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Lipoedema

- Lived Experiences, Functional Performance, and Psychological Well-Being in Affected Women

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The good physician treats the disease; the great physician treats the patient who has the disease.
Sir William Osler

Solum certum nihil esse certi.
In these matters, the only certainty is that nothing is certain.
Pliny the Elder

Table of contents

Abstract

Background:

Lipoedema is a chronic condition that predominantly affects women. It is characterised by an accumulation of adipose tissue in the extremities, accompanied by pain, a sense of heaviness, and easy bruising. Lipoedema does not respond to conventional weight-loss treatments, and no effective treatments are provided through subsidised healthcare. Recognition in healthcare is low, and lipoedema may be misdiagnosed as, for example, obesity. Lipoedema affects individuals through physical alterations which restrict movement and increase pain. Additionally, lipoedema is associated with reduced quality of life, increased risk of depression, and reduced psychological well-being.

Aim:

This thesis aimed to explore the lived experiences of women with medically verified lipoedema, including everyday lives and healthcare interactions. We also evaluated muscle strength, physical capacity, body composition, and health-related quality of life in a sample of women with verified lipoedema. In addition, psychological characteristics by perceived stress, anxiety, self-compassion, perfectionism, and impostor phenomenon were assessed.

Methods:

This thesis comprises five papers with both qualitative and quantitative approaches. In Paper I, a Priority-Setting Partnership was utilised within a national design to identify research questions prioritised by participants with lived experience of lipoedema and clinicians. Papers II and III were conducted with qualitative methods, collecting data through twelve semi-structured interviews in a sample of women with a verified lipoedema diagnosis. The transcripts of the interviews were analysed using qualitative content analysis to yield both manifest and latent content of data. In Paper IV, data were collected by measuring isometric strength and physical capacity in 18 women with lipoedema and by evaluating body composition using dual-energy X-ray absorptiometry. In addition, validated questionnaires were used to assess health-related quality of life, alcohol use, and physical activity. In Paper V, psychometric instruments were used in combination with RAND-36 to screen 18 women with lipoedema for signs of anxiety, stress, impostor phenomenon, perfectionism, self-compassion, and health-related quality of life.

Results:

Paper I: Ten questions from a total of 1314 submitted research questions were prioritised by representatives from individuals with lived experiences of lipoedema and clinicians. These ten questions were comprised of two tiers encompassing diagnostic methods, treatments, and treatment outcomes.

Papers II and III: Two themes emerged: “An uncertain uphill battle against a divergent body and societal ignorance” and “Pushing the barricaded doors to treatment and care while fighting to illuminate the shadows of lipoedema”. In Paper II, the women described how the condition made them feel trapped within their bodies and limited in their day-to-day activities. They also described social exclusion, while highlighting that emotional support from family and friends was an important aspect of their lives. In Paper III, their experiences of healthcare varied, but most were negative, characterised by limited or no support and treatment, disbelief, and being labelled obese by healthcare professionals. Financial limitations, varied treatment experiences, and a search for something that would alleviate their symptoms were also described.

Papers IV and V: In Paper IV, isometric strength and muscle mass according to DXA were unimpaired. The 30-second sit-to-stand test resulted in fewer repetitions performed, while the 6-minute walk test did not yield any significant deviation in distance. However, the participants experienced increased pain at completion of the 6-minute walk test. In Paper V, RAND-36 results showed lower scores across all subscales regarding quality of life. The subscales of role physical, role emotional, pain, and energy/fatigue displayed the lowest scores. There were signs of stress among one-third of the participants, but self-compassion scores were high: 88.9% (n=16) reported moderate to high self-compassion, and 50% (n=9) reported high self-compassion.

Conclusion:

Lipoedema significantly reduces the health-related quality of life and physical and mental well-being of affected women. Their experiences of healthcare indicate that the knowledge of lipoedema in healthcare is

limited, a lack of evidence-based care constrains women’s access to effective interventions, and substantial research gaps persist. The inadequacy of current diagnostic methods undermines clinical management and research comparability, making the development of such methods a critical priority.

Education for healthcare professionals regarding lipoedema, large multicentre studies of various treatments, and the implementation of effective treatments in healthcare settings are all necessary to reduce the consequences of lipoedema and to provide women diagnosed with lipoedema with care and support.

The findings regarding muscle strength, physical capacity, and body composition do not account for the symptoms described by participants and suggest that these symptoms are attributable to pain and adipose tissue accumulation. Objective and subjective perspectives should both be integrated in lipoedema consultation and treatment.

The psychometric findings differ between the qualitative studies and the rated health-related quality of life. It is imperative to consider protective psychological factors when planning lipoedema interventions.

Sammanfattning på svenska

Bakgrund:

Lipödem är en kronisk åkomma som nästan bara drabbar kvinnor. Den karakteriseras av en ansamling av fettvävnad på benen och ibland på armarna, tillsammans med smärta, tyngdkänsla och lätt att få blåmärken. Lipödem minskar inte med traditionell viktminskningsbehandling och få behandlingar ingår i den subventionerade sjukvården. Kunskapen om lipödem inom sjukvården är begränsad och sjukdomen kan därför felaktigt bli diagnostiserad som övervikt. Lipödem påverkar livskvaliteten och ger ökad risk för depression och sämre psykologisk hälsa och orsakar dessutom en kropp som begränsar rörligheten och ökar smärtan.

Syfte:

I andra studier ingår kvinnor som själva ställt diagnosen lipödem. Vi ville därför bara studera kvinnor med medicinskt diagnostiserat lipödem. Syftet med studierna var att hos kvinnor med lipödem utforska påverkan på vardagslivet och kvinnornas upplevelser av sjukvården. Vi studerade också fysisk förmåga, kroppssammansättning, självskattad livskvalitet, tecken på stress, ångest, självmedkänsla, perfektionism och s.k. bluffsyndrom.

Metoder:

Avhandlingen består av fem studier. I studie I gjordes en nationell identifiering av forskningsfrågor som prioriterades av personer med lipödem, anhöriga och kliniker som träffar personer med lipödem. I studierna II och III analyserades tolv intervjuer med kvinnor med lipödem med fokus på erfarenheter av att leva med sjukdomen och möten med sjukvården. Data från intervjuerna analyserades (med kvalitativ innehållsanalys) för att identifiera likheter och skillnader i berättelserna. I studie IV undersökte vi fysiska förutsättningar genom att mäta muskelstyrka och funktionell kapacitet samt mätning av kroppssammansättning hos 18 kvinnor med lipödem. Deltagarna fick också svara på enkäter för att kartlägga hälsorelaterad livskvalitet, alkoholanvändning och fysisk aktivitet. I studie V användes psykologiska skattningsskalor tillsammans med samma enkät för livskvalitet som i studie IV för att kartlägga tecken på ångest, stress, bluffsyndrom, perfektionism, självmedkänsla och hälsorelaterad livskvalitet.

Resultat:

Studie I: Tio frågor som var viktiga att studera prioriterades av de ursprungliga mer än 1300. Frågorna rankades till topp 5 och topp 6–10 och innehöll frågor relaterade till diagnostiska metoder, behandlingar och behandlingsresultat.

Studie II och III: Resulterade i två teman som illustrerar kvinnors erfarenhet av att leva med lipödem. I studie II beskrev kvinnorna hur sjukdomen fick dem att känna sig fångade i sin kropp och begränsade i sina vardagsaktiviteter. De beskrev socialt utanförskap, samtidigt som stöd från familj och vänner var viktigt. I studie III var erfarenheterna från sjukvården varierande, men ofta negativa, med begränsat eller obefintligt stöd och behandling samt misstro och risk att stämplas som överviktig av sjukvården. Finansiella begränsningar, olika erfarenheter av behandlingar och sökandet efter något för att ge symptomlindring beskrevs också.

Studie IV och V: I studie IV var både muskelstyrka och muskelmassa inom referensvärdena. I uppresningstestet genomförde deltagarna färre uppresningar. 6-minuters gångtest visade ingen avvikande gångsträcka, dock beskrev kvinnorna ökad smärta vid avslut av gångtestet. I studie V visade skattad livskvalitet lägre resultat på alla skalor, med de lägsta resultaten på fysiska och emotionella begränsningar, smärta och vitalitet. En tredjedel hade tecken på stress, men skattad självmedkänsla var hög.

Slutsats:

Lipödem minskar hälsorelaterad livskvalitet och det fysiska och psykiska måendet. Kvinnornas erfarenheter av sjukvård visar att kunskapen om lipödem är begränsad, tillgången till effektiva behandlingar är liten och mycket forskning saknas. Objektiva diagnostiska metoder behöver etableras för att kunna tillhandahålla sjukvård och forskning.

Utbildning för sjukvårdspersonal, stora studier av olika behandlingar och införande av dessa behandlingar i offentlig sjukvård behövs för att reducera konsekvenserna av lipödem och ge kvinnor med lipödem vård och stöd.

Fynden vid muskeltester, fysisk kapacitet och kroppsammansättning förklarar inte de symptom som beskrivs av deltagarna, utan tyder snarare på att de beror på smärta och fettvävens volym. Detta understryker behovet av att integrera både subjektiva och objektiva perspektiv i bedömning och behandling av lipödem.

Original papers

This thesis is based on the following papers, which are referred to by their Roman numerals I-V:

Paper I

Dahlberg J, Österberg M, Hellberg C, Stenman J, Fundell S, Andersson Å G, et al. Lipoedema research priorities: a Swedish priority-setting partnership for future treatment and diagnostic studies. *BMJ Open. 2025;15(8):e086869.*

Paper II

Dahlberg J, Nylander E, Persson M, Shayesteh A. An uncertain uphill battle – experiences and consequences of living with lipedema. *International Journal of Qualitative Studies on Health and Well-being. 2024;19(1):2300152.*

Paper III

Dahlberg J, Nylander E, Persson M, Shayesteh A. Struggles in Accessing Healthcare, the Experiences Made by Women with Lipedema in Sweden – A Qualitative Study. *International Journal of Women's Health. 2025;17:4949-60.*

Paper IV

Dahlberg J, Sandberg C, Holmlund M, Eriksson A, Nylander E, Shayesteh A. The Burden of Lipedema: A Cross-Sectional Study of Patient Reported Outcomes, Physical Performance, and Body Composition. *Submitted.*

Paper V

Dahlberg J, Nylander E, Boman J, Shayesteh A. Elevated stress and reduced quality of life despite preserved self-compassion in women with lipoedema. *Submitted.*

Papers I-III are reprinted with permission from the publishers.

Abbreviations

30STST	30-second Sit-To-Stand Test
6MWT	6-Minute Walk Test
AUDIT	Alcohol Use Disorder Identification Test
BMI	Body Mass Index
CIPS	Clance Impostor Phenomenon Scale
COREQ	Consolidated Criteria for Reporting Qualitative Research
CPQ-6	Clinical Perfectionism Questionnaire-6
CR10	Borg Category Ratio scale
DXA	Dual-energy X-ray Absorptiometry
GAD-2	Generalized Anxiety Scale-2
HDL	High-Density Lipoprotein
HRQoL	Health-Related Quality of Life
HRV	Heart rate variability
IQR	Interquartile range
JLA	James Lind Alliance Priority Setting Partnership
LCHF	Low-Carb, High-Fat
LDL	Low-Density Lipoprotein
MCS	Mental Component Summary
MLD	Manual Lymphatic Drainage
PCS	Physical Component Summary

PSS-4	Perceived Stress Scale-4
pts	Points
RAND-36	RAND 36-Item Health Survey
RPE	Borg Rating of Perceived Exertion scale
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
SCS-SF	Self-Compassion Scale Short Form
SD	Standard deviation
SRQR	Standards for Reporting Qualitative Research
VAS	Visual Analogue Scale

Introduction

Background

Lipoedema is a chronic condition predominantly affecting women and characterised by disproportionate accumulation of subcutaneous adipose tissue, primarily in the extremities (1-6). The condition typically presents with symmetrical enlargement of the hips, buttocks, thighs, and/or lower legs, while the upper body, hands, and feet are spared. This distinctive pattern of fat distribution results in marked body disproportion, with a relatively normal upper body in contrast to enlarged lower extremities (Figure 1) (1-6).

Figure 1. Illustration of a woman with lipoedema created with ChatGPT (OpenAI).

Note: *Image generated using ChatGPT (OpenAI) from an author-created prompt.*

In addition to increased adipose tissue volume, lipoedema is characterised by a range of symptoms which significantly contribute to physical discomfort and reduced health-related quality of life (HRQoL). These clinical features include pain, tenderness on palpation, a sensation of heaviness in the affected limbs, and the formation of haematomas with minimal or no apparent trauma (1-6). These manifestations distinguish lipoedema from generalised obesity and emphasise that the condition is a distinct pathological entity and not a cosmetic concern.

Although distribution is symmetric between the right and left sides, it is usually disproportionate relative to the upper body (3). This creates a distinct body shape, characterised by an unaffected torso and abdomen, with enlarged extremities, mainly the legs (3). This pattern is less commonly observed in clinical practice, as obesity, the most common comorbidity (7), would obscure the body shape (8). Involvement of the lower abdomen has been suggested (9), but current data are insufficient to support this claim. Lipoedema may also cause skin changes, including pits on the thighs, which women often describe as dimples or cellulite (6, 10). The woman may describe feeling cold in the affected tissues, a finding that can be objectively observed (6). The pain may be described as pressure, tenderness, and spontaneous pain (3). While lipoedema is often described as a progressive disorder (5), this notion has been challenged in consensus statements, which argue that disease progression is heterogeneous and, in many cases, remains stable over long periods (3, 8).

Diagnosis

There may be a delay in obtaining a lipoedema diagnosis due to limited knowledge and recognition among healthcare professionals, as well as the gradual progression of symptoms (11). Lipoedema is usually diagnosed using the criteria proposed by Wold et al. in 1951 (12) (Table 1) with modified versions reported in various publications (2, 5, 8, 13-15). Suggested addenda include arm involvement in 30% of cases, skin hypothermia, telangiectasias, a negative Stemmer sign, and disease onset at puberty, during pregnancy, or at menopause (5, 6, 13-15). The Stemmer sign, the inability to pinch a skinfold at the base of the second toe, indicates oedema in the feet and is associated with another condition, lymphoedema (16-18). It should be noted that clinical features of disproportionate adipose tissue without the other corresponding symptoms are *not* consistent with a diagnosis of lipoedema (3). So far, the diagnostic criteria consist of anamnesis and clinical examination. Some objective criteria, such as radiological examinations, blood tests, or tissue samples, have been suggested to aid in differentiating lipoedema from other conditions; however, none are officially approved for verifying the clinical diagnosis (3, 4, 19-21). Radiographic examinations and blood tests have been used to exclude other conditions which may mimic lipoedema, such as lymphoedema, venous oedema, thyroid disease, liver disease, and obesity (3, 14, 18). Accurate diagnosis is essential, as several conditions may resemble lipoedema and lead to misclassification, thereby impairing the validity of research findings.

Table 1. Diagnostic criteria for lipoedema according to Wold et al. (12).

Almost exclusively affecting women
Bilateral and symmetrical, with minimal involvement of the feet
Minimal pitting oedema
Pain, tenderness on pressure
Easy bruising
Persistent enlargement despite elevation of extremities or weight loss

Differential diagnosis and comorbidity

The most common comorbidities of lipoedema are obesity and overweight. Across studies, 70 to 95 per cent of patients with lipoedema have been reported to be overweight or obese (7, 8, 22, 23). Other reported comorbidities include hypothyroidism, hypertension (7), arthrosis (24), hypermobility spectrum disorders (25), and psychiatric disease (26). In a large consensus document, it was established that hypothyroidism is more prevalent in women with lipoedema and that lipoedema seems to be associated with connective tissue disorders in the hypermobility spectrum (4). In one small study comparing patients with lipoedema with age- and Body Mass Index (BMI)-matched controls, no differences in total cholesterol or triglycerides were observed, but high-density lipoprotein (HDL) cholesterol levels were elevated in the lipoedema group. Additionally, ratios used as predictors of metabolic disease, low-density lipoprotein (LDL)/HDL and triglycerides/HDL, were lower in the lipoedema group (27).

Several conditions may mimic lipoedema, delaying accurate diagnosis (3, 8, 13, 18, 24). The conditions most mistaken for lipoedema include lymphoedema, lipohypertrophy, and obesity, as well as chronic venous insufficiency, lipodermatosclerosis, Morbus Dercum, oedema due to internal disease, and oedema due to certain medications (13, 18, 24) (Table 2).

Table 2. Common differential diagnoses of lipoedema.

	Lipoedema	**Lymphoedema**	**Obesity**
Sex	Women	Both	Both
Pain	Yes	Rarely	Rarely
Turgor	Soft	Firm	Soft
Pitting oedema	Minimal	Pitting	None unless secondary venous oedema
Effect on elevation	No	Yes	No
Family history	Often	Rarely	Often
Age of onset	Puberty, pregnancy or menopause	Any age	Any age
Involvement of the feet	No	Yes	Sometimes
Symmetry	Symmetric	Sometimes symmetric	Symmetric
Bilateral	Bilateral	Uni or Bilateral	Bilateral
Easy bruising	Yes	No	No

Lipohypertrophy may present clinically with disproportionate adipose tissue accumulation in the legs and/or arms, similar to lipoedema, but without corresponding symptoms, such as pain (3, 8, 24). There is consensus that a body constitution associated with lipoedema is not diagnostic in the absence of corresponding symptoms (3).

Lymphoedema may occur as a primary condition or as a secondary result of treatments, surgery, trauma, or obesity (16, 17). While often located in an extremity, lymphoedema can also occur in other parts of the body (17, 18). Depending on the cause and location, it may be symmetrical, unilateral, or bilateral. When lymphoedema involves a leg, it typically affects the feet. Secondary skin changes may occur, it is not associated with increased bruising, and the Stemmer sign is often positive (16-18). **Obesity** is characterised by excessive adipose tissue throughout the body, with a distribution that may follow patterns described as android, i.e. a marked increase over the abdomen, or gynoid, i.e., a more peripheral increase, especially over the limbs and hips (28, 29). While pain can be present in obesity, it is not a main complaint and often localised to areas exposed to increased strain, such as the knees and hips (30, 31). Additionally, obesity may respond to dietary restrictions, unlike lipoedema (28).

Morbus Dercum has several subtypes, but it typically presents with painful lipomas, which may occur anywhere on the body and are associated with various symptoms, including gastrointestinal complaints, fatigue, telangiectasia around the lipomas, joint pain, and tachycardia (6, 32, 33). **Chronic venous insufficiency** is either unilateral or bilateral, usually affecting only the lower leg, and is often associated with a history of varicose veins, venous thromboembolism, pregnancy, and old age. It is distinctly associated with pitting oedema (34, 35). Secondary skin changes such as dermatitis, varicose veins, ulceration, and lipodermatosclerosis are also common (35, 36).

Classifications

The symptoms of lipoedema may manifest in different areas of the body, leading to a descriptive classification of distribution (type) and a classification of severity (stage). The anatomical areas used to specify the type are as follows: **I**. Hips, buttocks, and pelvis; **II**. Buttocks to knee; **III**. Buttocks to ankles; **IV**. Arms; **V**. Lower legs (6) (Figure 2). The types are not mutually exclusive; a patient may have a combination of two types, for example, both type II and type IV lipoedema. The stages describe disease severity and correlate with clinical findings. They are described as follows: stage 1, limited disease progression; stage 2, skin findings and pronounced tissue changes; and stage 3, further tissue changes, more fibrotic nodules, and overhanging tissue (2, 5, 6, 10, 15). Additionally, intermediate stages, 1.5 and 2.5, have been proposed, and stage 4 is sometimes used to describe lipoedema with concurrent lymphoedema (5, 6, 21).

The classification has been criticised for failing to account for the patient's subjective symptoms (3, 4, 8, 15). A person can have stage 3 lipoedema yet rate her pain lower than someone with stage 1 lipoedema and still be more hindered by her body. However, no standardised alternative to the established criteria exists that addresses these concerns (3).

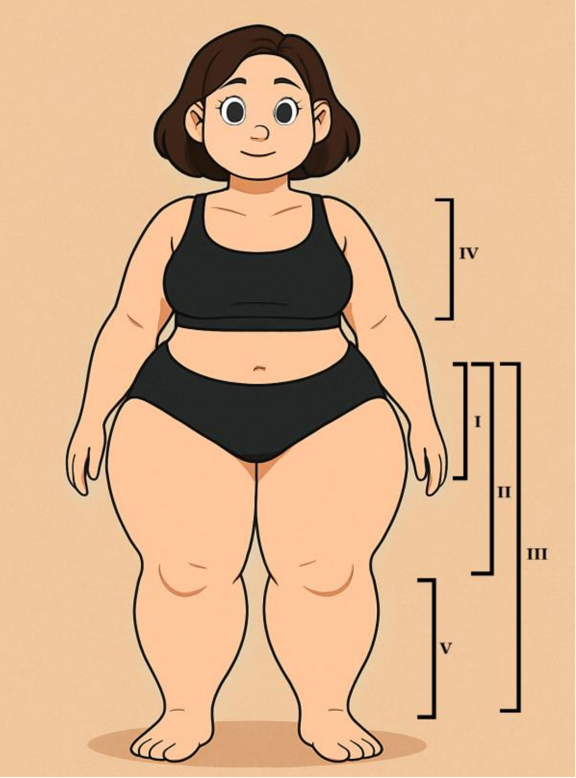

Figure 2. Schematic image illustrating the engaged parts of the body depending on the type of lipoedema. Image generated by generative AI and modified by the author.

Note: *Image generated using ChatGPT (OpenAI) from an author-created prompt and then altered.*

Psychological health and well-being

Lipoedema has been associated with reduced psychological well-being, including higher rates of depression, anxiety, and eating disorders (8, 23, 26, 37, 38). Although only one study to date has identified psychological distress preceding the onset of lipoedema symptoms (26), several studies report a significantly higher prevalence of psychiatric comorbidities among women with lipoedema compared to the general population (11, 23, 38, 39). Furthermore, studies examining HRQoL among patients with lipoedema consistently report more pain, reduced emotional well-being, and increased fatigue (7, 11, 23, 39-42).

The presence of psychiatric disorders, such as depression, eating disorders, and post-traumatic stress disorder, may affect the symptoms and management of lipoedema (3). Other psychological factors may also negatively influence individuals' psychological well-being. Perfectionism, the striving to meet excessively high expectations, has been linked to stress and impaired coping in individuals with chronic pain, as well as reduced health self-efficacy and poorer physical and mental health (43). Stress can contribute to reduced psychological well-being and may also affect pain processing, with repeated stress modifying the pain response through neurobiological changes in pain-processing pathways, i.e., stress-induced hyperalgesia (44). The impostor phenomenon, described as persistent self-doubt and feelings of intellectual fraudulence despite objective evidence of success, has been associated with depression and anxiety (45). Self-compassion, being inwardly kind to oneself in the face of pain and failure, is, on the other hand, seen as a protective factor associated with lower psychological distress, healthier behaviours, and better treatment adherence (43, 46-51). High self-compassion predicts lower anxiety and depression, as well as lower pain intensity in chronic pain (46). The occurrence of stress, anxiety, perfectionism, impostor phenomenon, and self-compassion has not previously been examined in lipoedema.

To achieve a positive treatment outcome, it is important to adopt an interdisciplinary approach when psychiatric conditions coexist with lipoedema (3, 8, 38, 52). Adequate treatment of psychiatric conditions is important because they can compromise self-management, and psychological adjustment has a major impact on the management of chronic conditions, such as lipoedema (52-54). Screening for psychological disorders, such as depression and eating disorders, using validated methods during the assessment of women with lipoedema is essential for providing adequate care.

Patient perspective and health-related quality of life

The impact of lipoedema on the lives of affected women has been examined in a few studies (55-57). However, all studies have recruited informants from patient associations and relied on self-reported diagnoses (55-57). An aspect described is an unreliable body and feelings of being trapped in a failing body, characterised by physical failings experienced alongside pain (55, 57). Feeling judged by their surroundings and experiencing social exclusion were also described, as were feelings of self-blame for their situation, despite needing social support to manage everyday life (55, 56). Obstacles in intimacy have been described, including avoidance behaviours, shame over their body, and challenges to romantic relationships, which were more pronounced at a younger age (56, 57). In interactions with healthcare, experiences of ignorance, being labelled obese, and receiving unhelpful advice have been described. Limited information on treatment recommendations has been reported; meanwhile, healthcare providers with experience of lipoedema have acknowledged that their symptoms exist, and the support received by these instances has been described by some (55, 56). These findings need to be further examined in women with a clinician-assessed lipoedema diagnosis, as research on self-reported diagnoses carries the risk of not accurately capturing the phenomenon.

Health-related quality of life (HRQoL) refers to how health affects an individual's ability to function and perceived well-being across different domains of life (58). Dimensions vary in focus; the physical domains reflect the extent of physical function, both in basic activities (such as bathing and dressing) and in work-based activities (housework and career). The mental domains are grounded in emotional well-being, including depression, happiness, anxiety, lethargy, and pain. HRQoL also encompasses social domains that reflect the ability to function in social interactions, such as with family and/or friends (58). Some studies have examined the complex phenomenon of HRQoL in lipoedema populations, with reduced HRQoL consistently reported (7, 11, 39, 40, 59). There remains a need to deepen the understanding of how lipoedema affects women’s HRQoL and how their experiences relate to objective findings.

Physical capacity and body composition

Objective examination of muscle strength and physical capacity is useful for understanding how a condition affects physical function. Isometric muscle strength is often assessed using a fixed dynamometer, which measures isometric strength in a specific joint angle. Lower extremity muscle strength in lipoedema has been examined in comparison with healthy controls matched for BMI and age and was found to be lower (60, 61).

Various measures of physical capacity are available; the 6-minute walk test (6MWT) and the 30-second sit-to-stand test (30STST) are well-established methods for assessing physical capacity across patient populations. The distance walked in the 6MWT is influenced by factors beyond physical fitness and capacity, including age, gender, weight, and height. Calculations can be made using these parameters to estimate the expected distance for a healthy individual, providing a reference distance for the examined individual (62, 63). The 6MWT has been assessed in lipoedema populations but has either lacked a distance for comparison (42), been compared with non-matched populations with fibromyalgia or obesity (60, 64), or compared with healthy controls matched for BMI and age, as well as % of calculated distance (61). Compared with fibromyalgia, the lipoedema group covered a longer distance; compared with obesity, the matched lipoedema sample walked a shorter distance, whereas the unmatched did not; and, when compared with the calculated distance, the lipoedema group covered a shorter distance (60, 61, 64). 30STST have been described in a lipoedema population compared with health controls matched for BMI and age, revealing fewer repetitions in the lipoedema group (61). Knowledge regarding muscle strength and functional capacity in persons with lipoedema is inconclusive and warrants further research.

Body composition refers to the distribution of fat mass, lean mass, and bone mineral content. Dual-energy X-ray Absorptiometry (DXA) uses low-dose X-rays to measure body composition and can be employed to assess the whole body or specific regions (65, 66). In lipoedema, DXA has primarily been investigated for diagnostic purposes but has also been used to characterise the distribution of fat mass, lean mass, and bone in women with lipoedema (19, 21, 67). The findings indicate increased fat mass in the arms and legs compared with age-matched controls (67) and in the legs compared with BMI-matched controls (21). However, no difference in lean mass was reported in these investigations. The relationship between muscle strength, estimated physical function, and body composition in lipoedema remains to be examined.

Aetiology/Pathogenesis

Lipoedema is commonly observed among family members, suggesting a hereditary component (1, 22). Pedigree analysis has suggested X-linked dominant or autosomal dominant inheritance with sex limitation (22). The frequent onset of lipoedema during periods of hormonal change, such as puberty, pregnancy, or menopause, has led to speculation about a hormonal component (3, 8). In addition, hormonal contraception has been described as a trigger for worsening symptoms (68). However, the disease may also present or progress at other times without apparent hormonal influence (3).

The exact pathogenesis of lipoedema remains unknown. Biopsied adipose tissue has been examined and compared with controls, revealing hypertrophic adipocytes in women with lipoedema, similar to those in women with obesity (69). Differences in adipocyte size have also been observed in thigh and abdominal biopsies. Compared with controls, women with stage II and stage III lipoedema had higher hypertrophic adipocyte levels in both regions; however, this was not the case in stage I lipoedema (27). Crown-like structures, in which macrophages encircle adipocytes, have been described but may also occur in adipose tissue in obesity (69, 70). An increase in macrophages in lipoedema adipose tissue has been shown, thought to be secondary to increased adipocyte necrosis, like that occurring in obesity (69, 70). This low-grade inflammation may contribute to the described pain (8, 69). Angiogenesis has been observed in the dermis of affected individuals; however, it was not observed in all cases examined. The increase in vasculature indicates localised hypoxia, which may contribute to chronic inflammation and the increased pain levels associated with lipoedema (69, 71).

Epidemiology

Reliable prevalence estimates for lipoedema are currently lacking, and prevalence in the adult female population is generally estimated to range from <1% to 12% (3, 4). This is due to frequent misdiagnosis, the absence of established diagnostic criteria, and the lack of extensive population-based studies. Additional factors may include population variations, over- or under-reporting of the condition, misdiagnosis as obesity, which can reduce diagnosis and alter patterns of healthcare seeking, and limited access to healthcare providers with experience of lipoedema.

The estimated prevalence of lipoedema remains uncertain, with various figures reported in the literature, yet no clear consensus has emerged. Most estimates come from lymphoedema clinics reporting their estimates of lipoedema among their patients, with figures ranging from 6.5% to 22.7% (24, 71-73). These figures do not represent the general population and, as such, are not suitable as evidence of prevalence. One of the most-cited figures is 11% of women with lipoedema; however, this estimate comes from an unpublished study (74) and has not undergone peer review. The most reliable figures for the general population to date come from Amato et al. (75), who administered a survey to screen for lipoedema symptoms to 253 women in Brazil, yielding a prevalence of 12.3%. This still has design limitations that reduce the reliability of the estimates, as all surveys are subject to response bias. There is a tendency towards higher response rates among participants who find the subject personally relevant, which may lead to an overestimation. Furthermore, the questionnaire employed is a symptom-screening instrument and cannot independently establish a diagnosis.

Treatment

Various treatments have been attempted for lipoedema, but high-quality studies are lacking, and the effects of different therapies remain to be evaluated (20). Treatment approaches have largely been adapted from those used for lymphoedema. Lipoedema treatment traditionally comprises both conservative and surgical approaches, including weight management, psychotherapy, compression therapy, and liposuction (2, 3, 8, 13, 15, 20, 76).

Weight loss and diets

Because increased adipose tissue is the primary manifestation of lipoedema, most patients attempt to lose weight through conventional methods. Although weight loss typically does not reduce the volume of lipoedema-affected limbs or other lipoedema-associated symptoms, limiting weight gain may reduce the risk of symptom exacerbation (3, 4, 6, 13, 15). Although lipoedema is generally not considered to be volume-reducing with exercise and diet, a small study tested a twice-weekly exercise programme for 6 weeks. The results showed improvements in pain, 6-Minute Walk Test (6MWT) distance, and muscle strength; however, these differences were not statistically significant compared with the control group (77). Other studies have examined whether exercise improves symptoms when used alongside other treatments, primarily compression therapy, with promising results (78-81).

The effects of diets have been a recurring topic in the literature, and several studies have examined them (82). The focus has primarily been on hypocaloric diets, specifically modified Mediterranean ketogenic or Low-Carb, High-Fat (LCHF) diets (82). One study found that higher serum inflammatory marker levels correlated with a higher dietary inflammatory index (83). While several studies on hypocaloric diets have reported findings consistent with reduced pain, volume, and weight, and improved HRQoL (84-88), a recent literature review identified substantial bias and significant variability in reported variables (82). Although the published literature includes findings supporting ketogenic hypocaloric diets, the evidence is insufficient to make general recommendations, and further studies are needed on the subject.

Currently, no large, randomised studies have examined the effects of weight-reducing treatments, such as GLP-1 receptor agonists, on lipoedema. However, theoretical support for a disease-modifying effect has been reported (89), and a case series of 5 patients treated with a GLP-1 receptor antagonist showed symptom improvement (90).

Compression therapy

Compression therapy has been used in various forms, including garments and manual lymphatic drainage (8, 20, 91). It is also recommended in several international treatment guidelines (2, 3, 76). Several studies have examined the use of compression garments, and although small, have shown promising results (79, 80, 91). The garments are often combined with moderate physical activity or exercise, and compression garments have been shown to improve symptoms more than physical activity alone (79, 80). Results have differed depending on whether improvement was confined to subjective symptoms or also included volume reductions relative to isolated physical activity (79, 80). These studies have limited follow-up of 4-8 weeks, and further studies with larger populations and longer follow-up are warranted to validate the durability of these results (79, 80).

An advanced pneumatic compression device has been described to improve subjective pain symptoms in lipoedema and to modulate intracellular and extracellular fluid volumes, as assessed by bioimpedance spectroscopy (92, 93). Manual lymphatic drainage (MLD), in various forms, has been used as a treatment modality, primarily to reduce pain and limb volume (94-97). Although promising, the type of therapy varies, with the two main approaches being MLD (96, 97) and subcutaneous adipose tissue therapy (94, 95). MLD has shown reductions in pain and volume after daily use with compression therapy for 4 to 6 weeks (78, 93, 98). However, larger studies with standardised treatment protocols are still lacking and are needed before a more generalised recommendation can be made.

Surgical management

Surgical management of lipoedema by liposuction is described as a treatment and, in some countries, is included in national guidelines (2-4, 15). The liposuction method varies, with tumescent and water-assisted liposuction being the most common; each method has advantages and disadvantages (59, 99-104). The methods remain to have complications, and discussions regarding the methods, postoperative care, and cannula size are ongoing to improve outcomes. Adverse effects of liposuction have been reported to include inflammation, infection, seroma, haematomas, erysipelas, necrosis, thrombosis, cutaneous sensory alterations, and hypokalaemia (101, 105-108). At present, it is not part of the Swedish healthcare system due to insufficient evidence for treatment and long-term follow-up (20). Promising reports on liposuction have been published (59, 103, 109-111), but results from extensive, prospective, multicentre studies are lacking.

Rationale – knowledge gaps

In 2018, a group of lipoedema patients in Västerbotten contacted regional healthcare authorities to raise awareness regarding the lack of adequate support within the Swedish publicly funded healthcare system. Their concerns were later reinforced in a 2021 systematic review by the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU), which identified substantial gaps in the evidence regarding diagnosis and treatment, as well as limited knowledge of patient and healthcare professional experiences and insufficient data for health economic evaluation (20). Together, these developments underscored the need for more systematic research in lipoedema.

Lipoedema has a detrimental impact on affected women and reduces their quality of life. Limited recognition among healthcare professionals contributes to delayed diagnosis, and the current healthcare system often restricts access to treatment. Despite a growing body of knowledge, current research mainly lacks the patient perspectives, leading to an incomplete understanding of how the condition affects individuals. This knowledge gap may impede both clinical management and the development of targeted interventions.

A combined qualitative and quantitative approach was considered valuable in addressing these gaps. Quantitative methods would enable the assessment of symptoms, functional limitations, and health-related quality of life. However, they would not fully capture the complex lived experiences of women with lipoedema. Hence, qualitative methods could address this issue by providing in-depth insights into patients' experiences that are not easily captured by standardised measures. Together, these approaches enabled a more comprehensive and nuanced understanding of the condition.

Aims

- Utilising a national, multiperspective approach to identify research priorities related to the diagnosis, treatment, and management of lipoedema.
- In a population of women with medically verified lipoedema:
    - Describe and analyse the experiences of everyday life and their disease.
    - Explore experiences of healthcare and treatments.
    - Measure physical capacity, body composition, and health-related quality of life.
    - Assess perceived stress, anxiety, self-compassion, perfectionism, and impostor phenomenon.

Materials and Methods

Thesis at a glance

Table 3. Overview of the thesis.

Paper	**I**	**II**	**III**	**IV**	**V**
Design	Mixed methods	Qualitative research interviews	Qualitative research interviews	Cross-sectional survey	Cross-sectional survey
Participants	255 at open survey 13 at final prioritisation	12 women with lipoedema	12 women with lipoedema	18 women with lipoedema	18 women with lipoedema
Data analysis	Priority-setting partnership	Qualitative content analysis	Qualitative content analysis	Descriptive statistics and analyses for differences and means	Descriptive statistics and analyses for differences and means
Outcome	Prioritised research questions	Descriptive Theme	Descriptive Theme	DXA, physical capacity, and HRQOL	Psychometric data (PSS-4, GAD-2, CPQ-6, CIPS, SCS-SF) and HRQOL

DXA, Dual-energy X-ray Absorptiometry; PSS-4, Perceived Stress Scale-4; GAD-2, Generalized Anxiety Scale-2; CPQ-6, Clinical Perfectionism Questionnaire-6; CIPS, Clance Impostor Phenomenon Scale; SCS-SF, Self-Compassion Scale Short Form; HRQoL, Health-Related Quality of Life.

Participants

Paper I

An open survey was hosted on the SBU website from May 2023 to September 2023. A total of 255 respondents submitted 1314 research questions. A total of 169 individuals expressed interest in participating in the open prioritisation process; 130 completed the first Delphi survey, and 123 completed the second. For the priority-setting meeting, 16 individuals were invited, while 13 participated. The participants consisted of seven healthcare professionals and six individuals with experience of lipoedema.

Papers II-V

Using purposive sampling, recruitment took place in Västerbotten County. The diagnosis of lipoedema was established when both the criteria proposed by Wold et al. (12) and the requirements of the Dutch guidelines for lipoedema (13) were met. In Papers II and III, ten potential informants were excluded due to comorbidities or communication difficulties. The remaining 14 informants were invited, and 12 women participated (Figure 3). For Papers IV and V, participants were recruited from the same sample as in Papers II and III, with a diagnosis date up to January 2024. A total of 26 potential participants were identified. However, five declined, and three were excluded due to acute illness, leaving 18 participants who completed the examinations. Of these, one declined Dual-energy X-ray Absorptiometry (DXA) because of early pregnancy (Figure 3).

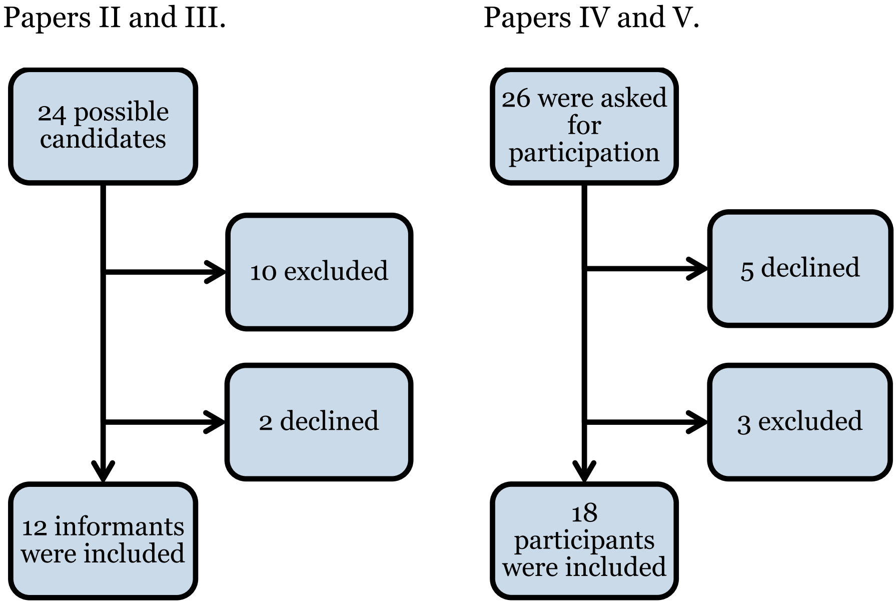

Figure 3. Inclusion process.

Open survey, Delphi survey, priority-setting meeting (Paper I)

The design consisted of several steps as described by the James Lind Alliance Priority Setting Partnership (JLA) (112), with modifications established by previous SBU projects. The research questions were collected through an open survey. The SBU team compiled the responses, removing duplicates and out-of-scope questions. Similar questions were grouped into broader topics, and all questions were categorised by topic. This resulted in 62 research questions included in the prioritisation process. The research questions generated by the initial survey were then processed through two sets of individualised prioritisations. Utilising a nominal group technique (113), the meeting was conducted in two sessions with an initial discussion in smaller groups and a final discussion in the whole group. Despite the instruction to have ranks 1-10, the group consensus was that there were only two tiers: the top 5 and the top 6-10 (Figure 4).

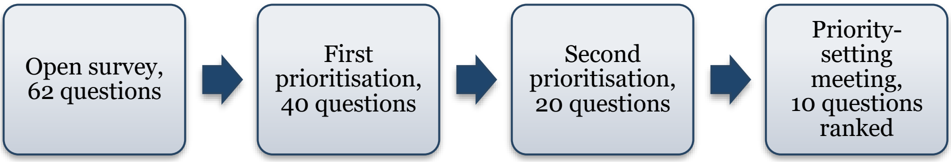

Figure 4. Prioritisation of research questions.

Interviews, questionnaires, rating scales

Interviews (Papers II and III)

Twelve informants participated in semi-structured interviews, supported by an interview guide explicitly developed by JD for the study (Supplement in Paper III). The first eight interviews were conducted in a neutral room, whereas the latter four, due to the COVID-19 pandemic, were conducted via video calls using either Zoom Video Communications, Inc.® or Microsoft® Teams®. JD conducted all interviews. The interviews lasted 50 to 90 minutes, were digitally recorded, and non-verbal cues, such as body language and emotional expression, were observed (114). The first were transcribed verbatim by JD, and the remaining were transcribed by two medical secretaries at the clinic.

Questionnaires (Papers IV and V)

The **RAND-36** is a validated questionnaire comprising 36 items, grouped into eight subscales that reflect physical and mental health dimensions. These subscales contribute to two summary measures: the Physical Component Score (PCS) and the Mental Component Score (MCS), each scored from 0 pts (worst health) to 100 pts (best health) (115, 116). RAND-36 has good reliability, with Cronbach's alpha > 0.80 for all subscales (116).

The Alcohol Use Disorders Identification Test (**AUDIT**) was developed by the World Health Organisation to identify hazardous alcohol consumption (117). The Swedish version has been validated (118) and comprises 10 multiple-choice items, yielding a total score ranging from 0 to 40 pts. In a Swedish context, a score of 6 or higher may indicate hazardous alcohol use (117, 118). It has a reported Cronbach's alpha = 0.95 (118).

The Swedish National Board of Health and Welfare developed two **control questions on physical activity** to assess everyday physical activity, exercise, and their combination (119). Responses result in a total score ranging from 3 to 19 pts. A score of 11 or higher indicates meeting the recommended level of physical activity, equivalent to at least 150 minutes of daily physical activity or 75 minutes of physical exercise per week (119, 120). The score has acceptable reliability with a Spearman's rho of 0.62 (121).

Rating scales (Paper IV)

The **Borg Rating of Perceived Exertion Scale** (RPE) was used to measure participants' physical effort, ranging from 6 ("no exertion at all") to 20 ("maximal exertion") (122). The scale is designed to approximate heart rate by multiplying the perceived exertion score by 10 (122).

The **Borg Category Ratio Scale** (CR10) is a subjective measure of perceived exertion, ranging from 0 ("nothing at all") to 10 ("extremely strong"), with an additional possibility indicating the "absolute maximum" (122). Participants used the scale to assess fatigue in the arm and leg, and shortness of breath.

The **Visual Analogue Scale** (VAS) is a self-reported, continuous, ungraded scale commonly used to assess subjective symptoms such as pain. It typically consists of a 100 mm-long horizontal line, anchored by verbal descriptors at the ends: "no pain" on the left and "worst pain" on the right (123, 124). Respondents indicate their symptom intensity by marking a point along the line, which is subsequently measured in millimetres, yielding a score between 0 and 100 mm (123, 124).

Psychometric characteristics (Paper V)

A collection of psychometric instruments was used to assess stress, anxiety, perfectionism, self-compassion, and the impostor phenomenon.

Perceived Stress Scale-4 (PSS-4) was utilised to assess perceived stress. Scores at 8 or below indicate normal stress levels, and scores of 9 or higher suggest elevated stress levels (125). PSS-4 has been validated in Swedish and has demonstrated an internal consistency with Cronbach's alpha of 0.77 (125, 126).

Generalised Anxiety Disorder Scale 2 (GAD-2) is a validated screening instrument for anxiety (127). Scores at 2 pts or under indicate no or mild anxiety symptoms, and scores of 3 pts or higher indicate risk for anxiety disorder and warrant further examination (127). The longer version, the Generalised Anxiety Disorder Scale 7, has been validated in Swedish, and the GAD-2 comprises the first two items (128). GAD-2 has a Cronbach's alpha of 0.92 and an intraclass correlation of 0.83 (127).

Clinical Perfectionism Questionnaire-6 (CPQ-6) assesses levels of perfectionism (129, 130). Interpretation is suggested as: 6-10 pts no problems, 11-15 pts moderate problems, 16-20 pts difficult problems, and 21-24 pts severe problems of perfectionism (131, 132). The Swedish version has demonstrated a test-retest correlation of r = 0.62 and an internal consistency of Cronbach's alpha 0.72 (129).

Self-Compassion Scale Short Form (SCS-SF) examines the presence of self-compassion, conceptualised as the ability to be understanding and accepting of one's own weaknesses (48). A mean score of 1.00-2.49 indicates low, 2.50-3.50 moderate, and 3.51-5.00 pts high self-compassion (48, 133). The Swedish translation of SCS-SF is a validated short form of the original Self-Compassion Scale (133, 134) and has a Cronbach's alpha of 0.85 (48).

Clance Impostor Phenomenon Scale (CIPS) assesses core characteristics of impostor phenomenon, including self-doubt, fear of failure, and perceived intellectual fraudulence (135, 136). It is interpreted as 20-40 pts: low levels of impostor characteristics; 41-60 pts: moderate levels; 61-80 pts: frequent experiences; and 81-100 pts: intense experiences of the impostor phenomenon. Holmes et al. (135) have suggested a total score of 62 pts or higher as a clinically relevant cut-off for significant impostor feelings. The original English version reported internal consistency with Cronbach's alpha ranging from 0.85 to 0.96 (135, 137). A Swedish version approved by Dr Clance was used but has not yet been validated (131, 132).

Physical examinations and radiological examinations

Data were collected on leg length, height, weight, blood pressure, and pain using VAS (123). The participants were then tested by two physiotherapy students, under the supervision of JD and CS, using a combination of tests in a standardised order as follows: isometric grip strength, isometric strength in the elbow and knee, the 30-second sit-to-stand test (30STST), and the 6-minute walk test (6MWT) (138-143). During the physical capacity tests, the VAS, Borg RPE, and Borg CR10

(122, 123, 144) rating scales were used to assess pain, exhaustion, exertion, and shortness of breath.

Isometric strength (Paper IV)

Isometric strength was assessed at the grip, elbow, and knee. Grip strength, measured by grip dynamometry, is an important predictor of health, muscular endurance, and overall strength (139). The best two out of three attempts were used for analysis.

Isometric elbow strength was measured while standing, with the arm in 90-degree flexion and the upper arm adducted (138). The participant held their hand in a supine position, gripping a dynamometer anchored to a small pallet on the floor (Image 1). Isometric knee strength was measured with the participant sitting on the gurney in 90 degrees of flexion at both the knee and hip, with their feet slightly above the floor (138). A dynamometer was affixed to the frame of the gurney and to the ankle, and the participant was instructed to perform a knee extension with maximum force (Image 1). The average of the two best results out of three attempts was used in the analysis.

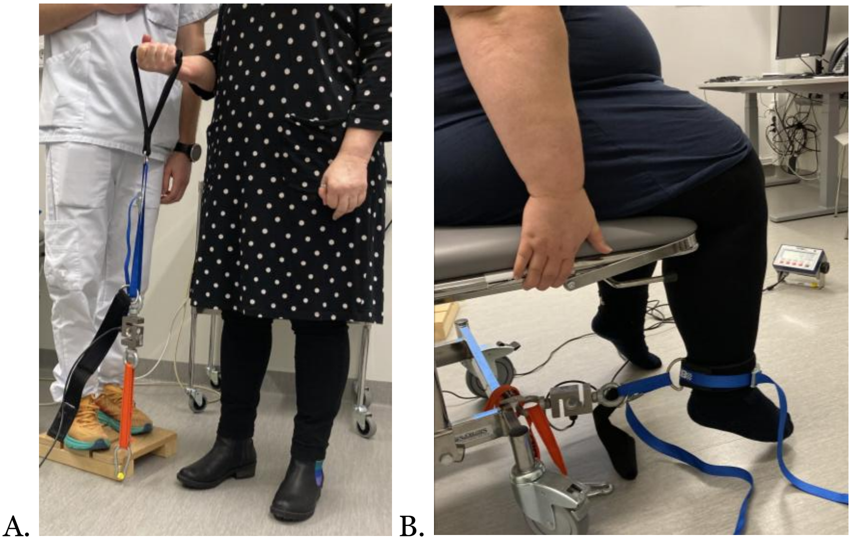

Image 1. Images from testing isometric strength in the elbow (A) and knee (B).

30-second sit-to-stand test and 6-minute walk test (Paper IV)

30STST is associated with anaerobic exercise performance and dynamic muscle contractions (140, 142, 145). The participant sat in a chair without armrests, a seat height of 46 cm, and both feet on the floor. After a few repetitions to familiarise themselves with the test procedure, the participants were instructed to perform as many repetitions as possible within a 30-second period.

6MWT correlates with peak work capacity and physical activity and is used for functional exercise performance (62). The test was conducted in accordance with the ERS/ATS guidelines (62, 146). After resting in a seated position for 15 minutes, the participants were instructed to walk as far as possible for 6 minutes. A 30-meter track was measured, with cones marking the turning point at each end of the track. They were allowed to use their habitual walking aid, if any, and standardised phrases of encouragement were read aloud every minute. After 6 minutes, the distance performed was measured.

Dual-Energy X-ray Absorptiometry (Paper IV)

Dual-energy X-ray Absorptiometry (DXA) was used to examine body composition. The method utilises X-rays, filtered through a specialised beam filter, to scan the entire body and measure bone mass and soft-tissue composition (65). DXA has previously been used in lipoedema and has been suggested as support in diagnosis, follow-up, and evaluation of treatments (19, 21, 147). In our study, 17 of 18 participants underwent DXA, with 1 participant opting out due to early pregnancy. The examinations were performed using the Lunar iDXA System (LU42295, GE Medical Systems, Madison, WI, USA). Lean mass was calculated as total body mass minus the mass of bone and fat, representing muscle mass. Appendicular lean mass constitutes the lean mass in the extremities.

Data analysis

Priority-setting partnership (Paper I)

From the initial survey, 1314 research questions were submitted by 255 participants. These were grouped, screened for duplicates, and refined. The groupings were: diagnostics, experience of treatment, organisation of care, education/information, and treatment, with treatment further subdivided by method type. The technique was inspired by the JLA method, as described in their guidebook (112), except for the individual prioritisation part, where we employed a two-step Delphi approach, and no JLA representative participated.

Qualitative content analysis (Papers II and III)

Qualitative content analysis addresses both manifest and latent meanings in text to distil and enhance understanding of the data (148). Using qualitative content analysis, described by Graneheim et al. (148, 149), the data were divided into meaning units, condensed meaning units, codes, subcategories, and categories, with one theme emerging in Papers II and III. Meaning units were parts of the text that contained information related to one another through context. Codes were used as short text descriptions without losing their core meaning. Subcategories described the "What?" and were composed of collections of codes (Table 4). By further abstracting the subcategories, they were grouped into categories. Categories were further abstracted to represent one theme, in our case, a metaphorical one, and the underlying meaning at an interpretable level, answering the question "How?" (149). In both Papers II and III, an inductive approach was used in the qualitative content analysis of the text.

Table 4. Examples of meaning units, codes, and subcategories.

Meaning unit*	**Code***	**Subcategory**
I know why things are the way they are. At times, the only thing I feel is: why did I have to develop lipoedema, a condition for which there is no help available? Why me?	Sometimes she wonders why she had to develop lipoedema, a condition without available support	Tackle anxiety and worries due to progressive deterioration
There was another occasion when I could not get into the clothes. Those are the moments when the frustration becomes overwhelming, when I just physically cannot fit into the clothes.	Could not fit into the clothes	Struggle with unfavourable physical symptoms

**During analysis, the meaning unit and code remained in Swedish, and the transformation to English began at the subcategory level.*

Statistical analysis (Papers IV and V)

Difficulties with sample identification, recruitment, and assessment of impaired physical abilities among patients with lipoedema affected the feasibility of sample size calculations. No formal power calculations were performed, which could affect the interpretability of the results. Data were compiled into tables and spreadsheets in Microsoft Excel (Microsoft Corp., Redmond, WA, USA). IBM SPSS Statistics version 29.0.1.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The lipoedema subgroups were categorised as stages 1 & 2 and stage 3, and the BMI subgroups were divided into obesity classes 1, 2, and 3, with one participant with a BMI below 30 kg/m^2 included in obesity class 1. Isometric grip, elbow flexion, and knee extension strength were calculated as the mean of the best two attempts.

Descriptive statistics were used to present background characteristics. Mean values were reported as mean ± SD and median values as median (IQR). A two-sided independent t-test was used to assess mean differences between the population and the lipoedema stage subgroups when the data were approximately normally distributed. When variables were not normally distributed, the Mann-Whitney U-test was used for analysis. Dichotomous variables were analysed using the chi-square test with Fisher's exact test. A one-way ANOVA with Bonferroni post hoc test was used to assess significant differences among BMI subgroups. The level of significance was set at $p<0.05$.

Ethical considerations

Autonomy was respected as all participants in the studies provided informed consent, received oral and written information about the study, and were able to ask questions prior to participation. Although the researcher, JD, was also the physician diagnosing the participants, the influence of this relationship was mitigated by ensuring that any prior healthcare relationships had ended and that no follow-up or treatments were scheduled before inclusion. All studies were conducted in accordance with the ethical standards set out in the Declaration of Helsinki. Ethical approval was obtained from the Swedish Ethical Review Authority: Paper I, 2022-01527-01; Papers II and III,2019-06344 and 2021-01138; Paper IV, 2023-06658-01; Paper V, 2022-01511-01 and 2023-06658-01.

For Papers II and III, we took additional care to adhere to the ethical principles of qualitative research (150) and the standards for reporting qualitative research (151, 152). Interviews may elicit experiences and emotions; therefore, informants were provided with contact information should they need support. Anonymity was ensured by coding all data and altering locations, names, and dates in the text to reduce the risk of identification. All published quotes were reviewed for identifying information before selection. Beneficence, defined as doing good and preventing harm, was observed: although the informant's individual benefits were limited, the risks were minimal. Justice, grounded in equal sharing and fairness, aims to ensure equal opportunities to participate in research and to prevent the exploitation of vulnerable informants. Although participation was limited to language requirements and a clinically verified lipoedema diagnosis, this research provides an important avenue for the informant’s voice and experiences.

Results

Research question prioritisation (Paper I)

Ten research questions were selected during the prioritisation process. These were divided into two distinct groups, with no internal ranking within each group (Table 5). Two questions related to diagnostics were chosen, with the rationale that a lack of a standardised diagnostic method would undermine research validity and that an established diagnostic method would improve care. Research outcomes were prioritised, as the same impact on validity was evident without patient-relevant outcomes. The effects of treatments were represented by several questions among the top ten, motivated by the need to determine whether a treatment should be used.

Table 5. The final, most important research questions, decided at the priority-setting meeting.

Highest priority
What diagnostic criteria are needed for a diagnosis of lipoedema? A secondary question was added: "How can lipoedema be detected early in the disease and in puberty?"
In lipoedema research, what are the important outcomes to be measured?
What are the effects of manual treatments?
What effect does liposuction have?
What are the effects of hormonal treatment/drugs in lipoedema?
High priority
Effect of interventions by health professionals with a focus on the patient's daily life, activity and function?
Can biomedical markers be identified and used to diagnose lipoedema?
Can food prevent and/or reverse lipoedema?
What effect does compression pump treatment have on lipoedema?
What is the effect of medical compression garments/compression therapy?

Experience from everyday life (Paper II)

From the data in Paper II, the overarching theme emerged as *"An uncertain uphill battle against a divergent body and societal ignorance"*. This theme reflected women's experiences of living with lipoedema and was derived from five categories and eleven subcategories (Table 6).

Table 6. Theme, categories, and subcategories of women's experience of lipoedema in everyday life.

Subcategory	Category	Theme
Become increasingly aware of one's body image	Captivated by a disintegrating body	An uncertain uphill battle against a divergent body and societal ignorance
Resign to the illness		
Struggle with unfavourable physical symptoms	Face the impairments of a chronic condition	
Be limited compared to others		
Have strategies for adapting to the condition		
Feel different and singled out	Experience social exclusion	
Face disbelief and receiving negative comments		
Have shifting experiences of relations and intimacy	Need emotional support to go on	
Be acknowledged for having problems		
Act as a detective searching for information	Mull over an insecure future	
Tackle anxiety and worries due to progressive deterioration		

Informants described how the condition affected their body image and how they felt trapped within their bodies, which, unable to improve their symptoms, led to surrendering to the disease. As women experienced the chronic nature of lipoedema and its accompanying restrictions, several informants chose to focus on aspects they could change to manage their situation, such as adapting clothing and equipment. Women also described withdrawing from social interactions due to body image struggles, which were marked by isolation, disbelief, and bullying. However, those who shared their experiences with family and friends found that it sometimes led to increased support and understanding.

Uncertainty about what the definition of lipoedema meant prompted a search for answers on social media and through patient associations. In addition, the lack of answers about the possible exacerbation of lipoedema created uncertainty about their future.

Experiences of healthcare and treatment (Paper III)

The theme *"Pushing the barricaded doors to treatment and care while fighting to illuminate the shadows of lipoedema"* emerged from the women's accounts of their encounters with healthcare and their experiences of different treatments. The theme comprises three categories and eight subcategories, highlighting the obstacles and challenges the women face (Table 7).

Table 7. Theme, categories, and subcategories of women with lipoedema's experiences of healthcare and treatment.

Subcategories	**Categories**	**Theme**
Experience societal inequality and a lack of support	Experiencing societal injustice and gatekeeping in healthcare services	Pushing the barricaded doors to treatment and care while fighting to illuminate the shadows of lipoedema
Hoping for changes in an imperfect system		
Search for an explanation of the disease	Combating prejudice and stigmatisation with increased awareness	
Face disbelief from healthcare professionals		
Restricted access due to treatment-related costs	Having a solid desire for improved and affordable treatment options	
Attempt to improve symptoms with conservative treatments		
Experience ambiguity regarding surgery and fears of complications		
Test alternative therapies		

Being met with disbelief by both political decision-makers and healthcare professionals was described as contributing to feeling disregarded by the system intended to support them. Many women reported having to actively seek information regarding lipoedema, as their concerns were frequently questioned or dismissed in healthcare settings. The women's search for effective treatments to alleviate their symptoms was further complicated by financial barriers and reports of variable treatment effectiveness. When treatments failed or were unavailable, some women tried alternative therapies, e.g. infrared sauna and self-administered lymphatic drainage, driven by the hope of reducing symptoms, including pain and volume.

Physical capacity and strength (Paper IV)

The mean muscle strength in grip, elbow flexion, and knee extension, measured with a dynamometer, did not differ from reference scores. For the 30-second sit-to-stand test (30STST), the younger participants (<60 years of age) performed fewer repetitions than the reference scores, whereas performance among women ≥60 years did not differ from the reference scores. During the 6-minute walk test (6MWT), the women walked farther than the calculated expected distance (63). Pain, self-rated by VAS during strength tests and 30STST, was only slightly increased compared to baseline, whereas after completion of the 6MWT, increased pain was reported.

Body composition (Paper IV)

DXA body composition analysis showed that participants with stage 3 lipoedema had higher subcutaneous adipose tissue, greater leg fat mass, and greater total body fat mass. As expected, the higher-BMI groups tended to have greater total fat mass and leg fat mass. The fat mass in the legs was 16381 ± 2532 g for participants in the lipoedema stage 1 & 2 group and 23195 ± 6005 g for the stage 3 group respectively. The total fat mass was 41214 ± 5732 g for those in stage 1 & 2 and 61519 ± 18659 g for stage 3. There was no difference in appendicular lean mass or visceral adipose tissue between the lipoedema or BMI groups.

RAND-36 (Papers IV and V)

In the RAND-36 subscales scores, role physical had the lowest mean at 22.22, followed by role emotional at 33.33, pain at 34.17, and energy/fatigue at 36.39. The component summary scores were 31.3 for PCS and 38.1 for MCS (Table 8). No difference was found between lipoedema stage 1 & 2 and stage 3. Findings compared to reference data are shown in Figure 5.

Table 8. RAND-36, results of subscales and summary scores for all participants.

RAND-36 subscales	Mean and median scores
Physical function†	52.50 (40.00)
Role physical†	0.00 (25.00)
Role emotional†	16.67 (66.67)
Energy/fatigue*	36.39 ± 16.79
Emotional well-being*	65.11 ± 13.07
Social functioning*	49.31 ± 23.67
Pain*	34.17 ± 16.91
General health*	39.44 ± 19.01
Health change†	25.00 (56.25)
Physical component summary*	31.3 ± 9.32
Mental component summary*	38.1 ± 9.56

**Normally distributed reported as mean ± SD and †non-normally distributed reported as median (IQR).*

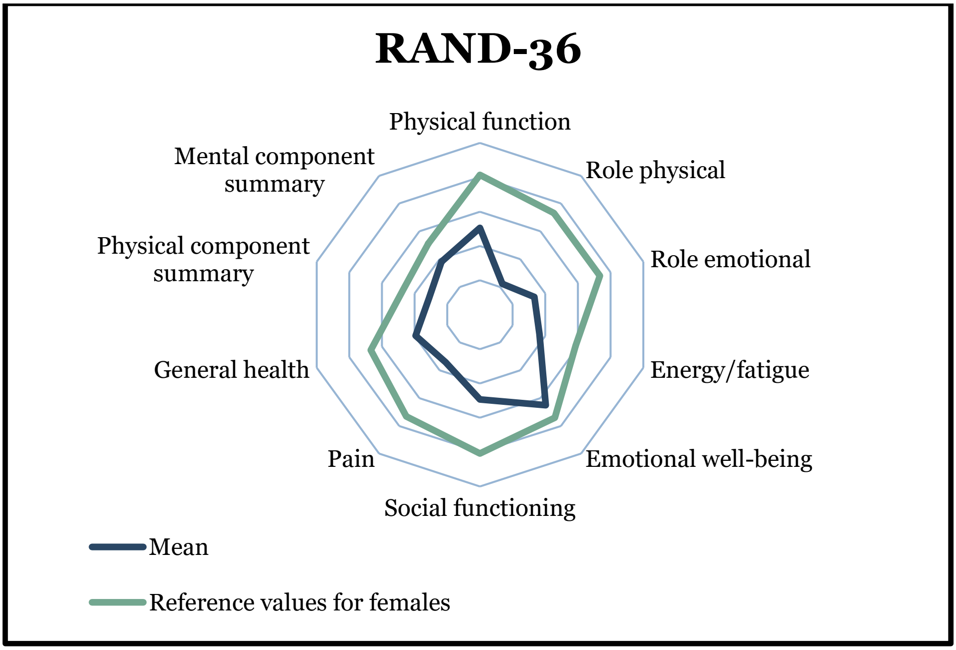

Figure 5. Mean results of RAND-36 in comparison with reference findings as reported for subscales by Ohlsson-Nevo 2021 and for PCS and MCS by Garratt 2017 (116, 153).

Psychometric characteristics (Paper V)

One third (n=6) had signs of elevated stress in the PSS-4, while 16.7% (n=3) had findings of elevated levels of anxiety in GAD-2. In the SCS-SF, 88.9% (n=16) reported moderate to high levels of self-compassion, of whom 9 (50%) reported high levels. Perfectionism was reported as 61.1% (n=11) for moderate, 33.3% (n=6) for difficult and none for severe levels of perfectionism. Regarding the impostor phenomenon, 27.8% (n=5) scored 62 or higher, indicating elevated levels of impostor feelings (Table 9). There were no differences between the lipoedema stage subgroups.

Table 9. Outcomes from psychometric instruments.

Psychometric instruments	**Mean ± SD**
PSS-4	6.7 ± 2.1
GAD-2	1.3 ± 1.6
SCS-SF	3.4 ± 0.7
CPQ-6	14.6 ± 2.8
CIPS	52.1 ± 17.8

Discussion

General discussion on main findings

The findings in this thesis highlight the multidimensional impact of lipoedema in women. The condition causes negative self-image, restricted social interactions, and a feeling of being trapped in their bodies. Additionally, the financial burden of lipoedema, including high treatment costs, recurring sick leave, and limitations on participation in work life, is a consequence that requires attention. Women with lipoedema reported recurring experiences of feeling disregarded by healthcare and social support systems, forcing them to fight for treatment and support. These findings highlight the importance for healthcare to recognise the diagnosis of lipoedema, validate patients' symptoms, and address structural barriers that currently limit access to appropriate care. Additionally, treatments need to be made available, and, in the absence of a curative option, supportive therapies such as compression therapy and manual treatments should be offered by healthcare to decrease the symptoms of lipoedema.

While quality of life regarding physical and mental health is reduced in lipoedema compared to the general population, as confirmed by our findings, objective physical tests conducted in the same study did not demonstrate reduced muscle strength or endurance. The latter finding was indirectly supported by DXA, which did not show reductions in muscle mass relative to age- and gender-reference scores. The location and accumulation of adipose tissue, rather than muscle function, could explain some of the impairments described in lipoedema. Since signs of anxiety and stress were relatively low, while feelings of self-compassion were elevated in our cohort, we interpret these findings as positive prognostic factors for women with lipoedema. Although further research on lipoedema is needed, including epidemiology, diagnostic processes, interventions, and broader health implications, our studies contribute to the puzzle of knowledge by providing data on the lived experiences and physical and mental health of individuals with lipoedema.

Discussion of results

Research prioritisation

Diagnostic methods for lipoedema were considered highly prioritised for both developing consensus criteria and identifying biomarkers. This matter was highly relevant in our work for diagnosing referrals from general practitioners, since patients seeking care often presented with symptoms requiring careful clinical assessment to distinguish lipoedema from other conditions. While somewhat established diagnostic criteria facilitated the process, several cases required discussion together with colleagues. Thus, the current diagnostic method for lipoedema has inherent limitations. The development of objective methods, such as biomarkers, would increase diagnostic accuracy, aid in difficult cases, and enable more valid studies of treatments.

The findings of Paper V indicated high self-compassion and signs of perfectionism, while health-related quality of life (HRQoL), according to RAND-36, was low in both the physical and mental components. Although signs of perfectionism were not severe, it may still impact treatment outcomes in individual cases. Perfectionism has previously been associated with poorer physical and mental health, for example, in chronic pain (43). Despite this, self-compassion was generally moderate to high, suggesting a protective factor supporting self-care and treatment adherence (46, 47, 50). Addressing reduced HRQoL should be central in healthcare settings when managing lipoedema, and healthcare professionals should take psychological factors into account when developing treatment plans.

Since no effective lipoedema treatment is available in subsidised care in Sweden due to insufficient evidence or a lack of standardised care pathways, patients often have limited access to appropriate management, as reported in one of our qualitative studies. This inequality in care not only contributes to delays in diagnosis and treatment but could also exacerbate physical symptoms, increase psychological distress, and reduce HRQoL. Increased sick leave and rising costs for workplaces and society could also be consequences of inadequate healthcare for patients with lipoedema. However, an important finding from our studies was relatively ordinary muscle strength and capacity, as the participants with lipoedema demonstrated the ability to perform at expected levels, and had moderate to high levels of self-compassion associated with adherence to treatments. All these findings could be positive signs for reversing patients' negative daily lives with appropriate care and innovative interventions.

A favourable treatment often described by informants was liposuction. Liposuction has shown promising results in several studies, but large, well-designed studies with established protocols are lacking. Theoretically, removing adipose tissue through liposuction would improve symptoms across all axes, but the intervention is not without complications. Despite this, liposuction is available and included in national guidelines in the US and Germany (2, 3). To improve the management and care of patients with lipoedema, there is a need for sufficiently powered, multi-centre, randomised intervention studies to establish the efficacy and safety of liposuction in lipoedema.

Qualitative findings in interviews

The two themes emerging from my studies were: “An uncertain uphill battle against a divergent body and societal ignorance” and “Pushing the barricaded doors to treatment and care while fighting to illuminate the shadows of lipoedema”.

Interviews examining experiences of lipoedema in everyday life contained findings that divided the informants' experiences. Most informants described a failing body, social exclusion, and uncertainty about the future, reflecting a significant impact on daily life. In contrast, some described supportive partners and family members, together with coping strategies, that illustrate attempts to build a functioning life in the face of a chronic illness. These findings of impairment and resourcefulness suggest that the lived experience of lipoedema cannot be characterised as purely negative but is contextual within individual and social contexts. Our findings add to the existing literature on women's experiences of lipoedema (55, 56) and provide additional information on worries about the future, impacts on work life, and attempts to cope with their situation.

Women's experiences of healthcare encounters were largely negative. All informants had sought medical support; however, the exclusion of their condition from subsidised care and the lack of treatments created conflicts in their interactions with healthcare providers when they did not get the help they sought. In addition, experiences of disbelief or dismissal further reduced their trust in healthcare professionals, increasing the likelihood that they would not seek medical attention in the future. Questioning the legitimacy of a care-seeker’s condition can affect a patient's psychological well-being and long-term interactions with healthcare providers (154). Societal and healthcare awareness are central to enabling women with lipoedema to have healthcare interactions without judgment and with positive outcomes. Previous research has reported similar experiences among women with lipoedema, including being dismissed by healthcare providers as obese and having limited access to treatment, which often proved unhelpful even when available (55, 56). The trust built during healthcare interactions appears pivotal to establishing a functional patient-physician relationship. A lack of validation often drives patients to seek alternative, complementary, non-evidence-based treatments (155).

Health-related quality of life

The participants reported RAND-36 scores below reference scores across all subscales, including PCS and MCS, indicating impaired HRQoL. Role physical, role emotional, pain, and energy/fatigue were the lowest. These results indicated the impact of lipoedema on general HRQoL, as reductions were not confined to specific domains and all subscales were reduced. Given the physical manifestations of lipoedema, the impact on PCS and physical subscales is plausibly associated; meanwhile, the findings for MCS and mental subscales may reflect the psychosocial burden described in Paper II. As Study IV and V were cross-sectional studies, no causal claims can be made; however, the findings indicated a connection between lipoedema and reduced HRQoL. Future studies should focus on the possible association between lipoedema and HRQoL. Interestingly, no significant difference in HRQoL was observed between lipoedema stage 1 & 2 and stage 3. This aligns with previous consensus statements that the commonly used staging system does not reflect the impact on a woman's life (3).

Body composition, muscle strength, and capacity

The participants demonstrated retained muscle strength and capacity besides the 30STST, with younger participants completing fewer repetitions than the reference scores for the 30STST. Sitting and standing at a rapid pace require coordination, balance, and strength. The movement differs from walking, and the location of adipose tissue might have influenced participants' results. Additionally, sitting and standing are vertical movements that work against gravity; greater weight would increase the energy and strength required for these movements.

DXA examinations showed more adipose tissue in the extremities relative to reference values, but the muscle mass remained at reference levels. In previous literature, appendicular lean mass in individuals with lipoedema has been reported to be comparable to that in healthy controls (21, 67). A possible explanation could be that the increased weight places a greater load on the musculature, leading to greater lean mass.

The delayed pain phenomenon described in Paper IV has, to our knowledge, not been previously described and may increase the understanding of the pain mechanism in lipoedema. A possible hypothesis could be referred to the experience of informants regarding a dynamic movement of adipose tissue relative to the underlying structures. This is also supported by informants describing compression and tight clothing as stabilising the tissues and thereby reducing pain. With low-grade inflammation and localised hypoxia being the primary suspects in the development of pain in lipoedema, physical activity that influences these mechanisms would likely increase pain levels. In addition, considering the effect of psychological factors on pain, a more relaxed environment for the informants, such as being at home and less active, may also contribute to the delayed onset.

Methodological considerations

Research prioritisation

Resources for research are limited; consequently, it is essential to prioritise available resources to promote medical research that addresses areas important to patients and clinicians. The method brings patients, carers, and clinicians together and identifies unanswered questions for specific health conditions. The inclusive structure is a methodological strength, as it enhances the legitimacy of the findings. However, the method has limitations. While it aims for equal representation and influence, participation is voluntary and may lead to overrepresentation of highly motivated individuals. In addition, although the JLA methodology is well established, the resulting priorities reflect the perspectives of those involved and should not be interpreted as universally generalisable. Rather, they represent stakeholder-defined uncertainties within the study's geographical and temporal context and are intended to guide future research.

Qualitative approach

Research interviews are a valuable method for exploring the lived experiences of women with lipoedema, given the limited amount of research and clinical understanding of the condition. The method provides a way for the informant to share the experiences in their own words and perspective. By enabling direct interaction between researchers and informants, the interviews captured variations in emotional, physical, and social challenges associated with lipoedema that could be difficult to investigate through surveys or other quantitative methods. The use of purposive sampling ensured that informants with relevant experiences contributed rich and meaningful narratives, while frequent debriefing sessions among the research team broadened analytical perspectives and strengthened the interpretation of both manifest and latent content (148, 149). Our study included only individuals with a physician-assessed diagnosis, whereas other studies utilised self-reported diagnoses. This methodological choice enhanced the credibility and clinical relevance of the findings, ensuring that experiences were collected from individuals with confirmed lipoedema rather than from potentially misclassified cases. However, a limitation could be the exclusion of mild or early-stage symptoms, which may narrow the breadth of experiences captured. Additionally, the interaction between the interviewer and informant may have shaped the narratives, introducing the possibility of the informant providing socially desirable responses, rather than their own experiences. However, frequent debriefing sessions, i.e., discussions between the primary researcher, JD, and the rest of the research group, AS, EN, and MP, were employed to broaden perspectives and incorporate other experiences into the analyses (156).

Health-related quality of life by RAND-36 and assessing psychological well-being

RAND-36 and SF-36 are broad questionnaires that enable researchers to compare results within and between populations. Both RAND-36 and SF-36 have also been applied to lipoedema populations in previous publications, often in conjunction with other general HRQoL instruments, such as EQ-5D-5L and WHOQOL-BREF, with findings similar across questionnaires (7, 11, 39, 40, 59). Arguments can be made for each questionnaire, but in the absence of a validated lipoedema-specific questionnaire, we believe the RAND-36 is the best option.

Psychological well-being and mental health have been described as essential in the management and treatment of lipoedema (2-4, 8). Psychological well-being is influenced by a multitude of factors, including personality traits, and has implications for reducing disease risk and promoting longevity (157). Methods for screening personality traits and psychological conditions exist in a multitude of versions. One of the main problems with utilising questionnaires is respondent fatigue; the longer the questionnaire, the higher the risk that responses are given by chance rather than by intention (158, 159). Shorter questionnaires, however, run the risk of losing their validity and reliability. Our solution was to utilise questionnaires in their shorter forms, most suited for screening for the condition, and, if positive, a more in-depth examination could be considered. The relatively small number of participants in Paper V is an important consideration when interpreting our questionnaire results. There is a risk that the observed results reflect individual variation rather than broader trends within the lipoedema population. This is particularly relevant for scoring-based measures, where extreme scores from few participants can disproportionately influence the results. Therefore, the findings should be interpreted with caution. However, our results provide valuable preliminary data that can aid hypothesis generation and enable future research with larger sample sizes.

Physical strength and functional capacity in relation to body composition

Grip strength has been reported to be an important predictor of good health, muscular endurance, and overall strength (139). When assessing functional capacity, several tests are available, including the 6-minute walk test and the 30-second sit-to-stand test, both of which have good reliability and validity in other chronic conditions (62, 140, 146, 160). Combining isometric strength tests with functional exercise capacity tests improves the accuracy of the results, as limitations in muscle strength would impair capacity tests but not vice versa. In lipoedema, engagement is asymmetrical, as only specific parts of the body are affected. Tests that assess grip, elbow, and knee strength do not provide exclusive data on the lipoedema-affected areas of the body. Combining these with functional tests, in which the whole body is activated rather than isolated muscle groups, provides a holistic description of the participants' capacity and still allows identification of whether their reported limitations are attributable to the lipoedema-affected areas.

Body composition, the distribution of adipose tissue, muscle, and bone in an individual, can be measured using various methods. Dual-energy X-ray absorptiometry (DXA) is one of the most widely used and reliable methods for this purpose (65). Collecting data on body composition, HRQoL, and physical strength and capacity provides a more comprehensive perspective, enabling comparisons among these domains.

Strengths and limitations

Validity and reliability

Validity, defined as the ability of a study to measure what it set out to measure, can be categorised into internal and external validity. Internal validity refers to the avoidance of systematic errors and bias, while external validity refers to whether the results can be extrapolated to the reader’s population (161-163). Reliability refers to the consistency of findings if the study is repeated in a different context, time, or situation (162, 163).

The **internal validity** of Papers IV and V was enhanced by using validated questionnaires, such as the RAND-36, the AUDIT, and physical activity questions. In addition, regarding the diagnostic criteria in the recruitment process, two diagnostic criteria were employed, those by Wold (12) and those by Halk (13), thereby increasing the specificity of the diagnostic method, and cases of uncertainty were discussed by JD with experienced colleagues, AS and EN. Keep in mind that higher specificity comes at the cost of sensitivity, as borderline cases in which symptoms did not meet the criteria might have been excluded from recruitment.

In smaller studies, **external validity** will be limited by small sample sizes, which reduce the sample's representativeness of the larger population. Individuals can have an unreasonable impact on the results. Therefore, the findings should be interpreted with caution, but they provide data enabling future studies with large sample sizes.

In Paper I, recruitment aimed to obtain a wide and representative sample, including patients, relatives, patient organisations, healthcare workers, and researchers. As recruitment was advertised on the SBU webpage and invitations were sent to relevant providers and organisations, the aim was to reach a diverse and representative population. Despite this, the volume of email in most organisations can drown out invitations, preventing them from reaching the intended recipients. In our results, most of the submitted research questions, as well as those interested in prioritisation, came from patients or patient organisations. This might generate a more one-sided view in the open survey from this perspective. Still, the prioritisation meetings had an even distribution of perspectives, allowing all perspectives to be heard and to influence the results.

The **reliability** of the physical tests and the questionnaires in Papers IV and V warrants discussion. While approaches such as test-retest can be used, they require additional resources and place greater demands on participants. The application of parallel-test reliability, however, to measure the same attribute using different methods was partially employed in Paper IV (163). Examining both isometric strength and physical capacity using different tests enabled comparison of results. The physical tests followed standardised protocols and the same sequence, additionally the participants were familiarised with the tests by performing a warm-up of the intended test prior to testing. For the psychometric instruments applied, GAD-2, PSS-4, SCS-SF, CIPS, and CPQ-6, all have demonstrated internal consistency with Cronbach's alpha > 0.70 (48, 125, 127, 129, 135, 137). Similarly, the RAND-36 and AUDIT both have Cronbach's alpha > 0.80, and the physical activity questions have a Spearman's rho of 0.62 (116, 118, 121).

Trustworthiness

The concept of trustworthiness in qualitative research has multiple aspects. Four key criteria are commonly used: credibility, transferability, dependability, and confirmability.

Credibility concerns the extent to which the data and analysis address the study's intended focus (149, 156, 163, 164). A diverse population with experience of the research subject can enrich the material and strengthen the credibility of the findings. Variations in age, disease duration, and disease severity provided a wide range of experiences among our informants (148, 149, 156). Illustrative quotations for each section further demonstrated the findings (149).

Member checks, in which informants read transcripts to allow corrections or present the results as a whole, are another method that can improve credibility (149, 156, 163). This risk, as well as the critique of member checks tending to favour interpretations that portray informants in the most favourable light, were reasons not to perform member checks on the results (163). Although in Papers II and III, whole-transcript member checks were conducted for the last four digitally conducted interviews, as the digital medium increased the risk of information being misinterpreted by the recording (165, 166).

Transferability, the ability to transfer findings to another context in qualitative research, could be limited (149, 156, 163, 164). Because the situation and population are unique, the findings may or may not be applicable in another context, leaving interpretation of transferability to the reader (148, 149, 156, 163, 164). By providing a rich description of the population's context with respect to age, geographic area, lipoedema diagnosis, stage, and interview method, our studies provide a framework for readers to interpret our findings (149, 163, 165, 166). In addition, to ensure that suitable information was provided for assessment, standardised methods for reporting qualitative research were employed, available in the publications, via the Consolidated Criteria for Reporting

Qualitative Research (COREQ) and Standards for Reporting Qualitative Research (SRQR) (151, 152).

A recurring issue in discussions of the transferability of results is the sample size, i.e., the number of informants in qualitative research (148, 167, 168). The purposive sampling employed aims to identify information-rich cases that provide material on experiences related to the purpose, without requiring a large sample of informants (164, 167). While no clear consensus exists on the optimal sample size for interviews, arguments have been made for small but rich samples (114, 167). With 12 interviews, each 50-90 minutes, a rich body of material with detailed descriptions was obtained and deemed sufficient, with no more than a few new experiences appearing in the final interviews (165, 166).

Dependability, defined as the extent to which the work would yield similar results if repeated with the same informants, methods, and contexts (149, 156, 163, 164). By providing rich descriptions of the methods and analyses employed, Papers II and III provide the necessary foundation for a recreation. As the situation cannot be recreated in its entirety, with the same researcher and informants, in the same context, the dependability is strengthened by the similar findings by comparing with other similar studies available (55-57). As the interview is co-created between the researcher and the informant, and the analysis is conducted between the researcher and the text, the researcher's pre-understanding influences the results (148). Given that JD is a physician working with lipoedema, prior experience of the condition was unavoidable; however, this knowledge could enable more specific follow-up questions.

Confirmability refers to whether the results are affected by personal interests and are free of researchers’ bias (156, 163, 164). Keeping the analysis and results objective and aligned with the informants' perspectives rather than the researcher's preferences can be achieved through various approaches. Collaboration on an interview, independent coding with collective comparison within the research group, and illustrative quotations that provide a clear thread between the interviews and the results all reduced the risk of external influence (163, 164). When there was disagreement regarding the coding or analysis, the group discussed possible interpretations until a consensus was reached.

Central to confirmability is **reflexivity**, which refers to researchers’ reflections on their pre-understanding and predispositions (163, 169).

While previous experience with the condition influenced the design of the interview guide, it may also have affected informants' willingness to participate, the information they chose to share during the interviews, and the conclusions drawn from the analysis. JD's prior knowledge aided in the design of the interview guide and the choice of questions, for example, the question of how, when, and where the informant received the diagnosis of lipoedema. The interview guide was a living document, and questions were adjusted between interviews. During data interpretation, the ongoing discussion within the research group on personal pre-understanding was maintained to ensure that the findings were grounded in the data rather than in personal perspectives. A reflexive journal documenting decisions and reflections during the research was kept by JD (163).

Conclusion

- The need for research on lipoedema regarding diagnostics, primary outcomes, and treatment effects is warranted. Prioritisation of these areas enables researchers and funders to focus resources on the most critical knowledge gaps.

- Experiences of 12 women with lipoedema in everyday life led to the theme: *An uncertain uphill battle against a divergent body and societal ignorance*. Lipoedema traps women in their own bodies while also restricting social interactions. These experiences were further complicated by financial constraints, with no expected improvement in symptoms. Preventing further decline in the physical and mental health of those affected and ensuring early identification of lipoedema should be a priority for healthcare.

- Investigating help-seeking and interactions with healthcare experiences among 12 women with lipoedema resulted in the theme: *Pushing the barricaded doors to treatment and care while fighting to illuminate the shadows of lipoedema*. The theme stems from the lack of available subsidised treatments and limited knowledge regarding lipoedema among healthcare professionals. The experience of not being recognised by healthcare professionals risks eroding trust in healthcare systems. Increased education and awareness among healthcare professionals should be central to optimal management and care of women with lipoedema.

- Women with lipoedema showed no reduction in muscle strength or capacity, except for the 30-second sit-to-stand test. They had greater adipose tissue volume in the arms and legs, but no reduction in muscle mass compared with reference scores. Health-related quality of life (HRQoL), as measured by the RAND-36, was lower across all domains among women with lipoedema compared with reference scores. These findings indicate that the impairments in HRQoL measured could be attributed to pain and adipose tissue accumulation rather than to muscle function.

- Women with lipoedema in this study demonstrated high signs of self-compassion, while some had elevated signs of perfectionism. The presence of feelings regarding impostor feelings, anxiety, or stress was limited. Self-compassion is positively associated with self-care and treatment outcomes, and it may support recovery with proper treatment and encourage adherence to treatment regimens.

Future research

Lipoedema remains a condition for which much remains unknown. The delayed pain observed in Paper IV, outside the scope, remains unexplained. This area could offer potential for future research into the characterisation of lipoedema pain and its manifestations.

Heart rate variability (HRV), which measures the time between heartbeats, is a marker of autonomic nervous system function. Reduced HRV has been associated with increased risk of cardiovascular disease, arrhythmias, and depression. Data on HRV among our participants have been recorded but not yet analysed. A low HRV could indicate an impact on systemic stress, possibly contributing to systemic symptoms and pain. As described previously, the pathophysiology of lipoedema remains a mystery. Future research into markers and diagnostic tools for lipoedema would be of great value to both patients and clinicians.

Additional research in larger cohorts is needed to better understand the functional limitations associated with lipoedema, particularly regarding participation in working life and patterns of sick leave.

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