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Effectiveness and safety of breast reduction surgery, compared with no surgery, in women with symptomatic breast hypertrophy

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Effectiveness and safety of breast reduction surgery, compared with no surgery, in women with symptomatic breast hypertrophy

[Effektivitet och säkerhet för bröstreduktionskirurgi, jämfört med ingen kirurgi, hos kvinnor med symtomgivande brösthypertrofi]

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1. Abstract

Background: Breast hypertrophy is a condition that may give rise to physical and/or psychosocial problems, such as pain, headache, postural changes, bra strap grooves, intertrigo, inability to participate in exercise and sports, bullying, body image problems and problems with poorly fitting clothes. The condition affects many women and approximately 1,000 breast reduction surgeries per year are performed in Sweden.

Objective: The objective of this Health Technology Assessment (HTA) was to assess whether breast reduction surgery in women with symptomatic breast hypertrophy and a BMI ≤ 35, is better than no surgery regarding mortality, health-related quality of life, depressive symptoms, anxiety symptoms, sexuality-related outcomes, work ability, sick leave, physical function, pain, patient experience, and whether the surgery is safe to perform.

Methods: A systematic literature search was conducted in June 2020 in PubMed/Medline, Embase, the Cochrane Library, PsycInfo, and a number of HTA databases. The included articles were critically appraised and certainty of evidence was assessed using the GRADE approach. Meta-analyses were performed when possible.

Main results: Fifteen articles were included in this HTA; eight reporting findings from four RCTs, three cohort studies, three case series, and one qualitative study describing results of breast reduction surgery in women with symptomatic breast hypertrophy. Most studies had serious study limitations and problems with directness. Three RCTs and two cohort studies showed significantly improved *health-related quality of life* in patients who had undergone breast surgery compared with controls; weighted mean difference in the RCTs was 0.14 (95% CI 0.10–0.17) when measured with SF-6D (score range 0.29–1.0), 7.0 (95% CI 4.4–9.5) for SF-36 physical summary score, and 9.8 (95% CI 6.2–13) for SF-36 mental summary score (both ranging 0–100). Three RCTs showed significantly reduced *depressive symptoms* after surgery and two showed reduced levels of anxiety symptoms after surgery compared with controls. One RCT and two cohort studies showed significantly improved *sexuality-related outcomes* after surgery compared with controls. Three RCTs and one cohort study showed reduced pain after surgery compared with controls. Most effect sizes exceeded the reported minimal important difference for the scale. Certainty of evidence for the above outcomes is low (GRADE ⊕⊕◯◯). Two RCTs and two cohort studies reported significantly improved *physical function* after surgery compared with controls (very low certainty of evidence, GRADE ⊕◯◯◯). None of the included studies reported data regarding *work ability or sick leave*. The qualitative study showed that women experienced benefits, e.g. improved quality of life, but also some drawbacks in the form of scarring, from breast reduction surgery. Three case series reported a 30-day mortality of zero. Major complications reported after breast reduction surgery ranged from 2.4% to 14% and minor complications from 2.4% to 69%. The most severe complications were venous thromboembolism and pulmonary embolism, while the most frequent were surgical site infections and wound healing problems.

Concluding remarks: In women with symptomatic breast hypertrophy, breast reduction surgery compared with no surgery, may result in clinically relevant improvement of HRQoL and sexuality-related outcomes, and reduction of depressive symptoms, anxiety symptoms, and pain (GRADE ⊕⊕◯◯). It is uncertain whether physical function is affected (GRADE ⊕◯◯◯). Complications include a few serious complications, e.g. venous thromboembolism and infections, even though the most frequent complications are less severe. Reported thirty-day mortality was zero. There is a need for large well designed RCTs evaluating the long-term efficacy of breast reduction surgery in women with thoroughly defined symptomatic breast hypertrophy, as well as studies exploring women's experience of having had the procedure.

2. Svensk sammanfattning – Swedish summary

Bakgrund: Brösthypertrofi är ett tillstånd som kan ge upphov till fysiska och/eller psykosociala problem, såsom smärta, huvudvärk, hållningsförändringar, avtryck i huden av bh-banden, hudinflammation, oförmåga att delta i träning och sport, mobbning, kroppsuppfattningsproblem och problem med dåligt passande kläder. Tillståndet drabbar många kvinnor och cirka 1000 bröstförminskningsoperationer per år utförs i Sverige.

Syfte: Att bedöma om bröstförminskning hos kvinnor med symtomgivande brösthypertrofi och BMI ≤ 35 är bättre än ingen operation avseende dödlighet, hälsorelaterad livskvalitet, depressions- och ångestsymtom, sexualitetsrelaterade utfall, arbetsförmåga, sjukfrånvaro, fysisk funktion, smärta och patientupplevelse samt är säker att utföra.

Metod: En systematisk litteratursökning genomfördes i juni 2020 i PubMed/Medline, Embase, Cochrane Library, PsycInfo och ett antal HTA-databaser. De inkluderade artiklarna granskades kritiskt, resultaten tabellerades och resultatens tillförlitlighet bedömdes med GRADE-metoden. Metaanalyser utfördes när så var möjligt.

Resultat: Denna HTA-rapport baseras på 15 artiklar: åtta artiklar med resultat från fyra randomiserade kontrollerade studier (RCT), tre kontrollerade kohortstudier, tre fallserier och en kvalitativ studie avseende kvinnors upplevelser av bröstförminskningskirurgi. De flesta studier hade allvarliga studiebegränsningar och problem med överförbarhet. Tre RCT och två kohortstudier visade förbättrad *hälsorelaterad livskvalitet* hos patienter som opererats jämfört med kontroller; vägd genomsnittlig skillnad i RCT:erna var 0,14 (95 % KI 0,10 – 0,17) uppmätt med SF-6D (poängintervall 0,29-1.0), 7.0 (95 % KI 4,4-9,5) för SF-36 fysisk och 9,8 (95 % KI 6,2–13) för mental komponentsumma (båda poängintervall 0-100). Tre RCT visade minskade *depressiva symtom* efter operation och två visade minskade *ångestsymtom* efter operation jämfört med kontroller. En RCT och två kohortstudier visade förbättrade sexualitetsrelaterade utfall efter operationen jämfört med kontroller. Tre RCT och en kohortstudie visade minskad *smärta* efter operationen jämfört med kontroller. De flesta effektstorlekar indikerade kliniskt relevant skillnad. Ovannämnda resultats tillförlitlighet bedömdes i samtliga fall som låg (GRADE ⊕⊕◯◯). Två RCT och två kohortstudier rapporterade bättre *fysisk funktion* efter operationen jämfört med kontroller (mycket låg tillförlitlighet, GRADE ⊕◯◯◯). Ingen av de inkluderade studierna rapporterade data om *arbetsförmåga* eller *sjukfrånvaro*. Den kvalitativa studien visade att kvinnor efter bröstförminskning upplevde fördelar, till exempel förbättrad livskvalitet, men också vissa nackdelar i form av exempelvis ärrbildning. Tre fallserier rapporterade att 30-dagarsdödligheten var noll. Frekvensen av allvarliga komplikationer efter bröstförminskning varierade från 2,4 % till 14 % och mindre allvarliga från 2,4-69 %. De allvarligaste, men mindre vanliga, komplikationerna var venös tromboembolism och lungemboli, medan de vanligaste var sårinfektioner och sårläkningsproblem.

Sammanfattning: Bröstförminskningsoperationer, jämfört med ingen operation, för kvinnor med symtomgivande brösthypertrofi kan resultera i kliniskt relevant förbättring av HRQoL och sexualitetsrelaterade utfall och minskning av depressions- och ångestsymtom samt smärta (GRADE ⊕⊕◯◯), medan det är osäkert huruvida fysisk funktion påverkas (GRADE ⊕◯◯◯). Komplikationer är vanliga och inkluderar också ett fåtal allvarliga komplikationer såsom venös tromboembolism och infektioner. De vanligaste komplikationerna är mindre allvarliga, såsom sårinfektioner och ärrproblem. Det finns behov av stora väldesignade RCT:er som utvärderar långtidseffekten av bröstförminskning hos kvinnor med väldefinierad grad av brösthypertrofi med symtom, liksom studier som undersöker kvinnors erfarenhet av att ha genomgått bröstförminskning.

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results. The Swedish summary is a brief plain language summary of the HTA intended for decision makers.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, 20 January 2020.

Regional board for quality assurance of activity-based HTA	
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Svanberg, Therese	HTA librarian
Svensson, Mikael	Health economist, Professor
Wallerstedt, Susanna	MD, Professor
Wartenberg, Constanze	Psychologist, PhD

DDS Doctor of dental surgery
MD Medical doctor
PhD Doctor of Philosophy
OD Odontology doctor
PT Physiotherapist
RN Registered Nurse

3. Summary of findings

Outcomes	Study design Number of studies	Absolute effect Breast reduction surgery vs control	Certainty of evidence GRADE
Critical outcomes			
Mortality	3 case series	30-day mortality was zero	Not assessed
Complications after breast reduction surgery	3 RCTs, 1 cohort study, 3 case series	Complication frequency rates: Minor complications 2.4% to 69% Major complications 2.4% to 14%	Not assessed
Health-related quality of life	3 RCTs, 2 cohort studies (only findings from RCTs presented)	<u>SF-6D</u> Mean (SD) at 6 months: 0.79 (0.11) vs 0.65 (0.10) WMD 0.14 (95% CI 0.10 to 0.17)[1] <u>SF-36 Physical summary score</u> Mean (SD) at 4-6 months: 51 (7.2) vs 43 (8.4) WMD 7.0 (95% CI 4.4 to 9.5)[1] <u>SF-36 Mental summary score</u> Mean (SD) at 4-6 months: 54 (11) vs 23 (11) WMD 9.8 (95% CI 6.2 to 13)[1]	⊕⊕◯◯[2]
Important outcomes			
Depressive symptoms	3 RCTs	<u>BDI</u> Mean (SD) at 4 months: 7.2 (9.9) vs 14 (11) WMD -6.5 (95% CI -12 to -1.2); p=0.01 <u>HADS Depression score</u> Mean (SD) at 6 months: 0.39 (0.27) vs 0.79 (0.27) WMD -0.4 (95% CI -0.52 to -0.28); p<0.001 <u>RBDI</u> Proportion reporting depression at 6 months: 7% vs 43%; p<0.01	⊕⊕◯◯[2]
Anxiety symptoms	2 RCTs	<u>HADS Anxiety score</u> Mean (SD) at 4 months: 5.0 (3.5) vs 9.6 (3.8) WMD -4.6 (95% CI -6.2 to -3.0); p<0.001 <u>RBDI</u> Proportion reporting anxiety at 6 months: 10% vs 34%; p=0.04	⊕⊕◯◯[2]
Sexuality-related outcomes	1 RCT, 2 cohort studies (only findings from RCT presented)	<u>FSFI</u> Mean (SD) at 6 months: 28 (6.9) vs 23 (9.3) WMD 5.0 (95% CI 0.69 to 9.3); p<0.001	⊕⊕◯◯[3]

Physical function	2 RCTs, 2 cohort studies (only findings from 2 RCTs reporting intergroup differences presented)	<u>HAQ-20</u> Mean (SD) at 6 months: 0.12 (0.23) vs 0.46 (0.30) WMD -0.34 (95% CI -0.45 to -0.23); p<0.001 <u>SF-36 physical summary score</u> Mean (SD) at 6 months: 52 (SD NR) vs 43 (SD NR); WMD 8.4 (95% CI 5.8 to 12); p<0.0001	⊕◯◯◯[4]
Pain	3 RCTs, 1 cohort study (only findings from RCTs presented)	<u>EQ-5D</u> Mean (SD) at 4 months: 1.5 (0.57) vs 2.1 (0.52) WMD -0.59 (95% CI -0.84 to -0.34); p<0.001 <u>FBAS</u> Mean difference: -46 (95% CI -50 to -41); p<0.0001 <u>VAS</u> Mean (SD) at 6 months: 1.3 (2.5) vs 5.3 (2.8) WMD -4.0 (95% CI -5.1 to -2.9); p<0.001	⊕⊕◯◯[2]
Work ability	Not reported in any of the included studies		
Sick leave	Not reported in any of the included studies		

CI: Confidence interval; RCT: Randomised controlled trial; WMD: Weighted mean difference; SF-6D: Short Form 6 dimensions, Health utility index score (range 0.29–1.00, higher better); SF-36: Short Form -36 Health Survey (36 items, range 0–100, higher better); BDI: Beck's Depression Inventory (range 0–63, lower better); HADS: Hospital Anxiety and Depression Scale (Depression score range 0–21, lower better, Anxiety score range 0–21, lower better); RBDI: Raitasalo's modification of the short form of the Beck Depression Inventory (range 0–39, lower better); FSFI: Female Sexual Function Index (higher better); HAQ-20: Stanford Health Assessment Questionnaire (range 0 (able) to 3 (disabled)); EQ-5D: The European Quality of Life-5 Dimensions (range NR, lower better); FBAS: Finnish Breast Associated Symptoms questionnaire (range 0–100, lower better); VAS: Visual analogue scale (range 0-10, higher better)

Footnotes:
[1]Results from meta-analysis of 2 RCTs
[2]Downgraded two steps due to serious study limitations and serious indirectness
[3]Downgraded two steps due to serious indirectness and serious imprecision
[4]Downgraded three steps due to serious study limitations, serious indirectness, and serious imprecision

Certainty of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4. Abbreviations/acronyms

BDI	Beck's Depression Inventory
BMI	Body mass index (kg/m^2)
CI	Confidence interval
DAS-59	Derriford Appearance Scale 59
EQ-5D	EuroQol-5 dimension
FBAS	Finnish Breast-Associated Symptoms questionnaire
FPQ	Finnish Pain Questionnaire
FSFI	Female Sexual Function Index
GRADE	The Grading of Recommendations Assessment, Development and Evaluation
HADS	Hospital Anxiety and Depression Scale
HAQ-20	Stanford Health Assessment Questionnaire
HTA	Health Technology Assessment
HRQoL	Health-Related Quality of Life
MD	Mean difference
MID	Minimal Important Difference
NAC	Nipple Areolar Complex
NSQIP	The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP®)
PICO	P= Patients, I= Intervention, C= Comparison, O=Outcome
QALY	Quality adjusted life years
RBDI	Raitsalo's modification of the BDI (Finnish modification)
RCT	Randomised controlled trial
SBU	Swedish Agency of Health Technology Assessment and Assessment of Social Services
SF-36	Short Form (36) Health Survey
SF-6D	Short Form Six-Dimension
SoS	Swedish National Board of Health and Welfare
SQoL-F	Sexual Quality of Life-Female
SU	Sahlgrenska University Hospital
VAS	Visual analogue scale
VGR	Region Västra Götaland
WMD	Weighted Mean Difference

5. Background

Disease/disorder of interest and its degree of severity

Breast hypertrophy (macromastia) is a condition that may give rise to one or several physical and/or psychosocial problems. Different definitions are used for breast hypertrophy. In the present HTA, we included studies of women with symptomatic breast hypertrophy regardless of what definitions of breast hypertrophy that were used in the included studies.

Definitions of breast hypertrophy

Volume-based definition according to the Swedish national guidelines for breast reduction

The Swedish guidelines (Abdiu et al., 2008) base the definition of breast hypertrophy on anthropomorphic measurements of mean breast volume (405 ml, median 359 ml) in a population of randomly chosen women (Loughry et al., 1989). Hypertrophy is defined as at least twice the mean volume in the anthropomorphic measurement studies; that is, a volume of >800 ml per breast. Previous Swedish studies, conducted before the guidelines were established, showed that many women who want a breast reduction have a volume of >800 ml (Atterhem et al., 1998; Sigurdson and Kirkland, 2006). However, there are a number of limitations regarding the use of breast volume as an indicator for surgery. Firstly, there are no conclusive studies determining what volume/weight, in relation to body habitus, that gives rise to physical and/or psychosocial symptoms. Secondly, the relationship between breast volume and breast weight is not clear-cut as different breasts have different density. The ratio between adipose tissue and breast tissue varies according to genetics and hormonal status and breast tissue weighs more than adipose tissue. Thirdly, breast volume measurements are uncertain (Hansson et al., 2014; Choppin et al., 2016).

The criteria of Sacchini et al

The criteria for breast hypertrophy by (Sacchini et al., 1991) are based on the mean measurement of the nipple to inframammary fold distance and the nipple to the lateral border of the sternum distance:

< 9 cm → small breasts
9-11 cm → normal sized breasts
> 11 cm → breast hypertrophy (Sacchini et al., 1991).

The criteria have never been validated scientifically.

Bra size

In some instances, bra size, typically cup D or larger, is used as a way of defining breast hypertrophy. However, cup size labelling is not standardised, and, e.g., one brand's C cup might equal another brand's B cup. The cup size is often based on the difference in breast circumference and rib cage circumference; that is, a difference of one inch (2.54 cm) constitute an A cup, two inches a B cup, etc. and consequently the actual volume of the cup is substantially different depending on the circumference of the rib cage. Moreover, the model of the bra, for example if it covers the entire or only part of the breast, creates different 'volumes'. Finally, there is a considerable difference in how women want their bra to fit; that is, women with identical breast volume might wear different bra sizes (Ringberg et al., 2006). In brief, the use of bra size to define breast hypertrophy is unprecise.

Gigantomastia

Sometimes, a breast size considerably larger than average is classified as gigantomastia. Some authors define the condition as breasts requiring a resection of >1500 grams per breast or as when the breast tissue constitutes more than three per cent of the patient's total body weight. Other definitions include excessive breast growth, often not self-limiting.

Gigantomastia is idiopathic and often induced by endogenous hormone production during pregnancy or puberty, or in rare cases by a pharmacological agent. Histopathologically, the condition is characterised by stromal and ductal hyperplasia, with dilatation, oedema, and an increase in oestrogen receptors (Dancey et al., 2008; Dafydd et al., 2011).

Physical and psychosocial consequences of breast hypertrophy

Physical symptoms of breast hypertrophy include muscle pain, such as back and shoulder pain, headache, postural changes, bra strap grooves, intertrigo, and inability to participate in exercise and sports (Kerrigan et al., 2001). Psychosocial symptoms of breast hypertrophy include sexual problems, bullying, body image problems and problems with poorly fitting clothes (Kerrigan et al., 2001).

Severity

Most of the symptoms described may impair health-related quality of life. Some of the symptoms, such as pain and inability to participate in sports, as well as sexual and body image problems, constitute a risk for permanent illness and in extreme cases disability.

Prevalence and incidence and number of patients per year who undergo current treatment regimen

The prevalence of breast hypertrophy is unknown and depends on how the condition is defined. According to the Swedish National Board of Health and Welfare (Socialstyrelsen, 2020) about 1,000 breast reductions are performed in Sweden per year and about 100 of these are performed at the Sahlgrenska university hospital. According to the American Society of Plastic Surgeons, about 100,000 breast reductions are performed in the United States yearly (American Society of Plastic Surgeons, 2019).

Present treatment

Surgical treatment

Breast hypertrophy is treated surgically with a breast reduction (reduction mammaplasty), an operation that is considered effective at reducing physical and psychosocial symptoms and improving quality of life (Lewin et al., 2019). However, a reduction in physical and psychosocial symptoms and an improved quality of life are also achieved when a breast reduction is performed for cosmetic reasons and therefore it is difficult to distinguish which patients should be operated in the public healthcare system (Klassen et al., 1996; Mello et al., 2010).

Indications for a rationed breast reduction

There is no general, globally agreed, consensus for when a breast reduction is indicated and should be rationed. In many countries the criteria vary according to local policies (Crittenden et al., 2020), and in the UK the situation has been described as a 'postcode lottery' (Wraight et al., 2007). The criteria are often based on some kind of volume measurement in normal weight patients, irrespective of the patient's other body habitus (Cook et al., 2003; King et al., 2005).
In healthcare systems with third party payers, such as the US system, insurance companies often define medical necessity for a breast reduction as amount of tissue that can be removed in a normal weight patient (Koltz et al., 2013). Nonetheless, symptom relief does not seem to be correlated to the amount of tissue resected (Spector et al., 2008).

What amount of breast tissue should be removed?

The Schnur Sliding Scale indicates average grams of tissue per breast to be removed according to calculated body surface. If a patient's body surface area and weight of resected tissue fall above the 22nd percentile, a breast reduction is classified as a medical necessity.

The method was developed for a study that evaluated whether patients request a breast reduction for medical or for cosmetic reasons, but not to establish which women should be granted an operation in the publicly funded healthcare system or have their operation covered by insurance (Schnur et al., 1991; Schnur, 1999).

Indications for breast reduction surgery according to the Swedish national guidelines for breast reduction

Indications for breast reduction surgery include the following criteria, which all must be fulfilled:

- Breast volume > 800 ml per breast (Abdiu et al., 2008), as measured with breast cups (Hansson et al., 2014).
- Physical and psychosocial symptoms of breast hypertrophy.
- BMI ≤ 25 for women < 50 years and ≤ 27 for women ≥ 50 years of age.
- Smoking cessation at least 4 weeks pre- and post-operatively (Abdiu et al., 2008).

The reason for the BMI and smoking requirements is that the risk for surgical complications increases with an increasing BMI and with smoking (Abdiu et al., 2008). The volume of 800 ml was chosen as this is twice the mean volume of an average breast (Loughry et al., 1989). In addition, previous Swedish studies, conducted before the guidelines were established, showed that many women who want a breast reduction have a volume of >800 ml (Atterhem et al., 1998; Sigurdson and Kirkland, 2006).

Non-surgical treatment for breast hypertrophy

Non-surgical treatment options for breast hypertrophy include physiotherapy, weight loss, and support bras. The evidence for their long-term effectiveness is unclear (Collins et al., 2002).

The normal pathway through the healthcare system and current wait time for medical assessment/treatment

Breast reductions are performed by plastic or general surgeons in most of Sweden's county as well as university hospitals. Most surgeries are performed as day surgery.

Present recommendations from medical societies or health authorities

There are Swedish national guidelines for breast reduction, published in 2008 (cf. above) (Abdiu et al., 2008), as part of *Nationella medicinska indikationer,* a collaborative project led by the Swedish Association of Local Authorities and Regions (*Sveriges kommuner och regioner*) and the Swedish National Board of Health and Welfare (*Socialstyrelsen*). They have not been formally modified or evaluated since they were published.

6. Health technology at issue: breast reduction surgery

The health technology at issue in this assessment is breast reduction surgery for women with breast hypertrophy, a surgical treatment modality that has been in use since many years.

There are many different surgical techniques described for breast reduction, varying mainly in skin incision/resection patterns and different pedicles on which the nipple-areolar complex (NAC) is moved. The two most commonly used skin resection patterns are the inverted-T (aka 'Wise pattern') (Wise, 1956) and a vertical pattern (aka e.g. 'Lejour', 'Lassus') (Lejour et al., 1990) (Hall-Findlay, 2004).

A pedicle is a partially detached piece of tissue with blood circulation, also called a flap.
Most pedicles are unipedicled, for example pedicles based superiorly (aka e.g. 'Weiner') (Weiner et al., 1973), inferiorly (aka e.g. 'Courtiss', 'Robbins') (Courtiss and Goldwyn, 1977; Robbins, 1977), laterally (aka eg 'Skoog') (Skoog, 1963), medially (aka e.g. 'Hall-Findlay') (Hall-Findlay, 2004) or superiomedially (aka e.g. 'Hauben', 'Orlando') (Hauben, 1984; Orlando and Guthrie, 1975). There are also different bi-pedicled flaps described, for example 'Strömbeck' (Strombeck, 1960) and 'McKissock' (McKissock, 1972). All pedicles are considered random flaps as the vascularisation of the nipple-areolar-complex comes from branches of the lateral thoracic, internal mammary, and other minor arteries in the area and is highly variable. Therefore, there is always a risk for NAC necrosis and wound healing problems when the NAC is moved (O'Dey et al., 2007). The most common complications after a breast reduction include delayed wound healing, fat necrosis, skin necrosis, and infection (Lewin et al., 2014).

7. Focused question

Is breast reduction surgery better than no surgery, in women with symptomatic breast hypertrophy and a BMI of ≤ 35, regarding HRQoL, depressive symptoms, anxiety symptoms, sexuality-related outcomes, work ability, sick leave, physical function, pain, and patient experience, and is it safe?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P	Women who seek health care for symptomatic breast hypertrophy and with a BMI ≤ 35[1]
I	Breast reduction surgery
C	C1: No treatment C2: Non-surgical treatment
O	**Critical for decision-making** Mortality Complications HRQoL (measured with validated scales) **Important for decision-making** Depressive symptoms (measured with validated scales) Anxiety symptoms (measured with validated scales) Sexuality-related outcomes (measured with validated scales) Work ability (measured with validated scales) Sick leave Physical function (measured with validated scales) Pain (measured with validated scales) Experiences of having a breast reduction

[1] The department currently mainly performs breast reduction surgery in women with a BMI<27, in accordance with the national Swedish guidelines (Abdiu et al., 2008). However, as the guidelines are not strictly evidence-based a wider range of BMI was included in the PICO.

8. Methods

Systematic literature search

During June 2020 two authors (AL, ME) performed systematic searches in PubMed, Medline, Embase, the Cochrane Library, PsycInfo and a number of HTA databases. Reference lists of relevant articles were scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, selected studies, and independently assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all authors. All authors read the articles independently and it was finally decided in a consensus meeting which articles should be included in the HTA report.

Critical appraisal and certainty of evidence

Included studies and their design and patient characteristics are presented in Appendix 2. Excluded studies and the reasons for exclusion are presented in Appendix 3.

The included RCTs, cohort studies, and qualitative study were critically appraised using modified checklists for quality assessment from the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU). Certainty of evidence was assessed using the GRADE approach (Atkins et al., 2004; GRADE Working group).

Data extraction was performed by one author and checked for accuracy by another. The results of each article were tabulated per outcome in Appendix 4. When possible, data were pooled and subjected to meta-analysis using RevMan 5.4. Unit of analysis was the patients. For most outcomes, meta-analysis was not possible due to heterogeneity in measures and follow-up time.

A summary result per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 9).

Patient involvement

Comments on the PICO and on the report were provided from a patient who had undergone breast reduction surgery and were considered in the formulation of the PICO and in the final report.

Ongoing research

A search in Clinicaltrials.gov (October 19, 2020) using the search terms ("Breast reduction" OR Reduction Mammoplasty OR Breast reduction OR Reduction Mastoplasty OR Gigantomastia Reduction OR Macromastia Reduction OR Hypermastia Reduction OR Large breast reduction OR breast assymmetry reduction OR Hypertrophic breast reduction) NOT (neoplasm OR tumor OR cancer OR malignant OR carcinoma) identified 91 trials.

9. Results

Search results and study selection

The literature search identified 1,355 articles after removal of duplicates. After screening titles and abstracts by two authors, 1,257 articles were excluded. Another 44 articles were excluded by two authors after reading the articles in full text. The remaining 54 articles were sent to all authors, and 15 articles were finally included in the assessment. A flowchart of the search results is presented in Appendix 1.

Included studies

Of the fifteen included articles, four were RCTs (reported in eight papers), three were cohort studies with a control group, three were case series, and one was a qualitative study (Appendix 2). The majority of the included studies compared surgical intervention with no treatment (C1). One study (Iwuagwu et al., 2006b) compared surgical intervention with physiotherapy (C2, non-surgical treatment). The RCTs had serious study limitations, indirectness, and/or imprecision. Methodological issues included unclear definition of breast hypertrophy, short follow-up, lack of blinding of patients or researchers, control groups constituting patients who were waiting for a breast reduction, and inter-group comparisons not being reported. Effects were measured using validated patient-reported outcome measures. The cohort studies had some study limitations in terms of poor evaluation of potential confounding, adherence, dropouts, and unclear definitions of breast hypertrophy. The qualitative study was assessed as being of moderate quality.

Results per outcome

Mortality (Appendix 4.1)

Three case series reported mortality. All three series are based on the NSQIP registry and therefore the cases are somewhat overlapping. No cases of 30-day mortality were reported by Fairchild et al. (2020) (0/283), Nelson et al. (2014) (0/2074), or by Simpson et al. (2019) (0/8108). However, one death was reported, by Fairchild et al. (2020), in the population with BMI>30 (not included in this HTA).

Complications (Appendix 4.2)

Three RCTs, one cohort study and three cases series based on register data reported surgical complications. The RCTs reported complications from the intervention groups. Reporting standards were heterogeneous, as complications were not predefined as, or divided into major and minor complications. Moreover, the articles did not state which complications were registered, how and by whom they were diagnosed, how they were defined, and whether registration was done prospectively or retrospectively. Detailed information regarding definitions of complications is given in Appendix 4.2.

For patients undergoing breast reduction the reported frequency of major complications varied from 2.4% to 14%, and frequency of minor complications from 2.4% to 69%. The lowest incidence was reported from a register study based on more than 8000 patients (Simpson et al., 2019) and the highest from an RCT with 40 patients in the intervention group (Saariniemi et al., 2008). The most severe complications reported were venous thromboembolism (0.2%, Nelson et al., 2014) and pulmonary embolism (3.4%, Saarinemi et al., 2008; 0.2%, Nelson et al., 2014), while the most frequent complications were surgical site infections and delayed wound healing. Two of the included studies showed that increased BMI was a risk factor for more complications (Fairchild et al., 2020; Nelson, et al., 2014).

Conclusion: The reported frequencies of complications after breast reduction in the included studies varied considerably and were often high. Minor complications are most frequent but severe complications also occur.

Health-related quality of life (Appendix 4.3)

Health-related quality of life was reported in three RCTs and two cohort studies. Two studies used the Short Form 6 Dimensions questionnaire (SF-6D) and three studies used the Short Form-36 Health Survey (SF-36) presenting both physical and mental summary scores, with two of the studies also using additional questionnaires. One study used the BREAST-Q questionnaire. Health-related quality of life was consistently improved for patients undergoing breast reduction mammoplasty when compared with the control group (no surgery) in all included studies.

Meta-analyses were performed for the studies using SF-6D and SF-36 (both physical and mental summary scores), including 142 and 155 patients, respectively (Figures 1-3). The weighted mean difference (WMD) for SF-6D (score range 0.29–1.0) was 0.14 (95% CI 0.10–0.17) six months after surgery. Minimal important difference (MID) for SF-6D has been suggested to be in the range of 0.01 to 0.10 (Walters and Brazier, 2005), implying that 0.14 is a clinically relevant difference in HRQoL. The WMD for the physical summary score of SF-36 was 7.0 (95% CI 4.4–9.5) and 9.8 (95% CI 6.2–13) for the mental summary score (both scores ranging 0–100), 4-6 months after surgery.

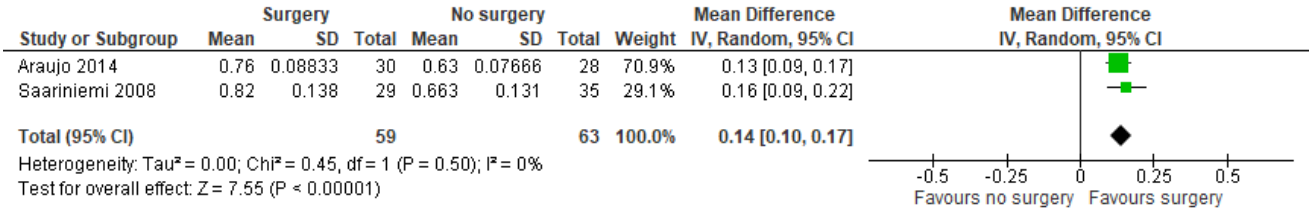

Figure 1. Meta-analysis of studies comparing reduction mammoplasty with no surgery.
Outcome: SF-6D (Health utility index score)

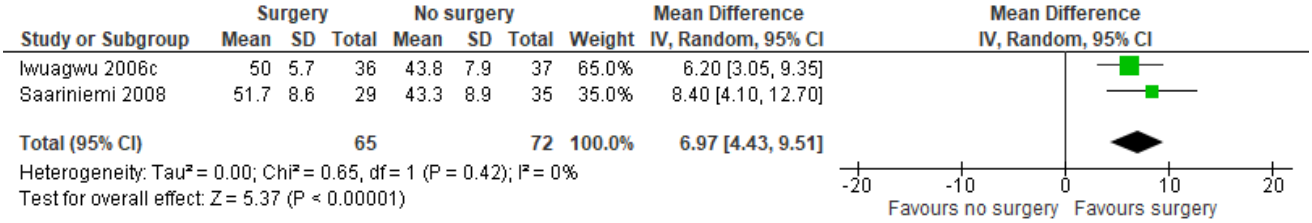

Figure 2. Meta-analysis of studies comparing reduction mammoplasty with no surgery.
Outcome: SF-36 (Physical summary score).

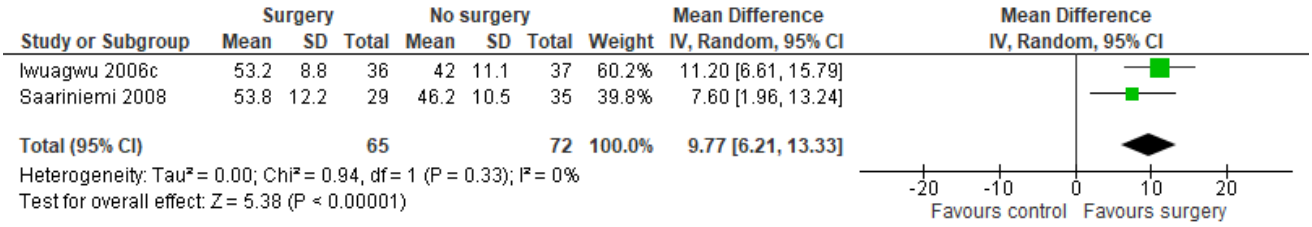

Figure 3. Meta-analysis of studies comparing reduction mammoplasty with no surgery.
Outcome: SF-36 (Mental summary score)

Conclusion: Breast reduction surgery compared with no surgery may result in a clinically relevant improvement in health-related quality of life in women with breast hypertrophy. Low certainty of evidence GRADE ⊕⊕◯◯).

Depressive symptoms (Appendix 4.4)

Depressive symptoms were reported in three RCTs (n= 215), all using different validated assessment tools and scores. Postoperative (4-6 months) depressive symptom rates were consistently lower in women undergoing breast reduction compared with no treatment or physiotherapy.

Beraldo and associates (2016) showed a difference in the BDI score (range 0–63) of 6.5 points six months after surgery (p=0.01) compared with no treatment (C1) (Beraldo et al., 2016). Converted to a percentage of the score in the control group this equals 6.5/14=53%, which is greater than the reported MID in BDI of 17.5% (Button et al., 2015). Iwuagwu et al. (2006b) showed a difference in the HADS depression score (range 0–3) of 0.4 points four months after surgery; p<0.001) compared with physiotherapy (C2), which equals a relative difference of 49%. This is just below the MID for HADS of 1.7 reported by Lemay et al. (2019), equalling a relative difference of 57%. Saarineemi et al. (2009) showed a difference in the RBDI (range 0–39) of 4 points four months after surgery (p<0.01), compared with no treatment (C1).

Conclusion: Breast reduction surgery compared with no surgery may result in a clinically relevant reduction in depressive symptoms in women with breast hypertrophy. Low certainty of evidence (GRADE ⊕⊕◯◯).

Anxiety symptoms (Appendix 4.5)
Anxiety symptoms were reported in two RCTs (n=155), using different validated assessment tools and scores. Postoperative anxiety symptom rates after four and six months were significantly lower in both studies (Iwuagwu et al., 2006b; Saarinemi et al., 2009) in women who had undergone breast reduction surgery. Iwuagwu et al. (2006b) presented a mean difference in HADS (range 0-21) of 4.6 points (p<0.001) four months after surgery in women undergoing breast reduction surgery compared to no treatment (C1), which exceeds the reported MID for HADS of 1.7 (Lemay et al., 2019). Saarinemi et al. (2009) showed a difference in RBDI (range 0-39) of 9 points (mean) (p=0.04) six months after surgery in women undergoing breast reduction surgery compared with physiotherapy (C2).

Conclusion: Breast reduction surgery compared with no surgery may result in a clinically relevant reduction in anxiety symptoms in women with breast hypertrophy.
Low certainty of evidence (GRADE ⊕⊕◯◯).

Sexuality-related outcomes (Appendix 4.6)
Sexuality-related outcomes were reported in one RCT and two cohort studies (n=262). All studies used different assessment tools and scores. Sexual function was significantly improved by breast reduction surgery compared with no surgical intervention in the RCT, as were sexual function, sexual well-being, and sexual quality of life in the cohort studies. Beraldo et al. (2016) reported a mean difference in FSFI (range 2-36) of 5.0 points six months after surgery (p<0.001), exceeding the reported MID of 4.2 (Krychman et al., 2018). Andrade et al. (2018) showed a mean difference in the sexual well-being domain of BREAST-Q (range 0-100) of 66 points up to 1 year after surgery (p=0.001), while Janik et al. (2019) reported a mean difference in SQoL-F (range 18-108) of 12 points (p<0.01), at an average of 24 months after surgery. All studies compared breast reduction surgery with no surgery (C1).

Conclusion: Breast reduction surgery compared with no surgery may result in a clinically relevant improvement in sexuality-related outcomes in women with breast hypertrophy.
Low certainty of evidence (GRADE ⊕⊕◯◯).

Work ability
Work ability was not reported in any of the included studies.

Sick leave
Sick leave was not reported in any of the included studies.

Physical function (Appendix 4.7)
Physical function was reported in two RCTs and two cohort studies (n=447), comparing patients with breast hypertrophy undergoing surgery and patients with breast hypertrophy with no surgical intervention. One RCT reported physical function in two papers (Neto et al., 2008; Freire et al., 2007). Physical function was assessed through different validated scales. Both RCTs had a follow-up of six months and both reported a significant improvement in physical function after surgery compared with controls. Freire et al. (2007) reported a mean difference in HAQ-20 score (range 0-3) of 0.34 points ($p<0.001$) six months after surgery. Neto et al. (2018), showed a mean difference in the Roland Morris questionnaire (range 0-24) of 5.0 points ($p<0.001$) six months after surgery. Saarimemi et al. (2008) reported a mean difference in SF-36 score of 8.4 points 4 (95% CI 5.8 to 12; $p<0.0001$) 6 months after surgery. The two cohort studies reported a significant intergroup difference in physical well-being ($p=0.001$), physical function ($p<0.05$), and daily activities ($p<0.005$). Andrade et al. (2018) describes a mean difference in Breast-Q score regarding physical function (range 0-100) of 31 points ($p=0.001$) after up to 12 months. Hermans et al. (2005) describes a significant mean difference in SF-36 score (range 0-100) of 7.3 points ($p<0.005$) and a 26% difference in patients reporting "no problems" regarding daily activities in the EQ-5D-questionnaire after up to 24 months. All studies compared breast reduction surgery with no surgery (C1).

Conclusion: It is uncertain whether breast reduction surgery compared with no surgery affects physical function in women with breast hypertrophy.
Very low certainty of evidence (GRADE ⊕◯◯◯).

Pain (Appendix 4.8)
Pain was reported in three RCTs and one cohort study (n= 420). All studies used different assessment tools with pain scores being part of HRQoL questionnaires. The RCTs all reported significantly reduced pain after breast reduction surgery compared with no surgery and the cohort study reported a significant decrease in pain-related outcomes after breast reduction surgery compared with no surgery (C1). Iwuagwu et al. (2006c) reported a mean difference in EQ-5D score (range 1-3) of 0.59 points four months after surgery ($p<0.001$), which exceeds the reported MID of 0.03 for the scale (Soer et al., 2012). Saarinemi et al. (2008), showed a mean difference in FBAS score (range 0-100) of 46 points ($p<0.0001$) and in FPQ score (range 0-100) of 20 points ($p<0.0001$), both six months after surgery. Freire et al. (2007) report differences in VAS (range 0-10) of 4 points ($p<0.001$) for lower back pain, 5.8 points ($p<0.001$) for shoulder pain and 4.2 points ($p< 0.001$) for neck pain, all six months after surgery. Reported MID for VAS is 0.9 points (Kelly, 1998). Hermans et al. (2005) describes a significant mean difference of 21 points ($p<0.001$) in SF-36 (range 0-100), a 38% difference in the number of patients reporting "no pain" in the EQ-5D questionnaire, and a 66% difference in patients reporting "almost never" in response to feeling pain in the DAS-59 questionnaire two years after surgery.

Conclusion: Breast reduction surgery compared with no surgery may result in a clinically relevant reduction of pain in women with breast hypertrophy.
Low certainty of evidence (GRADE ⊕⊕◯◯).

Experiences of having breast reduction surgery (Appendix 4.9)
One qualitative study reported women's experiences of having breast reduction surgery. The most common experienced advantages of breast reduction included increased physical activity, an increased choice in clothes, and a belief that they now cost the healthcare system less. The most common experienced disadvantages included scarring and loss of sensibility.

Conclusion: The women's experiences of breast reduction surgery were predominantly positive, with perceived improvement in both physical and mental wellbeing. Disadvantages included scarring and loss of sensibility.

10. Ethical aspects

Breast reduction surgery seems to improve health related quality of life, with the indications used in these studies. Indications for publicly funded breast reduction surgery is, however, the issue at hand. The lack of consensus regarding the definition of breast hypertrophy contributes to a large variability in indications from country to country and sometimes even from clinic to clinic, meaning that a breast volume accepted for reduction mammoplasty at one clinic might not be accepted at another clinic in a different region within the same public healthcare system. This variability in indications creates differences in both the amount of breast tissue removed and the proportion of the breast that is resected, which not only may affect the results of the procedure but also constitutes an ethical dilemma in that women are offered unequal treatment. Furthermore, no data are published on survival and this question has not been discussed at all.

We could not identify any high-quality studies. The studies included in this HTA report point in the same direction and indicate that breast reduction surgery has a positive effect on several of the endpoints defined in our PICO. Also, most studies have compared women who have had surgery with women still on a waiting list. This might influence the results, with women undergoing surgery being pleased for not having to wait. The short follow-up in many of the studies is also problematic as long-term effects (e.g. 24 months) might differ from those after six months. It would be interesting to study the cost effectiveness of breast reduction surgery. If resources are spent on a condition that could be described as not severe, a reduction in sick leave could perhaps regain the costs. However, as stated in chapter 12, no such studies are available.

The severity of breast hypertrophy can be experienced very differently in different persons. It can also be a pure cosmetic problem, rather than physically symptomatic. Performing a reduction mammoplasty based on too wide indications could affect the health of a third party if the procedure is occupying time in the operating theatre that could otherwise have been used for performing procedures with more evidence-based indications. Performed on strict indications it may not have any negative affect on the health of a third party. We have not identified anything that would violate the Human Dignity principle and that would violate the Swedish Discrimination act, as only women undergo reduction mammoplasty. In our PICO we excluded men and the operation performed for gynecomastia, as this is considered cosmetic surgery. Breast reduction surgery does not affect the patients' autonomy or integrity or that of their relatives in a negative way. It can be discussed whether there is evidence to suggest that the costs and effects of surgery are reasonable balanced.

The number of patients accepted for breast reduction surgery could be affected by resource and organisational limitations as the procedure is performed by the national health care and covered by health insurance. The procedure must be subjected to prioritisation, as all other non-life threating conditions. Accepting patients for reduction mammoplasty on too wide indications will consume resources that could otherwise have been spent elsewhere in the health care system. If, e.g., surgeons working both in the national health care system and as private entrepreneurs, are involved in this process they might give the procedure a lower priority with the intention to do theses surgeries in the private sector.

We have no data regarding long-term consequences. We do not know if post-surgery scarring of the breast gland might cause breast cancer diagnostic problems. Also, we do not know if breast reduction surgery affects survival.

To summarise, breast reduction surgery for breast hypertrophy is associated with several ethical issues. There is only limited evidence for the effectiveness and safety of the procedure. Indications for surgery are poorly defined and vary across studies.

11. Organisational aspects

Time frame for the putative introduction of the new health technology

Breast reductions are already performed within the public healthcare system in Sweden and at SU.

Present use of the technology in other hospitals in Region Västra Götaland

The majority of bilateral breast reductions performed due to breast hypertrophy are performed at SU. Therapeutic breast reductions and unilateral breast reductions as a symmetrising procedure after breast cancer are performed in most hospitals in VGR.

Consequences of the new health technology for personnel

Not applicable.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

Not applicable.

12. Economic aspects

The information in this section is based on operations performed in accordance with the current national Swedish guidelines. The number of operated patients annually could change if the criteria are changed, for example with regard to volume or BMI.

Present costs of the intervention health technology

Based on data from the SU in 2019 the cost per patient for breast reduction surgery varied from about 41,700 SEK to 82,600 SEK with a mean cost per patient of 58,000 SEK. This cost includes all costs for the surgery and costs related to any postoperative complications (e.g. hospital admission), but not any later revisits after discharge caused by complications.

Total difference in costs between breast reduction and no treatment

With around 100 annual operations and a cost per patient (per operation) of 58,000 SEK, the total difference in economic cost between breast reduction and no intervention is about 5.8 million SEK per year. If breast reduction surgery improves health-related quality of life and reduces depressive symptoms it is possible that such surgery may reduce future healthcare utilisation (and associated costs). Due to lack of data we have not included any such potential effects in the cost numbers reported above.

Possibility to adopt and use the technology within the present budget

Breast reduction surgery is currently used within the present budget. Given the higher healthcare costs for surgery compared with no intervention, as outlined above (at least in the short-term), the use of the surgery displaces other healthcare services.

Available economic evaluations or cost advantages/disadvantages

A total of five health economic articles were identified in the literature search, of which one was based on Swedish data from 1997 (Taylor et al., 2004) and two were based on data from Finland (Saariniemi et al., 2012; Tykkä et al., 2010). The studies generally reported results in terms of the cost per gained quality adjusted life year (QALY) that were very low, and in the range where they would be considered very cost-effective in relation to Swedish and Finnish health policy guidelines. However, the studies were all based on small sample sizes, assessed QALY benefits by the within-patient difference in HRQoL after-before the treatment (i.e. lacking control group) and partly made optimistic assumptions that the HRQoL benefits would last the rest of the lifetime. The studies did not specify a definition of the population or the condition. In sum, even though these studies reported favourable cost-effectiveness results, they should be interpreted very cautiously for the relevance of the PICO in this report.

13. Discussion

Summary of main results

The aim of this Health Technology Assessment was to study the effectiveness and safety of breast reduction surgery in women with breast hypertrophy, with an underlying focus on identifying specific indications for surgery related to breast size. The results showed that complications are frequent after breast reduction surgery, and that the risk for complications increases with a BMI>30. Regarding effects, breast reduction surgery may improve HRQoL and may reduce depressive symptoms, anxiety symptoms, and pain, compared with no surgery. It is uncertain whether breast reduction surgery improves physical function. Women's experiences of breast reduction surgery were predominantly positive, although postoperative infections and scarring also were reported.

Overall completeness and applicability of evidence

Several methodological limitations were identified in all included studies. Main issues included a lack of, or inconsistent, definition of breast hypertrophy and patients that are biased towards wanting a breast reduction, as well as short follow-up, lack of blinding, control groups being patients on a waiting list for a breast reduction, and that inter-group results sometimes were not reported. The results regarding the effect of breast reduction surgery on depression should be interpreted with caution, as the baseline values generally indicated no or mild depression.

None of the studies stated how complications were defined and whether they had been registered in a systematic and prospective fashion or not, which might explain the extraordinarily wide range of complication frequencies seen in the studies. Similar methodological problems have been seen previously in studies on breast reduction, where most studies only register surgical site complications in an undefined way and overall complication rates therefore often are underestimated (Winter et al., 2017). In one of few publications (Winter et al., 2017) on breast reduction where complications were classified according to a validated system, the complication frequency was 63%, albeit retrospectively registered. A prospective approach could give an even higher complication frequency. The most common type of complication (46%) was wound healing complications (Winter et al., 2017). The study by Winter and associates was not included in this review as the number of reported patients were 486, and the inclusion requirement of >1000 patients for case series was therefore not met. In this HTA, the lower complication rates are from publications reporting figures from the NSQIP registry (Fairchild et al., 2020; Nelson et al. 2014; Simpson et al, 2019). In the registry, wound complications are defined as "superficial infection, deep wound infection, deep or organ space infection, and wound dehiscence" (Simpson et al., 2019).

In Winter et al's study, the rate of such wound complications was 9%, and the rate of milder wound complications, not requiring an intervention, such as antibiotics or debridement, was 48%. Indeed, the studies included in this report with higher complications rates seem to have included all types of wound complications. Hence, complications are common but reported frequencies are dependent on how complications are defined and classified, which could explain the wide range of frequencies in this report.

Although a few definitions of breast hypertrophy exist (Sacchini et al., 1991; Ringberg et al., 2006; Abdiu et al., 2008), none of them have been validated as tools for prognostic purposes or as basis for indications for surgery. The clinical relevance of the definitions has never been investigated; that is, the relation between the definitions and physical and psychosocial problems have never been studied. Nonetheless, symptom relief does not seem to be correlated to the amount of tissue resected (Spector et al., 2008). Among the included studies, five described which definition of breast hypertrophy they had used, whereas ten articles did not. None of the used definitions has been validated, and therefore, we know very little about the severity of the breast hypertrophy in the women who were operated upon in the studies. Moreover, only seven of the studies reported the amount of breast tissue resected during the operations, which further complicates the evaluation of the effects of the intervention in relation to the severity of breast hypertrophy. The distinction between which patients should be operated on in the public healthcare system for 'medical reasons', and which patients should be referred to the private sector, is a well-known problem in plastic surgery (Sandman and Hansson, 2020).

In all included RCTs, patients who wanted a breast reduction were randomised to either surgery or to a waiting list for a breast reduction. Therefore, all the patients were biased towards a wish for a breast reduction and all the controls knew that they would receive a breast reduction eventually. It can be discussed whether such patients adequately represent an untreated control group. The practice also implies both unblinded patients and doctors.

Another issue limiting the directness of the results, is the short follow-up time in the included studies. According to basic plastic surgical principles, a final result can never be evaluated before at least a year has passed (Bond et al., 2008). Most of the included studies had a follow-up time of less than one year, and therefore the effects have not been measured on the final outcome of surgery. Patients who are treated with surgery they have requested themselves, initially experience a positive effect of the surgery that might diminish over time (Beard et al., 2013). Moreover, two of the four RCTs were conducted in Brazil, where cultural/aesthetic norms and perceived need for breast reduction surgery might differ from Sweden.

Agreements and disagreements with other studies and reviews

Our findings are in agreement with previous studies (Klassen et al., 1996; Chadbourne et al. 2001; Mello et al., 2010; Lewin et al., 2019). Previous studies and reviews present similar methodological limitations to those that are described in the present HTA.

Agreements and disagreements with the current Swedish guidelines

Regarding the validity of the current Swedish guidelines for a breast reconstruction (Breast volume > 800 ml per breast, physical and psychosocial symptoms of breast hypertrophy, BMI ≤ 25 for women < 50 years and ≤ 27 for women ≥ 50 years of age, and smoking cessation at least 4 weeks pre- and post-operatively) (Abdiu et al., 2008), none of studies fulfilling the PICO specifically studied the impact of different breast volumes on the effect and safety of breast reconstruction. However, the case series on complications clearly showed that a BMI equal to or higher than 30 increases the risk for complications by three-fold (Fairchild et al., 2020; Nelson et al., 2014). Moreover, the most serious complications, such as pulmonary embolism (Saariniemi et al., 2008) and death (Fairchild et al., 2020), occurred in patients with a high BMI.

Nonetheless, even though a high BMI clearly increases the risk for complications, there is no evidence on exactly where the BMI limit should be drawn. None of the included studies specifically included an analysis of women smoking. However, smoking is a known risk factors for wound healing complications (Pluvy et al., 2014), a type of complication that was very common in all of the included studies, indicating that all risk factors for wound healing problems should be eliminated. In summary, there is neither any specific evidence that the volume cut off should be 800 ml, nor that the BMI cut off should be 25/27, in all women.

Implications for research

Our findings imply that a study of definitions of breast hypertrophy, and clinical validation of them, are essential prerequisites for the development of evidence-based guidelines for breast reduction in the public healthcare system.

14. Future perspectives

Scientific knowledge gaps

There is a lack of high-quality studies that evaluate the results of breast reduction surgery and include a definition of breast hypertrophy. A breast reduction seems to have positive effects for women, but it is unclear which women benefit the most and which women should be offered a breast reduction in the public healthcare system.

To enable a more appropriate selection of patients that should be offered breast reduction surgery, future studies should focus on:

- Long-term efficacy
- The definition of breast hypertrophy and correlation with physical and mental symptoms.
- Cost-utility of breast reduction surgery compared with no surgery.
- Validation of definitions and classifications of complications after breast reduction.

There is also a need for more research on women's experiences before and after breast reduction surgery.

Ongoing research (Appendix 5)

The search in Clinicaltrials.gov 2020-10-19 identified 91 trials. Four of them were relevant for the PICO and the question at issue. Among those four, one was terminated and three were completed. Two trials, Beraldo et al. (2016) and Araujo et al. (2014), have been published and are included in the present HTA report and two are unpublished, thus far.

Of the two unpublished studies, one is an uncontrolled cohort study focusing on aesthetic outcome after breast reduction and mastopexy (NCT02016677) and the other is an RCT on physical activity and sexuality (NCT01297621).

15. Participants in the project

The question was nominated by

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Participating healthcare professionals

Håkan Hallberg, MD, PhD
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Max Petzold, Statistician, Professor
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All from Region Västra Götaland, HTA-centrum, Gothenburg, Sweden

Quality assurance meeting took place on 16 December 2020.

External reviewers

Michael Breimer, MD, PhD, Professor emeritus, University of Gothenburg, Sahlgrenska Academy, Department of Surgery, Gothenburg, Sweden
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Declaration of interests

None of the authors have any conflicts of interests to declare.

Project time

The HTA was accomplished during the period of 28 May 2020 – 20 January 2021.
Literature searches were made on 10 June 2020.

Appendix 1: PICO, study selection, search strategies, and references

Question(s) at issue:
Is breast reduction surgery better than no surgery, in women with symptomatic breast hypertrophy and a BMI of ≤ 35, regarding HRQoL, depressive symptoms, anxiety symptoms, sexuality-related outcomes, work ability, sick leave, physical function, pain, and patient experience, and is it safe?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P	Women who seek health care for symptomatic breast hypertrophy with a BMI ≤ 35
I	Breast reduction surgery
C	C1: No treatment C2: Non-surgical treatment
O	**<u>Critical for decision-making</u>** Mortality Complications HRQoL (measured with validated scales) **<u>Important for decision-making</u>** Depressive symptoms (measured with validated scales) Anxiety symptoms (measured with validated scales) Sexuality-related outcomes (measured with validated scales) Work ability (measured with validated scales) Physical function (measured with validated scales) Pain (measured with validated scales) Sick leave Experiences of having a breast reduction

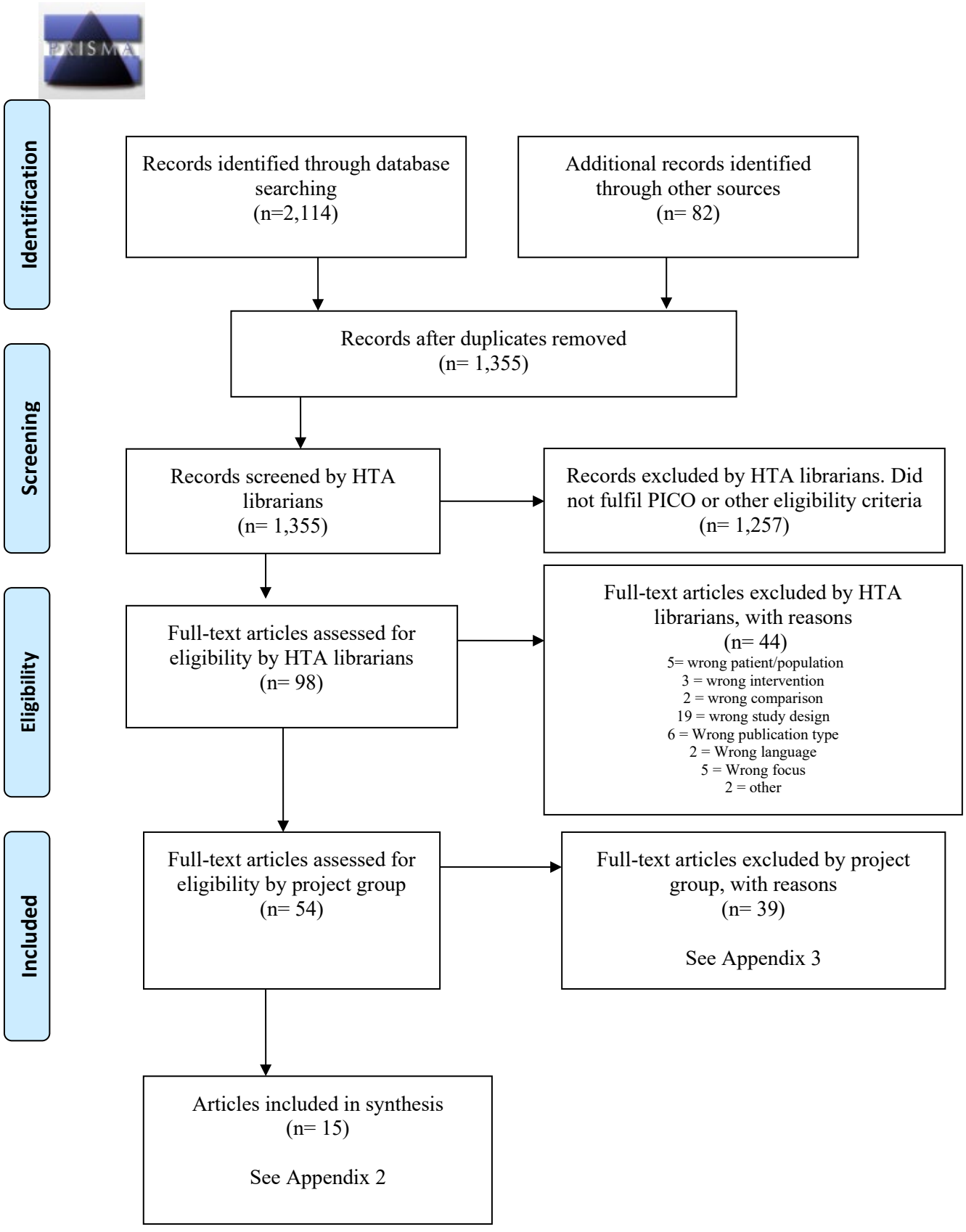
<u>Eligibility criteria</u>

Study design:
Systematic reviews (only commented on)
Randomised controlled trials
Non-randomised controlled studies ≥ 100 patienter
Case series if ≥ 1000 patients (only complications)
Case series (concerning death)
Qualitative studies

Language:
English, Swedish, Norwegian, Danish

Publication date: 1990-

Selection process – flow diagram



Modified from Moher et al., 2009

Database: Medline (OVID) Ovid MEDLINE(R) ALL 1946 to June 09, 2020
Date: 10 June 2020
No. of results: 934

#	Searches	Results
1	((Hypertrophy or Hypertrophies or Hypertrophied or Hyperplasia* or Asymmetr*) adj6 (Breast or Breasts or Mammary or Mammae or Mammaries)).ab,kf,ti.	2974
2	Hyperplasia/ or Hypertrophy/	54032
3	exp Breast/ or (Breast or Breasts or Mammary or Mammae or Mammaries).ab,kf,ti.	487688
4	2 and 3	3452
5	(Gigantomast* or Macromastia or Hypermastia or Large breast* or Hypertrophic breast*).ab,kf,ti.	1327
6	1 or 4 or 5	6161
7	Mammaplasty/ or (Mammaplast* or Mammoplast* or Mastoplast*).ab,kf,ti.	13845
8	(Correct* and (surg* or operative or operation* or procedur*)).ab,kf,ti.	149990
9	(Reduction or Reductions).ab,kf,ti.	1118093
10	7 or 8 or 9	1269430
11	6 and 10	1548
12	(animals not (animals and humans)).sh.	4672771
13	11 not 12	1513
14	(Cancer* or Malign* or Tumor* or Tumour* or Carcinom* or Sarcom* or Neoplasm* or Oncol* or Oncoplast* or oncogen* or Chemotherap* or Chemoradiotherap* or Radiochemotherap* or Chemoradiation or Immunoradiotherap* or Irradiation or Beamtherap* or Radiotherap* or Carcinogen* or Radiation*).ti.	2283937
15	13 not 14	1311
16	limit 15 to (yr="1990 -Current" and (danish or english or norwegian or swedish))	1004
17	(comment or editorial or letter).pt.	1853775
18	**16 not 17**	**934**

Database: PubMed
Date: 10 June 2020
No. of results: 204

Search	Query	Results
#26	**Search:** #23 AND #24 **Filters:** Danish, English, Norwegian, Swedish, from 1990 - 2020	**204**
#24	Search: (pubmednotmedline[sb] OR inprocess[sb] OR publisher[sb]) Filters: Danish, English, Norwegian, Swedish	4,165,856
#23	Search: #12 AND #18 Filters: Danish, English, Norwegian, Swedish	1,386
#19	Search: #12 AND #18	1,541
#18	Search: #13 OR #16 OR #17	1,258,672
#17	Search: Reduction[Title/Abstract] OR Reductions[Title/Abstract]	1,114,634
#16	Search: #14 AND #15	151,523
#15	Search: Surg*[Title/Abstract] OR Operative[Title/Abstract] OR Operation*[Title/Abstract] OR Procedur*[Title/Abstract]	3,099,145
#14	Search: Correct*[Title/Abstract]	625,328
#13	Search: Mammaplast*[Title/Abstract] OR Mammoplast*[Title/Abstract] OR Mastoplast*[Title/Abstract]	3,857
#12	Search: #9 or #10	9,067

#10	Search: Gigantomast*[Title/Abstract] OR Macromastia[Title/Abstract] OR Hypermastia[Title/Abstract] OR Large breast*[Title/Abstract] OR Hypertrophic breast*[Title/Abstract]	1,321
#9	Search: #7 and #8	7,928
#8	Search: Breast[Title/Abstract] OR Breasts[Title/Abstract] OR Mammary[Title/Abstract] OR Mammae[Title/Abstract] OR Mammaries[Title/Abstract]	479,119
#7	Search: Hypertrophy[Title/Abstract] OR Hypertrophies[Title/Abstract] OR Hypertrophied[Title/Abstract] OR Hyperplasia*[Title/Abstract] OR Asymmetr*[Title/Abstract]	323,703

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Database: Embase (OVID) 1974 to 2020 June 09
Date: 10 June 2020
No. of results: 911

#	Searches	Results
1	((Hypertrophy or Hypertrophies or Hypertrophied or Hyperplasia* or Asymmetr*) adj6 (Breast or Breasts or Mammary or Mammae or Mammaries)).ab,kw,ti.	3720
2	exp breast hyperplasia/	2532
3	exp breast hypertrophy/	1237
4	(Gigantomast* or Macromastia or Hypermastia or Large breast* or Hypertrophic breast*).ab,kw,ti.	1659
5	1 or 2 or 3 or 4	7301
6	exp breast reduction/	3015
7	(Correct* and (surg* or operative or operation* or procedur*)).ab,kw,ti.	204212
8	(Reduction or Reductions).ab,kw,ti.	1487672
9	(Mammaplast* or Mammoplast* or Mastoplast*).ab,kw,ti.	4770
10	6 or 7 or 8 or 9	1680968
11	5 and 10	1859
12	(animal not (animal and human)).sh.	1067242
13	11 not 12	1853
14	(Cancer* or Malign* or Tumor* or Tumour* or Carcinom* or Sarcom* or Neoplasm* or Oncol* or Oncoplast* or oncogen* or Chemotherap* or Chemoradiotherap* or Radiochemotherap* or Chemoradiation or Immunoradiotherap* or Irradiation or Beamtherap* or Radiotherap* or Carcinogen* or Radiation*).ti.	2845991
15	13 not 14	1529
16	**limit 15 to ((danish or english or norwegian or swedish) and yr="1990 -Current" and (article or article in press or conference paper or note or "review"))**	**911**

Database: The Cochrane library
Date: 10 June 2020
No. of results: 35
Trials (35)

ID	Search	Hits
#1	(((Hypertrophy or Hypertrophies or Hypertrophied or Hyperplasia* or Asymmetr*) NEAR/6 (Breast or Breasts or Mammary or Mammae or Mammaries)))	216
#2	MeSH descriptor: [Hyperplasia] this term only	611
#3	MeSH descriptor: [Hypertrophy] this term only	602
#4	#2 OR #3	1203
#5	MeSH descriptor: [Breast] explode all trees	732
#6	(Breast or Breasts or Mammary or Mammae or Mammaries):ti,ab,kw (Word variations have been searched)	47411
#7	#5 OR #6	47418
#8	#4 AND #7	59
#9	(Gigantomast* or Macromastia or Hypermastia or Large NEXT breast or Hypertrophic NEXT breast):ti,ab,kw (Word variations have been searched)	80
#10	#1 OR #8 OR #9	310
#11	MeSH descriptor: [Mammaplasty] this term only	265
#12	(Mammaplast* or Mammoplast* or Mastoplast*):ti,ab,kw (Word variations have been searched)	386
#13	((Correct* and (surg* or operative or operation* or procedur*))):ti,ab,kw (Word variations have been searched)	15378
#14	Reduction or Reductions	183549
#15	#11 OR #12 OR #13 OR #14	196997
#16	#10 AND #15	95
#17	Cancer* or Malign* or Tumor* or Tumour* or Carcinom* or Sarcom* or Neoplasm* or Oncol* or Oncoplast* or oncogen* or Chemotherap* or Chemoradiotherap* or Radiochemotherap* or Chemoradiation or Immunoradiotherap* or Irradiation or Beamtherap* or Radiotherap* or Carcinogen* or Radiation*	250894
#18	#16 NOT #17	50
#19	(clinicaltrials or trialsearch):so	327468
#20	#18 NOT #19 with Cochrane Library publication date Between Jan 1990 and Jun 2020	35

Database: APA PsycInfo
Date: 10 June 2020
No. of results: 30

#	Undran	Resultat
S15	**S12 NOT S13 Avgränsare - Publikationsdatum: 19900101-20200631; Språk: Danish, English, Norwegian, Swedish;**	**30**
S14	S12 NOT S13	39
S13	TI Cancer* or Malign* or Tumor* or Tumour* or Carcinom* or Sarcom* or Neoplasm* or Oncol* or Oncoplast* or oncogen* or Chemotherap* or Chemoradiotherap* or Radiochemotherap* or Chemoradiation or Immunoradiotherap* or Irradiation or Beamtherap* or Radiotherap* or Carcinogen* or Radiation*	46,067
S12	S5 AND S11	71
S11	S6 OR S7 OR S10	145,466
S10	S8 AND S9	13,232
S9	TI correct* OR AB correct* OR KW correct*	136,403
S8	TI (surg* or operative or operation* or procedur*) OR AB (surg* or operative or operation* or procedur*) OR KW (surg* or operative or operation* or procedur*)	298,295
S7	TI (Reduction OR Reductions) OR AB (Reduction OR Reductions) OR KW (Reduction OR Reductions)	132,666
S6	TI (Mammaplast* or Mammoplast* or Mastoplast*) OR AB (Mammaplast* or Mammoplast* or Mastoplast*) OR KW (Mammaplast* or Mammoplast* or Mastoplast*)	36
S5	S3 OR S4	1,039
S4	S1 AND S2	67
S3	TI (Gigantomast* OR Macromastia OR Hypermastia OR Large breast* OR Hypertrophic breast*) OR AB (Gigantomast* OR Macromastia OR Hypermastia OR Large breast* OR Hypertrophic breast*) OR KW (Gigantomast* OR Macromastia OR Hypermastia OR Large breast* OR Hypertrophic breast*)	976
S2	TI (Breast or Breasts or Mammary or Mammae or Mammaries) OR AB (Breast or Breasts or Mammary or Mammae or Mammaries) OR KW (Breast or Breasts or Mammary or Mammae or Mammaries)	18,868
S1	TI (Hypertrophy or Hypertrophies or Hypertrophied or Hyperplasia* or Asymmetr*) OR AB (Hypertrophy or Hypertrophies or Hypertrophied or Hyperplasia* or Asymmetr*) OR KW (Hypertrophy or Hypertrophies or Hypertrophied or Hyperplasia* or Asymmetr*)	29,100

The web-sites of **SBU** and **Folkehelseinstituttet** were visited
10 June 2020
Nothing relevant to the question at issue was found

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Appendix 2 – Characteristics of included studies

Author Year Country	Study design	Study duration (years) Follow-up (mean number of months)	Study groups; Intervention and control treatment	Patients (n)	Mean age (years)	Mean BMI	Smokers (n, %)	Definition of breast hypertrophy	Resection weight, g (mean)	Outcome variables (Appendix)
Araujo 2014 Brazil	RCT (cost-utility)	SD: NR FU: 6	I: Breast reduction surgery; conventional technique (inverted T-shaped scar and medial pedicle technique in most patients) C1: No treatment	60 I: 30 C: 30 >BMI 30 excluded)	I:32 C:35.5 (median)	I: 26.4 C: 26.3 (median)	NR	Classification by Sacchini et al	1200	HRQoL (4.3)
Beraldo 2016 Brazil	RCT (same RCT as above)	As above	As above	As above	As above	As above	NR	As above	As above	Depression (4.4) Sexual function (4.6)
Freire 2007 Brazil	RCT	SD: NR FU: 6	I: Breast reduction surgery; rigid outlining, transferring to opposite breast, preservation of papillary-areeola complex using fatty deral pedicle. Inverted T-shaped scar C1: Waiting list for reduction mammaplasty 6 months later	100 I: 50 C: 50 >BMI 30 excluded)	31.95	25.56	0	NR	1052.19	Complications (4.2) Physical function (4.7) Pain (4.8)
Neto 2008 Brazil	RCT (same RCT as above)	SD: 2.08 FU: 6	As above	As above	As above	As above	0	NR	As above	Physical function (4.7)

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Appendix 2 – Characteristics of included studies

Author Year Country	Study design	Study duration (years) Follow-up (mean number of months)	Study groups; Intervention and control treatment	Patients (n)	Mean age (years)	Mean BMI	Smokers (n, %)	Definition of breast hypertrophy	Resection weight, g (mean)	Outcome variables (Appendix)
Iwuagwu 2006b UK	RCT	SD: 1.67 FU: 4	I: Bilateral breast reduction surgery with an inferior pedicle C2: Physiotherapist-instructed upper body exercise 3 times/week while on wait list for surgery	73 I: 36 C: 37 No restriction related to BMI	39.15	28.5	NR	Bra cup size E or more in conjunction with symptoms in the upper body associated with mammary hypertrophy.	NR	Depression (4.4) Anxiety (4.5)
Iwuagwu 2006c UK	RCT (same RCT as above)	As above	As above	73 I: 40 C: 73	As above	As above	NR	As above	NR	Complications (4.2) HRQoL (4.3)
Saarinemi 2008 Finland	RCT	SD: NR FU: 6.35	I: Breast reduction surgery C1: Waiting list	82 I: 40 C: 42 No restriction related to BMI	46.35	29.65	NR	NR	670	HRQoL (4.3) Physical function (4.7) Pain (4.8)
Saarinemi 2009 Finland	RCT (same RCT as above)	As above	As above	As above	As above	As above	NR	NR	As above	Depression (4.4) Anxiety (4.5)
Andrade 2018 Brazil	Cohort	SD: 1 FU: 6 -12	I: Breast reduction surgery C1: Waiting list	100 I: 50 C: 50 BMI<30	I: 33 C: 31 (median)	I: 27 C: 26 (median)	NR	"By the criteria by Sacchini et al and Franco & Rebello"	1107	HRQoL (4.3) Sexuality-related outcomes (4.6) Physical function (4.6)
Hermans 2005 Netherlands	Cohort	SD: 2 FU: 25.4 (mean, intervention group)	I: Breast reduction surgery, modified Strömbäck procedure with mediocranial pedicle C1: Waiting list	165 I:94 C:71 BMI<30	37.3	25.65	NR	Cup size D or above	536	HRQoL (4.3) Physical function (4.6) Pain (4.8)

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Appendix 2 – Characteristics of included studies

Author Year Country	Study design	Study duration (years) Follow-up (mean number of months)	Study groups; Intervention and control treatment	Patients (n)	Mean age (years)	Mean BMI	Smokers (n, %)	Definition of breast hypertrophy	Resection weight, g (mean)	Outcome variables (Appendix)
Janik 2019 Poland	Cohort	SD: 0.25 months FU: 23.56 (mean)	I: Breast reduction surgery C1: Waiting list	102 I:75 C: 27	38	27.5	24%	NR	NR	Complications (4.2) Sexuality-related outcomes (4.6)
Fairchild 2020 USA	Case series	SD: 7 FU: 1	I: Breast reduction surgery	283 (not obese, (BMI<30);Not included because BMI<35 not separately reported: 259 (obese, BMI>30, range 32-38)	17 (median)	26 (median)	NR	NR	NR	Mortality (4.1) Complications (4.2)
Nelson 2014 USA	Case series	SD; 7 FU: 1	I: Breast reduction surgery	2074 (BMI<30); 1308 (BMI 30-34.9)	NR	NR	10%	NR	NR	Mortality (4.1) Complications (4.2)
Simpson 2019 USA	Case series	SD: 10 FU: 1	I: Breast reduction surgery	8180 (BMI <30); 4656 (BMI 30.1-35)	NR (solely reported for total cohort)	NR (solely reported for total cohort)	NR	NR	NR	Mortality (4.1) Complications (4.2)
Shakespeare 1999 UK	Qualitative	SD: 2,75 FU: 24	I: Breast reduction surgery	110	35	NR	NR	NR	NR	Experiences of breast reduction (4.9)

RCT: Randomised controlled trial; NR: Not reported; SD: Study duration; FU: Follow-up; BMI: Body mass index; HRQoL: Health-related quality of life

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Appendix 3. Excluded studies

Author, year	Reason for exclusion
Aravind, 2020	Wrong population; unclear BMI
Blaine, 2012	Wrong study design, unclear population
Chadbourne, 2001	Unclear population
Collins, 2002	Wrong population; unclear BMI
Crittenden, 2020	Unclear population; BMI <35 not reported separately
Crittenden, 2019	Case series n < 1000
Cruz, 2007	Wrong outcome
Cruz-Korchin, 2004	Wrong outcome
Eggert, 2009	Case series n < 1000
Fischer, 2014a	Duplicate data set
Fischer, 2014b	Duplicate data set
Fonseca, 2018	Wrong comparator, wrong outcome
Gust, 2013	Duplicate data set
Iwuagwu, 2005	Wrong outcome
Iwuagwu, 2006a	Wrong outcome
Karamanos, 2015	Wrong population; BMI partially >35 (BMI <35 not reported separately)
Kerrigan, 2002	Wrong population; BMI <35 not reported separately
Kordahi, 2015	Unclear population
Lonie, 2019	Unclear population
Manahan, 2015	Wrong population; BMI <35 not reported separately
Mian, 2020	Unclear population; BMI not reported
Nelson, 2014b	Duplicate data set
Nuzzi, 2017	Case series n < 1000
Ovadia, 2018	Unclear population, wrong comparison
Papanastasiou, 2019	Unclear population
Reardon, 2011	Unclear population; BMI not reported
Romeo, 2010	Wrong comparator; healthy women
Saariniemi, 2012	Wrong study design; cost utility
Sharma, 2014	Case series n <1000

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Appendix 3. Excluded studies

Author, year	Reason for exclusion
Shermak, 2011	Unclear population; BMI not reported
Singh, 2012	Unclear population and wrong outcome
Taylor, 2004	Wrong study design; cost effectiveness
Thoma, 2014	Wrong study design; cost effectiveness
Tykkä, 2010	Case series not reporting complications
Vairinho, 2018	Unclear population, wrong intervention and wrong outcome
Waltho, 2020	Wrong outcome, wrong population
Vidaeff, 2003	Wrong study design; case report
Woodman, 2007	Unclear population
Zhang, 2016	Wrong population; BMI <35 not reported separately (also: all case series with <1000 patients, except Nelson 2014 which is already included)

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.1
Outcome variable: Mortality

Author year country	Study design (scope)	Number of patients n=	With drawals - dropouts	Results	Comments	Directness*	Study limitations*	Precision*
				Reduction mammaplasty				
Fairchild 2020 USA	Case series	283 BMI<30	NA	30-day mortality: 0	NSQIP 2012-2017 register data. NSQIP data are prospectively collected and validated from medical records on preoperative risk factors, preoperative laboratory values, intraoperative variables, 30-day postoperative mortality, and 30-day morbidity. In the obese group (BMI>30) 1 death occurred (This group was not included in the HTA because women with BMI <35 was not reported separately)			
Nelson 2014 USA	Case series	2074 BMI<30	NA	30-day mortality: 0	NSQIP 2005-2011 register data. NSQIP data are prospectively collected and validated from medical records on preoperative risk factors, preoperative laboratory values, intraoperative variables, 30-day postoperative mortality, and 30-day morbidity.			
Simpson 2019 USA	Case series	8108 BMI<30	NA	30-day mortality: 0	NSQIP 2006-2015 register data. NSQIP data are prospectively collected and validated from medical records on preoperative risk factors, preoperative laboratory values, intraoperative variables, 30-day postoperative mortality, and 30-day morbidity.			

BMI: Body Mass Index (kg/m^2); NSQIP: The American College of Surgeons' National Surgical Quality Improvement Program; NA: not applicable

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Appendix 4.2
Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With drawals - drop-outs	Results Reduction mammaplasty	Comments	Directness*	Study limitations*	Precision*
Freire 2007 Brazil	RCT	50	4	<u>8 early complications (n=50, 16%)</u> 1 depressed nipple 6 delayed scar 1 seroma <u>8 late complications (6 months, n=46, 17%)</u> 6 hypertrophic scars 2 medial dog-ears	Early and late complications were not defined. Patients were evaluated 6 months after surgery.			
Iwuagwu 2006c UK	RCT	36	0	<u>3 major complications (n=36, 8.3%)</u> 2 major wound infections 1 haematoma drained <u>6 minor complications (6 months, n=16.7%)</u> 6 delayed wound healing	Major and minor complications were not defined. Patients were evaluated 4 months after surgery.			
Saariniemi 2008 Finland	RCT	40	11	<u>4 major complications (n=29, 13.8%)</u> 1 pulmonary embolism 2 haematomas evacuated 1 nipple necrosis <u>20 minor complications (n=29, 69%)</u> 12 minor infection with opening of wound 4 haematomas 3 ”dog ears” 1 minor nipple necrosis	Complications were not divided into major/minor or early/late. Patients were evaluated 6 months after surgery. The patient with pulmonary embolism was 57 years old, with a BMI of 32.3, smoked, and had hormone replacement treatment and medication for high blood pressure and hypercholesterolemia, but no thrombosis prophylaxis was given.			
Janik 2019 Poland	Cohort	28		<u>6 complications (21.4%)</u> 5 haematomas 1 nipple necrosis	Complications were not divided into major/minor or early/late. Patients were evaluated 12 to 36 months after surgery.			

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? Some problems
- Major problems

Appendix 4.2
Outcome variable: Complications

Author year country	Study design	Number of patients n=	With drawals - drop-outs	Results Reduction mammaplasty	Comments	Directness*	Study limitations*	Precision*
Fairchild 2020 USA	Case series	283 BMI<30	NA	<u>11 complication in 7 patients (2.5%)</u> 4 surgical site infections 2 30-day-readmissions 3 re-operations 2 wound-dehiscence	NSQIP 2012-2017 register data. NSQIP data are prospectively collected and validated from medical records on preoperative risk factors, preoperative laboratory values, intraoperative variables, 30-day postoperative mortality, and 30-day morbidity. A composite postoperative adverse events variable was created from a list of 21 individual adverse events. Patients were stratified by presence of obesity (body mass index ≥30 kg/m2). Obesity (BMI≥30) increased the odds of complications by 3-fold (adjusted for operative duration) (p=0.016). In the obese group 1 death and 1 sepsis occurred.			
Nelson 2014 USA	Case series	2074 BMI<30	NA	<u>104 patients had complications (5%)</u> 34 (1.6%) re-operations 48 (2.3%) superficial surgical site infection 6 (0.3%) deep surgical site infections 6 (0.3%) wound dehiscence 5 (0.2%) venous thromboembolism 5 (0.2%) pulmonary embolism 2 (0.1%) unplanned re-intubation 3 (0.1%) urinary tract infection 2 (0.1%) other bleeding	NSQIP 2005-2011 register data. NSQIP data are prospectively collected and validated from medical records on preoperative risk factors, preoperative laboratory values, intraoperative variables, 30-day postoperative mortality, and 30-day morbidity. Patients were categorised according to the World Health Organisation obesity classification. Data was analysed for surgical complications, wound complications, and medical complications within 30 days of surgery. Surgical complications were defined as an unplanned return to the operating room within 30 days and graft loss or failure. Wound complications included superficial surgical site infections (SSI), deep soft tissue infections, deep organ space infections, and wound dehiscence. Superficial SSI's were defined as infection involving only skin or subcutaneous tissue of the incision, with purulent drainage and physical exam findings including pain or tenderness, localised swelling, redness, or heat, which			

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Appendix 4.2
Outcome variable: Complications

* + No or minor problems
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Author year country	Study design	Number of patients n=	With drawals - drop-outs	Results Reduction mammaplasty	Comments	Directness*	Study limitations*	Precision*
					was ultimately opened by the surgeon or diagnosed by the surgeon. Deep soft tissue infections were infections involving deeper tissues (muscle or fascia), while organ space infections involve infection of spaces or organs different from that of the incision. Medical complications included any defined NSQIP endpoints such as pneumonia, pulmonary embolism, postoperative renal insufficiency (Creatinine >2 mg/dl), urinary tract infection (UTI), stroke, myocardial infarction (MI), symptomatic deep venous thrombosis (DVT), and sepsis. BMI > 40 was an independent risk factor for any early complication, OR 2.2 (p<0.001).			
Simpson 2019 USA	Case series	8108 BMI<30	NA	198 (2.4%) complications	NSQIP 2006-2015 register data. NSQIP data are prospectively collected and validated from medical records on preoperative risk factors, preoperative laboratory values, intraoperative variables, 30-day postoperative mortality, and 30-day morbidity. Our primary outcome was any major complications within 30 days. Major complication was defined as unplanned readmission or reoperation. Secondary outcomes were defined as wound complications (superficial infection, deep wound infection, deep or organ space infection, and wound dehiscence), medical complications (myocardial infarction, pneumonia, unplanned intubation, urinary tract infection, stroke, pulmonary embolism, deep vein thrombosis, renal insufficiency, sepsis, and death), and requirement for transfusion. Predictors are not given separately for BMI<30.			

BMI: Body Mass Index (kg/m^2); NSQIP: The American College of Surgeons' National Surgical Quality Improvement Program; NA: not applicable

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Appendix 4.3
Outcome variable: Health-related quality of life

Author year country	Study design	Number of patients	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention **Reduction mammoplasty** Mean (SD)	**Control** **No reduction mammoplasty** Mean (SD) P values of intergroup difference if not stated otherwise				
Araujo 2014 Brazil	RCT	60 I: 30 C: 30	2 1: 0 C: 2	SF-6D Median (range) Preop: 0.61 (0.45-0.83) 3 m: 0.75 (0.50-0.97) 6 m: 0.76 (0.44-0.97)	SF-6D Median (range) Preop: 0.61 (0.39-0.835) 3 m: 0.65 (0.43-0.83), p<0.001 6 m: 0.63 (0.42-0.88) p=0.008	SF-6D: Short Form 6 Dimensions questionnaire Scale 0.29-1.00 (1.00 denotes perfect health) (SF-36 measured but not reported)	?	?	?
Iwuagwu 2006c UK	RCT	73 I: 36 C: 37	0 I: 0 C: 0	FANLT Physical well-being: 24.2 (3.7) Social well-being: 24.6 (4.7) Emotional well-being: 17.3 (3.7) Functional well-being: 23.3 (5.2) SF-36 Physical component score: 50.0 (7.5) Mental component score: 53.2 (8.8)	FANLT Physical well-being: 19.2 (5.1) p<0.001 Social well-being: 20.7 (4.7) p = 0.002 Emotional well-being: 13.0 (3.5) p<0.001 Functional well-being: 17.1 (6.2) p<0.001 SF-36 Physical component score: 42.0 (9.6) p<0.001 Mental component score: 42.0 (11.1) p<0.001	FANLT: Functional Assessment of Non-Life-Threatening Conditions (higher score = better health, range not stated) SF-36: Short Form-36 Health survey (36 items, range 0–100, higher score = better health)	?	?	?

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- Major problems

Appendix 4.3
Outcome variable: Health-related quality of life

Author year country	Study design	Number of patients	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention **Reduction mammoplasty** Mean (SD)	**Control** **No reduction mammoplasty** Mean (SD) P values of intergroup difference if not stated otherwise				
				<u>EQ-5D</u> Self-care: 1.03 (0.18) Activities: 1.32 (0.61) Pain: 1.46 (0.57) Anxiety and depression: 1.21 (0.50)	<u>EQ-5D</u> Self-care: 1.05 (0.23) p=0.978 Activities: 1.48 (0.51) p=0.061 Pain: 2.05 (0.52) p<0.001 Anxiety and depression: 1.59 (0.55) p=0.006	EQ-5D (EuroQol): The European Quality of Life-5 Dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Range 1-3, lower score = better. 4 dimensions reported in article. All are validated HRQoL tools Control group underwent physiotherapy.			

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Appendix 4.3
Outcome variable: Health-related quality of life

Author year country	Study design	Number of patients	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention **Reduction mammoplasty** Mean (SD)	**Control** **No reduction mammoplasty** Mean (SD) P values of intergroup difference if not stated otherwise				
Saariniemi 2008 Finland	RCT	82 I: 40 C: 42	18 I: 11 C: 7	SF-36 Utility index score (SF-6D): 0.820 (SD NR) Physical component score: 51.7 (SD NR) Mental component score: 53.8 (SD NR) 15D index score 0.917 (SD NR)	SF-36 Utility index score (SF-6D): 0.663 (SD NR) MD 0.157 (95% CI 0.107 to 0.220) p<0.0001 Physical component score: 43.3 (SD NR) MD 8.4 (95% CI 5.8 to 11.8) p<0.0001 Mental component score: 46.2 (SD NR) MD 7.6 (95% CI 3.2 to 13.1) p<0.002 15D index score 0.861 (SD NR) MD 0.056 (95% CI 0.041 to 0.103), p<0.0001	SF-36: Short Form-36 Health survey (range 0-100, higher score = better health) SF-6D: Single health utility index score. Part of SF-36 (range 0.29-1.00, higher score = higher function) 15D: Finish QoL questionnaire (higher score = better health, range 0-1)	?/+	?	+

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- Major problems

Appendix 4.3
Outcome variable: Health-related quality of life

Author year country	Study design	Number of patients	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention **Reduction mammoplasty** Mean (SD)	**Control** **No reduction mammoplasty** Mean (SD) P values of intergroup difference if not stated otherwise				
Andrade 2018 Brazil	Cohort study	100 I: 50 C: 50	NR	Breast-Q Median (range) Satisfaction with breasts: 70 (30-100) Psychosocial well-being: 92 (0-100) Sexual well-being: 88 (21-100) Physical well-being: 79 (48-100)	Breast-Q Median (range) Satisfaction with breasts: 23 (0-50) p= 0.001 Psychosocial well-being: 33 (0-71) p = 0.001 Sexual well-being: 29 (0-78) p= 0.001 Physical well-being: 48 (0-83) p = 0.001	Breast-Q: Total scores ranging from 0-100. Higher score indicates greater satisfaction or better quality of life	+	-	?/+
Hermans 2005 Netherlands	Cohort study	165 I: 94 C: 71	10 I: 10 C: 0	SF-36 Physical function: 84.76 Pain: 77.65 Vitality: 67.01 Social activities: 83.69 Emotional status: 80.95 Mental health: 75.22 Physical activities: 76.19	SF-36 Physical function: 77.46, p<0.05 Pain: 57.00, p<0.001 Vitality: 56.83, p<0.01 Social activities: 68.30, p<0.001 Emotional status: 64.32, p<0.01 Mental health: 66.42, p<0.01 Physical activities: 65.85, p= NR	SF-36: Short Form-36 Health survey (higher score = better health, range 0-100)	?	?/-	?

Project: Effectiveness and safety of breast reduction surgery, compared with no surgery, in women with symptomatic breast hypertrophy

* + No or minor problems
? Some problems
- Major problems

Appendix 4.3
Outcome variable: Health-related quality of life

Author year country	Study design	Number of patients	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention **Reduction mammoplasty** Mean (SD)	**Control** **No reduction mammoplasty** Mean (SD) P values of intergroup difference if not stated otherwise				
				Health perceptions: 72.26 <u>EQ-5D</u> <u>Pain:</u> No problems: 51.2% Some problems: 44.0% Many problems: 4.8% <u>Daily activities:</u> No problems: 72.3% Some problems: 25.3% Many problems: 2.4%	Health perceptions: 65.42, p<0.05 <u>EQ-5D</u> <u>Pain:</u> No problems: 14.1%, p<0.001 Some problems: 78.9% Many problems: 7.0% <u>Daily activities:</u> No problems: 46.5%, p<0.005 Some problems: 50.7% Many problems: 2.8%	<u>EQ-5D:</u> The European Quality of Life-5 Dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). 3 answers possible within each dimension. Only 2 dimensions stated in article.			

SF-6D: Short Form 6 Dimensions questionnaire Scale; FANLT: Functional Assessment of Non-Life-Threatening Conditions; SF-36: Short Form-36 Health survey; MD: Mean difference; 15D: Finish QoL questionnaire; EQ-5D: The European Quality of Life-5 Dimensions, NR: Not reported; SD: Standard deviation

Project: Effectiveness and safety of breast reduction surgery, compared with no surgery, in women with symptomatic breast hypertrophy

Appendix 4.4
Outcome variable: Depression

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n= (I: Surgery C: no surgery)	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention **Reduction mammoplasty** Mean (SD)	**Control** **No surgery** Mean (SD) P values denote intergroup difference if not stated otherwise				
Beraldo 2016 Brazil	RCT	I: 30 C: 30	I: 1 C: 3	<u>Depression score (BDI)</u> Baseline: 12.4 (9.0) 3 months: 10.2 (9.9) 6 months: 7.2 (9.9) Intragroup change: Baseline to 3 and 6 months p < 0.001	<u>Depression score (BDI)</u> Baseline: 13.2 (9.6) p = 0.89 3 months: 13.0 (8.5) p = 0.12 6 months: 13.7 (10.5) p = 0.01 Intragroup change: Baseline to 3 and 6 months p = 0.89	Beck Depression Inventory (BDI) (21 items, range 0-63, higher score indicates worse depression) <10 = no or minimal depression 10-16 = mild depression 17-29 = moderate depression 30-63 = severe depression	?	?	?
Iwuagwu 2006b UK	RCT	I: 36 C: 37	0	<u>Depression score</u> Baseline: 0.69 (0.30) 4 months: 0.39 (0.27) <u>Proportion depressed (no. (%)):</u> Baseline: Normal score: 28 (78) Borderline score: 6 (17) Abnormal score: 2 (6) 4 months: Normal score: 34 (94) Borderline score: 1 (3) Abnormal score: 1 (3)	<u>Depression score</u> Baseline: 0.70 (0.29) 4 months: 0.79 (0.27) p<0.001 <u>Proportion depressed (no. (%)):</u> Baseline: Normal score: 27 (73) Borderline score: 8 (22) Abnormal score: 2 (6) 4 months: Normal score: 25 (67) Borderline score: 10 (27) Abnormal score: 2 (6) p<0.001	Hospital Anxiety and Depression Scale (HADS) (7 items, range 0-21. Higher score indicates worse depression) 0-7 ‘normal’ 8-10 ‘borderline’ ≥11 ‘clinical depression/anxiety’ Depression scores were transformed to appropriate a Gaussian distribution (1 + log 10)	?	?	?

Project: Effectiveness and safety of breast reduction surgery, compared with no surgery, in women with symptomatic breast hypertrophy

* + No or minor problems
? Some problems
- Major problems

Appendix 4.4
Outcome variable: Depression

Author year country	Study design	Number of patients n= (I: Surgery C: no surgery)	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention **Reduction mammoplasty** Mean (SD)	**Control** **No surgery** Mean (SD) P values denote intergroup difference if not stated otherwise				
Saariniemi 2009 Finland	RCT	I: 40 C: 42	I: 11 C: 7	<u>RBDI</u> <u>Depression</u> Baseline: 5 (2.5-6.5) 6 months: 0 (0.0-2.5) Median (interquartile) <u>Proportion depressed (no. (%)):</u> Baseline: 16 (55) 6 months: 2 (7)	<u>RBDI</u> <u>Depression</u> Baseline: 4 (1.0-8.0) 6 months: 4 (0.0-7.0) p<0.01 Median (interquartile) <u>Proportion depressed (no. (%)):</u> Baseline: 15 (43) 6 months: 15 (43) p<0.01	RBDI: Raitasalo's modification of the short form of the Beck Depression inventory (range 0-39, lower better) 5-7: mild depression 8-15: moderate depression >16: severe depression <u>Proportions:</u> Depressed = RBDI depression score > 4	?/+	?	+

BDI: Beck Depression Inventory; HADS; Hospital Anxiety and Depression Scale; RBDI: Raitasalo's modification of the short form of the Beck Depression Inventory

Project: Effectiveness and safety of breast reduction surgery, compared with no surgery, in women with symptomatic breast hypertrophy

Appendix 4.5
Outcome variable: Anxiety

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n= I: Surgery C: no surgery	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention **Reduction mammoplasty** Mean (SD)	**Control** **No surgery** Mean (SD) P values denote intergroup difference if not stated otherwise				
Iwuagwu 2006b UK	RCT	I: 36 C: 37	0	<u>Anxiety score</u> Baseline: 9.1 (3.9) 4 months: 5.0 (3.5) Baseline: No (%) Normal score: 12 (33) Borderline score: 11 (31) Abnormal score: 13 (36) 4 months: Normal score: 30 (83) Borderline score: 4 (11) Abnormal score: 2 (6)	<u>Anxiety score</u> Baseline: 9.1 (4.0) 4 months: 9.6 (3.8) p<0.001 Baseline: No (%) Normal score: 12 (32) Borderline score: 11 (30) Abnormal score: 14 (38) 4 months: Normal score: 10 (28) Borderline score: 10 (28) Abnormal score: 17 (47) p<0.001	Hospital Anxiety and Depression Scale (HADS) (7 items, range 0-21. Higher score indicates worse anxiety) 0-7 'normal' 8-10 'borderline' ≥11 'clinical depression/anxiety'	?	?	?
Saariniemi 2009 Finland	RCT	I: 40 C: 42	18 I: 11 C: 7	<u>RBDI</u> <u>Anxiety</u> No. (%) Baseline: 18 (62) 6 months: 3 (10)	<u>RBDI</u> <u>Anxiety</u> No. (%) Baseline: 18 (51) 6 months: 12 (34) p=0.04	Raitasalo's modification of the short form of the Beck Depression inventory (range 0-39, lower better) <u>Proportions:</u> Anxiety = RBDI anxiety score > 0	?/+	?	+

HADS: Hospital Anxiety and Depression Scale; RBDI: Raitasalo's modification of the short form of the Beck Depression inventory

Project: Effectiveness and safety of breast reduction surgery, compared with no surgery, in women with symptomatic breast hypertrophy

* + No or minor problems
? Some problems
- Major problems

Appendix 4.6
Outcome variable: Sexuality-related outcomes

Author year country	Study design	Number of patients n= (I: Surgery C: no surgery)	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention Reduction mammaplasty Mean (SD)	Control No surgery Mean (SD) Intergroup difference				
Beraldo 2016 Brazil	RCT	I: 30 C: 30	I: 1 C: 3	<u>Sexual function</u> Baseline: 24.7 (8.8) 6 months: 27.5 (6.9)	<u>Sexual function</u> Baseline: 23.9 (9.6) p=0.96 6 months: 22.5 (9.3) p<0.001	Female Sexual Function Index (FSFI). The questionnaire includes 19 questions on sexual activity during the last 4 weeks. It has 6 domains: desire, arousal, lubrication, orgasm, satisfaction, and discomfort/pain. A higher score means a better function. A total score of 26.55 or less indicates sexual dysfunction.	?	?	?
Andrade 2018 Brazil	Cohort	I: 50 C: 50	NR	<u>Sexual well-being</u> 6 months-1 year: 88 (21-100) median (range)	<u>Sexual well-being</u> 29 (0-78) median (range) p=0.001	Sexual well-being domain of BREAST-Q (reduction/ mastopexy module). Score 0-100, a higher score means better outcome. Baseline values are not given.	+	-	?/+
Janik 2019 Poland	Cohort	I: 75 C: 27	NR	<u>Sexual quality of life</u> 12-36 months: 76.7 (11.6) (mean follow-up 23.6 months) <u>Sexual function</u> 12-36 months: 27.4 (9.1) <u>Sexual well-being</u> 12-36 months: 72 (14)	<u>Sexual quality of life</u> 64.4 (13.7) p<0.01 <u>Sexual function</u> Pre-operative: 21 (11.4) p=0.03 <u>Sexual well-being</u> Pre-operative: 39.3 (14.5) p<0.01	Sexual Quality of Life-Female (SQoL-F): 18 items, each scored from 1-6, total score 18-108. Higher score better. Female Sexual Function Index (FSFI). Higher score better. Sexual well-being domain of BREAST-Q (reduction/ mastopexy module). Baseline values not reported.	+	-	-

Project: Effectiveness and safety of breast reduction surgery, compared with no surgery, in women with symptomatic breast hypertrophy

Appendix 4.7
Outcome variable: Physical function

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations *	Precision*
				Intervention **Reduction mammoplasty** Mean (SD)	**Control** **No surgery** Mean (SD) P values denote intergroup difference if not otherwise depicted				
Freire 2007 Brazil	RCT	100 I: 50 C: 50	8 I: 4 C: 4	HAQ-20 Pre-op: 0.44 (0.38) 6 months post-op: 0.12 (0.23)	HAQ-20 Baseline: 0.48 (0.40) 6 months after baseline: 0.46 (0.30) p<0.001	HAQ-20 has 8 dimensions that evaluate aspects of daily life: dress, get up without support, feed yourself, walk on the flat, take a shower, reach objects, grasp objects, domestic tasks. It gives a summary score between 0 (able) to 3 (disabled).	+	?/-	?
Neto 2008 Brazil	RCT (same as above)	100 I: 50 C: 50	8 I: 4 C: 4	Roland-Morris questionnaire Pre-op: 5.9 (4.9) 6 months post-op: 1.2 (1.9) Intragroup difference, p<0.001	Roland-Morris questionnaire Baseline: 6.2 (4.8) 6 months after baseline: 6.2 (3.9) Intragroup difference, N.S.	Roland-Morris questionnaire measures functional capacity and is scored from 0 (best performance) to 24 (worst performance) Intergroup difference NR	+	-	-
Saariniemi 2008 Finland	RCT	82 I: 40 C: 42	8 I: 11 C: 7	SF-36 physical summary score Pre-op: 42 (8.6) 6 months post-op: 51.7 (SD NR)	SF-36 physical summary score Baseline: 42.6 (8.9) 6 months after baseline: 43.3 (SD NR) MD 8.4 (95% CI 5.8 to 11.8), p<0.0001	The SF-36 physical summary score represents a norm-based scoring with a mean value of 50 and a SD of 10 (range 0-100). The higher the score, the greater the satisfaction. No MID is established.	?/+	?	+
Andrade 2018 Brazil	Cohort	100 I: 50 C: 50	0	Breast Q physical well-being Post-op median: 79 (48-100)	Breast Q physical well-being pre-op median: 48 (0-83) p=0.001	Total scores for the subscale physical well-being range from 0 to 100. The higher the score, the greater the satisfaction. There are no MID for subscales.	+	-	?/+
Hermans 2005 The	Cohort	165 I: 94 C: 71	10 I: 10 C: 0	SF-36 physical function Postop mean value after 12-24 months: 84.76	SF-36 physical function Before surgery 77.46 p<0.05	SF-36 is scored 0-100 where a higher score indicates better health status. MID not	?	?/-	?

Project: Effectiveness and safety of breast reduction surgery, compared with no surgery, in women with symptomatic breast hypertrophy

Appendix 4.7
Outcome variable: Physical function

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations *	Precision*
				Intervention **Reduction mammoplasty** Mean (SD)	**Control** **No surgery** Mean (SD) P values denote intergroup difference if not otherwise depicted				
Netherlands				<u>EQ 5D-daily activities</u> Postop mean after 12-24 months: No problems 72.3 Some problems 25.3 Many problems 2.4 <u>DAS-59 I have physical disabilities because of my features</u> 12-24 months postoperatively: Almost never 89% Sometimes 6% Always often 5%	<u>EQ 5D-daily activities</u> Before surgery No problems 46.5 Some problems 50.7 Many problems 2.8 p<0.005 <u>DAS-59 I have physical disabilities because of my features</u> Almost never 6% Sometimes 23% Always often 72% p=NS	possible to establish.			

DAS-59: Derriford Appearance Scale 59; EQ-5D: EuroQol 5 Dimensions; HAQ-20: Stanford Health Assessment Questionnaire; MID: Minimally clinically important difference; MD: Mean difference; NR: Not reported; NS: Non-significant; SF36: Short Form Health Survey 36

Project: Effectiveness and safety of breast reduction surgery, compared with no surgery, in women with symptomatic breast hypertrophy

Appendix 4.8
Outcome variable: Pain

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n= I: surgery C: no surgery	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention **Reduction mammoplasty** Mean (SD)	**Control** **No surgery** Mean (SD) P values denote intergroup assessment if not stated otherwise				
Iwuagwu 2006c UK	RCT	73 I: 36 C: 37	0	EQ-5D Pain: Baseline: 1.88 (0.46) 4 months: 1.46 (0.57)	EQ-5D Pain: Baseline: 1.94 (0.52) 4 months: 2.05 (0.52) p<0.001	EuroQol EQ-5D: The European Quality of Life-5 Dimensions. Pain assessment scores are part of the questionnaire. Lower score = less pain, range 1-3.	?	?	?
Saariniemi 2008 Finland	RCT	82 I: 40 C: 42	18 I: 11 C: 7	FBAS 11.8 (SD NR) FPQ 7.0 (SD NR)	FBAS 57.9 (SD NR) MD -46.1 (95% CI -49.8 to -40.7), p<0.0001 FPQ 26.5 (SD NR) MD -19.5 (95% CI -25.2 to -14.3), p<0.0001	FBAS: Finnish Breast Associated Symptoms questionnaire (Higher scores = more symptoms, range 0-100) FPQ: Finnish Pain Questionnaire (Higher scores = more pain, range 0-100)	?/+	?	+
Freire 2007 Brazil	RCT	100 I: 50 C: 50	8 I: 4 C: 4	VAS: Lower back Baseline: 5.7 (2.7) 6 months: 1.3 (2.5) Shoulders Baseline: 6.1 (2.7) 6 months: 1.1 (1.8) p<0.001 (intragroup difference) Neck Baseline: 5.2 (2.9) 6 months: 0.9 (1.3)	VAS: Lower back pain Baseline: 6.0 (3.3) 6 months: 5.3 (2.8) p<0.001 Shoulders Baseline: 6.2 (3.2) 6 months: 6.9 (2.6) p<0.001 NS (intragroup difference) Neck Baseline: 4.7 (3.6) 6 months: 5.1 (3.1)	VAS: Visual analogue scale (0: No pain, 10: Intense pain Same cohort as Neto et al. Lower back pain data identical.	+	?/-	?

Project: Effectiveness and safety of breast reduction surgery, compared with no surgery, in women with symptomatic breast hypertrophy

Appendix 4.8
Outcome variable: Pain

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n= I: surgery C: no surgery	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention **Reduction mammoplasty** Mean (SD)	**Control** **No surgery** Mean (SD) P values denote intergroup assessment if not stated otherwise				
				p<0.001 (intragroup difference)	p<0.001 NS (intragroup difference)				
Hermans 2005 Netherlands	Cohort	165 I: 94 C: 71	10 I: 10 C: 0	SF-36 Pain: 77.65 EQ-5D Pain: No problems: 51.2% Some problems: 44.0% Many problems: 4.8% DAS-59 Pain: Almost never: 68% Sometimes: 22% Always/Often: 10%	SF-36 Pain: 57.00 p<0.001 EQ-5D Pain: No problems: 14.1% Some problems: 78.9% Many problems: 7.0% p<0.001 DAS-59 Pain: Almost never: 2% Sometimes: 18% Always/Often: 80% p<0.001	SF-36: Short Form-36 Health survey (higher score = better health, range 0-100) EQ-5D: The European Quality of Life-5 Dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Only 2 dimensions stated in article DAS-59: Derriford Appearance Scale 59. Higher scores indicate greater problems. Pain scores were all part of QoL-questionnaires	?	?/-	?

NR: Not reported; NS: No significance; EQ-5D: The European Quality of Life-5 Dimensions; FBAS: Finnish Breast Associated Symptoms questionnaire; FPQ: Finnish Pain Questionnaire; VAS: Visual analogue scale; SF-36: Short Form-36 Health survey; DAS-59: Derriford Appearance Scale 59

Project: Breast reduction surgery, compared with no surgery, in women with breast hypertrophy

Appendix 4.9
Outcome variable: Experience of breast reduction surgery

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results	Comments
Shakespeare and Postle 1999 UK	Qualitative	110	50/110 (45%)	<u>Advantages:</u> The majority had very little or no pain (43/60) Patients reported an increased physical activity. 24 patients felt more fit and 19 patients reported weight loss. Forty-two patients believed that the operation had changed their lives to the better Almost all patients were pleased with an increased choice in clothes Three patients remarked that they believed they had cost the health care system less since the operation <u>Disadvantages:</u> Two patients reported a deterioration in self-image and quality of life One patient expressed regret Ten patients were unsatisfied with the scaring and expressed discomfort when wearing clothes Eight patients were dissatisfied with the nipple (loss of sensibility, misplacement, inversion) Two patients reported that they experienced more difficulty to interpret mammograms Two patients regretted not being able to breastfeed, postpartum, even though they had been informed about this preoperatively.	In-house constructed survey, analysed qualitatively by content analysis Semi-structured telephone interviews (n=10)

Appendix 5

Registered studies in ClinicalTrials.gov

NCT Number	Main scope	Status	Study design	URL
NCT01297621	Physical activity and sexuality after reduction mammaplasty	Completed	RCT	https://ClinicalTrials.gov/show/NCT01297621
NCT02016677	Esthetic outcomes of breast reduction surgery and /or mastopexy	Terminated	Cohort	https://ClinicalTrials.gov/show/NCT02016677
NCT01020422	Sexuality after reduction mammaplasty	Completed	RCT	https://ClinicalTrials.gov/show/NCT01020422
NCT00992368	Cost-effectiveness of reduction mammaplasty	Completed	RCT	https://ClinicalTrials.gov/show/NCT00992368

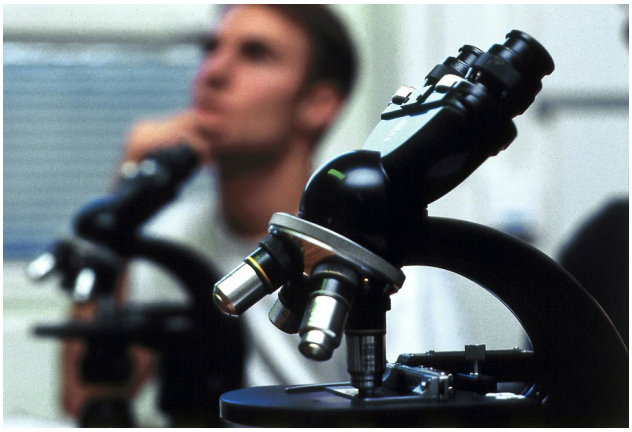
Innehållsdeklaration

Denna HTA-rapport är baserad på följande moment:

- [x] Metodbeskrivning
- [x] PICO
- [x] Uttömmande litteratursökning
- [x] Flödesschema
- [x] Urval relevans
- [x] Kvalitetsgranskning
- [x] Tabelldata
- [x] Sammanvägning av resultat
- [x] Metaanalys
- [x] Evidensgradering enligt GRADE
- [x] Sammanfattning
- [x] Ekonomi
- [x] Organisation
- [x] Etik
- [x] Pågående studier
- [x] Exkluderade artiklar
- [x] Expertgrupp deltar
- [x] Extern granskning
- [x] Kunskapsluckor identifierade
- [x] Jävsdeklaration inhämtad från projektdeltagarna

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

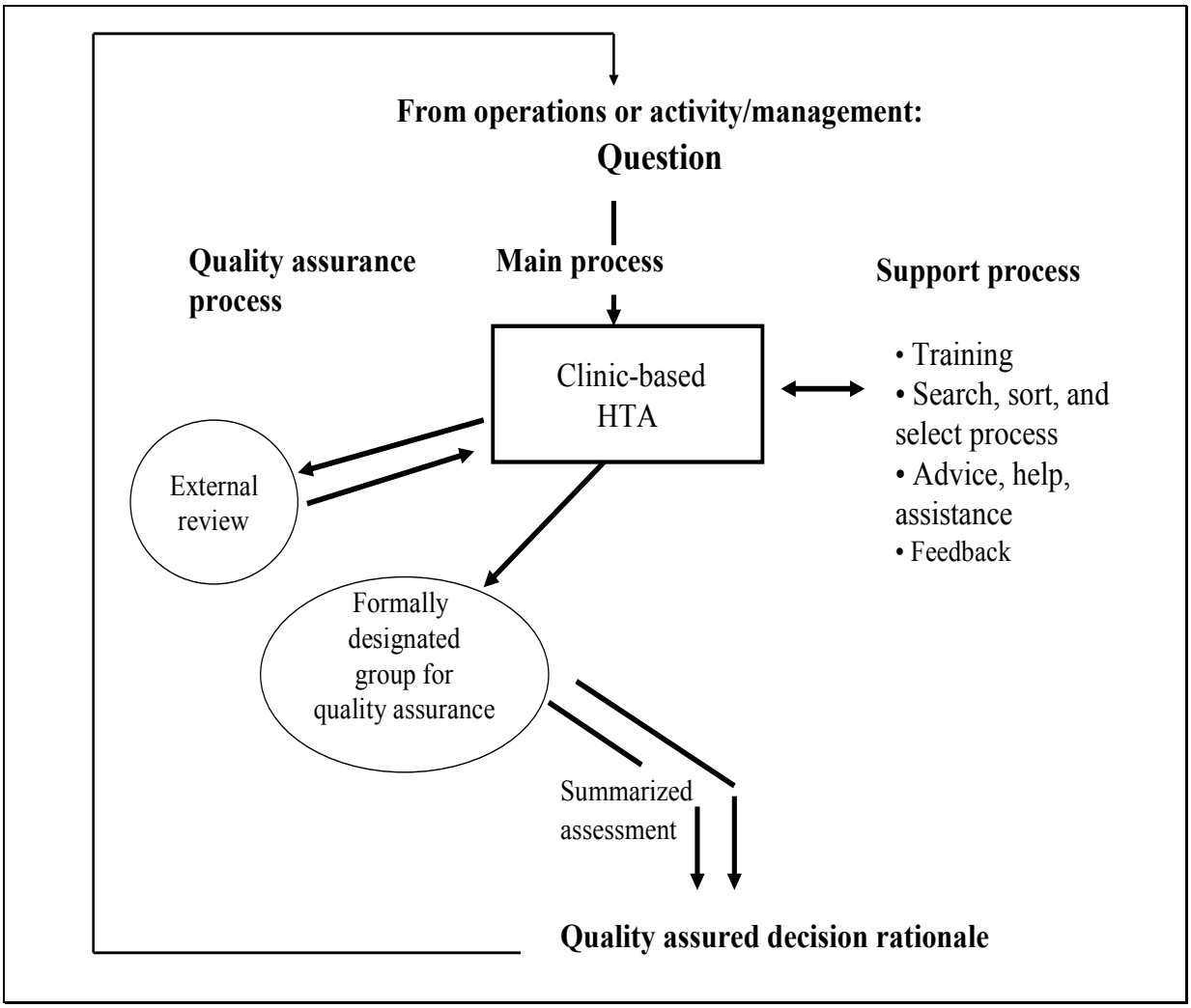
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the certainty of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High certainty of evidence	= (GRADE⊕⊕⊕⊕)
Moderate certainty of evidence	= (GRADE ⊕⊕⊕O)
Low certainty of evidence	= (GRADE ⊕⊕OO)
Very low certainty of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh
Professor, MD
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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