustrated by © Kari C. Toverud. All rights reserved
Aetiology and pathogenesis of pelvic girdle pain

The aetiology and pathogenesis of pregnancy-related pelvic girdle pain are not fully understood (39). Growing evidence suggests that the causes are multifactorial and complex (1, 40). Factors related to hormonal, biomechanical and physiological changes, which are considered normal during pregnancy, have been suggested as causal factors (41-44). Excessive loading of the pelvic ligaments may be caused by hormonal changes, muscle weakness, increased sensitivity due to previous overloading of ligaments, and increased weight gain during pregnancy (45). Pelvic girdle pain typically debuts during the first half of pregnancy, between gestational weeks 12 and 24 in most women (45), with peak pain intensity usually reported between gestational weeks 24 and 36 (9, 40). Several risk factors have been reported, among them a history of low back pain, previous trauma to the pelvis, pelvic girdle pain in previous pregnancies, strenuous work, multiparity, smoking, high body mass index, low educational level, early menarche, emotional distress, and low physical activity level before pregnancy (1, 8, 15, 46-51).

Pregnancy affects all body systems (1, 52), including the musculoskeletal system (43). Biomechanical explanatory factors that explain pelvic girdle pain are related to hormone-related increased joint mobility and changes in posture due to increased loading. As the uterus grows, weight gain shifts the centre of gravity anteriorly, leading to increased mechanical strain and excessive loading of the lower back and pelvic ligaments (53, 54). Altered biomechanics and the transmission of forces from the spine have been stated as common causes of pelvic girdle pain (55), where altered biomechanical loading and kinematics due to joint hypermobility can overload these joints (56). However, pregnancy-related pelvic girdle pain debuts during the first half of pregnancy, before the mechanical strain is noticeable, and typically resolves shortly after childbirth. This indicates that pregnancy-related factors may also affect structures in the pelvic area (12).

Hormonal regulation and pelvic girdle pain during pregnancy

Hormonal regulation during pregnancy, with the primary function of maintaining pregnancy and initiating delivery, is complex (1, 57). The level of the polypeptide hormone relaxin increases rapidly during the first weeks of pregnancy, peaking in gestational weeks 12–14, followed by a 50% gradual decrease which remains constant during the latter part of pregnancy (42, 58). The concentrations of oestrogen and progesterone increase gradually during pregnancy, with fluctuations in the latter (59). The hormonal impact on the connective tissue is not fully understood. Since ligaments, tendons and bones
contain receptors responsive to female sex hormones (60, 61), it has been suggested that the actions of female sex hormones affect the remodelling of soft tissues during pregnancy (62, 63), and may alter collagen protein synthetic response. This can impact the laxity of ligaments in the pelvic girdle and in the rest of the body (1), and may cause tissue alterations with increased pelvic motions (64) and thus constituting a possible cause of pelvic girdle pain (41, 42). The theory that pelvic girdle pain may be due to pelvic instability has been highlighted in several studies (1, 64). Changes in connective tissue during pregnancy may be of importance, as decreased collagen turnover in early pregnancy has been associated with the development of pelvic girdle pain (65).

However, the evidence regarding an association between relaxin, increased range of motion in the pelvic joints and pain is inconclusive (31, 35, 66, 67). Studies have reported associations between serum relaxin concentrations and pelvic girdle pain during and after pregnancy (41, 42), as well as no association (68). One study found no difference in mobility between symptomatic sacroiliac joints compared to asymptomatic joints (31). This was consistent with another study, which found an association between asymmetric mobility in the sacroiliac joints and pelvic pain during pregnancy (69) and postpartum (70).

A systematic review highlighted that pelvic joint mobility was greater in women with pelvic girdle pain in late pregnancy and within three weeks after childbirth compared to healthy controls (64). However, the large overlap in the range of symphyseal motion between the groups made it difficult to draw definitive conclusions regarding a possible relationship.

It has also been suggested that biopsychosocial factors are involved, as some women experience pelvic girdle pain very early in pregnancy when the mechanical load is negligible, and some women are more limited in their daily activities compared to others (3, 71). Women with pelvic girdle pain are more likely to have negative thoughts and fear-avoidance beliefs (72) compared to pain-free women.

Pregnancy-induced changes in the pelvic girdle

Hormonal influence and mechanical stress lead to changes in the pelvic girdle joints during pregnancy and delivery, where the relaxation of these joints is considered a normal physiological process before delivery (29, 43, 73). The width of the pubic symphysis is increased in parous women compared to nulliparous women, approximately 4–6 mm in non-pregnant women (74) and 3–11 mm postpartum (74, 75). The increased width of the pubic symphysis improves the dynamic ability of the birth canal (29, 74, 76). The widening of the pelvic joints starts around gestational weeks 10–12 (77), and the symphysis width increases steadily during pregnancy (29), returning to normal within one
to three months postpartum (74). There is no linear association between increased motions in pelvic joints and pelvic girdle pain, but symptoms are more likely with a symphysis width of $\geq 10 \text{ mm}$ (29, 78).

Ligaments are dense bands of connective tissue that connect bones across joints. Connective tissue provides support and is the most abundant tissue in the body. It can be found in cartilage, bone, ligaments, tendons, muscles, joint capsules, skin, internal organs, blood vessels and blood (79, 80). Connective tissue contains four types of macromolecules: collagen, elastin, glycoproteins and glycosaminoglycans. Collagens are the major component of the extracellular matrix and form the fibres that provide structure and strength to the connective tissues (79, 81). The effect of pregnancy on ligaments, in general, and in the pelvis, specifically, is demonstrated by hypertrophy and hyperaemia of ligaments, bone resorptions at ligament insertions with increased width of symphysis pubis and increased joint mobility (76, 82, 83). These changes may make the pelvic joint more flexible but could also affect its responses to mechanical loads (84). These modifications in the pelvic joints have been suggested as one of the causes of pelvic girdle pain (85, 86).

The increased ligament laxity and slightly larger range of movement in the pelvic joints during pregnancy must be compensated for by altered neuromotor control to counteract potential pelvic girdle pain (1, 87). With effective neuromuscular control, stability can be maintained with the minimum possible reaction force tailored to the current situation (1). An association between muscular dysfunctions and pelvic girdle pain during and after pregnancy has been demonstrated (44, 88, 89). However, the level of evidence for this association was found to be moderate, mainly due to selection bias (90). In addition to an increased width of the symphysis pubis, structural changes such as gas and bleeding in the pelvic joints, hyaline cartilage tears and bruises in the pubic bones have been seen in postpartum women (75).

Pregnancy-induced changes in joints other than the pelvic girdle joints

Pregnancy also affects the connective tissue in the body in general (91), with reported peaks of joint mobility in the second trimester of pregnancy (84). Increases in peripheral joint mobility during pregnancy have been reported, but the increases in range of motion were small (82, 85, 86, 92). One study reported increased mobility in the metacarpophalangeal joint of the index finger in late pregnancy compared to 15 weeks after childbirth (82). The largest increases were seen in women with previous pregnancies, with an average mean increase difference of $5^\circ$, which was confirmed in a later study (84).

Increased mobility in knees (93), mandibular joints (94) and wrists (91) during pregnancy has also been reported. However, increased concentrations
of female hormone during pregnancy did not correlate with increased peripheral joint mobility (91, 92). The tendon collagen fractional synthesis rate is lower in women than in men, but it was not affected by the menstrual phase, during which concentrations of female hormones changed (95).

The association between peripheral joint mobility and pregnancy-related low back pain

Two studies examined the association between peripheral joint mobility and pregnancy-related low back pain using passive abduction (ulnar deviation) of the left fourth finger (85, 86). The first study showed an increased abduction of the finger, on average about 2°, from early pregnancy to 13 weeks postpartum, but with a wide dispersion of the angle. Women with low back pain in late pregnancy and postpartum exhibited an increased range of motion, and a larger proportion of them had previous pregnancies compared to pain free women (85). In the other study, women who had previously given birth had, on average, 2° higher range of motion in early pregnancy compared to first-time mothers, but their mobility did not increase during pregnancy. In first-time mothers, the range of motion increased by an average of about 2° during pregnancy, but the peripheral joint mobility was lower among women with low back pain (86). Finger joint laxity during pregnancy has been highlighted as a proxy of general joint laxity, reflecting a constitutional weakness of connective tissue (85). This was supported by the fact that the majority of the stiffness of the metacarpophalangeal joints of the hand results from the capsule ligament complex and not the muscle-tendon units (96).

Generalised joint hypermobility

Joint hypermobility was first mentioned by Hippocrates in the 4th Century BC, where unstable elbows were described as ‘flabby and atonic’ (97). The clinical significance of the hypermobile joint was recognised towards the end of the 19th century (98). The phenomenon of large articular laxity that might have an impact on a variety of symptoms was first described in 1967 by Kirk and colleagues (99), followed by revised diagnostic criteria (100). Today, joint hypermobility is often described as the ability of joints to move beyond their normal ranges along physiological axles, with respect to age, gender and ethnicity (101, 102). A range of motion above the mean plus two standard deviations is considered hypermobile (103). It can be divided into localised joint hypermobility (LJH; joint hypermobility in one or a few sites), generalised joint hypermobility (GJH; joint hypermobility at multiple sites, usually 5 or more), peripheral joint hypermobility (PJH; joint hypermobility in hands and
feet) and historical joint hypermobility (HJH; joint hypermobility at a younger age). Joint hypermobility is a sign, not a diagnosis (102), and is often synonymous with joint laxity or double-jointedness, describing an excess of joint motion due to reduced stiffness of capsules, tendons, and ligaments (104).

There are wide ethnic and geographic variations in the prevalence of generalised joint hypermobility (101, 105-107). It is more often seen in Asian and African populations compared to Caucasians (106), with a reported prevalence of approximately 5–10% in female Western populations (108-110). A recent study concluded that the risk of self-reported pelvic girdle pain during and after pregnancy was higher for women of South Asian and Middle Eastern origin compared to women of Western origin (111).

Musculoskeletal problems are proposed to be more prevalent in individuals with joint hypermobility because of the increased ratio of type III to type I collagen, leading to more stretchy and perhaps more fragile tissues (112). Symptomatic generalised joint hypermobility was previously referred to as ‘joint hypermobility syndrome’ (106). It has been associated with musculoskeletal pain (113-116), both acute, recurrent (117, 118) and chronic (56, 119), as well as impaired proprioception, muscle weakness (120) and lack of endurance (121). However, generalised joint hypermobility can also be asymptomatic (102, 115). This raises the question whether hypermobility has any bearing on the occurrence of pregnancy-related pelvic girdle pain.

There is a continuous spectrum of phenotypes between asymptomatic, non-syndromic joint hypermobility and hypermobile Ehlers-Danlos Syndrome (102). The identification of novel genes related to clinical variants of Ehlers-Danlos Syndrome has underscored the difficulty in distinguishing patients with symptomatic joint hypermobility from those with heritable connective tissue disorders (122), where Ehlers-Danlos Syndrome hypermobility type is the most frequent (104). The “New framework for classification of joint hypermobility and related conditions” established ‘the hypermobility spectrum disorders’ to identify discrete subtypes bridging the gap between asymptomatic joint hypermobility and hypermobile Ehlers-Danlos Syndrome (104).

Generalised joint hypermobility is a collagen phenotype that affects the entire body (120, 123). It is often congenital, possibly an inherited trait, with similarities to heritable connective tissue disorders, such as fragile connective tissue (104, 123). Heritable connective tissue disorders are characterised by genetic defects in protein synthesis, which is particularly abundant in connective tissue (79, 124). The genetic components in generalised joint hypermobility and associated phenotypes are largely unknown (125, 126), and a genetic marker for hypermobile Ehlers-Danlos Syndrome type is still lacking (104, 122). Further research is needed to differentiate between joint hypermobility spectrum disorder and hypermobile Ehlers-Danlos Syndrome (39). Structural abnormalities of collagen fibrils have been seen in many diseases characterised by generalised joint hypermobility, where the latter is proposed to reflect the constitutional weakness in the connective tissue (127).
Assessment of generalised joint hypermobility

Assessment of generalised joint hypermobility can be done either visually or measured with a goniometer. The reliability increases with the latter (128), although a variability of ±5 degrees is accepted (129). The first criteria for assessing joint hypermobility were presented by Carter and Wilkinson in 1964 (130) and were modified by Beighton et al. for an epidemiological study in 1973, as an screening instrument for generalised joint hypermobility (131). The Beighton score has since been used as a diagnostic tool and is the most common method for assessing generalised joint hypermobility (103, 123, 132). It includes measurements of thumbs, fifth fingers, elbows, knees and forward bending. Each hypermobile joint scores one point, with a total score ranging from 0 to 9. To identify generalised joint hypermobility in adults, cut-off levels of ≥4 or ≥5 have mostly been used, but today, a cut-off ≥5 points is recommended, including historical information (132). The Beighton score is quick and easy to perform. However, it covers only five joints, in particular hinge joints, and is an “all-or-nothing-test” with no indication regarding the degree of hypermobility.

The Contompasis score is a modification of the Beighton score with one additional joint included (foot flexibility test/calcaneus tilt) and a graded rating scale based on the degree of hypermobility, resulting in a total score range from 22 to 72 (133). The Hospital del Mar criteria offer a broader assessment of joint mobility by evaluating nine joints on the non-dominant side, including ball-and-socket-joints, and incorporating a question about bruises (134).

The Upper Limb Hypermobility test (135) and the Lower Limb Assessment Score (136) are two recently developed assessment scores for identifying upper- and lower hypermobility, as well as generalised joint hypermobility in commonly affected joints. However, their clinical utility for diagnosis needs to be further studied (116, 137).

For questionnaire surveys, the 5-part self-reported questionnaire (5PQ) is the most commonly used method to identify past and present generalised joint hypermobility (138), with a cut-off level of ≥2 positive answers out of 5 questions.

Comparisons between studies are challenging since a gold standard for the assessment of generalised joint hypermobility is lacking (117). There is still no consensus regarding assessments, with significant methodological differences regarding which joints to include, test performances and defined cut-off points (139-141). These differences may impact prevalence estimates, highlighting an urgent need for structured and standardised assessments (132, 139, 142).
Generalised joint hypermobility and pregnancy-related pelvic girdle pain

In some studies, women with hypermobile joints have been reported to have a higher risk of developing pregnancy-related pelvic girdle pain compared to women with normal joint mobility (39, 143). The pelvic joints are perhaps more sensitive for load and prone to develop pain, especially in individuals with fragile connective tissue (112, 144), such as those with generalised joint hypermobility with slow or delayed healing (143). However, the association between generalised joint hypermobility and pelvic girdle pain during pregnancy is scarcely investigated, and the evidence is inconclusive (14, 145), perhaps due to differences in study design, assessment methods and diagnostic definitions. One study found an association between self-reported joint hypermobility and low back- and pelvic pain six months postpartum (146), and a recent study found that a Beighton score $\geq 6$ was a risk factor for low back pain two years after delivery (147). The prevalence of generalised joint hypermobility among female patients with chronic myofascial pelvic pain was also higher compared to the general population (148).

Overweight during pregnancy

Overweight (body mass index $\geq 25$kg/m$^2$) and obesity (body mass index $\geq 30$kg/m$^2$) are rapidly increasing worldwide (149, 150), including women of reproductive age (149, 151). Overweight and obesity are associated with increased risks of foetal and maternal complications, as well as increased health risks for mother and child later in life (152, 153). In addition, pregnancy itself often leads to weight gain, and weight retention one year after childbirth predicts future overweight 15 years later (154).

A high body mass index is associated with various disabling musculoskeletal conditions in adults, such as osteoarthritis, low back pain and soft tissues complaints, for instance (155). It is also a risk factor for developing pregnancy-related pelvic girdle pain (8, 48), with a dose–response relation (48). In addition, a high body mass index is associated with less recovery from pelvic girdle pain 3–6 months after childbirth (51, 146, 156).

A recent study found that pregnant women with a combination of generalised joint hypermobility and a pre-pregnancy body mass index $\geq 25$ kg/m$^2$ reported higher evening pain intensity compared to women with normal joint mobility and body mass index $< 25$ kg/m$^2$ (157). These factors have also been associated with recurrent or continuous lumbar pelvic pain six months after childbirth (146).
Pain intensity and measurements of pain

Pelvic girdle pain intensity increases during pregnancy (12), with an average rating between 50 mm and 60 mm on a 100 mm visual analogue scale, and it decreases after childbirth (11, 12, 158). The intensity of pelvic girdle pain during pregnancy seems to be more severe compared to low back pain, contrary to what women have reported after childbirth. High pain intensity during pregnancy has also been associated with poorer recovery (17). The visual analogue scale (0–100 mm) is one of the most frequently used instruments to assess pain intensity (159, 160). It is valid, reliable and appropriate for use in clinical practice (161).

Measuring pain is a challenge, however. Although the measurement scales are reliable, valid and easy to use, they are unidimensional and cannot cover the multidimensional aspects of experiencing pain (162). Pain is a subjective feeling that varies due to many factors, such as personality, earlier painful events, emotional state, context and the cause of pain (160). This can result in that the same estimated number on the pain assessment scale can express “average everyday pain” for one patient and “barely tolerable” for another (105). Comparisons of pain intensity between studies are also challenged due to when the pain is assessed and the specific type of pain being evaluated, for instance, “pain intensity at the moment” and/or “worst pain felt during the last week” (12), “pain in the morning” and/or “pain in the evening” (163), pain related to activities (164) or pain “on average” and/or “peak episodes” (19).

Physical disability in pregnancy

Complications such as nausea, vomiting, overweight, hypertension, gestational diabetes, preeclampsia and the risk of preterm birth can affect physical ability and health during and after pregnancy (152, 165). However, pelvic girdle pain has a major impact on health and socioeconomics in European countries, particularly as it typically affects the working population, leading to an increased risk of sick-leave and disablement (1, 166, 167). Pelvic girdle pain is a major cause of sick leave (16, 168), significantly affecting daily activities during (13, 20, 169) and after pregnancy (170). A study in Norway involving 283 women found that those experiencing pain in all three pelvic joints reported the highest disability scores (169). Pelvic girdle pain combined with low back pain during pregnancy also adversely affected health and function (13).

Affected women often struggle with frustration, guilt, irritability and dissatisfaction at not being able to carry out their normal lives (171). Symptoms of pelvic girdle pain are intermittent (172), time-dependent and related to weight-bearing activities (7), leading to reduced endurance capacity and difficulties in walking, standing, sitting, lying down and turning over in bed (45,
172-174). The pain generally starts within 30 minutes (172). A catching of the leg when walking has been identified as a specific symptom in women with dorsal pelvic pain, where twisting, climbing stairs and unequal weight bearing in standing can worsen the symptoms (19). Approximately 50% of affected women report that pain limits their daily activities (5), and may be one of the explanations for the reported drop in physical activity levels during pregnancy (175, 176). Studies of physical activity in pregnancy often focus on exercise and leisure-time activity, but caregiving and indoor household activities are essential parts of physical activity behaviour and contribute significantly to the total activity level (176, 177).

Similar to women affected by pain during pregnancy, those experiencing dorsal pelvic pain six months postpartum also reported difficulties with daily activities (170). Women with persistent pelvic girdle pain struggle to cope with everyday life and manage feelings of frustration, physical limitations, disappointments and future worries (178). Their worries and concerns about their condition can impact their recovery negatively (179).

Generalised joint hypermobility and physical disability

The association between generalised joint hypermobility and physical disability in non-pregnant cohort is limited and presents conflicting results. One study involving 72 young females found that generalised joint hypermobility was negatively associated with physical activity level, walking distance and jumping capacity, even after controlling for age, body mass index and musculoskeletal complaints (180). A recent study focusing on women of reproductive age with generalised joint hypermobile reported some differences in muscle strength and daily function compared to normative values. However, the reported correlations were moderate or low, indicating a complex relationship between strength, muscle properties and function (181). Another study reported that women with generalised joint hypermobility, especially those with symptomatic hypermobility, exhibited altered movement patterns during stair climbing compared to women with normal joint mobility (182). However, the differences were small, perhaps because of a roof effect. Climbing a six-step staircase is perhaps not challenging enough for the target group? A retrospective Brazilian study involving 482 individuals with joint hypermobility, aged between 1 and 76 years, showed that higher Beighton scores were indicative of motor implications (183). In a review study from 2020, the authors suggested that to explain disability in individuals with generalised joint hypermobility, both physical and psychological components should be included, since pain-related fear may be an underlying mechanism that explains the association between these components (119). In another study by these authors, however, they found no differences in physical functioning and pain-related fear
among hypermobile and non-hypermobile adolescents with chronic musculo-skeletal pain (184). Another study with pregnant women found no association between generalised joint hypermobility, defined as a Beighton score $\geq 4$, and physical disability in late pregnancy (185).

Prognosis

For most women, pelvic girdle pain tends to regress between one to six months postpartum (1, 186-188). However, comparisons between studies are difficult because pelvic girdle pain is often included as "low back pain", and study designs differ (1). The prevalence of PGP declines to 7% in all women within the first three months postpartum (1). One study reported that women with symphysis pain alone had the best prognosis, while those with pain in all pelvic joints had the worst prognosis (186). Factors such as previous back pain, high pain intensity, early onset of pain, higher body mass index, emotional distress, joint hypermobility and a high number of positive pelvic pain provocation tests impact the prognosis negatively (146, 147, 187, 189, 190).

Despite an overall good prognosis, some women will continue to experience persistent pain for years after childbirth (158, 186). A difficulty regarding comparisons between studies on prognosis is that many studies only report the prevalence of pain and do not assess its severity or associated disabilities, such as pain intensity, sleep disturbances or work ability (40). In a cohort of women referred for physiotherapy during pregnancy because of pelvic girdle pain, disabling pain was experienced in 10%, 18 months postpartum (191). Severe pain has been reported in 5 to 7% of women up to three years postpartum (192, 193). In a long-term follow-up study conducted 11 years postpartum (response rate 70%), 10% of the respondents were classified as having pregnancy-related pelvic girdle pain, with decreased ability to perform daily activities (190). In another long-term follow-up study, the prevalence of self-reported pelvic girdle pain “to a various degree” was 40%, with a high prevalence of widespread pain 12 years after childbirth; however, the response rate was 47% (194). Identifying this subgroup of women early in pregnancy is important because the transition from acute to chronic pain is complex (190) and may lead to long-term sick leave (194). In addition, passive coping strategies, fear-avoidance beliefs, anxiety and depression, and an unhealthy lifestyle all have the potential to exacerbate pain and physical disability (71, 72, 156, 187, 195, 196) and affect recovery after childbirth, increasing the risk of developing chronic pain (179).
Prevention and treatment

Since pelvic girdle pain can be considered as a special form of low back pain, it is important to distinguish between the conditions to be able to offer adequate treatment (1, 197). Currently, the evidence regarding the preventive effect of physical activity on the risk of developing pelvic girdle is conflicting (198-200). Many women benefit from stabilisation exercises to reduce pelvic pain intensity and improve physical ability, especially after pregnancy (201-203). The heterogeneous interventions provide limited scientific evidence that exercise reduces pelvic girdle pain (198). A critical review concluded that ‘Exercises need to be meaningful to the patient, relevant for daily activities, individualized according to patient preferences, guided and supervised to secure performance and quality’ (204).

Numerous treatment methods for pregnancy-related pelvic girdle pain and disability have been tested in studies with different designs, durations of follow-ups and different outcome measures. This leads to a limited and divergent scientific basis for manual treatment (205, 206), pelvic girdle belts (203), transcutaneous electrical stimulation and acupuncture (207), yoga (208), progressive muscle relaxation (209) and kinesio taping (210). Future large randomised studies are needed to validate the effect of treatment interventions. A collaborative model of pelvic girdle pain was recently developed, representing the collective view of a group of experts (211). Additionally, a core outcome set for research and clinical practice has recently been proposed (212). Based on the complex multifactorial range of causes, a flexible biopsychosocial (71, 115) and person-centred care approach is needed. From an overall health perspective, it is also important to encourage a healthy lifestyle in order to reduce pregnancy-related complications (152) and prevent the development of chronic pelvic pain (196).

The rationale for the thesis

The aetiology and pathogenesis explaining how healthy young women within a few months of pregnancy can become severely disabled by pelvic girdle pain that can persist for several years in some women are not fully understood. The limited knowledge about factors involved in the development of pregnancy-related pelvic girdle pain and the recovery process after childbirth leaves us with a lack of effective preventive measures and treatment interventions.

Generalised joint hypermobility has been associated with musculoskeletal pain, but it can also be asymptomatic. Few studies have investigated this association during and after pregnancy. A possible association between generalised joint hypermobility, pelvic girdle pain and physical disability during and after pregnancy is even less studied. In addition, comparisons between
studies are hampered because a gold standard regarding the assessment of generalised joint hypermobility is lacking. There is variability in starting positions for the measurements, reference points for the goniometer, and whether the movement is active or passive, and the performance of the test, which may lead to different interpretations. Within this thesis, I want to use reliable measurement methods to study whether general joint hypermobility is associated with pelvic girdle pain and physical disability during and after pregnancy. We hypothesise that women with generalised joint hypermobility, due to an inherent derangement of the stable connective tissue and defective connective tissue repair, are at a higher risk of experiencing disabling pregnancy-related pelvic girdle pain.
Aims

The overall aim was to investigate whether generalised joint hypermobility increases the risk of pelvic girdle pain and physical disability during and after pregnancy.

Study I:
To investigate the inter- and intra-rater reliability for measurements of range of motion in joints, included in three hypermobility assessment methods using a structured protocol.

Study II:
To study the association between self-reported generalised joint hypermobility, measured using the 5PQ, and the presence of pelvic girdle pain during pregnancy, identified using pain drawings and reported for the entire pregnancy and in each trimester.

Study III:
To investigate whether clinically assessed generalised joint hypermobility was associated with an increased risk of pelvic girdle pain and high pain intensity during and after pregnancy. A further aim was to explore if body mass index in early pregnancy influenced this risk.

Study IV:
To study the development of physical disability from early pregnancy to nine months postpartum based on pelvic girdle pain, generalised joint hypermobility and early-pregnancy overweight. Secondary aims were to explore how pelvic girdle pain limited daily activities during and after pregnancy, and if the time of onset of pelvic girdle pain and high levels of physical disability during pregnancy were associated with physical disability nine months postpartum.
Methods

This thesis comprises four original studies based on three different study samples. A methodological overview of the studies is presented in table 1.

Table 1. Methodological overview of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study sample</th>
<th>Design</th>
<th>Data</th>
<th>Point of measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>49 women and men for inter-rater reliability. 29 women and men for intra-rater reliability</td>
<td>Inter- and intra-rater reliability study with a test re-test design</td>
<td>Repeated clinical assessment</td>
<td>Inter-rater reliability: ≥30 min - ≤7 hours Intra-rater reliability: ≥7 days - ≤14 days</td>
</tr>
<tr>
<td>II</td>
<td>2217 pregnant women</td>
<td>Retrospective cohort study</td>
<td>Questionnaires, Pain drawing</td>
<td>Early pregnancy: gestational week 11 (median range 3-36), Late pregnancy: gestational week 33 (median range 18-40)</td>
</tr>
<tr>
<td>III</td>
<td>356 pregnant women</td>
<td>Prospective cohort study</td>
<td>Questionnaires, Pain drawing, Clinical assessments</td>
<td>Early pregnancy: gestational week ≤15, Late pregnancy: gestational week 36, Nine months postpartum</td>
</tr>
<tr>
<td>IV</td>
<td>355 pregnant women</td>
<td>Prospective longitudinal cohort study</td>
<td>Questionnaires, Pain drawing, Clinical assessments</td>
<td>Early pregnancy: gestational week ≤15, Late pregnancy: gestational week 36, Nine months postpartum</td>
</tr>
</tbody>
</table>
Settings, recruitment procedure and participants

Study I

The first study was conducted in a rehabilitation centre within primary care in Stockholm, Sweden. All 250 employees of a rehabilitation company received information about the study via e-mail and were invited to participate. The first 50 individuals who agreed to participate and who met the inclusion criteria (men and women aged between 18 and 65 years) were consecutively recruited for the inter-rater measurements. Subsequently, the first 30 participants who agreed to participate in the intra-rater measurements were consecutively recruited for test-retest assessment. Exclusion criteria were joint inflammatory signs, spasticity, joint-replacement, musculoskeletal injuries during the past 3 months and not fluent in the Swedish language. One participant was excluded because of injury. The study was conducted between October 2014 and June 2015. We followed the “Guidelines for Reporting Reliability and Agreement Studies” (GRAAS) (213) and “Quality Appraisal of Reliability Studies” (QAREL) (214).

Study II

In this study, data from the longitudinal Swedish Pregnancy Planning Study (SWEPP) were used. Of the 215 antenatal clinics (ANC) invited, in central and in northern Sweden, 153 clinics participated. All pregnant women in Sweden are offered maternal healthcare free of charge, provided by a midwife. The midwives gave written and verbal information about the study and invited the pregnant women to participate when they came to the ANCs for registration, from September 2012 to July 2013. There were no exclusion criteria.

The SWEPP-study is based on three questionnaires: the baseline questionnaire completed at registration (Q1), the second questionnaire administered around, estimated, gestational weeks 33–35 (Q2) and a third questionnaire distributed one year after expected delivery (Q3). There were no exclusion criteria, and non-Swedish-speaking participants could answer the questionnaires in languages other than Swedish or through interviews. We only used data from the Swedish questionnaires (Q1 and Q2), as they included a pain drawing. Swedish-speaking women who agreed to participate completed Q1 either at the ANC or at home, returning it in a prepaid envelope. A total of 4,884 women received the Swedish version of Q1, and 3,327 women (68%) responded, with 3,154 agreeing to participate in the follow-up (Q2) of which 2,455 women responded.

The data for the exposure variable, self-reported generalised joint hypermobility, was collected in Q2. After merging data from Q1 and Q2, 2,452 women were identified as having answered both the questionnaires. We then excluded 235 women because of miscarriage or missing data on gestational
weeks and/or the occurrence of generalised joint hypermobility. Our final study population included 2,217 women who had responded to the Swedish version of both Q1 and Q2, were pregnant at baseline and had complete data on gestational weeks and generalised joint hypermobility status (Figure 2).

Figure 2. Data management of the Swedish questionnaires in study I

Studies III and IV

Pregnant women attending three maternity care centres in two medium-sized cities in the middle of Sweden were consecutively invited when they came for registration on their first visit. Midwives invited the women to participate in Uppsala Pelvic Pain Study (UPPS) and offered written information on site or sent it by mail. Women who were interested in participating or wanted more information sent an email to the research group. An appointment for the first study visit was booked by telephone, during which time further information was also provided. Inclusion criteria were an ongoing pregnancy of ≤15 completed gestational weeks according to the last menstrual period and the ability to read Swedish. Women with recent musculoskeletal injury or severe pain that prevented joint mobility measurement were excluded from the assessment of generalised joint hypermobility. If needed, the gestational age was revised after the ultrasound examination. During the study period, from February 2014
to June 2019, approximately 8,000 women attended the maternity care centres. The number of these women that the midwives invited to participate in the study is not known.

Data collection procedures

Study I

A structured protocol was developed to standardise the measurement of joint range of motion in 12 single joints (Study I, Additional file 1). The protocol was an expansion from the original versions of three hypermobility assessments scales: the Beighton score (BeS), the Contompasis score (CS) and the Hospital del Mar criteria (HdM) (Study I, Additional file 2). The protocol described the starting position for the measurement, positioning of the goniometer, anatomical landmarks, stabilisation of adjacent structures and performances, active or passive movement, and the protocol was illustrated with photographs. Two physiotherapists (rater A and rater B), each with extensive clinical experience in examining patients with joint hypermobility, assessed all participants. Before the start of the study, the two raters underwent unblinded training on three occasions until a consensus was reached regarding how to standardise the performance and to ensure similar interpretations of the assessments. This pilot cohort included 21 individuals. Joint hypermobility assessments were conducted using a standard goniometer (Medema Brodin, Kista Sweden, 31 cm or 21 cm with a 180° protractor and movable arms), with the smaller goniometer used for measuring the fifth finger and the big toe. Each joint measurement was registered to the nearest 1-degree.

Self-reported sociodemographic data were obtained using a questionnaire (Table 2). The participants’ joint range of motion was measured in separate examination rooms. Participants wore shorts and tank tops and were not allowed to warm up before the measurements. The assessing rater marked reference dots on anatomical landmarks according to the protocol and removed them after each assessment session. Before each measurement, participants received both oral and visual instructions from the rater on how the test would be performed. Participant were instructed to stop the passive movement when they experienced that their joints reached an end-range position. The rater examined if further movement of the joint was possible without causing pain. During the active range of motion measurement, the rater asked the participant: “Is this your maximum range of motion?” and examined if the participant could move the joint further without experiencing pain.

The raters conducted measurements with a minimum of 30 minutes and a maximum of 7 hours between the assessments for inter-rater reliability. They were blinded to each other’s results. After each examination session, the test
protocol was placed in a sealed envelope. Both the test protocols and envelopes were labelled with the same unique code for identification in later analysis. To avoid recall bias in the intra-rater reliability study, rater B repeated the measurements between \( \geq 7 \) to \( \leq 14 \) days after the first occasion. These measurements were taken at the same time of the day as the first occasion. To ensure that the time intervals between measurements were adhered to and that the order of the joint measurements varied, a timetable was used. For both inter- and intra-rater reliability assessments, the order of joint measurements changed every third assessment day, beginning with the end of the protocol.

Study II

All data in the Swedish Pregnancy Planning Study were collected with questionnaires and a pain drawing. A questionnaire was provided to Swedish-speaking women by the midwife to fill out either at the clinic or at home and return by post in a prepaid envelope. If the questionnaire was not returned within two weeks, a reminder was sent by text message or email. The first questionnaire (Q1) was filled out in gestational week 11 (median range 3–36) and included questions about sociodemographic characteristics, general health and lifestyle. The baseline data are presented in table 2. The second questionnaire (Q2) was filled out in gestational week 33 (median range 18–40) and included a questionnaire to identify women with generalised joint hypermobility.

Both Q1 and Q2 included a pain drawing, where the women could indicate any pain locations. To divide the different pain areas on the body, a template was used during the data analysis that was not visible to the women when they marked their areas of pain on the pain chart (Figure 3). The marked areas of pain were manually transferred to a computer software programme (Draw Survey, KLONK, Denmark) by two external assistants. A total of 300 pain drawings were entered beforehand for training purpose. Various devices such as a computer mouse, roller mouse and touch pad were tested, with the best results obtained for computer- and roller mouse, with the latter being mostly used in the study. The pain locations were transferred to the computer software programme using anatomical landmarks on the drawings as reference points, to achieve the best possible transfer of the marked pain locations from paper to the computer. To make sure that the transmission had been performed correctly, without yielding pain locations other than those reported on paper, all data input was double-checked.

Studies III and IV

Data were collected on three occasions: visit 1 \((\leq 15 \text{ GW})\), visit 2 \((36 \text{ GW})\) and visit 3 \((9 \text{ months postpartum})\), using self-reported web-based questionnaires
and clinical examinations. The baseline data are presented in table 2. Additionally, a pain drawing on paper was also included, with additional questions about pain onset in relation to the current pregnancy and pain intensity. The same template used in Study II to divide the different pain locations on the body was also used in Studies III and IV, and it was not visible to the women when they marked their areas of pains on the pain drawing (Figure 3). The transmission procedure for the marked pain locations to a computer software programme (Draw Survey, KLONK, Denmark) was the same as in Study I.

The weight (kg) and height (cm) were clinically assessed, and BMI was calculated. One of the assessors (city A: a general practitioner or a physiotherapist, city B: two physiotherapists) conducted the clinical examinations at the end of the visits and remained blinded to all self-reported data.

Assessment of generalised joint hypermobility was done only at the first visit and was performed first during the clinical examination to ensure that the range of motion would not be affected by other tests, such as screening for neurological symptoms and tests for function and pain. The joint mobility measurements were performed according to the structured protocol developed in Study I (Study I, Additional file 1).

Figure 3. A pain drawing to mark pain locations. The red borders indicate pelvic girdle pain, but these were not visible to the women.
Table 2. Overview of baseline data in Studies I–IV

<table>
<thead>
<tr>
<th>Variables</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Origin (European, yes/no)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Body mass index /overweight (kg/m², BMI ≥ 25 yes/no)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Parity (first time mother, yes/no)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Education (university degree, yes/no)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Partnership (having a partner, yes/no)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>History of low back pain (yes/no)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of pelvic girdle pain (yes/no)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-pregnancy tobacco use (1 month, yes/no)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms (HADS-D, 0–21)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary exercise (yes/no)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalised joint hypermobility (yes/no)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a) Hospital Anxiety and Depression Scale, depressive part (HADS-D), a 7-item 4-point Likert scales, sum score range 0–21, a higher sum equals more symptoms, b) Pulse-raising leisure time exercise ≥2 times/week three months before pregnancy, c) Beighton score ≥5 of 9 points
An overview of the variables and the used measures are displayed in Table 3.

Table 3. Overview of the data collection methods used in Studies I–IV

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measures</th>
<th>Items</th>
<th>Response scale</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalised joint hypermobility</td>
<td>Beighton score</td>
<td>5</td>
<td>0–9 rating scale</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Generalised joint hypermobility</td>
<td>Contompasis score</td>
<td>6</td>
<td>22–72 rating scale</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalised joint hypermobility</td>
<td>Hospital del Mar criteria</td>
<td>9</td>
<td>0–10 rating scale</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Generalised joint hypermobility (self-reported)</td>
<td>Five-part Questionnaire</td>
<td>5</td>
<td>0–5 rating scale</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pelvic girdle pain location (self-reported)</td>
<td>Pain drawing</td>
<td>1</td>
<td>Markings within predefined areas for pelvic pain</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pelvic girdle pain location (clinically assessed)</td>
<td>Pain drawing, verified modified posterior pelvic pain provocation test for dorsal pain and symphysis pubis pain provocation test for ventral pain</td>
<td>1</td>
<td>Markings within defined areas for pelvic pain, verified 0–1 (no-yes)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic girdle pain intensity (self-reported)</td>
<td>Visual Analogue Scale</td>
<td>2</td>
<td>0–100 rating scale</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical disability (self-reported)</td>
<td>Disability Rating Index</td>
<td>12</td>
<td>0–100 rating scale</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Generalised Joint Hypermobility

In the first study, generalised joint hypermobility was assessed through clinical measurements in joints included in three assessment scores (Study I, Additional file 1). The Beighton score (131) includes five measurements:

1) first finger opposition (the thumb to the ventral aspect of the forearm),
2) fifth finger extension (≥90°),
3) elbow extension (≥10°),
4) knee extension (≥10°),
5) low back forward bending (placing the palms flat on the floor with the knees in full extension).

The first four measurements are performed bilaterally, resulting in a total score ranging from 0 to 9. Cut-off values of ≥4/9 and ≥5/9 (Study I) and ≥5/9 (Studies III–IV) were used for the Beighton score. The Beighton score has shown acceptable reliability, but with shortcomings on its validity (132).

The Contompasis score (133) encompasses all assessments from the Beighton score, supplemented by an additional assessment, namely, the foot flexibility test (calcaneal stance position) for assessment of valgus tilt. All joint measurements are performed bilaterally except for forward bending of the lower back. The Contompasis score utilises a graded scoring system based on the degree of mobility, where 2 to 4 or 6 points are given, resulting in a total score between 22 and 72. A cut-off level of ≥30 points was used to define generalised joint hypermobility (study I). The assessment scores were modified for the elbow, knee and for the metacarpophalangeal joint of the fifth finger because the range of motion in degrees was insufficiently graded in the original description, and some degrees were represented in two score levels. The Contompasis score has not been sufficiently tested for reliability or validity (132, 133).

The Hospital del Mar criteria (134) includes measurements of nine joints and a question about easy bruising: “Do you get bruises easily after minimal trauma”? The assessed joints include: passive apposition of the thumb, passive dorsiflexion of the fifth finger, passive hyperextension of the elbow, external shoulder rotation, hip abduction, patella hypermobility (medial a/o lateral slide), ankle and foot hypermobility (dorsiflexion and eversion), dorsiflexion of the first metatarsophalangeal joint, and knee hyper flexion. These joints are assessed unilaterally on the non-dominant side. Each hypermobile joint scores one point, resulting in a total score from 0 to 10. Cut-off values ≥4 and ≥5 were used for the Hospital del Mar criteria (Study I). Some of the assessment scores were modified compared to the original description. For example, passive opposition of the thumb was measured with a goniometer instead of a ruler, where <15 degrees on the goniometer corresponded to <21 mm on a ruler. Due to the lack of reference values regarding hypermobility for the ankle...
and patella, ≥45 degrees were defined as hypermobility for the ankle and ≥2 of 4 quadrants in medial or lateral sliding were defined as translational hypermobility for the patella. The Hospital del Mar criteria has not been sufficiently tested for reliability or validity (132, 134).

Self-reported general joint hypermobility (Study II) was collected through the 5PQ, where each affirmative answer yields one point (range score 0–5):

1) Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2) Can you now (or could you ever) bend your thumb to touch your forearm?
3) As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4) As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
5) Do you consider yourself double-jointed? (138).

The recommended cut-off value of ≥2 affirmative answers was used to define generalised joint hypermobility, and the 5PQ was also used as a continuous variable in additional analyses. The 5PQ was reported to be an effective method to identify generalised joint hypermobility, validated against the Beighton score with an age-dependent cut-off (215). However, the reliability, different aspects of validity and responsiveness are not fully described for this instrument (132).

Pelvic girdle pain location

The presence of pelvic girdle pain was indicated on a pain drawing (Studies II–IV). Markings between the posterior iliac crest and the gluteal fold, and/or pain in the pubic symphysis or the groins, were defined as pelvic girdle pain (Figure 2). In Studies III and IV, a woman was diagnosed with pelvic girdle pain if the location of the marking on the pain drawing was verified by ≥1 positive provocation test: ipsilateral posterior pelvic pain provocation test (P4) for dorsal pain and symphysis pubis pain provocation test for ventral pain (1, 2). The P4 test was modified to a semi-quantitative test with predefined loads (1kg, 5kg, 10kg or 15 kg) applied to the flexed knee to exert load along the longitudinal axis of femur. The test was considered positive when a familiar pain was felt in the posterior part of the pelvis on the provoked side, and the lowest painful load was recorded. Palpation of the pubic symphysis was conducted with the woman in a supine position. The assessor palpated gently along the pubic symphysis. The test was considered positive if the palpation caused pain, persisting >5 seconds after the removal of the assessor’s hand (yes/no). The validity of these tests is difficult to assess because of the lack of a gold standard.
Pelvic girdle pain intensity
Pelvic girdle pain intensity regarding “pain right now” and “worst pain last week” was rated using a Visual Analogue Scale (VAS) with anchors of 0 (no pain) and 100 (worst imaginable pain) (Study III). VAS is reliable in assessing low back pain severity (216), but more studies on content validity, test-retest reliability, measurement error, and responsiveness are necessary (217). The pain intensity was divided into four categories (0 = no pain, 1–38 = mild pain, 39–57 = moderate pain, and ≥58 = severe pain (218).

Physical disability
To measure self-reported physical disability, the Disability Rating Index (DRI) was used (Study IV). The DRI covers 12 non-specific activities of daily life, including dressing without help, outdoor walks, climbing stairs, sitting for a longer time, standing bent over a sink, carrying a bag, making a bed, running, light work, heavy work, lifting heavy objects and participating in exercise/sports (219). The ability to perform each activity is indicated by the woman using VAS 100 mm, from 0 (without difficulty) to 100 (not capable at all). The mean value of the 12 answers is then calculated. Regarding the ability to perform the activities, a value of 0–24 on the VAS is interpreted as “no problem”, 25–49 as “some difficulty”, 50–74 as “with difficulty”, 75–99 as “with great difficulty and VAS 100 as “impossible” (220). The DRI was used both as a continuous variable and as a dichotomous variable with a cut-off ≥ 25 (“some difficulty” yes/no). The DRI has been tested for reliability and validity (219).

Data management and analyses
The analyses were performed using the R.version 3.3.1 (The R Project for Statistical Computing, Vienna, Austria) (Study I), STATA V.14.0 (Stata Corp, Texas, USA) (Studies II–IV) and R version 4.2.2 along with the packages lme4 and emmeans (Study IV). All tests were two-sided, and a significance level of 5% was chosen for all analyses. An overview of the data analysis methods is displayed in Table 4.
Table 4. Overview of data analysis methods in Studies I–IV

<table>
<thead>
<tr>
<th>Analyses</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
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<tbody>
<tr>
<td><strong>Descriptive statistics</strong></td>
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<tr>
<td>Mean (SD)</td>
<td>X</td>
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<td>Median (IQR or range)</td>
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<td>Number (proportions)</td>
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<tr>
<td><strong>Reliability and agreement</strong></td>
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<tr>
<td>Intra-class correlations, two-way random effects model, ICC (2.1) with 95% confidence intervals</td>
<td>X</td>
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<tr>
<td>Standard error of measurement (SEM), Percentage of agreement</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Cohen's Kappa (κ)</td>
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<tr>
<td>Prevalence-adjusted bias-adjusted kappa</td>
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<tr>
<td><strong>Inferential analyses</strong></td>
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<tr>
<td><strong>Parametric</strong></td>
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<tr>
<td>Two-sample t-test / Unpaired Student’s t-test</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Linear mixed model with random intercept</td>
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<td><strong>Non-parametric</strong></td>
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<tr>
<td>Mann-Whitney U test</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Uni- and multivariate logistic regression</td>
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<tr>
<td>Ordinal logistic regression</td>
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<tr>
<td>Proportional test</td>
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</table>

**Descriptive statistics**

Descriptive data are presented for Studies I–IV. Continuous variables are presented as means with standard deviations (SD), and ordinal data are presented as medians with interquartile ranges (IQRs) or as ranges (min-max). Nominal data are presented as absolute numbers and proportions (%). The distribution of continuous data was evaluated using histograms. Other statistical methods for each study are described below.

**Study I**

The inter- and intra-rater reliability for the quantitative measurements regarding range of motion (degrees) in each individual joint and for total scores of the hypermobility assessment methods were analysed using the intra-class correlations, two-way random effects model, ICC (2.1), with 95% confidence intervals (CI). ICC was also used for the total score of the hypermobility assessment methods, as they were based on the measured degrees in the included joints. An ICC-score of < 0.40 is interpreted as poor, 0.40–0.59 as fair/moderate, 0.60–0.74 as good and ≥75 as excellent (221). The absolute reliability was presented as standard error of measurement (SEM) using the residual mean square error from two-way repeated measures ANOVA. The total percentage of agreement (Pa) for prevalence of positive findings regarding binary variables was calculated using Cohen’s Kappa (κ). With a kappa value of
<0.00, the strength of the agreement is interpreted as poor, 0.00–0.20 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial and ≥ 0.80 = almost perfect (222). The prevalence-adjusted bias-adjusted kappa (PABAK) was calculated in addition to the obtained value of kappa since prevalence and bias can affect the magnitude of the kappa coefficient. To obtain a power of 80% with a significance level at 0.05, the sample size was determined based on an ICC score of at least 0.82, where a score of 0.6 or higher would be considered acceptable.

**Study II**

Group differences between women with or without self-reported generalised joint hypermobility were assessed using the two-sample t-test and Mann-Whitney U test for continuous data, and test of proportions for categorical data. The association between generalised joint hypermobility and the presence of pelvic girdle pain during the entire pregnancy and in each trimester was estimated as crude and adjusted odd ratios with 95% confidence intervals (CI) using univariate and multivariate binary logistic regression analyses. Adjustments for age and ethnicity were made based on directed acyclic graphs (Figure 3) and a literature search. Due to the wide time interval for answering Questionnaire 1 and Questionnaire 2, overlapping between some women, the pregnancy period was divided into trimesters. Cluster robust standard error was used for the analyses of the entire period of pregnancy and trimesters 2 and 3. To test linear trends across the number of positive responses to the 5PQ, positive responses were modelled as a continuous variable. Additional analyses were conducted in strata of women on previously known risk factors using proportional tests (Study II, Additional file 1). Furthermore, to analyse the drop-outs from early to late pregnancy, participant characteristics and pain at baseline between those who dropped out and those who remained were compared. All tests were two-tailed.
Figure 4. A directed acyclic graph illustrating a causal model of the association between generalised joint hypermobility and pelvic girdle pain during pregnancy

**Study III**

Group differences between women with or without generalised joint hypermobility were assessed using the proportion test and the Mann–Whitney U test. The association between generalised joint hypermobility and the presence of pelvic girdle pain was estimated as crude and adjusted odd ratios, with 95% confidence interval (CI), using logistic regression analyses. This association was further analysed in subgroups of women who differed in combinations of generalised joint hypermobility and body mass index. Due to the high occurrence of zero values on the visual analogue scale among the women, differences in pain intensity associated with generalised joint hypermobility were estimated using both crude and adjusted odds ratios, employing ordinal logistic regression analyses and testing for adherence to the proportional odds assumption. Based on directed acyclic graphs and a literature search, the regression analyses were all adjusted for age and origin. If the association between generalised joint hypermobility and pelvic girdle pain differed in relation to parity, time for pelvic girdle pain onset and early-pregnancy BMI ≥25 kg/m² were tested in sensitivity analyses.

**Study IV**

The development of physical disability during and after pregnancy was estimated as crude and adjusted mean differences using the linear mixed model. A random intercept was used to account for within-individual correlation. Based on directed acyclic graphs, the regression analyses for pelvic girdle pain in relation to physical disability were adjusted for age, depressive symptoms, pre-pregnancy pulse-raising exercise ≥ two times/week and overweight. For
generalised joint hypermobility in relation to physical disability, the regression model was adjusted for age. For overweight in relation to physical disability, the regression model was adjusted for age, university degree, depressive symptoms, parity, pre-pregnancy heart-rate-increasing exercise ≥ twice/week and pre-pregnancy tobacco use.

Differences in the time of onset of pelvic girdle pain during pregnancy and physical disability nine months postpartum were presented as crude and adjusted odds ratios with 95% confidence interval (CI), using logistic regression analyses. Adjustments were made for age, as recommended for the disability rating index, and for depressive symptoms based on a >10% change in the beta-coefficient. Differences between the proportion of physical disability nine months postpartum and the level of physical disability during pregnancy were analysed using the Mann-Whitney U test.

Ethical considerations

The major hormonal changes that occur during pregnancy, accompanied by subsequent physical and mental changes, can make the pregnant woman feel extra sensitive and vulnerable. The regular follow-up by midwives at maternity care centres provides security during what may otherwise be an uncertain and sometimes anxious period in life. In the patient-caregiver relationship, the caregiver is often at an advantage. This aspect is very important to consider when asking patients to participate in a study. It is essential to ensure that patients are aware that participation in the study is voluntary and that they can cancel their participation at any time without having to give an explanation, and that continued care will not be affected. To maintain the autonomy of women in this decision, they must be thoroughly informed about the study in advance. This includes information about the purpose of the study, what participation entails and that all data are coded and anonymised, as well as how the data will be stored. The written information about the study that the participants received contained contact information for the responsible researchers for the studies. All participating women provided their written informed consent (Studies I, III and IV). In Study II, for Swedish-speaking women, the return of the completed questionnaire was regarded as providing informed consent. The clinical measurements and tests conducted in Studies I, III and IV are used in daily practice in primary care and have been used in previous studies.

Ethical approval was granted by the Regional Ethics Review Board of Stockholm, Sweden, for Study I (Drn 2014/665-31/4), and the Regional Ethical Board in Uppsala, Sweden, provided ethical approval for Study II (Drn 2010/085) and for Studies III–IV (Drn 2013/186).
Results

Study I

The inter- and intra-rater reliability for measurements of generalised joint hypermobility

Structured assessments of joint mobility, measured in degrees using a goniometer, were reliable both between and within assessors. The inter- and intra-rater reliability for the total scores of the three hypermobility assessment methods included in the study were found to be good to excellent (ICC 2:1 0.72–0.82 and 0.76–0.86, respectively). (Table 5).

Table 5. Inter- and intra-rater reliability for the total score of three hypermobility methods: the Beighton score (BS), Hospital del Mar Criteria (HdM) and Contompasis score (CS).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Inter-rater reliability</th>
<th>Intra-rater reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypermobility instrument</td>
<td>Rater A mean (SD)</td>
<td>Rater B mean (SD)</td>
</tr>
<tr>
<td>BS</td>
<td>1.4 (1.4)</td>
<td>1.3 (1.4)</td>
</tr>
<tr>
<td>HdM</td>
<td>2.7 (1.4)</td>
<td>2.6 (1.5)</td>
</tr>
<tr>
<td>CS</td>
<td>28.9 (4.3)</td>
<td>28.1 (4.1)</td>
</tr>
</tbody>
</table>

Intra-rater reliability

| | Rating 1 mean (SD) | Rating 2 mean (SD) | P-value | Intra class correlation [2.1] (95% CI) | Standard error of measurement |
| BS | 1.4 (1.6) | 1.1 (1.4) | 0.11 | 0.76 (0.54–0.88) | 0.7 |
For the 18 included joints, the inter- and intra-rater reliability was deemed good to excellent in all but three of the measured joints (ICC 2:1 0.67–0.91). In all but one joint, the differences between the raters were within 5 degrees, and within 3 degrees between test-retest assessments. The highest agreement for positive findings of hypermobility regarding the total scores was observed for the Beighton score and the Hospital del Mar Criteria. The agreement between the raters ranged from 80% to 98%, and within the rater from 72% to 97%. The prevalence- and bias-adjusted kappa (PABAK) values ranged from moderate to almost perfect for both inter- and intra-rater reliability ($\kappa$=0.59–0.96) and ($\kappa$=0.45–0.93), respectively for the total scores.

### Study II

The association between self-reported generalised joint hypermobility and pelvic girdle pain during pregnancy

Self-reported generalised joint hypermobility was seen in 28.7% of the women. These women were more likely to report pelvic girdle pain during pregnancy compared to women without generalised joint hypermobility (47.9% versus 41.0%, $p < 0.001$). The association remained even after adjusting for age and ethnicity (origin outside Europe) 1.27 (95% CI: 1.11–1.47). Moreover, the adjusted odds ratio for pelvic girdle pain increased with an increasing number of positive answers to the 5PQ. The association between self-reported generalised joint hypermobility and pelvic girdle pain was most prominent in early pregnancy. This was supported by the fact that the difference in prevalence between the groups was greatest in trimester 1 (31.6% versus 22.0%, $p = 0.01$), with an adjusted odds ratio of 1.54 (95% CI: 1.20–1.96), for pelvic girdle pain in women with generalised joint hypermobility. However, the differences between the groups decreased as the pregnancy progressed. In trimester 3, 63.0% of women with generalised joint hypermobility reported pelvic girdle pain compared to 57.8% of women without generalised joint hypermobility ($p = 0.02$), with an adjusted odds ratio of 1.20 (95% CI: 0.99–1.45).
Study III

The association between clinically assessed generalised joint hypermobility and pelvic girdle pain during and after pregnancy

The prevalence of clinically assessed generalised joint hypermobility was 9.6% (n = 34). A higher proportion of women with clinically assessed generalised joint hypermobility, had pelvic girdle pain in early pregnancy compared to women without generalised joint hypermobility, 47.1% versus 32.6%. However, the estimate was imprecise, with an age- and origin- adjusted odds ratio of 1.76 (95% CI: 0.86–3.62). The difference in proportions of pelvic girdle pain between the groups decreased and disappeared in late pregnancy and nine months postpartum, indicating that women with generalised joint hypermobility had no increased risk of experiencing pelvic girdle pain during or after pregnancy. Nevertheless, these women reported higher pelvic pain intensity in early pregnancy, with an adjusted odds ratio of 2.07 (95% CI: 1.04–4.15. A higher proportion of these women also reported pelvic girdle pain onset before the current pregnancy compared to women with normal joint mobility (29.4% versus 14.3%, p = 0.02). Among women with pregnancy-induced pelvic girdle pain during the current pregnancy (n = 192), the proportion of women with onset in early pregnancy was higher for those with generalised joint hypermobility, 46.2% compared to 32.4% (p = 0.31). Additionally, women with a combination of generalised joint hypermobility and a body mass index ≥25m² had the highest odds of pelvic girdle pain in early pregnancy, with an adjusted odds ratio of 6.88 (95% CI: 1.34–35.27).

Study IV

Physical disability increased during pregnancy but had a positive postpartum prognosis, regardless of pelvic girdle pain. The more demanding and vigorous activities resulted in the highest disability scores, and the highest scores were seen among women with pelvic girdle pain in both early and late pregnancy. Generalised joint hypermobility had no influence on physical disability during or after pregnancy. However, being overweight in early pregnancy had some impact on the disability score during pregnancy. Approximately 8.8% of the women reported physical disability of varying degrees, nine months postpartum. The remaining impact on physical disability was associated with early onset of pelvic girdle pain, age- and depressive symptoms, with an adjusted odds ratio 4.90 (95% CI: 1.45–16.51) and with higher disability scores in early and late pregnancy.
Discussion

Main findings
This thesis is based on four studies investigating the reliability of assessing generalised joint hypermobility and its association with pelvic girdle pain and physical disability during and after pregnancy.

Using a goniometer and following a structured protocol, the inter- and intra-rater reliability was found to be good to excellent for the total score of three joint hypermobility assessment scales and for the majority of the included joints.

There was an association between self-reported generalised joint hypermobility and pelvic girdle pain during pregnancy, most prominent in the first trimester of pregnancy.

Women with clinically assessed generalised joint hypermobility had an adjusted odds ratio of 1.76 (95% CI: 0.86–3.62) for experiencing pelvic girdle pain in early pregnancy compared to those without generalised joint hypermobility, although this estimate was imprecise.

Furthermore, women with generalised joint hypermobility reported higher pain intensity in early pregnancy compared to those without.

In early pregnancy, women with a combination of generalised joint hypermobility and a body mass index $\geq$ 25 kg/m$^2$ had the highest risk of pelvic girdle pain.

Women experiencing pelvic girdle pain in both early and late pregnancy reported the highest physical disability scores during pregnancy. Generalised joint hypermobility had no impact on the development of physical disability during or after pregnancy.

Early onset of pelvic girdle pain and higher physical disability scores during pregnancy were associated with persistent physical disability 9 months postpartum.

Interpretation of the results
Following a structured protocol and with an inter- and intra-rater reliability between 0.72–0.82 and 0.76–0.86, respectively, for the Beighton score, Contompasis score and Hospital del Mar criteria, the assessments methods for generalised joint hypermobility were interpreted as reliable (221). This was
supported by the suggestion that kappa values ≥0.60 are sufficient as a research and clinical tool (223). All kappa values for joints measurements included in the Beighton score were above 0.60. Within this assessment instrument, measurements of elbow mobility had the lowest kappa values. This might be due to their composition with an adjacent valgus angle. This can complicate the measurement of extension in the joint and give an impression of hypermobility. Hip abduction (included in Hospital del Mar) and calcaneus tilt (included in the Contompasis score) showed just fair/moderate inter- and intra-rater reliability, perhaps due to insufficient stabilisation during hip measurement and asymmetric load while standing.

Is generalised joint hypermobility a risk factor for pelvic girdle pain?

Generalised joint hypermobility has been associated with musculoskeletal pains (99, 113). However, the association between generalised joint hypermobility and pregnancy-related pelvic girdle pain has been scarcely studied and with conflicting results (14, 145, 185). Comparisons between studies are challenged by differences in assessing generalised joint hypermobility and in defining pelvic girdle pain. We hypothesised that generalised joint hypermobility was a risk factor for pregnancy-related pelvic girdle pain. This was confirmed in Study II, where self-reported data from 2,217 pregnant women showed an association during pregnancy, with the largest difference between the groups in early pregnancy, 31.6% versus 22.0%, with an age- and origin-adjusted odds ratio of 1.54 (95% CI: 1.20–1.96). We found no other study that had used the 5PQ to assess generalised joint hypermobility during pregnancy. However, one study that examined this relationship using survey-based data found that women who had been diagnosed as having hypermobile joints were at an increased risk of experiencing low back- and pelvic pain during pregnancy (14). Nonetheless, comparison with our study is difficult due to the methodological differences. In the other retrospective study, women were asked after delivery if they had experienced low back or pelvic pain at any time during pregnancy, with no further information provided regarding how they were diagnosed with joint hypermobility.

Study III, aimed to investigate whether clinically assessed generalised joint hypermobility and test-verified pelvic girdle pain were consistent with the results from Study II. We also wanted to investigate whether women with generalised joint hypermobility had an earlier onset of pelvic girdle pain and higher pain intensity compared to those without generalised joint hypermobility. The disadvantage of clinically collected data from a prospective cohort study is that it is time-consuming and may, therefore, provide too small sample to study. This can cause problems with statistical power and increased risk of type II errors.
With an age and origin adjusted odds ratio of 1.76 (95% CI: 0.86–3.62), we concluded that the estimate regarding whether women with generalised joint hypermobility had an increased risk of pelvic girdle pain in early pregnancy was imprecise. Additionally, the differences between the groups narrowed and disappeared in late pregnancy and nine months postpartum. However, we cannot completely exclude the possibility that women with generalised joint hypermobility may have a certain risk of experiencing problems earlier in pregnancy compared to those with normal joint mobility, as they reported higher levels of pelvic girdle pain in early pregnancy. Both Studies II and III showed that the differences between the groups decreased and disappeared in late pregnancy and postpartum. Notably, women with a combination of generalised joint hypermobility and a body mass index $\geq 25$ kg/m$^2$ had the highest odds of experiencing pelvic girdle pain in early pregnancy. Our results were partly in accordance with another study, which also used clinical assessed data (157). They reported an 11% difference in the prevalence of pelvic girdle pain between women with and without generalised joint hypermobility at gestational week 30, with the highest proportion of pelvic girdle pain observed in women with a combination of pelvic girdle pain and a pre-pregnancy body mass index $\geq 25$ kg/m$^2$. Similarly, in that study, the confidence intervals were wide, and the estimates were imprecise. However, unlike in our study, where we examined “worst possible pelvic pain in the past week”, the other study examined “worst evening pain when going to bed”. Additionally, they found that pain intensity was only increased in women with a combination of pelvic girdle pain and a pre-pregnancy body mass index $\geq 25$ kg/m$^2$. In addition, the Beighton score $\geq 4$ showed no association with worst evening pain intensity in late pregnancy, in another study (185).

Clinically assessed data regarding generalised joint hypermobility and pelvic girdle pain are mostly based on small studies (147, 157, 185), with one exception (145), indicating that further research would benefit from larger-scale studies (39). It is also important to remember that, despite the strain that an ongoing pregnancy has on the weight-bearing joints and their adjacent connective tissue (54), many women with generalised joint hypermobility remain symptom-free during pregnancy.

For most women, the prognosis of pelvic girdle pain after pregnancy is good, with spontaneous regression of symptoms within one to six months postpartum (51, 187). However, several factors have been associated with persistent pelvic girdle pain postpartum, including a history of lumbar pelvic pain, high levels of pain during pregnancy, a large number of positive provocation tests, fear-avoidance beliefs (224, 225), early onset of pain during pregnancy and multiparity (111). A total of 23.3% of the women in our study had pelvic girdle pain nine months after pregnancy (Study III). This relatively high prevalence of pelvic girdle pain postpartum may be explained by the fact that 15.7% of women had the onset of pelvic girdle pain before the current pregnancy. In contrast to other studies (146, 147), the proportion with remaining
pelvic girdle pain nine months postpartum was not greater for women with generalised joint hypermobility in our study. However, low back pain was included in the outcome in the other two studies, and Long et al. used a Beighton score $\geq 6$ as cut-off level for generalised joint hypermobility. Moreover, chronic myofascial pelvic girdle pain in women has also been associated with generalised joint hypermobility (148).

The development of physical disability during and after pregnancy

The development of physical disability increased during pregnancy but had a good prognosis postpartum (Study IV). In total, 8.8% of the women had remaining physical disability nine months after delivery, with the majority reporting a disability index ranging from 25 to 49, interpreted as "some difficulty in performing" activities (220). Our study confirmed that perceived physical disability varies widely among women (169), despite the majority of women having a good overall ability to cope with daily activities. It was mainly at the end of pregnancy that the more physically demanding activities could be difficult for the women. This was also previously reported for women with pain and activity limitations postpartum (170). Moreover, women without pelvic girdle pain reported some difficulties in coping with these activities at the end of pregnancy. The highest disability rating scores during pregnancy were seen in women with pelvic girdle pain in both early and late pregnancy, which confirms pain as a driver for pregnancy-related physical disability (13, 169). Decreased capacity for walking and jumping has previously been reported in non-pregnant women with generalised joint hypermobility (180), but generalised joint hypermobility had minimal impact on the development of physical disability during or after pregnancy in our study. Our result is in agreement with another study, which used a lower cut-off value for the Beighton score and found no association between generalised joint hypermobility and disability rating index in gestation week 30 (185).

A high body mass index, which is a known risk factor for pelvic girdle pain (48), had a small impact on physical ability during but not after pregnancy. It is of great importance that pregnant women are able to manage their everyday life because the level of physical activity often decreases during pregnancy, and an unhealthy lifestyle increases the risk of long-term pain (196). It was perhaps somewhat surprising that neither hypermobility nor overweight affected physical ability to a greater extent, as they hypothetically could have adversely affected weight-bearing activities and endurance in pregnant women with pelvic girdle pain. However, early onset of pelvic girdle pain as well as higher levels of physical disability during pregnancy were associated with physical disability scores 9 months postpartum. The generalised joint hypermobility likely affects pregnant women in the same way as the rest
of the population, with some experiencing problems while others remain asymptomatic (116).

Methodological considerations

Due to a number of limitations and methodological considerations, the findings in this thesis should be interpreted with caution.

Are the currently available measurement tools for generalised joint hypermobility reliable?

Studying a phenomenon that lacks a golden standard, which applies to both the assessment and the classification of generalised joint mobility, poses great challenges. Reliability and validity are fundamental components for the quality of a measuring instrument (226). Numerous questions were raised before work on this thesis began. First, are we measuring the right joints to identify generalised joint hypermobility? Although the Beighton score is the most widely used assessment scale for generalised joint hypermobility, and included in previous and present diagnostic criteria for hypermobility syndromes (142), the Beighton score was developed for another purpose, namely screening in large populations (131). No scientific explanation was found for the selection of the included joints or the chosen cut-off levels for hypermobility in these joints, which has also been highlighted in a recent review (142).

Investigating the validity of joint mobility measurements is beyond the scope of this thesis; however, in the first study, we wanted to determine whether the assessment method we used in the clinic is reliable. The degree of error inherent in measurements can be gauged through studies of reliability and agreement (227, 228). Variations among assessors and in sample characteristics, the type of instrument used, as well as the measurement level and statistical model utilised, all affect reliability and agreement (213). In order to optimise the reliability of measurements and minimise measurement errors, we followed guidelines for reliability studies when planning the study (213, 214). As test performances between the studies differed or were not presented in detail, including factors such as starting positions, stabilisation of adjacent joints and if the range of motion was active or passive, an assessment protocol for joint mobility measurement across three assessment instruments was created. The aim of the protocol was to standardise joint mobility measurements, with optimal positions for the range of movement in each individual joint. Although the inter- and intra-rater reliability regarding the assessment of generalised joint mobility was found to be good to excellent, the reliability of measurements for each individual joint was not consistent. A better fixation
of the pelvis when measuring hip abduction, as well as better control of symmetrical load when measuring the calcaneus tilt while standing, could possibly have improved the reliability of these measurements. This discrepancy may also be due to the fact that, in the training phase, we did not specify a level of agreement of 80%, as recommended, to end method practice (229). It may also be due to the goniometer, where a variation of ±5 degrees has been reported (230). However, new digital assessment tools can likely make measurements faster and more precise (231).

Which and how many joints should be included for diagnostic purposes have been questioned (110, 134). A recent review from 2021 questioned the validity of the Beighton score, citing its failure to demonstrate hypermobility in joints other than those included. It recommended that the Beighton score should not be used as the principal tool for identifying generalised joint hypermobility, or used alone for excluding the presence of the condition (142). Castori et al. 2017 proposed that a definition of generalised joint hypermobility should include joint hypermobility simultaneously across the four limbs and axial skeleton (104). However, this proposal has not been further studied, and the distribution of hypermobile joints varies among different individuals. In addition, a decreased range of motion is often seen on the dominant side (142, 232), which also appeared in most of our measurements. Given that there is no official gold standard for testing the validity of the Beighton score, assessments of its sensitivity and specificity are hampered, which increases the risk of misleading results. Cut off-levels have varied between ≥4 and ≥5 for adults, and have been based on a cut-off value for each joint that was considered positive either when the range of movement reached the cut-off value or exceeded it (141). We found no scientific explanation for the use of these cut-off values, either for the individual joints or for the total score. Despite the above discussed disadvantages and uncertainties, the Beighton score was used for assessing generalised joint hypermobility in Study III and IV. A review of clinical assessment methods for classifying generalised joint hypermobility in 2017 recommended the Beighton score for clinical use, with a cut-off level of ≥ 5/9 for women of reproductive age, even though more studies on its validity were requested (132).

Although clinical measurements are recommended for assessing generalised joint hypermobility, survey studies can be suitable for collecting data from a large number of participants (132). The self-reported 5PQ is the most frequently used questionnaire assessment method for classifying current or past generalised joint hypermobility (138), as used in Study II. It is reported to have good reproducibility and satisfactory sensitivity and specificity (138), but reliability, validity and responsiveness are not fully described (132, 215, 233). The five-part questionnaire has the advantage of not being joint-specific. However, ensuring accurate interpretation of the questions is essential, which was not possible in Study II, where the questionnaires were sent to the participants by mail. The prevalence of generalised joint hypermobility at 28.7% is
higher than the estimated 5%–10% prevalence among women in the Western populations (108, 109). This increased prevalence is perhaps a result of different interpretations, posing a risk of misclassification and an underestimation of the association between self-reported generalised joint hypermobility and pelvic girdle pain during pregnancy.

Can we trust the diagnostic criteria for pelvic girdle pain?

A gold standard for the diagnosis of pelvic girdle pain is lacking (234). In Study II-IV, the commonly accepted definition of pelvic girdle pain was used, but without including the radiation to the posterior thigh, as was defined in “The European Guidelines for the diagnosis and treatment of pelvic girdle pain” (1). However, women may have been misclassified regarding pelvic girdle pain in our studies. All data in Study II were self-reported, and a woman was defined as having pelvic girdle pain if she marked pain within the defined area on a pain chart (Figure 3). Pain drawings were also used in Study III and IV to identify pelvic girdle pain, which, in addition, underwent verification through clinical tests to be defined as having pelvic girdle pain. Pain drawing is a common tool to map the distribution of pain. Even though the method is quick and easy to complete and shows sufficient reliability for making clinical decisions (235, 236), it has its drawbacks. Some individuals are very careful when marking their pain, while others draw the areas as broad and even outside the contours of the pain template. We did not calculate the marked area, but excessive marking may have resulted in adjacent areas being incorrectly registered as painful. In addition, the transfer of pain drawings from paper to digital software programme may have introduced a systematic bias because pain areas are drawn slightly smaller on paper (237), and this method is not validated. Thus, this may have led to a slightly higher prevalence of pelvic girdle pain overall. The digitisation of these pain drawings creates unprecedented opportunities to collect data and will catapult the quantification of pain into a new field ripe for breakthrough discoveries (238).

The European guidelines recommend that pelvic girdle pain should be reproducible by clinical tests and present a battery of pain provocation and functional tests (1). In order to minimise the examination time, we chose two confirmatory tests in Study III and IV: ipsilateral posterior pelvic pain provocation test for dorsal pain (169) and palpation of the symphysis for ventral pain (2). These tests had the highest sensitivity and specificity; however, by not using all tests, the risk of misclassification may have increased.

For the purpose of diagnosis, a clinical test must be valid. The posterior pelvic pain provocation test is valid (169). However, the modified semi-quantitative posterior pelvic pain test that we constructed to quantify how much load the dorsal sacroiliac joint was subjected to was not validated. Instead of
using the assessor's hand to apply load along the longitudinal axis of the femur, we used four pre-defined loads (1kg, 5kg, 10kg, 15 kg), weight cuffs, from lightest to heaviest. This might have affected the outcome of the test.

Pain intensity ratings are very common in clinical studies, even though it provides an endemic picture of a complex phenomenon (162). Pelvic girdle pain intensity fluctuates throughout pregnancy and is influenced by weight-bearing activities and reduced endurance (172). To capture these pain fluctuations, women were asked to estimate "worst pain last week" on a visual analogue scale ranging from 0 to 100 mm. However, this may have introduced a risk for recall bias, and the pain assessment might have been more reliable using a pain diary or responding to a smartphone mobile app, a painometer, at certain time points (239). Nonetheless, new equipment must be tested for, among others, feasibility, responsiveness, validity and reliability before it can be implemented in research.

Is the Disability Rating Index a valid tool to assess physical disability in pregnancy?

We used the Disability Rating Index (219) to follow the development of physical disability from early pregnancy to nine months postpartum (Study IV). This rating index is a self-rated measure of perceived physical functional limitation, related to 12 non-specific everyday activities, primarily intended for patients with low back pain. However, the index has previously been used on pregnant cohorts (20, 185, 240). The rating scores in our study are in agreement with previous studies for the corresponding time period in pregnancy (16, 20, 169, 185). In contrast to pelvic girdle pain, generalised joint hypermobility had no effect on physical ability during or after pregnancy. Being overweight in early pregnancy was associated with a slight increase in the index. However, because most items of the disability rating index do not specify the level of effort, such as walking distance, time interval, or weight, the instrument may not fully capture women's reduced endurance for weight-bearing activities (172). The Pelvic Girdle Questionnaire has the ability to capture differences in load and endurance, but it is a condition-specific measure for women with pelvic girdle pain (241). No available data on threshold values for clinically significant changes regarding the disability rating index within the target group were found. Consequently, we used the 25-step intervals outlined in the user manual to relate the estimates with the degree of impact on physical disability (220).
Confounding

A confounding factor is a variable that can distort the association between an exposure and an outcome, i.e. the result can depend on another variable. Confounding factors are an imminent threat to the validity of observational studies, and an appropriate selection of confounders to control is, therefore, essential (242). Despite the limitations of using observational study designs, we aimed to explore the possible causal relationship between generalised joint hypermobility and pelvic girdle pain (Study II and III). This could be achieved through causal inference (243). Causal inference studies require careful consideration of confounding, particularly in observational research. The recommended variable selection methods include:

1. The historical approach to defining a confounder, i.e. ‘Any third variable that is associated with the exposure of interest, is a cause of the outcome of interest and does not reside in the causal pathway between the exposure and outcome’. Additionally, based on prior knowledge, to purposefully select variables that fit the criterion.
2. Causal models using directed acyclic graphs (DAGs) (243).

Causal models can be visualised using a directed acyclic graph, where unidirectional arrows represent the known causal effects (243). The causal pathway visualises the association between the exposure and the outcome to be studied. Based on the above recommendations for observational causal inference studies, the relationship between generalised joint hypermobility and pelvic girdle pain was adjusted for age and ethnicity/origin (Study II and III). The latter served as a proxy for genetics in the model. Since a lower incidence of generalised joint hypermobility has been reported in Caucasians compared to individuals of other origins, we defined women with at least one non-European parent as "non-European origin". However, lack of detailed information about origin and genetics may have introduced bias, in our studies.

In order to identify confounding factors for the association of physical disability with pelvic girdle pain, generalised joint hypermobility and obesity, separate DAGs were created for each studied relationship. However, constructing a DAG can be challenging, and even minor errors in directionalities can lead to incorrect inferences, which we cannot rule out in our models.

The risk of type II error

When drawing conclusions from studies with small study samples, there is a risk of type II errors (244). We cannot rule out that low statistical power has influenced our results in Study III and IV. In Study II, a greater proportion of women with self-reported generalised joint hypermobility reported pelvic gir-
Pain in early pregnancy compared to women without generalised joint hypermobility, 31.6% versus 22.0%, with an adjusted odds ratio of 1.54 (95% CI: 1.20–1.96). With a larger sample size in Study III, the association between generalised joint hypermobility and pelvic girdle pain in early pregnancy (adjusted odds ratio 1.76; 95% CI: 0.86-3.62) would probably have reached statistical significance.

External validity and transferability

Study I
Following a structured protocol, the results in Study I are valid for standardised measurement of joint mobility using a goniometer for the majority of the 12 joints, performed on healthy adult women and men by an experienced assessor. We measured joint mobility in the general adult population in order to be able to generalise to a wider context, with an expected greater variation in range of motion among participants. Generalisability regarding the inter- and intra-assessor reliability of joint mobility measurements for pregnant women is, therefore, low. A future reliability study of joint mobility measurements and the assessment of generalised joint hypermobility needs to be conducted, where a digital measuring instrument can be tested at the same time.

Study II
In Study II, women were recruited from 153 antenatal clinics from various parts of Sweden. Among all approached women, 61% completed the study (n = 3390), and 98% answered the Swedish questionnaire. Only questionnaires in Swedish were included because those in other languages did not include a pain map. In addition, we only included women who answered both questionnaire 1 and questionnaire 2 because the exposure variable, self-reported generalised joint hypermobility, was asked in questionnaire 2. A greater proportion of the women who were lost to follow-up after questionnaire 1 had non-European origin, was multiparous and a smaller proportion had a university degree. However, only a 2% difference between the groups was noted regarding the occurrence of pelvic girdle pain in early pregnancy. This reduces the generalisability to include pregnant women with European origin, who can read and understand Swedish and are willing to participate in research studies. Of the women who answered both questionnaire 1 and questionnaire 2 in Swedish, 56% had previously given birth, 50% had a university education and 5.6% had an origin outside Europe.
Studies III and IV

The generalisability of the findings in Study III and IV may be low due to the small sample size. Larger studies, preferably from several clinics, are needed, as the prevalence of generalised joint hypermobility is low. Participating in a clinical trial involves several sacrifices, including the participant having to travel to the clinic, having the will and the ability to set aside time and being motivated to participate. We do not know how many women were asked to participate in the study, but about two-thirds of those who participated were recruited from a university town. This might introduce a selection bias, as educational level is an important factor influencing interest in participating and completing a study. Approximately 70% of the participating women had a university education. Level of education is also associated with socio-economic standard and healthy lifestyle habits (245). Women who were lost to follow-up for visit 2 or visit 3 (Study III and IV) did not differ in baseline characteristics from those who completed the studies.
Conclusions

This thesis showed that repeated standardised measurements of joint mobility using a goniometer, encompassing joints included in three assessment scales for generalised joint hypermobility, showed high to excellent inter- and intra-rater reliability when following a structured protocol. Self-reported generalised joint hypermobility was associated with pelvic girdle pain during pregnancy. The biggest differences compared to women without generalised joint hypermobility were seen in early pregnancy. When generalised joint hypermobility was clinically assessed, women with generalised joint hypermobility reported higher pelvic girdle pain intensity during this period of pregnancy. However, the highest risk of pelvic girdle pain in early pregnancy was observed in women with a combination of generalised joint hypermobility and overweight during the same period. There were no differences seen between the groups in late pregnancy or nine months postpartum.

The physical ability was negatively affected by pregnancy, particularly evident in women with pelvic girdle pain both in late and early pregnancy, whereas generalised joint hypermobility had no impact and overweight had negligibly impact. The prognosis was good and nine months postpartum had most women regained their physical ability. The remaining impact on physical disability postpartum was associated with early pain onset and a higher disability index in both early and late pregnancy.

Clinical implications

When generalised hypermobility is suspected, a standardised joint mobility measurement using a goniometer is reliable for assessing its presence. Our findings indicate that women with generalised joint hypermobility may experience more pelvic girdle pain and higher pain intensity earlier in pregnancy compared to women with normal joint mobility. Therefore, women with early pain onset may benefit from an assessment of generalised joint hypermobility, in conjunction with clinical examination of pain and function. As women with pelvic girdle pain in both early and late pregnancy reported the highest disability index among all women, and considering that the remaining impact on physical disability nine months postpartum was associated with early pain onset and higher disability scores during pregnancy, it becomes important to
identify women experiencing pelvic girdle pain and disability early in pregnancy. Early management strategies may reduce their risk of developing long-term pain and disabilities after pregnancy.

Future research

The findings of this thesis prompt several suggestions for future research. There is still a need for an international consensus regarding the selections of joints that should be included in the assessment of generalised joint hypermobility. Moreover, the development of flexible digital instruments would probably increase the reliability of joint mobility measurements in the future and needs to be tested for both reliability and validity. The association between generalised joint hypermobility and pelvic girdle pain needs to be investigated in larger studies. It is also important to determine if the group differences diminish and disappear in late pregnancy and postpartum, as our studies indicate. The risk of pregnant women with a combination of generalised joint hypermobility and overweight also needs to be investigated in larger studies, as our study showed that the risk of pelvic girdle pain in early pregnancy may be particularly high for these women. Furthermore, the “Disability Rating Index” may not be challenging enough to measure physical disability during pregnancy, as the instrument does not provide information regarding the duration or load of various activities. Therefore, it would perhaps be beneficial to use the “Pelvic girdle questionnaire” as the outcome variable in future studies on the relationship of generalised joint hypermobility to provide more decisive insights.
Sammanfattning på svenska


I detta avhandlingsarbete var det övergripande syftet att undersöka om generell ledöverrörlighet ökar sannolikheten för att drabbas av bäckensmärta och fysisk funktionsnedsättning under och/eller efter graviditeten.

I studie I undersökte hur tillförlitligt det var att mäta ledrörligheten när resultaten jämfördes mellan olika bedömare och när mätningen upprepades av samma bedömare. Tillförlitligheten undersöktes för ledrörlighetsmätning i 12 leder hos 49 vuxna personer. I Studie II undersökt sambandet mellan självrapporterad generell ledöverrörlighet och bäckensmärta under graviditeten hos 2 217 kvinnor. I studie III undersökt sambandet mellan kliniskt bedömd generell ledöverrörlighet och bäckensmärta under och efter graviditeten hos 356 kvinnor. Studie IV fokuserade på utvecklingen av fysisk funktionsnedsättning från tidig graviditet till nio månader efter förlossningen i relation till bäckensmärta, generell ledöverrörlighet och övervikt, samt om tidig debut av bäckensmärta och graden av fysisk funktionsnedsättning under graviditeten var associerad med fysisk funktionsnedsättning nio månader efter graviditeten.

Tidig debut av bäckensmärter under graviditeten och högre skattning av påverkan på funktion under graviditeten var associerade med fysisk funktionsnedsättning nio månader efter förlossningen.

Kvinnor som upplever bäckensmärta tidigt i graviditeten, vilket kvinnor med generell ledöverrörlighet tenderar att göra, kan ha nytta av en bedömning av generell ledöverrörlighet, eftersom de kan uppleva mer intensiv smärta under denna tidiga period jämfört med normalrörliga kvinnor. Det är också angeläget att utveckla metoder för att förebygga och hantera bäckensmärter, med tanke på dess starka samband med fysisk funktionsnedsättning under och efter graviditeten samt att tidig debut av bäckensmärta och ett högre invaliditetsindex under graviditeten är prediktorer för fysisk funktionsnedsättning nio månader efter förlossningen, med en ökad risk för långvarig smärta.
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A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)