Shadi-Afarin Ghassemi Jahani

Thalidomide Embryopathy

Orthopaedic Aspects, Degenerative Changes and Quality of Life at Age 45

Department of Orthopaedics,
Institute of Clinical Sciences at
Sahlgrenska Academy, University of Gothenburg,
Gothenburg, Sweden 2016

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Shadi-Afarin Ghassemi Jahani, 2016,
ghasemi.shadi@gmail.com

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"When I want to understand what is happening today or try to decide what will happen tomorrow, I look back."

– Omar Khayyám (1048-1122)

Contents

1. Abstract

In the late 1950s and early 1960s, a sudden peak was seen among children with different, severe malformations, caused by the intake of the drug thalidomide during pregnancy. Among other featured malformations, so-called thalidomide embryopathy (TE), the most obvious were seen in the extremities. In this thesis, orthopaedic problems, physical function and quality of life in a cohort of survivors with TE in Sweden, around 45 years of age, were investigated.

The study group of 31 individuals with TE underwent a clinical examination, computed tomography (CT) of the pelvis and lower limbs (Study I) and MRI of the cervical spine (Study II) and answered several questionnaires (Studies I, III, IV). For evaluations of function, the "Disability in Shoulder Arm and Hand" (DASH) and "Rheumatoid Arthritis Outcome Score" (RAOS) were used (Study I). Health-related quality of life was evaluated by the Short Form-36 (SF-36) and Euro Qol-5 Dimensions (EQ-5D) (Study III) and the level of independence was evaluated by a modified General Function Score (GFS) and WHO questionnaire (Study IV).

The individuals with TE had a number of different malformations in the extremities. Five individuals were identified as having a proximal femoral focal deficiency (PFFD). The whole group had a high prevalence of moderate osteoarthritis in their hip and knee joints and reported greater disability in terms of upper limb function compared with the general population. The individuals with PFFD reported significantly poorer lower extremity function than the rest of the group (Study I). Individuals with TE demonstrated a high frequency of degenerative changes in the cervical spine compared with a control group (Study II). Individuals with TE reported a reduction in physical quality of life measured by both the SF-36, i.e. the Physical Composite Summary Score (PCS), and EQ-5D. Their mental quality of life was not affected, when measured by either the SF-36 Mental Composite Summary Score (MCS) or the EQ-5D. A relationship between low PCS and the number of extremities involved, as well as with the DASH score and the RAOS's pain subscore (Study III), was observed. Individuals with TE generally demonstrated a high level of independence, as the majority were employed and participated in physical activities (Study IV).

In conclusion, middle-aged individuals with TE demonstrated an increased risk of degenerative changes in both larger joints and the cervical spine. Individuals with PFFD were most affected in terms of physical function, daily activities and quality of life. Despite a decrease in physical function in the overall group, their mental quality of life was not affected. ■

2. Sammanfattning på svenska

Talidomid var tidigare känt som en ofarlig medicin för behandling av vissa smärtsamma neuropatiska symptom och fungerade även som sömnmedel och mot illamående. Då den inte var ett barbiturat, och därmed ansågs ofarlig, kom den att också ges till gravida kvinnor. Samtidigt som användningen av Talidomid ökade på slutet av 50-talet och i början av 60-talet, steg antalet barn födda med svåra missbildningar, s.k. Thalidomide Embryopathy (TE) i nästan hela världen. Många foster dog till följd av missbildningarna. En del barn dog i samband med födelsen eller direkt efter födelsen. Den faktiska siffran av drabbade barn och foster kommer därför för alltid att förbli okänd. I Sverige föddes över 100 barn med TE. De är idag drygt 50 år gamla. Hittills har kunskapen om långtidseffekten av de ortopediska missbildningarna, främst i extremiteter, samt effekten på livskvalitet hos dessa individer varit mycket begränsad.

I denna avhandling ingår långtidsuppföljning av individer med TE, med fokus på ortopediska besvär, framför allt med avseende på utveckling av artros i nedre extremiteter och halsrygg, fysisk funktion och livskvalité. Alla medlemmar i ”Föreningen för de Neurosedyn skadade” kontaktades och inbjöds att delta i studien. Trettio-tre accepterade, men två exkluderades pga. allvarligt nedsatt hälsotillstånd. I delarbete I belystes utvecklingen av artros i höft- och knäleder, samt funktionsnivå i övre och nedre extremiteterna. Spiral CT-undersökning av nedre extremiteter, inklusive bäckenet användes för evaluering av artrosgrad. Validerade frågeformulär, d.v.s. Rheumatoid Arthritis Outcome Score (RAOS), användes för evaluering av funktion i nedre extremiteterna och Disability in Arm, Shoulder and Hand (DASH) för övre extremiteterna. Fem individer hade grava missbildningar i nedre extremiteterna bestående av Proximal Femoral Focal Deficiency, (PFFD). Resultatet pekade på en ökning av artros hos individer med TE jämfört med normal befolkningen i samma åldersgrupp. Gruppen med PFFD hade också sämre ADL funktion.

I delarbete II undersöktes förekomsten av missbildningar och diskdegeneration (DD) i halsryggen. Tjugo-sju av 31 patienter genomgick magnetkameraundersökning (MRI) av halsryggen och jämfördes med en frisk kontrollgrupp. Resultatet visade förhöjd frekvens av tidig diskdegeneration i halsryggen hos individer med TE jämfört med kontrollgruppen, sannolikt orsakat av ökad belastning på halsryggen. I delarbete III belystes hälsorelaterad livskvalitet hos patienter med TE. Validerade frågeformulär; SF-36 och EQ-5D användes för utvärdering. Signifikant lägre värde för övergripande fysisk funktions mätt med SF-36, förelåg hos TE individer jämfört med den allmänna populationen. Den mentala livskvaliteten, mätt både med SF-36 och EQ-5D, var däremot lika hos individerna med TE och den allmänna populationen. ▸

Delarbete IV fokuserar på de ortopediska ingrepp och de extra hjälpinsatser som patienter med TE har och här studerades hur muskuloskeletala missbildningar kan påverka funktion och behovet av insatser i det vardagliga livet. Resultatet visar att individer med PFFD har signifikant större behov av tid för ADL och de med gravt handikapp större behov av anpassat arbete och hem. Sammanfattningsvis har individer med TE många olika typer av missbildningar i extremiteterna vilket bl.a. innebär ökad risk för tidig diskdegeneration i halsryggen och ökad risk för artrosutveckling i de stora lederna. Den fysiska funktionen, dagliga aktiviteter samt generell livskvalitet var mest påverkad hos individer med PFFD. Trots att den fysiska livskvaliteten var signifikant sämre för individer med TE jämfört med individer i samma åldersgrupp, påverkades den mentala livskvaliteten inte nämnvärt. ■

3. List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals

Paper I: Long-term follow-up of thalidomide embryopathy; malformations and development of osteoarthritis in the lower extremities and evaluation of upper extremity function
Ghassemi Jahani S. A., Danielson B., Karlsson J., Danielsson A.J.
J Child Orthop. 2014;8(5):423-33

Paper II: Degenerative changes in the cervical spine are more common in middle-aged individuals with thalidomide embryopathy than in healthy controls
Ghassemi Jahani S. A., Danielsson A.J., Ab-Fawaz R., Hebelka H., Danielson B., Brisby H.
PLoS One. 2016 May 13;11(5):e0155493.
doi: 10.1371/journal.pone.0155493. eCollection 2016.

Paper III: Health related quality of life and function in middle-aged individuals with thalidomide embryopathy
Ghassemi Jahani S.A., Karlsson J., Brisby H., Danielsson A.J.
Accepted. J Child Orthop.

Paper IV: Middle-aged individuals with thalidomide embryopathy have undergone few surgical limb procedures and demonstrate a high degree of physical independence
Ghassemi Jahani S.A., Danielsson A.J., Karlsson J., Brisby H.
Submitted

4. Abbreviations

BOA	Bättre omhändertagande av Artros
CTR	Control
DASH	Disability in Arm, Shoulder and Hand
DD	Disc degeneration
EQ-5D	EuroQol-5 Dimensions
FDA	Food and Drug Administration
FFdN	Föreningen för de Neurosedynskadade
GFS	General Function Score
MRI	Magnetic Resonance Imaging
OA	Osteoarthritis
PACS	Patient Archiving Community System
PFFD	Proximal Femoral Focal Deficiency
RAOS	Rheumatoid Arthritis Outcome Score
ROM	Range of Motion
SF-36	Short-Form 36
Spiral CT	Spiral Computed Tomography
SPSS	Statistical Package for the Social Sciences
TE	Thalidomide Embryopathy

5. Definitions

Ahlbäck's classification: The Ahlbäck's classification system estimates the severity of osteoarthritis in the knee joint, in patients with chronic knee pain. The Ahlbäck's classification is divided into five grades with increasing severity.

Amelia: Congenital absence of an arm or leg.

Aitken's Classification: Classification of proximal focal femoral deficiency, PFFD, most widely used according to Aitken, which is based on the anatomic relationship between the acetabulum and the proximal end of the femur, with four classes; Class A-D.

Birth defect: A defect that is present at birth.

Crohn's disease: An idiopathic inflammatory bowel disorder that can affect the entire gastrointestinal tract, from the mouth to the anus. Patients frequently have abdominal pain, fever and/or diarrhoea with the frequent passage of blood or mucus or both.

Duane syndrome: A congenital eye-movement disorder defined by limited outward gaze and retraction of the eye on attempted inward gaze and sometimes narrowing of the palpebral fissure of the same eye.

Embryopathy: A developmental abnormality of an embryo or foetus especially when caused by a disease.

Gillespie classification: Classification and management of congenital abnormalities of the femur. Two groups are defined; Group I with a congenital short femur and Group II (true proximal femoral focal deficiency), where a true deficit exists in the proximal femur regardless of whether or not the femoral head and acetabulum are present. ▸

Kaposi's sarcoma: Kaposi's sarcoma (KS) is a lymphoangio-proliferative neoplasm induced by human herpes virus 8 (HHV-8). There are four clinical variants; classical, African endemic, AIDS related and KS caused by iatrogenic immunosuppression. It can be associated with the use of immunosuppressive therapy in organ transplant and in patients who receive immunosuppression for other indications, such as autoimmune disorders.

Leprosy: A chronic mycobacterial infection caused by Mycobacterium leprae. It is an infectious disease causing an inflammatory process in the tissues causing disfiguring cutaneous lesions, peripheral nerve injuries, osteoarticular deformity, limb loss and dysfunction, blindness and skin stigmata.

Malformation: Irregular, anomalous, abnormal, or faulty formation of a structure

Multiple myeloma: Multiple myeloma (MM) is a neoplasm of a post-germinal centre, terminally differentiated B cells, a kind of blood cancer. It is characterised by a multifocal proliferation of long-lived plasma cells within the bone marrow and is associated with skeletal destruction, immune suppression and end-organ sequelae, such as kidney, liver or brain failure.

Pfirrman Classification: MRI classification system originally for lumbar disc degeneration. This classification is based on five grades; Grade I-V.

Phocomelia: An abnormality of development, in which the upper part of an arm or leg is missing so the hands or feet are attached to the body.

Teratogenic: Any agent that interferes with normal embryonic development: such as alcohol, thalidomide, rubella or misoprostol.

Thalidomide: Phthalimido glutarimide

Thalidomide embryopathy: Malformations caused by thalidomide during early pregnancy in individuals with featured malformations most striking in the extremities, but the ears, eyes and inner organs may also be affected.

Van Nes rotationplasty: Van Nes rotationplasty or distal femoral rotation osteotomy. This surgical procedure always involves the distal femur in a short femur so that the foot would face backwards. This allows the patient's foot to have weight bearing on the below-knee portion of the lower-leg prosthesis.

Z-score: A z-score is a measurement of the number of standard deviations below or above the general population mean a measured score is. It is a way to measure an individual's result compared with the average national population's mean result for that specific variable.

6. Introduction

Thalidomide embryopathy (TE) is a condition caused by the drug thalidomide and includes different developmental organ malformations, most strikingly in the extremities. In the late 1950s and the beginning of the 1960s, a dramatic increase in children born with severe malformations of the extremities led to the suspicion and subsequent confirmation of the teratogenicity of thalidomide.

At that time, treatment options were sparse and individuals with TE had no possibilities other than to cope with the situation. Several publications described the findings of TE during the 1960s and 1970s (Lenz, 1961, Lenz, 1962, McBride, 1961, McBride, 1977, Ruffing, 1977, Ruffing, 1980). The severe limb deformities led to a severe physical handicap, often in combination with a significant mental burden.

For many years, the condition did not attract much attention, but, in recent years, a number of studies of mental status (Imai et al., 2014), dental status (Ekfeldt and Carlsson, 2008) and facial palsy (Sjögreen and Kiliaridis, 2012) in individuals with TE have been published (Jankelowitz et al., 2013, Shiga et al., 2015, Nicotra et al., 2016). How these individuals have managed in terms of their musculoskeletal manifestations over the years is not well known. There is a general lack of long-term follow-up studies from an orthopaedic perspective of this and other similar congenital limb deficiencies. This is the reason why the studies within this thesis were initiated and performed.

6.1 Musculoskeletal malformations of the limbs

6.1.1 Embryological background

Normally, the limbs start to develop towards the end of the fourth week after fertilisation. Their development and growth is from proximal to distal. The limbs are made up of four segments, the root, the proximal segment (with one bone), the middle segment (with two bones) and the distal segment (with several bones) (Herring, Fifth edition). The limbs start to rotate in the seventh week after fertilisation and the forelimbs rotate laterally 90° with lateral positioning of the thumb, while the hind limbs rotate medially 90°, positioning the big toe medially. In the 12th week after fertilisation, the ossification centres have reached their final localisation in the long bones. Malformations are structural defects that arise from an interruption in normal organogenesis during the second month after gestation. Most of them occur in the early period of limb development, during the 5th or 6th weeks after fertilisation. Examples include syndactylies

and proximal focal deficiency. Drugs that affect development during early pregnancy, such as thalidomide, will therefore affect the development of the limbs.

Other failures of normal growth and development are deformations (caused by mechanical stress leading to a deformed limb, such as malposition of the foot called calcaneovalgus foot), disruptions (caused by extrinsic factors such as constricting amniotic bands or drugs) or dysplasias (structural defects caused by abnormal tissues, for example achondroplasia or spondyloepiphyseal dysplasia) (Herring, Fifth edition).

All limb deficiencies are categorised into two groups: terminal (the missing segment is at the end of the extremity) and intercalary (the missing part is within the extremity, i.e. the proximal and the distal parts are present). Both can be either transverse (amputation) or paraxial (longitudinal). Transverse deficiencies are when the limb is normally developed until the missing segment. Longitudinal (paraxial) deficiencies are the reduction or absence of one or more elements within the long axis of the limb, sometimes with normal development of the limb distal to the affected part. The malformations found in thalidomide embryopathy are described below.

6.1.2 Congenital limb deficiencies

Upper limbs

The main function of the upper limb is to serve as a gripping tool and, if objects are too far away, to position the arm so that the object can be reached. The ability to reach and grip objects is essential for the independence of the individual. Malformations causing decreased hand function, sometimes in combination with shortening or deformity of the arm, therefore affect the ability to use the arm/hand as a gripping tool. In the most severe cases with bilateral malformations, no gripping ability exists on either side, which leads to the individual learning to use his/her feet to function as gripping tools, sometimes in combination with the teeth.

In the event of insufficient function of the lower limbs, the upper limbs can also be used to support body balance. In individuals with severe lower limb deficiencies, proper arm function is essential to the ability to move. Examples of malformations in the upper extremities are radius or ulnar deficiency or aplasia, and hand and finger malformations.

Amelia, phocomelia

Amelia is when the limb is completely absent and no part of a proximal or distal part of an extremity (or several extremities) has developed (Figure 1).

The definition of phocomelia is when the arm and forearm in the upper limbs or the thigh and leg in the lower limbs are absent, i.e. the hands or feet are attached directly to the trunk.

Phocomelia can also differ in severity, where the total absence of the long bones is the most severe form.

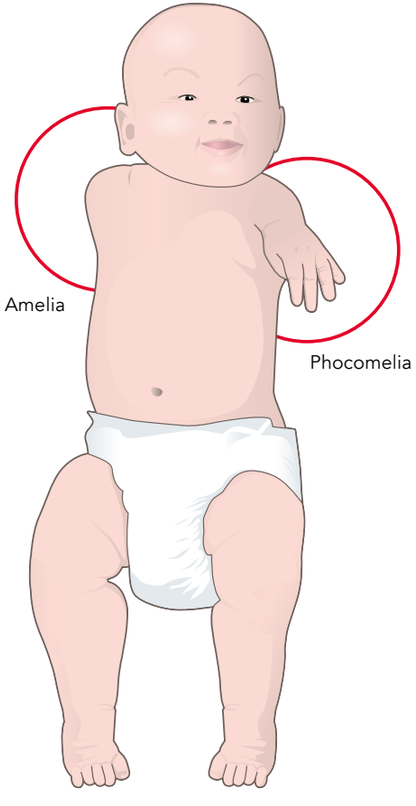


Figure 1: Phocomelia on the left side and amelia on the right side

Lower limbs

The main function of the lower limbs is to support the body during standing and to provide the ability for locomotion. Malformations affecting limb length are deleterious for the independence of an individual. These malformations include proximal focal femoral deficiency and tibia/fibular aplasia or hypoplasia, as well as congenital amputations.

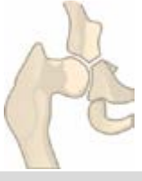
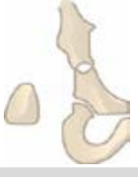
Amelia, phocomelia

See above for the upper extremities

Proximal femoral focal deficiency (PFFD)

PFFD is one of the severe lower limb malformations, where the femur is shorter than normal and the femoral neck and shaft are often not connected to each other. In most cases of PFFD, the cause is unknown. If significant shortening exists, it may be accurately diagnosed prenatally with sonography. There is a large variation in the severity of the malformation, from only a slightly shorter femur to a virtually non-existent femoral diaphysis and with absence of the hip. Two major descriptions/classifications exist and are described in detail. The Aitken (Aitken, 1969), Figure 2, and the Gillespie classifications (Gillespie and Torode, 1983). The Gillespie classification (Group I and II) is based on the clinical appearance and possible outcome of treatment, while the Aitken classification is a detailed anatomic description. The Aitken classification is one of the classification systems that is used most frequently clinically to describe the malformation in PFFD and includes four types; A, B, C or D.

Figure 2: Aitken types A, B, C and D

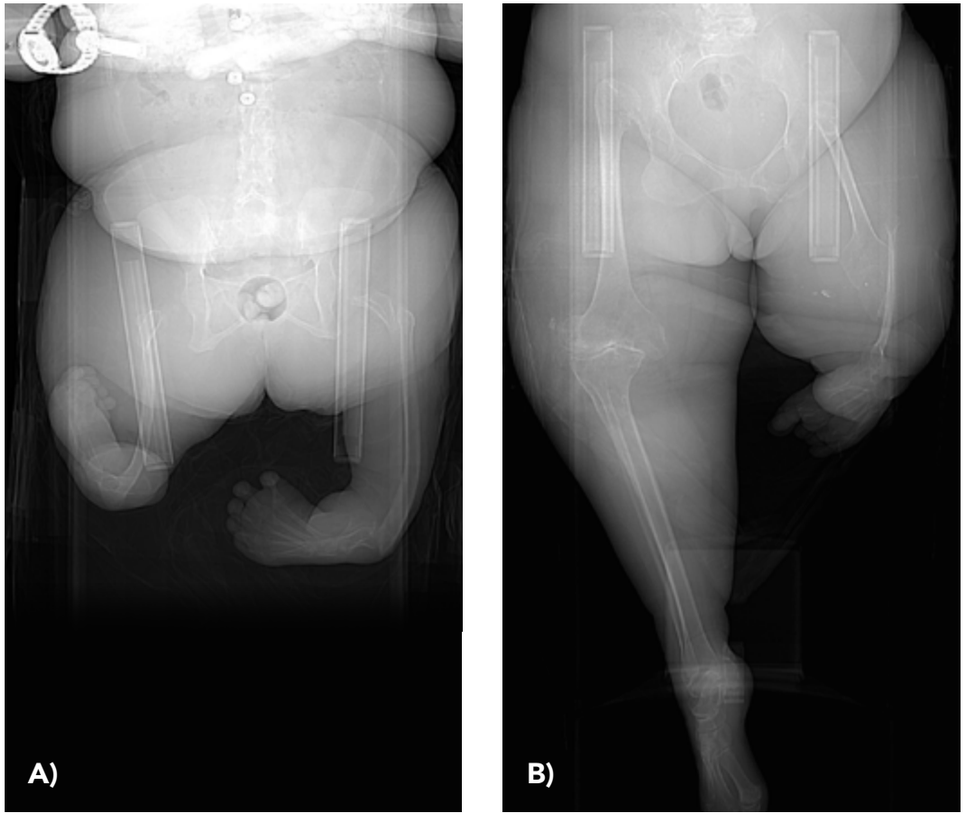
Type	A	B	C	D
				
Femoral head	Present	Present	Absent or represented by an ossicle	Absent
Acetabulum	Normal	Adequate or moderately dysplastic	Severely dysplastic	Absent Obturator foramen enlarged
Pelvis squared in bilateral cases				
Femoral segment	Short	Short, usually proximal bony tuft	Short, usually proximally tapered	Short, deformed
Relationship between different components of the femur and acetabulum at skeletal maturity	Osseous connection between components of the femur is present Femoral head in the acetabulum Subtrochanteric varus angulation, often with pseudoarthrosis	No osseous connection between the head and shaft Femoral head in the acetabulum	May be an osseous connection between the shaft and proximal ossicle No articular relationship between the femur and acetabulum	None

The Gillespie classification of PFFD is based on clinical appearance and possible outcome of treatment. Two groups are defined; Group I with congenital short femur, and Group II (true proximal femoral focal deficiency), where a true deficit exists in the proximal femur whether or not the femoral head and acetabulum are present.

There is further a more recent classification from 1990, also according to Gillespie and based on the treatment outcome. (Herring, Fifth edition)

Clinically, patients with PFFD who have a significant femoral shortening have a characteristic appearance; the thigh on the affected side is very short, the hip is flexed and abducted and the entire limb may be externally rotated. The knee often has a flexion contracture and, with the very short femur, the foot is at the level of the contralateral knee (if a normal contralateral knee exists) (Fig 3. A, B) The flexion contractures of the hip and knee make the limb appear to be shorter than it actually is. Most children with unilateral PFFD are able to compensate for the short limb by standing with weight-bearing on the knee on the non-affected side, when trying to move (Figure 4).

Figure 3: Two individuals with PFFD with **A)** Aitken's "D" bilateral and **B)** Aitken's "C" bilateral



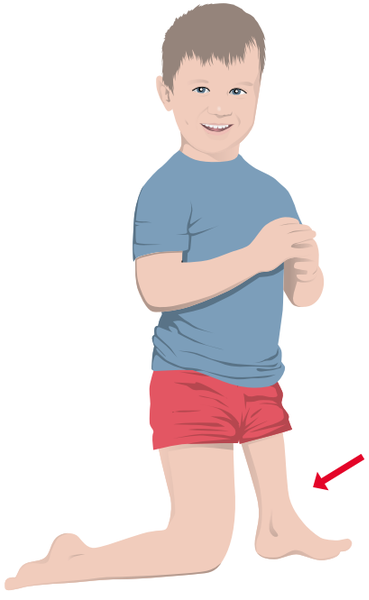


Figure 4: Child with significant shortening of one leg

6.1.3 Treatment of congenital limb deformities/malformations

Limb shortening has historically mainly been treated conservatively with various types of prosthesis, making standing or gripping easier. Due to the lack of a proper grip function, an absent or deficient thumb could surgically be replaced by another finger by a surgical procedure, a so-called pollisation. Arthrodesis of the knee has also been used to increase the stability of the limb. A deformed foot or knee could either be corrected to a straighter position or amputated to make the use of a prosthesis less troublesome. Re-directional osteotomies of the long bones, such as radial osteotomies or osteotomies of the lower leg, have also been performed from an early stage.

In 1950, Van Nes described a rotationplasty, which was used for children with a PFFD with a short femur. The fairly normal foot located at the level of the knee of the normal leg was rotated posteriorly through a distal femoral rotation osteotomy, leaving the foot pointing posteriorly instead of anteriorly. This allows the ankle joint to act as a simulated knee joint, while providing motor and sensory control of the prosthetic knee (Figure 5). One drawback of this method is that the rotationplasty can have cosmetic disadvantages for some patients. This method has not been used very often in Sweden, possibly due to the cosmetic disadvantages. In a long-term follow-up of individuals treated with Van Nes rotationplasty, it was found that the individuals had an acceptable level of function and quality of life (Ackman et al., 2013). For the individuals that were born during the 1960s, the procedures mentioned above were the only ones that were available. It was not until the late 1980s that lengthening procedures were made possible by the use of the Ilizarov frame (Ilizarov and Deviatov, 1971, Dal Monte and Donzelli, 1987). Today, children born with significant limb shortening in Sweden are followed from an early stage and

evaluated for localisation and the type of malformation with CT and/or MRI. The extent and classification of the malformations in combination with expected and observed growth will advise on treatment potential.

Generally, prosthetic management is started early, at the time when normal use of the affected limb begins. For upper limb deficiencies, the timing of prosthetic management is early, with a fitted passive prosthesis at the time children need to balance, when they begin to sit (around six months). Children with lower limb deficiencies require prosthesis management at a later stage, approximately the time they start to rise and walk (around nine to 16 months) (Herring, Fifth edition, Mayer et al., 2011). Modern prosthetic techniques nowadays allow children with limb deficiency to walk at almost the same age as normal children. Training and the development of the prosthesis have to be adjusted in harmony with the children's developmental status. It is important to evaluate whether the goal is to aim for limb correction, to be able to use an external prosthesis, or whether the goal is to lengthen the limb, to get the foot on the ground for walking. For children with the most severe malformations and where no reconstructive surgery is available, an external prosthesis will be introduced. Early surgery might be performed by correcting or amputating parts that make prosthetic use less problematic. The stability of the hip and upper femur must be evaluated and surgery is sometimes needed to achieve stability. The Van Nes rotationplasty can be considered when knee fusion or femoral-to-pelvis fusion is considered, but this procedure has not been used extensively in Sweden. If the aim of the treatment is walking without prosthesis, the reconstruction and stabilisation of the hip, knee, foot and ankle may normally need to be performed. For the knee, an arthrodesis for stabilisation might be an option. Limb lengthening is then part of the treatment plan and the lengthening often needs to be repeated several times during the growth period in order to keep up with the growth of the normal leg. Stabilisation of the upper femoral part and surgery at the level of the femoral neck are often part of the initial treatment protocol.

The medical team has to present different treatment options to the child and parents and decisions must be made in consensus. The timing is essential when it comes to different types of surgery for children with congenital limb deficiencies. One important factor is to try to let families with children with similar conditions meet in order to obtain an improved understanding of both the deficiency and possible treatment options (Herring, Fifth edition).

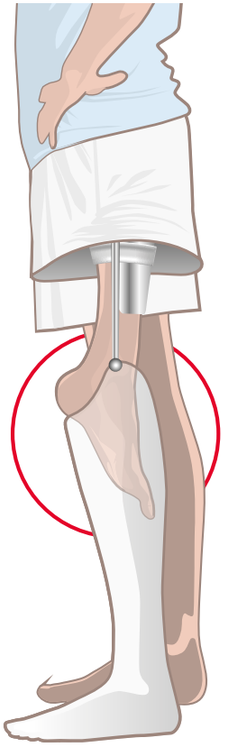


Figure 5: Operated short left thigh with Van Nes rotationplasty. The foot is backwards and placed in the prosthesis.

6.2 The history of thalidomide

6.2.1 Historical background

Thalidomide was launched in Europe on 1 October 1957 (Kida and Lenz, 1968, Vargesson, 2013), by the Chemie Grünenthal chemical company in West Germany, as a sedative with the positive attribute of being non-addictive and non-barbiturate (Vargesson, 2013, Vargesson, 2015). The drug was not lethal in high doses and, as an overdose had never produced fatal poisoning (Taussig, 1962, Nilsson, 2004), it was considered safe to keep it at home. Thalidomide was added to other drugs when sedation was required, for people suffering from headache, asthma, migraine and coughing, for example, and was further sold as a tranquiliser (Taussig, 1962). The drug was used for insomnia, under preoperative conditions, for relieving tension and anxiety, gastric hyperactivity and gastric and peptic ulcers. Drugs containing thalidomide were initially used without prescriptions. Symptoms of polyneuropathy, such as marked paresthesia in the hands and toes, were first noticed as coldness of the extremities, slight ataxia and nocturnal cramps in the leg muscles in some patients, long before the malformations appeared (Leslie Florence, 1960). These side-effects were first noticed by Dr. Leslie Florence who suspected thalidomide in four of his patients after long use of the drug. The anti-emetic capacity of the drug, together with the belief of no side-effects, opened another treatment field for morning sickness in pregnant women (Lenz, 1985, Smithells and Newman, 1992, Vargesson, 2015). Thalidomide was sold and distributed in 46 countries (Kida and Lenz, 1968, Ances, 2002); 11 European countries, seven African countries, 17 Asian countries and under different names in 11 other countries in the western hemisphere (Kida and Lenz, 1968, Yllner, 2007, Vargesson, 2015). In the United States of America (USA), thalidomide was known in the market as Kevadone®, but it was never released for sale, thanks to the cautiousness of Mrs. Frances Oldham Kelsey, at that time a medical officer and a reviewer for the US Food and Drug Administration (FDA) (Taussig, 1962, Kelsey, 1963). She had read about peripheral neuritis, reported as a side-effect of thalidomide (Leslie Florence, 1960). She realised that, even though the drug was given to pregnant women, no investigation into the safety of the drug for the embryo had ever been performed. Soon after the introduction of thalidomide to be used for hyperemesis during the late 1950s, a sudden peak in congenital malformations appeared in different countries worldwide. Several physicians in different countries started to wonder (Kida and Lenz, 1968, McCredie, 2009) why thousands of children with rare malformations were born during this time period (Taussig, 1962). The varieties of malformations appearing after the intake of thalidomide were later called thalidomide embryopahy (TE) or thalidomide syndrome (Lenz, 1962, Kida and Lenz, 1968, Vargesson, 2013).

Table 1: Frequency of children born with thalidomide embryopathy in different countries between 1957-1964

West Germany	>3,000
United Kingdom	≈ 450
Japan	≈ 300
Sweden	115
Brazil	≈ 90
Italy and Canada	≈ 80 each
Taiwan, Australia, New Zealand, Finland	≈ 30 each
Other countries	< 25

Number of children born with thalidomide embryopathy worldwide

According to the Japanese report (Kida and Lenz, 1968), the rate of survival from thalidomide in West Germany, Sweden and Canada was almost 70%, while it was approximately 40% in Japan. The number of reported cases in different countries is shown in Table 1.

In Hungary, Israel and Belgium, children with TE were also born, but the number is unknown (Somers, 1962, Heyne, 1963, Dolev, 2001). In addition to the increased number of live-born children with congenital malformations, many foetuses with even more severe malformations died before or at birth (Strömland and Miller, 1993). It is estimated that approximately 40% of infants with TE died before their first birthday (Lenz, 1985, Smithells and Newman, 1992, McCredie, 2009, Vargesson, 2013). As a result, the true number of foetuses affected by thalidomide is still unknown (Strömland and Miller, 1993, Vargesson, 2015).

6.2.2 History of thalidomide in different countries

Thalidomide in West Germany

With the increasing number of children born with unknown and in some cases severe malformations of different organs and especially malformed extremities at the beginning of the 1960s (Vargesson, 2013), two independent doctors from two different continents became suspicious. They alerted the medical society to thalidomide's possible side-effects (Leslie Florence, 1960, Lenz, 1961, McBride, 1961, Taussig, 1962).

The first warning came on 8 November 1961, when Dr Widukind Lenz (1919-1995), a paediatrician from the University of Hamburg, expressed his concern about the relationship between the increased number of new-borns with congenital malformations and thalidomide (Lenz, 1961, Taussig, 1962). On 16 November the same year (Lenz, 1962), he also expressed his concern on the phone to the drug company, which soon became known as "the Lenz warning" (Kida and Lenz, 1968). Dr. Lenz had recognised an increased frequency and different types of malformation in several new-born children. The most common malformation was phocomelia, which had long been known as a rare malformation, with the typical morphology of the hands directly attached to the shoulders, similar to the flippers of a seal (Taussig, 1962, McCredie, 2009). Phocomelia was often combined with different malformations of internal organs such as duodenal stenosis, anal atresia, heart anomalies, the absence or duplication of internal organs like the kidneys and malformations of the ears and/or eyes (Miller and Stromland, 1992, Miller and Strömland, 1999) but without any familial history (McCredie, 2009). Hoping to find the cause in the environment (Taussig, 1962), for the almost 3,000 children born with these malformations in West Germany, Dr Lenz personally asked 46 mothers and 41 of them had used the drug (McCredie, 2009). On 18 November 1961, at a paediatric congress in Dusseldorf, he expressed his concern directly to his colleagues and subsequently published them in a German medical journal (Lenz, 1961, Taussig, 1962). A colleague asked about Contergan® and was concerned about his wife who had used the drug during her pregnancy. The baby was born malformed and this can be regarded as the first prospective case study of thalidomide (McCredie, 2009). Dr Lenz and a lawyer, who also had a son born with severe malformations of the upper extremities related to the drug, started to collect more information about other children with the same kind of malformations by simply asking the parents. They thus started a campaign against the drug company in Germany. It only took 10 days after the "Lenz warning" for the drug to be withdrawn from the market in Germany. On 26 November, the company withdrew the drug in West Germany and the whole of Europe; 33 days after the Lenz warning (McCredie, 2009, Taussig, 1962).

Thalidomide in Sweden

In Sweden, the drug was sold under the name Neurosedyn® and was licensed by Astra (McCredie, 2009, Yllner, 2007). It was available on the market between January 1959 and December 1961 (Agerberg, 2011). Regrettably, it took several weeks to withdraw the drug from the market after the very first information and warnings about its serious side-effects were released in Sweden (TT-Reuter, 1961, Agerberg, 2011). The medical authorities received information about the side-effects of the drug but were not effective enough to withdraw the drug directly (McCredie, 2009) and, in addition, no general information was given to the public. This lack of public information resulted in the continued use of the drug, which had also been purchased and stored in several homes before the withdrawal, and this probably caused more children to be born with malformations. The first warning and information to the public in Sweden was given on 14 March 1962 (Yllner, 2007). Soon after, several parents with affected children set up "The Thalidomide Society" in Sweden. The society engaged a layer, Henning Sjöström, and asked him for his help in suing the drug company, which was the first trial and legal follow-up for those affected by Neurosedyn® in Sweden. Henning Sjöström won the lawsuit, which resulted in an economic insurance for all the affected children in Sweden. The TE diagnose for all children at this time, were set by a single paediatrician and based on the observed malformations (Winberg, 1964b, Winberg, 1964a). The Thalidomide Society was later taken over by the children with TE themselves. In Sweden, as in many other countries, the thalidomide disaster led to the initiation of centres for health surveillance and health registers; the Swedish register of congenital malformation (Källen et al., 1984), the congenital surveillance system in Canada (Froster-Iskenius and Baird, 1989) and subsequently to the Uppsala Monitoring Centre, UMC, http://www.who-umc.org. The aim was to improve worldwide patient safety, in collaboration with the World Health Organisation (WHO), (Kelsey, 1967, Froster-Iskenius and Baird, 1989, Agerberg, 2011). One of the main purposes of the UMC related to pharmacovigilance is to support good decision-making in terms of the benefits and risks of treatment options for patients using different drugs.

Thalidomide in Japan

In Japan, the drug formula was changed, which explains why no patent was needed to produce the drug in that country. The drug was then sold under different names. Every belief and major opinion leaned towards its harmlessness and the risk of teratogenicity was neither considered nor accepted. The way this drug was handled by the government and the circumstances related to its production in Japan are the reason why the drug was still sold nine months after its withdrawal in Europe (Kida and Lenz, 1968). The complete withdrawal of the drug in Japan came at the end of 1963 (Kida and Lenz, 1968, McCredie, 2009).

Figure 6: Mrs Frances Oldham Kelsey (1914-2015) (photo from US National Library of Medicine, https://www.nlm.nih.gov)

Thalidomide in the United States

Mrs Frances Oldham Kelsey, Figure 6, became one of America's most celebrated public servants by not approving thalidomide in the USA. Frances Oldham Kelsey, PhD, MD, earned her MD and PhD in pharmacology at the University of Chicago. She was practising medicine in 1960 when she was offered the chance to become a medical officer at the FDA. In the USA, the applications to distribute the drug were sent to the FDA. Shortly after assuming her position, she was assigned to review a new drug application for thalidomide. Despite the global popularity of this drug and despite constant and increasing pressure from the drug company to approve the application, Dr Kelsey asked for evidence that the drug was safe, as she had studied the effect on the metabolism of mothers and embryos and had seen the diverse effects of different drugs in different individuals (Kelsey et al., 1945). Moreover, thalido-

mide had mostly been used by women after the birth of their children (Taussig, 1962, Kelsey, 1967,). Her decision not to approve the drug was supported by her colleagues and superiors. Frances Kelsey wrote in her Autobiographical Reflections (FRANCES OLDHAM KELSEY):
I came on the first of August 1960 and I think I got the thalidomide application in early September 1960. I believe it was the second one that was given to me. I was the newest person there and pretty green, so my supervisors decided, "Well, this is a very easy one. There will be no problems with sleeping pills".

"…..the peripheral neuritis did not seem the sort of side-effect that should come from a simple sleeping pill…"

It is worth mentioning the reaction towards a new medical officer, who also happened to be a woman, in what was then most definitely a man's world in science. As described by Dr Kelsey on 10 August, she was called "unreasonable and irresponsible". To his credit, Dr Kelsey's boss, Julius Hauser, decided to back his young pharmacologist. Thalidomide was not licensed for use in the USA between 1957 and 1961, due to the fact that Dr Frances Kelsey did not approve its applications. By doing so, Dr Kelsey undoubtedly prevented thalidomide-induced birth defects and deaths and without doubt prevented a disaster in the USA. For this, she received the nation's highest federal civilian service award, presented by President John F. Kennedy in 1962 (Vargesson, 2013). She died on 7 August 2015 at the age of 101 years. In the USA, only 17 children with TE have been identified, of which seven cases were caused by drugs sold outside the USA (Lary et al., 1999). The drug regulations were neither common, nor strict, at this time period and the most striking aims were to make money after the Second World War in Europe (McCredie, 2009). Dr Frances Kelsey published several papers on improving drug testing and safety and started the basics of drug testing and investigations which led to the regulations used today. Her pioneering work subsequently changed the global rules for drug introduction (Kelsey, 1967, Kelsey, 1988, Nilsson, 2004, Agerberg, 2011).

6.2.3 Mechanism of action

Over the years, many theories have been presented regarding the way thalidomide actually causes birth defects.

Pharmacokinetics

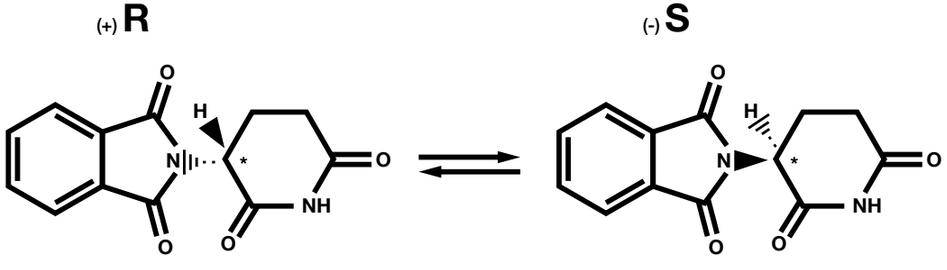


Figure 7: Thalidomide

Thalidomide is a derivate of glutamic acid, an essential amino acid, which is important for the function of the brain and during muscle development (Vargesson, 2013). Thalidomide consists of two linked rings, a glutarimide ring and a pthalimide ring (Vargesson, 2015), and exists in two isometric forms which interconvert into one another spontaneously in physical conditions (PH 7), Figure 7. R (+)-thalidomide and S (-)-thalidomide (Franks et al., 2004), the two isomers, have different responsibilities. R (+) is responsible for the sedative effect of the drug and S (-) is responsible for its teratogenicity by inhibiting the tumour necrosis factor (TNF) (Franks et al., 2004). This conversion of the two isomers makes it very difficult to isolate them from one another in clinical applications (Franks et al., 2004, Vargesson, 2009). The thalidomide molecule is believed to have an active half-life of around 8-12 hours. Thalidomide is metabolised in the liver through the involvement of the hepatic enzyme P450 (Franks et al., 2004, Lu et al., 2004).

Effects during embryonic development

Thalidomide acts during embryonic development in a time-sensitive window (Lenz and Knapp, 1962, Kida and Lenz, 1968, Miller and Strömland, 1999, Vargesson, 2013). The critical time for thalidomide to act is 20-36 days after fertilisation or 34 to 50 days after the last menstrual period (Kida and Lenz, 1968, Smithells and Newman, 1992, Miller and Strömland, 1999), (Table 2). It has been reported that 50 mg of the drug administered to pregnant women during the time-sensitive window would cause birth defects in approximately 50% of the foetuses, demonstrating the high teratogenicity of the drug (Vargesson, 2013). Nevertheless, some studies have also reported an even higher risk and claim that no pregnancy period would be safe, regardless of when thalidomide is consumed during a pregnancy (Smithells and Newman, 1992). These reports on the critical times are based on interviews with the mothers of malformed children, performed by their physicians (Lenz, 1961, McCredie, 2009). It is important to mention that, although investigations initially identified a time-sensitive window during the first trimester (Kida and Lenz, 1968, Strömland and Miller, 1993, Miller and Stromland, 2011), it has recently been suggested that exposure to thalidomide at a later time during foetal development would affect other organs. It has been reported about autism in individuals with TE in a Swedish population with individuals with TE (Strömland et al., 1994). There has also been suggested that later exposure could affect angiogenesis in the brain, causing cell death and subsequent afflictions like epilepsy and autism (Smithells and Newman, 1992, Miller et al., 2005). Taken as a whole, thalidomide is also considered harmful after what is known as the time-sensitive window (Hallene et al., 2006, Miller and Stromland, 2011).

Anti-angiogenic effect

Blood vessels are important for normal embryonic development and supply tissues with nutrition and oxygen. Blood vessels develop in two steps, vasculogenesis and angiogenesis. The first is the migration of the endothelial cells towards one another to make the vascular tubes and the next step is when the tubes form a complex network of vessels in the tissues of the embryo (Vargesson, 2013). Thalidomide is anti-angiogenic, which makes the drug suitable for treatment in some cancer therapies (D'Amato et al., 1994). The effect of thalidomide on vessel formation has also been suggested as a reason for limb teratogenesis (Therapontos et al., 2009). The loss of blood vessel formation during early foetal development is usually lethal, or may cause serious malformations, similar to the action of other anti-angiogenic teratogenic drugs, such as sodium valproate (Whitsel et al., 2002). However, whether the anti-angiogenic effect is responsible for limb defects has not been confirmed in vivo. There are further suggestions that thalidomide may affect limb development by inducing changes in gene expression (Lebrin et al., 2010), but the mechanism by which thalidomide might target limb gene expression is unknown. It has further been suggested that the loss of newly formed and immature blood vessels is the primary cause of thalidomide teratogenesis (Therapontos et al., 2009). Even if the exact mechanism is not known,

thalidomide is able to interfere with angiogenesis and inhibit the formation of new blood vessels that are important for the normal development of the embryo (Kenyon et al., 1997).

Anti-inflammatory capacity

Thalidomide has an anti-inflammatory capacity due to the inhibition of tumour necrosis factor (TNF) by enhancing mRNA degradation (Moreira et al., 1993) and further by COX-2 inhibition in monocytes and macrophages (Payvandi et al., 2004). Since TNF is an important factor in regulating the inflammatory response to different injuries and other stimuli, thalidomide is a potent substance when it comes to reducing inflammation in autoimmune diseases, like multiple myeloma, (Hideshima et al., 2000), erythema nodosum keprosum (Jurado et al., 2015) and Crohn's disease or ulcerative colitis in children (Yang et al., 2015).

Neurotoxicity

One of the earliest reports on the side-effects of thalidomide related to polyneuritis (Leslie Florence, 1960). This was reported after long use (between 18 months to more than two years) of thalidomide, (Leslie Florence, 1960, Taussig, 1962).

In addition to the high teratogenicity of the drug, thalidomide has neurotoxic effects on the peripheral motor nerves (Clemmensen et al., 1984, Oshima et al., 2006, Svetlana Balkanov et al., 2014, Yang et al., 2015)), as well as the sensory nerves (Fullerton and Kremer, 1961, Fullerton and O'Sullivan, 1968, Schwab et al., 1984, Nicotra et al., 2016). The exact mechanism for this is not known. A study of the sural nerve in rabbits with thalidomide-induced treatment has shown (Schwab et al., 1984) early toxic neuropathies with morphological findings in the central nervous system (CNS), as well as in the peripheral nervous system (PNS). In a recent study of peripheral nerves, dysfunction in both large sensory nerve fibres and small sensory fibres in the peripheral nerves was seen (Nicotra et al., 2016). It has still not been clarified whether or not these findings are a result of a direct effect of thalidomide exposure. Jankelowitz et al. have described peripheral neuropathy occurring in the median nerve at wrist level, which is mainly compressive neuropathy and due to the mechanism of overusing abnormal upper limbs for activities of daily living (Jankelowitz et al., 2013).

It has also been claimed that exposure to thalidomide during the foetus-sensitive period causes ear and cranial nerve (CN) abnormalities and deficits causing Duane's syndrome (DS) (CN 6) or other abnormalities of the facial nerve and aberrant tearing (Miller and Stromland, 2011). Injury to the neural crest has also been suggested (McCredie, 1976) and it could affect the migration of the neural crest and the nerve innervation of tissues and result in limb formation failure. The limbs are, however, not innervated until late in the foetal period (Martin and Lewis, 1989). The fact remains that the teratogenicity of the drug causing a direct injury to the neural crest has not been clarified (Vargesson, 2013).

6.2.4 Malformations and defects

Thalidomide is a powerful human teratogenic agent, inducing a high frequency of severe and life-threatening birth defects when ingested during early pregnancy (Stromland et al., 1991, Strömland and Miller, 1993, Miller and Strömland, 1999). The mortality of foetuses and infants due to TE, especially related to serious internal organ damage, is estimated to be almost 40% (Smithells and Newman, 1992, Vargesson, 2013). Featured malformations appear due to the teratogenicity of thalidomide leading to TE. Phocomelia, amelia, three phalangeal thumbs, spine malformations, ear and eye abnormalities, blindness, deafness, abnormalities of internal organs such as agenesis of the gall bladder, anomalies of the vascular systems (Björck and Wanhainen, 2007, Tajima et al., 2016) and inner genital absence or duplication are the most common malformations in TE. Abnormalities of the lower limbs are less common than those of the upper limbs, but the exact reason for this is unclear (Winberg, 1964c, Newman, 1985, Newman, 1986, Castilla et al., 1996). Bilateral limb defects are classical in individuals with TE, but the malformations do not need to be similar to one another (Castilla et al., 1996, Vargesson, 2015). Although unilateral damage is not considered to be a feature hallmark of TE, several cases have nonetheless been reported (Schmidt and Salzano, 1980). Many individuals with TE have been shown to have abnormal posture and scoliosis in particular has been reported (Kida and Lenz, 1968, Ruffing, 1980).

Malformations of the limbs

Amelia /phocomelia

Amelia means that a limb is completely absent and no part of a proximal or distal part of an extremity (or several extremities) has developed (Figure 1).

The definition of phocomelia is that the arm and forearm of the upper limbs or the thigh and leg in the lower limbs are absent, i.e. the hands or feet are attached directly to the trunk. The most striking limb defect as a result of thalidomide is phocomelia, where the proximal parts of the extremities are under-developed or not developed at all (Leck and Millar, 1962, Smithells, 1973, Newman, 1986). Phocomelia can also differ in severity. The total absence of the long bones is the most severe form. For the upper extremities, the hands are then directly attached to the trunk with only a flipper-like structure.

Other malformations of the extremities also exist. Some examples are radial hypo/aplasia, with radial bowing of the lower arm as a result, and finger anomalies where the most striking is absence or hypoplasia of the thumb, or three-phalangeal thumbs. PFFD with significant shortening of the thigh and hypo- or aplasia of either tibia or fibula are other malformations seen in individuals with TE.

Malformations/effects on the central nervous system

The anti-angiogenetic effect of thalidomide has been investigated in vitro to explain malformations of the cortical development in the brain (Hallene et al., 2006). It has been suggested that, with anti-angiogenesis caused by thalidomide, new blood vessels in the brain would not develop and this might lead to brain cell necrosis and death. The protein cereblon has been identified as a primary target for thalidomide as a thalidomide-binding protein in humans (Ito et al., 2010). Cereblon is not only involved in the anti-inflammatory effect of thalidomide (Broyl et al., 2013), it is also a gene related to mental retardation (Xin et al., 2008). In the epidemiological Swedish study by Strömland et al., in 1994, there was an increased incidence of autism in thalidomide survivors compared with the rest of the population (Stromland et al., 1994).

Other organ defects

Several kinds of malformation of other organs have been reported. They include malformations of the eyes and ears, causing problems like hearing impairment, deafness and blindness (Livingstone, 1965, Miller et al., 2008). Facial damage; Duane syndrome (DS) is characterised by an abduction deficit of the abducens nerve (CN 6), with secondary aberrant innervations of

the lateral rectus by the oculomotor nerve (CN 3). DS is frequently observed after thalidomide exposure (Miller and Stromland, 1991). After limb malformations, eye abnormalities are the second most frequent manifestation of thalidomide embryopathy in living subjects (Miller and Stromland, 1991, Jankelowitz et al., 2013). Malformations of the spine, such as vertebral column fusion ((Edwards and Nichols, 1977, Ruffing, 1978, Newman, 1985), have also been mentioned. Internal organ defects have further been described for the urinary tract, kidneys, heart and genital organs (Chamberlain, 1989).

Table 2: The pattern of how different malformations occur during the time-sensitive window (Strömland and Miller, 1993)

Days after last menstrual period	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53
Mean age of the foetus	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
Age in weeks	3		4							5							6			
Sensitive phase to thalidomide	Anotia					Ear malformation														
		Thumb aplasia/ hypoplasia																		
							Amelia and phocomelia of the upper limbs													
								Amelia or phocomelia of the lower limbs												

6.2.5 The medicolegal aspects of thalidomide

When the reason for the malformations in TE became publicly known, legal processes against the company in West Germany and Sweden started (McCredie, 2009, Agerberg, 2011). It took years for the individuals with TE to receive any compensation and recognition during the course of legal standards of proof and causation (Bernstein, 1997, McCredie, 2009). The processes started by acknowledging the special needs of these children as they grew. Those with the most severe malformations of the extremities, in combination with malformations of the ears and eyes, often became institutionalised. As the cost increased and compensation became known and accepted, mothers who had denied using the drug came forward, as did physicians who admitted prescribing the drug (McCredie, 2009). In West Germany, special orthopaedic clinics and special schools for the care of these children were started all over the country and children with these deformities received a great deal of medical attention (von Pawel, 1972). Despite the increased knowledge and improved treatment opportunities nowadays, the dark side remains and children are still being born with these limb defects, in Brazil, for example (Castilla et al., 1996, Vianna et al., 2011, Vianna et al., 2013). This is mostly the result of the culture of medication-sharing in society. Pregnant mothers and leprosy patients, or those with a disease but without an awareness of being pregnant, have been sharing/using the drugs. The less stringent policy for prescription and the misunderstanding of drug labelling have also added to the situation in Brazil (Vargesson, 2013, Vargesson, 2015). Thalidomide caused the largest man-made medical disaster to date (Vargesson, 2013, Vargesson, 2015), but, at the same time, it opened the door to today's knowledge of drug toxicology and forever changed the way new drugs are tested and marketed both now and in the future.

6.2.6 The use of thalidomide today

Thalidomide has been re-marketed (Lary et al., 1999) and, nowadays, it is used for the treatment of a number of different diseases (Lowell, 1995). Because of its anti-inflammatory action on mycobacterium leprae (Sheskin, 1965, Vargesson, 2013), leprosy has been treated with thalidomide since 1965, in addition to other autoimmune disease like arthritis and sarcoidosis. Further, gastro-intestinal diseases, such as Crohn's disease and hereditary haemorrhagic haemangioectasy, are treated with thalidomide (Ladizinski et al., 2010, Lebrin et al., 2010). The anti-angiogenentic effect of thalidomide has been used in the treatment of a few cancer diseases (D'Amato et al., 1994, Franks et al., 2004) like multiple myeloma (Giles, 2002) Kaposi's sarcoma in AIDS (Little et al., 2000, Wu et al., 2005), renal cell cancer (Stebbing et al., 2001) and prostate cancer (Song et al., 2015). Thalidomide has been licensed around the world since 1998 (Vargesson, 2013); in the USA since 2005-2006 (Castaneda et al., 2008), according to a risk minimisation program called the Celgene REMS (Risk Evaluation and Mitigation Strategy) Program, similar to the Thalidomide Celgene Pregnancy Prevention Programme. The programme must be complied with, by all male (Zeldis et al., 1999, Teo et al., 2001, Ances, 2002) and female patients using the drug. This programme is known as the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) (Zeldis et al., 1999). It requires prescribers to certified patients to be well informed. In Sweden, there are strict rules related to how and to what extent the drug may be used. Thalidomide must never be used by women who are pregnant or by women who could become pregnant. A female patient or a female partner of a male patient, as thalidomide is also found in semen (Teo et al., 2001), is considered to have child-bearing potential, unless she meets at least one of the following criteria: http://www.fass.se

- *Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year, but not following cancer therapy*
- *Premature ovarian failure confirmed by a specialist gynaecologist*
- *Previous bilateral salpingo-oophorectomy, or hysterectomy*
- *XY genotype, such as Turner's syndrome, uterine agenesis.*

Women with childbearing potential must be made aware of the risk of congenital malformation in the unborn child. These women must be informed and understand the need for effective contraception, without interruption, four weeks before starting treatment, throughout and four weeks after the treatment. As thalidomide is found in semen (Teo et al., 2001), male patients taking thalidomide must also follow certain rules. The patients, both men and women, must confirm that they understand all the conditions and use an effective method for contraception. A pregnancy test must ensure that a female patient is not pregnant when she starts a treatment with thalidomide. The test should be repeated every four weeks, including four weeks after interrupting or ending the treatment.

6.2.7 The Swedish Thalidomide Society

"Föreningen för de Neurosedynskadade" (FFdN)
(www.thalidomide.org)
FFdN is the Swedish name for The Swedish Thalidomide Society which collaborates with other thalidomide societies in other countries and gives continuous information to its members.

6.3 Instruments and methods for studying musculoskeletal malformations and function

6.3.1 Imaging investigations

Conventional plain radiography (X-ray) can be used for the general screening of malformations of the limbs and spine, for example. However, computed tomography (CT) is preferable for detailed information on existing malformations involving the skeleton. When performed as a spiral CT, the radiation dose is lower, but sufficient information can still be obtained. For osteoarthritis, plain radiographs taken with the patient in a standing position for weight-bearing are normally used. However, a spiral CT may also yield information for the evaluation of osteoarthritis (OA) of the hip and knee joints (Li et al., 2016). Magnetic resonance imaging (MRI) is used when information on soft tissues, cartilage and nerve compromise is required. For example, MRI can be used to detect degenerative changes in the spine and intervertebral discs, where plain radiography and CT are less sensitive to early changes (Resnick, 1985).

For different locations in the body, different evaluation scales are also sometimes used for CT and MRI findings. For the evaluation of disc degeneration in MRI, the most used classification is the Pfirrmann grading. The Pfirrmann classification is based on nucleus structure, distinction between nucleus/annulus, signal intensity and disc height respectively, using the grades I-V (Pfirrmann et al., 2001) Figure 8, Table 3.

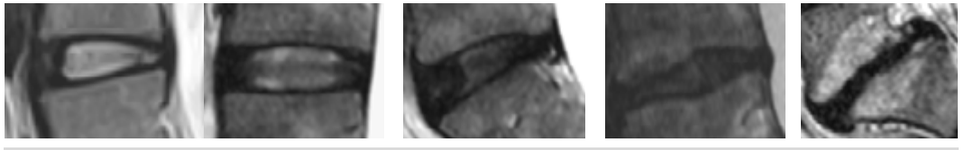


Figure 8: Different degrees of disc degeneration according to Pfirrmann captured in MRI

Table 3: Pfirrmann's classification of disc degeneration (Pfirrmann et al., 2001)

Grade	Nucleus structure	Distinction nucleus/ annulus	Signal intensity	Disc height
I	Homogeneous, white	Clear	High	Normal
II	Inhomogeneous+/- grey line	Clear	High	Normal
III	Inhomogeneous, grey	Unclear	Intermediate	Normal to slight decrease
IV	Inhomogeneous, grey or black	Lost	Intermediate/low	Normal to intermediate decrease
V	Homogeneous, black	Lost	Low	Collapsed

6.3.2 Patient-reported outcome measurements (PROM)

Generic health-related Qol questionnaires

The definition of health according to the WHO is not only the absence of sickness but also a state of physical, mental and social well-being. There are several tools for measuring health-related quality of life. The most frequently used ones are the Short Form-Health Survey with 36 items (SF-36) developed by the RAND Corporation, a non-profit research organisation in the USA, and the EuroQol 5 Dimensions (EQ-5D), developed by European research partners.

SF-36 (Short Form-36)

The SF-36 is a well-known validated instrument for measuring both physical and mental components of health quality (Ware and Sherbourne, 1992). A validated Swedish translated version of this questionnaire has been presented and recently used (Sullivan and Karlsson, 1998, Danielsson et al., 2001). It is based on self-reported patient information. The SF-36 evaluates the physical as well as the mental health through 36 questions. The answers are calculated into subscores: the physical scores; Physical Function (PF), Role Physical (RP), Bodily Pain (BP) and General Health (GH), and the mental scores; Vitality (VT), Social Function (SF), Role Emotional (RE) and Mental Health (MH). The scores are between 0-100, where the sum of 100 indicates the best function.

Two summary scores can also be calculated using the subscores, a physical composite summary score (PCS), mainly based on the four physical subscores and a mental composite summary score (MCS), mainly based on the four mental subscores. The normal value of this is 50. This questionnaire has previously been used in orthopaedic populations (Danielsson et al., 2001).

EQ-5D (Euro-Qol 5D)

The EQ-5D is a standardised non-disease-specific questionnaire to describe and value health-related quality of life (Brooks, 1996). The EQ-5D is a self-reported health report of the respondent's situation at the time of questioning and can be used in both postal surveys to evaluate the result of a treatment in a population and in face-to-face interviews. The EQ-5D covers the following five dimensions: mobility, self-care (i.e. hygiene), usual activities (i.e. ADL), pain/discomfort and anxiety/depression or stress. Every dimension is presented with three alternatives as follows; "no problems", "some problems" and "severe problems".

The result is subsequently presented as 1, 2 or 3 and is then translated according to the health-related quality tariff system (Brooks, 1996, Burstrom et al., 2001, Burstrom et al., 2014). The best overall descriptive result is 1 and the worst is zero. Negative values are sometimes measured in the tariff system, meaning conditions worse than death. It also includes a VAS scale for the individual's perception of his/her current health state, which will result in a value between 0 and 100 (worst to best).

The EQ-5D has also previously been used in orthopaedic as well as other studies (Hansson et al., 2006, Sandberg et al., 2015).

Disease-specific validated questionnaire

RAOS, Rheumatoid Arthritis Outcome Score

The RAOS (Fries et al., 1980, Bellamy et al., 1988, Roos et al., 1998) is a disease-specific validated instrument for evaluating both symptoms and functional impairment in persons with lower extremity impairment and it has been translated into Swedish (Bremander et al., 2003). The RAOS can be used for both short- and long-term evaluation; to assess changes over time, for instance, week to week, induced by a treatment (medication, operation, physical therapy) or over years such as following up an outcome after surgery. The RAOS is self-reported and evaluates hips/knees/feet and associated problems. It is a 42-item instrument and covers five relevant dimensions and subscales; pain, other symptoms, function in daily living (ADL), function in sport and recreation (Sport/Rec) and knee-related quality of life (QOL). Each item is answered as "None", "Mild", "Moderate", "Severe" and "Extreme" and is scored as 0-4. The result is the

sum of the total score for each subscale divided by the possible maximum score for the scale. One hundred indicates no symptoms and 0 indicates extreme symptoms.

DASH, Disability in Arm Shoulder and Hand

The DASH is a well-known, validated instrument describing the degree of disability experienced by individuals with upper-limb disorders. The DASH is also used to monitor changes in symptoms and function over time (Atroshi et al., 2000). The DASH Outcome Measurement is a 30-item, self-reported questionnaire designed to measure physical function and symptoms in people with any kind of musculoskeletal disorder of the upper limbs.

The DASH Outcome Measurement includes two components:

1) The main part (mandatory) evaluates disability and symptoms using 30 items, all scored 1-5

2) The optional high performance Sport/Music or Work sections with four items each with the possibility to score between 1 and 5.
At least 27 of the 30 items in the main part must be answered in order to have obtained a reliable score. No item can be missed in the optional part for this score to be calculated. A higher score indicates greater disability and the scores are reported between 0-100, with 0 as the best value.

General Function Score (GFS)

The GFS is a disease-specific instrument used initially to evaluate physical disability in patients with low back pain (LBP) (O. Hägg, 2001). It focuses on the ability to perform 17 daily living activities. The alternatives for answers are scored with “can perform”, “can perform with difficulty” and “cannot perform”. The total score is given as a percentage between 0 and 100, where “0” represents no physical disability or dependence and “100” represents maximum physical disability and dependence. The GFS has also been validated for nine and 11 questions (O. Hägg, 2001).

6.4 Current knowledge of the long-term outcome in TE

Most individuals with TE are now over 50 years old. With ageing, there is a deterioration of the joints and other organs as part of the physiological ageing process. This might lead to the need for extra help or aids to perform tasks that were previously performed by the TE individuals themselves. The long-term effects of TE and other similar limb deformities on function, quality of life and mental parameters have been only sparsely studied.

The dental status of the same individuals as in the orthopaedic studies in this thesis was studied (Ekfeldt and Carlsson, 2008) and revealed that the teeth in some individuals with TE are used as tools; however, the teeth are mostly affected by a negative effect of frequent regurgitations. Kowalski performed a clinical follow-up of 28 individuals with TE in Brazil (Kowalski et al., 2015), focusing primarily on the late effect on other organs rather than degenerative changes in the joints and reported, for example, on dental loss and progressive deafness. They also reported the early onset of cardiovascular diseases and a higher frequency of psychological disorders. There are also previous studies focusing on the psychological effects of TE and demonstrating more anxiety in TE individuals (Imai et al., 2014). Shiga et al. demonstrated an increased frequency of dyslipidemia in individuals with TE (Shiga et al., 2015) and also a higher than 50% prevalence of hypertension in this group. It is, however, not clear if these findings are related to lifestyle, such as less physical activity or smoking. Studies have further demonstrated evidence of a high frequency of peripheral nerve dysfunction in middle-aged TE individuals (Kowalski et al., 2015, Nicotra et al., 2016). To the best of our knowledge, there have been no studies clarifying the level of degenerative changes in the hip and knee joints and the spine in this group. No long-term studies of individuals with TE, focusing specifically on orthopaedic problems, physical function or quality of life, have previously been performed. This is one of the most important reasons why the studies in this thesis were initiated.

7. Aims

The overall aim of this thesis was to investigate different health parameters in a middle-aged cohort of individuals with thalidomide embryopathy (TE).

The more specific aims in this cohort of middle-aged TE individuals were:

- To characterise the types of malformation in the upper and lower extremities and how these affect function, as measured by validated questionnaires (Study I)
- To investigate the radiological appearance, as well as clinical signs of osteoarthritic changes in the hips and knees, in the TE cohort and to relate them to clinical signs (Study I)
- To examine the presence of malformations and degenerative changes in the cervical spine using MRI and to compare the findings with those in an age- and gender-matched control group (Study II)
- To investigate HRQL, both overall and for physical and mental health respectively, and to compare these scores with a population-based control group of similar age (Study III)
- To look for correlations between HRQL and limb malformations (Study III)
- To study the need for orthopaedic care, including surgical correction of the limbs, technical aids such as prosthesis and orthoses or walking aids, disability adjustment of the workplace and/or home and functions in daily life and participation in physical activities (Study IV)

8. Material and Methods

8.1 Study set-up

All the studies in this thesis are derived from a multi-disciplinary cohort study of middle-aged Swedish individuals with TE. Apart from the orthopaedic studies, the overall study plan included investigations by other specialists focusing on speech pathology, dentistry, neuropsychology and ophthalmology. To be able to collect information in all these areas, without too much travelling, the participants were invited to take part in a visit at which all the examinations and interviews were planned to occur during a single day. Participants were invited through "The Swedish Association for Thalidomide Embryopathy" and came from different parts of Sweden. Three participants were living abroad, one person was visiting his hometown in Sweden from the USA and two were living in Norway. The study was performed at Sahlgrenska University Hospital, Gothenburg, Sweden.

8.1.2 The participants

The Swedish Association for Thalidomide Embryopathy had 108 members at the time the study was planned. Due to the strict rules of the association, all contacts with its members had to be made through the association. The invitations were sent out by the association and no reminder was allowed to be sent to those who did not respond. A total of 31 individuals, 18 males and 13 females, with a mean age of 45.8 (range 45-50) participated in Studies I, III and IV. Twenty-seven individuals from the whole group, 16 men and 11 women with a mean age of 46.2 /range (45-50), accepted the invitation for MRI and participated in Study II.

The number of invited and participating individuals in the four studies within the thesis is shown in Table 4.

Table 4: Flow chart of invited and included individuals in Studies I-IV

All members 108				
Declined 24	Invited 84			
	Accepted 33	Declined 18	Did not respond 33	
	Participants			
	Studies I, III and IV 31	Excluded 1 [1)]	Excluded 1 [2)]	
	Study II 27	Excluded 1 [3)]	Excluded 2 [4)]	Declined 1

[1)] Severe mental problem, [2)] Stroke, [3)] Metal clips in the head, [4)] Claustrophobia

Controls (Study II): Twenty-seven age- and gender-matched individuals were collected from the group of patients who had undergone MRI investigation of the whole spine between 2003 and 2014 at Sahlgrenska University Hospital in Gothenburg. None of them had any previous specific cervical pathology according to the referrals and they were included as a control group for comparison with the TE group, in terms of the presence of degenerative changes to the cervical spine.

8.1.3 Grouping of the participants in different studies

The TE participants were grouped into different subgroups based on the degree of malformation/s for comparisons and evaluations of function and HRQL.

- According to the presence of an anatomic pincer grasp with proper opposition of the thumb. Those with no/a unilateral pincer grip (n=20) versus a bilateral pincer grasp (n=11) (Studies I, III)
- According to the presence of extremity/ies with major malformation (n=15) versus no extremity with major malformation (n=16). (Just finger and toe malformations did not count as major deformities.) (Studies I, III)
- According to a functional hand-grip function, for one or no hand (n=4) versus both hands (n=27). A hand was defined as a palm with two fingers (Study I)
- According to proximal focal femoral deficiency (PFFD) with the absence of the femoral head or acetabulum (n=5) (based on a CT scan and Gillespie classification) (Gillespie and Torode, 1983) versus those without PFFD (n=26) (Studies I, III and IV)
- According to the need for additional help during daily life, such as personal assistance, disability-adapted home and/or work. Group A (n=12), who needed additional help versus Group B (n=19), without additional help requirements (Study IV).

The different subgroups used for comparison between one another in different studies are shown in Table 5.

Table 5: Different subgroups and control subjects used for comparison in the four studies

All, n=31	Study I	Study II	Study III	Study IV
Control group, n=27		X		
PFFD, n=5, No PFFD, n=26	X		X	X
Anatomic pincer grasp in one or no hand, n=20, versus bilateral pincer grip, n=11	X			
Functional hand-grip function (in one or no hand), n=4, versus bilateral functional hand grip, n=27	X			
Need for some type of additional help during daily life (Group A), n=12, versus no need for additional help in daily life (Group B), n=19				X
Major malformations in at least one extremity, n=15, versus no severe malformation in any of the extremities, n=16	X		X	

8.1.4 Study focus and questionnaires

Study I focuses on an evaluation of malformations and the degree of degenerative changes of the large joints of the lower limbs (CT and clinical examination) and related to function of upper and lower limbs (using DASH and RAOS questionnaires respectively).

Study II focuses on the development of degenerative changes of the cervical spine as evaluated by MRI examinations.

Study III focuses on health-related quality of life, measured with SF-36 and EQ-5D, and its relationship with malformations and function of the limbs, as evaluated by the DASH and RAOS.

Study IV focuses on the ability to handle daily living, evaluated by the GFS questionnaires and study-specific questions.

Table 6 summarizes methods used in Study I-IV.

Table 6: Investigations and instruments used in the different studies

Instrument	Clinical examination	CT	MRI	Questionnaires					
				SF-36	EQ-5D	RAOS	DASH	GFS	Others
Study I	X	X				X	X		X
Study II	X		X						X
Study III	X			X	X	X	X		X
Study IV								X	X

8.2 Methods

8.2.1 Clinical examinations (Studies I, II, III, IV)

In the evaluation procedure for all participants, a thorough inspection and examination of all four limbs, as well as the whole spine, were performed.

All the participants gave their consent to participate in the study. They were all examined clinically by the same orthopaedic surgeon. All visible malformations on the extremities were documented. All digits were counted for both hands and feet. Range of motion (ROM) measurements of all joints present in the upper and the lower extremities were performed. The Myrin instrument (Malmstrom et al., 2003) was used to measure the ROM of the cervical spine. A neurological examination including motor and sensory functions in both upper and lower extremities was performed. Lachman's test was performed for evaluating of sagittal knee stability.

8.2.2 Validated questionnaires (Studies I, II, III, IV)

All the participants answered disease-specific questionnaires. To evaluate the function of the upper limbs, the DASH (Disability in Arm, Shoulder and Hand) (Atroshi et al., 2000) was used and, for the evaluation of function in the lower limbs, the RAOS (Rheumatoid Arthritis Outcome Score) (Bremander et al., 2003) was used. To evaluate the general function in the group, the disease-specific validated questionnaire, the GFS (General Function Score) (O. Hägg, 2001), was filled in by all participants. The GFS questionnaire was adjusted to some extent, in order to suit the participants of this study. Firstly, in the original version of the GFS, there is a question about the spine. This specific question was removed to make sure that participants would not relate their answers primarily to a spinal condition or disorder. Secondly, to the three answer options for each question in the original questionnaire, a fourth option was added ("need help to perform") to collect information about whether the person needed the aid of an assistant to perform a specific task. To evaluate health-related quality of life, the two validated self-reported instruments, the SF-36 (Short form- 36) (Ware and Sherbourne, 1992) and the EQ-5D (Euro Qol- 5 dimensions) (Brooks, 1996) that previously was used in a Swedish population (Hansson et al., 2006), were used. The SF-36's two summary components, Physical and Mental Composite Summary scores (PCS, MCS), and each subscore (PF, RP, BP, GH, VT, SF, RE and MH) are presented separately. To evaluate the reported level of quality of life as measured by the SF-36, the patients' results were compared with the national general population using z-scores. This measures the number of standard deviations (SD) below or above the population mean for the specific score. For each subscore the z-score of each individual was calculated; the difference between the individual domain score value and the reference mean (according to age and gender) for that specific subscale was calculated and it was then divided by the reference SD. These z-scores were used for statistical calculations.

8.2.3 Study-specific questionnaires (Studies I, II, III, IV)

A study-specific questionnaire about other diseases related or unrelated to TE, family situation and other sociodemographic data, such as number of children, occupational status and educational degree, was used. Information about previous surgeries and the age of the participant at the time of surgery was also collected. Questions on whether additional external help was needed, such as a personal assistant, disability-adjusted home or adjustments at work, were also included. Moreover, the questionnaires covered information about the use of walking aids and external prostheses, as well as the time every individual spent on managing ADL in the morning and in the evening before bedtime. The WHO questionnaire for the evaluation and measurement of the effect of stress in relation to health (Rosengren et al., 1993) includes questions about smoking, family status and other sources of stress. The parts of the WHO questionnaire in which the stress scores are related to physical activities during both work and spare time were used (Wiklund and Karlberg, 1991, Danielsson et al., 2001).

8.3 Imaging investigations

8.3.1 Computed tomography (Study I)

All patients underwent a spiral computed tomography, CT, in order to evaluate osteoarthritis (OA) of the joints in the lower extremities. Spiral CT was preferred because of the low radiation dose, i.e. none exceeded 2.2 mGy/cm. All CT investigations were performed without contrast injections at Sahlgrenska University Hospital in Gothenburg. CT was performed in the supine position and did not include any weight-bearing on the knees. A modified scale of the Ahlbäck lassification (Ahlback, 1968, Ahlback and Rydberg, 1980) was therefore constructed to evaluate signs of OA and included grade "0", grade "1" and grade "2". Grade 0 indicated "no sign of OA", Grade 1 indicated "mild OA", defined by the reduced height of the joint space and/or a few osteophytes, and Grade 2 indicated "severe OA", where cysts and osteophytes were detected. The hip joints were evaluated as one "anatomic organ", while the knee joints were divided into three parts, the medial, the lateral and the femoro-patellar compartments. All variables from the spiral CT were evaluated by two independent radiologists and were re-evaluated by an orthopaedic surgeon and a paediatric orthopaedic surgeon.

8.3.2 Magnetic resonance imaging (Study II)

The study group

Twenty-seven of 31 participants in the overall individuals with TE in the study group underwent MRI investigation of the cervical spine. One person had a metal clip in the brain due to a neurosurgical procedure during the 1980s, after a traumatic event. One person declined to undergo MRI and two individuals were excluded due to claustrophobia, Table 4. Magnetic Resonance Imaging (MRI) was performed at Sahlgrenska University Hospital in Gothenburg for the majority of the participants. Seven participants preferred to have an MRI at their regional hospital due to difficulty travelling. The same MRI protocol for the cervical spine was used in all investigations. All images and variables were evaluated by the same radiologists at Sahlgrenska University Hospital in Gothenburg. The MRIs were performed in 2008 and the mean age of the patients was 46.2 years, SD/range (1.0/ 45-50).

The MRI examinations were performed with sagittal T1-weighted and T2-weighted images and axial T2-weighted images. For all sequences, the field of view (FOV) was 10 cm and the slice thickness 3-6 mm. In the group of individuals with TE, both sagittal and axial sequences were used for the assessment of disc bulge, herniation and foraminal stenosis.

The control group

Twenty-seven age- and gender-matched controls (CTR) who underwent an MRI during the period 2003-2014 with no evidence of cervical pathology according to the referrals were included. For most of the controls, only sagittal images were available (axial images were only included if any pathology was seen in the sagittal images).

Evaluations of all MRIs

The Pfirrmann classification was used for the evaluation of disc degeneration (Pfirrmann et al., 2001). For both TE and controls, all intervertebral discs were evaluated for narrowing of disc space (≥ 25% loss of height), presence of anterior or posterior osteophytes, anterior or posterior disc bulge, disc herniation, foraminal stenosis, anterior compression of the dural sac and the presence of malformations such as block vertebrae (Fardon and Milette, 2001). All variables were analysed for each segment in all individuals with TE and controls (CTR) (n=27 in TE and controls respectively) and also evaluated based on the total number of segments in all 27 individuals (n=135 in individuals with TE and controls respectively). The comparison of disc bulge/herniation and foraminal stenosis between the two groups of TE and controls was only possible based on sagittal images.

9. Statistical methods

Study I: Distributions of variables were given as the mean, standard deviations (SD) and ranges, i.e. mean, SD/(range). For comparisons between two groups, the Mann-Whitney non-parametric U-test was used for continuous variables. When comparing two groups, the Mantel-Haenszel chi-square test for ordered categorical variables was used. Wilcoxon signed-rank test was used when comparing two related samples.

Study II: For comparisons between the two groups, Fisher's exact test was used for dichotomous variables and the Mantel-Haenszel chi-square exact test was used for ordered categorical variables. The chi-square exact test was used for unordered categorical variables and the Mann-Whitney U-test was used for continuous variables. The Cohen's kappa coefficient statistic (k) was used to assess the inter-observer (between the observers) and intra-observer (within the observer) agreement. The statistical analyses were performed using SPSS software version 19.

Study III: The results relating to continuous variables, as well as changes in continuous variables, are described with n, the mean, SD and range for each group, i.e. mean, SD/(range). The results of the SF-36 were presented with the mean (95% confidence interval, CI), while those of the EQ-5D were presented with the mean (SE), according to the most used standards for these questionnaires. The results for categorical variables including dichotomous variables were given as numbers and percentages.

To compare continuous variables between two groups, the Mann-Whitney U-test was used and, to compare dichotomous variables between two groups, Fisher's exact test was used. For comparisons between two groups in terms of ordered categorical variables, the Mantel-Haenszel chi2 test was used and, for non-ordered categorical variables, the chi-square test was used. Wilcoxon signed-rank test was used when comparing two related samples.

Correlations were analysed using Spearman's rank correlation. Statistical analyses were performed using version 9 of the SAS System for Windows and version 19 of the Statistical Package for the Social Sciences, SPSS.

Study IV: For comparisons between the groups, the Mann-Whitney U-test was used for continuous variables and Fisher's exact test was used for dichotomous categorical variables. For ordered categorical variables, the Mantel-Haenszel chi2 test was used. All the data were processed in SPSS version 23.

In all the studies, the significance tests were two-tailed and conducted at the five per cent significance level.

10. Summary of papers

10.1 Study I

"Long-term follow-up of thalidomide embryopathy: malformations and development of osteoarthritis in the lower extremities and evaluation of upper extremity function"

Background: Individuals born with TE have different malformations, often of the extremities. With ageing, there is a risk of deterioration in joints in the extremities and this may have a greater effect on physical function in individuals with extremity malformations than in persons without malformations. The study was designed to assess long-term degenerative changes and the function of the lower extremities and upper extremities.

Method: Thirty-one individuals from the Association for Thalidomide Embryopathy in Sweden agreed to participate in the study. All the participants answered validated disease-specific questionnaires. All the participants underwent spiral CT of the lower extremities including the pelvis, for evaluations of osteoarthritis (OA).

Results: Several other diseases were noted in the individuals with TE, such as asthma (3/31), sleep apnoea (2/31), migraine (2/31), hypertension (2/31), stroke (1/31) and breast cancer (1/31).

Malformations were located in both upper and lower limbs. Malformations of the upper extremities are as shown in Table 7.

Table 7: Musculoskeletal malformations in the upper limbs in the 31 individuals with thalidomide embryopathy

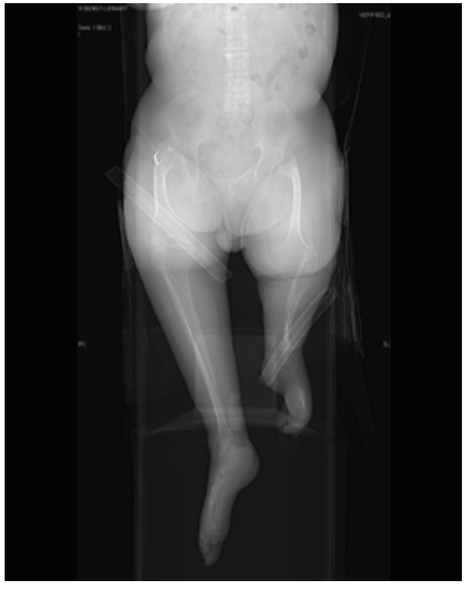
	n (%)
UPPER EXTREMITY	
At any location of the upper extremity	27(87)
Shoulder	5 (16)
Elbow/forearm	11 (36)
Hand	25 (81)

CT scans showed fulfilled criteria for PFFD according to Aitken's classification in five individuals with severe malformations of the lower extremities. These findings were combined with upper extremity malformations in all five individuals. Three of five individuals had bilateral PFFD (Table 8). It was not possible to establish the diagnosis of OA of the hips in individuals with PFFD due to severe malformations (Figure 9).

Table 8: Description of the five individuals with TE, who had proximal femoral focal deficiency (PFFD)

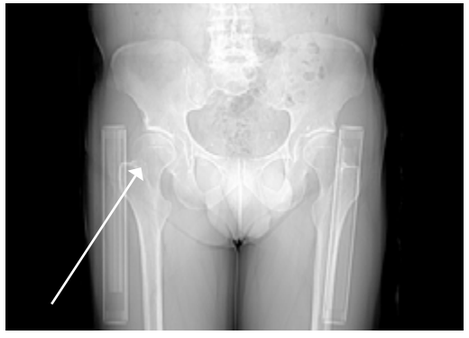
Individual with PFFD	**I**		**II**		**III**		**IV**		**V**	
	R*	**L***	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**
Lower extremities										
Hip/femur										
PFFD, type acc. to Gillespie/Aitken†	II/B	No	II/D	II/D	II/C	No	I/C	II/C	I/D	II/D
Knee										
Hypoplastic lateral femoral condyle‡		●							●	●
Intercondylar notch hypoplasia		●				●	●			
Lower leg										
Tibia or fibula hypoplasia/aplasia			●	●	●	Absent	●	●		●
Foot						Absent				
Equinus and varus position				●			●	●	●	●
Equinus and cavus position	●	●								
Significant limb shortening	●		●	●	●	●	●	●	●	●

Figure 9: Individual with bilateral PFFD.



In the group without PFFD (n=26), other deformities of the femoral head and the knees were also noted. Twenty-seven knees in these individuals (27/52) had hypoplastic lateral femoral condyles and 34/52 (65%) of all the hips that were studied were found to have a minor deformity, Table 9. (Figures 10 and 11)

Figure 10: Deformed femoral head



Three individuals (of 26) had a positive Lachman test. One (of 26) had undergone an anterior cruciate ligament reconstruction following a trauma.

Figure 11: Hypoplastic lateral femoral condyle

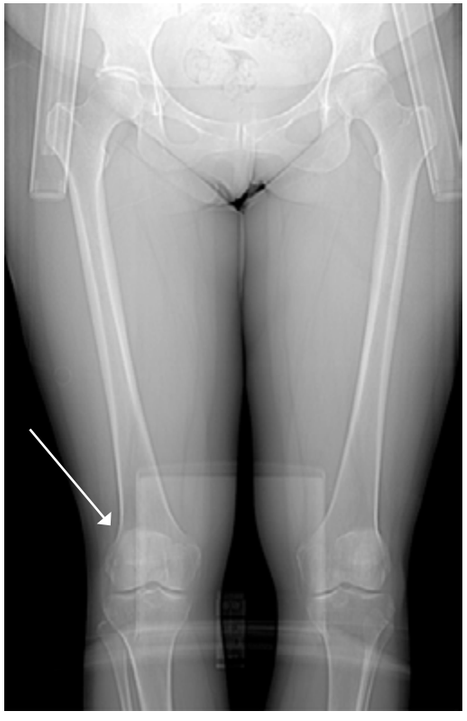


Table 9: Description of the 26 individuals with TE but not PFFD
n (%) or mean, (SD)/(range)

	n (%)
Hip/femur	
Malformations	
Deformed femoral head *	34 (65)
Knee	
Malformations	
Hypoplastic lateral femoral condyle **	27 (52)
Proximal tibia adapted to the hypoplastic lateral femoral condyle	20 (39)
Intercondylar notch hypoplasia	26 (50)

* See Figure 10
** See Figure 11

Osteoarthritis of the hip and knee joints in the group without PFFD: (n=26)

The hip joint was evaluated as a whole (one joint), while the knee joint was divided and evaluated in three compartments, the medial, lateral and patello-femoral compartments (Tables 10-11).

There were 7/26 individuals (27%) with bilateral OA of different grades of the hip joints. Ten of 26 individuals (39%) had some degree of OA in one of their hips. Severe OA was found in nine hip joints and three of seven individuals with bilateral OA of the hips had severe OA.

Table 10: Occurrence and location of osteoarthritis of the hip joint in the 26 individuals with TE but no PFFD
n (%)

	Grade 0 No OA	Grade 1 Mild OA	Grade 2 Severe OA
Hip joint			
Right *	15 (58)(60)	5 (19)(20)	5 (19)(20)
Left	18 (69)	4 (15)	4 (15)
Occurrence of OA at any side versus bilaterally, regardless of the grade			
Occurrence of OA on any side	10 (39)		
Bilateral OA of all grades	7 (27)		

*Evaluation in one person was not possible due to hip replacement. The percentages have therefore been counted again for the total number of 30 for the right hips.

In fifteen/26 (58%) individuals with TE and without PFFD, some OA in the knees (in any compartment) was diagnosed.

In nine/26 (35%) individuals with TE and without PFFD, OA was observed in the knees bilaterally. OA was located in the medial knee compartment rather than in the lateral knee compartment (12 versus 4, medial and lateral respectively).

Table 11: Occurrence and location of osteoarthritis, OA, in the knee joint in the 26 individuals with TE but no PFFD
n (%)

	Grade 0 No OA	Grade 1 Mild OA	Grade 2 Severe OA
Knee joint			
Right			
Medial	14 (54)	5 (19)	7 (26)
Lateral	22 (84)	4 (15)	-
Patello-femoral	20 (77)	5 (19)	1 (4)
Left			
Medial	15 (58)	7 (27)	4 (15)
Lateral	25 (96)	1 (34)	-
Patello-femoral	25 (96)	1 (34)	-
Occurrence of OA at any side versus bilaterally, regardless of the grade			
Occurrence of OA on any side	15 (58)		
Bilateral OA of all grades	9 (35)		

Lower extremity function (RAOS)

Evaluation of the RAOS in the entire group of individuals with TE revealed good function in general, with a high score on all subscales. Comparisons between the two subgroups with and without PFFD revealed significantly lower scores for ADL, sport/recreation and quality of life for the PFFD group (Table 12).

Table 12: Results for the RAOS score
mean, (SD)/(range) or n (%)

			Occurrence of PFFD *		
	N	All	No n=26	Yes n=5	p -value
Pain	31	78.5 (21) (36-100)	80.4 (20) (36-100)	68.1 (24) (47-100)	n.s. (p=0.31)
Symptoms	31	78.6 (18) (32-100)	80.2(18.0) (32-100)	70.0 (17) (50-89)	n.s. (p=0.20)
ADL †	30 ‡	83.1 (20) (40-100)	87.3(17) (41-100)	55.9 (13) ‡ (40-71)	p=0.0076
Sport & Recreation	31	61.9 (36) (0-100)	72.1(30.) (10-100)	9.0 (10) (0-25)	p=0.0007
Quality of Life	31	66.1 (26) (19-100)	71.2(25 (19-100)	40.0 (17) (25-69)	p=0.016

* PFFD = Proximal Focal Femoral Deficiency
† ADL = Activities of daily living
‡ One patient did not answer all items

Upper extremity function (DASH)

To compare function between the group with a major malformation of at least one extremity (15/31) and the group without major malformation in any extremity (16/31), the DASH was used (Table 13). A further comparison of function, evaluated with the DASH, was performed in those with an anatomic pincer grasp versus those without (n=20 versus n=11) and those with a functional hand-grip function and those without (n=27 versus n=4). There were no significant differences between the subgroups, either for the total DASH score or for the optional parts of the DASH.

Table 13: Results for the DASH questionnaire and its subscores for evaluations of upper extremity function in 31 individuals with TE
mean, (SD)/(range) or n (%)

			No of extremities with major malformations		
	N	All	0 n=16	1-4 n=15	p -value
Total DASH score	31	20.5 (16) (0-73)	14.3 (12) (0-46)	25.5 (17) (0-73)	p=0.015
Work score	25 *	13.3 (18) (0-69)	10.1 (13) (0-38) n=12	15.4 (21) (0-69) n=13	n.s. (p=0.62)
Sports/Music score	13 *	22.1 (24) (0-69)	19.5 (27) (0-69) n=8	21.9 (22) (0-56) n=5	n.s. (p=0.45)

* n = some individuals did not answer all questions

Conclusion: Degenerative changes are more frequent in the hip and knee joints in individuals with TE than in a general population. The function in the upper limbs was reduced in the total group compared with the general population, but the difference in DASH scores for the study group and the general population did not reach a level considered to reflect clinical relevance i.e. mean/SD 20.5/ 15.5 versus 14.0/15.4 for the general population with a difference of 6.5. (A difference of 10 point would be the minimal clinical relevance). There was a significantly reduced function in the upper extremities in those with major malformation of any extremity compared with the rest of the group.

10.2 Study II:

"Degenerative changes in the cervical spine are more common in middle-aged individuals with thalidomide embryopathy than in healthy controls"

Background: Degenerative changes may not be limited to the extremities in TE individuals. The aim of this study was to study the presence of degenerative changes in the cervical spine in TE and to compare them with an age-matched group of healthy controls.

Methods: All 31 individuals from Study I were invited to undergo an MRI of the cervical spine. Twenty-seven underwent the MRI, two had claustrophobia, one rejected the invitation and one had to be excluded because of a metal chip in the head after head trauma surgery, Table 4. Twenty-seven age- and gender-matched controls were collected from the PACS at the Department of Radiology at Sahlgrenska University Hospital (Table 14).

Table 14: Gender and age of TE versus controls in Study II

Variables	TE	Control	p-value
Male	16(59)	15(56)	p=0.452 (n.s.)
Female	11(41)	12(44)	
Age, mean (SD)	46.2(1.0)	46.1(1.9)	p=0.4982 (n.s.)

Disc degeneration (DD) was evaluated on MRI investigations using Pfirrmann classification.

Results: ***MRI findings in individuals with TE and controls:*** A higher frequency of cervical segments with disc degeneration (DD) was found in the individuals with TE than in the controls. The same relationship was observed for cervical foramina, i.e. the individuals with TE had a higher frequency of affected foramina (Table 15).

Table 15: Correlation, DD, number of affected foramina and affected medulla in the two groups of TE and controls

Number of degenerated discs	TE (n = 27) n(%)	CTR (n = 27) n(%)	p-value
0	3 (11)	9 (33)	<0.001
1	2 (7)	3 (11)	
2	6 (22)	11 (41)	
3	6 (22)	4 (15)	
4	10 (37)	0 (0)	
Number of affected foramina on any side*			
0	3 (11)	15 (56)	p=0.002
1	8 (30)	2 (7)	
2	3 (11)	4 (15)	
3	4 (15)	5 (19)	
4	3 (11)	1 (4)	
5	2 (7)	0	
6	3 (11)	0	
7	0	0	
8	1 (4)	0	
9	0	0	
10	0	0	

***** All 10 foramina, left and right

The majority of DD occurred in the lower segments in both groups and more specifically at the C5-C6 and C6-C7 levels. However, DD was also noted in other cranial segments, like the C3-C4 and C4-C5 in the group of individuals with TE, but rarely in controls.

An evaluation of DD in all segments for the TE group and compared with controls indicated more severe DD, i.e. Pfirrmann grades IV and V, in the lower segments of the cervical spine in the TE group. Osteophytes and disc protrusions were also found at a higher frequency in the individuals with TE than in controls, $p<0.001$ (Table 16). MRI with an affected C4-C5 segment is illustrated in Figure 12.

Table 16: Pfirrmann's classification of disc degeneration in all 135 evaluated disc levels and comparison between the discs in individuals with TE and CTR

Disc signal (Pfirrmann), (n = 135)	TE n(%)	CTR n(%)	p-value
I	0 (0)	2 (2)	p<0.001
II	4 (3)	49 (36)	
III	62 (46)	68 (50)	
IV	51 (38)	15 (11)	
V	18 (13)	1 (1)	
Osteophytes (n =135)			
Yes	64 (47)	32 (24)	p<0.001
Disc protrusion (n=135)			
Yes	39 (29)	12 (9)	p<0.001

The frequency of foraminal stenosis and nerve root compression in TE control groups is shown in Table 17.

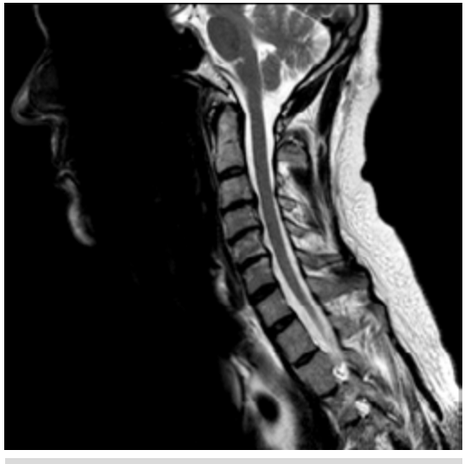


Figure 12: Sagittal image from an MRI of the cervical spine in an individual with TE

Table 17: All foramina on the right and left side together for each group (n=270)

Foramen (R + L, n = 270)	TE n(%)	CTR n(%)	p-value
No compromise	196 (73)	241 (89)	p<0.001
Narrowing, normal nerve root	33 (12)	24 (9)	
Narrowing, nerve root compressed	41 (15)	5 (2)	

Conclusion: Individuals with TE demonstrated a higher frequency of disc degeneration in the cervical spine and a change in the load on the cervical spine might be a contributory factor.

10.3 Study III

"Health-related quality of life and function in middle-aged individuals with thalidomide embryopathy"

Background: Degenerative changes in the joints in the extremities and within the cervical spine might have a direct effect on the physical function of individuals with TE in general. However, it is valuable to understand whether these changes, and perhaps the impaired function, could affect the health-related quality of life as measured using validated questionnaires. The aim of this study was to evaluate the effect of limb malformations on health-related quality of life (HRQL) and the relationships between HRQL and function of the extremities in a group of individuals with TE.

Methods: All participants in Study I were included. The SF-36 and EQ-5D scores were used to evaluate self-reported health-related quality of life. The validated disease-specific questionnaires for evaluation of the upper and lower extremities, i.e. the DASH and RAOS respectively, were used for the evaluation of HRQL in relation to physical function.

Results: Data on musculoskeletal malformations are reported in Study I (Tables 7, 8). Data on other organ malformations in individuals with TE are shown in Table 18. All numbers represent occurrence in number of patients, regardless of whether it is uni- or bilateral.

Table 18: Other organ malformations in 31 individuals with TE

OTHER MALFORMATIONS	
Ear: hearing deficit	6 (19)
Facial nerve palsy	3 (10)
Duane's syndrome	9 (29)
Inconcomitant gaze	10 (32)
Tearing while eating	5 (16)
Other internal anomalies	10 (32)

Sociodemographic data

Sociodemographic conditions are presented in Table 19. Twenty-four individuals (77%) were currently working and 15/31 (60%) worked full time. Despite major limb deformities, only four of 15 (27%) individuals were sick-listed or retired. Only one individual, with major limb malformations, reported a living situation with heavy stress. The group with major limb deformity/ies did not differ from those without any major limb malformations for any of the variables listed in Table 19.

Table 19: Self-reported sociodemographic status in 31 individuals with TE
n(%)

	All patients n=31	Occurrence of major malformations in any of the limbs		
		No n=16	Yes n=15	p-value
Family situation				
Marital status				
Never married	5(16)	2(13)	3(20)	
Married/cohabiting	25(81)	13(81)	12(80)	n.s. (0.55)
Divorced/widowed	1(3)	1(6)	0	
No of individuals without children	9(29)	5(31)	4(27)	n.s. (0.89)
Education, highest achieved level < 7 y of school attendance	0	0	0	
High school, completed or not	4 (13)	3 (19)	1 (7)	
Vocational school	3 (10)	1 (6)	2 (13)	n.s. (0.69)
College, completed or not	15 (48)	8 (50)	7 (47)	
Graduate school	9 (29)	4 (25)	5 (33)	
Working life				
Employment				
Currently working	24 (77)	13 (81)	11 (73)	
Housewife	1 (3)	1 (6)	0	n.s. (0.41)
Sick listed or retired	6 (19)	2 (13)	4 (27)	
Working time Working full time (of those working)	15 (62)	9 (69)	6 (55)	n.s. (0.32)

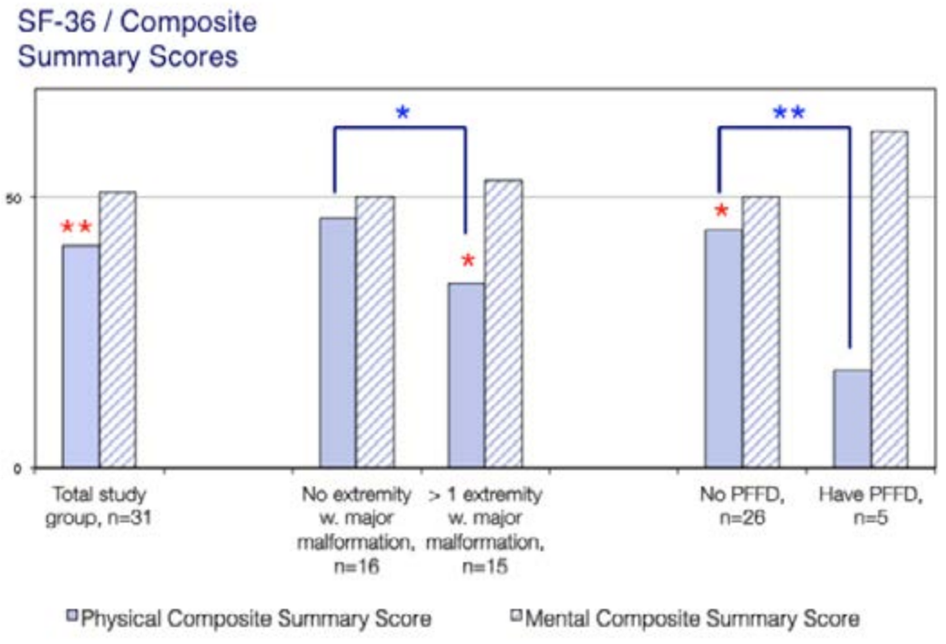
Quality of life, generic questionnaires

Physical and mental composite scores of SF-36

The Physical Composite Summary score for the entire group (n=31), mean 40.6 (95% CI 35.4; 45.8), was significantly lower than that of the population-based control group (Figure 13). Individuals with limb/limbs with major deformity/ies had a significantly lower physical HRQL as measured by the Physical Composite Summary score compared with those without any extremities with major deformities (mean 34.6 versus 45.8, p=0.040). The group with PFFD also reported a significant reduction in the Physical Composite Summary score, compared with the rest of the group (mean 18.3, vs. 44.0, p=0.00031).

The Mental Composite Summary score had a mean of 51.5 (95% CI 47.1; 56.0) for the full study group and no differences were noted between the subgroups. No differences were found in the z-score analyses in relation to the control group for the full study group or for the subgroups.

Figure 13: Physical and Mental Composite summary scores in the total study group, in individuals with major malformation and in individuals with/without PFFD



Composite scores of the SF-36 in the full study group and analyses of the subgroups. Summary scores of fifty represent a level regarded as normal.
Comparisons in relation to national norms (z-scores): *=p<0.05, **= p<0.01 (red color, located just above the respective bar)
Comparisons between groups: *=p<0.05, **= p<0.01 (blue color, located at the top of the figure)

SF-36 subscores

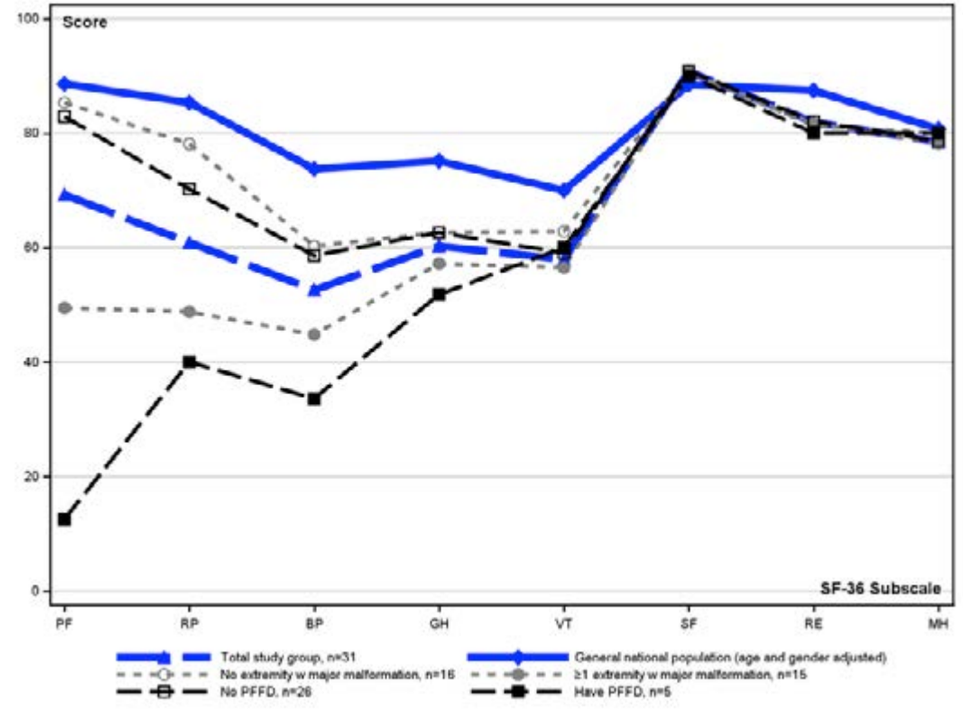
Low levels for physical quality of life were reported for the whole group; Role Physical (mean 65.3, 95% CI 51.4; 79.3), Bodily Pain (mean 54.6, 95% CI 44.6; 64.5) and General Health (mean 60.9, 95% CI 53.0; 68.7) were all significantly lower than the values for the population-based control group. The Vitality score had a mean of 59.2 (95% CI 51.4; 67.0) for the individuals with TE, also significantly lower than the values for the population-based control group.

Individuals with and without major limb deformity/ies did not differ significantly in any of the subscores. The measured z-scores showed statistically significant differences in relation to the population-based controls in the group with major deformities for the physical subscales, as well as for the Vitality score. The other mental subscales, however, differed neither significantly between the subgroups nor in relation to the population-based control group.

The individuals with PFFD (n=5) had significantly poorer physical quality of life compared with those without PFFD (n=26), the Physical Function score was a mean of 12.5 (95% CI 6.4; 31.4) compared with a mean of 82.9 (95% CI 75.1; 90.7, p=0.0015), while the score for Bodily Pain was a mean of 33.6 (95% CI 18.0; 49.2) compared with a mean of 58.6 (95% CI 47.5; 69.7, p=0.044) respectively in the two groups.

The group without PFFD had significantly lower z-scores compared with the population-based control group for Bodily Pain, General Health and Vitality. In the group with PFFD, the z-scores for Physical Function showed a mean of -4.3, i.e. reflects a level four times lower than that of the general population, but still no statistically significant difference was found. For the mental subscales, no significant differences were noted between the two subgroups or when compared with the general population. The outcome for HRQL measured by the SF-36 is shown in Figure 14.

Figure 14: Comparison of all the subscales in both the Physical and the Mental HRQL for all the subgroups compared with the values for the general Swedish national population



Result from all the subscores in SF-36 and the physical and mental composite summary scores and result from the z-scores are shown in Tables 20 to 22.

Table 20: Health related quality of life in 31 patients with thalidomide embryopathy. Results of SF-36 subscores and composite summary scores of the full study group and subgroups. P-values represent results of comparisons between the subgroups. (p-values showing significant differences have been highlighted)

Mean (95% CI)

	Total n=31	No of extremities with major malformations			Occurrence of PFFD b)		
		No extremity n=16	> 1 extremity n=15	p-value	No n=26	Yes n=5	p-value
SF-36 Domains							
Physical Functioning a)	73.5 (62.1; 84.9)	85.3 (76.0; 94.7)	60.0 (38.8; 81.2)	ns (p=0.055)	82.9 (75.1; 90.7)	12.5 (-6.4; 31.4)	p=0.0015
Role Physical	65.3 (51.4; 79.3)	78.1 (61.4; 94.9)	51.7 (29.2; 74.2)	ns (p=0.073)	70.2 (55.3; 85.0)	40.0 (-7.1; 87.1)	ns (p=0.13)
Bodily Pain	54.6 (44.6; 64.5)	60.3 (44.0; 76.5)	48.5 (36.0; 61.1)	ns (p=0.26)	58.6 (47.5; 69.7)	33.6 (18.0; 49.2)	p=0.044
General Health	60.9 (53.0; 68.7)	62.6 (50.2; 75.0)	59.0 (46.8; 71.2)	ns (p=0.58)	62.6 (54.4; 70.9)	51.8 (12.4; 91.2)	ns (p=0.37)
Vitality	59.2 (51.4; 67.0)	62.8 (51.1; 74.6)	55.3 (43.9; 66.7)	ns (p=0.36)	59.0 (50.4; 67.7)	60.0 (30.6; 89.4)	ns (p=0.98)
Social Functioning	90.7 (83.4; 98.0)	90.6 (79.6; 101.6)	90.8 (79.9; 101.8)	ns (p=0.77)	90.9 (82.2; 99.5)	90.0 (77.0; 103.0)	ns (p=0.20)
Role Emotional	81.7 (70.0; 93.5)	81.2 (62.9; 99.6)	82.2 (65.3; 99.1)	ns (p=0.82)	82.1 (68.7; 95.4)	80.0 (43.0; 117.0)	ns (p=0.71)
Mental Health	78.8 (73.1; 84.6)	80.0 (70.5; 89.5)	77.6 (70.1; 85.1)	ns (p=0.44)	78.6 (71.9; 85.3)	80.0 (67.3; 92.7)	ns (p=0.91)
Composites (50 +/- 10)							
Physical Composite Summary Score a)	40.6 (35.4; 45.8)	45.8 (40.1; 51.6)	34.6 (25.9; 43.4)	p=0.040	44.0 (39.4; 48.7)	18.3 (7.9; 28.7)	p=0.0031
Mental Composite Summary Score a)	51.5 (47.1; 56.0)	49.8 (43.4; 56.2)	53.5 (46.6; 60.4)	ns (p=0.66)	49.9 (45.2; 54.5)	62.1 (47.2; 77.0)	ns (p=0.093)

a)= The Physical Functioning score could be calculated for 30 patients only, which is the base for the two composite scores and the Physical function score.
b)= PFFD = proximal Femoral Focal Deficiency

Table 21: Health related quality of life in 31 patients with thalidomide embryopathy, presented as SF-36 Z-scores of the respective groups and subgroups. P-values represent results of comparisons between the subgroups. (p-values showing significant differences have been highlighted)

Mean (95% CI)

	Total n=31	No of extremities with major malformations			Occurrence of PFFD b)		
		No extremity n=16	> 1 extremity n=15	p-value	No n=26	Yes n=5	p-value
Normalized Subscales							
Physical Functioning SWEv1 Z a)	-0.86 (-1.50; -0.22)	-0.17 (-0.66; 0.32)	-1.65 (-2.84; -0.45)	ns (p=0.052)	-0.33 (-0.76; 0.104)	-4.29 (-5.41; -3.17)	p=0.0016
Role Physical SWEv1 Z	-0.68 (-1.15; -0.21)	-0.242 (-0.80; 0.32)	-1.14 (-1.90; -0.38)	ns (p=0.11)	-0.52 (-1.02; -0.02)	-1.52 (-3.14; 0.10)	ns (p=0.24)
Bodily Pain SWEv1 Z	-0.72 (-1.08; -0.36)	-0.500 (-1.08; 0.08)	-0.95 (-1.40; -0.49)	ns (p=0.22)	-0.574 (-0.98; -0.17)	-1.46 (-1.98; -0.95)	ns (p=0.059)
General Health SWEv1 Z	-0.631 (-0.99; -0.27)	-0.55 (-1.10; -0.001)	-0.71 (-1.25; -0.18)	ns (p=0.62)	-0.55 (-0.92; -0.19)	-1.03 (-2.77; 0.71)	ns (p=0.44)
Vitality SWEv1 Z	-0.46 (-0.80; -0.13)	-0.301 (-0.79; 0.19)	-0.64 (-1.14; -0.13)	ns (p=0.36)	-0.48 (-0.84; -0.11)	-0.40 (-1.73; 0.92)	ns (p=0.98)
Social Functioning SWEv1 Z	0.10 (-0.25; 0.45)	0.10 (-0.43; 0.63)	0.11 (-0.42; 0.63)	ns (p=0.75)	0.11 (-0.31; 0.52)	0.089 (-0.54; 0.72)	ns (p=0.44)
Role Emotional SWEv1 Z	-0.20 (-0.62; 0.22)	-0.21 (-0.87; 0.44)	-0.18 (-0.78; 0.42)	ns (p=0.80)	-0.19 (-0.67; 0.29)	-0.24 (-1.55; 1.07)	ns (p=0.84)
Mental Health SWEv1 Z	-0.09 (-0.38; 0.20)	-0.03 (-0.50; 0.45)	-0.16 (-0.55; 0.22)	ns (p=0.45)	-0.11 (-0.44; 0.24)	-0.03 (-0.71; 0.65)	ns (p=1.00)
Normalized Composites							
Physical Composite SWEv1 Z a)	-0.94 (-1.46; -0.42)	-0.42 (-0.99; 0.16)	-1.54 (-2.41; -0.66)	p=0.040	-0.60 (-1.06; -0.13)	-3.17 (-4.21; -2.13)	p=0.0031
Mental Composite SWEv1 Z a)	0.15 (-0.29; 0.60)	-0.02 (-0.66; 0.62)	0.351 (-0.34; 1.04)	ns (p=0.66)	-0.01 (-0.48; 0.45)	1.21 (-0.28; 2.70)	ns (p=0.093)

a)= The Physical Functioning score could be calculated for 30 patients only, which is the base for the two composite scores and the Physical function score.
b)= PFFD = proximal Femoral Focal Deficiency

Table 22: Health related quality of life in 31 patients with thalidomide embryopathy, presented as SF-36 Z-scores of the respective groups and subgroups. "P-values within group" represent results of comparison with the normal population. (p-values showing significant differences have been highlighted)

Mean (95% CI)

	The full study group		No of extremities with major malformations				Occurrence of PFFD b)			
	n=31	p-value within group	No extremity n=16	p-value within group	> 1 extremity n=15	p-value within group	No n=26	p-value within group	Yes n=5	p-value within group
Normalized Subscales										
Physical Functioning SWEv1 Z a)	-0.86 (-1.50; -0.22)	ns (p=0.050)	-0.17 (-0.66; 0.32)	ns (p=0.81)	-1.65 (-2.84; -0.45)	p=0.023	-0.33 (-0.76; 0.104)	ns (p=0.35)	-4.29 (-5.41; -3.17)	ns (p=0.13)
Role Physical SWEv1 Z	-0.68 (-1.15; -0.21)	ns (p=0.087)	-0.242 (-0.80; 0.32)	ns (p=0.85)	-1.14 (-1.90; -0.38)	p=0.020	-0.52 (-1.02; -0.02)	ns (p=0.42)	-1.52 (-3.14; 0.10)	ns (p=0.13)
Bodily Pain SWEv1 Z	-0.72 (-1.08; -0.36)	p=<.0001	-0.500 (-1.08; 0.08)	p=0.037	-0.95 (-1.40; -0.49)	p=0.0012	-0.574 (-0.98; -0.17)	p=0.0026	-1.46 (-1.98; -0.95)	ns (p=0.063)
General Health SWEv1 Z	-0.631 (-0.99; -0.27)	p=0.0010	-0.55 (-1.10; -0.001)	ns (p=0.063)	-0.71 (-1.25; -0.18)	p=0.012	-0.55 (-0.92; -0.19)	p=0.0032	-1.03 (-2.77; 0.71)	ns (p=0.19)
Vitality SWEv1 Z	-0.46 (-0.80; -0.13)	p=0.017	-0.301 (-0.79; 0.19)	ns (p=0.32)	-0.64 (-1.14; -0.13)	p=0.024	-0.48 (-0.84; -0.11)	p=0.023	-0.40 (-1.73; 0.92)	ns (p=0.44)
Social Functioning SWEv1 Z	0.10 (-0.25; 0.45)	ns (p=0.063)	0.10 (-0.43; 0.63)	ns (p=0.27)	0.11 (-0.42; 0.63)	ns (p=0.16)	0.11 (-0.31; 0.52)	ns (p=0.051)	0.089 (-0.54; 0.72)	ns (p=1.00)
Role Emotional SWEv1 Z	-0.20 (-0.62; 0.22)	ns (p=0.92)	-0.21 (-0.87; 0.44)	ns (p=0.61)	-0.18 (-0.78; 0.42)	ns (p=0.79)	-0.19 (-0.67; 0.29)	ns (p=0.72)	-0.24 (-1.55; 1.07)	ns (p=0.75)
Mental Health SWEv1 Z	-0.09 (-0.38; 0.20)	ns (p=0.80)	-0.03 (-0.50; 0.45)	ns (p=1.00)	-0.16 (-0.55; 0.22)	ns (p=0.59)	-0.11 (-0.44; 0.24)	ns (p=0.78)	-0.03 (-0.71; 0.65)	ns (p=0.81)
Normalized Composites										
Physical Composite SWEv1 Z a)	-0.94 (-1.46; -0.42)	p=0.0027	-0.42 (-0.99; 0.16)	ns (p=0.23)	-1.54 (-2.41; -0.66)	p=0.0067	-0.60 (-1.06; -0.13)	p=0.036	-3.17 (-4.21; -2.13)	ns (p=0.13)
Mental Composite SWEv1 Z a)	0.15 (-0.29; 0.60)	ns (p=0.38)	-0.02 (-0.66; 0.62)	ns (p=1.00)	0.351 (-0.34; 1.04)	ns (p=0.24)	-0.01 (-0.48; 0.45)	ns (p=0.87)	1.21 (-0.28; 2.70)	ns (p=0.13)

a)= The Physical Functioning score could be calculated for 30 patients only, which is the base for the two composite scores and the Physical function score.
b)= PFFD = proximal Femoral Focal Deficiency

EQ-5D

Table 23 shows the results of the EQ-5D analyses. The five dimensions of the EQ-5D were not affected by the presence of major deformities of the extremities. The EQ-5D Index was significantly lower in the individuals with PFFD compared with those without PFFD (mean 0.35 vs. 0.66, p=0.035). Moreover, a similar difference was observed for the mobility and the usual activities subscales.

Table 23: Health-related quality of life as measured by the EQ-5D in 31 individuals with TE

	All n=31	Occurrence of PFFD b)			National population c)
		No n=26	Yes n=5	p-value	
Health profile					
Mobility a)				p=0.018	
I have no problems walking about	24 (80.0%)	23 (88.5%)	1 (25.0%)		94 %
I have some problems walking about	6 (20.0%)	3 (11.5%)	3 (75.0%)		6 %
I am confined to bed	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Self-care				ns (1.00)	
I have no problems with self-care	28 (90.3%)	24 (92.3%)	4 (80.0%)		98.5 %
I have some problems washing or dressing myself	2 (6.5%)	1 (3.8%)	1 (20.0%)		1.5 %
I am unable to wash or dress myself	1 (3.2%)	1 (3.8%)	0 (0.0%)		
Usual activities				p=0.0098	
I have no problems performing my usual activities	23 (74.2%)	22 (84.6%)	1 (20.0%)		91.5 %
I have some problems performing my usual activities	8 (25.8%)	4 (15.4%)	4 (80.0%)		8.2 %
I am unable to perform my usual activities	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Pain/discomfort				ns (0.14)	
I have no pain/discomfort	5 (16.1%)	5 (19.2%)	0 (0.0%)		61.1 %
I have moderate pain/discomfort	17 (54.8%)	15 (57.7%)	2 (40.0%)		38.9 %
I have extreme pain/discomfort	9 (29.0%)	6 (23.1%)	3 (60.0%)		
Anxiety/depression				ns (0.29)	
I am not anxious or depressed	22 (71.0%)	17 (65.4%)	5 (100.0%)		73.9 %
I am moderately anxious or depressed	9 (29.0%)	9 (34.6%)	0 (0.0%)		26.1 %
I am extremely anxious or depressed	0 (0.0%)	0 (0.0%)	0 (0.0%)		
EQ-5D Index, mean (SE)	0.61 (0.12)	0.66 (0.12)	0.31 (0.41)	p=0.035	
EQ VAS rating, mean (SE)	69 (3.0)	69.8 (7.1)	65.4 (3.4)	ns (0.61)	

a) n=30
b) PFFD=proximal focal femoral deficiency
c) (Burstrom et al., 2001, Burstrom et al., 2014)
mean (95% CI) or n (%)

Function of the upper and lower limbs in relation to HRQL

Upper extremities

As reported in Study I, the DASH disability/symptoms score, evaluating the function of the upper extremities, was 20.5 (SD 15.6) for the entire study group. The group with major limb deformity/ies (mean 25.3, SD 17.3) showed significantly reduced upper extremity function compared with those without any major limb deformities (mean 14.3, SD 12.1, p=0.015). Even the group with PFFD had a significantly reduced upper extremity function (mean 34.3, SD 6.3) compared with those without PFFD (mean 17.9, SD 15.5, p=0.0040). The physical quality of life (PCS) from the SF-36 questionnaire correlated with upper extremity function measured by the DASH and number of extremities (rs = -0.72, p<0.0001) (Table 24).

Lower extremities

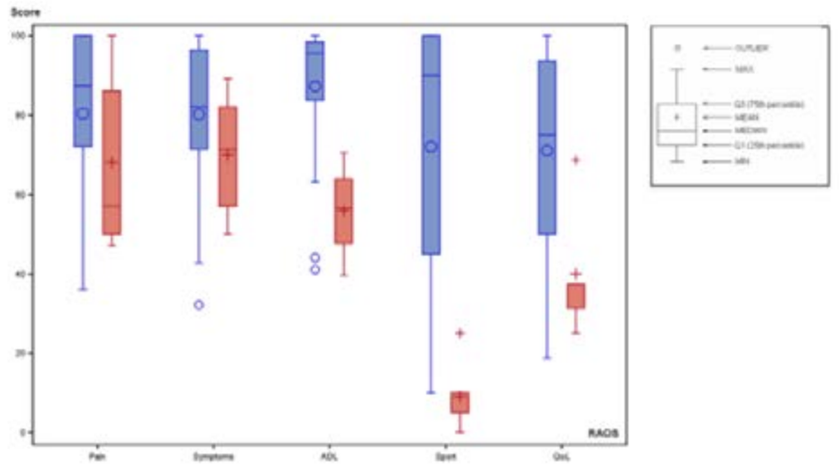
The function of the lower limbs as measured by the RAOS score is presented in Table 12 (Study I) (Figure 15). Correlations were found between the PCS and the pain subscore of the RAOS as well as with the number of extremities with major malformations rs = 0.53, p=0.0028 and rs = -0.39, p=0.035 respectively (Table 24).

The total score for the EQ-5D also correlated strongly with both the DASH disability/symptoms score and the RAOS pain score (r= -0.74, p<0.0001) and (r=0.61, p=0.0003) respectively.

Table 24: Correlation analyses between health-related quality of life and functional scores in 31 patients with TE

	DASH ground score	RAOS pain	Number of extremities w. major malformations (0-4)
SF-36			
Physical Composite Summary Score	-0.72 p<.0001	0.53 p=0.0028	-0.39 p=0.035
Mental Composite Summary Score	0.17 ns (p=0.36)	0.056 ns (p=0.77)	0.085 ns (p=0.66)
EQ-5D			
Aggregated score	-0.74 p<.0001	0.61 p=0.0003	-0.18 ns (p=0.33)

Figure 15: Lower extremity function in Pain, Symptoms, Activities of Daily Living, Sport/Recreation and QOL measured using the RAOS in 31 individuals with TE



Conclusion: Individuals with TE demonstrated a significantly lower physical quality of life (PCS in SF-36) compared with population-based controls. Mental quality of life was not affected compared with the reference population, however. The outcome of the EQ-5D strengthened this result by demonstrating a negative effect on the subscores of mobility and ADL in individuals with TE compared with the population-based controls and no effect on the HRQL subscore in terms of anxiety and depression.

10.4 Study IV

"Middle-aged individuals with thalidomide embryopathy have undergone few surgical limb procedures and demonstrate a high degree of physical independence"

Background: Individuals with TE are now in middle age. Some of them have been using orthotic aids for mobility since childhood, such as lower extremity prosthesis. Some of them need disability adaptation for home or work. How dependent/independent individuals with TE are, in terms of the need for technical aids or the need for an assistant or other additional help to deal with daily life, is not clarified.

Methods: The 31 TE individuals in Study I were investigated with regard to the need for walking aids and the disability adjustment of their workplace and home, as well as activities of daily living, ADL, and physical function. All data on previous surgeries on the upper and lower extremities and the age of individuals at the time of the procedures were collected using study-specific questionnaires. Information about the time taken to perform ADL in the morning and evening was also collected. Group A was defined as the individuals in need of additional help and Group B as the individuals without any need for any extra help.

Results: The group of individuals with TE had undergone 27 surgeries, most on the upper extremities and after the age of 18 years. A decompression of the medial nerve at the wrists was performed after the age of 18 on the upper extremities in four individuals, whereas in two it was performed bilaterally. Nine surgeries were performed on the lower extremities, the majority on the individuals with PFFD and mostly before the age of 18 (Table 25).

Table 25: Surgical procedures performed on the individuals with PFFD

Extremities	Type of surgery	Age at the time of surgery
Upper limbs	One CTS*	**>18**
	Three surgeries on the wrist in two patients	**<18**
	One unspecific arm surgery	**<18**
Lower limbs	Amputation of a foot in one patient	**<18**
	Arthrodesis of a knee in one patient	**<18**
	Two surgeries for a clubfoot in two patients	**<18**
	Hip surgery during childhood in two patients	**<18**

* CTS: Carpal Tunnel Syndrome

All the individuals with PFFD used some kind of walking aid(s) indoors/outdoors and three of them used orthotic devices on the lower extremities. Eighty per cent, i.e. four in five, had some type of additional help and disability adjustment for home or work or both (Table 26).

Table 26: Comparison between the two groups with and without PFFD

	TE, n=31 n(%)	Non-PFFD, n=26 n(%)	PFFD, n=5 n(%)
Walking aid			
Indoors*	5(16)	0	5 (100)
Outdoors*	6(19)	1 (4)	5 (100)
Orthotic devices			
Lower limb	4(13)	1 (4)	3 (60)
Disability-adjusted home			
Yes	7(23)	3 (12)	4 (80)
Would like	1(3)	0	1 (20)
Disability-adjusted workplace**			
Yes	9 (29)	6 (23)	3 (60)

- Thalidomide embryopathy (TE) (n=31) individuals with and without proximal focal femoral deficiency (PFFD) (n=5) and (n=26) respectively
- * Two wheelchair-bound individuals
- ** 29 answered the question

A comparison between the two groups with and without PFFD according to the modified GFS revealed a significantly lower score for the group with PFFD, mean 41, SD 15. This group also needed a longer time to prepare and perform their daily ADL in the morning (p=0.032), but the time before bedtime was not longer for the same group. The results are shown in Table 27.

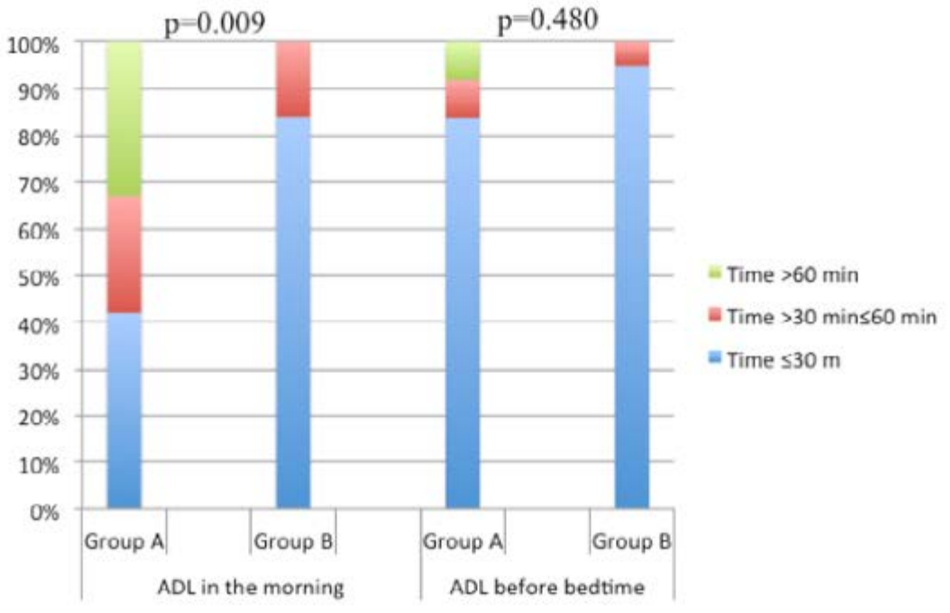
Table 27: Modified General function scores and time for ADL in the morning and evening for the total group of individuals with TE and those with and without PFFD

Mean (SD)/range or n(%)

Physical function	All n=31 n(%)	No PFFD n=26 n(%)	PFFD n=5 n(%)	p-values
Modified GFS	12.6(21) /(0-66)	7.2(18) /(0-66)	41(15) /(25-56)	p=0.001
Time for ADL				
Morning				
≤ 30 minutes	21(68)	20(77)	1(20)	
> 30 min ≤ 60 minutes	6(19)	4(15)	2(40)	p=0.032
> 60 minutes	4(13)	2(8)	2(40)	

The time needed for morning ADL for the group with additional help and extra adjustment at work/home (Group A) was significantly longer, despite their extra help and adjustments. For the time needed before bedtime, there was no significant difference between the two groups, A and B respectively (Figure 16).

Figure 16: Time needed for ADL in the morning and before bedtime for the two groups A (those with additional disability adaptation) and B (those without any adaptation or adjustment in their daily life)



The majority of the group with TE participated in some kind of activity in their spare time. A few performed heavy labour and participated in regular training (Table 25).

Table 28: Different stress levels in the two groups with and without PFFD, during work or spare time

Working time	All n(%)	Not PFFD n(%)	PFFD n(%)
Sedentary	13(46)	10(42)	3(75)
Light work with some physical activity	8(29)	7(29)	1(25)
Relatively heavy labour	5(18)	5(21)	0
Heavy manual labour	2(7)	2(8)	0
Leisure time			
Mainly sedentary	7(23)	4(15)	3(60)
Light exercise and training	14(45)	13(50)	1(20)
Regular training and exercise	9(29)	8(31)	1(20)
Serious training and competitive sports	1(3)	1(4)	0

Conclusion: Individuals with TE are mostly active employees and report physical independence despite their malformations.

11. Discussion

In this thesis, extremity malformations and musculoskeletal degenerative changes in a group of middle-aged individuals with TE were studied. The overall aim was to investigate the long-term effects of these changes on different health and function parameters. Taken together, this group of individuals with TE have a high frequency of osteoarthritis (OA) in the hip and knee joints, but without major self-reported functional impairment and pain. They also have an increased frequency of disc degeneration (DD) in the cervical spine compared with a control group.
It is important to note that, despite relatively low self-reported Physical Composite Summary Scores (PCS) on the SF-36 form, indicating physical impairments, most of these individuals regard themselves as independent. Moreover, they have a high mental quality of life measured by the SF-36's Mental Composite Summary Score (MSC). The majority of the individuals with TE were not affected by daily stress, were employed and were involved in regular physical activities, despite their malformations.

Lower extremities

Malformations of the lower extremities

In the 31 individuals with TE participating in the studies within this thesis, the majority had lower extremities with a normal external appearance. There were also other minor deformities and some of those could only be detected by the radiographic investigations. One had undergone total hip replacement surgery.

Five of 31 had severe malformations of the lower limbs, where evaluations of the CT scans identified them as having proximal femoral focal deficiency (PFFD) on one or both sides, as shown in Study I.

PFFD is a rare abnormality of the proximal femur with an overall incidence of one (1) in 52,000 live births (Biko et al., 2012, Bedoya et al., 2015). Bilateral PFFD is even more uncommon and is only present in 15% of all individuals with PFFD (Bedoya et al., 2015, Herring, Fifth edition). In the present cohort of 31 individuals with TE, 5/31 (16%) had PFFD and three of five (60%) had bilateral manifestations. There were also malformations in terms of tibia hypo-/aplasia and/or fibula hypo-/aplasia and malformations of the feet represented. Furthermore, these five individuals all had upper limb malformations. As a result, they were significantly more affected physically than the rest of the group, which strengthens the opportunity to detect differences when comparing them in the subgroup analyses.

In the clinical examination of the subgroup without PFFD (26/31), the anterior cruciate ligament (ACL) of three individuals was assessed as affected. The absence of ACL in dysplastic knees is well known and has also been previously reported (Thomas et al., 1985, Kaelin et al., 1986). Notch hypoplasia was further noted in 26/52 (50%) of the knees in the individuals with TE. Notch hypoplasia has also been reported in patients with hypoplasia of the intercondylar part of the distal femur (Stanitski and Kassab, 1997, Stevens and Arms, 2000). A hypoplastic lateral femoral condyle is another finding described in patients with congenital longitudinal deficiencies of the lower extremities (Manner et al., 2006) and was found in 27/52 (52%) of the knee joints in the present study group. Knee joint dysplasia occurs most often in the distal femur, but it may also be located in the proximal part of the tibia (Manner et al., 2006). The appearance of the proximal tibia may adapt to the hypoplastic lateral femoral condyle and this was noted in 20/52 (40%) of the individuals in our study group. The adaptation of the proximal tibia, as a hypoplastic tibia plateau, together with a leg length discrepancy, has been described as being associated with genu valgum (Ring, 1959). The exact clinical impact or functional effects of these findings are not clarified. However, it is important to recognise deformities causing genu valgum when planning and performing total knee arthroplasty (TKA), as this may require changes in the surgical procedure (Matsuda et al., 2004).

Knee and hip osteoarthritis

Osteoarthritis (OA) of the hip joints was found in 10/26 (40%) of individuals with TE without PFFD and in 7/26 (27%) in the hip joints bilaterally. OA was not evaluated in the hip joints in the group with PFFD, because, if there was a joint, it was too difficult to classify the degree of OA, because of the severe malformations.

OA of the hip joint is reported to be less common than OA of the knee joint in the general population (Guillemin et al., 2011, Thorstensson et al., 2011, Cross et al., 2014, Malm et al., 2015). The global age-standardised prevalence of symptomatically and radiographically confirmed hip joint OA was 0.85% in 2010 (Cross et al., 2014). Guillemin reported the prevalence of OA in knee and hip joints in individuals between 40 and 75 years to be less than 1% in the hip joint and 2.1% in the knee joint (Guillemin et al., 2011).

Since the frequencies of OA were based on CT imaging in the present study, with no loading on the extremities, it is difficult to compare the present results with investigations of other populations where other diagnostic criteria have been used. The diagnosis of OA in hip and knee joints is most often decided by a radiographic investigation, but it may also be determined based on the description of clinical symptoms (Bedson and Croft, 2008). There is often a discrepancy between radiographic OA findings in larger joints and clinical symptoms, such as pain or stiffness (Bedson and Croft, 2008). The burden of OA is therefore best described by both clinical symptoms and radiological features (Wanka and Dixon, 1964, Amor, 1989). According to the Swedish registry of osteoarthritis and the organisation for better management of patients with osteoarthritis almost 15% of the population between 35 and 55 years have pain in one knee, most probably indicating OA in the affected joint, while OA may only be visualised on radiographs in approximately 5%, *http://utv.boaregistret.se/en/default.aspx*, (Thorstensson et al., 2011). According to the BOA organisation, approximately 10% of the men and 18% of the women older than 60 years in the general population have OA of a hip joint, characterised by groin pain or other OA symptoms such as stiffness. The RAOS subscale for pain and the OA rate did not correlate in the present study, either for hip or knee joints. This indicates a discrepancy between the symptoms and the radiographic (CT) findings in the group of individuals with TE, as in the rest of the population.

Lower extremity function

The function of the lower extremities was measured using the RAOS in the individuals with TE in the present study. The RAOS score demonstrated a high score (good function) in general and the same was seen for most of its subscales. The highest score was observed for ADL, with a mean/(range) of 83/(40-100). As might be expected, the individuals with PFFD had a more affected function compared with those without PFFD. This was reported for the three subscales of ADL, Sport/Recreation and QOL. Moreover, OA in the hip joints either uni- or bilaterally in the individuals with TE had a negative effect on ADL, measured by the RAOS. There was, however, no evidence that OA in the knee joints had the same clinical impact on physical function in the TE group. In a survey comprising 1,910 patients with rheumatoid arthritis (RA), Malm et al. used the RAOS self-reported questionnaire. The function, in terms of ADL and Sport/Recreation, for the individuals most affected by RA, was significantly lower, compared with those less affected (Malm et al., 2015). In the present study, OA was detected by CT and without any reported clinical symptoms. In spite of this, the relatively high frequency of mild OA in the hip joints had a negative effect on the overall result for ADL measured by the RAOS. The negative effect on ADL related to the existence of OA may be caused by inflammation causing some stiffness and pain, even if not reported or detected by the instruments that were used. These symptoms may also be present with a low degree of OA (Myers et al., 1990). It is possible to wonder why the knee OA did not have a similar effect on the RAOS score. The reason for this might simply be the way these joints were evaluated; the three compartments of the knee joint, medial, lateral and patello-femoral compartments, were evaluated and summarised, but the hip joint was evaluated as one entity. This resulted in the recording of every mild degree of OA in every compartment for the knees, possibly leading to an overestimation of the frequency of OA in the knees.

Upper extremities

Malformations of the upper extremities

In 28/31 of the individuals with TE, some kind of malformation of the upper limbs was present. Striking examples were radial bowing of the forearms in eleven individuals (11/31) and, in terms of the hands, affection of the thumb, either three phalangeal and/or malformed or totally absent. Thirty-one of 62 thumbs were absent, whereas 11/31 had a bilateral absence of the thumbs and 9/31 individuals with TE had a unilateral absence of the thumb. In previous studies, upper limb malformations in the individuals with TE have been shown to be more common than lower limb malformations (Lenz and Knapp, 1962, Kida and Lenz, 1968, Smithells and Newman, 1992). The reason for this is not clear, but it can be speculated on. Thalidomide is active in a limited time-sensitive window of embryonic development and this period has also been named “the critical period”. This period occurs between day 20 and 36 after fertilisation or 35 to 50 days after the last menstrual period (Lenz and Knapp, 1962, Strömland and Miller, 1993, Vargesson, 2013). The upper and lower extremities start to develop when the foetus is about five weeks old. The lower limb bud normally starts to grow several hours to a day later than the upper limb bud (Herring, Fifth edition, Vargesson, 2015). Thalidomide has an active half-life of around 8-12 hours (Vargesson, 2015). It is therefore likely that a single dose in the early stage of a pregnancy could affect only the upper extremities, while several doses over a few days would be needed to affect the lower extremities as well (Vargesson, 2015).

Upper extremity function

To evaluate the function of the upper extremities, the DASH, a self-reported questionnaire evaluating the function of the upper limbs, was used (John et al., 2010, Ruckenstuhl et al., 2014). The DASH total score showed lower function (higher score) in the total TE group than the American-based norm (Jester et al., 2005), mean/SD 20.5/15.5 and 14.0/15.4 respectively ($p=0.035$). Although there was a significant difference between the groups, this difference was not considered clinically meaningful, since the difference was only 6.5 points. Gummesson et al. demonstrated that a score difference of 10 points in the DASH instrument is needed to reflect clinically relevant changes (Gummesson et al., 2003).

Different subgrouping of the 31 individuals was performed related to the function of the upper limbs (based on anatomic pincer grasp and hand-grip function). The upper extremity function, evaluated by the DASH, did not show any significant differences between any of the subgroups. However, when comparing individuals with major malformation of the extremity/ies (n=15), no matter whether it was the upper or lower extremity/ies, with individuals without extremity malformations, a significant difference in the total DASH score was revealed. This strengthens the theory that major malformations, regardless of localisation in the lower or upper extremities, may adversely affect physical function in general and, in particular, the function of the upper limbs. There were no differences between the groups with and without major malformations in terms of work activities and sports/music, evaluated in the optional part of the DASH instrument.

Most of the surgeries performed in the group of individuals with TE were performed before the age of 18, in terms of both the upper and lower extremities. Carpal tunnel syndrome (CTS) appears to be a relatively common problem in adulthood and four individuals had undergone surgery to decompress the median nerve. Two individuals had been treated for bilateral CTS. Median nerve compression has previously been reported in individuals with TE (Oshima et al., 2006, Jankelowitz et al., 2013), but the prevalence is not well described. CTS has also been reported as a side-effect when using thalidomide in the treatment of lupus erythematosus (Clemmensen et al., 1984, Delforge et al., 2010).

Cervical spine

A high frequency of disc protrusions, vertebral osteophytes, foraminal narrowing and loss of disc signal was found in the TE individuals, compared with a healthy, age-matched control group. These findings may indicate the early development of disc degeneration (DD) in individuals with TE. However, the exact mechanism for this observation is unclear. Since the individuals with TE have different extremity malformations, most frequently in the upper extremities (Kida and Lenz, 1968, Kowalski et al., 2015, Vargesson, 2015), one explanation of these degenerative changes might be a change in the load on the cervical spine. In a previous study, a change in the load on the cervical spine has been reported to cause cervical DD in African head bearers, related to long-term head load-bearing (Echarri and Forriol, 2005).
Somewhat surprising, no malformations of the cervical spine were found in any of the individuals in the investigated group since Tajima et al reported that five out of 22 individuals with TE had a block vertebrae in the cervical spine, using CT (Tajima et al., 2016). In our 27 individuals studied by MRI of the cervical spine, only three had completely anatomically normally developed upper limbs and hands. In addition to upper limb malformations, five of 27 also had PFFD. Ekfeldt et al. have reported that using the teeth as tools is not rare for individuals with TE (Ekfeldt and Carlsson, 2008), which would suggest that this group may have altered load and movements, including maximum flexion and/or lateral bending of their cervical spine. The effect of a repetitive moderate load on the intervertebral cervical discs is, however, not well known (Masoudi et al., 2015). Another theory could be that the drug thalidomide itself affects the intervertebral discs and causes early DD, possibly already initiated during the embryonic period, as thalidomide is anti-inflammatory and inhibits tumour necrosis factor (TNF) (Moreira et al., 1993, Payvandi et al., 2004). Currently, there is no knowledge related to intervertebral discs in individuals with TE to clarify this hypothesis.

A Myrin goniometer was used to measure the range of motion (ROM) in the cervical spine and demonstrated reduced ROM in all directions of the cervical spine in individuals with TE compared with what has been reported by Malmström et al. in 60 healthy volunteers, 20-60 years of age (Malmstrom et al., 2003). Since the group investigated by Malmström et al. also included individuals younger than the individuals with TE in the present study, it is not possible to determine whether the differences were caused by age, the presence of degenerative changes or some other parameters (muscle shortening, tissue “stiffness” and so on).

Health-related quality of life

“Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” according to the WHO’s definition (http://www.who.int/about/definition/en/print.html). This is one of the reasons why measuring health-related quality of life is currently an important complement in the evaluation of overall health. The aim of health-related quality of life (HRQL) instruments is to evaluate individuals of different ages in a population to obtain knowledge about the way the health status of different medical conditions affects quality of life, both at individual level and at group level.

The survivors of the thalidomide catastrophe are now over 50 years of age. They often have multiple anomalies including musculoskeletal disorders. To assess HRQL in individuals with TE, the SF-36 and EQ-5D were used in this study.

In the total group of 31 individuals with TE, poorer physical quality of life measured by the SF-36 Physical Composite Summary score and the physical subscores was found compared with a population-based control group. The SF-36 has recently been used in a German population with TE which has been reported on but not scientifically published, “Klase Peters 2015” http://www.thalidomidetrust.org/public/thalidomide-health-information. One hundred and eighty-six individuals were evaluated using the SF-36 and EQ-5D. The PCS and MCS for the group were reported to be significantly lower than those of the normal German population.

Further, Nippert et al. reported on HRQL in 166 women with TE evaluated by WHO QOL-BREF (Nippert et al., 2002). A comparison between this group and a control group revealed poorer QOL in individuals with TE, as well as a higher frequency of early retirement.

In spite of impaired physical quality of life in the individuals with TE in this thesis, Mental Quality of Life as measured by the SF-36 Mental Composite Summary score and the mental subscores was not affected. This result is contradictory to that reported in previous studies, where a negative effect on the mental health of individuals with TE has been reported (Imai et al., 2014, Kowalski et al., 2015). Kowalski at al. demonstrated a high level of psychological

disorders (52%) in a study of 28 individuals, which should be compared with the expected prevalence of 25%-30% with psychological disorders in the Brazilian population. This was, however, solely based on a retrospective review of medical records and did not involve any validated instrument/questionnaire (Kowalski et al., 2015). Imai et al. also studied the psychological effects of TE, using the "General Health Questionnaire-28" (Sterling, 2011), which was developed as a screening tool to detect the risk of developing psychiatric disorders in an individual. Imai et al. reported a prevalence of almost 41% suffering from or at risk of psychiatric disorders in a group of 22 individuals with TE (Imai et al., 2014).

Moreover, it is noteworthy that, just as with the SF-36 MCS, the mental domains of the HRQL instrument in the EQ-5D did not demonstrate any effect on the mental quality of life of the TE individuals in the present cohort. All the subgroups evaluated in this study also reported low scores for PCS and normal scores for MCS, compared with the population-based controls for the SF-36. For example, in those with at least one extremity malformation (n=15), the PCS was lower than that in the population-based controls, but the MCS did not differ significantly in the individuals with TE compared with the population-based controls. The same result was reported for individuals with and without PFFD compared with the population-based controls, in terms of both MCS and PCS.

The concept of a clinically meaningful difference is important when evaluating the results of HRQL instruments. This allows for evaluations of whether results found to be statistically significant also have any clinical impact. The huge number of articles published on this concept reveals the difficulties and complexity of this matter. For the present study, it is enough to state that the difference noted between all subgroups for PCS are well above what some authors have regarded as a clinically meaningful difference (over 6-8), (Ware and Sherbourne, 1992, Crosby et al., 2003).

There was a positive correlation between the physical quality of life, PCS, and the function in the upper extremities measured by the DASH in the individuals with TE in the present study. The same relationship was seen for PCS and the pain subscore for lower extremity function measured by the RAOS. The results of Study I also demonstrated that malformations in more than one limb in individuals with TE resulted in a higher DASH score, indicating more disability.

For the EQ-5D, the results from the aggregated subscales also correlated with poorer function in the upper extremities and pain in the lower extremities, measured by the DASH and the RAOS respectively. However, no correlation was found between the EQ-5D and the number of malformed extremities. The two subscales of the EQ-5D measuring physical function, i.e. mobility and ADL, were lower in the group with PFFD compared with the no-PFFD individuals, indicating a poorer physical quality of life for those with PFFD. These results were thereby in agreement with the result shown by the SF-36.

The Mental Quality of Life, MCS, correlated to neither the DASH nor the RAOS result. Ruckenstuhl et al. demonstrated a strong correlation between the DASH score and MCS of the SF-36 in a 10-year follow-up study of patients after surgical treatment of a lower arm fracture (Ruckenstuhl et al., 2014). Those with better arm function, i.e. lower DASH scores, had better mental quality of life measured by the SF-36. Mental quality of life in that study was related to the DASH score evaluating function after treatment, i.e. where the physical function had changed over time. As different from this, the present study's SF-36 MCS was related to a DASH score evaluating function in the upper limbs in individuals with their malformations and lack of certain functions since childhood. In other words, a person born with congenital malformations of the upper and lower extremities might have a low physical function detected by the DASH, but this might not negatively affect the individual's mental status as much as if an individual experiences a deterioration in function, caused by some type of acquired injury.

Another factor that may have influenced the reported HRQL and in particular the mental health of the studied individuals with TE is the economic security in Swedish society. In Sweden, the medico-legal process for individuals with TE started at an early stage. It resulted in a life-long yearly payment to individuals with TE leading to a form of "economic independence", as well as improved social security. This was due to a settlement between all the individuals with TE in Sweden and the drug company that sold the drug that was reached during the trial agreement in 1969 (Strömland and Miller, 1993, Yllner, 2007). In addition, a payment of 500,000 SEK/person was given as an ex gratia payment from the government in Sweden to all thalidomide survivors in Sweden (Berith Josefsson, 2011). This economic security has probably had a positive effect on this group's mental quality of life. Another factor that may have been important for the positive mental quality of life experienced by the group of individuals with TE could be that they reported a high level of independence in overall terms. For example, they had a high rate of employment (77%), which is known to influence mental health positively (Waddell G, 2006, Curnock et al., 2016).

Daily life and adjustments and technical aids related to physical function

For most of the individuals with TE, the orthotic devices used during childhood for the upper and lower extremities were not well designed. They were often heavy and clumsy and therefore both painful and difficult to use (Yllner, 2007). All the efforts during childhood and adolescence focused for the most part on the adjustment of these orthoses with a view to achieving the same mobility as that of individuals without any malformations. The idea of disabled adjustments by stimulating existing functions, i.e. making activities of daily life (ADL) adjusted and possible to perform but in a different manner, had not been processed at that time.

At the time of this study, the individuals with TE had reached middle age and technical aids were used by all the individuals in the group with PFFD. These aids were almost exclusively used to improve mobility, such as orthoses for the lower limbs or a wheelchair. None of the TE individuals in this study used any orthotic devices for the upper limbs.

The present study cohort did not differ from the rest of the Swedish population in terms of sociodemographic data. Nor did they differ in comparison with individuals with TE in other countries, such as Brazil, where children with TE are still being born (Schuler-Faccini et al., 2007). Kowalski et al. demonstrated that 12/28 of the individuals with TE in their survey had a high-school or postgraduate education (Kowalski et al., 2015) and only one individual was illiterate due to severe malformations in all four extremities in combination with deafness and a subsequent inability to learn sign language. In the present study group, almost 50% had attended college and 1/3 had obtained a university degree. In a recent study, sixteen of 28 (57%) were employed (Kowalski et al., 2015), which can be compared with the results of the present study, with almost 80% employment in the studied individuals. Imai et al. reported that 10/22 individuals were employed (Imai et al., 2014).

Most individuals with TE in the present study spent less than 30 minutes in the morning and evening for morning or bedtime procedures, i.e. activities of daily life (ADL) management. One-third of the group had disability-adjusted workplaces and fewer than 1/3 had disability-adjusted homes. These two facts could have indirectly enhanced the self-estimated level of well-being in mental quality of life (MCS), as mentioned earlier. The modified general function score (GFS) also demonstrated an overall high level of independence in the group, despite a few individuals needing assistance in everyday life.

Although the majority of TE individuals reported a lower physical quality of life than the general population, both in the subgroups and for the total group, 1/3 took part in regular training and 14 (45%) performed at least light exercise every week. The ability to participate in regular physical exercise is an important factor for an individual to remain happy and healthy. In a study of Swedish adults with congenital heart disease, the management of physical exercise was one of the self-reported variables clearly associated with a good health status (Sandberg et al., 2015). Deformities of the large joints with an increased risk of OA development, as has been seen in individuals with TE, might change the way these individuals perform physical exercise. Inactivity has a number of well-known negative effects on both health and well-being (Chaput et al., 2014, Kaminsky et al., 2016) and it is therefore important to encourage these individuals to perform physical activities and especially to suggest different types of activity that they are able to perform.

12. Strengths and limitations

To our knowledge, this is the first long-term follow-up cohort focusing on different aspects of orthopaedic problems and quality of life measurements in individuals with thalidomide embryopthy (TE). Some of the instruments and methods used here, such as the SF-36, EQ-5D and MRI for detecting degenerative changes in the cervical spine, have not previously been scientifically reported in this patient group. Although the number of participants was limited to 31 individuals, this is, in comparison with other studies of individuals with TE performed worldwide, a relatively large cohort. Another strength of the study is the detailed evaluation of the general HRQL by SF-36 by measuring the z-scores. This allows for a reliable comparison between the subgroups and the general sex and age-matched populations group.

There are, however, several limitations in the studies in this thesis. Even if the cohort is larger than that in most similar studies, the main limitation was the limited number of individuals available for participation in the study. This is, of course, explained in part by the fact that TE is a rare condition, but it is also due to the difficulty involved in getting individuals with TE to participate in this study. One third of the known individuals with TE who received the invitation to participate never responded. Moreover, due to the strict rules of "The Swedish Thalidomide Society", no reminders were allowed. Another reason for the low acceptance rate might have been the life-long media attention these individuals have lived with, in combination with several studies previously performed on this group. Another factor that may have made some of the individuals with TE, and especially those with severe malformations of the extremities, unwilling to participate, is their difficulty when it comes to travelling. It is therefore likely that the study group might be somewhat skewed towards individuals who are less impaired, with fewer malformations.

Another limitation for the orthopaedic parts of the overall multidisciplinary study was that almost all the data collection, for all disciplines, had to be performed during one day for each participant. This naturally restricted the amount of time each individual could spend on orthopaedic questionnaires and clinical and imaging investigations.

When it came to the information about previous surgeries, this information was self-reported, as the old medical records were not possible to retrieve, and the true number of surgeries might therefore be higher. Moreover, it was not possible to retrieve old radiographs for comparison and no evaluation of the development of degenerative changes over time could therefore be performed. Moreover, the large variety of malformations of the extremities in the examined individuals in this study makes it difficult to aggregate and interpret some of the data at group level; however, the subgrouping of an already limited cohort is far from ideal and sometimes impossible.

13. Conclusions

- A large variety of malformations in both the lower and upper extremities were detected in individuals with TE. For the upper extremities, most individuals had an anatomic pincer grasp or some kind of hand-grip function and function measured by the DASH. They did not demonstrate a clinically significant reduction compared with the reference values from a healthy population. In the lower extremities, proximal femoral focal deficiencies (PFFD) were present in 5/31 individuals. These individuals had lower function as measured by the RAOS in comparison with the rest of the TE group.

- The individuals with TE had a high frequency of osteoarthritis (OA) of the hip and the knee joints but with limited clinical impact.

- An increased frequency of degenerative changes, in terms of both disc degeneration and foraminal affection, was detected with MRI of the cervical spine, in comparison with a control population.

- HRQL, measured by the SF-36 and EQ-5D, demonstrated that individuals with TE had an unaffected mental quality of life, while their physical quality of life was significantly lower compared with the population-based control group. In the subgroup with PFFD, as well as in the subgroup with more than one extremity with malformations, poorer physical quality of life was seen in the SF-36 than in the rest of the TE individuals.

- Few individuals with TE had undergone surgery on their extremities. The majority of the individuals with TE had an active working life, were employed, performed physical activity regularly during their spare time and regarded themselves as being highly independent in daily life.

14. Future perspectives

Thalidomide will remain a link to one of the worst human medical catastrophes to date. There are, however, also individuals not exposed to thalidomide but born with congenital malformations of the extremities. The information in this thesis might therefore be useful in order to better understand the difficulties people with extremity malformations might face with normal physiological ageing.

Today, perhaps somewhat surprisingly, the drug thalidomide has found a new and widespread use. Thalidomide's strong anti-inflammatory capacity is currently used to treat mycobacterium leprae, multiple myeloma, Kaposi's sarcoma, inflammatory bowel disease, Crohn's disease and ulcerative colitis, as well as some other conditions of malignant diseases. The drug has a continuous and rapid interchange between the two isomers, S (-); teratogenic and R (+); anti-inflammatory. It has been difficult to develop only the anti-inflammatory form of the drug, without risking that the teratogenic isomer will act. However, recently at the "Legacy of Thalidomide Seminar-30th September" meeting at the University of York in England, it was reported that there is ongoing research aiming to develop a harmless derivate of the drug with only anti-inflammatory effects. Several different derivates are currently under investigation and patented. The challenge is how these drugs can be tested in humans and how such a drug should be marketed. The controversy of a "harmless" drug would still be alive.

One challenge the Brazilian health-care system is dealing with is the poor health education and the culture of widespread sharing of medicines from one individual to another. On the label of the thalidomide drug used in Brazil, there is a "warning" with a picture of a pregnant woman and a red cross over it. This "warning" is often totally misunderstood and interpreted as if the drug is a contraceptive medication!

For the present and the future, there is a need to spread information about thalidomide embryopathy, as long as the drug is on the market, for whatever indications.

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16. References

ACKMAN, J., ALTIOK, H., FLANAGAN, A., PEER, M., GRAF, A., KRZAK, J., HASSANI, S., EASTWOOD, D. & HARRIS, G. F. 2013. Long-term follow-up of Van Nes rotationplasty in patients with congenital proximal focal femoral deficiency. Bone Joint J, 95-B, 192-8.

AGERBERG, M. 2011. Allt började med Neurosedyn katastrofen. (Everything started with the Neurosedyn disaster). Läkartidningen. Sweden.

AHLBACK, S. 1968. Osteoarthrosis of the knee. A radiographic investigation. Karolinska Instituter.

AHLBACK, S. & RYDBERG, J. 1980. [X-ray classification and examination technics in gonarthrosis]. Lakartidningen, 77, 2091-3, 2096.

AITKEN, G. T. 1969. Proximal femoral focal deficiency-definition, classification, and management. In Proximal Femoral Focal Deficiency. A Congenital Anomaly, pp. 1-22. Washington, DC ,National Academy of Sciences 1969.

AMOR, B. 1989. [Early diagnosis of osteo-arthrosis of the hips and knees]. Rev Prat, 39, 559-63.

ANCES, B. M. 2002. New concerns about thalidomide. Obstet Gynecol, 99, 125-8.

ATROSHI, I., GUMMESSON, C., ANDERSSON, B., DAHLGREN, E. & JOHANSSON, A. 2000. The disabilities of the arm, shoulder and hand (DASH) outcome questionnaire: reliability and validity of the Swedish version evaluated in 176 patients. Acta Orthop Scand, 71, 613-8.

BEDOYA, M. A., CHAUVIN, N. A., JARAMILLO, D., DAVIDSON, R., HORN, B. D. & HO-FUNG, V. 2015. Common Patterns of Congenital Lower Extremity Shortening: Diagnosis, Classification, and Follow-up. Radiographics, 35, 1191-207.

BEDSON, J. & CROFT, P. R. 2008. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. BMC Musculoskelet Disord, 9, 116.

BELLAMY, N., BUCHANAN, W. W., GOLDSMITH, C. H., CAMPBELL, J. & STITT, L. W. 1988. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol, 15, 1833-40.

BERITH JOSEFSSON, J. W. 2011. Barnen som samhället svek- åtgärder med anledning av övergrepp och allvarliga försummelser i samhällsvården. Statens offentliga utredningar SOU 2011:9. Stockholm, Sweden

BERNSTEIN, A. 1997. Formed by thalidomide: mass torts as a false cure for toxic exposure. Columbia Law Rev, 97, 2153-76.

BIKO, D. M., DAVIDSON, R., PENA, A. & JARAMILLO, D. 2012. Proximal focal femoral deficiency: evaluation by MR imaging. Pediatr Radiol, 42, 50-6.

BJÖRCK, M. & WANHAINEN, A. 2007. Knivigt fall från Uppsala. Kärl. 20070226 ed.

BREMANDER, A. B., PETERSSON, I. F. & ROOS, E. M. 2003. Validation of the Rheumatoid and Arthritis Outcome Score (RAOS) for the lower extremity. Health Qual Life Outcomes, 1, 55.

BROOKS, R. 1996. EuroQol: the current state of play. Health Policy, 37, 53-72.

BROYL, A., KUIPER, R., VAN DUIN, M., VAN DER HOLT, B., EL JARARI, L., BERTSCH, U., ZWEEGMAN, S., BUIJS, A., HOSE, D., LOKHORST, H. M., GOLDSCHMIDT, H., SONNEVELD, P., DUTCH-BELGIAN, H. G. & GERMAN, G. G. 2013. High cereblon expression is associated with better survival in patients with newly diagnosed multiple myeloma treated with thalidomide maintenance. Blood, 121, 624-7.

BURSTROM, K., JOHANNESSON, M. & DIDERICHSEN, F. 2001. Swedish population health-related quality of life results using the EQ-5D. Qual Life Res, 10, 621-35.

BURSTROM, K., SUN, S., GERDTHAM, U. G., HENRIKSSON, M., JOHANNESSON, M., LEVIN, L. A. & ZETHRAEUS, N. 2014. Swedish experience-based value sets for EQ-5D health states. Qual Life Res, 23, 431-42.

CASTANEDA, C. P., ZELDIS, J. B., FREEMAN, J., QUIGLEY, C., BRANDENBURG, N. A. & BWIRE, R. 2008. RevAssist: a comprehensive risk minimization programme for preventing fetal exposure to lenalidomide. Drug Saf, 31, 743-52.

CASTILLA, E. E., ASHTON-PROLLA, P., BARREDA-MEJIA, E., BRUNONI, D., CAVALCANTI, D. P., CORREA-NETO, J., DELGADILLO, J. L., DUTRA, M. G., FELIX, T., GIRALDO, A., JUAREZ, N., LOPEZ-CAMELO, J. S., NAZER, J., ORIOLI, I. M., PAZ, J. E., PESSOTO, M. A., PINA-NETO, J. M., QUADRELLI, R., RITTLER, M., RUEDA, S., SALTOS, M., SANCHEZ, O. & SCHULER, L. 1996. Thalidomide, a current teratogen in South America. Teratology, 54, 273-7.

CHAMBERLAIN, G. 1989. The obstetric problems of the thalidomide children. BMJ, 298, 6.

CHAPUT, J. P., CARSON, V., GRAY, C. E. & TREMBLAY, M. S. 2014. Importance of all movement behaviors in a 24 hour period for overall health. Int J Environ Res Public Health, 11, 12575-81.

CLEMMENSEN, O. J., OLSEN, P. Z. & ANDERSEN, K. E. 1984. Thalidomide neurotoxicity. Arch Dermatol, 120, 338-41.

CROSBY, R. D., KOLOTKIN, R. L. & WILLIAMS, G. R. 2003. Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol, 56, 395-407.

CROSS, M., SMITH, E., HOY, D., NOLTE, S., ACKERMAN, I., FRANSEN, M., BRIDGETT, L., WILLIAMS, S., GUILLEMIN, F., HILL, C. L., LASLETT, L. L., JONES, G., CICUTTINI, F., OSBORNE, R., VOS, T., BUCHBINDER, R., WOOLF, A. & MARCH, L. 2014. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis, 73, 1323-30.

CURNOCK, E., LEYLAND, A. H. & POPHAM, F. 2016. The impact on health of employment and welfare transitions for those receiving out-of-work disability benefits in the UK. Soc Sci Med, 162, 1-10.

D'AMATO, R. J., LOUGHNAN, M. S., FLYNN, E. & FOLKMAN, J. 1994. Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci U S A, 91, 4082-5.

DAL MONTE, A. & DONZELLI, O. 1987. Tibial lengthening according to Ilizarov in congenital hypoplasia of the leg. J Pediatr Orthop, 7, 135-8.

DANIELSSON, A. J., WIKLUND, I., PEHRSSON, K. & NACHEMSON, A. L. 2001. Health-related quality of life in patients with adolescent idiopathic scoliosis: a matched follow-up at least 20 years after treatment with brace or surgery. Eur Spine J, 10, 278-88.

DELFORGE, M., BLADE, J., DIMOPOULOS, M. A., FACON, T., KROPFF, M., LUDWIG, H., PALUMBO, A., VAN DAMME, P., SAN-MIGUEL, J. F. & SONNEVELD, P. 2010. Treatment-related peripheral neuropathy in multiple myeloma: the challenge continues. Lancet Oncol, 11, 1086-95.

DOLEV, E. 2001. [The thalidomide story: the Israeli chapter]. Harefuah, 140, 795-7.

ECHARRI, J. J. & FORRIOL, F. 2005. Influence of the type of load on the cervical spine: a study on Congolese bearers. Spine J, 5, 291-6.

EDWARDS, D. H. & NICHOLS, P. J. 1977. The spinal abnormalities in thalidomide embryopathy. Acta Orthop Scand, 48, 273-6.

EKFELDT, A. & CARLSSON, G. E. 2008. Dental status and oral function in an adult group of subjects with thalidomide embryopathy - a clinical and questionnaire study. Acta Odontol Scand, 66, 300-6.

FARDON, D. F. & MILETTE, P. C. 2001. Nomenclature and classification of lumbar disc pathology. Recommendations of the Combined task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology. Spine (Phila Pa 1976), 26, E93-E113.

FRANCES OLDHAM KELSEY, P. D., M. D. Autobiographical reflection, USA.

FRANKS, M. E., MACPHERSON, G. R. & FIGG, W. D. 2004. Thalidomide. Lancet, 363, 1802-11.

FRIES, J. F., SPITZ, P., KRAINES, R. G. & HOLMAN, H. R. 1980. Measurement of patient outcome in arthritis. Arthritis Rheum, 23, 137-45.

FROSTER-ISKENIUS, U. G. & BAIRD, P. A. 1989. Limb reduction defects in over one million consecutive livebirths. Teratology, 39, 127-35.

FULLERTON, P. M. & KREMER, M. 1961. Neuropathy after intake of thalidomide (distaval). Br Med J, 2, 855-8.

FULLERTON, P. M. & O'SULLIVAN, D. J. 1968. Thalidomide neuropathy: a clinical electrophysiological, and histological follow-up study. J Neurol Neurosurg Psychiatry, 31, 543-51.

GILES, F. J. 2002. The emerging role of angiogenesis inhibitors in hematologic malignancies. Oncology (Williston Park), 16, 23-9.

GILLESPIE, R. & TORODE, I. P. 1983. Classification and management of congenital abnormalities of the femur. J Bone Joint Surg Br, 65, 557-68.

GUILLEMIN, F., RAT, A. C., MAZIERES, B., POUCHOT, J., FAUTREL, B., EULLER-ZIEGLER, L., FARDELLONE, P., MORVAN, J., ROUX, C. H., VERROUIL, E., SARAUX, A. & COSTE, J. 2011. Prevalence of symptomatic hip and knee osteoarthritis: a two-phase population-based survey. Osteoarthritis Cartilage, 19, 1314-22.

GUMMESSON, C., ATROSHI, I. & EKDAHL, C. 2003. The disabilities of the arm, shoulder and hand (DASH) outcome questionnaire: longitudinal construct validity and measuring self-rated health change after surgery. BMC Musculoskelet Disord, 4, 11.

HALLENE, K. L., OBY, E., LEE, B. J., SANTAGUIDA, S., BASSANINI, S., CIPOLLA, M., MARCHI, N., HOSSAIN, M., BATTAGLIA, G. & JANIGRO, D. 2006. Prenatal exposure to thalidomide, altered vasculogenesis, and CNS malformations. Neuroscience, 142, 267-83.

HANSSON, E., HANSSON, T. & JONSSON, R. 2006. Predictors for work ability and disability in men and women with low-back or neck problems. Eur Spine J, 15, 780-93.

HERRING, J. A. Fifth edition. Tachdjian's Pediatric Orthopaedics, Fifth edition, pages 951-1003.

HEYNE, D. 1963. [Initial statistical elements relative to congenital malformations in Belgium]. Arch Belg Med Soc, 21, 186-98.

HIDESHIMA, T., CHAUHAN, D., SHIMA, Y., RAJE, N., DAVIES, F. E., TAI, Y. T., TREON, S. P., LIN, B., SCHLOSSMAN, R. L., RICHARDSON, P., MULLER, G., STIRLING, D. I. & ANDERSON, K. C. 2000. Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. Blood, 96, 2943-50.

ILIZAROV, G. A. & DEVIATOV, A. A. 1971. Surgical elongation of the leg. Ortop Travmatol Protez, 32, 20-5.

IMAI, K., IIDA, T., YAMAMOTO, M., KOMATSU, K., NUKUI, Y. & YOSHIZAWA, A. 2014. Psychological and mental health problems in patients with thalidomide embryopathy in Japan. Psychiatry Clin Neurosci, 68, 479-86.

ITO, T., ANDO, H., SUZUKI, T., OGURA, T., HOTTA, K., IMAMURA, Y., YAMAGUCHI, Y. & HANDA, H. 2010. Identification of a primary target of thalidomide teratogenicity. Science, 327, 1345-50.

JANKELOWITZ, S. K., SPIES, J. M. & BURKE, D. 2013. Late-onset neurological symptoms in thalidomide-exposed subjects: a study of an Australasian cohort. Eur J Neurol, 20, 509-14.

JESTER, A., HARTH, A. & GERMANN, G. 2005. Measuring levels of upper-extremity disability in employed adults using the DASH Questionnaire. J Hand Surg Am, 30, 1074 e1-1074 e10.

JOHN, M., PAP, G., ANGST, F., FLURY, M. P., LIESKE, S., SCHWYZER, H. K. & SIMMEN, B. R. 2010. Short-term results after reversed shoulder arthroplasty (Delta III) in patients with rheumatoid arthritis and irreparable rotator cuff tear. Int Orthop, 34, 71-7.

JURADO, F., RODRIGUEZ, O., NOVALES, J., NAVARRETE, G. & RODRIGUEZ, M. 2015. Lucio's leprosy: a clinical and therapeutic challenge. Clin Dermatol, 33, 66-78.

KAELIN, A., HULIN, P. H. & CARLIOZ, H. 1986. Congenital aplasia of the cruciate ligaments. A report of six cases. J Bone Joint Surg Br, 68, 827-8.

KAMINSKY, L. A., BRUBAKER, P. H., GUAZZI, M., LAVIE, C. J., MONTOYE, A. H., SANDERSON, B. K. & SAVAGE, P. D. 2016. Assessing Physical Activity as a Core Component in Cardiac Rehabilitation: A position statement of the American Association of Cardiovascular and Pulmonary Rehabilitation. J Cardiopulm Rehabil Prev, 36, 217-29.

KELSEY, F. E., OLDHAM, F. K. & GEILING, E. M. 1945. Studies on antimalarial drugs; the metabolism of quinine and quinidine in birds and mammals. J Pharmacol Exp Ther, 85, 170-5.

KELSEY, F. O. 1963. Drug Embryopathy: The Thalidomide Story. Md State Med J, 12, 594-7.

KELSEY, F. O. 1967. Events after thalidomide. J Dent Res, 46, 1201-5.

KELSEY, F. O. 1988. Thalidomide update: regulatory aspects. Teratology, 38, 221-6.

KENYON, B. M., BROWNE, F. & D'AMATO, R. J. 1997. Effects of thalidomide and related metabolites in a mouse corneal model of neovascularization. Exp Eye Res, 64, 971-8.

KIDA, M. & LENZ, W. 1968. Thalidomide embryopathy in Japan. Arch Kinderheilkd. 1968/09/01 ed.

KOWALSKI, T. W., SANSEVERINO, M. T., SCHULER-FACCINI, L. & VIANNA, F. S. 2015. Thalidomide embryopathy: Follow-up of cases born between 1959 and 2010. Birth Defects Res A Clin Mol Teratol.

KÄLLEN, B., RAHMANI, T. M. & WINBERG, J. 1984. Infants with congenital limb reduction registered in the Swedish Register of Congenital Malformations. Teratology, 29, 73-85.

LADIZINSKI, B., SHANNON, E. J., SANCHEZ, M. R. & LEVIS, W. R. 2010. Thalidomide and analogues: potential for immunomodulation of inflammatory and neoplastic dermatologic disorders. J Drugs Dermatol, 9, 814-26.

LARY, J. M., DANIEL, K. L., ERICKSON, J. D., ROBERTS, H. E. & MOORE, C. A. 1999. The return of thalidomide: can birth defects be prevented? Drug Saf, 21, 161-9.

LEBRIN, F., SRUN, S., RAYMOND, K., MARTIN, S., VAN DEN BRINK, S., FREITAS, C., BREANT, C., MATHIVET, T., LARRIVEE, B., THOMAS, J. L., ARTHUR, H. M., WESTERMANN, C. J., DISCH, F., MAGER, J. J., SNIJDER, R. J., EICHMANN, A. & MUMMERY, C. L. 2010. Thalidomide stimulates vessel maturation and reduces epistaxis in individuals with hereditary hemorrhagic telangiectasia. Nat Med, 16, 420-8.

LECK, I. M. & MILLAR, E. L. 1962. Incidence of malformations since the introduction of thalidomide. Br Med J, 2, 16-20.

LENZ, W. 1961. Missbildungen nach Medikamen-Einnahme während der Gravidatät. (Childhood malformation after nkake of Medication during pregnancy). Dtsch Med Wochenschr 86, 2555.

LENZ, W. 1962. Thalidomide and congenital abnormalities. Lancet, 1, 271-272.

LENZ, W. 1985. Thalidomide embryopathy in Germany, 1959-1961. Prog Clin Biol Res, 163C, 77-83.

LENZ, W. & KNAPP, K. 1962. Thalidomide embryopathy. Arch Environ Health, 5, 100-5.

LESLIE FLORENCE, A. 1960. Is thalidomide to blame? Br Med J, 2, 1954.

LI, Q., AMANO, K., LINK, T. M. & MA, C. B. 2016. Advanced Imaging in Osteoarthritis. Sports Health, 8, 418-28.

LITTLE, R. F., WYVILL, K. M., PLUDA, J. M., WELLES, L., MARSHALL, V., FIGG, W. D., NEWCOMB, F. M., TOSATO, G., FEIGAL, E., STEINBERG, S. M., WHITBY, D., GOEDERT, J. J. & YARCHOAN, R. 2000. Activity of thalidomide in AIDS-related Kaposi's sarcoma. J Clin Oncol, 18, 2593-602.

LIVINGSTONE, G. 1965. Congenital Ear Abnormalities Due to Thalidomide. Proc R Soc Med, 58, 493-7.

LOWELL, B. 1995. Growing interest in thalidomide. GMHC Treat Issues, 9, 4-6.

LU, J., HELSBY, N., PALMER, B. D., TINGLE, M., BAGULEY, B. C., KESTELL, P. & CHING, L. M. 2004. Metabolism of thalidomide in liver microsomes of mice, rabbits, and humans. J Pharmacol Exp Ther, 310, 571-7.

MALM, K., BERGMAN, S., ANDERSSON, M., BREMANDER, A. & GROUP, B. S. 2015. Predictors of severe self-reported disability in RA in a long-term follow-up study. Disabil Rehabil, 37, 686-91.

MALMSTROM, E. M., KARLBERG, M., MELANDER, A. & MAGNUSSON, M. 2003. Zebris versus Myrin: a comparative study between a three-dimensional ultrasound movement analysis and an inclinometer/compass method: intradevice reliability, concurrent validity, intertester comparison, intratester reliability, and intraindividual variability. Spine (Phila Pa 1976), 28, E433-40.

MANNER, H. M., RADLER, C., GANGER, R. & GRILL, F. 2006. Knee deformity in congenital longitudinal deficiencies of the lower extremity. Clin Orthop Relat Res, 448, 185-92.

MARTIN, P. & LEWIS, J. 1989. Origins of the neurovascular bundle: interactions between developing nerves and blood vessels in embryonic chick skin. Int J Dev Biol, 33, 379-87.

MASOUDI, A., FAMA, D., YOGANANDAN, N. & SNYDER, B. 2015. Methodology to Calibrate Disc Degeneration in the Cervical Spine During Cyclic Fatigue Loading. Biomed Sci Instrum, 51, 222-9.

MATSUDA, S., MIURA, H., NAGAMINE, R., MAWATARI, T., TOKUNAGA, M., NABEYAMA, R. & IWAMOTO, Y. 2004. Anatomical analysis of the femoral condyle in normal and osteoarthritic knees. J Orthop Res, 22, 104-9.

MAYER, A., TIHANYI, J., BRETZ, K., CSENDE, Z., BRETZ, E. & HORVATH, M. 2011. Adaptation to altered balance conditions in unilateral amputees due to atherosclerosis: a randomized controlled study. BMC Musculoskelet Disord, 12, 118.

MCBRIDE, W. G. 1961. Thalidomide and congenital anomalies. Lancet, 2, 1358.

MCBRIDE, W. G. 1977. Thalidomide embryopathy. Teratology, 16, 79-82.

MCCREDIE, J. 1976. Neural crest defects. A neuroanatomic basis for classification of multiple malformations related to phocomelia. J Neurol Sci, 28, 373-87.

MCCREDIE, J. 2009. History, heresy and radiology in scientific discovery. J Med Imaging Radiat Oncol, 53, 433-41.

MILLER, M. T. & STROMLAND, K. 1991. Ocular motility in thalidomide embryopathy. J Pediatr Ophthalmol Strabismus, 28, 47-54.

MILLER, M. T. & STROMLAND, K. 1992. The study of malformations "by the company they keep". Trans Am Ophthalmol Soc, 90, 247-60; discussion 260-3.

MILLER, M. T., STROMLAND, K., VENTURA, L., JOHANSSON, M., BANDIM, J. M. & GILLBERG, C. 2005. Autism associated with conditions characterized by developmental errors in early embryogenesis: a mini review. Int J Dev Neurosci, 23, 201-19.

MILLER, M. T. & STROMLAND, K. K. 2011. What can we learn from the thalidomide experience: an ophthalmologic perspective. Curr Opin Ophthalmol, 22, 356-64.

MILLER, M. T. & STRÖMLAND, K. 1999. Teratogen update: thalidomide: a review, with a focus on ocular findings and new potential uses. Teratology, 60, 306-21.

MILLER, M. T., STRÖMLAND, K. & VENTURA, L. 2008. Congenital aberrant tearing: a re-look. Trans Am Ophthalmol Soc, 106, 100-15; discussion 115-6.

MOREIRA, A. L., SAMPAIO, E. P., ZMUIDZINAS, A., FRINDT, P., SMITH, K. A. & KAPLAN, G. 1993. Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. J Exp Med, 177, 1675-80.

MYERS, S. L., BRANDT, K. D., EHLICH, J. W., BRAUNSTEIN, E. M., SHELBOURNE, K. D., HECK, D. A. & KALASINSKI, L. A. 1990. Synovial inflammation in patients with early osteoarthritis of the knee. J Rheumatol, 17, 1662-9.

NEWMAN, C. G. 1985. Teratogen update: clinical aspects of thalidomide embryopathy--a continuing preoccupation. Teratology, 32, 133-44.

NEWMAN, C. G. 1986. The thalidomide syndrome: risks of exposure and spectrum of malformations. Clin Perinatol, 13, 555-73.

NICOTRA, A., NEWMAN, C., JOHNSON, M., EREMIN, O., FRIEDE, T., MALIK, O. & NICHOLAS, R. 2016. Peripheral Nerve Dysfunction in Middle-Aged Subjects Born with Thalidomide Embryopathy. PLoS One, 11, e0152902.

NILSSON, R. 2004. Control of chemicals in Sweden: an example of misuse of the "precautionary principle". Ecotoxicol Environ Saf, 57, 107-17.

NIPPERT, I., EDLER, B. & SCHMIDT-HERTERICH, C. 2002. 40 years later: the health related quality of life of women affected by thalidomide. Community Genet, 5, 209-16.

HÄGG O., P. F., ROMBERG K., NORDWALL A. 2001. The General Function Score: a usefull tool for measurment of ohysical disability, validity and reliability. Eur Spine J, 10, 203-210.

OSHIMA, Y., OKUTSU, I., HAMANAKA, I. & MOTOMURA, T. 2006. Carpal tunnel syndrome accompanying radial dysplasia due to thalidomide embryopathy. J Hand Surg Br, 31, 342-4.

PAYVANDI, F., WU, L., HALEY, M., SCHAFER, P. H., ZHANG, L. H., CHEN, R. S., MULLER, G. W. & STIRLING, D. I. 2004. Immunomodulatory drugs inhibit expression of cyclooxygenase-2 from TNF-alpha, IL-1beta, and LPS-stimulated human PBMC in a partially IL-10-dependent manner. Cell Immunol, 230, 81-8.

PFIRRMANN, C. W., METZDORF, A., ZANETTI, M., HODLER, J. & BOOS, N. 2001. Magnetic resonance classification of lumbar intervertebral disc degeneration. Spine (Phila Pa 1976), 26, 1873-8.

RESNICK, D. 1985. Degenerative diseases of the vertebral column. Radiology, 156, 3-14.
RING, P. A. 1959. Congenital short femur; simple femoral hypoplasia. J Bone Joint Surg Br, 41-B, 73-9.

ROOS, E. M., ROOS, H. P., LOHMANDER, L. S., EKDAHL, C. & BEYNNON, B. D. 1998. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. J Orthop Sports Phys Ther, 28, 88-96.

ROSENGREN, A., ORTH-GOMER, K., WEDEL, H. & WILHELMSEN, L. 1993. Stressful life events, social support, and mortality in men born in 1933. BMJ, 307, 1102-5.

RUCKENSTUHL, P., BERNHARDT, G. A., SADOGHI, P., GLEHR, M., HOLZER, L. A., LEITHNER, A., WOLF, M. & GRUBER, G. 2014. Quality of life after volar locked plating: a 10-year follow-up study of patients with intra-articular distal radius fractures. BMC Musculoskelet Disord, 15, 250.

RUFFING, L. 1977. Evalulation of thalidomide children. Birth Defects Orig Artic Ser, 13, 287-300.

RUFFING, L. 1978. [Ankylosing spinal changes in thalidomide embryopathies]. Verh Dtsch Ges Rheumatol, 5, 427-31.

RUFFING, L. 1980. [The spine in the thalidomide-embryopathy]. Fortschr Med, 98, 405-9.

SANDBERG, C., ENGSTROM, K. G., DELLBORG, M., THILEN, U., WADELL, K. & JOHANSSON, B. 2015. The level of physical exercise is associated with self-reported health status (EQ-5D) in adults with congenital heart disease. Eur J Prev Cardiol, 22, 240-8.

SCHMIDT, M. & SALZANO, F. M. 1980. Dissimilar effects of thalidomide in dizygotic twins. Acta Genet Med Gemellol (Roma), 29, 295-7.

SCHULER-FACCINI, L., SOARES, R. C., DE SOUSA, A. C., MAXIMINO, C., LUNA, E., SCHWARTZ, I. V., WALDMAN, C. & CASTILLA, E. E. 2007. New cases of thalidomide embryopathy in Brazil. Birth Defects Res A Clin Mol Teratol, 79, 671-2.

SCHWAB, B. W., AREZZO, J. C., PALDINO, A. M., FLOHE, L., MATTHIESSEN, T. & SPENCER, P. S. 1984. Rabbit sural nerve responses to chronic treatment with thalidomide and supidimide. Muscle Nerve, 7, 362-8.

SHESKIN, J. 1965. Thalidomide in the Treatment of Lepra Reactions. Clin Pharmacol Ther, 6, 303-6.

SHIGA, T., SHIMBO, T. & YOSHIZAWA, A. 2015. Multicenter investigation of lifestyle-related diseases and visceral disorders in thalidomide embryopathy at around 50 years of age. Birth Defects Res A Clin Mol Teratol.

SJÖGREEN, L. & KILIARIDIS, S. 2012. Facial palsy in individuals with thalidomide embryopathy: frequency and characteristics. J Laryngol Otol, 126, 902-6.

SMITHELLS, R. W. 1973. Defects and disabilities of thalidomide children. Br Med J, 1, 269-72.

SMITHELLS, R. W. & NEWMAN, C. G. 1992. Recognition of thalidomide defects. J Med Genet, 29, 716-23.

SOMERS, G. S. 1962. Thalidomide and congenital abnormalities. Lancet, 1, 912-3.

SONG, L., ZHOU, X. & LI, X. 2015. Phase II trial of granulocyte-macrophage colony-stimulating factor plus thalidomide in older patients with castration-resistant prostate cancer. Mol Clin Oncol, 3, 865-868.

STANITSKI, D. F. & KASSAB, S. 1997. Rotational deformity in congenital hypoplasia of the femur. J Pediatr Orthop, 17, 525-7.

STEBBING, J., BENSON, C., EISEN, T., PYLE, L., SMALLEY, K., BRIDLE, H., MAK, I., SAPUNAR, F., AHERN, R. & GORE, M. E. 2001. The treatment of advanced renal cell cancer with high-dose oral thalidomide. Br J Cancer, 85, 953-8.

STERLING, M. 2011. General Health Questionnaire - 28 (GHQ-28). J Physiother, 57, 259.

STEVENS, P. M. & ARMS, D. 2000. Postaxial hypoplasia of the lower extremity. J Pediatr Orthop, 20, 166-72.

STRÖMLAND, K., MILLER, M. & COOK, C. 1991. Ocular teratology. Surv Ophthalmol, 35, 429-46.

STRÖMLAND, K., NORDIN, V., MILLER, M., AKERSTROM, B. & GILLBERG, C. 1994. Autism in thalidomide embryopathy: a population study. Dev Med Child Neurol, 36, 351-6.

STRÖMLAND, K. & MILLER, M. T. 1993. Thalidomide embryopathy: revisited 27 years later. Acta Ophthalmol (Copenh), 71, 238-45.

STRÖMLAND, K., NORDIN, V., MILLER, M., AKERSTROM, B. & GILLBERG, C. 1994. Autism in thalidomide embryopathy: a population study. Dev Med Child Neurol, 36, 351-6.

SULLIVAN, M. & KARLSSON, J. 1998. The Swedish SF-36 Health Survey III. Evaluation of criterion-based validity: results from normative population. J Clin Epidemiol, 51, 1105-13.

SVETLANA BALKANOV, K., SOTIROVA, T., GENADIEVA, S. S., CEVRESKA, L., STOJANOVIK, A. & BALKANOV, T. 2014. Adverse effects of thalidomide administration, in patients with myeloma multiplex? Mater Sociomed, 26, 134-6.

TAJIMA, T., WADA, T., YOSHIZAWA, A., MASUDA, T., OKAFUJI, T., NAKAYAMA, T. & HASUO, K. 2016. Internal anomalies in thalidomide embryopathy: results of imaging screening by CT and MRI. Clin Radiol, 71, 1199 e1-7.

TAUSSIG, H. B. 1962. Thalidomide and phocomelia. Pediatrics, 30, 654-9.

TEO, S. K., HARDEN, J. L., BURKE, A. B., NOORMOHAMED, F. H., YOULE, M., JOHNSON, M. A., PETERS, B. S., STIRLING, D. I. & THOMAS, S. D. 2001. Thalidomide is distributed into human semen after oral dosing. Drug Metab Dispos, 29, 1355-7.

THERAPONTOS, C., ERSKINE, L., GARDNER, E. R., FIGG, W. D. & VARGESSON, N. 2009. Thalidomide induces limb defects by preventing angiogenic outgrowth during early limb formation. Proc Natl Acad Sci U S A, 106, 8573-8.

THOMAS, N. P., JACKSON, A. M. & AICHROTH, P. M. 1985. Congenital absence of the anterior cruciate ligament. A common component of knee dysplasia. J Bone Joint Surg Br, 67, 572-5.

THORSTENSSON, C., DAHLBERG, L., CEDERLUND, I. & GARELLICK, G. 2011. Bättre Omhändertagande av patienter med Artros (BOA)

(The BOA register annual report 2011, Better management of patients with OsteoArthrtis). Registercentrum Västra Götaland, 413 45 Göteborg, Sweden.

TT-REUTER. 1961. Tyskt sömnmedel förmodas farligt under havandeskap. Svenska dagbladet, 27 Nov.

VARGESSON, N. 2009. Thalidomide-induced limb defects: resolving a 50-year-old puzzle. Bioessays, 31, 1327-36.

VARGESSON, N. 2013. Thalidomide Embryopathy: An Enigmatic Challenge. International Scholarly Research Notices, 2013.

VARGESSON, N. 2015. Thalidomide-induced teratogenesis: history and mechanisms. Birth Defects Res C Embryo Today, 105, 140-56.

VIANNA, F. S., LOPEZ-CAMELO, J. S., LEITE, J. C., SANSEVERINO, M. T., DUTRA MDA, G., CASTILLA, E. E. & SCHULER-FACCINI, L. 2011. Epidemiological surveillance of birth defects compatible with thalidomide embryopathy in Brazil. PLoS One, 6, e21735.

VIANNA, F. S., SCHULER-FACCINI, L., LEITE, J. C., DE SOUSA, S. H., DA COSTA, L. M., DIAS, M. F., MORELO, E. F., DORIQUI, M. J., MAXIMINO, C. M. & SANSEVERINO, M. T. 2013. Recognition of the phenotype of thalidomide embryopathy in countries endemic for leprosy: new cases and review of the main dysmorphological findings. Clin Dysmorphol, 22, 59-63.

VON PAWEL, B. 1972. Social integration of dysmelic children caused by thalidomide in normal school classes. Psychol Prax, 46, 25-46.

WADDELL G, G. K. A. 2006. IS WORK GOOD FOR YOUR HEALTH AND WELL-BEING?, UK, The Stationery Office.

WANKA, J. & DIXON, A. S. 1964. Treatment of Osteo-Arthritis of the Hip with Indomethacin. A Controlled Clinical Trial. Ann Rheum Dis, 23, 288-94.

WARE, J. E., JR. & SHERBOURNE, C. D. 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care, 30, 473-83.

WHITSEL, A. I., JOHNSON, C. B. & FOREHAND, C. J. 2002. An in ovo chicken model to study the systemic and localized teratogenic effects of valproic acid. Teratology, 66, 153-63.

WIKLUND, I. & KARLBERG, J. 1991. Evaluation of quality of life in clinical trials. Selecting quality-of-life measures. Control Clin Trials, 12, 204S-216S.

WINBERG, J. 1964a. Investigation on the Possible Relation of Fetal Injuries and Drugs. Iv. Retrospective Study on Drug Consumption among Mothers with Malformed Children. Sven Lakartidn, 61, 814-831, 890-902.

WINBERG, J. 1964b. Investigation on the Possible Relation of Fetal Injuries and Drugs. Iv. Retrospective Study on Drug Consumption among Mothers with Malformed Children. Sven Lakartidn, 61, 890-902.

WINBERG, J. 1964c. Utredning rörande det eventuella sambandet mellan fosterskador och läkemedel. III. Skelett missbildningar av Talidomidtyp i Sverige under åren 1960-1962. Svenska läkartidningen. Sweden, Stockholm.

WU, J. J., HUANG, D. B., PANG, K. R., HSU, S. & TYRING, S. K. 2005. Thalidomide: dermatological indications, mechanisms of action and side-effects. Br J Dermatol, 153, 254-73.

XIN, W., XIAOHUA, N., PEILIN, C., XIN, C., YAQIONG, S. & QIHAN, W. 2008. Primary function analysis of human mental retardation related gene CRBN. Mol Biol Rep, 35, 251-6.

YANG, C., SINGH, P., SINGH, H., LE, M. L. & EL-MATARY, W. 2015. Systematic review: thalidomide and thalidomide analogues for treatment of inflammatory bowel disease. Aliment Pharmacol Ther, 41, 1079-93.

YLLNER, N. 2007. Just a little withe sleeping pill. "Bara en liten vit sömntablett. ", Sweden, Recito.

ZELDIS, J. B., WILLIAMS, B. A., THOMAS, S. D. & ELSAYED, M. E. 1999. S.T.E.P.S.: a comprehensive program for controlling and monitoring access to thalidomide. Clin Ther, 21, 319-30.

Appendix

Study design questionnaire

Namn.....Personnummer.....

Adress.....

Telefon hem.....Telefon arbete.....

Vilket är ditt nuvarande civilstånd?

☐ Gift/ sammanboende
☐ Skild
☐ Änka/ änklig
☐ Ensamboende

Hur många barn har du?

☐ 0 ☐1 ☐2 ☐3 ☐4 ☐ fler än 4

ARBETE

Nuvarande yrke.....

Hur mycket arbetar du? (gäller senaste året)

☐ Heltid ☐ Deltid, ange omfattning: .....

Hur är arbetstiden förlagd? (gäller senaste året)

☐ Dagtid ☐ Nattetid

Har du skiftarbete?

☐ Nej ☐ Ja

Jag arbetar inte utanför hemmet p.g.a. att jag är (gäller senaste året)

☐ Föräldraledig
☐ Arbetslös sedan.....(mån, år)
☐ Sjukskriven pga.....sedan.....(mån, år)
☐ Sjukbidrag/ pension p.g.a.....sedan.....(år)
☐ Studerar
☐ Annat, ange vad:.....

Har du varit tvungen att arbeta mindre än heltid p.g.a. din neurosedynskada?

☐ Nej ☐ Ja, hur mycket?.....

Har din make/maka/sambo varit tvungen att minska sin arbetstid p.g.a. din neurosedynskada?

☐ Nej ☐ Ja, hur mycket?.....

UTBILDNING

Vad har du för skolutbildning? Kryssa i för det alternativ som stämmer

☐ mindre än 7 år i skolan
☐ mellan 7-9 år i skolan
☐ yrkesskola, fackskola
☐ Gymnasieskola
☐ Oavslutad högskola/universitet
☐ Högskola eller universitet

Har du gått i någon form av specialförskola, specialskola (t ex särskola, skola för rörelsehindrade) eller specialklass (t ex syn- eller hörselklass, obsklass)?

.....

Har du haft några speciella svårigheter inom något/några ämnesområden?

☐ Läs- och/eller skrivsvårigheter?.....

☐ Inom andra ämnesområden?.....

Har du fått speciellt stöd inom något/några ämnesområden?

☐ Läs- och/eller skrivsvårigheter?.....

☐ Inom andra ämnesområden?.....

Har du någon gång tidigare blivit testad av psykolog, tex genomfört ett begåvningstest?

☐ Nej ☐ Ja

Ange i så fall (så gott du vet och minns) typ av test, när och var detta genomfördes?

.....

ÖVRIGA SJUKDOMAR

Har du någon sjukdom eller åkomma som du behandlas för förutom din neurosedynskada? (Frågan gäller både nu och tidigare)

☐ Nej ☐ Ja. Vilken eller vilka sjukdomar? .....

.....

Tar du regelbundet någon medicin? (gäller senaste året)

☐ Nej ☐ Ja Ange namn på medicin och dos:.....

.....

Namn.....Personnummer.....

PROBLEM FRÅN RÖRELSEAPPARATEN

1. Använder du gånghjälpmedel eller stöd för att förflytta dig inomhus?

☐ Nej ☐ Ja

2. Vilken typ av hjälpmedel? ☐ Kryckor ☐ Rollator ☐ Rullstol

☐ Annat hjälpmedel, vilket.....

3. Använder du gånghjälpmedel eller stöd för att förflytta dig ute?

☐ Nej ☐ Ja

4. Vilken typ av hjälpmedel? ☐ Kryckor ☐ Rollator ☐ Rullstol

☐ Annat hjälpmedel, vilket.....

5. Har du någon skena eller stöd för benet?

☐ Nej ☐ Ja

6. Vilken typ av hjälpmedel? ☐ Inlägg ☐ Specialanpassade skor

☐ Skena för fot/ underben ☐ Protes, vilken typ?.....

☐ Annat hjälpmedel, vilket.....

7. Hur mycket använder du dina hjälpmedel?

☐ Inte alls ☐ Högst 1 tim/dag

☐ Mellan 1-6 tim/dag ☐ Mer än 6 tim/dag

8. Har du någon skena eller stöd för armen?

☐ Nej ☐ Ja, vilken typ?.....

9. Hur mycket använder du den dagligen?

☐ Inte alls ☐ Högst 1 tim/dag

☐ Mellan 1-6 tim/dag ☐ Mer än 6 tim/dag

10. Bor du i handikappanpassad bostad?

☐ Nej ☐ Ja

11. Hur är bostaden anpassad?.....

12. Om du inte har sådan bostad, tycker du att du skulle behöva ha handikappanpassad bostad?

☐ Nej ☐ Ja

13. Varför?.....

14. Har du fått anpassning av din arbetssituation, t.ex. hjälpmedel, ändring av din arbetsplats etc.?

☐ Nej ☐ Ja

15. Vilken typ av anpassning?..... .....

16. Har du personlig asisstent?

☐ Nej ☐ Ja.

17. Hur många timmar om dagen?.....

18. Har du känt dig stressad? Med stress menar vi att man känner sig spänd, retlig, nervös, ångestfylld eller har svårigheter med sömnen p.g.a. exempelvis förhållanden i arbetet eller hemmet etc. Har du upplevt detta?

☐ Har aldrig upplevt detta
☐ Har upplevt någon stressperiod
☐ Någon stressperiod under senaste fem åren
☐ Flera stressperioder under senaste fem åren
☐ Ständig stress det senaste året
☐ Ständig stress under de senaste fem åren

VANLIGA AKTIVITETER

19. Hur mycket tid brukar du behöva för dina vardagliga rutiner exempel morgonrutiner, innan du är klar på morgonen?

☐ 30 minuter ☐ En timma ☐ Mer än en timma

20. ...och för kvällsrutiner, innan du kommer i säng?

☐ 30 minuter ☐ En timma ☐ Mer än en timma

21. Markera med ett kryss (x) på var rad hur du klarar dessa aktiviteter. Du kan välja mellan att du klarar, klarar det dåligt eller inte alls, samt om du får eller behöver hjälp för att klara av det.

	Klarar	Klarar dåligt	Klarar inte själv	Får hjälp med (anhörig, assistent, etc.)
a. Duscha	☐	☐	☐	☐
b. Klä på sig	☐	☐	☐	☐
c. Ta på skor	☐	☐	☐	☐
d. Luta sig över handfat	☐	☐	☐	☐
e. Bädda säng	☐	☐	☐	☐
f. Äta	☐	☐	☐	☐
g. Laga mat	☐	☐	☐	☐
h. Diska	☐	☐	☐	☐
i. Dammsuga	☐	☐	☐	☐
j. Handla	☐	☐	☐	☐
k. Bära matkasse	☐	☐	☐	☐
l. Gå i trappor	☐	☐	☐	☐
m. Sitta längre än 30 min.	☐	☐	☐	☐
n. Gå längre än 30 min.	☐	☐	☐	☐
o. Stå längre än 30 min.	☐	☐	☐	☐
p. Lyfta mer än 10 kg	☐	☐	☐	☐

22. **Hur mycket rör du dig och anstränger dig kroppsligt i ditt arbete?**
Vi vill veta hur kroppsligt ansträngande ditt arbete är. De yrken som finns upptagna i nedanstående grupper är bara exempel. Frågan gäller det senaste året.

☐ Sittande arbete: du har övervägande stillasittande arbete och går inte mycket under arbetstiden.
Exempel på sådana arbeten är skrivbordsarbete, urmakeri och montering av lättare delar.

☐ Lätt, men något rörligt arbete: du har ett arbete där du går ganska mycket, men ej bär eller lyfter tyngre saker.
Exempel på sådana arbeten är rörligt expeditionsarbete, lätt industriarbete, förmanssysslor, sådan undervisning där man går mycket, arbete som affärsbiträde, sjuksköterska, hemsamarit med få lyft, hemarbete utan småbarn.

☐ Måttligt tungt arbete: du går mycket och lyfter dessutom ganska mycket eller går mycket uppför trappor eller backar.
Exempel är brevbäring, arbete vid tyngre industri, arbete som lokalvårdare, kökspersonal, hemarbete med småbarn.

☐ Tungt arbete: du har ett tungt kroppsarbete, lyfter tunga föremål och anstränger dig mycket kroppsligt.
Exempel är skogsarbete, fiske med tunga redskap, byggnadsgrovarbete.

23. **Hur mycket rör du dig och anstränger dig kroppsligt på fritiden?**
Om din aktivitet varierar mycket mellan t.ex. sommar och vinter, så försök att ta ett genomsnitt. Frågan gäller det senaste året.

☐ Stillasittande fritid: du ägnar dig mestadels åt läsning, TV, bio eller annan stillasittande sysselsättning på fritiden.

☐ Måttlig motion på fritiden: du promenerar, cyklar eller rör dig på annat sätt under minst fyra timmar i veckan.
I detta inräknas också gång eller cykling till och från arbetet samt söndagspromenader, ordinärt trädgårdsarbete, fiske, bordstennis, bowling.

☐ Regelbunden motion och träning: du ägnar dig åt t.ex. löpning, simning, tennis, badminton, motionsgymnastik, studsmatta eller liknande, som motionssport.
Tyngre trädgårdsarbete och liknande räknas till denna grupp. Observera att det skall vara 2-3 timmar i veckan.

☐ Hård träning eller tävlingssport: du ägnar dig åt hård träning och tävling i löpning, orientering, skidåkning, simning, fotboll, handboll etc., regelbundet och flera gånger i veckan.

TIDIGARE OPERATIONER

24. Har du blivit opererad i arm eller hand?

☐ Nej ☐ Ja. Beskriv närmare: .....

.....

	När?	Var?/ Vilket sjukhus?	Vilken typ av operation?
Operation nr 1			
Operation nr 2			
Operation nr 3			
Operation nr 4			

25. Har du blivit opererad i ben eller fot?

☐ Nej ☐ Ja. Beskriv närmare: .....

.....

	När?	Var?/ Vilket sjukhus?	Vilken typ av operation?
Operation nr 1			
Operation nr 2			
Operation nr 3			
Operation nr 4			

26. Har du blivit opererad i ryggen?

☐ Nej ☐ Ja. Beskriv närmare: .....

HUR PÅVERKAS DITT LIV AV DIN SKADA OCH/ELLER ANDRA PROBLEM

27. Har du någon sjukdom eller åkomma som du behandlas för förutom din neurosedynskada? (Frågan gäller både nu och tidigare)

☐ Nej ☐ Ja

28. Vilken eller vilka sjukdomar? .....

29. Har du varit i kontakt med nedanstående vårdpersonal senaste året, pga. din neurosedyn skada?

Vård personal	Nej	Ja	Hur ofta?
Läkare			
Psykolog			
Kurator			
Sjuksköterska			
Annan			

30. Har du varit inlagd på sjukhus senaste året p.g.a. din neurosedyn skada?

☐ Nej ☐ Ja

31. Hur många gånger o hur länge?.....

32. Behöver du specialtransportmedel, tex. färdtjänst för att kunna ta dig till och från sjukhus, eller andra instanser?

☐ Nej ☐ Ja

33. Hur ofta råkar du ut för olyckhändelser som beror på din neurosedyn skada, under senaste halvåret (t.ex. klämt dig, skurit dig, snubblat eller liknande) ?

☐ Dagligen
☐ En gång per vecka eller färre
☐ En gång i månad eller färre
☐ Ganska sällan
☐ Aldrig

34. Har du p.g.a. din neurosedynskada varit tvungen att ersätta material i hemmet oftare än vad som är brukligt, eftersom dessa gått sönder?

☐ Nej ☐ Ja

35. .....till vilken kostnad?.....

36. Har du känt att du p.g.a. din neurosedynskada blivit särbehandlad på olika myndigheter?

Försäkringskassan	☐ Nej	☐ Ja
Försäkringsbolag	☐ Nej	☐ Ja
Arbetsgivaren	☐ Nej	☐ Ja

37. Har du någon gång varit sjukskriven mer än en månad p.g.a. följder av din neurosedynskada?

☐ Nej ☐ Ja

38. Orsak?.....

.....

39. När i så fall:

	Hur många gånger?	Hur länge?
Sista året		
För mer än ett år sedan men mindre än fem år sedan		
Mer än fem år sedan		

40. Har du varit sjukskriven för andra sjukdomar?

☐ Nej ☐ Ja

41. Vilken eller vilka sjukdomar?.....

.....

42. När i så fall:

	Hur många gånger?	Hur länge?
Sista året		
För mer än ett år sedan men mindre än fem år sedan		
Mer än fem år sedan		