Liposuction versus conservative therapy for patients with lipoedema in Germany: a multicentre, randomised controlled clinical trial

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Summary

Background Lipoedema is a painful, chronic disease of the subcutaneous adipose tissue, predominantly affecting women. Conservative complex decongestive therapy is the standard of care but offers limited symptom relief. Liposuction appears to be a promising approach but lacks evidence of effectiveness and safety. The aim of this trial was to show superiority of liposuction compared with conservative therapy regarding relevant pain reduction with reasonable safety.

Methods In this multicentre, randomised controlled trial at 11 German centres, eligible women with stage I, II, or III lipoedema and leg pain of at least 4 points on a 0–10 numeric rating scale received conservative therapy for up to 7 months and then were randomly assigned to liposuction or conservative therapy (2:1) stratified by lipoedema stage and study site. For all visits involving an assessment, patches were applied to the legs of all patients, and patients were instructed not to reveal the treatment they had received, in order to mask the assessor. The primary endpoint was reduction of patient-reported leg pain by at least 2 points after 12 months, and missing assessment was considered non-successful.The primary outcome was analysed in the intention-to-treat population which included all randomly assigned patients, and safety analysis included all enrolled patients. A long-term follow-up of 36 months is ongoing. This study is registered at ClinicalTrials.gov, NCT04272827.

Findings Of 1973 patients screened between Jan 19, 2021, and June 7, 2022, 453 were enrolled, and 410 were randomly assigned to the liposuction group (n=278) or to the conservative therapy group (n=132). All 410 patients were included in the intention-to-treat analysis (mean age 42·9 [SD 10·6]; ethnicity data were not collected). After 12 months, 190 (68%) of 278 randomisly assigned patients undergoing liposuction achieved the primary endpoint of pain reduction versus ten (8%) of 132 randomly assigned to conservative therapy (odds ratio 26·2 [95% CI 13·1–52·5]; p<0·0001). Adverse events occurred in 124 (47%) of 265 patients undergoing liposuction, and 20 (8%) of 265 were rated as serious. In the conservative therapy group, 30 (21%) of 145 patients reported adverse events, and five (3%) 145 were rated as serious. Secondary endpoints regarding quality of life showed greater improvement in the liposuction group.

Interpretation Liposuction was superior to conservative therapy in reducing leg pain and improving quality of life in patients with lipoedema, but was associated with a higher rate of serious adverse events. Liposuction has the potential to be a promising treatment option for patients with lipoedema.

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Introduction

Lipoedema is characterised by the symmetrical accumulation of adipose tissue, predominantly in the lower extremities, but at times also the upper extremities, sparing the trunk, hands and feet, and occurring almost exclusively in women.[1,2] In most cases, the onset of lipoedema occurs during puberty.[2,3] Patients present with non-pitting, bilateral swelling, pain upon touch, and pronenesss to haematomas.[1] Current data suggest a prevalence of approximately 10% among adult women.[4] Although the exact pathophysiology of lipoedema remains to be fully elucidated, increased permeability of capillaries and disturbed lymphatic microcirculation appear to be two important factors.[5,6]

In western Europe, the standard treatment for lipoedema is conservative complex decongestive therapy, combining manual drainage, compression stockings, and physical activity.[7,8] This approach reduces pain and perceived tension and pressure, but is a lifelong treatment process.[9]

Data from patient cohorts indicate that liposuction effectively reduces pain and increases quality of life.[10–12] The German S2k guideline for lipoedema emphasises liposuction as an alternative treatment option in refractory disease.[7] The prevailing lipoedema surgery is wet-technique liposuction with tumescence anaesthesia and blunt atraumatic cannulas, causing minimal trauma

Research in context

Evidence before this study

The current standard of care for patients with lipoedema is conservative complex decongestive therapy, compromising compression, manual lymphatic drainage, physical activity, and skin care. Conservative therapy has been shown to reduce oedema but has limited effects on pain, the key symptom of lipoedema, and cannot stop disease progression. Liposuction has emerged as a treatment option, especially in refractory disease. To identify studies comparing efficacy and safety of liposuction and conservative therapy for lipoedema we searched PubMed, Embase, and the Cochrane Library for articles published up to Dec 1, 2025, using the search terms "lipoedema" AND "liposuction" AND ("decongestive therapy" OR "physiotherapy" OR "compression") without language restrictions. Only small, uncontrolled case series and retrospective cohort studies were found, that suggested liposuction might improve pain, haematoma proneness, and impairment in quality of life in patients with lipoedema. High-quality evidence from large randomised controlled trials evaluating efficacy and safety of liposuction for lipoedema was scarce.

Added value of this study

The LIPLEG trial is the first multicentre, randomised controlled trial comparing liposuction with conservative therapy in patients with lipoedema. Liposuction showed superiority over conservative therapy for the primary endpoint, the relevant reduction in patient-reported leg pain by at least 2 points on a numerical rating scale 12 months after completion of treatment. The findings were consistent across all lipoedema stages. Liposuction resulted in significant improvements in quality of life, physical health, and haematoma proneness, while these did not change much with conservative therapy alone. In this study, most patients in the liposuction group received concomitant conservative therapy, underscoring that reduction in pain and functional improvements were primarily attributed to the surgical intervention. As expected, more adverse events occurred in the liposuction group, but they were mostly of mild-to-moderate intensity. No unexpected or life-threatening events occurred. These results substantially raise the level of evidence for treatments of lipoedema.

Implications of all the available evidence

The LIPLEG trial proves that liposuction offers a substantial reduction in patient-reported pain and improvements in quality of life in all lipoedema stages compared with conservative therapy. These findings align with previous case reports but provide the first high-quality evidence of a randomised controlled trial. The results have changed health-care policy in Germany, resulting in the incorporation of liposuction in the catalogue of services reimbursed by the German statutory health insurances. Further research should focus on long-term efficacy and safety of liposuction, as this study reports the results of the 12 months' analysis. Ongoing follow-up up to 36 months will be published as soon as available. Recurrence rates, and the influence of the liposuction technique used should be further elucidated. Comparable studies in health-care systems other than Germany are encouraged to investigate different study populations.

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to nerves and vessels.[13,14] The aim of this randomised, controlled, multicentre LIPLEG trial was to demonstrate whether liposuction is superior to conservative treatment in patients with lipoedema, regarding relevant pain reduction with reasonable safety.

Methods

Study design

The LIPLEG trial was a multicentre, randomised controlled trial conducted at 11 sites throughout Germany. Study sites were hospitals and outpatient practices for dermatology or plastic surgery with documented experience in liposuction as lipoedema treatment and qualification to conduct a clinical trial. Conservative therapy was required to be performed by an experienced physiotherapist. Detailed information on the study is provided in the trial protocol, available within the appendix (pp 39–100).

Representatives of patient initiatives were involved in the development of the study design. The trial was conducted in accordance with the International Conference on Harmonization for Good Clinical Practice and the ethical considerations of the Declaration of Helsinki. The trial protocol and amendments were approved by the independent ethics committee at each participating site (Ethics Committee of the Hesse State Chambers of Physicians; reference number Az. 2019–1377-evBO). Following the trial initiation, the protocol was amended to refine the study procedures, eligibility criteria outcome definitions, the description of the randomisation methodology, and to introduce pandemic-related considerations. A summary of changes is provided in the appendix (pp 35–38).

A full list of all sites and corresponding ethics approvals is given in the appendix (p 5). The trial was registered on Feb 4, 2020, at ClinicalTrials.gov (NCT04272827; current status is not recruiting and expected to be active until the end of 2026). The protocol was previously published.[15] In this Article we present results up to the 12-month follow-up (recruitment and 12-month visit completed). The trial is still ongoing; long-term follow-up will last for a total of 36 months. After the 12-month visit, the conservative therapy group was offered liposuction. The protocol and statistical analysis plan are presented in the appendix (pp 39–100, 101–124).

See Online for appendix

Participants

Before trial initiation, a central online registration portal was established, allowing patients with lipoedema to register their interest in study participation via an online form. The number of registrations substantially exceeded the 450 minimum participants required; thus, a lottery-based selection was performed. Selected patients were allocated to a trial site according to the nearest postal code. Then, patients were contacted by the trial site and assessed for eligibility by structured telephone interviews. Patients considered eligible were invited for an onsite screening visit with a clinical examination to assess inclusion and exclusion criteria.

We enrolled women aged 18 years or older with a diagnosis of lipoedema stage I, II, or III, and an average leg pain of at least 4 points on a 0–10 numeric rating scale during the previous 4 weeks. Key exclusion criteria were concurrent lipoedema of the arms interfering with the primary end point of leg pain, previous liposuctions, non-lipoedema fat disorders, pregnancy, breastfeeding, or contraindications to clinical trial interventions. A full list of eligibility criteria is provided in the trial protocol in the appendix (pp 42–43). All patients provided written informed consent before study participation.

Randomisation and masking

Patients were randomised to liposuction group or conservative therapy group (2:1; to increase participation rates) using the web-based randomisation service ALEA Version 17.1 or higher (FormsVision BV, Abcoude, Netherlands), The randomisation was based on permuted blocks of varying length using a pseudo-random number generator and was stratified by lipoedema stage and trial site. Only ALEA service administrators of the Institute of Medical Statistics and Computional Biology (IMSB) not otherwise involved in the trial had access to the concealed randomisation sequence. Local researchers only had access to patients of their own study site. Masked assessors were excluded from any access to ALEA or other information about randomisation.

All assessments were performed by a single assessor at each trial site who had no knowledge of treatment allocation. To achieve masking of the assessor at each visit, surgical scars were taped by unmasked study personnel before each visit, with dummy patches in the control group, and patients were asked not to disclose the treatment they received to the masked study personnel performing the assessments. After assessment, data were entered into electronic case report forms by unmasked study personnel. Statisticians were unmasked when finalising the programming of the statistical analysis for the endpoints.

Procedures

After enrolment, all patients received conservative complex decongestive therapy for 1 month to reduce any pre-existing oedema, followed by another 6 months to maintain the achieved results and to ensure equal baseline conditions for all patients before randomisation. After this run-in period, patients were randomly assigned. Patients in the intervention group received wet-technique liposuction in up to four surgical sessions with optional concomitant conservative therapy. Patients in the control group were treated with conservative therapy alone for another 12 months and were offered liposuction thereafter. Liposuction was performed by experienced dermatologists or plastic surgeons who had performed at least 30 liposuctions on patients with lipoedema in the past 2 years. Conservative therapy was performed by experienced physiotherapists with a certificate in lymphatic drainage and at least 2 years of experience in lipoedema treatment. The treatment regimen could be adapted to the participants' individual situation. The surgeons performed liposuction in accordance with the local standard of the respective trial site. For this purpose, trial sites received guidance on volumes for infused tumescent solution as well as the allowable volume of liposuction aspirate, while the specific wet-technique liposuction approach was at the discretion of the surgeon. The tumescent solution before each liposuction or, in the case of water-jet assisted liposuction, during liposuction was limited to a maximum volume of 10% of the patient's bodyweight. The absolute maximum of the infused solution was set at 8 L per procedure, and the maximum volume of suctioned adipose tissue to 6 L for a bodyweight of 80 kg or less per procedure, and to 8 L for patients weighing more than 80 kg. The tumescent solution consisted of sodium chloride solution with variable additives of amide local anaesthetics, adrenaline, sodium bicarbonate, and triamcinolone. Additives and their concentration could differ between study sites according to local standard.

Both groups were assessed at randomisation, at 6 months, and at 12 months. At each visit, a clinical examination and assessments for the primary and secondary endpoints were performed. Patient characteristics were collected at baseline as well as randomisation, ethnicity was not part of the data collection. Adverse events were assessed non-systematically and monitored throughout the study by questioning patients during their visits. Surgical site abscess, post-surgical decrease in haemoglobin, post-operative pain, and others were classified as prespecified events in this regard. Before liposuction, an electrocardiogram, laboratory, and pregnancy tests were done. Full visit schedule, assessments, and datapoints are provided in the trial protocol in the appendix (pp 39–100). The full follow-up will last 36 months; the last patient's final visit is expected to take place in August, 2026.

Outcomes

The primary endpoint was binary (successful *vs* non-successful) and derived from the patient-reported average

leg pain intensity in the past 4 weeks, measured on a numerical rating scale (German pain questionnaire, range 0–10; higher score indicates higher pain intensity).[16] Success was defined as a reduction of at least 2 points assessed at 12 months after completion of liposuction or at 12 months after randomisation in the conservative therapy group. Patient-reported and other secondary endpoints were also measured at 12 months and included: change in average leg pain intensity in the past 4 weeks;[16] physical and mental component of the 36-Item Short Form Health Survey (SF-36, range 0–100; higher score indicates higher quality of life);[17] the Dermatology Life Quality Index (DLQI, range 0–30; higher score indicates lower quality of life);[18] the domains physical health, psychological health, social relationship and environment as well as items G1 rating quality of life and G4 content with quality of life of the World Health Organization Quality of Life–Brief Version (WHOQOL-BREF, range 0–100; higher score indicates higher quality of life);[19] susceptibility to depression in Patient Health Questionnaire-9 (PHQ-9, range 0–27; higher score indicates more severe depression symptoms);[20] general impairment of the legs (range 0–10; higher score indicates higher impairment);[10] haematoma proneness of the legs (range 0–10; higher score indicates higher tendency to develop haematomas);[10] movement restriction in Lower Extremity Functional Scale (range 0–80; higher score indicates higher disability);[21] and bodyweight (additional endpoint).

For assessment of safety, data on adverse events and dropouts due to serious adverse events were collected for up to 12 months. All adverse events occurring during the trial were documented in the patient medical records and the electronic case report form, including date and time of onset and resolution, severity, causal relationship with conservative therapy or liposuction, seriousness, and treatments given due to adverse events. Assessment for adverse events and serious adverse events was performed by the trial physician. All adverse events were coded according to MedDRA Version 27. Information on serious adverse events was immediately sent to the principal coordinating investigator via an automatic email notification directly from the database. The risk–benefit ratio was checked by the principal coordinating investigator based on a list of adverse events that had occurred up to that point. Moreover, an independent Data Monitoring Committee monitored the safety of participants during the study twice a year.

Statistical analysis

The rate of success in each lipoedema stage was expected to be at least 40% in the liposuction group and 10% in the conservative therapy group.[10] This corresponds to a minimum targeted effect of an absolute risk difference of 30% and an odds ratio (OR) of 6 in favour of the liposuction group, which aims to create a balance of treatment effect and risk burden. Accounting for stratification and dropout (in total about 20%), our sample size calculation resulted in a requirement of 450 patients in order to be able to randomly assign at least 405 patients (135 per stage) for the primary analysis, and in order to provide evidence of the hypothesised effect both overall and within the three individual stages (90% power, 5% two-sided significance level; further details are given in the trial protocol [appendix p 93]). An interim efficacy analysis was not planned.

The primary analysis included all patients randomly assigned as the intention-to-treat population. The primary endpoint was evaluated by Cochran–Mantel–Haenszel test stratified by lipoedema stage at a two-sided significance level of 5% (H_0: OR=1 *vs* H_A: OR≠1).[22] When statistically significant, equality of the success rates in each stage was assessed by Fisher's exact test (hierarchical test strategy). A missing primary endpoint was considered as non-successful. As a secondary analysis, the mean change in pain intensity from randomisation was evaluated using a restricted maximum likelihood-based mixed model for repeated measures (MMRM). The overall model (pooling all stages) included fixed categorical effects for treatment group, visit time, study site (pooled for sites with <10 patients), and stage, alongside a treatment-by-visit interaction term. Age and baseline pain intensity (at randomisation) were included as continuous fixed covariates. Analogous analyses were subsequently conducted for each stage independently. To ensure model convergence, numerical optimisation was performed using a sequential combination of nlminb, BFGS, and L-BFGS-B algorithms. To model within-subject correlations and time-specific variances, a heterogeneous first-order autoregressive covariance structure was specified. This structure assumes an autoregressive correlation pattern in which correlations decay exponentially with increasing temporal separation, while permitting unequal variances at each timepoint. Denominator degrees of freedom were estimated using the Satterthwaite approximation. To account for partial nesting (clustering by surgeon), pain intensity was additionally analysed using a linear mixed-effects model. This model incorporated a random intercept for surgeon (restricted to the patient's first assigned surgeon) in addition to the same fixed effects utilized in the MMRM. Furthermore, a post-hoc analysis of the primary endpoint was conducted using a partially nested mixed-effects logistic regression, adjusting for the fixed effects of treatment group and stage, alongside a random effect for surgeon. The intraclass correlation coefficient was calculated to assess the clustering of treatment outcomes among patients treated by the same surgeon. Further secondary endpoints were analysed in the same way as the primary endpoint. Secondary analyses were performed without controlling for multiple testing error. Evaluation of adverse events was performed as treated (safety population). Adverse events were listed and summarised by seriousness, severity, causal relation, treatment group,

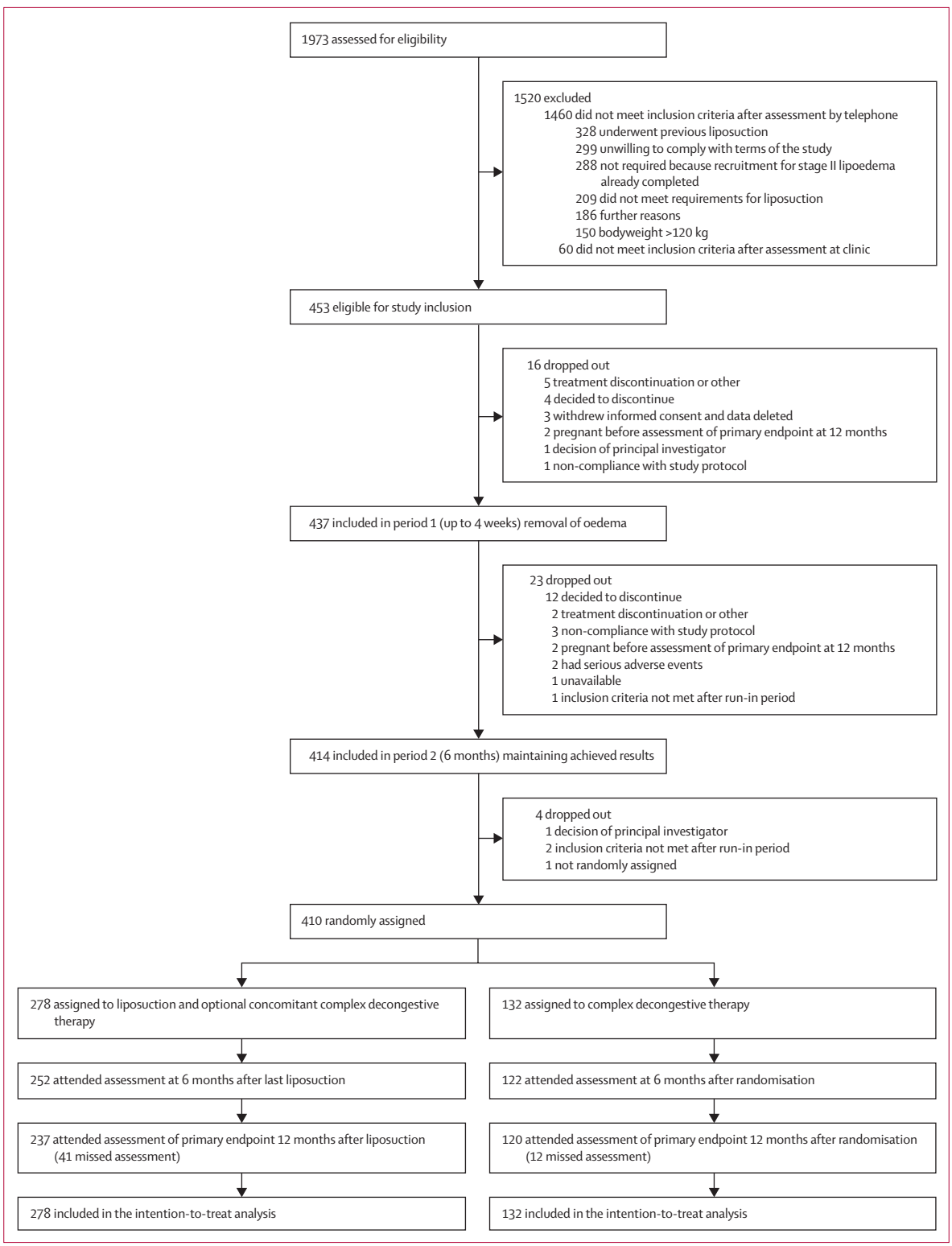


Figure 1: **Trial profile**
After the 12-month visit, the conservative therapy group was offered liposuction. Both groups will be followed up until 36 months. The final analysis will be performed after the study is completed.

and prespecified category (appendix p 6). Every 6 months a report of all adverse events was made available to the Data Monitoring Committee (appendix p 59).

Details on documentation and reporting period are given in the appendix (pp 94–96). The analysis examines the number of events and the number of patients affected, including comparisons of different groups or time periods regarding severity, duration, causal relation, and resolution of harms.

Descriptive statistics were summarised as mean, SD, and percentiles (quantitative variables) or as absolute and relative frequencies (qualitative variables). Binary endpoints were reported as ORs along with 95% CIs and adverse events with risk difference and corresponding 95% CIs. Analyses were conducted using SPSS (version 28 or higher) and R (version 4.5.1 or higher [R Core Team]). Further details of the statistical analysis can be found in the statistical analysis plan in the appendix (pp 101–124).

Role of the funding source

The clinical trial was publicly funded by the Federal Joint Committee of the self-government of physicians, dentists, hospitals, and health insurance funds in Germany. With the participation of patient representatives, the committee identified the research question and provided guidance on study design. The protocol was written by the trial sponsor (Medical Centre Darmstadt), the Clinical Trial Centre Cologne (CTCC), and the IMSB in Cologne. The sponsor was responsible for oversight of trial progress, data quality, and patient safety. CTCC performed data management, project management, and monitoring. IMSB was responsible for sample size calculation, randomisation, and analysis of trial data. The funder had no role in study conduct, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 19, 2021, and June 7, 2022, 1973 potential participants were prescreened via structured telephone interviews, 453 patients were enrolled, 43 patients dropped out between enrolment and before randomisation (including three patients who withdrew consent), and 410 patients were randomly assigned to the liposuction group (n=278) or to the conservative therapy group (n=132). All 410 patients were included in the intention-to-treat analysis of the primary outcome (figure 1). Patient characteristics and endpoint values at randomisation were balanced (table 1; appendix p 7).

12 months after last liposuction or after randomisation into the conservative therapy group, 190 (68%) of 278 (SD 2·80) patients in the liposuction group achieved a reduction of at least 2 points on the numeric rating scale versus ten (8%) of 132 (SD 2·3) in the conservative therapy group. There was a significant difference in leg pain reduction between the two treatment groups (OR 26·2 [95% CI 13·1–52·5]; p<0·0001; figure 2, appendix p 8). No patient in the conservative therapy group received liposuction within 12 months post randomisation. In the liposuction group, 216 (82%) of 265 patients underwent power-assisted liposuction and 49 (18%) of 265 underwent water-jet assisted liposuction (table 2); if multiple operations were performed, each patient received only one technique. Liposuction treatment is completed at different timepoints for each patient, with a median of 112 days between first to last liposuction in all stages. In the liposuction group, 203 (73%) of 278 patients received concomitant conservative therapy, and after their last liposuction, 184 (69%) of 265 patients who were operated on continued conservative therapy.

Statistically significant differences in reduction of pain between the two treatments were found across all

	Liposuction (n=278)	Conservative therapy (n=132)
Demographics		
Age, years*	43 (10·5)	43 (10·8)
Height, cm	167·0 (5·9)	166·6 (6·5)
Bodyweight, kg	89·5 (17·1)	91·2 (16·7)
Body fat (%)	43·7 (9·6)	45·0 (8·4)
BMI (kg/m²)	32·1 (6·1)	32·9 (5·9)
Waist circumference, cm	95·6 (13·5)	96·6 (11·7)
Hip circumference, cm	115·8 (13·4)	117·2 (11·8)
Waist-to-hip ratio	0·83 (0·08)	0·83 (0·07)
Waist-to-height ratio	0·57 (0·08)	0·58 (0·07)
Lipoedema stage		
Stage I	90 (32%)	42 (32%)
Stage II	95 (34%)	45 (34%)
Stage III	93 (34%)	45 (34%)
Patient-reported outcomes and other outcomes		
Average leg pain intensity	6·2 (1·6)	6·3 (1·6)
PHQ-9 depression	8·9 (5·4)	8·3 (5·0)
SF-36 mental health component	40·7 (14·0)	42·6 (14·1)
SF-36 physical health component	37·4 (8·8)	37·7 (9·0)
DLQI	9·2 (7·7)	9·1 (7·4)
WHOQOL-BREF, G1 rating quality of life	56·1 (20·2)	60 (20·2)
WHOQOL-BREF, G4 content with quality of life	36 (20·7)	40·5 (22·8)
WHOQOL-BREF, D1 physical health	52·6 (17·9)	55·4 (19·2)
WHOQOL-BREF, D2 mental health	54·9 (18·3)	57·4 (18·3)
WHOQOL-BREF, D3 social relationships	67 (18·4)	67·6 (20·4)
WHOQOL-BREF, D4 environment	71·5 (14·1)	74 (15·7)
General impairment (legs)	7·4 (1·7)	7·5 (1·4)
Haematoma proneness (legs)	8·2 (2·2)	8·5 (2·0)
Movement restrictions (Lower Extremity Functional Scale, sum)	48·6 (17·3)	48·5 (17·3)
Number of oedemas	0·5 (1·5)	0·5 (1·3)

Data are n (%), median (IQR), or mean (SD), collected at randomisation. Body measurements were missing in less than 2% of cases. Lipoedema stage I is defined as soft, homogeneous increase of subcutaneous adipose tissue, stage II as increased volume with nodular subcutaneous adipose tissue and uneven skin surface, and stage III is characterised by large nodules, tender, hanging flaps of adipose tissue and skin, especially on the thighs and knees.[1] PHQ=Patient Health Questionnaire. SF-36=36-Item Short Form Health Survey. DLQI=Dermatology Life Quality Index. WHOQOL-BREF=World Health Organization Quality of Life–Brief Version. *Age on day of consent.

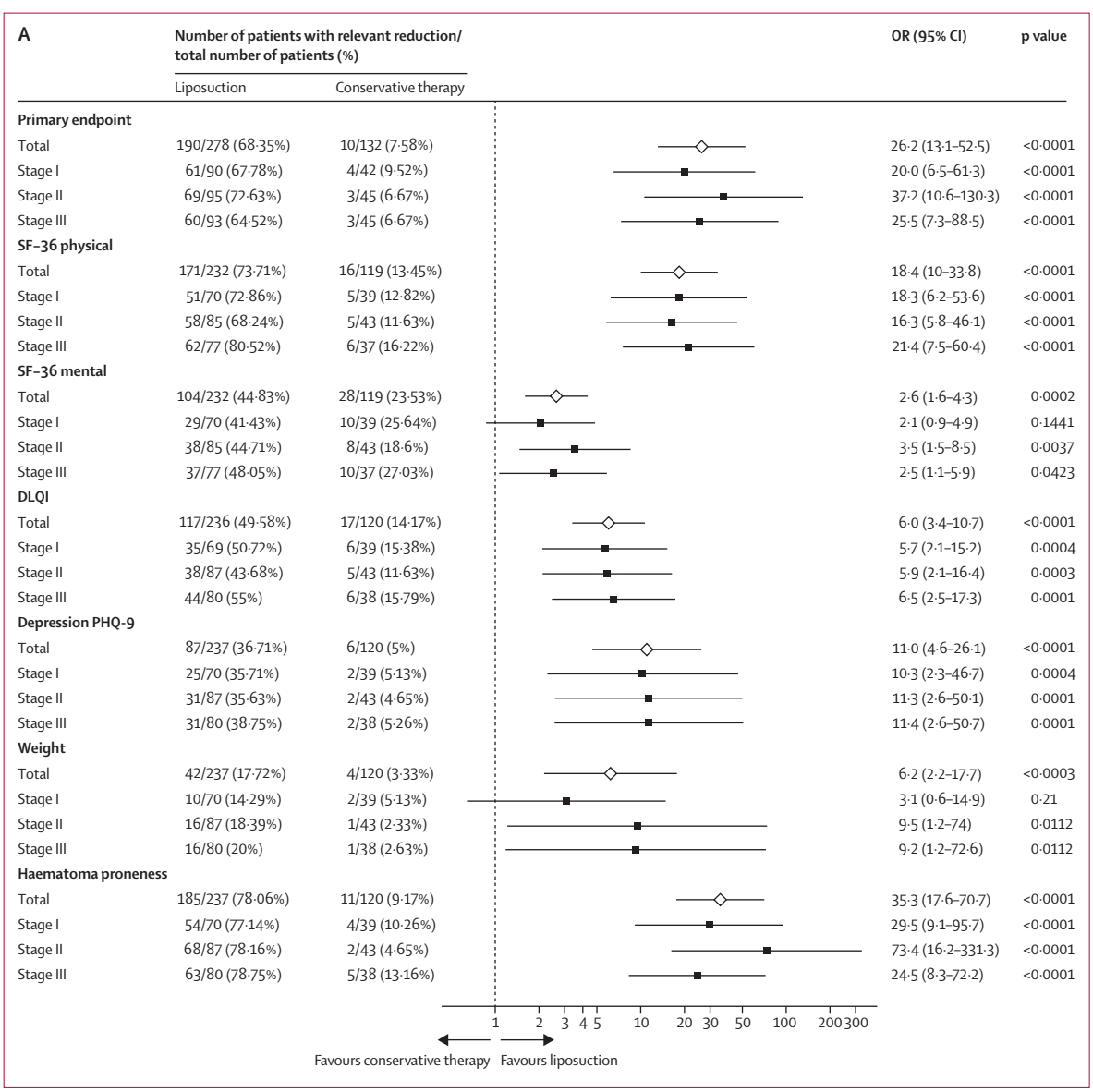
Table 1: **Patient characteristics in the intention-to-treat population**

three lipoedema stages: 67·78% (SD 4·9) with liposuction versus 9·52% (4·80) with conservative therapy in stage I (OR 20·0 [95% CI 6·5–61·3]; p<0·0001), 72·63% (4·60) with liposuction versus 6·67% (3·70) with conservative therapy in stage II (OR 37·2 [10·6–130·3]; p<0·0001), and 64·52% (5·00) with liposuction versus 6·67% (3·70) with conservative therapy in stage III (OR 25·5 [7·3–88·5]; p<0·0001; figure 2; appendix pp 9–10).

At randomisation, the mean pain intensity was 6·2 (SD 1·6) in the liposuction group versus 6·3 (1·6) in the conservative therapy group. At 12 months post randomisation, there was a reduction in pain intensity in the liposuction group down to 2·6 (SD 2·5), while there was no difference in the conservative therapy group (6·6 [SD 1·5]; table 3).

For the physical component of subjective health as measured by SF-36 questionnaire, improvement was achieved with liposuction compared with conservative therapy, within each lipoedema stage and across all stages (OR 18·4 [95% CI 10·0–33·8]; p<0·0001). The mental health component also improved with liposuction compared with conservative therapy (OR 2·6 [1·6–4·3]; p=0·0002).

The DLQI and WHOQOL-BREF to assess quality of life and the PHQ-9 to assess susceptibility to depression improved within 12 months after liposuction compared with conservative therapy across and within all lipoedema stages. No improvement was observed for the social domain of WHOQOL-BREF in stages I and III, or the environmental domain in stage III. Overall and



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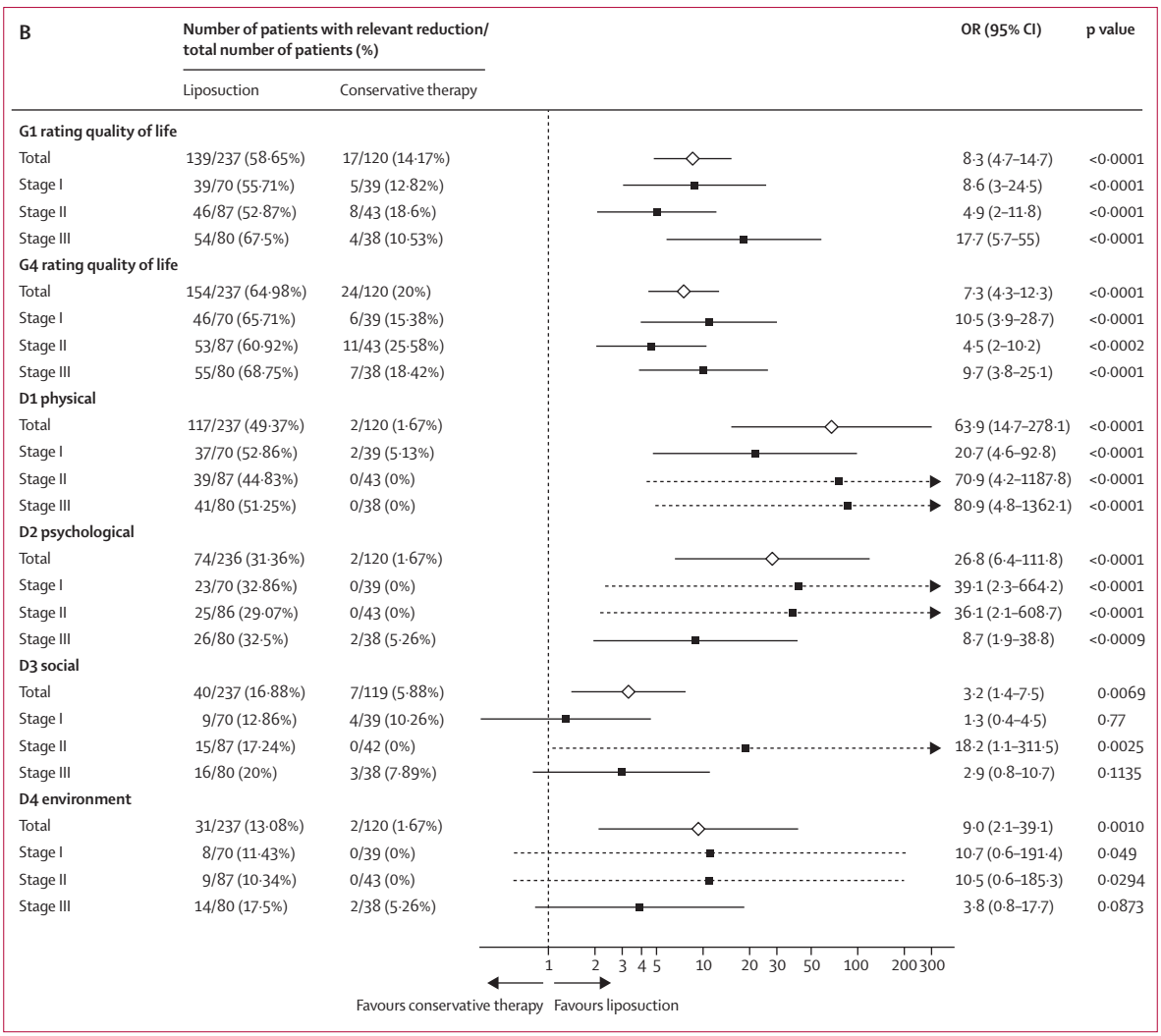

Figure 2: **Forest plot of primary and secondary endpoints**
(A) Results of the primary endpoint: relevant improvement of pain 12 months after start of conservative therapy or last liposuction, and relevant improvement of further secondary endpoints. A missing primary endpoint was considered non-successful (liposuction: 41 of 278; conservative therapy: 12 of 132). (B) Results of the secondary endpoints: WHO-BREF domains and selected items. Odds ratios and corresponding confidence intervals with dashed lines were computed using the Haldane–Anscombe correction, whereby 0·5 was added to each cell in contingency tables containing empty cells. Visual display of upper limits of confidence intervals was cut off at 300. OR=odds ratio. PHQ=Patient Health Questionnaire. SF-36=36-Item Short Form Health Survey. DLQI=Dermatology Life Quality Index. WHOQOL-BREF=World Health Organization Quality of Life–Brief Version.

within stages II and III, patients experienced weight reduction , but not in stage I. The proportion of patients showing improvement in haematoma proneness was larger in the liposuction group compared with conservative therapy (figure 2). After adjusting for partial nesting, the effects remained in a similar range or even increased (eg, for the primary endpoint; appendix pp 15–33).

The safety population included all patients based on the treatment they received (liposuction: n=265; conservative therapy: n=145, including 13 patients who were randomly assigned to liposuction, but who discontinued before undergoing their first liposuction). In the liposuction group, 124 (47%) of 265 patients reported at least one adverse event. In 45 (36%) of 124 patients, the event was possibly treatment related. In two patients in the liposuction group, an adverse event was possibly related to liposuction with concomitant conservative therapy. In the conservative treatment group, 30 (21%) of 145 patients reported at least one adverse event. This indicated a risk difference of 26·1 (95% CI 16·3–34·8) percentage points for patients receiving liposuction compared with conservative therapy, with respect to the occurrence of at least one adverse event. Since the first liposuction, 20 patients reported at least one serious adverse event, in the conservative therapy group five patients had at least one serious adverse event (risk difference 4·1 [95% CI

	Stage I	Stage II	Stage III	All stages
Liposuction technique details				
Liposuction performed	85/90 (94%)	92/95 (97%)	88/93 (95%)	265/278 (95%)
Power-assisted technique	75/85 (88%)	72/92 (78%)	69/88 (78%)	216/265 (82%)
Water-jet assisted technique	10/85 (12%)	20/92 (22%)	19/88 (22%)	49/265 (18%)
Liposuctions per patient				
1	2/85 (2%)	0/92 (0%)	0/88 (0%)	2/265 (1%)
2	18/85 (21%)	11/92 (12%)	1/88 (1%)	30/265 (11%)
3	15/85 (18%)	30/92 (33%)	11/88 (13%)	56/265 (21%)
4	50/85 (59%)	51/92 (55%)	76/88 (86%)	177/265 (67%)
Aspirate volume, L				
First liposuction	4·29 (1·87); n=85	5·17 (2·14); n=90	5·18 (2·03); n=87*	4·89 (2·05); n=262
Second liposuction	3·98 (1·66); n=83	4·76 (1·89); n=90	4·77 (1·66); n=88	4·51 (1·78); n=261
Third liposuction	2·87 (0·98); n=65	3·33 (1·32); n=79	4·72 (3·72); n=87	3·72 (1·61); n=231
Fourth liposuction	2·69 (0·80); n=50	3·21 (1·14); n=51	4·01 (1·11); n=76	3·41 (1·18); n=177
Median duration, days				
Randomisation to first liposuction	23 (15–27)	20 (9–25)	22 (15–27)	22 (13–27)
First to last liposuction	106 (75–125)	105 (84–122)	126 (112–139)	112 (91–129)

Data are n/N (%), median (IQR), or mean (SD) with n. Of 278 patients randomly assigned to the liposuction group, 265 had at least one liposuction. 13 patients discontinued after randomisation and before first liposuction. *The aspirate volume in the first liposuction was missing in one patient.

Table 2: **Details of liposuction**

	Descriptive analysis			Estimates from mixed model for repeated measures*		
	At randomisation	After 12 months	Change from randomisation	After 12 months	Change from randomisation	p value
All stages						
Conservative therapy	6·3 (1·6); 132	6·6 (1·5); 120	0·30 (1·33); 120	6·38 (5·98 to 6·77)	0·41 (–0·02 to 0·81)	..
Liposuction	6·2 (1·6); 275	2·6 (2·5); 237	–3·74 (2·43); 237	2·34 (2·05 to 2·63)	–3·63 (–3·92 to –3·33)	..
Difference between treatments	..	..	..	–4·04 (–4·49 to 3·59)	–4·04 (–4·49 to 3·59)	<0·0001
Stage I						
Conservative therapy	6·0 (1·5); 42	6·3 (1·6); 39	0·23 (1·22); 39	5·99 (5·21 to 6·77)	0·48 (-0·30 to 1·26)	..
Liposuction	5·5 (1·5); 90	1·8 (2·1); 70	–3·87 (2·24); 70	1·85 (1·22 to 2·48)	–3·76 (–4·39 to –3·12)	..
Difference between treatments	..	..	..	–4·24 (–4·99 to –3·49)	–4·24 (–4·99 to –3·49)	<0·0001
Stage II						
Conservative therapy	6·3 (1·3); 45	6·7 (1·5); 43	0·49 (1·37) 43	6·22 (5·58 to 6·86)	-0·16 (–0·48 to 0·80)	..
Liposuction	6·4 (1·5); 95	2·7 (2·5); 87	–3·69 (2·42) 87	2·37 (1·91 to 2·82)	–3·68 (–4·14 to –3·23)	..
Difference between treatments	..	..	..	–3·85 (–4·58 to –3·12)	–3·85 (–4·58 to –3·12)	<0·0001
Stage III						
Conservative therapy	6·8 (1·9); 45	6·8 (1·5); 38	0·16 (1·39) 38	6·90 (6·09 to 7·71)	0·57 (–0·24 to 1·38)	..
Liposuction	6·8 (1·6); 90	3·1 (2·7); 80	–3·67 (2·62) 80	2·92 (2·30 to 3·53)	–3·41 (–4·02 to –2·79)	..
Difference between treatments	..	..	..	3·98 (–4·87 to –3·09)	3·98 (–4·87 to –3·09)	<0·0001

Data present the average leg pain intensity in the past 4 weeks assessed at randomisation and after 12 months. Descriptive results are given as mean (SD); n. Estimated marginal means were derived from mixed models for repeated measures and are presented along with 95% CIs. The difference between treatments was calculated as liposuction minus conservative therapy. *Covariates appearing in the models are evaluated at the following values. All stages: pain intensity at randomisation=5·96, age=42; interaction term: treatment group × visit: F=0·99, df= 356·29; stage I: pain intensity at randomisation=5·48, age=39; interaction term: treatment group × visit: F=0·09, df=107·76; stage II: pain intensity at randomisation=6·05, age=44; interaction term: treatment group × visit: F=2·63, df=128·11; stage III: pain intensity at randomisation=6·32, age=44; interaction term: treatment group × visit: F=0·10, df=115·61.

Table 3: **Leg pain intensity in the intention-to-treat population**

–1·5 to 8·7]). Adverse events expected to be more frequent after liposuction were prespecified in the study protocol. Of the 20 patients with serious adverse events in the liposuction group, 11 patients had a prespecified serious adverse event while no prespecified serious adverse event occurred during conservative therapy (risk difference 4·2 [0·4–7·5]). In the liposuction group, 30 patients experienced a surgical site infection,

	Liposuction (n=265)	Conservative therapy (n=145)	Risk difference (95% CI; liposuction–conservative therapy)
Adverse events			
Patients without any adverse events	141 (53·2%; 47·2 to 59·1)	117 (80·7%; 73·5 to 86·3)	−27·5 (−36·0 to −17·8)
Patients with at least one adverse event	124 (46·8%; 40·7 to 53·0)	30 (20·7%; 14·4 to 28·2)	26·1 (16·3 to 34·8)
Severity			
Patients with at least one severe adverse event	11 (4·2%; 2·1 to 7·3)	6 (4·1%; 1·5 to 8·8)	0 (−5·4 to 4·2)
Patients with at least one moderate adverse event	54 (20·4%; 15·7 to 25·7)	15 (10·3%; 5·9 to 16·5)	10 (2·1 to 16·9)
Patients with at least one mild adverse event	59 (22·3%; 17·4 to 27·8)	9 (6·2%; 2·9 to 11·5)	16·1 (8·7 to 22·5)
Serious adverse events			
Patients with at least one serious adverse event	20 (7·5%; 4·7 to 11·4)	5 (3·4%; 1·1 to 7·9)	4·1 (−1·5 to 8·7)
Patients with at least one serious prespecified adverse event	11 (4·2%; 2·1 to 7·3)	0 (0%; 0 to 2·5)	4·2 (0·4 to 7·5)
By prespecified category			
Erysipelas	4 (1·5%; 0·4 to 3·8)	0 (0%; 0 to 2·5)	1·5 (−1·9 to 4·1)
Post-surgical decrease in haemoglobin	4 (1·5%; 0·4 to 3·8)	0 (0%; 0 to 2·5)	1·5 (−1·9 to 4·1)
Surgical site abscess	3 (1·1%; 0·2 to 3·3)	0 (0%; 0 to 2·5)	1·1 (−2·2 to 3·5)
Post-surgical pain	1 (0·4%; 0 to 2·1)	0 (0%; 0 to 2·5)	0·4 (−2·9 to 2·4)
Patients with at least one prespecified adverse event			
Post-surgical decrease in haemoglobin	15 (5·7%; 3·2 to 9·2)	..	..
Surgical site abscess*	5 (1·9%; 0·6 to 4·3)	..	..
Erysipelas	15 (5·7%; 3·2 to 9·2)	0 (0%; 0 to 2·5)	5·7 (1·7 to 9·4)
Seroma	10 (3·8%; 1·8 to 6·8)	0 (0%; 0 to 2·5)	3·8 (0·1 to 7·0)
Venous thrombosis	3 (1·1%; 0·2 to 3·3)	0 (0%; 0 to 2·5)	1·1 (−2·2 to 3·5)
Perioperative or postoperative pain	2 (0·8%; 0·1 to 2·7)	0 (0%; 0 to 2·5)	0·8 (−2·3 to 3·0)
Pulmonary embolism	1 (0·4%; 0 to 2·1)	1 (0·7%; 0 to 3·8)	−0·3 (−4·0 to 1·8)
By system organ class			
Blood and lymphatic system disorders	3 (1·1%; 0·2 to 3·3)	0 (0%; 0 to 2·5)	1·1 (−2·2 to 3·5)
Ear and labyrinth disorders	1 (0·4%; 0 to 2·1)	0 (0%; 0 to 2·5)	0·4 (−2·9 to 2·4)
Gastrointestinal disorders	3 (1·1%; 0·2 to 3·3)	0 (0%; 0 to 2·5)	1·1 (−2·2 to 3·5)
General disorders and administration site conditions	2 (0·8%; 0·1 to 2·7)	0 (0%; 0 to 2·5)	0·8 (−2·5 to 3·0)
Infections and infestations	4 (1·5%; 0·4 to 3·8)	0 (0%; 0 to 2·5)	1·5 (−1·9 to 4·1)
Injuries, poisoning, and procedural complications	2 (0·8%; 0·1 to 2·7)	0 (0%; 0 to 2·5)	0·8 (−2·5 to 3·0)
Musculoskeletal and connective tissue disorders	0 (0%; 0 to 1·4)	1 (0·7%; 0 to 3·8)	−0·7 (−4·4 to 1·2)
Neoplasms benign, malignant and unspecified	2 (0·8%; 0·1 to 2·7)	0 (0%; 0 to 2·5)	0·8 (−2·5 to 3·0)
Nervous system disorders	1 (0·4%; 0 to 2·1)	1 (0·7%; 0 to 3·8)	−0·3 (−4·0 to 1·8)
Reproductive system and breast disorders	1 (0·4%; 0 to 2·1)	2 (1·4%; 0·2 to 4·9)	−1·0 (−5·0 to 1·3)
Respiratory, thoracic and mediastinal disorders	1 (0·4%; 0 to 2·1)	0 (0%; 0 to 2·5)	0·4 (−2·9 to 2·4)
Skin and subcutaneous tissue disorders	1 (0·4%; 0 to 2·1)	0 (0%; 0 to 2·5)	0·4 (−2·9 to 2·4)
Surgical and medical procedures	0 (0%; 0 to 1·4)	1 (0·7%; 0 to 3·8)	−0·7 (−4·4 to 1·2)
Vascular disorders	0 (0%; 0 to 1·4)	1 (0·7%; 0 to 3·8)	−0·7 (−4·4 to 1·2)
Causal relation to liposuction			
Possibly related	45 (17%; 12·7 to 22·1)	..	..
Not related	79 (29·8%; 24·4 to 35·7)	..	..
Causal relation to conservative therapy			
Possibly related†	2 (0·8%; 0·1 to 2·7)	0 (0%; 0 to 2·5)	0·8 (−2·5 to 3·0)
Not related	122 (46%; 39·9 to 52·2)	30 (20·7%; 14·4 to 28·2)	25·3 (15·5 to 34·0)

Data are given as n (%; 95 % CI) and indicate the frequency of patients with at least one event in the period from randomisation (conservative group) or from first liposuction (liposuction group), respectively, to the 12-month visit. The severity of adverse events is assessed by evaluating each patient based on the event with the highest intensity. Patients were counted once per prespecified category. 13 patients who were randomly assigned to the liposuction group and discontinued before the first liposuction were evaluated in the conservative therapy group. In only two cases did a serious adverse event result in study discontinuation; in one instance (liposuction group), a serious infection developed after the first surgery, which precluded further treatment in the surgical group. The other case (control group) involved a diagnosis of multiple sclerosis that led to discontinuation. No serious adverse event resulted in death. Of the serious adverse events which occurred after the first liposuction, two were reported as condition improving, all others as resolved without sequelae. *One patient with both a surgical site abscess and erysipelas after the first liposuction terminated study participation prematurely (serious adverse event, lipoedema stage I). †Two patients had a seroma (non-serious, mild intensity) that occurred after the second liposuction; both events were reported as causally related to liposuction and to conservative therapy.

Table 4: **Adverse events in the safety population**

including erysipelas or abscess; 15 patients had a postoperative decrease in haemoglobin, ten patients developed a seroma, and three developed venous thrombosis. Two patients reported severe postoperative pain following liposuction. One pulmonary embolism occurred in the liposuction group and one in the conservative therapy group. In the liposuction group, ten of the possibly treatment-related adverse events were classified as serious. This included postoperative decrease in haemoglobin in four patients, surgical site abscess in two patients, erysipelas in two patients, severe postoperative pain in one patient, and vertigo in one patient. Two patients discontinued the study due to a serious adverse event. One patient discontinued before liposuction due to diagnosis of multiple sclerosis and one patient discontinued due to a surgical site abscess and erysipelas after first liposuction (table 4). More detail on adverse events before randomisation and after randomisation under liposuction and conservative therapy can be found in the appendix (pp 11–14).

Discussion

The LIPLEG trial is the first multicentre, randomised controlled trial evaluating treatment for lipoedema. The key finding was that significantly more patients with lipoedema experienced leg pain relief after liposuction than with conservative complex decongestive therapy. We found that relevant reduction of leg pain was 26-fold more likely with liposuction than with conservative treatment, with the lower border of the confidence interval being 13·1 exceeding the anticipated OR of 6. Data were consistent for all lipoedema stages combined, and within each stage. Although 36-month follow-up is pending, the primary endpoint of pain reduction of at least 2 points on a numeric rating scale was achieved at 12 months, after completion of the allocated treatment.

For many years, conservative therapy has been the gold standard in lipoedema care.[7,8] However, conservative treatment has a limited effect on pain, the main symptom of lipoedema, and only has temporary effects on oedema and haematoma proneness.[9] Therefore, more effective treatment options are needed. Wet-technique liposuction is a surgical, potentially disease-modifying alternative to merely symptom-modifying conservative treatment.[7,8,14] This technique employs tumescent anaesthesia, infiltrating adipose tissue with highly diluted amide anaesthetics, and subsequent liposuction using either power or water-jet assistance.[13] Several uncontrolled case series reported on the potential of liposuction to reduce pain and improve quality of life in patients with lipoedema, but the quality of evidence provided by these studies remained unsatisfactory.[10–12] Because there is currently no consensus liposuction technique in lipoedema, the LIPLEG trial allowed real-world practice (ie, liposuction was performed in accordance with the local standard of the respective trial site). Hence, most patients received power-assisted liposuction and tumescent anaesthesia solutions could differ on each trial site. Study sites were selected based on their experience in lipoedema surgery and their qualification to participate in clinical trials.

Improved quality of life through liposuction has been reported in the past, but the effect was limited due to less convincing trial designs with small sample sizes, single-centre approach, or lack of randomisation.[10–12] In the LIPLEG trial, relevant improvements in mean pain intensity, quality of life, physical health, and haematoma proneness were achieved with liposuction, while these patient-reported outcomes remained mostly unchanged when receiving conservative therapy alone. Liposuction might enhance body image, self-esteem, and social participation. Potential downstream benefits, including reductions in obesity-related comorbidities, venous diseases, or musculoskeletal disorders, may become evident.[23] The absence of significant improvements in lipoedema stage I for the mental component of the SF-36, social domain of the WHOQOL-BREF, and weight might reflect the lower disease burden in early-stage disease. Functional, social, and weight-related impairments might be limited, leaving less scope for measurable benefits of liposuction. In lipoedema stage III, no significant improvements were observed in social and environmental domains of the WHOQOL-BREF, suggesting that these aspects of quality of life might need interventions beyond liposuction.

Due to the trial design, the analysis for the primary and secondary outcomes were done at different timepoints. As conservative therapy is currently the standard therapy regimen, every symptomatic patient should receive conservative therapy as a start of treatment. If no substantial symptom relief is achieved after an adequate period of conservative therapy, liposuction can be considered.[7,8] This was ensured by the run-in period of up to 7 months. Aspirate volume limits each surgical session to ensure patient safety. Thus, liposuction might need to be done in several sessions. Consequently, liposuction treatment is completed at different timepoints for each patient. We ensure comparability by analysing primary and secondary endpoints 12 months after the last liposuction in the intervention group, and 12 months after randomisation in the control group.

While undergoing liposuctions, most patients received concomitant conservative therapy to optimise postoperative swelling and bruising and sustain functional improvements. 12 months after the final liposuction, the proportion of patients requiring adjuvant conservative therapy decreased to 69%. Previous evidence showed a substantial decline in the need for continued conservative therapy following liposuction, which in some cases was no longer necessary.[24] These observations suggest that the need for ongoing conservative therapy following liposuction might gradually decrease with longer-term follow-up. The observation that patients in the liposuction group were significantly more likely to

achieve the primary endpoint, despite most of them receiving concomitant conservative therapy versus conservative therapy alone, emphasises the substantial effect of liposuction on pain relief.

In the present trial, liposuction, as well as conservative therapy, were well tolerated. Previous studies considered wet-technique liposuction a safe procedure.[25–27] Safety of both wet-techniques (ie, power or water-jet assisted) was found to be comparable in previous analyses.[28,29] As expected for a surgical intervention, a higher number of adverse events occurred in the liposuction group than in the conservative therapy group, and more events were considered treatment-related. The most frequent adverse events were prespecified in the study protocol and included postoperative decreases in haemoglobin, as can be expected with the extensive subcutaneous wound surface, and surgical site infections. The number of serious adverse events was significantly higher in the liposuction group, as expected for a surgical intervention compared with conservative therapy, and prespecified serious adverse events exclusively occurred in the liposuction group. One patient discontinued the study due to a surgical site abscess and erysipelas following the first liposuction. Apart from this case, most adverse events in the liposuction group were of mild-to-moderate intensity. No unexpected and no potential life-threatening events were observed.

The LIPLEG study employed a more rigorous approach than previously seen in published evidence, by using a randomised, controlled trial design with masked outcome assessors. Furthermore, the relatively high number of participants led to significant results in all relevant endpoints. Findings from this trial (ie, the superiority of liposuction over conservative therapy in terms of pain reduction and improvement in quality of life), in all stages of lipoedema, prompted the incorporation of liposuction into the catalogue of services reimbursed by the German statutory health insurances. This decision might have the potential to result in cost savings for the German health-care system by reducing the need for lifelong conservative therapy, by lowering rates of sick leave from work, and fewer lipoedema-related disability claims. However, health-economic analysis was not a subject of the LIPLEG trial.

Trial limitations include variability within surgical techniques as well as within conservative therapy. Currently, there is no established standard technique in either liposuction or conservative therapy for lipoedema. Further research to establish the most efficient and safe procedure protocols are encouraged. Additionally, there is a lack of long-term efficacy and safety outcomes for liposuction in patients with lipoedema; in particular, recurrence rates, need for repeated procedures, and sustainability of pain reduction need to be further elucidated. We did not want to postpone reporting the 12-month analysis, therefore we will address the long-term efficacy and safety in the 36-month follow-up. A previous, smaller study demonstrated stable efficacy and safety results for up to 12 years after liposuction.[30] Considerable efforts were made to maintain masking of the outcome assessors during study visits, including taping of potential scars and instructing patients to not disclose their allocated treatment. Nevertheless, the visible change of body contour and fat distribution after liposuction introduced an inherent risk of unmasking, which could have led to bias. For both ethical and methodological reasons, the use of sham surgery as a control was not deemed feasible. The study was conducted exclusively in Germany and findings might not be fully reproducible in other health-care systems. Additionally, even though the sample size was high compared with previous evidence on treatment options for lipoedema, the sample size might not be sufficient to detect very rare safety events. However, one advantage of the LIPLEG study was that liposuction was available to all patients during the later course of the study, meaning that the final safety analysis will be based on a larger dataset. The analysis for the primary and secondary endpoints of intervention and control groups was performed at different timepoints because liposuction treatment often requires multiple sessions to be completed for an individual. Hence, we selected to evaluate the endpoints 12 months after completion of liposuction. This approach might have had an influence on the effect sizes. Another factor that particularly affected the liposuction group was the COVID-19 pandemic, which led to rescheduled appointments, missed visits, and even study withdrawals. Although most of the reasons for missed visits and endpoint assessments were similar in both groups, the pandemic-related missing data might have introduced bias. In the primary analysis, missing values were classified as non-successful, which means that the effect on the primary endpoint is underestimated. Furthermore, these results were supported by sensitivity analyses. Overall, the effect of the COVID-19 pandemic was found to be negligible.

The aim of the study was to evaluate whether liposuction leads to substantial pain reduction in patients with lipoedema, regardless of the liposuction technique used. The higher number of patients undergoing power-assisted liposuction than undergoing water-jet assisted liposuction might have influenced outcomes. The effect of the liposuction techniques, especially on leg pain, post-surgical complications, and long-term success of liposuction, with a potential need for repeated interventions or prolonged conservative therapy, should be further investigated. Furthermore, ethnicity should be part of future research to make results more generalisable. Additionally, the primary endpoint of at least 2 points reduction of pain on the numeric rating scale is a subjective, patient-reported outcome, which might have led to bias. Unfortunately, no objective measurements for pain in patients with lipoedema are validated. The fact that pain is the key symptom of

lipoedema may justify a patient-reported outcome as the primary endpoint.

The original decision to conduct this trial answered a request submitted by patients. In summary, patients with lipoedema undergoing liposuction were more likely to achieve significant leg pain relief at 12 months when compared to conservative therapy. Quality of life improved across multiple measured dimensions. Liposuction was associated with a higher rate of serious adverse events of mostly mild-to-moderate intensity. In conclusion, liposuction appears to be a safe and effective treatment for lipoedema and can be considered in patients at all stages.

Contributors

MP, OAC, and MH obtained funding. MP, OAC, SS, and DK participated in trial design and coordinated the trial. MP, OAC, DK, MIS, PS, and WM contributed to drafting the manuscript. MH, WM, and PS participated in the trial design, conducted sample size calculation and the statistical analysis, wrote the statistical analyses plan, and analysed the collected data. MP, SS, MK, MEC, DR, K-HB, MG, JS, and ZT recruited patients, conducted the study intervention, and collected data. MP interpreted the data. All authors contributed, reviewed, and approved the final version of the manuscript, and with the sponsor vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. MP and OAC directly accessed and verified the underlying data. All authors had full access to all the data and accept final responsibility for the decision to submit for publication.

Declaration of interests

OAC declares grants from iMi, iHi, DFG, BMFTR, Cidara, DZIF, EU-DG RTD, F2G, Gilead, G-BA, MedPace, MSD, Mundipharma, Octapharma, Pfizer, and Scynexis; consulting fees from AbbVie, AiCuris, Basilea, Cidara, Elion, Gilead, GSK, IQVIA, Janssen, MedPace, Menarini, Melinta, Mundipharma, Octapharma, Pardes, Pfizer, PSI, Scynexis, Seqirus, and Shionogi; speaker fees from Abbott, AbbVie, Hikma, Asahi Kasei, AstraZeneca, Gilead, GSK, Knight, InfectoPharm, Ipsen, Medscape, WebMD, MSD, Moderna, Mundipharma, Noscendo, Paul-Martini-Stiftung, Pfizer, Sandoz, Seqirus, Shionogi, Universimed, and Vitis; and participation on a Data Safety Monitoring Board or Advisory Board for AstraZeneca, Cidara, IQVIA, Janssen, MedPace, Melinta, PSI, Pulmocide, and Vedanta. All other authors declare no competing interests.

Data sharing

Deidentified participant data can be made available to researchers upon reasonable academic request 1 year after completion of the trial. Requests should be submitted to the corresponding author for consideration (oliver.cornely@uk-koeln.de). Access will be granted through a secure data environment. The protocol and statistical analysis plans are available in the appendix and further study-related documents can also be made available.

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