Systematic Review Report

Systematic Review of Selected Adverse Outcomes and Symptoms in Women with Silicone Gel Breast Implants

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Introduction

For decades, there has been concern that silicone breast implants may be associated with numerous diseases and symptoms among the women in whom they have been implanted. Developed in the early 1960s, silicone gel prostheses have been used for breast reconstruction after mastectomy, to correct congenital breast defects, and for aesthetic breast augmentation. The structure and composition of the silicone gel and shell have changed over the decades to improve the aesthetic look and feel of the implant and to reduce complications such as contracture, silicone leakage, and rupture. The current generation of implants, in use since the mid-1990s, consists of a semi-solid cohesive silicone gel, and an elastic silicone shell. They are available in round and teardrop (anatomic) shapes and with smooth and textured surfaces. Textured surfaces keep the implant in one position and decrease capsular contracture.[1] In 2012, more than 300,000 women underwent breast augmentation and about 92,000 women underwent breast reconstruction with silicone implants in the United States, accounting for a 16% increase since 2000.[2]

Silicone implants have been controversial due to allegations and conflicting evidence of increased risk of developing several diseases, in particular connective tissue diseases (CTD)—such as systemic lupus erythematosus, scleroderma (systemic sclerosis), rheumatoid arthritis, and fibromyalgia—neurologic diseases, certain cancers, reproductive and lactation problems, harms to offspring, and other conditions. There have been continued concerns and claims of potentially serious systemic problems related to silicone implants, that the silicone gel inside the implant shell, can cause connective tissue or other autoimmune diseases such as rheumatoid arthritis and lupus, neurological disorders, cancer, and even new silicone-related diseases.[3-5] Originally, concerns about cancer arose from studies that linked silicone in the implant with the development of cancerous tumors in mice.[6-8] Early studies in humans, however, have not demonstrated increased risk of these diseases in humans.[9-11] Despite these concerns, it was recognized that there were limited data on rare events and long-term outcomes in women with silicone implants. In 1999, the Institute of Medicine (IOM) published a comprehensive report of the existing literature and ongoing studies on breast implants that concluded that there was no evidence that silicone breast implants caused systemic health effects such as cancer or autoimmune disease.[3]

In response to the concerns of iatrogenic disease, the U.S. Food and Drug Administration (FDA) reclassified breast implants as Class III medical devices in 1988 and required the submission of premarket approval applications from manufacturers in 1991.[12]The following year, silicone implants were removed from the market in the U.S. except for their use in approved clinical studies. FDA-approved silicone implants were reintroduced to the market starting in 2006. Since November 2006, FDA approval of new silicone implants have been conditional on the manufacturers conducting post-approval studies to to better understand the long-term performance and safety of silicone breast implants, specifically to monitor for previously unrecognized adverse events.[12]

In June 2011, the FDA reported an update on the safety of silicone gel-filled breast implants.[13] Their review found important limitations to the evidence that precluded definitive conclusions, including issues related to low follow-up rates (rare events), problems with follow-up within studies, and limited long-term follow-up data. However, they concluded the evidence failed to support an association between silicone implants and CTD, pregnancy or fertility problems, difficulty breastfeeding, suicide, or cancer with the possible exception of the rare

development of anaplastic large cell lymphoma (ALCL). The FDA conclusions are consistent with a 1998 report by the National Science Panel for CTD and 1999 report by the IOM for CTD, various cancers, neurologic diseases, pregnancy, lactation, and offspring.[3,14] All concluded that the evidence is limited and flawed.

In 2012, the FDA and American Society of Plastic Surgeons (ASPS) amended their existing Cooperative Research and Development Agreement (CRADA) to explore the development of a National Breast Implant Registry for post-market surveillance of breast implants, including silicone implants.[15]The ASPS and The Plastic Surgery Foundation (PSF) solicited this systematic review to summarize the state of the literature on specific safety outcomes in women with silicone gel breast implants for the purpose of informing the development of the registry.

Methods

A draft protocol was written by the ASPS and The PSF. In conjunction with The PSF, an Advisory Panel was convened to refine the protocol. We included representatives from ASPS and The PSF, industry representatives, FDA liaisons, a women's health research advocate, and plastic surgeons (see acknowledgments). The Advisory Panel did not participate in the conduct of the systematic review and the systematic review team retained independence regarding final decisions and conclusions. The Advisory Panel also commented on a draft version of the report.

Study Selection

We conducted literature searches of studies in MEDLINE, Embase, and Ovid Healthstar (inception – 30 June 2015), as well as the Cochrane Central Trials Registry and Cochrane Database of Systematic Reviews (through 1st Quarter, 2015). Additional citations were solicited from the Advisory Panel. The search included a broad range of search terms for silicone gel implants and outcomes of interest (see **Appendix A** for complete search strings). We utilized a screening program, *Abstrackr*, to assist in manual double-screening of abstracts for eligible articles for full-text screening (http://abstrackr.cebm.brown.edu/).[16] Four researchers screened all abstracts in duplicate after an iterative training period to ensure that all screeners agreed upon the eligibility criteria. Citations that include both the words "silicone" and "breast" were double-screened, with group reconciliation; other citations were single-screened. We also screened reference lists of existing systematic reviews and selected narrative reviews for additional relevant articles. Retrieved full-text articles were rescreened for eligibility. The reasons for excluding these articles are tabulated in **Appendix B**.

We included studies conducted in people with silicone breast implants. This included women with any history of silicone breast implants, regardless of whether they were explanted, revised or replaced, regardless of reason for implantation, and regardless of country. We excluded studies that included only women with a given set of signs or symptoms (e.g., women with joint pain) or that included only women seen at a non-plastic-surgery specialty clinic (e.g., women evaluated by a rheumatologist) who were then compared regarding whether they had breast implants.

We included all types of silicone gel-filled breast implants (implants that have both a silicone gel filling and a silicone shell), with the exception of implants produced by Poly Implant Prothese, since these had a defective manufacturing technique and were recalled. We also excluded studies of injected silicone and tissue expanders. We included all generations, shapes, sizes, brands and manufacturers of silicone gel implants. At least half the implants in each study

group had to be silicone gel (as opposed to saline), but we included studies that did not specify the percentage of implants that were silicone gel. We did not require a comparator, but for comparators we included study groups with no implants (including the general population) and saline breast implants.

As determined with the Advisory panel, we included the following outcomes: primary breast cancer, lymphoma (except ALCL) and hematologic cancers, and cancers of the cervix, uterus, endometrium, vulva, brain, and lung; connective tissue, rheumatologic, and auto-immune diseases; neurologic diseases; reproductive difficulties and complications; lactation difficulties; offspring diseases and congenital malformations; suicide; and clinical depression. We also included signs and symptoms that could be attributable to connective tissue, rheumatologic, auto-immune, and neurologic diseases. We included all study designs, including prospective and retrospective, comparative and non-comparative, and case-control. We excluded case reports, case series, letters and comments. We included studies in all languages, all publication dates, and follow-up durations. Non-English language publications (which were in French and Spanish) were extracted and confirmed by researchers able to read the relevant languages.

Data Extraction and Assessment

Data from each study were extracted by one experienced methodologist. The extraction was reviewed and confirmed by at least one other methodologist. Data were extracted into customized forms in the Systematic Review Data Repository (SRDR) [and will be available] at http://srdr.ahrq.gov. Relevant data captured included publication information, study design, intervention and comparator arm descriptions, baseline characteristics, outcome definitions, results, and study quality (described below).

When reported, we captured data on whether implants were used for reconstruction or augmentation; whether implants were revised or removed and not replaced; demographic features (e.g., age, race, socioeconomic status), and country. We also captured data on the type of gel (e.g., cohesive), the type of shell surface (i.e., smooth vs. textured), the implant shape (i.e., anatomic vs. round), and the manufacturer or brand. When extracting clinical outcomes, we preferentially included confirmed over self-reported diagnoses. For breast cancer, we restricted extraction to primary breast cancer occurring in women with breast augmentation.

To assess study quality, we applied an adaptation of the McMaster Quality Assessment Scale of Harms (McHarm) Tool.[17] As relevant, we also applied selected quality questions from the Newcastle-Ottawa Quality Assessment Scales for case-control and observational studies.[18]The quality questions are listed in **Appendix C.5** (Study Quality).

We also qualitatively assessed the plausibility for adverse events to be related to the silicone exposure based on the Bradford Hill considerations.[19] To understand the degree to which the studies provide plausible evidence of causality between silicone gel implants and the outcomes, we used the Bradford Hill considerations related to observational studies and looked within and across studies for evidence regarding strength of association, consistency, specificity (between factor and effect), temporal relationship (the effect occurring after the exposure, with a reasonable delay), and biological gradient(based on size of implant/volume of silicone gel and analyses of possible risk reduction after implant removal).

Because associations found in observational studies are often spurious (likely due to multiple testing and publication bias), the Bradford Hill considerations for causality includes large associations. Bradford Hill contended that the stronger the association, the more likely it is that

the exposure is causative to the outcome. A small association does not rule out a causal effect, but larger associations are more likely to be causal. A common rule rule of thumb to define strong associations is an ES ≥2.0 (or ≤0.5); i.e., at least a doubling (or halving) of risk.

Associations shown to be consistent in different people, in different settings, and across different samples (e.g., studies) are more likely to be causative. The strength of the association may vary in different settings, but the directionality of association should be consistent (assuming biases do not confound the associations). Ideally, consistency should be shown both within studies (e.g., between subgroups) and across studies.

The more specific the analyzed exposure is to the putative causative agent, the greater the probability of a causal relationship. For our purposes, the putative agent is silicone gel; therefore, studies of only silicone gel implants are more convincing regarding possible causality than studies of all breast implants, particularly those with low percentages of women with silicone gel implants. However, this assumption may be faulty, since both silicone gel-filled and saline-filled breast implants contain an outer shell of silicone elastomer (polydimethylsiloxane) and that this portion of the device is what has direct contact with the patient's tissue. Exposure to the internal silicone gel would be expected only in the case of rupture or leakage. Comparisons both within studies (of subgroups of women with silicone gel or saline implants) or across studies with different percentages of women having silicone gel implants can address the question of specificity.

Clearly, the outcome must occur after the exposure for the agent (silicone gel) to be appropriately implicated. Studies that clearly evaluate only outcomes that occur after breast implantation (after a reasonable delay to allow the outcome conditions to develop) provide superior evidence of association and causality. Studies that fail to differentiate between outcomes (e.g., symptoms or depression) that occurred after implantation from outcomes that may have existed prior to implantation are flawed.

Evidence of a biological gradient, where greater exposure is associated with greater outcome incidence, is also consistent with causality; although the presence of the exposure may be sufficient. Applying this factor to silicone gel breast implant exposure, however, is problematic, since it is likely that if silicone gel is causative to any of the evaluated outcomes, the amount of silicone a woman is exposed to is greater than any threshold exposure. Nevertheless, we looked for evidence of biological gradient (both within and across studies) of differences in association between breast implant size (a proxy for amount of silicone gel exposure) and whether there is a change in association in women whose implants are removed (and thus their exposure decreases).

Bradford Hill also considers plausibility of the mechanism between cause and effect, coherence between epidemiological and animal or laboratory models, experimental evidence, and analogy with similar factors. However, the body of evidence considered in this review does not address these factors, so they are not included.

The plausibility questions asked for individual studies are listed in **Appendix C.6** (Bradford Hill Considerations, By Study).

Data Synthesis

Study data were analyzed for each outcome of interest. From each study we captured, as reported, or calculated, when possible, the number and percent of women with breast implants who had each outcome of interest. From studies that compared women with and without implants or with silicone implants versus non-silicone implants, we captured the numbers of

women with and without outcomes in both groups, and the reported comparison results and measures of variability of the estimates. These metrics included adjusted and unadjusted odds ratios (OR), risk ratios (RR), hazard ratios, and incidence rate ratios, standardized incidence, mortality, and hospitalization ratios. When comparison results were not reported, we calculated unadjusted ORs. When there were no events in a single group, we added 0.5 to each cell of the 2x2 table to estimate the OR. For all results, we captured or estimated the 95% confidence intervals.

The factors for which each metric was adjusted, when reported, are listed. We categorized adjustments as inadequate, adequate, or unclear. Inadequate adjustments adjusted only for, at most, age, race, time since implant, and calendar year. These analyses do not account for important confounders between women's decision to have an implant and the outcome, such as tobacco use, weight, or other risk factors for the outcome. Adequate adjustments account for these other possible confounders (e.g., education, family history, hormone use, depression, pregnancy history, alcohol use). Analyses were categorized as unclear if the factors being adjusted for were not adequately reported. By definition, standardized incidence ratios (SIR) are standardized by age, time period (year), and sometimes race. They cannot be adjusted for an adequate range of confounders, but are possibly less susceptible to selection bias with complete, validated reporting.

For each outcome, we tabulated all relevant studies. They are listed with the comparative studies first (followed by single group studies), then by the percent of women with silicone gel breast implants (from 100% down, followed by studies with no data on the percent with silicone implants), then alphabetically by study name. When studies reported data for both all breast implants and the subgroup of women with silicone gel implants, both sets of data are included. Because many studies had multiple articles with different sets of outcomes, we assigned each study a name, usually based on where the study was conducted. The study names and all associated articles are matched in **Appendix C.1** (Study Characteristics).

For each outcome, we conducted meta-analyses when basic criteria were met. For ES measures (i.e., OR, RR, hazard ratio), if at least three studies (or independent sets of cohorts) provided sufficient data (to calculate an ES and its standard error), we conducted random-effects model meta-analyses with the empirical Bayes method;[20] if this method failed to converge, the residual maximum likelihood method was used. We report the chi-squared P value for heterogeneity and the I^2 statistic.[21] For the purpose of meta-analysis, we treated all ES measures as being equivalent. We conducted separate, secondary meta-analyses for studies (or within-study subgroups) of 100% silicone gel implants. We separately meta-analyzed direct within-study comparisons with a control group and SIRs (with a general population "control group"). We preferentially used adjusted values, when reported. When studies reported data at multiple time points, we preferentially used data from the longest follow-up period, unless there was a large drop-off in the number of women with data in later time points. When studies compared women with breast implants to multiple control groups of women, we conducted sensitivity analyses using either comparison. For meta-analyses with at least five studies (or independent sets of cohorts), we conducted cumulative meta-analyses (based on years of follow-up and the calendar year when recruitment ended, the final year that implants were placed within a study)[22] and sensitivity analyses removing outlier studies when there was heterogeneity. For meta-analyses with at least 10 studies, we evaluated the potential for publication bias with funnel plots and Egger's tests for small study effects.[23,24] We evaluated whether there were outlier studies and looked for differences across studies to explain heterogeneity in association results. In particular,

we evaluated by meta-regression differences based on whether outcomes were ascertained by registry or physical examination (versus by questionnaire) and whether outcomes were clearly incident since implantation (versus possible prevalence at the time of implantation).

To estimate the summary percent of women with each outcome, we performed random effects model meta-analyses of the arcsine-transformed proportion of women with the outcome, regardless of the number of studies.[25] The arcsine-transformed proportion was used to minimize bias due to the non-normal distribution when proportions are close to 0.[1] However, when meta-analysis gave an implausible summary estimate, the exact proportion and confidence interval (CI) were calculated for the total number of events and women at risk.[26]

All analyses were performed in Stata version 13 (StataCorp, College Station, Texas) with the metareg, metaprop, metacum, metafunnel, and metabias functions. Cumulative meta-analyses were drawn in Excel version 14.0 (Microsoft, Redmond, Washington). For disease outcomes for which there is limited or suggestive evidence of an association (see next section) that had a statistically significant association between breast implants and the outcome by meta-analysis of direct comparisons, we estimated a range of numbers-needed-to-harm (or "treat"), the number of women who would receive a breast implant that may result in one additional (or one fewer) woman having the outcome. This range was based on the 95% CI of the summary ES and the estimated percent of women with implants who had the outcome in the studies (and its 95% CI).

In the text, we describe relevant within-study subgroup analyses (e.g., by age group). For selected outcomes with heterogeneity in estimates across a sufficient number of studies, we attempted to compare the studies based on differences across them (e.g., based on type of gel or country).

Summary of Findings

For each outcome, we summarized the evidence in one of four categories as described in **Table 1**. These categories were based on criteria used by the IOM Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides,[3] modified in discussion with our Advisory Panel. Despite use of a standardized method to categorize the summary of the evidence for each outcome, it is important to note that the criteria used are arbitrary (not based on empirical evidence) and the categorization relies on judgments, which may vary based on one's perspective. Each outcome was categorized by one researcher and confirmed by a second. Disagreements were resolved through discussion, as needed.

[1] The proportions were were transformed with the Freeman-Tukey double arcsine method with the following equation: $t = \arcsin (r/(n + 1))^{1/2} + \arcsin ((r + 1)1(n + 1))^{1/2}$, where r is the number of events and n is the number of subjects, where the proportion = r/n. This approach is used to normalize the distribution of estimates of proportions, which are otherwise bounded by zero, and to avoid using continuity corrections.

Table 1. Categories and Criteria for Summary of Findings

Finding	Criteria*
Sufficient Evidence of an Association	Evidence is sufficient to conclude that there is a positive (or inverse) statistically significant, strong association. A positive (or inverse) association has been observed between silicone gel breast implants (or breast implants†) and the outcome with an adjusted risk ratio‡ ≥2.0 (or ≤0.5) in at least 2 studies free of major bias and confounding or by meta-analysis of such studies.§ The associations are consistent across studies (and within subgroups of women within studies, if reported).
Limited/Suggestive Evidence of an Association	Evidence is suggestive of a positive (or inverse) association between silicone gel breast implants (or breast implants†) and the outcome, but is limited because chance, bias, and confounding could not be ruled out with confidence, there is inconsistency in the associations found across studies, or the association is small (adjusted risk ratio‡>0.5 and <2.0) within studies or by meta-analysis. For example, two studies did not adequately account for confounding but found a strong association (adjusted risk ratio‡ ≥2.0 or ≤0.5) and other studies are non-significant but consistent in direction of the association.
Inadequate/Insufficient Evidence to Determine Whether an Association Exists	The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to adequately control for confounding, have major bias, or major imprecision within studies or by meta-analysis.‖
Limited/Suggestive Evidence of No Association	Several studies free of major bias and confounding are mutually consistent in not showing a positive or negative association, within studies or by meta-analysis, between exposure to silicone gel breast implants (or breast implants*) and the outcome.

* For all criteria, studies are qualitatively weighted by the adequacy of their accounting for confounding (see footnote §), their lack of major bias, and their sample size. Studies that report only unadjusted outcomes or are small (<10 events [women with outcomes] per variable included in the model adjusting for confounders) are given less weight in the summary of findings.

† Where appropriate, findings are specific to evidence for silicone gel breast implants or for all breast implants.

‡ Or other comparative metric.

§ Adequate accounting for confounding requires adjustment for more than the women's age, the time since surgery, and the calendar year of implantation. Adjustment for confounders must attempt to account for underlying differences between women who choose to have breast implants and women without implants and for factors associated with the outcome (e.g., smoking for cancer outcomes). Exposure and outcome must be confirmed (e.g., by medical record or physical examination) and free from recall and other biases. Outcomes must clearly occur after breast implantation.

‖ Major imprecision: Relative risk (or comparable metric) has a 95% confidence interval that extends beyond both 0.5 and 2.0.

Results

The literature search yielded 5171 citations. An additional 11 studies were added by Advisory Panel members. From these, 207 articles were provisionally accepted for review based on abstracts and titles, of which 18 were found from existing systematic reviews (**Figure 1**). After screening the full text, 55 studies (in 79 publications[27-74,9,11,75-78,78-99]) met the inclusion criteria. The most frequent reasons for rejection were that the articles were not primary studies of women with implants (30 articles), there were no outcomes of interest reported (21 articles), they were case reports or case series (15 articles), they included only women with implants who had specific complaints or referred to specialty (e.g., rheumatology) clinics and thus no data about rates or incidence were available (14 articles), or they did not report additional data beyond the included articles (11 articles). See **Appendix B** for the list of rejected studies and the reasons for rejection. For outcomes with available data, we collected prevalence or incidence information for the general population of adult women in the U.S. But because women who have breast implants are dissimilar to people in the general (e.g., by age, race, weight, smoking status), the data from (unadjusted) general population surveys are not directly comparable. Studies that use these data have adjusted for population differences with standardized incidence ratios and are included for each outcome. We, therefore, provide these data for interested readers, but relegate them to **Appendix D** and do not make inferences based on the general population outcome rates.

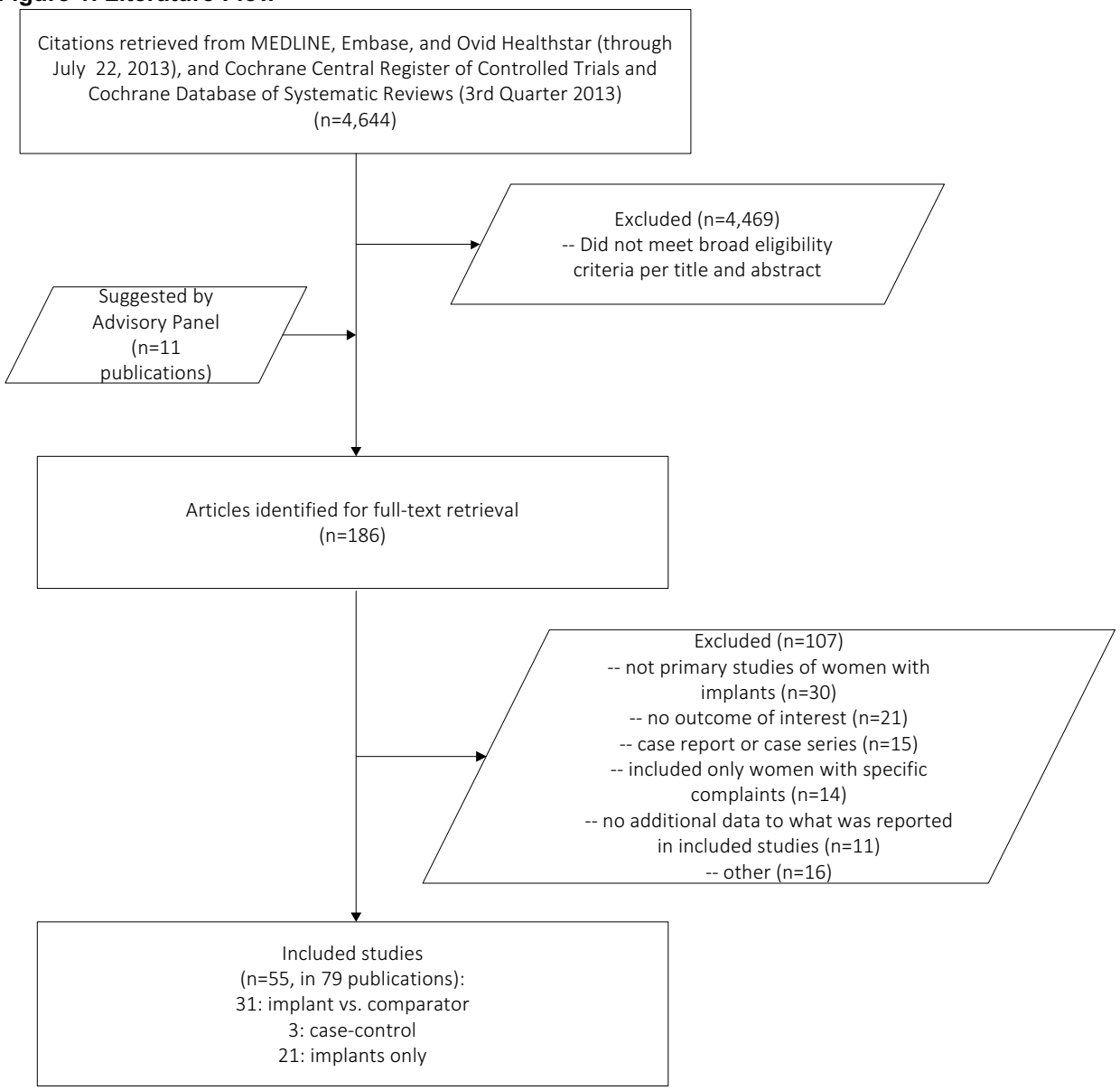
For all studies, the extracted data are summarized in **Appendix C**, with separate appendix sections for the study characteristics (Appendix C.1), study arm details (Appendix C.2), baseline characteristics (Appendix C.3), results by study (Appendix C.4), study quality (Appendix C.5), and causality items (Appendix C.6). The study characteristics section (Appendix C.1) matches each study by its name and included publications.

Among the 55 included studies, 31 compared women with implants to controls—either no implants, general population, other cosmetic surgeries, or saline implants (one study). However, many of these studies did not report comparative data (implant versus no implant) for all reported outcomes. An additional three studies were case-control. There were 21 studies that included only women with implants, one of which compared two different brands of silicone gel implants (Allergan vs. Mentor). Particularly among several of the Scandinavian studies, there is likely to be some overlap in included women; although, we attempted to sort articles into non-overlapping studies as much as possible. There were 27 studies that reported data for only women with silicone gel implants (100% silicone). Among the remaining 28 studies, 14 did not report the percent of implants that were silicone gel; the remaining 14 included between 50% and >90% silicone gel implants.

Study quality was assessed for each cohort depending on the study design. Only about half the studies (30/55; 55%) reported on exposure ascertainment, 24 of which (44%) verified the breast implant exposure through a secure medical record and five studies (9%) relied on a written self-report. Also, only about half the studies (28/55; 51%) explicitly reported on the assessment of the outcome, with 11 reports citing a secure record (20%), 12 with self-reported outcomes (22%), four independent blind assessments (7%), and one clinical examination with lab tests (2%). About half the studies (28/55; 51%) provided sufficient information to confirm that outcomes of interest were not present at the start of each study. The large majority clearly reported both eligibility criteria (89%) and results without any discrepancies (93%). Most (71%) of the cohort pre-defined their harms in the protocol and similarly 73% used an active collection of harms data, while fewer than half (36%) incorporated a passive harms collection. Only four studies did not report on number of withdrawals during the study. Among the comparative

studies, only one-third (9/27) adequately accounted for possible confounders. While overall, studies provided clear reporting of the population of interest, relied on secure records, and actively collected results data (versus self-reporting), many suffered from the major flaw of not conducting appropriate statistical analyses to compare women with implants to women without implants. Namely, they either failed to adjust for a comprehensive list of possible confounders or they provided only raw counts (which allowed only unadjusted analyses to be conducted). Since in all (non-randomized) observational studies it is highly likely that the study groups differ by factors other than the intervention of interest (breast implants), for an unbiased assessment of the association between the implant and the outcomes, it is critical that proper adjustment for confounders be instituted. Furthermore, half the studies did not explicitly ascertain that the outcomes were not present at the time of implantation, a critical feature to determine whether the implant may be a cause of the outcomes.

Figure 1. Literature Flow



Regarding issues related to causality across studies, for the issue of consistency within studies, we examined whether the studies reported outcomes for distinct *a priori* defined groups (e.g., different centers, cities, or populations). Only the manufacturers who provided evidence to the FDA and Health Canada (Allergan, Mentor, and Sientra) collected and reported data separately for distinct groups of women (namely, by augmentation or reconstruction and by primary or revision surgery). We found no clear differences across these four groups of women, but the studies did not directly analyze the comparisons across the groups. As is highlighted for each outcome, most of the comparative evidence is for any breast implant versus no implant; only 30% (9/30) of the comparative studies are specific to silicone gel implants. The issue of temporality was an important concern. Among comparative studies, almost half (14/30) of the comparative studies did not provide sufficient descriptions of their methods to confirm that all reported outcomes occurred after breast implant surgery. This was particularly an issue for the CTDs and CTD-related symptoms, for which the time of onset of disease or symptoms was not stated and may have existed prior to implantation. This was also the case for more than half (12/22) of the single group studies. None of the studies evaluated either the effect of implant size (silicone gel volume) on the strength of association or whether any associated risk decreases after removal of the silicone gel implant.

Within-study subgroup analyses that were reported are noted below under each outcome. However, only a few studies reported such within-study subgroup analyses and none of them explicitly reported an appropriate statistical analysis to determine whether any possible differences across subgroups are statistically significant. Evaluating implant and patient factors across studies was particularly problematic since most studies included women with any breast implant and, with rare exceptions, it was not possible to determine which implants, fill material, specific silicone gel material, shell material, implant shape, manufacturer, or brand were used. For the few comparative studies that were restricted to a specific brand, there was no way to determine whether there were differences in associations between those usually single studies and the other studies reporting a given outcome. For all outcomes, we highlighted the silicone gel implant studies versus the studies that included all breast implants. When there was statistical heterogeneity across the comparative studies (when the reported associations differed among studies), we attempted to explain the differences based on major differences across studies such as the percent of women with silicone gel implants, the country or region of the study, and when the study was conducted. However, this type of analysis was usually not feasible due to small numbers of studies or lack of data.

The Results section is structured by outcome category. The outcomes were categorized as: 1) cancer; 2) connective tissue, rheumatologic, and auto-immune diseases; 3) symptoms of connective tissue, rheumatologic, and auto-immune diseases; 4) neurologic diseases; 5) symptoms of neurologic diseases; 6) reproductive issues, including lactation; 7) offspring issues; and 8) mental health issues (depression and suicide). Within each category, outcomes are presented in alphabetical order (unless there is an overarching outcome, such as “any CTD”, which is presented first).

Cancer

Brain Cancer

Thirteen studies reported brain cancer outcomes (**Table 2, Figures 2 & 3**). None of the studies reported an *a priori* list of which specific brain cancers were analyzed. Only the South 18 Centers study noted that brain metastases were included in their analysis; most of the reported brain cancers in this study were glioblastomas.

The three studies that compared women with implants versus without implants had conflicting estimates of the comparative risk of brain cancer ranging from 0.21 to 2.9. However, the studies all had very few women with brain cancer so that the confidence intervals about the estimates were very wide. Thus, the studies were statistically homogeneous and yielded a summary ES of 0.76 (95% CI 0.11, 5.34) (**Figure 2**). The South 18 Centers study reported an adequately adjusted analysis.[31] The study found a large ES (2.9), but this was statistically non-significant. Using the standard error implied by the unadjusted OR yielded a very wide 95% confidence interval (CI 0.34, 24.8). Three of the studies analyzed women with only silicone gel implants. Seven of the studies reported SIR compared with the general population; five provided sufficient data to allow meta-analysis (**Figure 3**). The studies were homogeneous yielding a non-significant SIR of 1.41 (95% CI 0.91, 2.19); two additional studies with insufficient data to be included in the meta-analysis, however, reported opposite, non-significant SIRs (0.73 and 0.6). Two studies reported subgroup analyses. The South 18 Centers study reported no difference in association by type of implant (silicone gel, double lumen, saline), age at time of implantation, calendar year of implantation (through 1988), or years since implantation. The Sweden/Denmark Public-Private study also reported no difference by years since implantation. The four studies with at least 10 women diagnosed with brain cancer (South 18 Centers, Sweden/Denmark Public-Private, Ontario/Quebec, and Swedish Inpatient Register) all included only women receiving implants for augmentation; so no comparison with women who had reconstruction was possible.

Across the 13 studies (and across the eight studies with 100% silicone gel implants), 0% to 0.5% of women developed brain cancer over 3 to 24 years of follow-up. Pooled across the eight studies with 100% silicone gel implants 0.02% (95%CI 0.01, 0.03) developed brain cancer after implantation. Across all 13 studies 0.10% (95% CI 0.08, 0.13) developed brain cancer.

Overall, there is insufficient evidence to determine whether an association exists between breast implants and brain cancer. The associations across studies are not consistent in direction or statistical significance. Therefore, the currently available epidemiologic evidence does not support an increased risk of brain cancer after breast implantation.

Table 2. Brain Cancer

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Connecticut[69]	100	4 y	No implant (tubal ligat)	0/680 (0%)	3/1022 (0.3%)	ORcalc 0.21 (0.01, 4.15)	
Mentor (MemoryGel/MemoryShape) Post-Approval Study[59]	100	5 y		1/41451 (0.002%)	--	SMR 0.6	
South 18 Centers[31]	100	12 y	Cosm surg	5/3701 (0.14%)	1/2203 (0.05%)	Adj RR 2.9 (NS) (0.34, 24.8)†	**Ad**: A, R, T, O1
	50		Gen pop	11/7447 (0.15%)	--	SIR 2.16 (1.2, 3.89)	
Finland hospitals[63]	>90	8 y		2/2171 (0.09%)	--	SIR 1.0 (0.17, 3.5)	
Sweden/Denmark Public-Private[77]	80	17 y	Gen pop	17/6222 (0.27%)	--	SIR 1.20 (0.70, 1.93)	
Ontario/Quebec[100]	66	24 y	Cosm surg	25/24558 (0.10%)	26/15893 (0.16%)	Adj RR 0.67 (0.38, 1.16)	**Inad:** A, Y
			Gen pop		--	SIR 0.73 (NS)	
Los Angeles[101]	nd	18 y	Gen pop	5/3139 (0.16%)‡	--	SIR 1.03 (0.33, 2.41)	
Swedish Inpatient Register[102]	nd	18 y	Gen pop	11/3486 (0.32%)	--	SIR 1.3 (0.6, 2.3)	
Allergan (Inamed/Natrelle Round) Cohort[88]	100	4 y		1/715 (0.14%)			
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	7 y		0/941 (0%)			
Mayo Clinic[45]	100	4 y		1/200 (0.5%)			
Mentor (MemoryGel Round) Cohort[87]	100	3 y		0/1007 (0%)			
Mentor (MemoryShape/CPG Anatomic) Cohort[91]	100	6 y		0/955 (0%)			
Summary Implant vs. No Implant	**100% (n=3)**					**0.21 (0.01, 4.15) 2.9 (0.34, 24.8) SMR 0.6**	
	Any, Direct comparisons (n=3)					**0.76 (0.11, 5.34) P het=0.31, I^2=14%**	
	Any, With SIR data (n=7)					**5 studies: 1.41 (0.91, 2.19) P het=0.56, I^2=0% 6th study: 0.73 (NS) 7th study: 0.6**	
	Any, Adequate adjustment (n=1)					**2.9 (0.34, 24.8)**	
Summary Percent Implant	**100% (n=8)**			**0.02% (0.01, 0.03)#**			
	Any (n=13)			**0.10% (0.08, 0.13)#**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O1 = Other: “predictors of cancer”

† 95% confidence interval derived from unadjusted odds ratio standard error.
‡ Denominator based on data from 2007 report.[44]
# Exact proportion

Figure 2. Brain Cancer (Direct Comparisons)

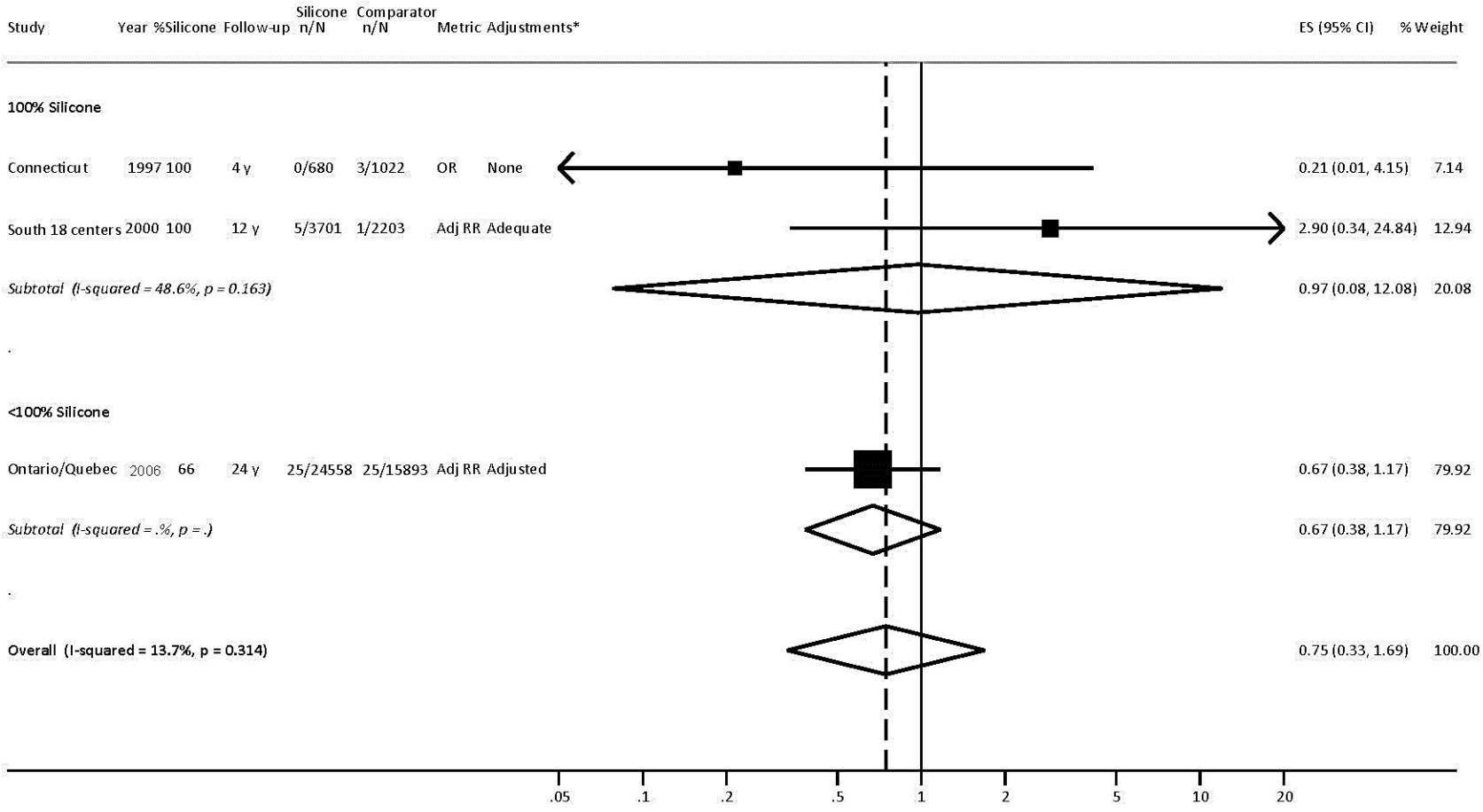
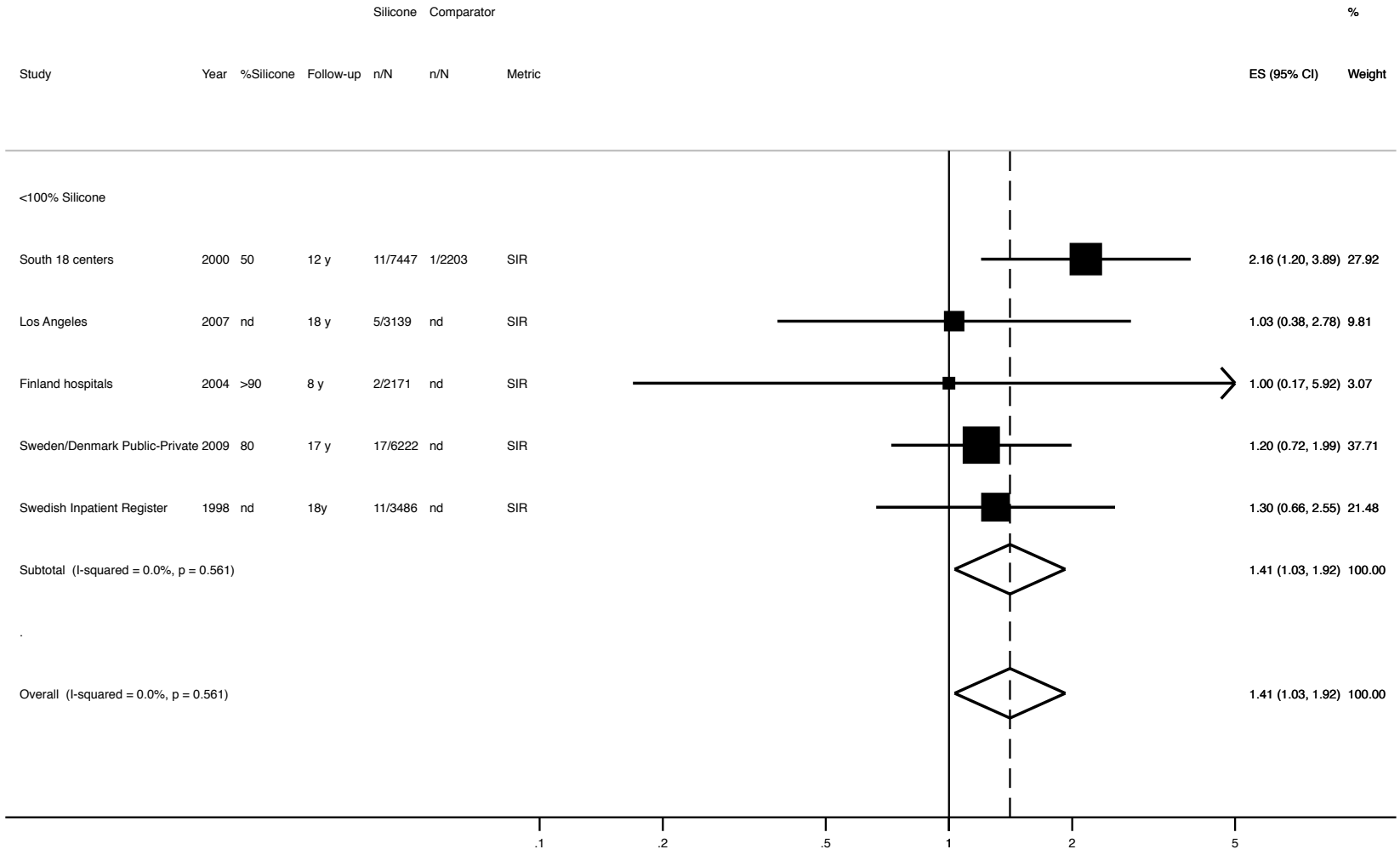


Figure 3. Brain Cancer (Standardized Incidence Ratios)



Breast Cancer, Primary

Twenty-two studies reported primary breast cancer outcomes in women who had augmentation surgery, two of which had two cohorts each of women with implants (Alberta Health Care Data and Allergan vs. Mentor)[36,67] (**Table 3**; **Figures 4-9**). Only one comparative study (implant vs. no implant) evaluated only women with silicone gel implants; in the other 10 comparative studies between 50% and over 90% of implants were silicone gel (or no data were provided). One study (Atlanta/Seattle/NJ) was a case-control study of women with or without breast cancer.[29] All studies, including the single study of 100% silicone gel implants, found that women with implants were at *lower* risk of developing breast cancer; five of the analyses (in four studies) were statistically significant. Among the comparative studies, all but two (WHI OS and South 18 Centers) obtained outcome data (reports of breast cancer) from medical records or registries. However, it is unlikely that misclassification of cancer occurred in the two studies that obtained outcome data from patient questionnaires.

The one comparative study of 100% silicone gel implants found a statistically non-significant relative reduction in breast cancer (RR = 0.67). Pooling the six studies that reported within-study direct comparisons (**Figure 4**) yielded a homogeneous reduced risk: summary ES = 0.63 (95% CI 0.54, 0.73). The two of these studies that adequately (or unclearly; see Table 3) adjusted their analyses found non-significant reduced risk (RR = 0.84 and 0.64). However, it is important to note that neither study clearly listed what factors were adjusted for and it is likely that not all the following important possible confounders were included: body mass index, exercise, smoking, oral contraceptive use, parity, age at first birth, bra cup size, and family history of breast cancer. The seven studies that reported SIR also found a statistically significant reduced risk (**Figure 5**); the summary SIR across six of these studies was 0.76 (95% CI 0.64, 0.91), though with moderate heterogeneity.

As noted, the meta-analysis of the direct comparisons was homogeneous. Thus, sensitivity analyses did not provide insights into differences across studies or substantially alter the summary estimate. While the meta-analysis of SIR was heterogeneous, there was no clear outlier among the included studies. The two studies at the extremes closest to or furthest from a null ES were not clearly different from the other studies. Sequentially removing them in sensitivity analyses reduced the heterogeneity but did not substantially alter the summary ES estimate or its statistical significance. Cumulative meta-analyses of the direct comparisons (**Figures 5& 6**) and SIR (**Figures 7 & 8**) by the calendar year that recruitment of women into the studies ended or by follow-up duration did not show trends over time.

All studies analyzed incident breast cancer since breast implant augmentation. Among the studies that analyzed SIR there was no difference in association between those that determined the outcome from registry or medical record data versus from patient questionnaire (P=0.24).

Based on the pooled ES and the pooled risk of primary breast cancer, the risk difference (RD) between women with and without implants—the absolute percentage of women who would have breast cancer associated with their implant (assuming the association is causal)—ranges from −0.26% (95% CI −0.31, −0.20) to –0.44% (95% CI −0.52, −0.35).

Five of the studies reported subgroup analyses. These included the Ontario/Quebec, South 18 Centers, Atlanta/Seattle/NJ, Finland Hospitals, and Sweden/Denmark Public-Private studies. Although estimates of associations between breast implants and breast cancer varied in different subgroups, none of the five studies reported a significant difference in association for age at implant or time since implant. In addition, no significant differences were found for calendar

years of implant (four studies, through 1988, 1989, 1995, and 1999) and bra cup size pre-implant (two studies). The Ontario/Quebec study also found no evidence of a difference between those with silicone gel and saline implants, polyurethane-coating, or by fill volume. The Atlanta/Seattle/NJ study found no difference based on the women's body mass index.

Across the 19 studies with adequate data, between 0% and 2.6% developed breast cancer over 3 to 17 years of follow-up. Pooled, 0.9% (95% CI 0.7, 1.2) of women with implants developed breast cancer. Restricted to the 9 studies of women with silicone gel implants, 0.6% (95% CI 0.3, 1.0) developed breast cancer. As would be expected, studies with longer duration of follow-up had greater percentages of women with breast cancer (P=0.04), but there was no significant difference by the percent of women with silicone gel implants (P=0.11). Only a single study was specific to silicone gel implants. In all studies the primary breast cancers occurred after implantation.

There is suggestive evidence of an association between breast implants and primary breast cancer. The evidence suggests that women with breast implants may have a small (about 15% to 35%) decreased risk of developing primary breast cancer compared with women without breast implants. The evidence is insufficient regarding the association specifically with silicone gel implants, per se, but a single study is consistent with the studies of all breast implants. The weak strength of the association (<50% reduction in risk) and questions about whether the studies have (or can) sufficiently adjust for important confounders related to how women who choose to undergo breast augmentation differ from the general population in terms of overall health status and family history of breast cancer yield an evidence base that does not provide sufficient evidence to support causality between silicone gel implants and reduced risk of primary breast cancer.

Table 3.Breast Cancer, Primary

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Connecticut[69]	100	4 y	No implant (tubal ligat)	4/680 (0.6%)	9/1022 (0.9%)	RR 0.67 (0.20, 2.17)	
Finland hospitals[63]	>90	8 y	Gen pop	7/2171 (0.3%)	--	SIR 0.5 (0.2, 1.0)	
Sweden/Denmark Public-Private[77]	80	17 y	Gen pop	84/6222 (1.4%)	--	SIR 0.73 (0.58, 0.90)	
WHI OS[84]	67	nd	No implant	30/1250 (2.4%)	3524/86208 (4.1%)	ORcalc 0.58 (0.37, 0.90)	
Ontario/Quebec[100]	66	20 y	Cosm surg	414/24558 (1.7%)	457/15893 (2.9%)	Adj RR 0.60 (0.53, 0.69)	**Inad:** A, Y
			Gen pop		--	SIR 0.54 (P<0.05)	
South 18 Centers[31]	50	12 y	Cosm surg	136/7447 (1.8%)	60/2203 (2.7%)	Adj RR 0.84 (NS) (0.62,1.14)†	**Ad**: A, R, T, O1
			Gen pop		--	SIR 0.96 (0.8, 1.1)	
Alberta Health Care Data[36]	nd	5 y	Gen pop	Cohort 1: nd/10835		SIR 0.85 (0.58, 1.19)	
			Gen pop	Cohort 2: nd/10368		SIR 0.81 (0.53, 1.18)	
Atlanta/Seattle/NJ†[29]	nd	7 y	No implant	36 implants / 2174 breast cancer (1.7%)	44 implants / 2009 no breast cancer (2.2%)	Case-Control Adj RR 0.64 (0.4, 1.0)†	**Unc:** O2
Los Angeles[101]	nd	18 y	Gen pop	59/3139 (1.9%)‡	--	SIR 0.60 (0.45, 0.77)	
Swedish Inpatient Register[102]	nd	18 y	Gen pop	53/3486 (1.5%)	--	SIR 0.7 (0.6,1.0)	
Sydney[47]	nd	16 y	No implant	2/458 (0.4%)	6/687 (0.9%)	RR 0.50 (0.10, 2.48)	
Allergan (Inamed/Natrelle Round) Cohort[88]	100	10 y		7/602 (1.2%)			
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	9 y		6/648 (0.9%)			
Mayo Clinic[45]	100	4 y		2/200 (1.0%)			
Allergan vs. Mentor[67]	100	10 y		0/118 (0.0%)			
Allergan vs. Mentor[67]	100	10 y		3/117 (2.6%)			
Mentor (MemoryGel Round) Cohort[87]	100	9 y		2/697 (0.3%)			
Mentor (MemoryShape/CPG Anatomic) Cohort[91]	100	8 y		7/696 (1.0%)			
Sientra[89]	100	3 y		3/1477 (0.2%)			
Massachusetts General Hospital[49]	73	7 y		0/106 (0.0%)			
Puerto Rico[41]	nd	nd		4/1682 (0.2%)			
Tucson[48]	nd	9 y		18/1968 (0.9%)			

continued

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Summary Implant vs. No Implant	100% (n=1)					0.67 (0.20, 2.17)	
	Any, Direct comparisons (n=6)					0.63 (0.54, 0.73) P het=0.53, I^2=0%	
	Any, SIR (n=7)					6 studies: 0.76 (0.64, 0.91) P het=0.051, I^2=52% 8th study: 0.54 (P<0.05)	
		Confirmed diagnosis (n=5)				0.71 (0.56, 0.89)	P btw = 0.24
		Self-reported diagnosis (n=2)				0.85 (0.65, 1.11)	
	Any, Adequate or unclear adjustment (n=2)					0.84 (0.62,1.14) 0.64 (0.4, 1.0)	
Summary Percent Implant	100% (n=9)			0.6% (0.3, 1.0)			
	Any (n=19)			0.9% (0.7, 1.2)			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O1 = Other: “predictors of cancer”
O2 = Other: “extraneous variables”

† 95% confidence interval derived from unadjusted odds ratio standard error.
‡ Denominator based on data from 2007 report.[44]

Figure 4. Breast Cancer, Primary (Direct Comparisons)

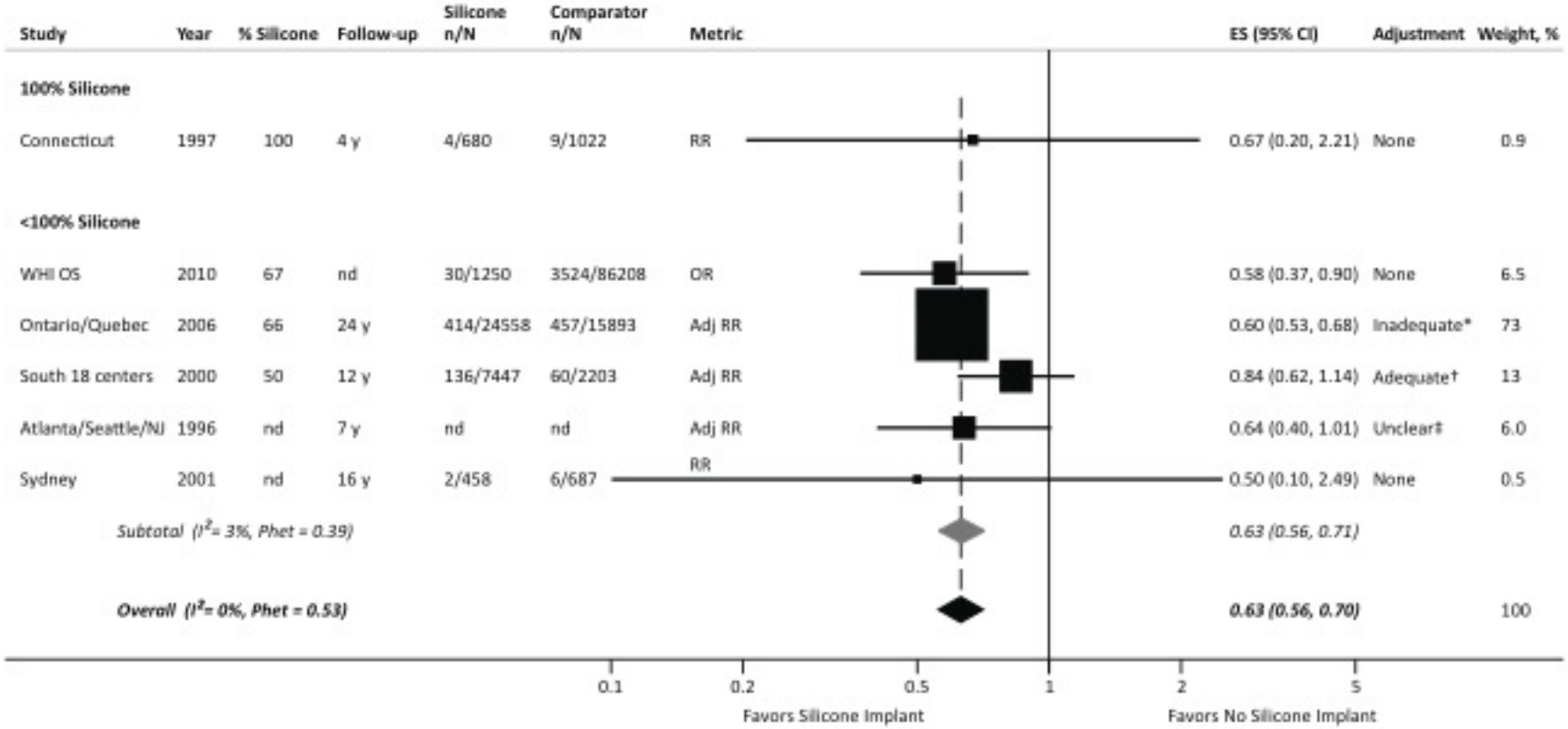


Figure 5. Breast Cancer Effect Size, Cumulative Meta-Analysis by End-Entry Date

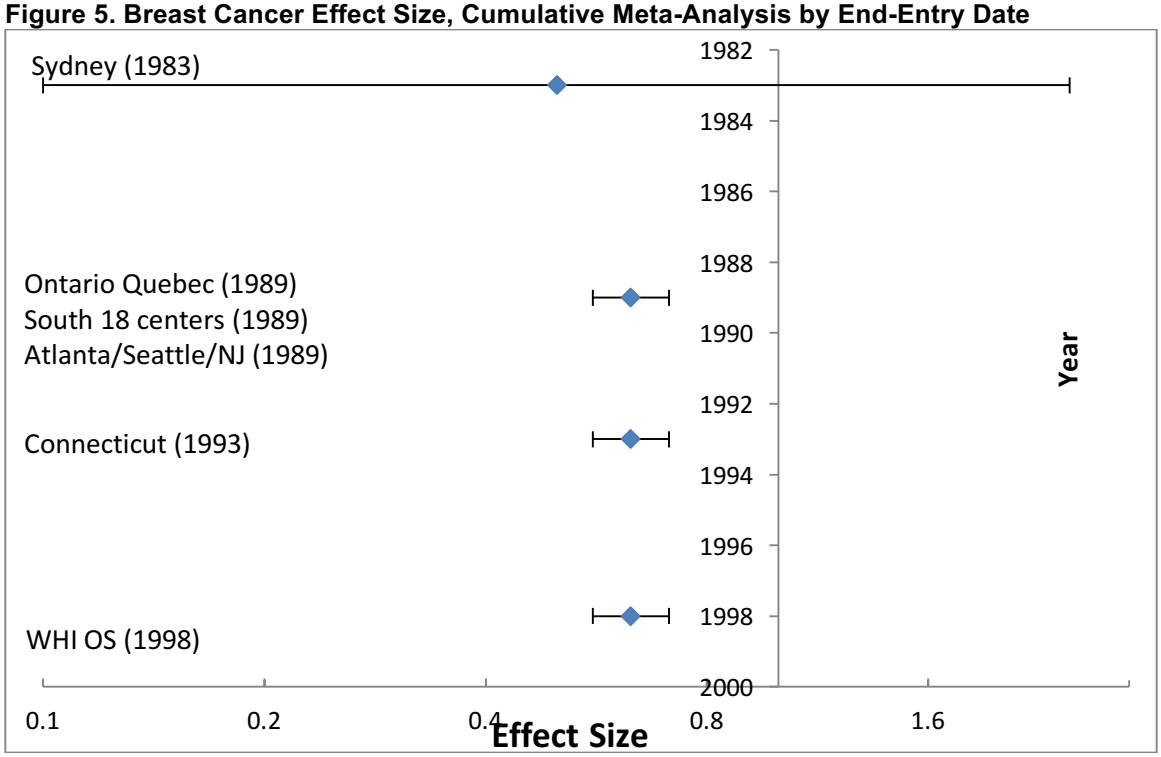


Figure 6. Breast Cancer Effect Size, Cumulative Meta-Analysis by Follow-Up Duration

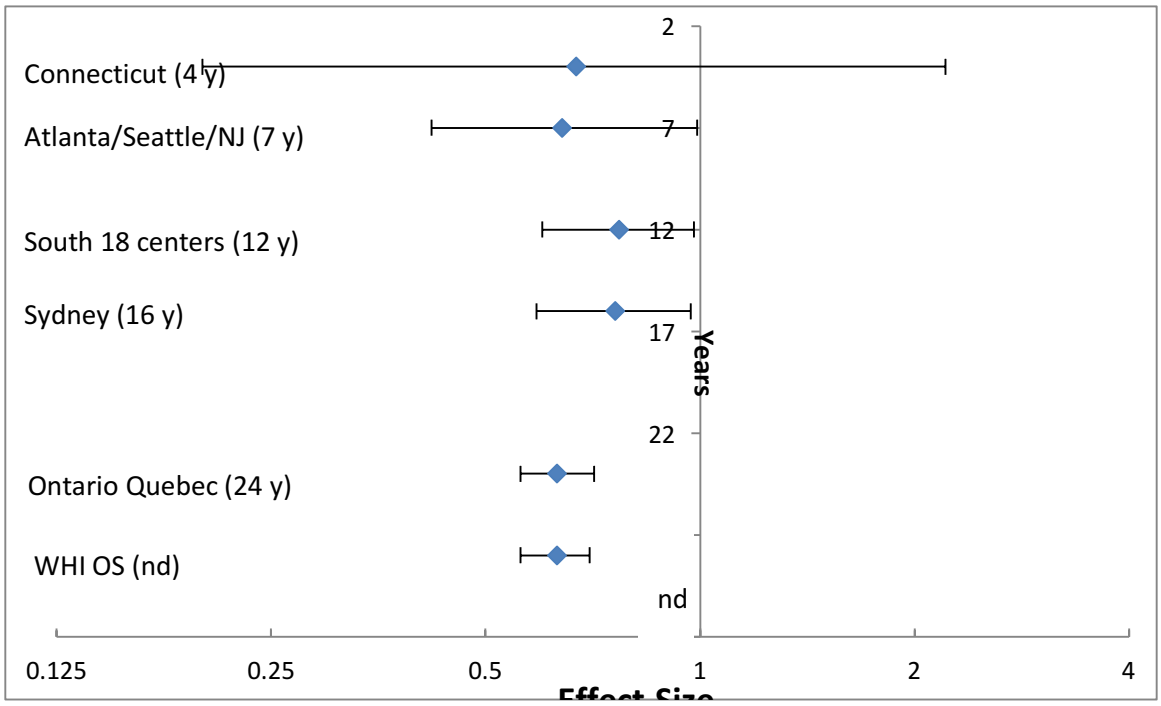


Figure 7. Breast Cancer, Primary (Standardized Incidence Ratios)

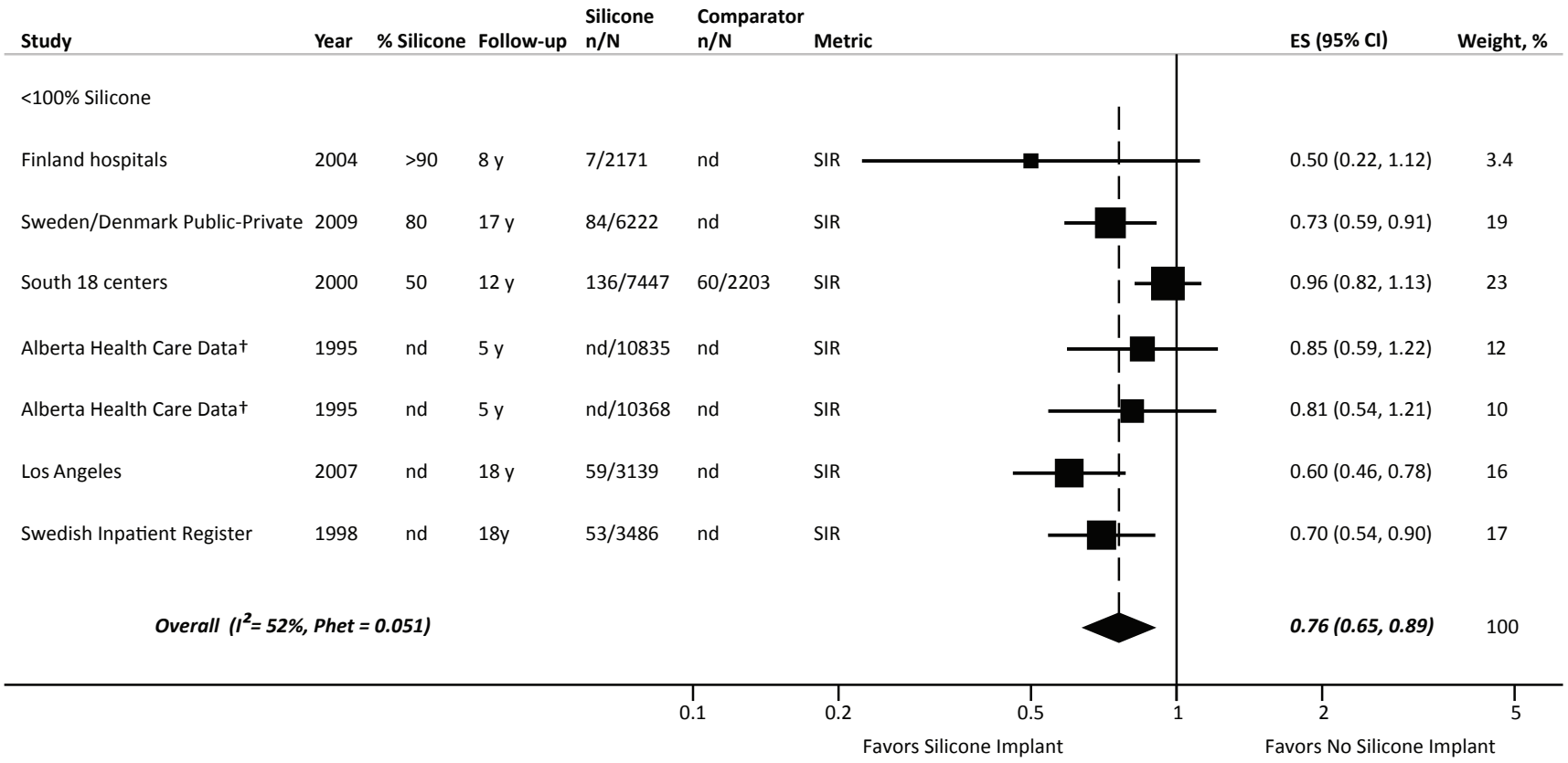


Figure 8. Breast Cancer SIR, Cumulative Meta-Analysis by End-Entry Date

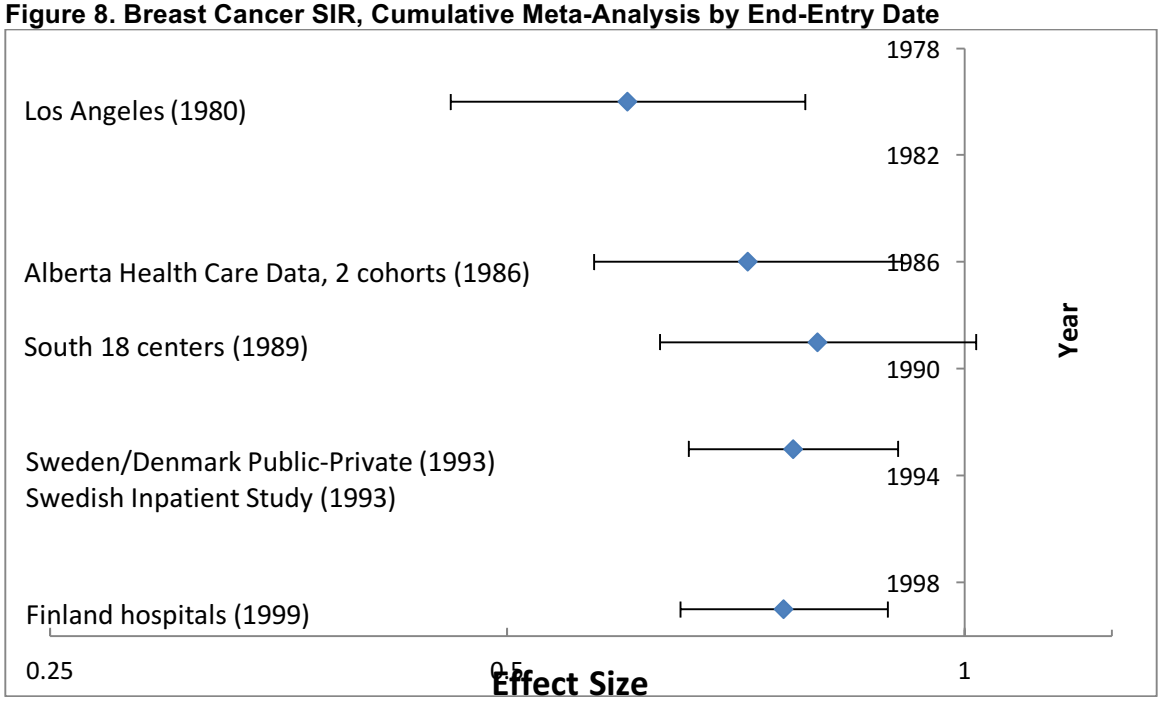
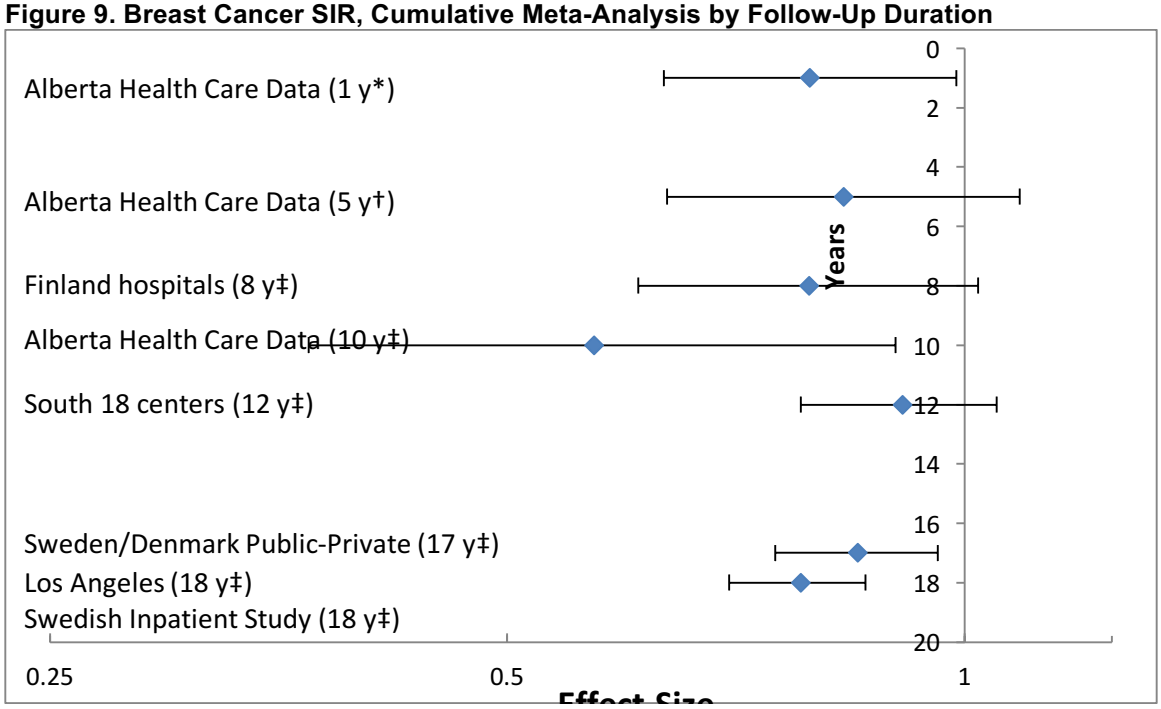


Figure 9. Breast Cancer SIR, Cumulative Meta-Analysis by Follow-Up Duration



* Using 1 year results from Alberta Health Care Data
† Using 5 year results from Alberta Health Care Data
‡ Using 10 year results from Alberta Health Care Data

Cervical Cancer

Eleven studies reported cervical cancer outcomes in women with breast implants (**Table 4**; **Figures 10 & 11**). Only one comparative study (implant vs. no implant) evaluated only women with silicone gel implants; in the other five comparative studies between 50% and 80% of implants were silicone gel (or no data were provided).

The one study of only silicone gel implants found a statistically non-significant relative reduction in cervical cancer (calculated OR = 0.17), but there were no cases of cervical cancer among women with implants. Pooling the three studies that reported within-study direct comparisons (**Figure 10**) yielded an imprecise estimate of no association with a summary ES of 1.04 (95% CI 0.18, 6.00), with no significant heterogeneity. The one study with adequate adjustment reported a highly non-significant estimate favoring a positive association (RR = 1.78; 95% CI 0.7, 4.8). The six studies that reported SIR were heterogeneous, with estimates ranging from 0.83 to 3.18. Pooling five of these studies (**Figure 11**) resulted in no significant association: summary SIR 1.58 (95% CI 0.74, 3.35).

The Ontario/Quebec study found no evidence of a difference by age at implant, time since implant, calendar year of implant (through 1989), or between those with silicone gel and saline implants, polyurethane-coating, or by fill volume.[34]

Across the 11 studies (and across the five studies with 100% silicone gel implants), between 0% and 0.5% of women developed cervical cancer over 3 to 24 years of follow-up (3 to 7 years of follow-up for studies with 100% silicone gel implants). Across all 10 studies, 0.2% (0.1, 0.3) of women with implants developed cervical cancer. Only one of the women in the studies restricted to women with silicone gel implants developed cervical cancer, yielding an estimate of 0.02% (95% CI 0.003, 0.17).

Overall, there is insufficient evidence to determine whether an association exists between breast implants and cervical cancer. The studies were imprecise and found inconsistent associations. Meta-analyses did not yield precise, homogeneous estimates of associations.

Table 4. Cervical Cancer

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Connecticut[69]	100	4 y	No implant (tubal ligat)	0/680 (0.0%)	4/1022 (0.4%)	ORcalc 0.17 (0.01, 3.09)	
Finland hospitals[63]	>90	8 y		1/2171 (0.1%)	--	SIR 1.0 (0.0, 5.6)	
Sweden/Denmark Public-Private[77]	80	17 y	Gen pop	19/6222 (0.3%)	--	SIR 1.03 (0.62, 1.61)	
Ontario/Quebec[100]	66	24 y	Cosm surg	64/24558 (0.3%)	40/15893 (0.3%)	Adj RR 0.94 (0.63, 1.40)	**Inad:** A, Y
			Gen pop		--	SIR 0.83 (NS)	
South 18 Centers[31]	50	12 y	Cosm surg	40/7447 (0.5%)	5/2203 (0.2%)	Adj RR 1.78 (0.7, 4.8)	**Ad**: A, R, T, O1
			Gen pop		--	SIR 3.18 (2.3, 4.3)	
Los Angeles[101]	nd	18 y	Gen pop	7/3139 (0.2%)†	--	SIR 1.19 (0.47, 2.45)	
Swedish Inpatient Register[102]	nd	18 y	Gen pop	12/3486 (0.3%)	--	SIR 1.3 (0.7, 2.2)	
Allergan (Inamed/Natrelle Round) Cohort[88]	100	4 y		1/715 (0.1%)			
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	7 y		0/941 (0.0%)			
Mentor (MemoryGel Round) Cohort[87]	100	3 y		0/1007 (0.0%)			
Mentor (MemoryShape/CPG Anatomic) Cohort[91]	100	6 y		0/955 (0.0%)			
Summary Implant vs. No Implant	**100% (n=1)**					**0.16 (0.01, 3.09)**	
	Any, Direct comparisons (n=3)					**1.04 (0.18, 6.00) P het=0.23, I^2=31%**	
	Any, SIR (n=6)					**5 studies: 1.58 (0.74, 3.35) P het=0.001, I^2=80% 6th study: 0.83 (NS)**	
	Any, Adequate adjustment (n=1)					**1.78 (0.7, 4.8)**	
Summary Percent Implant	**100% (n=5)**			**0.02% (0.003, 0.17)‡**			
	Any (n=11)			**0.2% (0.1, 0.3)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O1 = Other: "predictors of cancer"
† Denominator based on data from 2007 report.[44]
‡ Exact proportion

Figure 10.Cervical Cancer (Direct Comparisons)

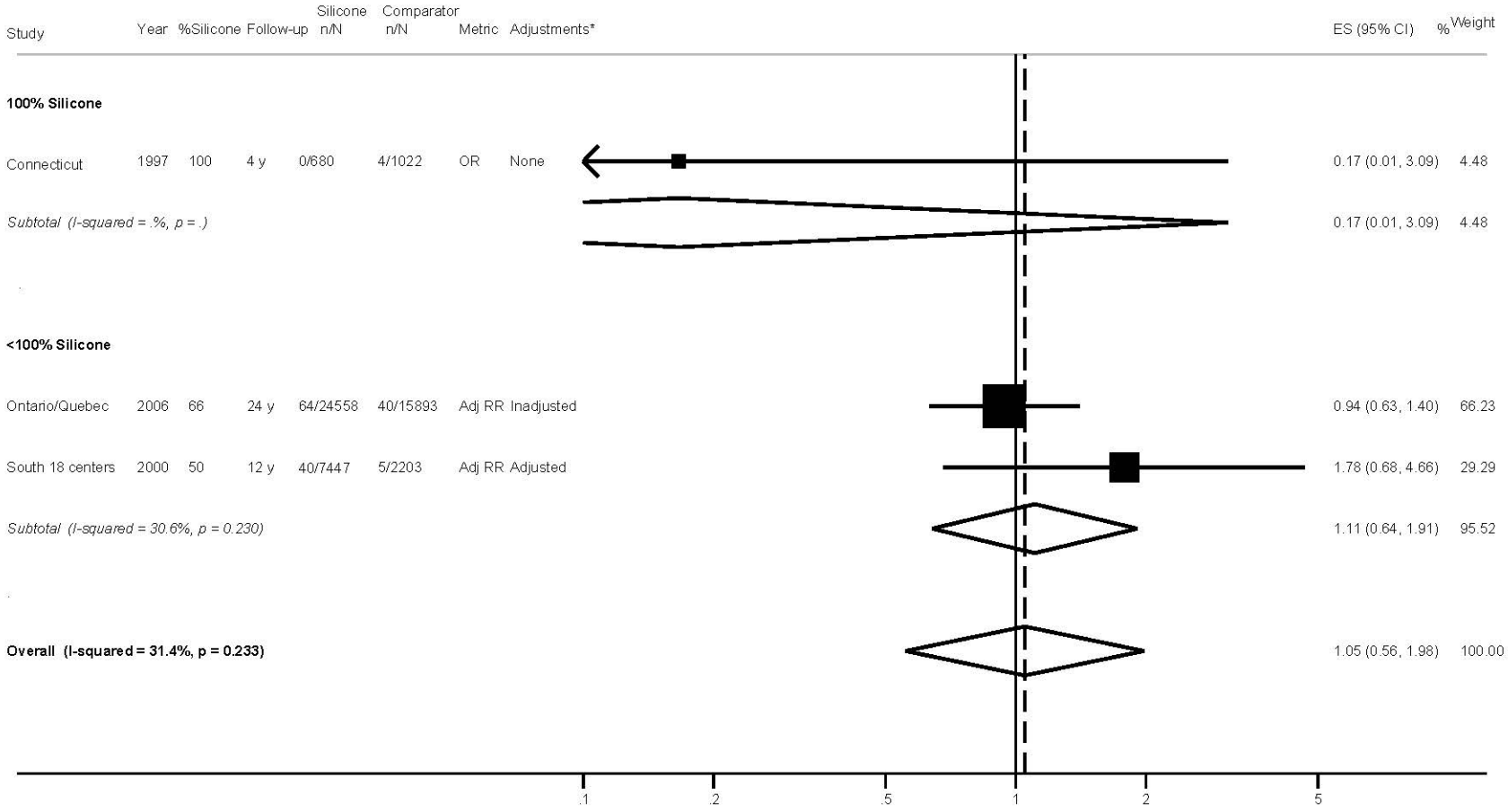
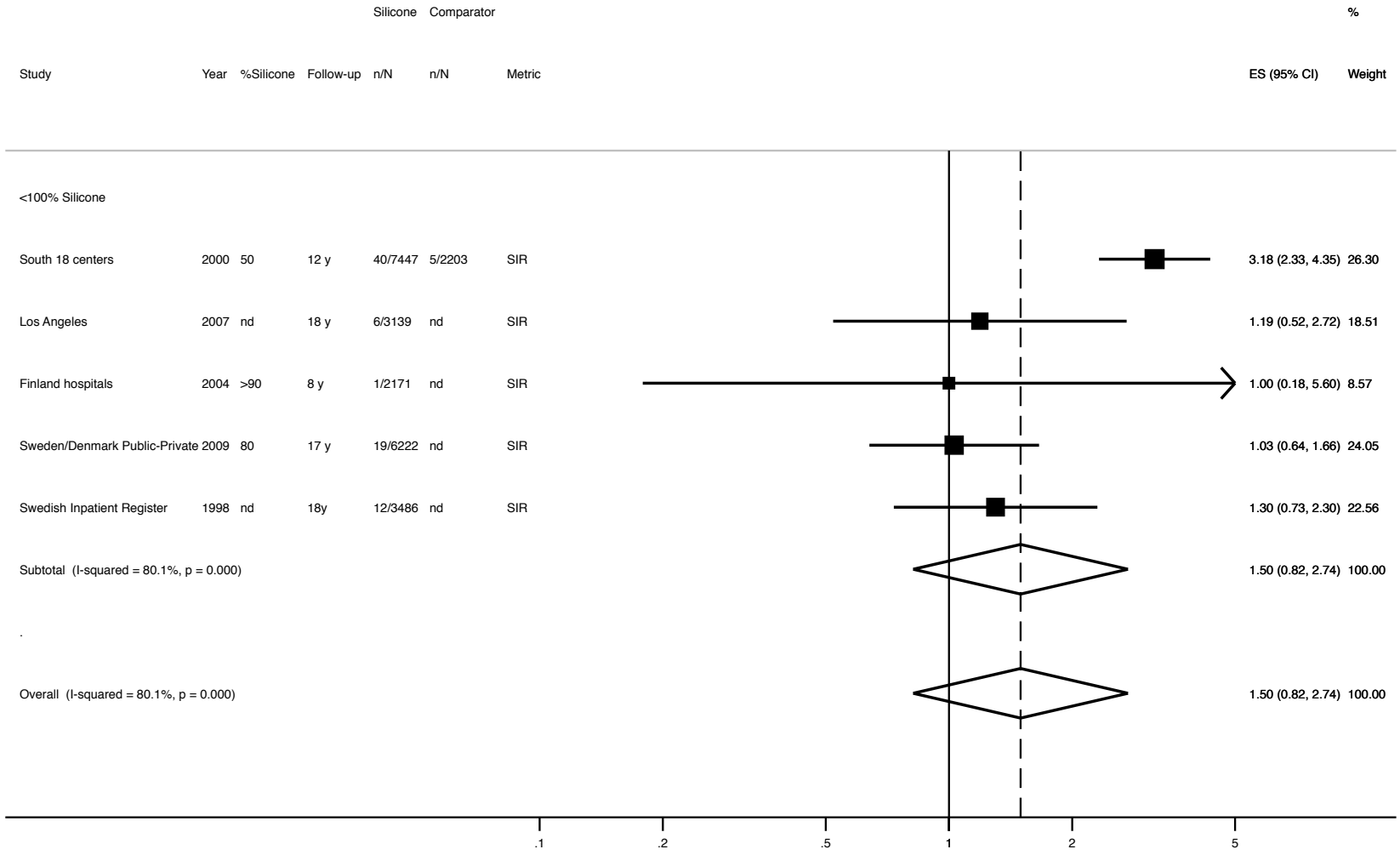


Figure 11. Cervical Cancer (Standardized Incidence Ratios)



Endometrial Cancer

Only two studies reported endometrial cancer outcomes (**Table 5**). Neither evaluated only women with silicone gel implants. Both studies confirmed incident cancer diagnoses through medical records or a cancer registry. The single study with a direct within-study comparison compared women with implants (66% silicone gel) to women without implants, with a mean follow-up duration of 24 years. The (inadequate) adjusted RR for endometrial cancer was 0.55 (95% CI 0.38, 0.78). The studies both reported SIR estimates suggesting fewer cases of endometrial cancer in women with breast implants, but only one was statistically significant.

Based on the single study with a direct comparison and its estimate of the risk of endometrial cancer, the RD between women with and without implants—the absolute percentage of women who would have endometrial cancer associated with their implant (assuming the association is causal)—ranges from −0.29% (95% CI −0.57, −0.10) to −0.46% (95% CI −0.91, −0.16).

The Ontario/Quebec study found no evidence of a difference by age at implant, time since implant, calendar year of implant (through 1989), or between those with silicone gel and saline implants, polyurethane-coating, or by fill volume. Across the two studies 0.3% (95% CI 0.01, 0.4) had endometrial cancer. Neither study was specific to silicone gel implants; although, in all studies the cancers occurred after implantation.

There is limited or suggestive evidence of an association between breast implants and endometrial cancer; however this conclusion is based on only two studies, only one of which provided an inadequately adjusted direct comparison. Women with breast implants may have a large (about 50%) decreased risk of developing endometrial cancer than women without breast implants. The evidence is insufficient regarding the association specifically with silicone gel implants, per se. While the association found in the studies was strong, the evidence base is small, consisting of only two comparative studies in which only 63 women with breast cancer had endometrial cancer and the studies failed to adjust for important possible confounders between the decision to undergo breast implantation and endometrial cancer. The studies do not provide sufficient evidence to determine if a true association exists and, therefore, whether silicone gel implants may have a causal link to endometrial cancer.

Table 5.Endometrial Cancer

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Ontario/Quebec[100]	66	24 y	Cosm surg	52/24558 (0.2%)	71/15893 (0.4%)	Adj RR 0.55 (0.38, 0.78)	**Inad:** A, Y
			Gen pop		--	SIR 0.44 (P<0.05)	
Los Angeles[101]	nd	18 y	Gen pop	11/3139 (0.4%)†	--	SIR 0.73 (0.36, 1.30)	
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=1)					**0.55 (0.38, 0.78)**	
	Any, SIR (n=2)					**0.44 (P<0.05)** **0.73 (0.36, 1.30)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=2)			**0.3% (0.01, 0.4)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.

† Denominator based on data from 2007 report.[44]

Hodgkin Lymphoma

Five studies reported on Hodgkin lymphoma (**Table 6**). One non-comparative study evaluated only women with silicone gel implants. In the four comparative studies, 50% to over 90% of women had silicone gel implants (or data were not reported).

One study reported a direct comparison of women with implants and women with other cosmetic surgery. Fewer women with breast implants had Hodgkin lymphoma after 12 years, but the outcome was rare resulting in an imprecise estimate. All four comparative studies reported SIRs, all of which were statistically non-significant with a range of estimates of 0 to 2.0.

In the single study of only women with silicone gel implants, 0.5% developed Hodgkin lymphoma. Across the five studies, 0.06% (95% CI 0.03, 0.10) developed Hodgkin lymphoma over 4 to 17 years of follow-up.

There is insufficient evidence to determine whether an association exists between breast implants and Hodgkin lymphoma. The studies found imprecise, inconsistent associations.

Leukemia

Five studies reported on leukemia, four of which provided comparative analyses (**Table 7, Figure 12**). One study reported a direct comparison in a population of women only with silicone gel implants and also reported an SIR of their full population of women, 50% of whom had silicone gel implants. The percentage of women with silicone gel implants in other studies fell between these extremes, or was not reported.

Two studies compared women with implants to women with other cosmetic surgery, one of which evaluated only women with silicone gel implants. Both found similar associations (1.66 and 1.34) that were imprecise due to the rarity of leukemia in the studies. The study that evaluated only women with silicone gel implants provided the only adequate analysis, based on adjustment for "predictors of cancer."[31] All five studies reported SIR analyses. These ranged from 0 to 2.19; all were non-significant. Meta-analysis of the three studies that provided sufficient data (**Figure 12**) yielded an imprecise summary SIR of 1.54 (95% CI 0.45, 5.22), with little statistical heterogeneity.

The single study of only women with silicone gel implants found that 0.08% of these women developed leukemia over 12 years of follow-up. Across the five studies, 0.10% developed leukemia after 8 to 24 years of follow-up.

There is insufficient evidence to determine whether an association exists between breast implants and leukemia. Imprecise and inconsistent associations were reported in the studies.

Table 6. Hodgkin Lymphoma

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Finland hospitals[63]	>90	8 y		0/2171 (0.0%)	--	SIR 0.0 (0.0, 7.8)	
Sweden/Denmark Public-Private[77]	80	17 y	Gen pop	2/6222 (0.03%)	--	SIR 1.15 (0.15, 4.16)	
South 18 Centers[31]	50	12 y	Cosm surg	6/7447 (0.08%)	1/2203 (0.05%)	Adj RR 0.11 (NS) (0.01,1.21)†	**Ad**: A, R, T, O1
			Gen pop		--	SIR 0.46 (NS)	
Swedish Inpatient Register[102]	nd	18 y	Gen pop	2/3486 (0.05%)	--	SIR 2.0 (0.5,8.0)	
Mayo Clinic[45]	100	4 y		1/200 (0.5%)			
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons, Adequate adjustment (n=1)					**0.11 (0.01,1.21)**	
	Any, SIR (n=4)					**1.15 (0.15, 4.16)** **0.46 (NS)** **2.0 (0.5,8.0)** **0 (0, 7.8)**	
Summary Percent Implant	**100% (n=1)**			**0.5% (0.07, 3.6)‡**			
	Any (n=5)			**0.06% (0.03, 0.10)‡**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O1 = Other: "predictors of cancer"

† 95% confidence interval derived from unadjusted odds ratio standard error.
‡ Exact proportion

Table 7.Leukemia

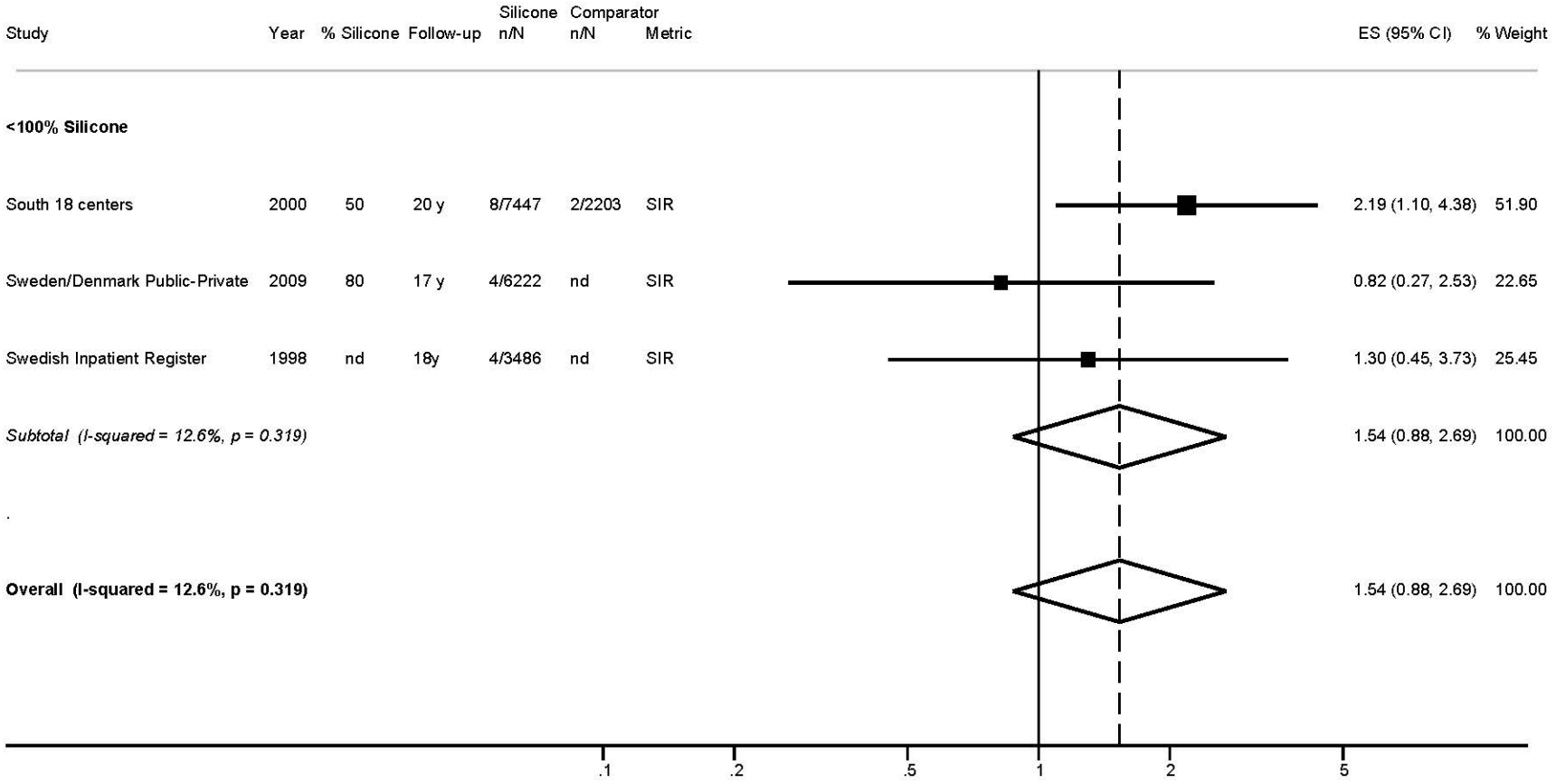
Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
South 18 Centers[31]	100	12 y	Cosm surg	3/3701 (0.08%)	2/2203 (0.09%)	Adj RR 1.66 (NS) (0.28, 9.94)†	**Ad**: A, R, T, O1
	50		Gen pop	8/7447 (0.11%)	--	SIR 2.19 (1.1, 4.4)	
Finland hospitals[63]	>90	8 y		0/2171 (0%)	--	SIR 0.0 (0.0, 7.8)	
Sweden/Denmark Public-Private[77]	80	17 y	Gen pop	4/6222 (0.06%)	--	SIR 0.82 (0.22, 2.09)	
Ontario/Quebec[100]	66	24 y	Cosm surg	27/24558 (0.11%)	16/15893 (0.10%)	Adj RR 1.34 (0.72, 2.51)	**Inad:** A, Y
			Gen pop		--	SIR 0.75 (NS)	
Swedish Inpatient Register[102]	nd	18 y	Gen pop	4/3486 (0.15%)	--	SIR 1.3 (0.4, 3.3)	
Summary Implant vs. No Implant	**100% (n=1)**					**1.66 (0.28, 9.94)**	
	Any, Direct comparisons (n=2)					**1.66 (0.28, 9.94)** **1.34 (0.72, 2.51)**	
	Any, SIR (n=5)					**3 studies:** **1.54 (0.45, 5.22)** **P het=0.32, I^2=13%** **4th study: 0 (0, 7.8)** **5th study: 0.75 (NS)**	
	Any, Adequate adjustment (n=1)					**1.66 (0.28, 9.94)**	
Summary Percent Implant	**100% (n=1)**			**0.08% (0.03, 0.24)**			
	Any (n=5)			**0.10% (0.05, 0.12)‡**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O1 = Other: "predictors of cancer"

† 95% confidence interval derived from unadjusted odds ratio standard error.
‡ Exact proportion

Figure 12. Leukemia(Standardized Incidence Ratios)



Lung Cancer

Twelve studies reported on lung cancer (**Table 8, Figure 13**), six of which provided comparative analyses. Two of the comparative studies analyzed only women with silicone gel implants, comparing them with women who had either other cosmetic surgery or tubal ligations. One additional study, in which 66% of the women had silicone gel implants, directly compared them with women having other cosmetic surgery. Seven of the studies reported SIR analyses. Among the comparative studies, all except the South 18 Centers obtained outcome data (reports of lung cancer) from medical records or registries. However, it is unlikely that misclassification of cancer occurred in the one study that obtained outcome data from patient questionnaires.

The two direct comparisons of women with only silicone gel implants yielded non-significant positive associations (1.50 and 2.6), one of which was highly imprecise. The only study that reported an adequate adjustment found no significant association (but did not report a confidence interval). Furthermore, this study reported only that they adjusted for "predictors of cancer." It is unclear whether this included tobacco smoking, which is highly likely to be a confounder. The third study with a direct comparison found a smaller, also non-significant, association (adjusted RR = 1.18; 95% CI 0.97, 1.44). The seven studies that analyzed SIR for lung cancer yielded values between 0.2 and 2.2, four of which were statistically significant. Meta-analysis of the five SIR estimates with sufficient data (**Figure 13**) yielded a summary SIR of 1.82 (95% CI 1.37, 2.42), with no statistical heterogeneity. The other two studies, omitted from the meta-analysis because no variance data were reported, reported SIRs of 0.2 and 1.04. The studies that determined outcome based on registries or medical records found similar associations as those that were based on patient questionnaires (P=0.35).

Three studies analyzed the association between breast implants and lung cancer by subgroups. The South 18 Centers study found an apparent trend related to years since implant such that the RR was 2.85 after ≥15 years, 2.02 at 10-14 years, 1.81 at 5-9 years, and 1.09 at <5 years.[31] However, they did not analyze whether this trend was statistically significant. The Sweden/Denmark Public-Private study reported no significant difference by duration since implant, but noted a statistically significant association at 15-19 years (RR=2.52; 95% CI 1.2, 4.6) and non-significant associations at other times, including ≥20 years (RR 0.88 to 1.66).[77] The Ontario/Quebec study also found no difference by time since implant.[100] The South 18 Centers and Ontario/Quebec studies also reported no difference by age at implant, calendar year of implant (through 1988 or 1989), or type of implant (South: silicone gel vs. double lumen vs. saline; Ontario/Quebec: silicone gel vs. saline). Lastly, the Ontario/Quebec study also found no evidence of a difference by whether the implant was polyurethane-coated, or by fill volume.

Across the 12 studies, follow-up ranged from 3 to 24 years after implantation and 0% to 1.5% of women with implants developed lung cancer. In summary, 0.20% (95% CI 0.02, 0.66) developed lung cancer. In the eight studies where all women received silicone gel implants, between 0% and 0.65% of women developed lung cancer between 3 and 12 years of follow-up. Across these eight studies, 0.007% (95% CI 0.002, 0.02%) developed lung cancer. The five studies with at least 10 women diagnosed with lung cancer (South 18 Centers, Sweden/Denmark Public-Private, Ontario/Quebec, Los Angeles, and Swedish Inpatient Register) all included only women receiving implants for augmentation; so no comparison with women who had reconstruction was possible. Two of the studies were specific to silicone gel implants, one of which conducted an adequate adjustment (assuming that smoking was included among "predictors of cancer"), but yielded a non-significant association.

There is limited or suggestive evidence of an association between breast implants and lung cancer. The evidence suggests that women with breast implants may have about a small (ES <2.0) 80% increased risk of developing lung cancer compared with women without breast implants. However, this conclusion is based largely on SIR data and the only study with an adequate adjustment (probably including smoking status) found a non-significant association (in women with only silicone gel implants). The studies do not provide sufficient evidence to determine if a true association exists and, therefore, whether silicone gel implants may have a causal link to lung cancer.

Table 8. Lung Cancer

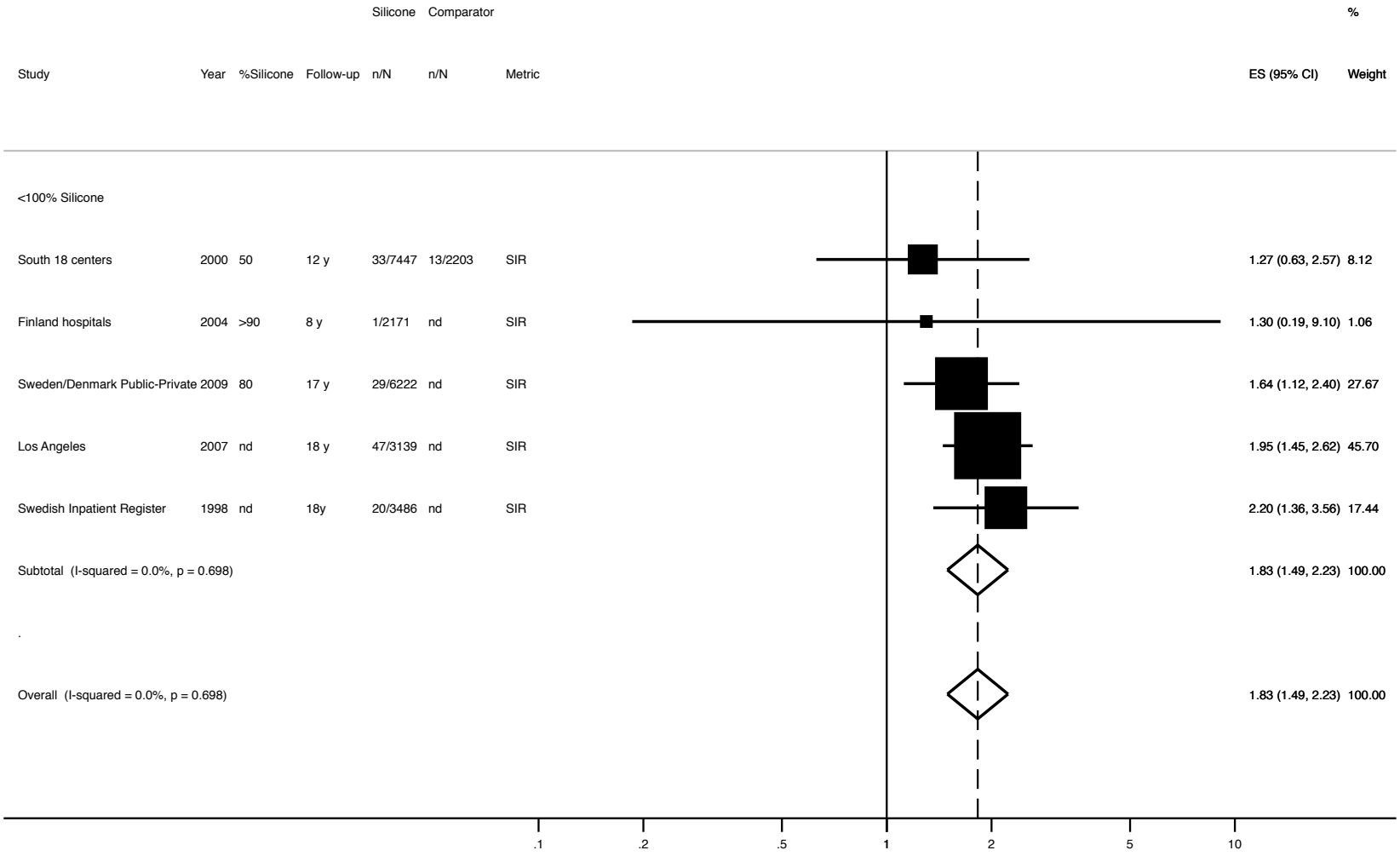
Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Connecticut[69]	100	4 y	No implant (tubal ligat)	2/680 (0.3%)	2/1022 (0.2%)	ORcalc 1.50 (0.21, 10.7)	
Mentor (MemoryGel/MemoryShape) Post-Approval Study[59]	100	5 y		3/41451 (0.01%)	--	SMR 0.2	
South 18 Centers[31]	100	12 y	Cosm surg	24/3701 (0.65%)	13/2203 (0.59%)	Adj RR 2.6 (NS)†	**Ad**: A, R, T, O1
	50		Gen pop	33/7447 (0.44%)	--	SIR 1.27 (1.1, 4.5)	
Finland hospitals[63]	>90	8 y		1/2171 (0.1%)	--	SIR 1.3 (0.0, 7.0)	
Sweden/Denmark Public-Private[77]	80	17 y	Gen Pop	29/6222 (0.5%)		SIR 1.64 (1.10, 2.36)	
Ontario/Quebec[100]	66	24 y	Cosm surg	271/24558 (1.1%)	167/15893 (1.1%)	Adj RR 1.18 (0.97, 1.44)	**Inad:** A, Y
			Gen pop			SIR 1.04 (NS)	
Los Angeles[101]	nd	18 y	Gen pop	47/3139 (1.5%)‡	--	SIR 1.95 (1.43, 2.59)	
Swedish Inpatient Register[102]	nd	18 y	Gen pop	20/3486 (0.6%)	--	SIR 2.2 (1.3, 3.4)	
Allergan (Inamed/Natrelle Round) Cohort[88]	100	4 y		0/715 (0%)			
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	7 y		0/941 (0%)			
Mentor (MemoryGel Round) Cohort[87]	100	3 y		0/1007 (0%)			
Mentor (MemoryShape/CPG Anatomic) Cohort[91]	100	6 y		0/955 (0%)			
Summary Implant vs. No Implant	**100% (n=3)**					**1.50 (0.21, 10.7)** **2.6 (NS)** **SMR 0.2**	
	Any, Direct comparisons (n=3)					**1.50 (0.21, 10.7)** **2.6 (NS)** **1.18 (0.97, 1.44)**	
	Any, SIR (n=7)					**5 studies:** **1.82 (1.37, 2.42)** **P het=0.69, I^2=0%** **6th study: 1.04 (NS)** **7th study: 0.2**	
	Any, Adequate adjustment (n=1)					**2.6 (NS)**	
Summary Percent Implant	**100% (n=8)**			**0.007% (0.002, 0.02)#**			
	Any (n=12)			**0.2% (0.02, 0.66)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O1 = Other: “predictors of cancer”

† The 95% confidence interval derived from unadjusted odds ratio standard error yielded a statistically significant association; therefore omitted.
‡ Denominator based on data from 2007 report.[44]
# Exact proportion

Figure 13. Lung Cancer (Standardized Incidence Ratios)



Multiple Myeloma

Five studies reported on multiple myeloma, three of which provided comparative results (**Table 9**). The three comparative studies included 50%, 66%, or no data reported on the number of women with silicone gel implants. None of the studies provided adjusted analyses.

The single study that provided a direct comparison against women with other cosmetic surgery, had only a single woman (who did not have a breast implant) who developed multiple myeloma after 12 years of follow-up. All four comparative studies reported SIR analyses. Reported SIRs were low (0.46 and 0.7) but non-significant in two studies and not fully evaluable in the other two studies since no women in the implant cohorts developed multiple myeloma.

In the single study of women only with silicone gel implants, 0.11% developed multiple myeloma within 7 years of follow-up. Across the five studies, 0.014% developed multiple myeloma between 7 and 18 years of follow-up.

Overall, there is insufficient evidence to determine whether an association exists between breast implants and multiple myeloma. The studies provided imprecise estimates of association.

Non-Hodgkin Lymphoma

Eight studies reported on the development of non-Hodgkin lymphoma (**Table 10, Figure 14**). Five of the studies provided comparative analyses; between 50% and 80% of the women had silicone gel implants (or no data were reported).

Two studies (with 66% and 50% of the implants being silicone gel) compared women with and without implants. Both analyses were adjusted, but only one conducted an adequate analysis. Both found no significant association. Six of the studies reported SIR analyses. These estimates ranged from 0.7 to 3.7; all were statistically non-significant. Four of the studies provided sufficient data to allow meta-analysis (**Figure 14**), which resulted in a homogeneous, non-significant summary SIR (1.30; 95% CI 0.63, 2.71). The two remaining studies had SIR estimates below 1.

In the two studies of women only with silicone gel implants, 0.2% developed non-Hodgkin lymphoma within 4 and 7 years of follow-up. Across the eight studies, 0.1% developed non-Hodgkin lymphoma between 4 and 24 years of follow-up.

Overall, there is insufficient evidence to determine whether an association exists between breast implants and non-Hodgkin lymphoma. The few studies yielded often imprecise, somewhat inconsistent estimates.

Table 9. Multiple Myeloma

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Finland hospitals[63]	>90	8 y		0/2171 (0%)	--	SIR 0.0 (0.0, 19.0)	
Ontario/Quebec[34]	66	15 y	Gen pop	3/24558 (0.01%)	--	SIR 0.46 (0.09, 1.33)	
South 18 Centers[31]	50	12 y	Cosm surg	0/7447 (0%)	1/2203 (0.05%)	ORcalc 0.10 (0.004, 2.42)	
			Gen pop		--	SIR 0	
Swedish Inpatient Register[102]	nd	18 y	Gen pop	1/3486 (0.03%)	--	SIR 0.7 (0.0, 4.1)	
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	7 y		1/941 (0.1%)			
Summary Implant vs. No Implant	**100% (n=0)**					**No Data**	
	Any, Direct comparisons (n=1)					**0.10 (0.004, 2.42)**	
	Any, SIR (n=4)					**0.46 (0.09, 1.33)** **0 (0, 19.0)** **0 (NS)** **0.7 (0.0, 4.1)**	
Summary Percent Implant	**100% (n=1)**			**0.1% (0.02, 0.6)**			
	Any (n=5)			**0.014% (0.006, 0.033)***			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Exact proportion

Table 10. Non-Hodgkin Lymphoma

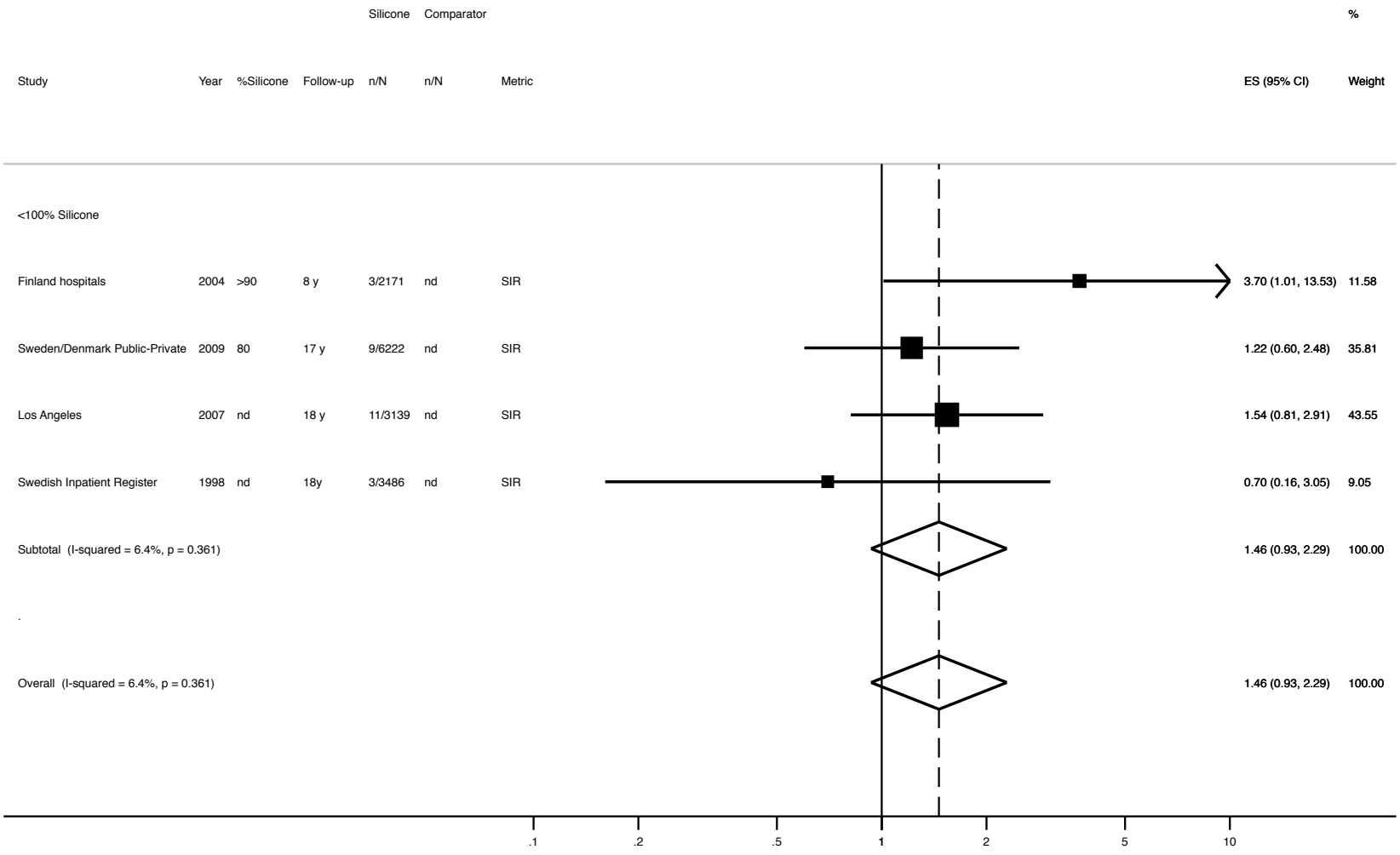
Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Finland hospitals[63]	>90	8 y		3/2171 (0.1%)	--	SIR 3.7 (0.8, 10.7)	
Sweden/Denmark Public-Private[77]	80	17 y	Gen pop	9/6222 (0.1%)	--	SIR 1.22 (0.56, 2.32)	
Ontario/Quebec[34]	66	24 y	Cosm surg	63/24558 (0.3%)	45/15893 (0.3%)	Adj RR 1.03 (0.70, 1.52)	**Inad:** A, Y
			Gen pop		--	SIR 0.84 (NS)	
South 18 Centers[31]	50	12 y	Cosm surg	6/7447 (0.1%)	4/2203 (0.2%)	Adj RR 0.55 (NS) (0.16, 1.95)†	**Ad**: A, R, T, O1
			Gen pop		--	SIR 0.72 (NS)	
Los Angeles[101]	nd	18 y	Gen pop	11/3139 (0.4%)‡	--	SIR 1.54 (0.77, 2.75)	
Swedish Inpatient Register[102]	nd	18 y	Gen pop	3/3486 (0.09%)	--	SIR 0.7 (0.1, 1.9)	
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	7 y		1/941 (0.1%)			
Mayo Clinic[45]	100	4 y		1/200 (0.5%)			
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=2)					**1.03 (0.70, 1.52)** **0.55 (0.16, 1.95)**	
	Any, SIR (n=6)					**4 studies:** **1.30 (0.63, 2.71)** **P het=0.81, I^2=84%** **5th study: 0.84 (NS)** **6th study: 0.72 (NS)**	
	Any, Adequate adjustment (n=1)					**0.97 (0.53, 1.76)**	
Summary Percent Implant	**100% (n=2)**			**0.2% (0.04, 0.7)#**			
	Any (n=8)			**0.1% (0.07, 0.22)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O1 = Other: "predictors of cancer"

† 95% confidence interval derived from unadjusted odds ratio standard error.
‡ Denominator based on data from 2007 report.[44]
# Exact proportion

Figure 14. Non-Hodgkin Lymphoma (Standardized Incidence Ratios)



Uterine Cancer

Six studies reported on the cancer of the uterus (**Table 11**). Three of the studies (one of which was restricted to women with silicone gel implants) provided comparative analyses.

The two direct comparison studies, one of which included only women with silicone gel implants and the other of which provided an adequate adjustment, yielded non-significant and imprecise associations between breast implants and uterine cancer. Three studies reported SIR analysis, which were inconsistent (0.7, 0.74, and 1.15) and non-significant.

Across the six studies, follow-up ranged from 3 to 17 years and between 0% and 0.2% of women with implants developed uterine cancer. The summary estimate was that 0.1% (95% CI 0.04, 0.02) developed uterine cancer. However, among three studies restricted to women with silicone gel implants, only one woman had uterine cancer, or 0.04% (95% CI 0.005, 0.3).

Overall, there is insufficient evidence to determine whether an association exists between breast implants and uterine cancer. The few studies yielded often imprecise, inconsistent estimates.

Vulvar Cancer

Six studies reported on vulvar cancer (**Table 12**), two of which provided comparative analyses. The comparative study included women only 50% of whom had silicone gel implants or provided no data. The Los Angeles study obtained cancer data from medical records while the South 18 Centers study asked patients about their cancer history in a questionnaire. However, it is unlikely that misclassification of cancer occurred in this study.

The one study that provided a direct comparison with women with other cosmetic surgery conducted an adequate analysis. It found a non-significant, imprecise association. The two comparative studies found consistent statistically significant SIR estimates (2.51 and 3.14).

None of the women in the four studies with 100% silicone gel implants developed vulvar cancer (95% CI 0%, 0.2%). Across all six studies, 0.11% (0.07, 0.18) developed vulvar cancer. Neither of the studies was specific to silicone gel implants.

While the two SIR analyses found significant associations, the single direct comparison, which was adequately adjusted found no significant association. Thus, overall, there is insufficient evidence to determine whether an association exists between breast implants and vulvar cancer.

Table 11. Uterine Cancer

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Connecticut[69]	100	4 y	No implant	0/680 (0%)	4/1022 (0.4%)	ORcalc 0.17 (0.01, 3.09)	
Finland hospitals[63]	>90	8 y		1/2171 (0.1%)	--	SIR 0.7 (0.0, 4.0)	
Sweden/Denmark Public-Private[77]	80	17 y	Gen pop	10/6222 (0.1%)	--	SIR 0.74 (0.35, 1.36)	
South 18 Centers[31]	50	12 y	Cosm surg	17/7447 (0.2%)	8/2203 (0.2%)	Adj RR 0.9 (NS) (0.39, 2.09)†	**Ad**: A, R, T, O1
			Gen pop		--	SIR 1.15 (NS)	
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	7 y		1/941 (0.1%)			
Mentor (MemoryGel Round) Cohort[87]	100	3 y		0/1007 (0%)			
Summary Implant vs. No Implant	**100% (n=1)**					**0.17 (0.01, 309)**	
	Any, Direct comparisons (n=2)					**0.17 (0.01, 309)** **0.9 (0.39, 2.09)**	
	Any, SIR (n=3)					**0.74 (0.35, 1.36)** **0.7 (0.0, 4.0)** **1.15 (NS)**	
	Any, Adequate adjustment (n=1)					**0.9 (NS)**	
Summary Percent Implant	**100% (n=3)**			**0.04% (0.005, 0.3)‡**			
	Any (n=6)			**0.1% (0.04, 0.2)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O1 = Other: "predictors of cancer"

† 95% confidence interval derived from unadjusted odds ratio standard error.
‡ Exact proportion

Table 12. Vulvar Cancer

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
South 18 Centers[31]	50	12 y	Cosm surg	6/7447 (0.1%)	1/2203 (0.05%)	Adj RR 1.24 (NS) (0.15, 10.3)†	**Ad**: A, R, T, O1
			Gen pop		--	SIR 2.51 (1.2, 3.9)	
Los Angeles[101]	nd	18 y	Gen pop	10/3139 (0.3%)‡	--	SIR 3.14 (1.50, 5.77)	
Allergan (Inamed/Natrelle Round) Cohort[88]	100	4 y		0/715 (0.0%)			
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	7 y		0/941 (0.0%)			
Mentor (MemoryGel Round) Cohort[87]	100	3 y		0/1007 (0.0%)			
Mentor (MemoryShape/CPG Anatomic) Cohort[91]	100	6 y		0/955 (0.0%)			
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons, Adequate adjustment (n=1)					**1.24 (0.15, 10.3)**	
	Any, SIR (n=2)					**2.51 (1.2, 3.9)** **3.14 (1.50, 5.77)**	
Summary Percent Implant	**100% (n=4)**			**0% (0, 0.2)‡**			
	Any (n=6)			**0.11% (0.07, 0.18)‡**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O1 = Other: "predictors of cancer"

† 95% confidence interval derived from unadjusted odds ratio standard error.
‡ Denominator based on data from 2007 report.[44]
# Exact proportion

Connective Tissue, Rheumatologic, and Auto-Immune Diseases

Amyloidosis

A single study of women, at most 84% of whom had a silicone gel implant, found no cases of amyloidosis after 13 years of follow-up (**Table 13**). The studies do not provide evidence regarding the association between silicone gel implants and amyloidosis.

Ankylosing Spondylitis

Two comparative studies from Scandinavia, both with women with implants of any type, found non-significant, imprecise associations between implants and ankylosing spondylitis (**Table 14**). The two studies differed in their estimates (OR = 0.3 and 3.2), but there were only nine cases of ankylosing spondylitis across both study groups in both studies, yielding very wide confidence intervals. In the two studies, after 9 or 13 years of follow-up, 0.04% (95% CI 0.01, 0.10) had ankylosing spondylitis. There is insufficient evidence to determine whether an association exists between breast implants and ankylosing spondylitis.

Chronic Fatigue Syndrome

One comparative study of women, 50% of whose implants were silicone gel, and two single-group studies evaluated chronic fatigue syndrome (**Table 15**). The comparative study conducted an adequately adjusted analysis and found an adjusted RR of 2.4 (95% CI 1.6, 3.6) for developing chronic fatigue syndrome during 12 years of follow-up after breast implantation. While the study was adequately adjusted (adjusting for factors associated with chronic fatigue such as education and family history), found a strong association (ES ≥2.0), and evaluated only new diagnoses since implantation, the study was not specific to silicone gel implants.

The study reported no difference in association by age at implant, time since implant, or calendar year of implant (through 1992).The range of risk of disease across studies was wide, from 0.4% to 9.0%, likely due to varying definitions of chronic fatigue syndrome. Pooling of all three studies or just the two studies with 100% silicone gel implants yielded a summary 3.3% who had chronic fatigue syndrome with a wide 95% confidence intervals; for silicone gel studies the CI was 0 to 17%.

There is insufficient evidence to determine whether an association exists between breast implants and chronic fatigue syndrome. While a single study found a strong association after adequate adjustment, there are no confirmatory studies.

Dermatomyositis

A single study compared women with and without breast implants (with an unreported percentage of silicone gel implants) and reported an SIR for dermatomyositis (**Table 16**). Only one woman in the study was given the diagnosis; thus the comparative risk of disease and the SIR were imprecise. The study found that 0.01% (95% CI 0.002, 0.10) of women with implants had dermatomyositis after 9 years of follow-up after breast implantation. There is insufficient evidence to determine whether an association exists between breast implants and dermatomyositis.

Note: See “Dermatomyositis and Polymyositis”, next.

Table 13. Amyloidosis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Denmark Public-Private[53]	≤84	13 y	No implant	0/2761 (0%)	0/8787 (0%)	No events	
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=1)					**No events**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=1)			**0% (0, 0.3)***			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Exact proportion

Table 14. Ankylosing Spondylitis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Denmark Public-Private[53]	≤84	13 y	Cosm Surg	1/2761 (0.04%)	5/8787 (0.06%)	ORcalc 0.63 (0.07, 5.45)	
Swedish Inpatient Register[79]	nd	9 y	Br Reduc	3/7431 (0.04%)	0/3351 (0.0%)	ORcalc 3.16 (0.16, 61.2)	
			Gen Pop		--	SHR 0.74 (0.35, 1.36)	
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=2)					**0.63 (0.07, 5.45)** **3.16 (0.16, 61.2)**	
	Any, SIR (n=1)					**0.74 (0.35, 1.36)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=2)			**0.04% (0.01, 0.10)***			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Exact proportion

Table 15. Chronic Fatigue Syndrome

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
South 18 Centers[32]	50	12 y	Cosm surg	246/7234 (3.4%)	27/2138 (1.3%)	Adj RR 2.4 (1.6, 3.6)	**Ad**: A, R, T, O3
Mentor (MemoryGel Round) Cohort[87]	100	9 y		4/1008 (0.4%)			
Birmingham, AL[35]	100	20 y		31/344 (9.0%)			
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons, Adequate adjustment (n=1)					**2.4 (1.6, 3.6)**	
Summary Percent Implant	**100% (n=2)**			**3.3% (0, 16.7)**			
	Any (n=3)			**3.3% (0.6, 7.9)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O3 = Other: "specific predictors of CTDs ([e.g.,] education, family history)"

Table 16. Dermatomyositis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Swedish Inpatient Register[79]	nd	9 y	Br Reduc	1/7433 (0.01%)	0/3353 (0%)	ORcalc 1.35 (0.06, 33.2)	
			Gen Pop		--	SHR 3.4 (0.1, 19.1)	
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=1)					**1.35 (0.06, 33.2)**	
	Any, SIR (n=1)					**3.4 (0.1, 19.1)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=1)			**0.01% (0.002, 0.10)***			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.
* Exact proportion

Dermatomyositis and Polymyositis

Five studies reported on combined dermatomyositis and polymyositis (**Table 17, Figure 15**). None of the studies were restricted to women with silicone gel implants. The diagnoses were rare.

Four of the studies reported direct comparisons with women without breast implants or with other cosmetic surgery; however, in one of these studies no women received the combined diagnosis. Meta-analysis of the three remaining studies (**Figure 15**) yielded a homogeneous, but imprecise summary ES = 1.97 (95% CI 0.08, 15.3).

Across the five studies 0.01% (95% CI 0.008, 0.02) of the women were given the diagnoses of dermatomyositis or polymyositis.

There is insufficient evidence to determine whether an association exists between breast implants and combined dermatomyositis and polymyositis.

Fibromyalgia

Eleven studies reported on fibromyalgia, four of which were comparative (**Table 18, Figure 16**). The only comparative study restricted to silicone gel implants used what appeared to be a historical control. They reported a RR of 1.08 with a 1-sided P value of 0.7. The three studies that compared all breast implants with no implants also found no significant associations. The pooled ES across the four studies was 1.20 (95% CI 0.83, 1.72) with no statistical heterogeneity (**Figure 16**). The South 18 Centers study provided the only adequately adjusted analysis (adjusting for "specific predictors of connective tissue diseases" including education and family history).[32] This study found no significant association. They also reported no difference in association by age at implant, time since implant, or calendar year of implant (through 1992). A single study reported a standardized hospitalization ratio (SHR), which was non-significant (SHR = 1.6; 95% CI 0.9, 2.7).

The 11 studies had a wide variation in the reported prevalence of fibromyalgia, likely due to different definitions of the disease, ranging from 0.1% to 2.4% for 10 studies and 14% for one study from Alabama. The pooled prevalence for women with silicone gel implants (8 studies) was 1.0% (95% CI 0.3, 2.1) and across all 11 studies of breast implants 1.1% (95% CI 0.3, 2.2).

Overall, there is insufficient evidence to determine whether an association exists between breast implants and fibromyalgia. The studies consistently found small (ES <2.0) non-significant associations, but the studies lack the power to distinguish between a real, small association and no association.

Table 17. Dermatomyositis & Polymyositis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Denmark Reconstruction[50]	≥84	7 y	No implant	0/1435 (0%)	1/3952 (0.03%)	ORcalc 0.91 (0.04, 22.5)	
Denmark Public-Private[53]	≤84	13 y	Cosm Surg	2/2761 (0.07%)	4/8787 (0.05%)	Adj HR 2.8 (0.4, 20.4)	**Inad:** A, Y
Women's Health Cohort Study[75]	70	4 y	No implant	0/3950 (0%)	1/19897 (0.005%)	ORcalc 1.68 (0.07, 41.2)	
Sydney[47]	nd	16 y	No implant	0/458 (0%)	0/687 (0%)	No events	
Nurses Health Study[85]	74	nd		12/87501 (0.01%)			
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=3)					**1.97 (0.08, 15.3) P het=0.84, I^2=0%**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=5)			**0.01% (0.008, 0.02)†**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.

† Exact proportion

Figure 15. Dermatomyositis & Polymyositis

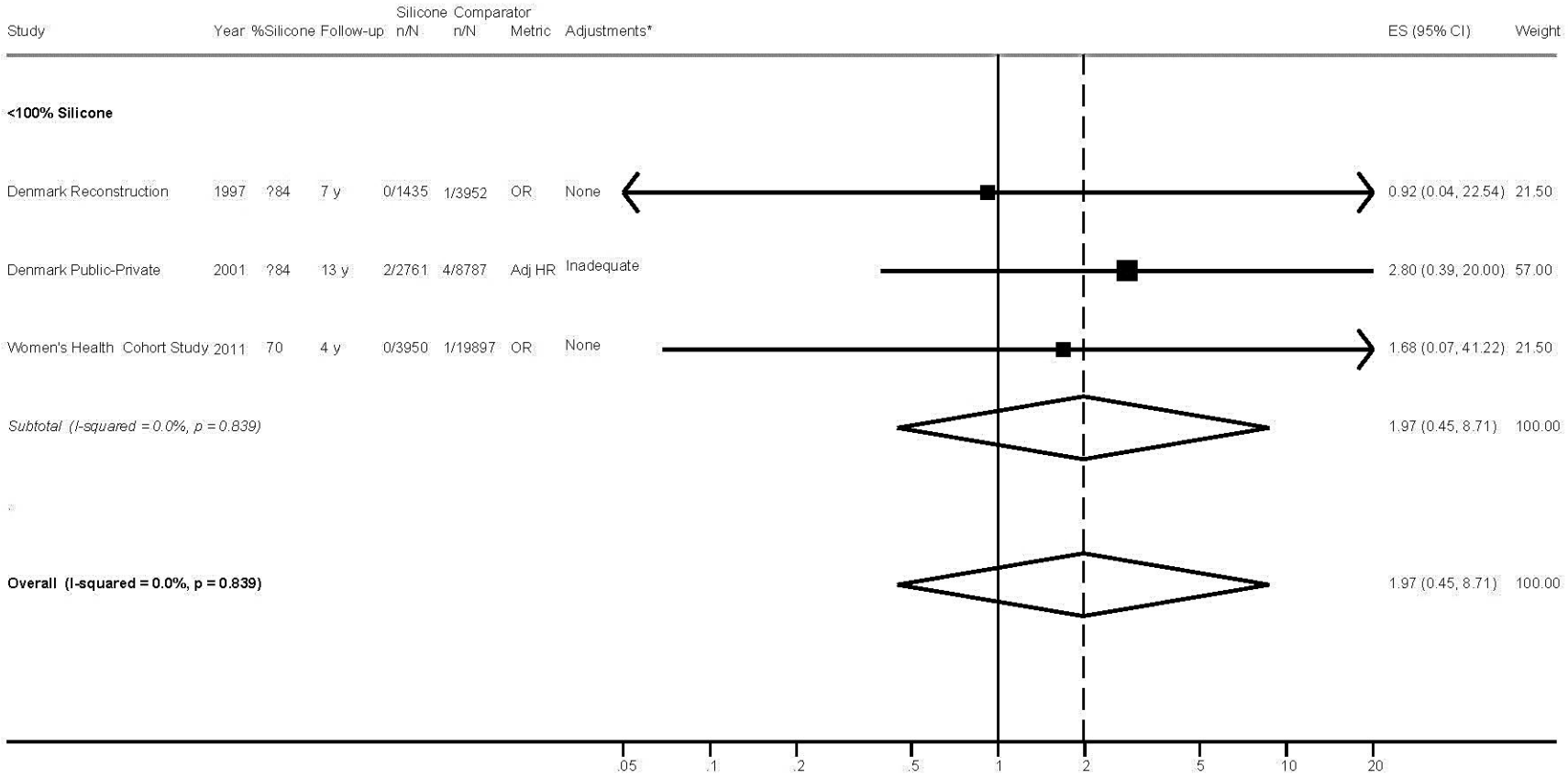


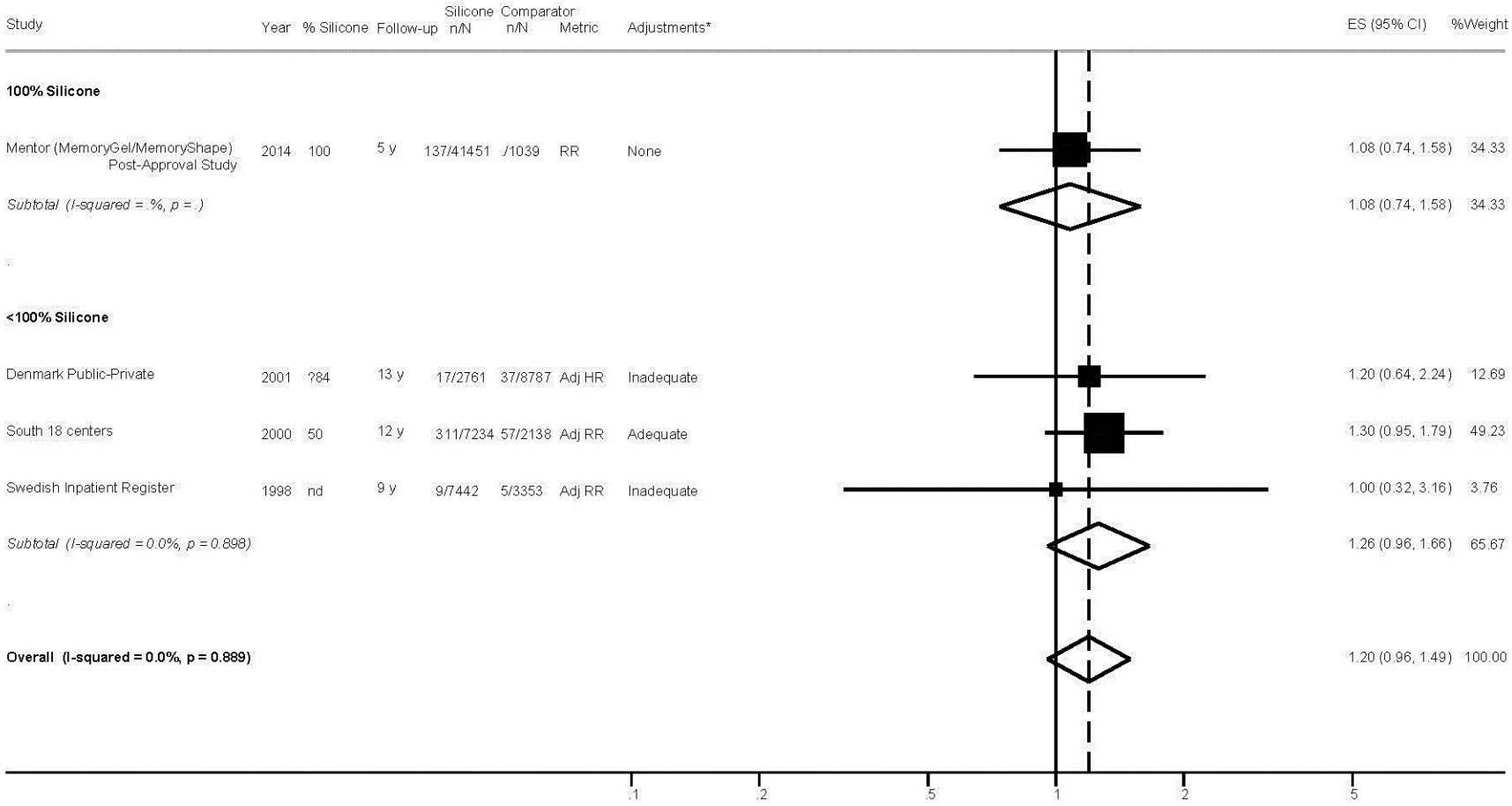
Table 18. Fibromyalgia

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Mentor (MemoryGel/MemoryShape) Post-Approval Study[59]	100	5 y	Hist Cx	137/41451 (0.3%)	nd/1039	RR 1.08 (0.74, 1.58)	
Denmark Public-Private[53]	≤84	13 y	Cosm Surg	17/2761 (0.5%)	37/8787 (0.4%)	Adj HR 1.2 (0.6, 2.1)	**Inad:** A, Y
South 18 Centers[32]	50	12 y	No implant	311/7234 (4.3%)	57/2138 (3%)	Adj RR 1.3 (0.9, 1.7)	**Ad**: A, R, T, O3
Swedish Inpatient Register[79]	nd	9 y	Br Reduc	9/7442 (0.1%)	5/3353 (0.15%)	Adj RR 1.0 (0.3, 3.0)	**Inad:** A, Y
			Gen Pop		--	SHR 1.6 (0.9, 2.7)	
Allergan (Inamed/Natrelle Round) Cohort[88]	100	10 y		3/715 (0.4%)			
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	7 y		2/941 (0.2%)			
Birmingham, AL[35]	100	20 y		47/344 (14%)			
Mentor (MemoryGel Round) Cohort[87]	100	9 y		7/1008 (0.7%)			
Mentor (MemoryShape/CPG Anatomic) Cohort[91]	100	8 y		2/955 (0.2%)			
Sientra[89]	100	3 y		2/1788 (0.1%)			
San Diego[95]	100	7 y		3/125 (2.4%)			
Summary Implant vs. No Implant	**100% (n=1)**					**1.08 (0.74, 1.58)**	
	Any, Direct comparisons (n=4)					**1.20 (0.83, 1.72) P het=0.89, I^2=0%**	
	Any, SIR (n=1)					**1.6 (0.9, 2.7)**	
	Any, Adequate adjustment (n=1)					**1.3 (0.9, 1.7)**	
Summary Percent Implant	**100% (n=8)**			**1.0% (0.3, 2.1)**			
	Any (n=11)			**1.1% (0.3, 2.2)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O3 = Other: “specific predictors of CTDs ([e.g.,] education, family history)”

Figure 16. Fibromyalgia



Hashimoto Thyroiditis

Four studies reported on Hashimoto thyroiditis, two of which were comparative (**Table 19**). Both comparative studies included women with all types of breast implants. The studies from Denmark and Olmstead County had different rates of diagnosis of Hashimoto, which may represent different thresholds for diagnosis or underlying differences in the study populations. However, both found no evidence for an association between breast implants and Hashimoto thyroiditis, with wide confidence intervals.

The other two, single-group, studies included only women with silicone gel implants, both had similar percentages of women with disease at 7 and 9 years after implantation yielding a pooled estimate of 0.1% (95% CI 0, 0.3). Due to the influence of the outlier study from Minnesota, across all studies the summary percentage was somewhat higher at 0.2% (95% CI 0, 0.8%).

There is insufficient evidence to determine whether an association exists between breast implants and Hashimoto thyroiditis. The rarity of the outcome resulted in imprecise estimates of any association.

Mixed Connective Tissue Disease

Only the Nurses Health Study reported on mixed CTD in women with silicone gel implants (**Table 20**). No women in the study were given the diagnosis yielding a risk of 0% (95% CI 0, 0.009). However, they did not report the percentage in women without implants. The studies do not provide evidence regarding the association between silicone gel implants and mixed CTD.

Monoclonal Gammopathy of Undetermined Significance (MGUS)

Only the Nurses Health Study reported on MGUS (**Table 21**). They restricted their analysis to women with silicone gel implants. They found an OR of 0.9 (95% CI 0.1, 5.5). In the group of women with silicone gel implants, 0.9% (95% CI 0.2, 3.1) had a diagnosis of MGUS. There is insufficient evidence to determine whether an association exists between breast implants and MGUS.

Polyarteritis Nodosa

Two comparative studies from Scandinavia reported on polyarteritis nodosa in women with breast implants of any type (**Table 22**). Both studies had few events, despite including over 22,000 women, with no events in one study group in both studies. Thus, the estimates of association are highly imprecise. One study reported a SHR, which was also imprecise, with wide confidence intervals. Overall, 0.01% (95% CI 0.001, 0.07) of women with breast implants had polyarteritis nodosa. There is insufficient evidence to determine whether an association exists between breast implants and polyarteritis nodosa.

Table 19. Hashimoto Thyroiditis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Denmark Public-Private[53]	≤84	13 y	Cosm Surg	0/2761 (0%)	2/8787 (0.02%)	ORcalc 0.64 (0.03, 13.3)	
Olmstead County, MN[54]	78	8 y	No implant	10/749 (1.3%)	21/1498 (1.4%)	ORcalc 0.95 (0.45, 2.03)	
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	7 y		1/941 (0.1%)			
Mentor (MemoryGel Round) Cohort[87]	100	9 y		1/1008 (0.1%)			
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=2)					**0.64 (0.03, 13.3)** **0.95 (0.45, 2.03)**	
Summary Percent Implant	**100% (n=2)**			**0.1% (0, 0.3)**			
	Any (n=4)			**0.2% (0, 0.8)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Table 20. Mixed Connective Tissue Disease

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Nurses Health Study[85]	74	nd		0/87501 (0%)			
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
Summary Percent Implant	**100% (n=1)**			**0% (0, 0.009)***			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Exact proportion

Table 21. Monoclonal Gammopathy of Undetermined Significance

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Nurses Health Study[68]	100	nd	No implant	2/235 (0.9%)	5/288 (2%)	OR 0.92 (0.13, 5.5)	
Summary Implant vs. No Implant	**100% (n=1)**					**0.92 (0.13, 5.5)**	
Summary Percent Implant	**100% (n=1)**			**0.9% (0.2, 3.1)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Table 22. Polyarteritis Nodosa

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Denmark Public-Private[53]	≤84	13 y	Cosm Surg	0/2761 (0%)	4/8787 (0.05%)	ORcalc 0.35 (0.02, 6.57)	
Swedish Inpatient Register[79]	nd	9 y	Br Reduc	1/7442 (0.01%)	0/3353 (0%)	ORcalc 1.35 (0.06, 33.2)	
			Gen Pop		--	SHR 3.1 (0.1, 17.3)	
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=2)					**0.35 (0.02, 6.57)** **1.35 (0.06, 33.2)**	
	Any, SIR (n=1)					**3.1 (0.1, 17.3)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=2)			**0.01% (0.001, 0.07)***			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Exact proportion

Polymyalgia Rheumatica

Two comparative studies reported on polymyalgia rheumatica (**Table 23**). The study from Houston was restricted to women with silicone gel implants, but had only one woman with the diagnosis in their small study. The Swedish study included women with all breast implant types. Both studies yielded imprecise estimates of association. Overall, 0.1% (95% CI 0, 0.4) of women with breast implants had polymyalgia rheumatica. One study reported a SHR, which was also imprecise. There is insufficient evidence to determine whether an association exists between breast implants and polymyalgia rheumatica.

Note: See "Temporal Arteritis & Polymyalgia Rheumatica" below.

Polymyositis

One comparative and one small single group study reported on polymyositis (**Table 24**). The comparative study included women with all breast implant types and had only two women with polymyositis, yielding an imprecise estimated OR of 0.5 (95% CI 0.03, 7.2). The study also reported an imprecise SHR. No women in the small study of women with silicone gel implants had the disease. Across the two studies, 0.01% (95% CI 0.002, 0.09) had polymyositis. There is insufficient evidence to determine whether an association exists between breast implants and polymyositis.

Psoriatic Arthritis

Two Scandinavian comparative studies reported on psoriatic arthritis in women with any type of breast implant (**Table 25**). Both had few women with the diagnosis in at least one study group, resulting in imprecise associations. In one study, the SHR was also imprecise. Across the two studies 0.01% (95% CI 0.001, 0.07) of women with breast implants had psoriatic arthritis. There is insufficient evidence to determine whether an association exists between breast implants and psoriatic arthritis.

Table 23. Polymyalgia Rheumatica

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Houston[11]	100	nd	No implant	1/308 (0.3%)	0/408 (0.0%)	ORcalc 3.99 (0.16, 98.2)	
Swedish Inpatient Register[79]	nd	9 y	Br Reduc	6/7442 (0.1%)	1/3353 (0.03%)	ORcalc 2.70 (0.33, 22.5)	
			Gen Pop		--	SHR 1.4 (0.5, 3.1)	
Summary Implant vs. No Implant	**100% (n=1)**					**3.99 (0.16, 98.2)**	
	Any, Direct comparisons (n=2)					**3.99 (0.16, 98.2)** **2.70 (0.33, 22.5)**	
	Any, SIR (n=1)					**1.4 (0.5, 3.1)**	
Summary Percent Implant	**100% (n=1)**			**0.3% (0.1, 1.8)**			
	Any (n=2)			**0.1% (0, 0.4)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Table 24. Polymyositis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Swedish Inpatient Register[79]	nd	9 y	Br Reduc	1/7442 (0.01%)	0/3353 (0%)	ORcalc 1.35 (0.06, 33.2)	
			Gen Pop		--	SHR 1.7 (0, 9.4)	
San Diego[95]	100	7 y		0/125 (0%)			
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=1)					**1.35 (0.06, 33.2)**	
Summary Percent Implant	**100% (n=1)**			**0% (0, 6.5)***			
	Any (n=2)			**0.01% (0.002, 0.09)†**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Exact proportion

Table 25. Psoriatic Arthritis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Denmark Public-Private[53]	≤84	13 y	Cosm Surg	1/2761 (0.03%)	11/8787 (0.13%)	ORcalc 0.29 (0.04, 2.24)	
Swedish Inpatient Register[79]	nd	9 y	Br Reduc	0/7442 (0%)	2/3553 (0.06%)	ORcalc 0.10 (0.005, 1.99)	
			Gen Pop		--	SHR 0 (0, 3.2)	
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=2)					**0.29 (0.04, 2.24)** **0.10 (0.005, 1.99)**	
	Any, SIR (n=1)					**0 (0, 3.2)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=2)			**0.01% (0.001, 0.07)***			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Exact proportion

Rheumatoid Arthritis

Eighteen studies have reported on rheumatoid arthritis, of which 11 are comparative studies (**Table 26**, **Figures 17-21**). The comparative studies included between 50% and 100% (or no data) of women with silicone gel implants and had follow-up between 4 and 16 years (or no data). Of the 11 comparative studies, five obtained outcome diagnoses through medical records or national registries, three confirmed diagnoses by medical examination (Alberta Health Registry, SE Scotland, Sydney), one did not report how outcomes were obtained (Mentor Post-Approval Study), but two obtained outcomes only from patient questionnaires (Women's Health Cohort, WHI OS). This latter method is potentially problematic for rheumatologic diseases.

Three of the comparative studies were restricted to women with silicone gel implants, one of which compared women with implants to a historical control. Among these studies, the effect sizes were all non-significant and ranged from 0.86 to 1.46. By meta-analysis, the summary ES was homogeneous and statistically significant at 1.44 (95% CI 1.05, 1.97).

The 11 comparative studies reported direct comparisons with women with no implants, other cosmetic surgery, or breast reduction surgery; the results were heterogeneous with comparative rates ranging from 0.86 to 5.5. Two of the studies found statistically significant results (Denmark Reconstruction: OR = 5.5 [95% CI 1.01, 30]; South 18 Centers adjusted RR 1.9 [95% CI 1.4, 2.7]). Across all 11 comparative studies, the pooled ES (**Figure 17**) was statistically significant at 1.38 (95% CI 1.06, 1.80) with statistical heterogeneity (P heterogeneity = 0.005, I^2 = 60%). None of the studies was an outlier in its estimate of association. However, the WHI OS study was a relatively large study with a precise, but unadjusted estimate (calculated OR = 1.01; 95% CI 0.98, 1.05), which was closer to the null than most other studies.[84] In sensitivity analysis, removing this study yielded a larger summary ES = 1.58 (95% CI 1.30, 1.91), which was statistically homogeneous (P heterogeneity = 0.83, I^2 = 0%).

Two of the studies conducted adequate adjustments, controlling for body mass index, tobacco use, hormone replacement therapy, history of breast cancer, and age in the Women's Health Cohort Study,[75] and education, family history, age, race, time since implant, and calendar year of implant in the South 18 Centers study.[32] However, as noted above, the Women's Health Cohort Study may suffer from misclassification bias since rheumatoid arthritis diagnoses were obtained by questionnaire only. The two studies had conflicting results of an imprecise, non-significant adjusted RR = 1.3 (95% CI 0.56, 3.04) in the Women's Health Cohort Study and a near-large, statistically significant adjusted RR = 1.9 (95% CI 1.4, 2.7) in the South 18 Centers study. One study reported a non-significant SHR (1.0; 95% CI 0.6, 1.5).

Cumulative meta-analyses of the direct comparisons by the calendar year that recruitment of women into the studies ended (**Figure 18**) or by follow-up duration (**Figure 19**) did not show trends over time, except for the influential effect of the WHI OS study. Funnel plots were drawn to evaluate possible publication bias. Plotting all studies (**Figure 20**) may indicate missing studies with inverse associations (ES <1.0). However, this plot may again be driven by the WHI OS study. Excluding that study (**Figure 21**), the funnel plot does not suggest evidence of publication bias.

No differences in association were found between studies that determined the outcome based on medical records (or physical examination) versus patient questionnaire (P=0.86), between studies that explicitly analyzed incident disease (since implantation) versus those that may have included prevalent disease (at the time of implantation) (P=0.68), or between studies of augmentation or reconstruction (P=0.81). The effect did not vary by mean duration of follow-up

after implantation (P=0.58) or the reported percent of implants that were silicone gel (P=0.65). The South 18 Centers study reported no difference in association by age at implant, time since implant, or calendar year of implant (through 1992).

Based on the pooled ES and the pooled risk of rheumatoid arthritis, the RD between women with and without implants—the absolute percentage of women who would have rheumatoid arthritis associated with their implant (assuming the association is causal)—ranges from 0.008% (95% CI 0.001, 0.013) to 0.27% (95% CI 0.05, 0.44).

Among the nine studies of women all of whom had silicone gel implants, there was a wide range in the percentage of women with rheumatoid arthritis, ranging from 0 to 2% over 3 to 10 years of follow-up after implant. The pooled percentage was 0.2% (95% CI 0.07, 0.4) for women with silicone gel implants. Across all studies, up to 5.4% of women were diagnosed with rheumatoid arthritis. The pooled percentage for women with any breast implant was higher than women with any breast implant at 0.6% (95% CI 0.3, 1.0). There was no association across studies between the percentage of women with rheumatoid arthritis and mean duration of follow-up after implantation (P=0.12). Among studies that reported the percent of implants that were silicone gel, the higher the percent of silicone gel implants the lower the percent with rheumatoid arthritis. However, the eight silicone gel implant studies did not have a significantly different percentage than the 10 all-implant studies (P=0.30). While the highest percentage of women with rheumatoid arthritis were found in US-studies, across studies the rates were not significantly different in the US than Europe or Canada (P=0.76).The two studies specific to silicone gel implants found similar or null associations as the summary of all 10 studies.

In summary, there is limited or suggestive evidence of an association between breast implants and rheumatoid arthritis. Women with breast implants may have an about 40% increased risk of developing rheumatoid arthritis than women without breast implants, but this summary association is small (ES <2.0) and heterogeneous, warranting a cautious interpretation. The evidence is insufficient regarding the association specifically with silicone gel implants, but these studies are consistent with the studies of all breast implants. The studies do not provide sufficient evidence to determine if a true association exists and, therefore, whether silicone gel implants may have a causal link to rheumatoid arthritis.

Table 26. Rheumatoid Arthritis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
SE Scotland[9]	100	6 y	**No Implant**	**1/207 (0.5%)**	**1/88 91%)**	**OR 0.42 (0.03, 6.83)**	
			Cosm Surg	0/110 (0%)	0/128 (0%)	--	
Mentor (MemoryGel/MemoryShape) Post-Approval Study[59]	100	5 y	Hist Cx	160/41451 (0.4%)	nd/1039	RR 1.46 (1.06, 2.02)	
Italy[81]	100	5 y	No implant	2/102 (2%)	2/102 (2%)	ORcalc 1.00 (0.14, 7.24)	
Denmark Reconstruction[50]	≥84	7 y	No implant	4/1435 (0.3%)	2/3952 (0.05%)	ORcalc 5.52 (1.01, 30.2)	
Denmark Public-Private[53]	≤84	13 y	Cosm Surg	17/2761 (0.6%)	53/8787 (0.6%)	Adj HR 1.3 (0.7, 2.5)	**Inad:** A, Y
Women's Health Cohort Study[75]	70	4 y	No implant	12/3950 (0.3%)	32/19897 (0.2%)	Adj RR 1.3 (0.56, 3.04)	**Ad**: A, O4
WHI OS[84]	67	nd	No implant	67/1241 (5.4%)	4545/85350 (5.3%)	ORcalc 1.01 (0.98, 1.05)	
South 18 Centers[32]	50	12 y	Cosm Surg	258/7234 (3.6%)	499/2138 (23%)	Adj RR 1.9 (1.4, 2.7)	**Ad**: A, R, T, Y, O5
Alberta Health Registry[46]	nd	nd	Cosm Surg	11/1112 (1%)	6/727 (0.8%)	Adj RR 1.44 (0.50, 4.15)	**Inad:** A, T
Swedish Inpatient Register[79]	nd	9 y	Br Reduc	11/7442 (0.1%)	5/3553 (0.2%)	Adj RR 1.3 (0.7, 2.5)	**Inad:** A, Y
			Gen Pop		--	SHR 1.0 (0.6, 1.5)	
Sydney[47]	nd	16 y	No implant	3/458 (0.7%)	2/687 (0.03%)	RR 2.26 (0.38–13.6)	
Allergan (Inamed/Natrelle Round) Cohort[88]	100	10 y		4/715 (0.6%)			
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	7 y		1/941 (0.1%)			
Mentor (MemoryGel Round) Cohort[87]	100	9 y		3/1008 (0.3%)			
Mentor (MemoryShape/CPG Anatomic) Cohort[91]	100	8 y		3/955 (0.3%)			
Sientra[89]	100	3 y		1/1788 (0.1%)			
San Diego[95]	100	7 y		0/125 (0%)			
Nurses Health Study[85]	74	nd		392/87501 (0.4%)			
Summary Implant vs. No Implant	**100% (n=3)**					**1.42 (1.04, 1.95)** **P het=0.64, I^2=0%**	
	Any, Direct comparisons (n=11)					**1.38 (1.06, 1.80)** **P het=0.005, I^2=60%**	
		Augmentation (n=6)				**1.66 (1.20, 2.29)**	**P btw = 0.81**
		Reconstruction (n=3)				**1.93 (0.45, 8.31)**	
		Confirmed diagnosis (n=8)				**1.41 (0.88, 2.27)**	**P btw = 0.86**
		Self-reported diagnosis(n=3)				**1.35 (0.95, 1.92)**	
	Any, SIR (n=1)					**1.0 (0.6, 1.5)**	
	Any, Adequate adjustment (n=2)					**1.3 (0.56, 3.04)** **1.9 (1.4, 2.7)**	
Summary Percent Implant	**100% (n=9)**			**0.2% (0.07, 0.4)**			
	Any (n=18)			**0.6% (0.03, 1.0)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O4 = body mass index, tobacco use, hormone replacement therapy, history of breast cancer
O5 = education, family history

Figure 17. Rheumatoid arthritis

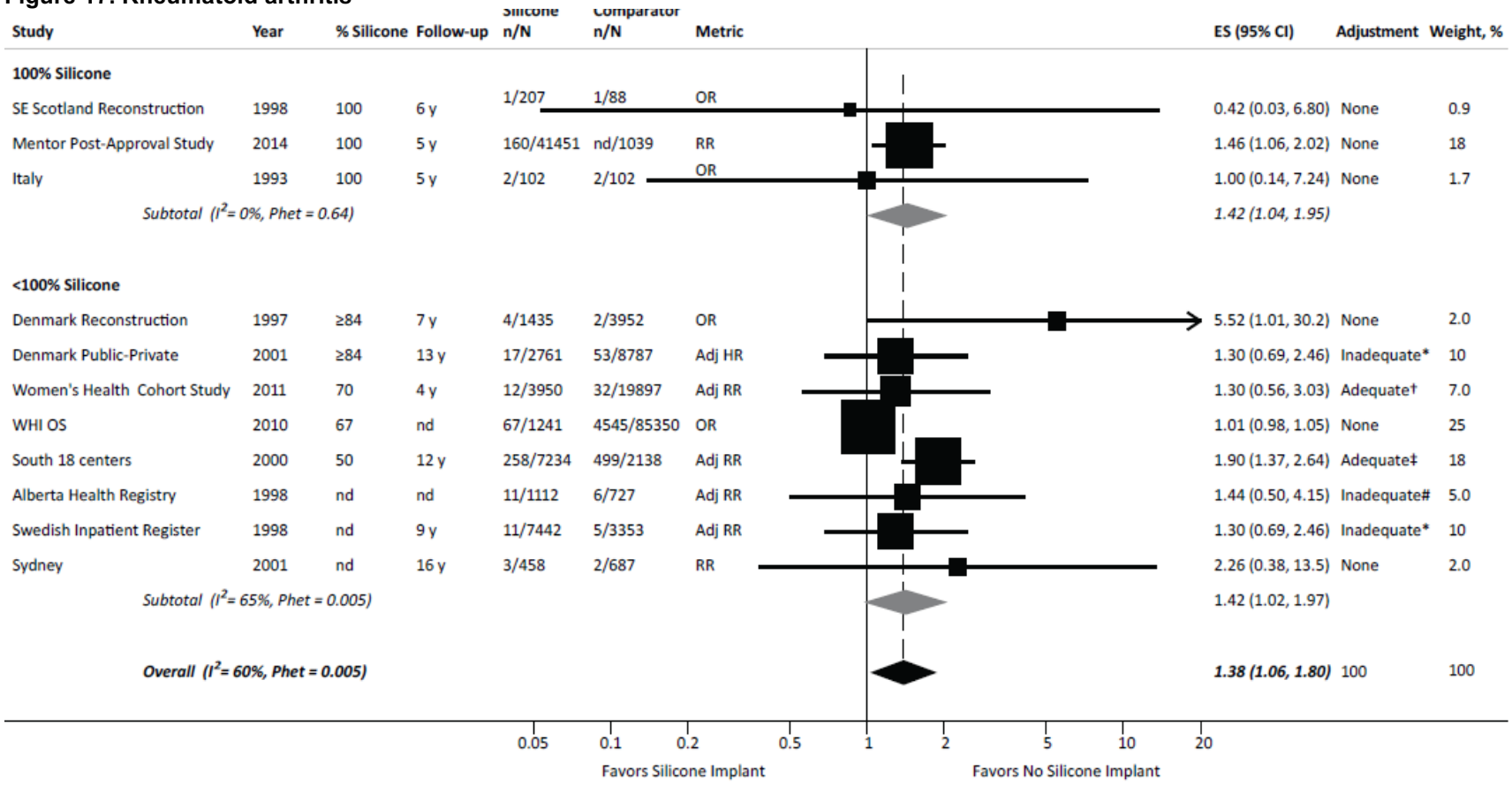


Figure 18. Rheumatoid Arthritis, Cumulative Meta-Analysis by End-Entry Date

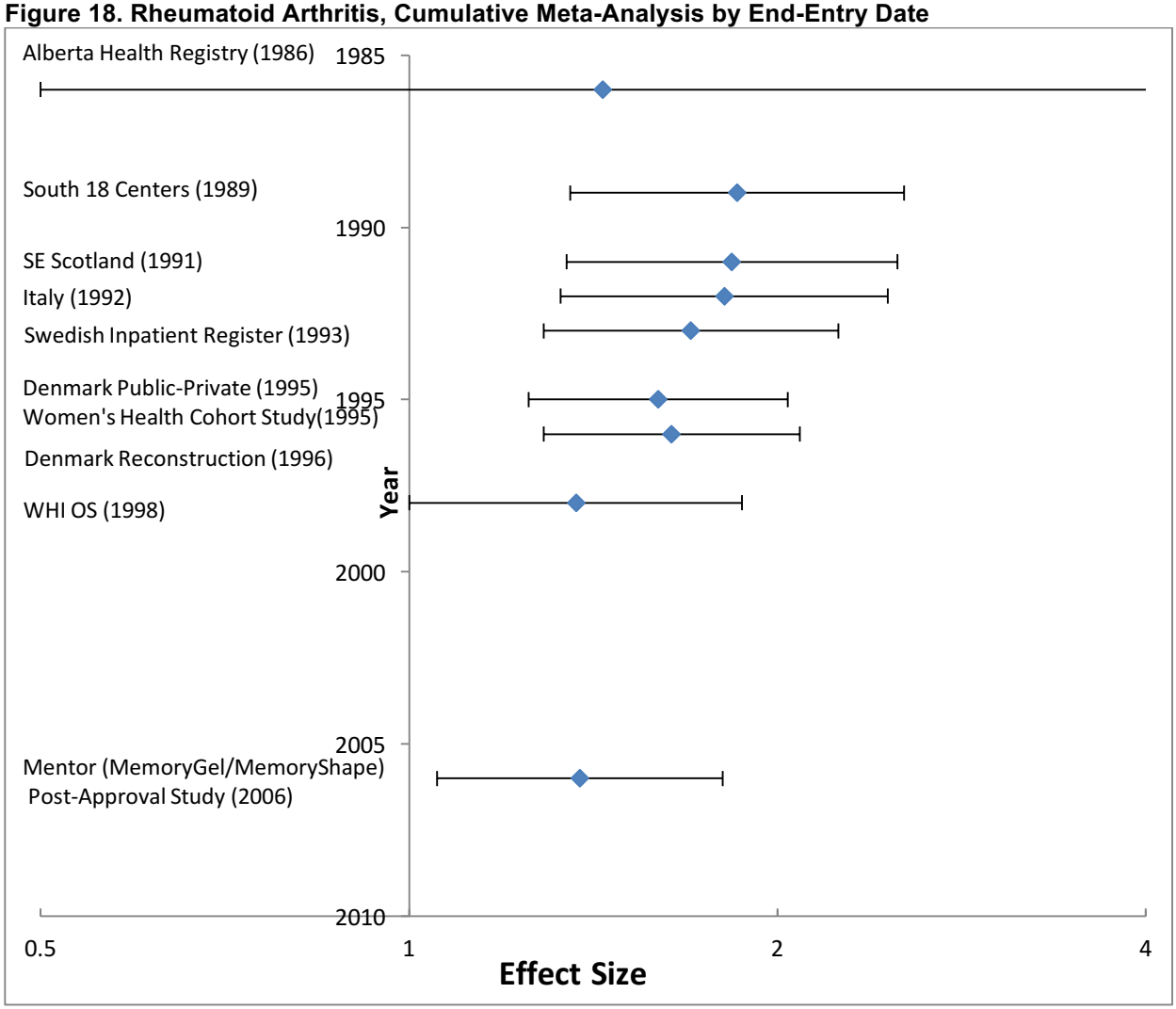


Figure 19. Rheumatoid Arthritis, Cumulative Meta-Analysis by Follow-Up Duration

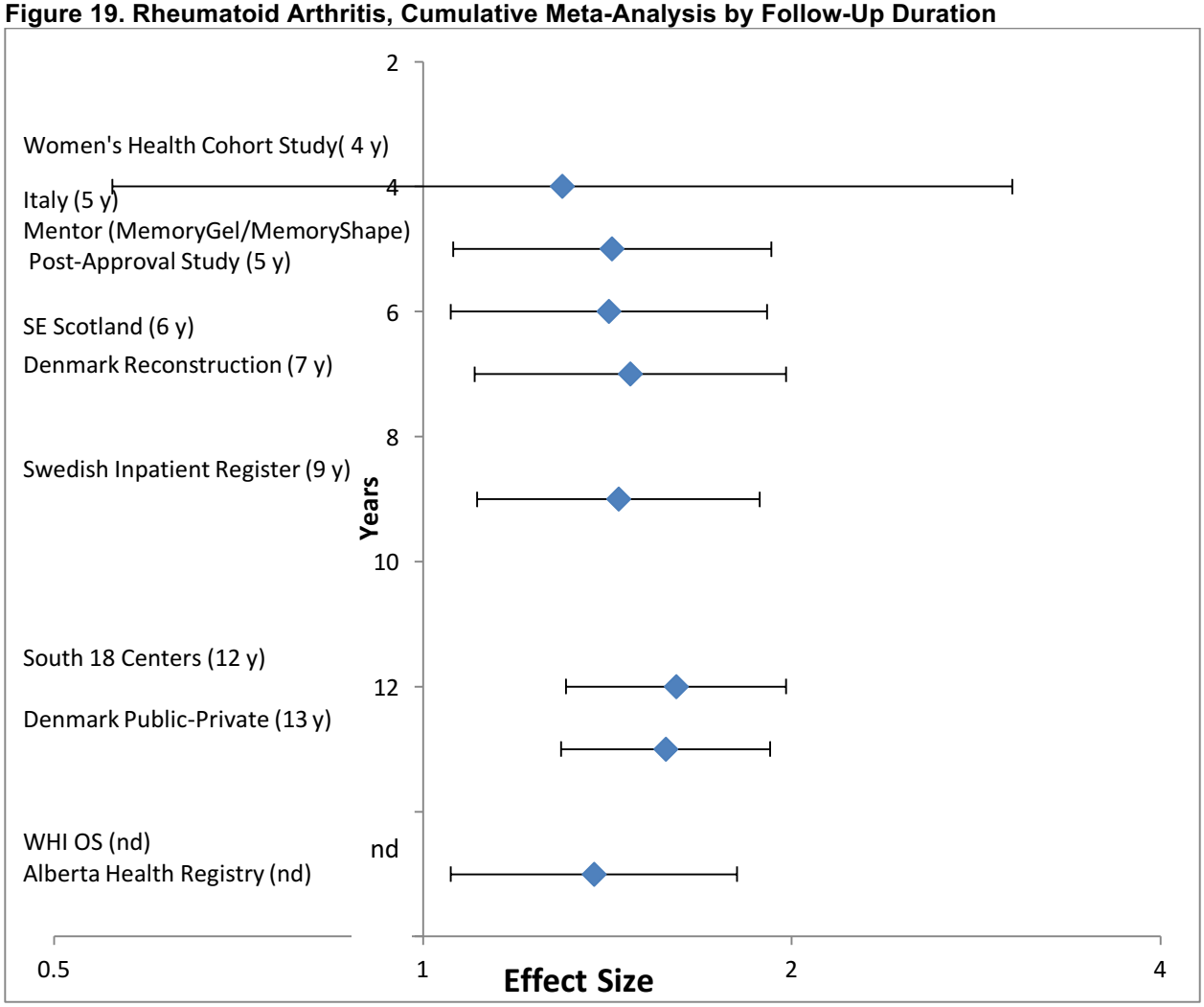
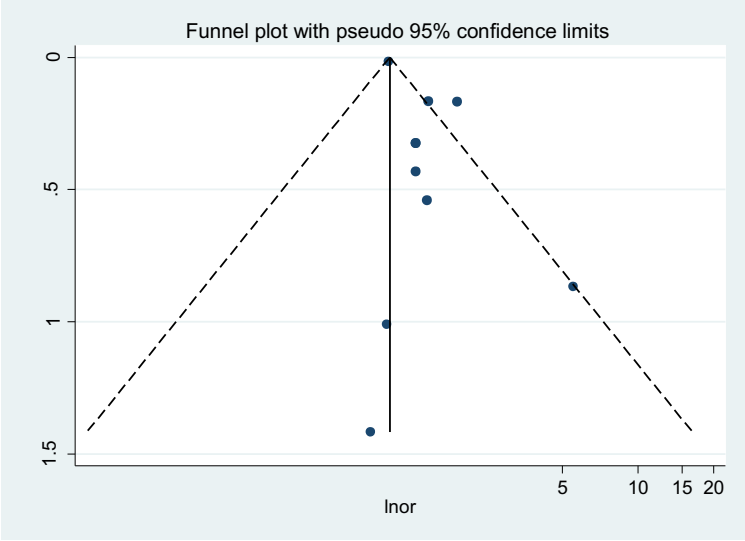
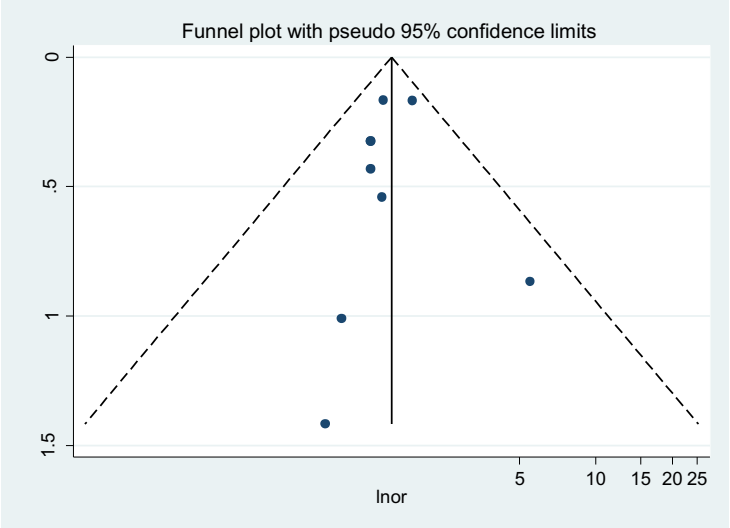


Figure 20. Rheumatoid arthritis: Funnel Plot



Egger test: Test of H_0: no small-study effects; P = 0.030

Figure 21. Rheumatoid arthritis: Funnel Plot Without WHI OS Study



Egger test: Test of H_0: no small-study effects; P = 0.72

Sarcoidosis

Three comparative studies of all breast implants versus no implants evaluated sarcoidosis (**Table 27, Figure 22**). All studies gave imprecise estimates but consistently found lower rates of sarcoidosis among women with implants. The summary ES was homogeneous but non-significant at 0.34 (95% CI 0.02, 5.56). One study reported a consistent and non-significant SHR. The studies also had a consistent percentage of women with sarcoidosis. The pooled percentage was 0.03% (95% CI 0.01, 0.09).

Overall, there is insufficient evidence to determine whether an association exists between breast implants and sarcoidosis. The studies were consistent but imprecise and the meta-analysis did not yield a sufficiently precise estimate to provide sufficient evidence.

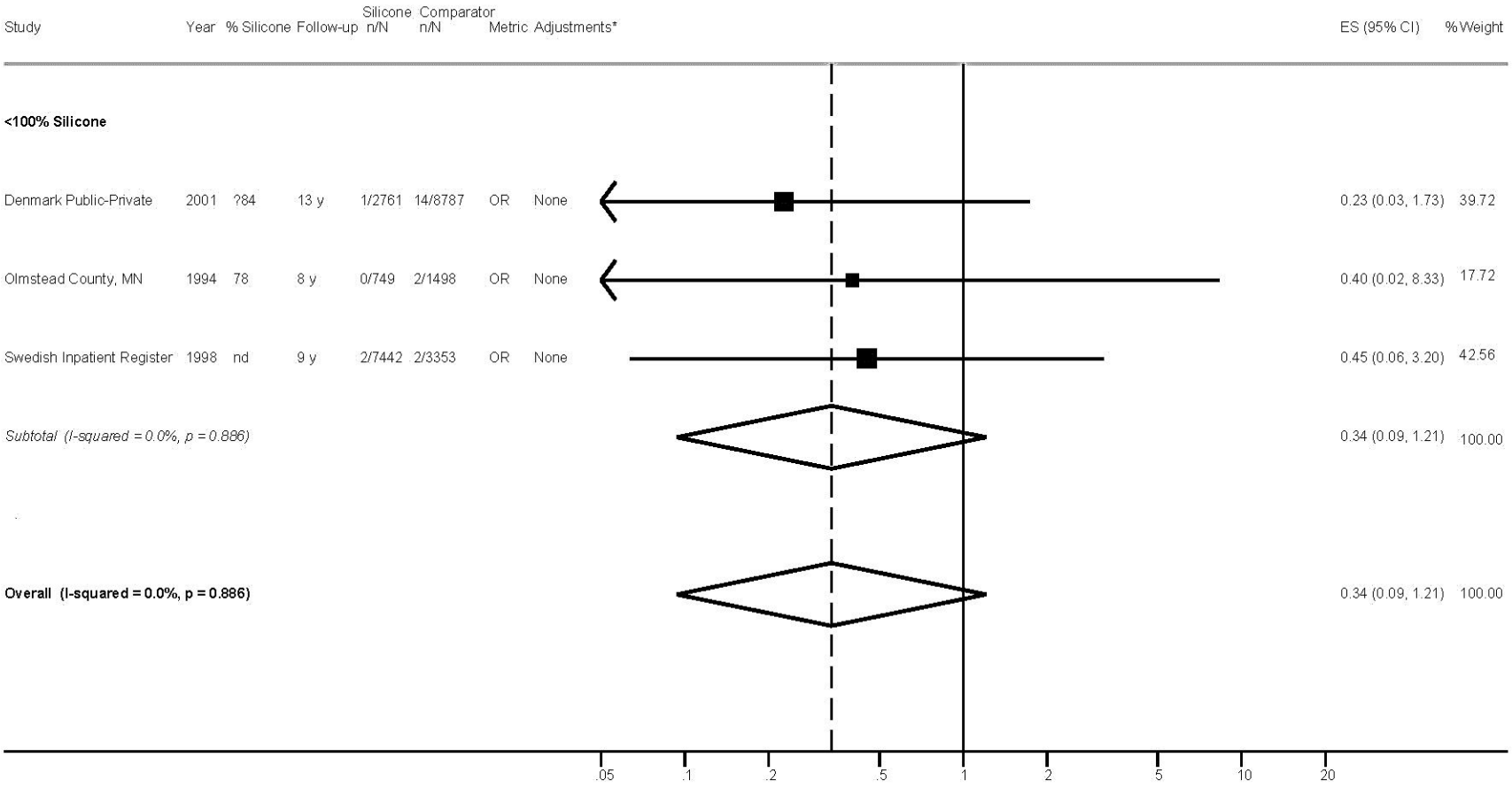
Table 27. Sarcoidosis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Denmark Public-Private[53]	≤84	13 y	Cosm Surg	1/2761 (0.03%)	14/8787 (0.2%)	ORcalc 0.23 (0.03, 1.73)	
Olmstead County, MN[54]	78	8 y	No implant	0/749 (0%)	2/1498 (0.1%)	ORcalc 0.40 (0.02, 8.33)	
Swedish Inpatient Register[79]	nd	9 y	Br Reduc	2/7442 (0.03%)	2/3553 (0.06%)	ORcalc 0.45 (0.06, 3.20)	
			Gen Pop		--	SHR 0.6 (0.1, 2.1)	
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=3)					**0.34 (0.02, 5.56) P het=0.89, I^2=0%**	
	Any, SIR (n=1)					**0.6 (0.1, 2.1)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=3)			**0.03% (0.01, 0.09)***			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Exact proportion

Figure 22. Sarcoidosis



Scleroderma

Eighteen studies evaluated scleroderma (**Table 28**, **Figures 23-25**). Eleven of the studies were comparative; however, only three of these were specific to women with silicone gel implants. The comparative studies included between 50% and 100% (or no data) of women with silicone gel implants and had follow-up between 4 and 16 years (or no data).

Among the comparative studies of women with only silicone gel implants, the Mentor MemoryGel/MemoryShape post-approval study compared their longitudinal cohort against a historical control; they reported a RR of 2.95 with a 1-sided P value of 0.094.[59] A case control study from Michigan was underpowered and yielded an imprecise (inadequately) adjusted OR = 1.3 (95% CI 0.27, 6.23).[37] Two small studies, from Tampa and Italy, had no women with scleroderma.[81]

The nine comparative studies of any breast implant type (with events to analyze) were all statistically non-significant with mostly imprecise estimates that ranged from 0.09 (Alberta Health Registry[36]) to 3.0 (South 18 Centers[32]). When pooled, the summary ES remained non-significant at 1.38 (95% CI 0.60, 3.17) with a small degree of heterogeneity (P heterogeneity = 0.26, I^2=20%).

Only the South 18 Centers study conducted an adequate adjustment, controlling for education, family history, age, race, time since implant, and calendar year of implantation.[32] The study yielded the largest ES across studies, but still non-significant (adjusted RR = 3.0; 95% CI 0.8, 10.9). One study reported an imprecise, non-significant SHR (1.0; 95% CI 0.6, 1.5).

Cumulative meta-analyses of the direct comparisons by the calendar year that recruitment of women into the studies ended (**Figure 24**) or by follow-up duration (**Figure 25**) did not show trends over time. The South 18 Centers study reported no difference in association by age at implant, time since implant, or calendar year of implant (through 1992). Across studies, no factors significantly differentiated studies from each other.

No difference in association was found between studies that clearly analyzed only incident disease (since implantation) versus those that may have included prevalent disease (at the time of implantation) (P=0.96). However, the two studies that determined outcome based on patient questionnaire (Mentor Post-Approval Study and South 18 center) found stronger associations (ES = 2.97; 95% CI 1.0001, 8.84) than the seven studies that relied on medical records or physical examination (SE = 0.92; 95% CI 0.36, 2.36); though this difference was not statistically significant (P=0.096).

Across the 17 studies (excluding the case-control study), with mean durations of follow-up since implantation from 3 to 20 years, the range of scleroderma percentage was 0% to 0.9% (in the 20 year follow-up study). Studies with longer mean duration had higher percentages of women with scleroderma (P=0.03), although non-significantly, so if the 20 year follow-up study (Birmingham, AL) was excluded (P=0.07) the pooled percentage was 0.06% (95% CI 0.03, 0.10). The nine studies restricted to silicone gel implants had a similar pooled percentage of 0.05% (95% CI 0.03, 0.07).

Overall, the evidence is insufficient to determine if there is an association between breast implants and scleroderma, particularly silicone gel implants. The studies were inconsistent with each other. Meta-analysis of studies based on confirmed diagnoses of scleroderma was imprecise.

Table 28. Scleroderma

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Mentor (MemoryGel/MemoryShape) Post-Approval Study[59]	100	5 y	Hist Cx	20/41451 (0.05%)	nd/1039	RR 2.95 (0.85, 10.3)	
Tampa[96]	100	nd	No implant	0/222 (0%)	0/80 (0%)	No events	
Italy[81]	100	5 y	No implant	0/102 (0%)	0/102 (0%)	No events	
Michigan[37]†	100	nd	No implant	2 implants / 274 scleroderma (0.8%)†	12 implants / 1183 no scleroderma (1.0%)†	Adj OR 1.3 (0.27, 6.23)†	**Inad:** A, R
Denmark Reconstruction[50]	≥84	7 y	No implant	1/1435 (0.07%)	1/3952 (0.03%)	ORcalc 2.76 (0.17, 44.1)	
Denmark Public-Private[53]	≤84	13 y	Cosm Surg	3/2761 (0.1%)	5/8807 (0.06%)	Adj HR 1.7 (0.4, 7.7)	**Inad:** A, Y
Women's Health Cohort Study[75]	70	4 y	No implant	1/3950 (0.03%)	4/13897 (0.03%)	ORcalc 0.88 (0.10, 7.87)	
South 18 Centers[32]	50	12 y	Cosm Surg	23/7234 (0.3%)	3/2138 (0.14%)	Adj RR 3.0 (0.8, 10.9)	**Ad**: A, R, T, Y, O5
Alberta Health Registry[46]	nd	nd	Cosm Surg	0/1112 (0%)	3/727 (0.4%)	ORcalc 0.09 (0.005, 1.80)	**Inad:** A, T
Sydney[47]	nd	16 y	No implant	1/458 (0.2%)	1/687 (0.15%)	RR 1.5 (0.09, 24)	
Swedish Inpatient Register[79]	nd	9 y	Br Reduc	1/7442 (0.01%)	3/3353 (0.1%)	ORcalc 0.15 (0.02, 1.44)	
			Gen Pop		--	SHR 0.8 (0, 4.4)	
Allergan (Inamed/Natrelle Round) Cohort[88]	100	4 y		1/715 (0.1%)			
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	7 y		1/941 (0.1%)			
Birmingham, AL[35]	100	20 y		3/344 (0.9%)			
Mentor (MemoryGel Round) Cohort[87]	100	9 y		1/1008 (0.1%)			
Sientra[89]	100	3 y		0/1788 (0%)			
San Diego[95]	100	7 y		0/125 (0%)			
Nurses Health Study[85]	74	nd		14/87501 (0.02%)			
Summary Implant vs. No Implant	**100% (n=2)**					**2.95 (0.85, 10.3)** **1.3 (0.27, 6.23)**	
	Any, Direct comparisons (n=9)					**1.38 (0.60, 3.17)** **P het=0.26, I^2=20%**	
	Augmentation (n=5)					**0.86 (0.13, 5.58)**	**P btw = 0.57**
	Reconstruction (n=1)					**2.76 90.02, 3.82)**	
	Confirmed diagnosis (n=7)					**0.92 (0.36, 2.36)**	**P btw = 0.096**
	Self-reported diagnosis (n=2)					**2.97 (1.00,8.84)**	
	Any, SIR (n=1)					**0.8 (0, 4.4)**	
	Any, Adequate adjustment (n=1)					**3.0 (0.8, 10.9)**	
Summary Percent Implant	**100% (n=9)**			**0.05% (0.03, 0.07)‡**			
	Any (n=17)			**0.06% (0.03, 0.10)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.

O5 = education, family history

† Case control study
‡ Exact proportion

Figure 23. Scleroderma

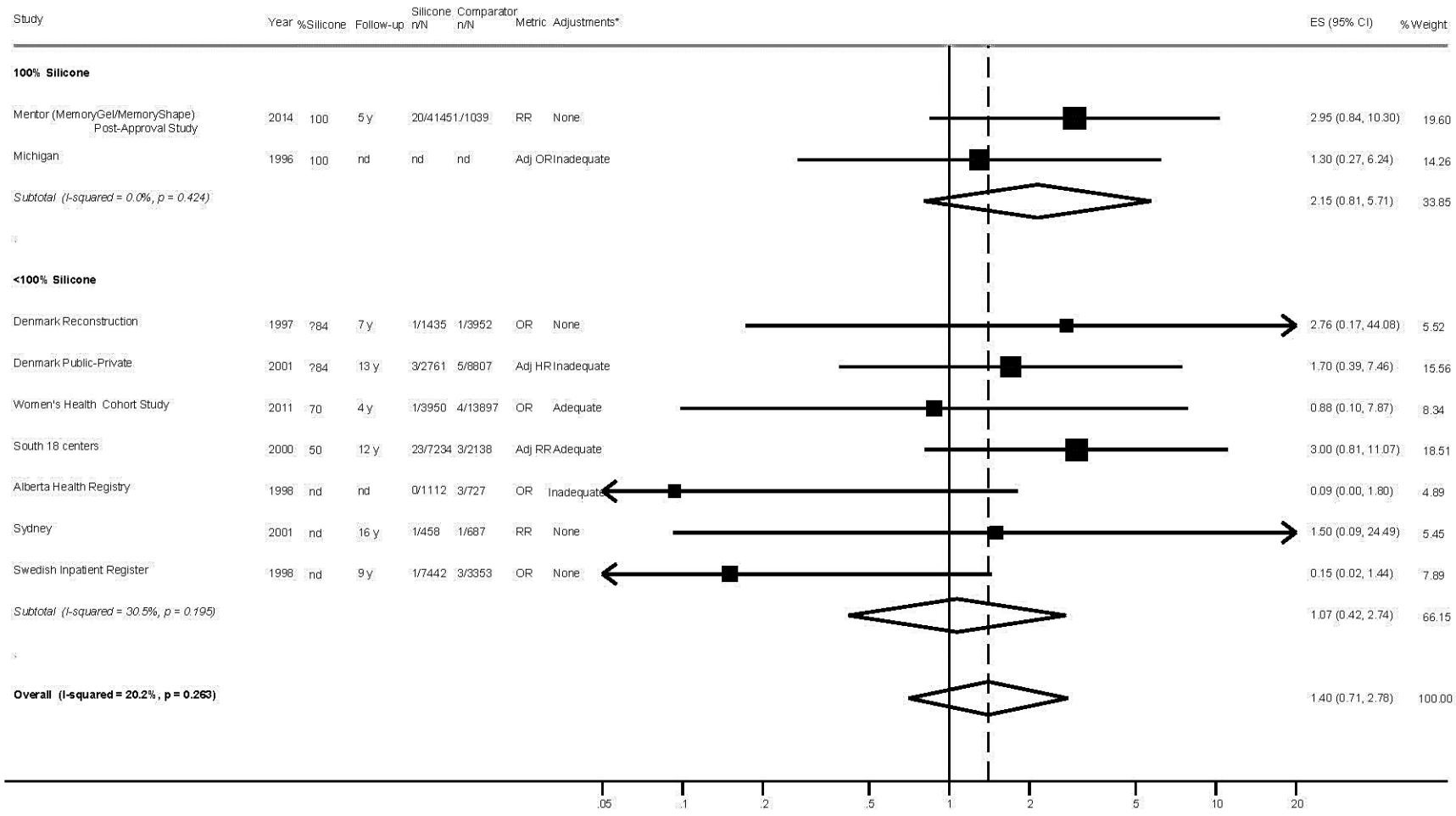


Figure 24.Scleroderma: Cumulative Meta-Analysis by End-Entry Date

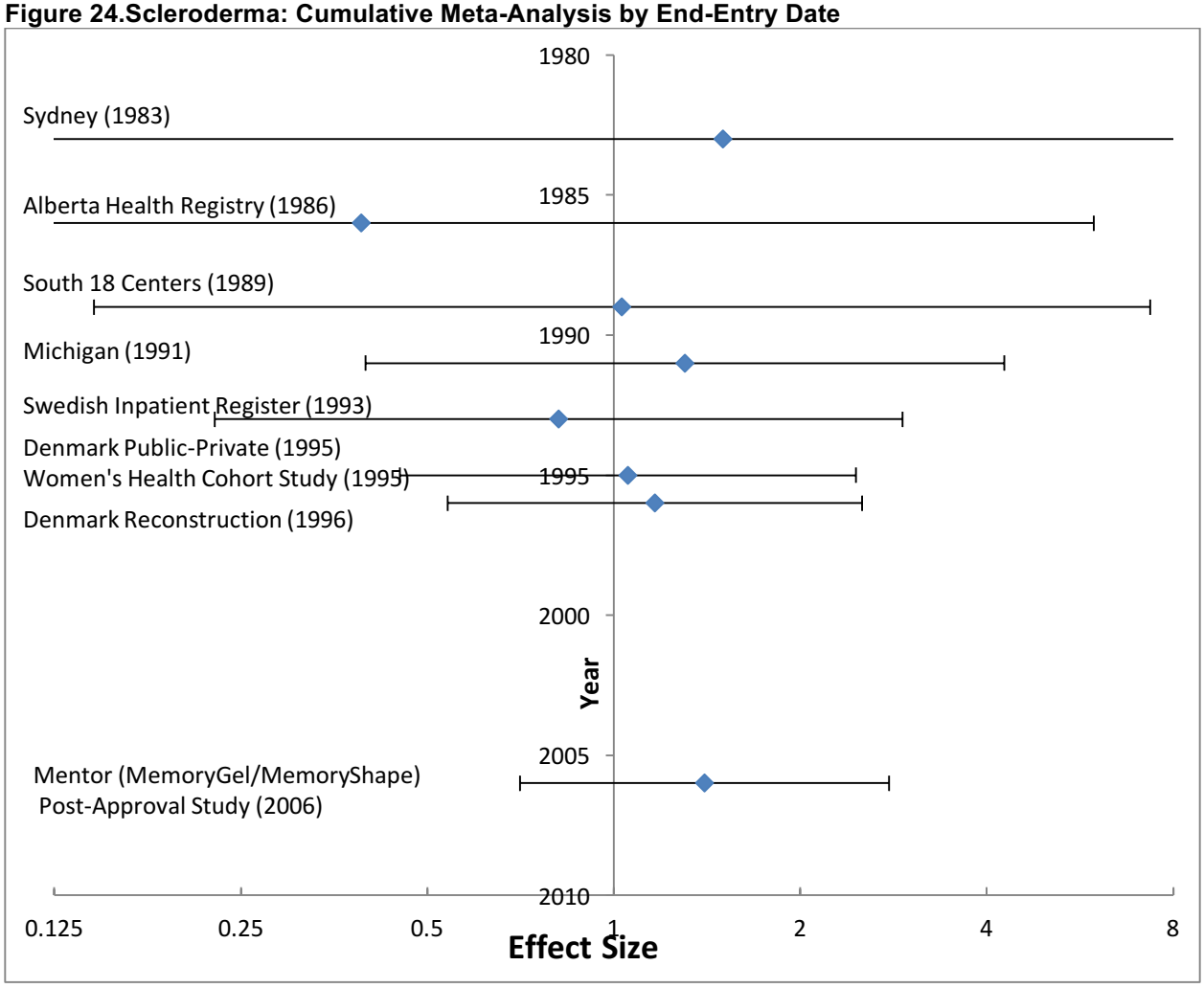
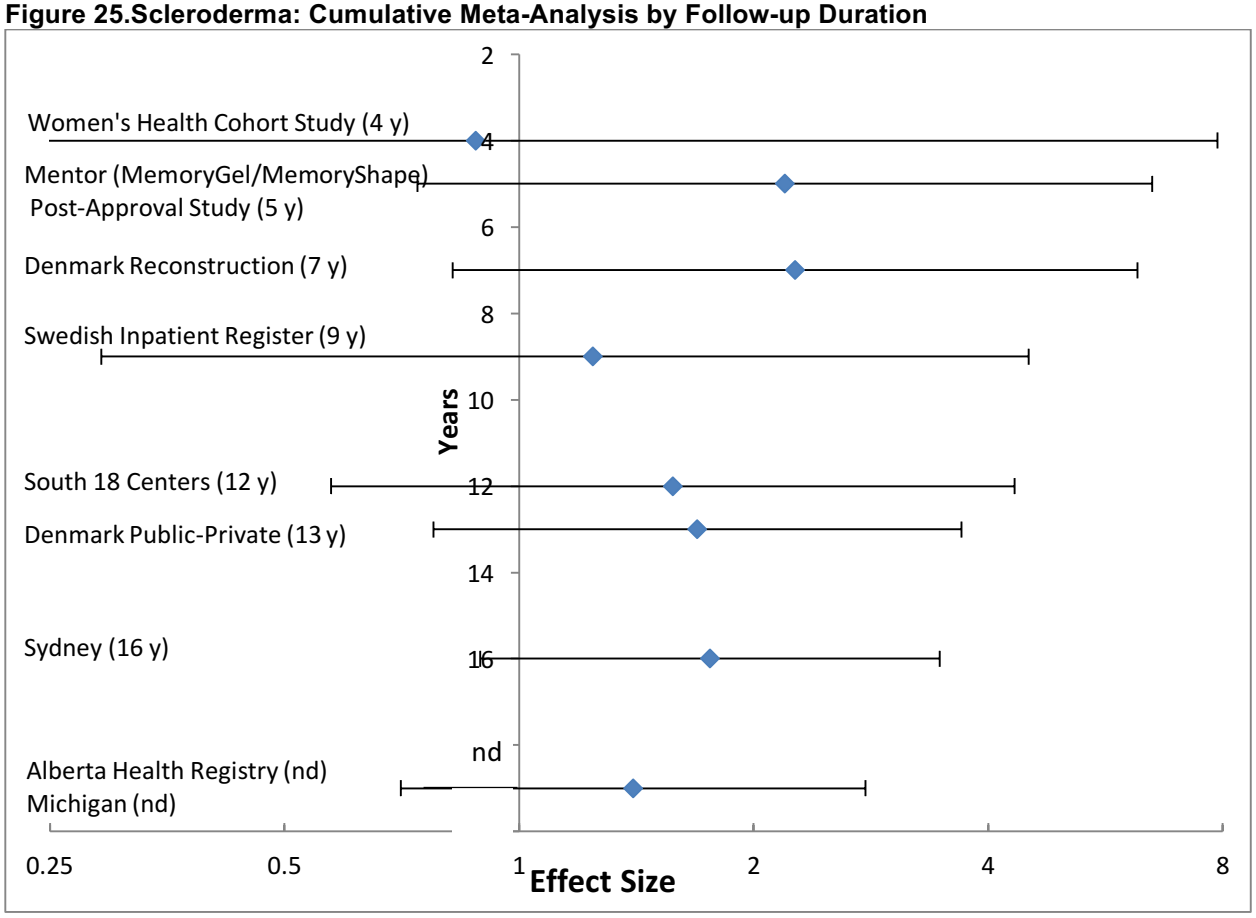


Figure 25.Scleroderma: Cumulative Meta-Analysis by Follow-up Duration



Sjögren Syndrome

Twelve studies reported on Sjögren syndrome, seven of which provided comparative analyses, but only one of which was specific to women with silicone gel implants (**Table 29**, **Figures 26-28**). The comparative studies included between 50% and 100% (or no data) of women with silicone gel implants and had follow-up between 4 and 20 years (or no data).Of the seven comparative studies, three obtained outcome diagnoses through medical records or national registries, one confirmed diagnoses by medical examination (Alberta Health Registry), one did not report how outcomes were obtained (Mentor Post-Approval Study), but one obtained outcomes only from a patient questionnaire (Women's Health Cohort, WHI OS). This latter method is potentially problematic for rheumatologic diseases. All studies evaluated incident disease since the time of implantation.

The only comparative study that focused on silicone gel implants compared a longitudinal cohort of women with Mentor implants to a historical control. They reported a RR of 6.64 with a 1-sided P value of <0.002. This study met three items related to causality with a strong association (OR>2.0), specificity to silicone gel implants, and temporality that the disease arose after surgery. However, the comparator group is a historical control for which no data are provided and it is unclear whether proper adjustment for possible confounders was performed. The remaining six comparative studies had a wide range of associations from a non-significant OR of 0.39 to a highly significant adequately adjusted RR of 11.7. Pooling all seven studies yielded a just-significant summary ES of 2.92 (95% CI 1.01, 8.47) with modest heterogeneity (P heterogeneity = 0.17, I^2=34%). Given the wide heterogeneity across studies, none was clearly an outlier. Removing the study with the largest ES (though with a wide confidence interval), the South 18 Centers study, shrank the summary ES somewhat and resulted in a non-significant summary association (ES = 2.24; 95% CI 0.96, 5.23), but lowered the degree of heterogeneity only modestly (I^2 = 15%). Likewise, removing the study with the smallest ES (also with a wide confidence interval), the Women's Health Cohort Study, increased the summary ES somewhat (ES = 3.47; 95% CI 1.48, 8.13) but also had a small effect on heterogeneity (I^2 = 27%).

Only the South 18 Centers study conducted an adequate adjustment, controlling for education, family history, age, race, time since implant, and calendar year of implantation.[32] As noted, the study yielded the largest ES across studies (adjusted RR = 11.7; 95% CI 2.5, 54.9). One study reported an imprecise, non-significant SHR (1.8; 95% CI 0.4, 5.4).

Cumulative meta-analyses of the direct comparisons by the calendar year that recruitment of women into the studies ended (**Figure 26**) or by follow-up duration (**Figure 27**) did not show trends over time. The South 18 Centers study reported no difference in association by age at implant, time since implant, or calendar year of implant (through 1992). The two studies that determined outcome based on patient questionnaire (Mentor Post-Approval Study and South 18 center) found stronger associations (ES = 8.21; 95% CI 2.38, 28.4) than the five studies that relied on medical records or physical examination (SE = 1.26; 95% CI 0.36, 4.46), which was a statistically significant difference (P=0.042).

Based on the summary ES from direct comparisons and the summary percent of women with implants with Sjögren syndrome, the RD between women with and without implants—the absolute percentage of women who would have Sjögren syndrome associated with their implant (assuming the association is causal)—ranges from 0.007% (95% CI 0.002, 0.009) to 0.13% (95% CI0.03, 0.17).

Across the 12 studies, the percentage of women with Sjögren syndrome ranged from 0% to 0.9% (with 30 years of follow-up after implantation). The summary percent of women with

Sjögren syndrome across all studies of breast implants was 0.1% (95% CI 0.01, 0.2). The same summary percent was found among the five studies restricted to women with silicone breast implants, with a wider confidence interval: 0.1% (95% CI 0, 0.4). Studies with longer mean duration of follow-up after implantation had marginally significantly higher percent of women with disease (P=0.052).

Overall, the evidence is insufficient to determine if there is an association between breast implants and Sjögren syndrome. While one adequately adjusted study found a large (ES >2.0), significant association, it (and the other study with a strong association) determined outcome based on questionnaire, which may result in bias if women with implants are more likely to incorrectly self-diagnose with Sjögren syndrome than women without implants. Overall, the studies were inconsistent with each other. Meta-analysis of studies based on confirmed diagnoses of scleroderma was imprecise.

Table 29. Sjögren Syndrome

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Mentor (MemoryGel/MemoryShape) Post-Approval Study[59]	100	5 y	Hist Cx	30/41451 (0.1%)	nd/1039	RR 6.64 (2.01, 21.9)	
Denmark Reconstruction[50]	≥84	7 y	No implant	1/1435 (0.07%)	1/3952 (0.03%)	ORcalc 2.76 (0.17, 44.1)	
Denmark Public-Private[53]	≤84	13 y	Cosm Surg	2/2761 (0.1%)	9/8787 (0.1%)	Adj HR 1.3 (0.3, 7.2)	**Inad:** A, Y
Women's Health Cohort Study[75]	70	4 y	No implant	0/3950 (0%)	6/19897 (0.03%)	ORcalc 0.39 (0.02, 6.88)	
South 18 Centers[32]	50	12 y	Cosm Surg	43/7234 (0.6%)	2/2138 (0.1%)	Adj RR 11.7 (2.5, 54.9)	**Ad**: A, R, T, Y, O5
Alberta Health Registry[46]	nd	nd	Cosm Surg	5/1112 (0.5%)	4/727 (0.6%)	Adj RR 0.99 (0.17, 5.94)	**Inad:** A, T
Swedish Inpatient Register[79]	nd	9 y	Br Reduc	3/7442 (0.04%)	0/3353 (0%)	ORcalc 3.16 (0.16, 61.1)	
			Gen Pop		--	SHR 1.8 (0.4, 5.4)	
Birmingham, AL[35]	100	20 y		3/344 (0.9%)			
Mentor (MemoryGel Round) Cohort[87]	100	9 y		2/1008 (0.2%)			
Mentor (MemoryShape/CPG Anatomic) Cohort[91]	100	8 y		2/955 (0.2%)			
San Diego[95]	100	7 y		0/125 (0%)			
Nurses Health Study[85]	74	nd		2/87501 (0.002%)			
Summary Implant vs. No Implant	**100% (n=1)**					**6.64 (2.01, 21.9)**	
	Any, Direct comparisons (n=7)					**2.92 (1.01, 8.47) P het=0.17, I^2=34%**	
	Confirmed diagnosis (n=5)					**1.26 (0.36, 4.46)**	**P btw = 0.042**
	Self-reported diagnosis (n=2)					**8.21 (2.38, 28.4)**	
	Any, SIR (n=1)					**1.8 (0.4, 5.4)**	
	Any, Adequate adjustment (n=1)					**11.7 (2.5, 54.9)**	
Summary Percent Implant	**100% (n=5)**			**0.1% (0, 0.4)**			
	Any (n=12)			**0.1% (0.01, 0.2)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O5 = education, family history

Figure 26.Sjögren Syndrome

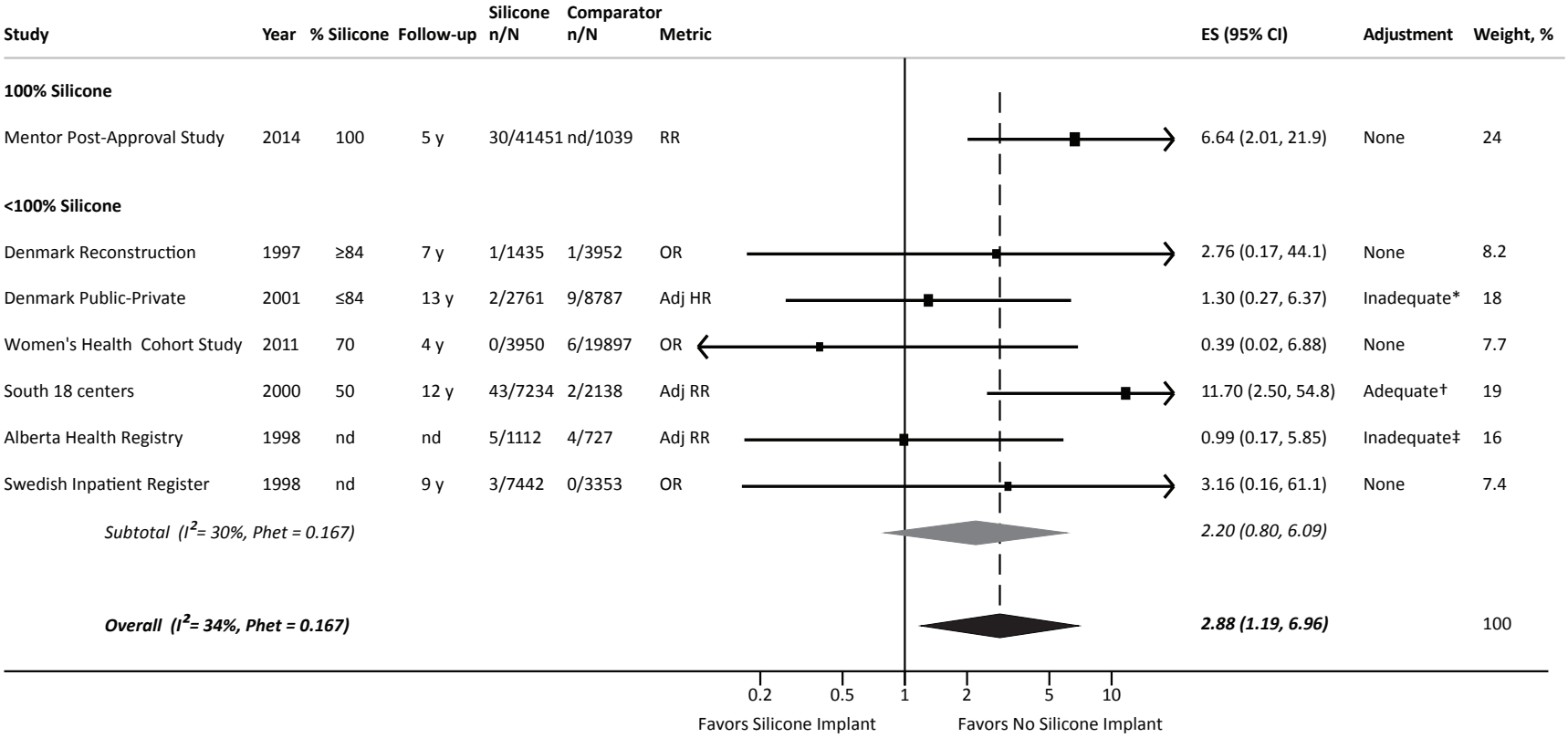


Figure 27.Sjögren Syndrome: Cumulative Meta-Analysis by End-Entry Date

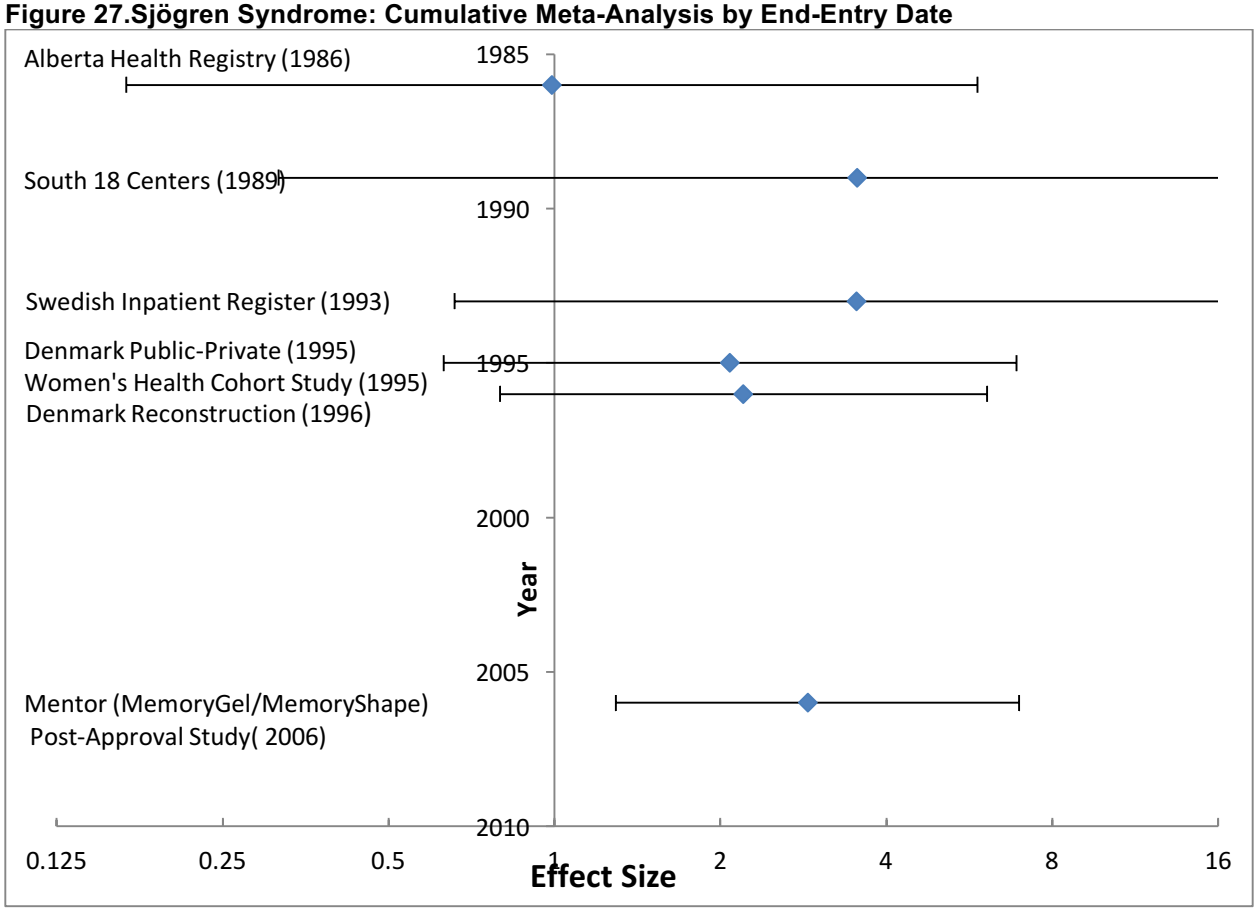
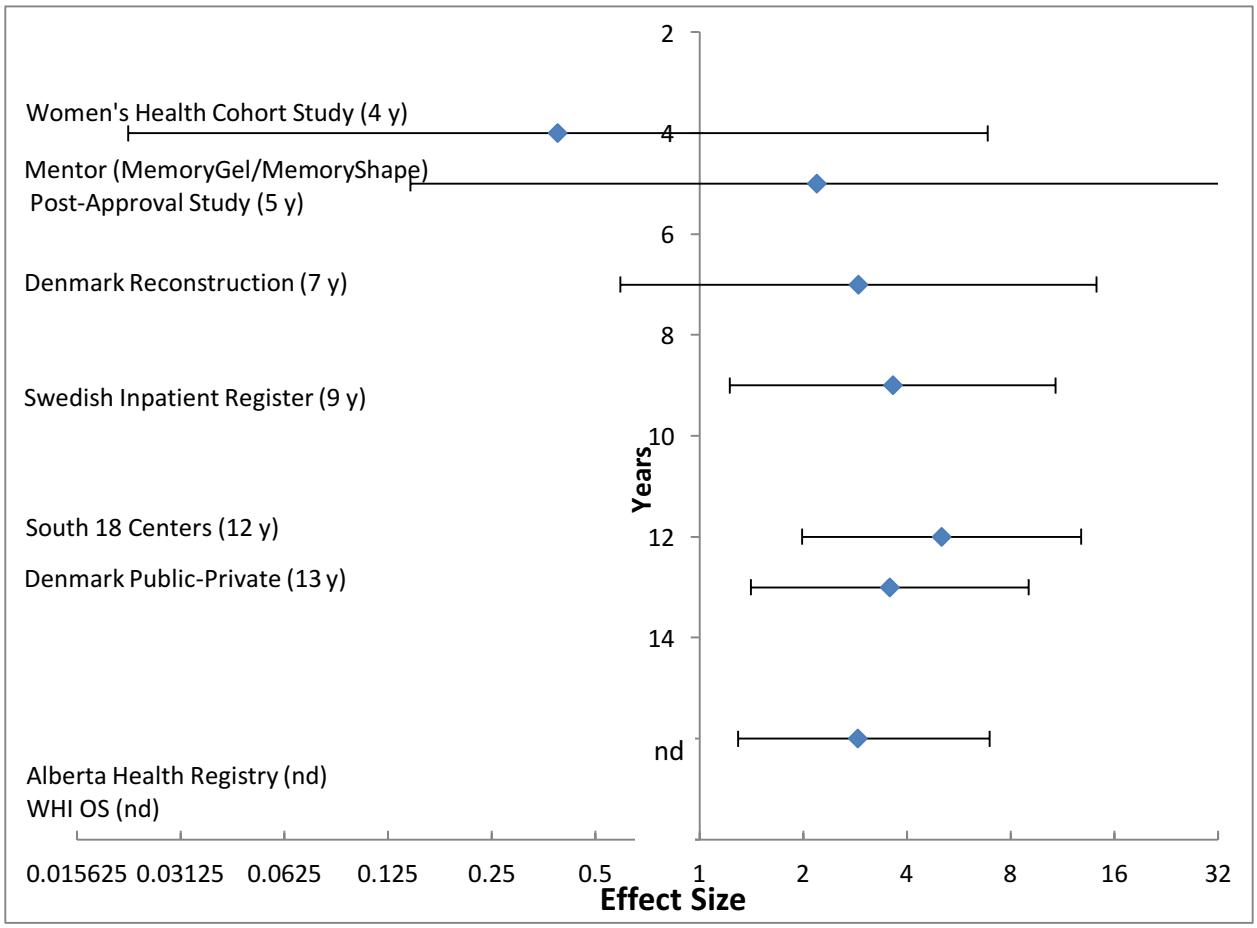


Figure 28.Sjögren Syndrome: Cumulative Meta-Analysis by Follow-Up Duration



Systemic Lupus Erythematosus (SLE)

Sixteen studies evaluated SLE, of which 10 provided comparative analyses. (**Table 30**, **Figure 29**). The comparative studies included between 50% and 100% (or no data) of women with silicone gel implants and had follow-up between 4 and 16 years (or no data). All studies evaluated incident SLE since the time of implantation.

Two comparative studies evaluated only women with silicone gel implants. One compared women with Mentor implants to a historical control. They reported a RR of 1.02 with a 1-sided P value of 0.57. The second study, from Tampa, had no women with SLE. The remaining comparative studies were mostly imprecise due to few diagnoses of SLE and had a wide range of ES estimates ranging from 0.18 to 5.04. Across the nine studies with direct comparisons (and women with SLE diagnoses), the pooled ES was non-significant at 1.28 (95% CI 0.76, 2.14), though with statistical heterogeneity (P heterogeneity = 0.03, I^2 = 54%).

Only the South 18 Centers study conducted an adequate adjustment, controlling for education, family history, age, race, time since implant, and calendar year of implantation.[32] The study yielded a significant adjusted RR = 2.1 (95% CI 1.1, 4.2). One study reported a non-significant SHR (1.8; 95% CI 0.7, 3.7).

No difference was found between the three studies that relied on patient questionnaire for the diagnosis of SLE and the studies that confirmed diagnosis by medical record review or physical examination (P=0.20). Cumulative meta-analyses of the direct comparisons by the calendar year that recruitment of women into the studies ended (**Figure 30**) or by follow-up duration (**Figure 31**) did not show trends over time. Driven by the results of the WHI OS and South 18 Centers—which had about 10 times the percentage of women with disease than other studies and the lowest percentage of women with silicone gel implants—studies with higher percentages of women's implants being silicone gel had smaller ES of association (P=0.032); similarly, studies with a lower percentage of women with SLE in the implant groups also had smaller ES of association (P=0.011). Restricting the meta-analysis to the four studies with at least 70% silicone gel implants, the summary ES was 1.06 (95% CI 0.63, 1.81); also including the four studies that did not report what percentage of women had silicone gel implants (i.e., excluding only WHI OR and South 18 Centers), the summary OR was 0.99 (95% CI 0.81, 1.22). The South 18 Centers study reported no difference in association by age at implant, time since implant, or calendar year of implant (through 1992).

Across the 16 studies, the percentage of women with SLE ranged from 0% to 1.2% over 3 to 20 years of follow-up after implantation. The summary percent of women with SLE across all studies of breast implants was 0.2% (95% CI 0.06, 0.3). The same summary percent was found among the seven studies restricted to women with silicone gel breast implants, with a wider confidence interval: 0.2% (95% CI 0, 0.5). Studies with longer mean duration of follow-up after implantation had a significantly higher percentage with disease (P=0.012).

Two of the studies had large ESs (≥2.0) for new diagnoses since implantation, one of which conducted adequate adjustment, but neither of these studies was specific to silicone gel implants.

Overall, the evidence is insufficient to determine if there is an association between breast implants and SLE, particularly silicone gel implants. While two large studies found a significant doubling of risk, overall, the summary estimate is non-significant and these studies were outliers also, in having only two-thirds or fewer women with silicone gel implants and also having a percentage of women with SLE about 10-times higher than other studies. Furthermore, the

higher the percentage of women in the study who had silicone gel implants, the smaller the association between implants and SLE.

Table 30. Systemic Lupus Erythematosus

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Mentor (MemoryGel/MemoryShape) Post-Approval Study[59]	100	5 y	Hist Cx	23/41451 (0.1%)	nd/1039	RR 1.02 (0.82, 1.27)	
Tampa[96]	100	nd	No implant	0/222 (0%)	0/80 (0%)	No events	
Denmark Reconstruction[50]	≥84	7 y	No implant	1/1435 (0.1%)	2/3952 (0.1%)	ORcalc 1.38 (0.12, 15.2)	
Denmark Public-Private[53]	≤84	13 y	Cosm Surg	2/2761 (0.1%)	13/8787 (0.2%)	ORcalc 0.49 (0.11, 2.17)	
Women's Health Cohort Study[75]	70	4 y	No implant	2/3950 (0.1%)	2/19897 (0.01%)	ORcalc 5.04 (0.7135.8)	
WHI OS[84]	67	nd	No implant	15/1220 (1.2%)	462/85127 (0.5%)	ORcalc 2.28 (1.36, 3.83)	
South 18 Centers[32]	50	12 y	Cosm Surg	72/7234 (1.0%)	10/2138 (0.5%)	Adj RR 2.1 (1.1, 4.2)	**Ad**: A, R, T, Y, O5
Alberta Health Registry[46]	nd	nd	Cosm Surg	3/1112 (0.3%)	3/727 (0.4%)	Adj RR 0.94 (0.17, 5.23)	**Inad:** A, T
Sydney[47]	nd	16 y	No implant	0/458 (0%)	3/587 (0.5%)	ORcalc 0.18 (0.01, 3.53)	
Swedish Inpatient Register[79]	nd	9 y	Br Reduc	3/7442 (0.04%)	3/3353 (0.1%)	Adj RR 0.7 (0.3, 1.6)	**Inad:** A, Y
			Gen Pop	7/7442 (0.09%)	--	SHR 1.8 (0.7, 3.7)	
Birmingham, AL[35]	100	20 y		8/344 (0.04%)			
Mentor (MemoryGel Round) Cohort[87]	100	9 y		1/1008 (0.1%)			
Mentor (MemoryShape/CPG Anatomic) Cohort[91]	100	8 y		4/955 (0.4%)			
Sientra[89]	100	3 y		0/1788 (0%)			
San Diego[95]	100	7 y		0/125 (0%)			
Nurses Health Study[85]	74	nd		96/87501 (0.1%)			
Summary Implant vs. No Implant	**100% (n=1)**					**1.02 (0.82, 1.27)**	
	Any, Direct comparisons (n=9)					**1.28 (0.76, 2.14) P het=0.03, I^2=54%**	
	Augmentation (n=6)					**0.98 (0.38, 2.49)**	**P btw = 0.81**
	Reconstruction (n=1)					**1.38 (0.04, 50.7)**	
	Confirmed diagnosis (n=6)					**0.84 (0.36, 1.97)**	**P btw = 0.20**
	Self-reported diagnosis (n=3)					**1.57 (0.88, 2.78)**	
	Any, SIR (n=1)					**1.8 (0.7, 3.7)**	
	Any, Adequate adjustment (n=1)					**2.1 (1.1, 4.2)**	
Summary Percent Implant	**100% (n=7)**			**0.2% (0, 0.5)**			
	Any (n=16)			**0.2% (0.06, 0.3)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.

A = age, R = race, T = time since surgery, Y = calendar year.
O5 = education, family history

Figure 29. Systemic Lupus Erythematosus

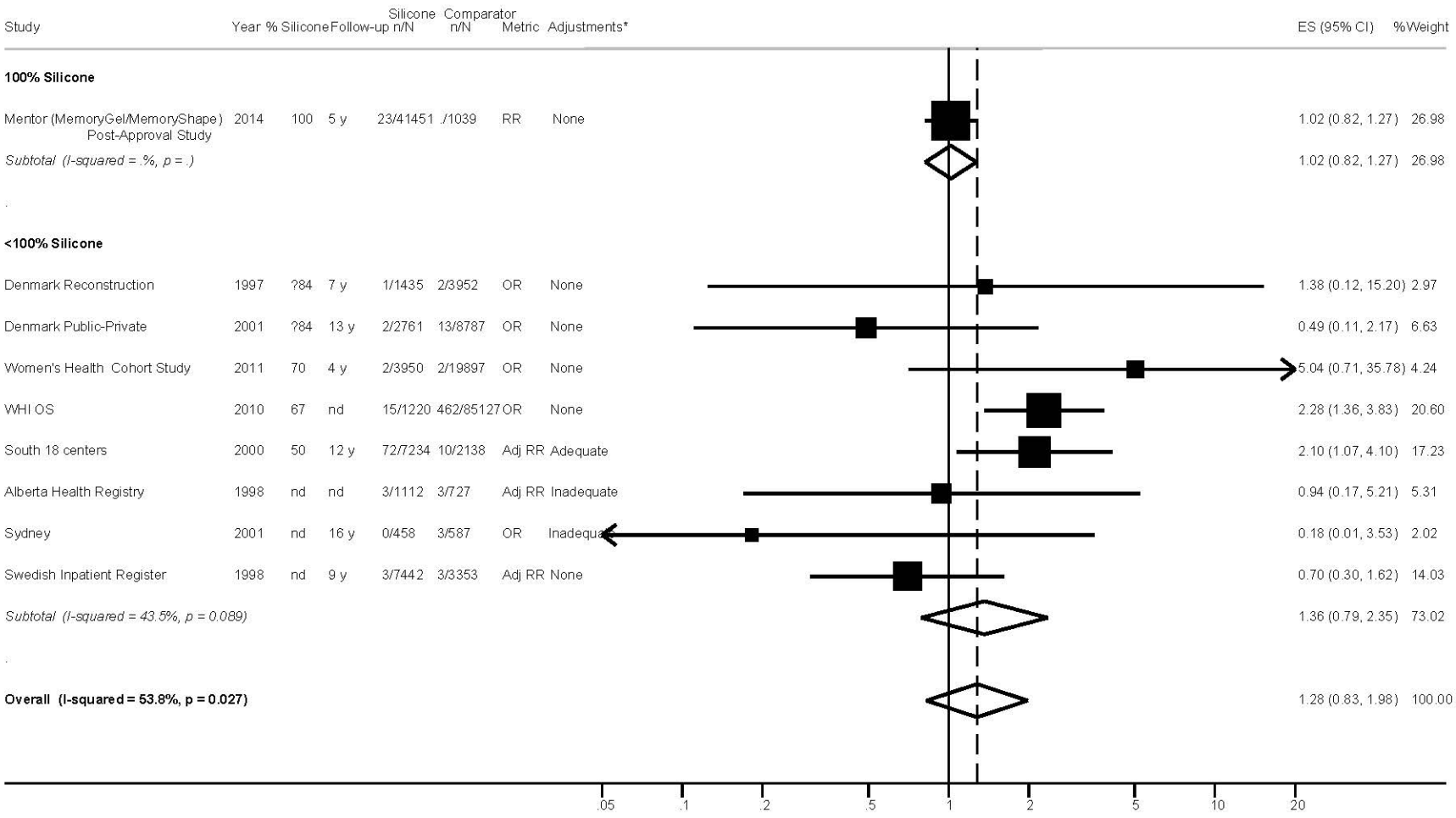


Figure 30.SLE: Cumulative Meta-Analysis by End-Entry Date

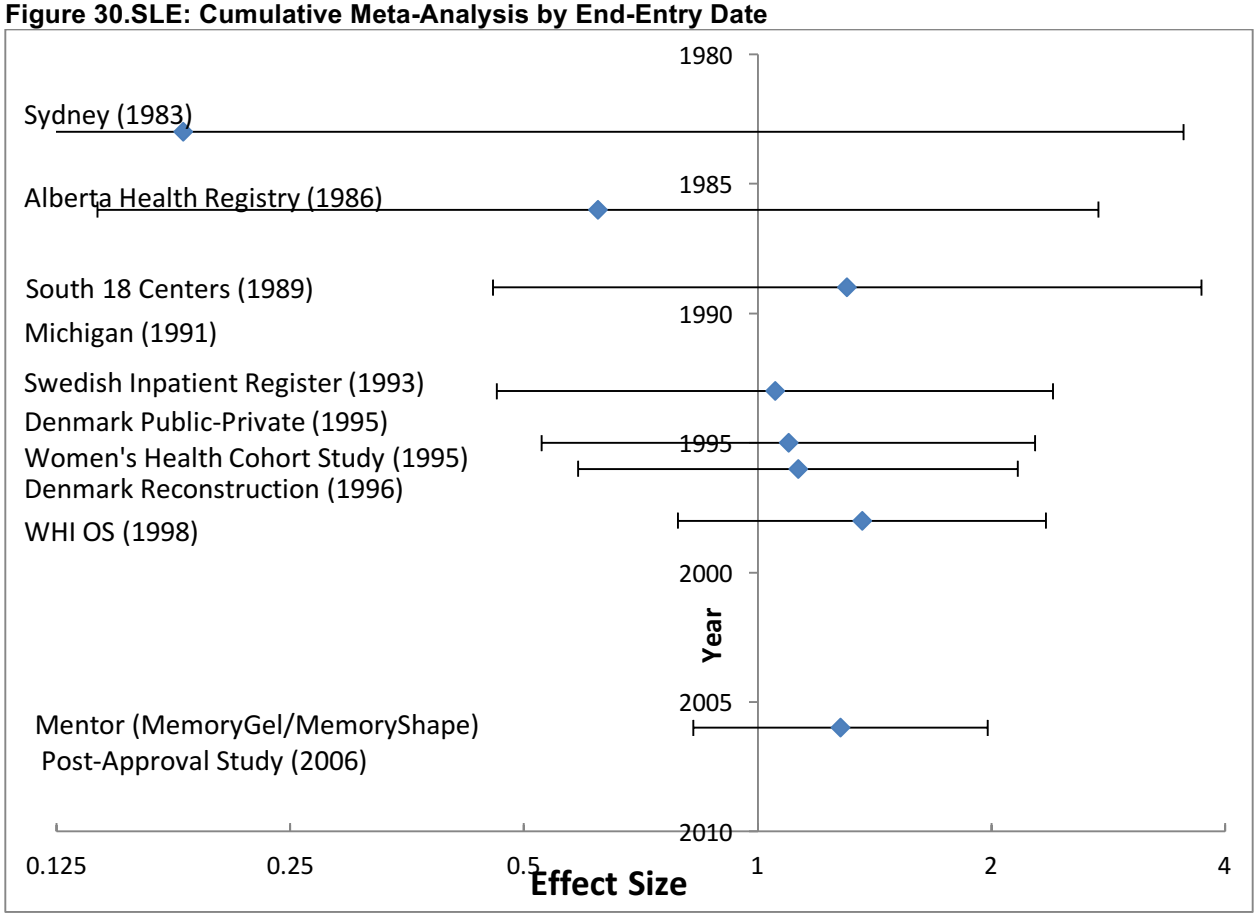
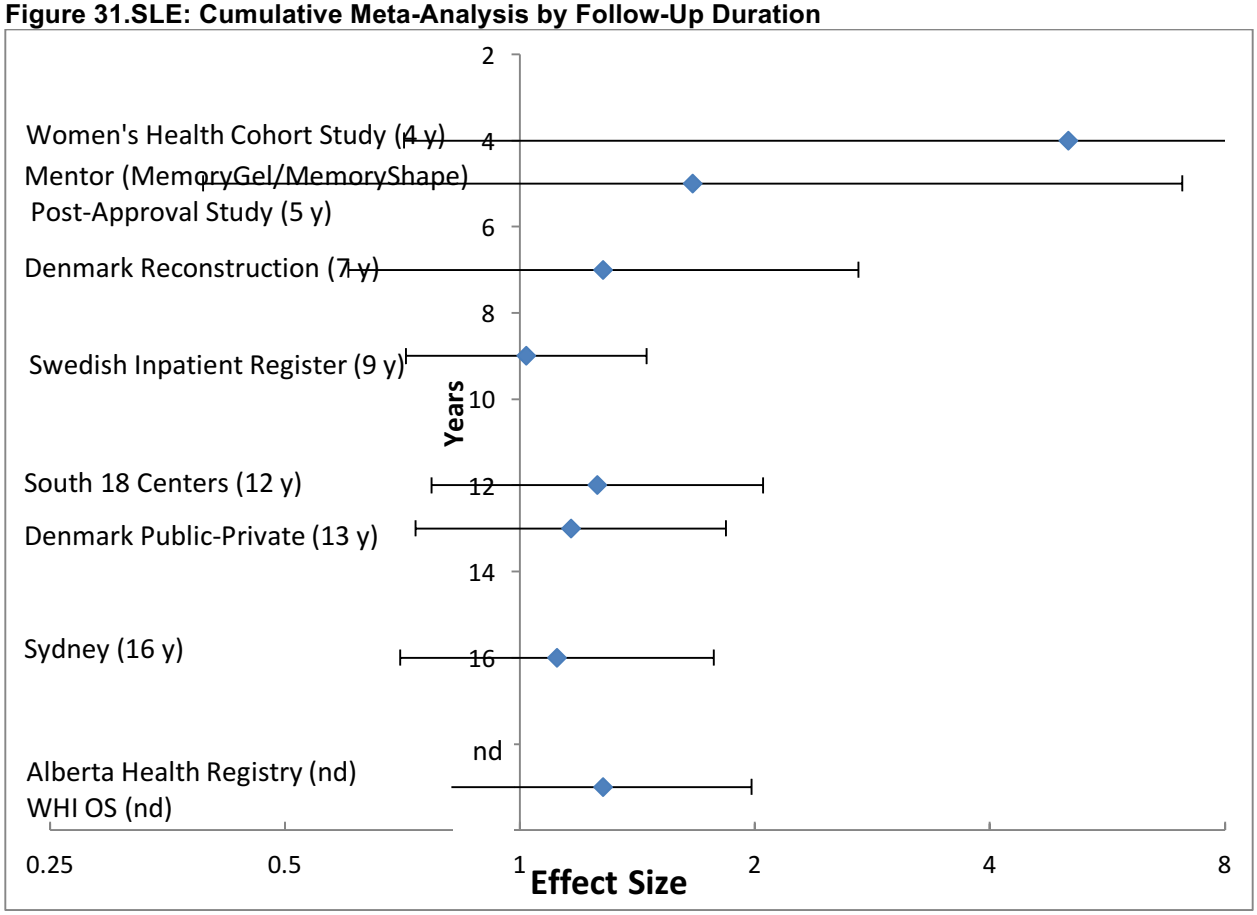


Figure 31.SLE: Cumulative Meta-Analysis by Follow-Up Duration



Temporal Arteritis

A single Swedish study reported on temporal arteritis (**Table 31**). The study did not report the percentage of women with silicone gel implants. Only a single woman among more than 10,000 had the diagnosis. The study also reported an imprecise, non-significant SHR. In the study, 0.01% (95% CI 0.002, 0.10) of the women with implants had temporal arteritis. The evidence is insufficient to determine if there is an association between breast implants and temporal arteritis.

Note: See the "Temporal Arteritis and Polymyalgia Rheumatica" section, following.

Temporal Arteritis and Polymyalgia Rheumatica

A single Danish study reported on the combined diagnosis of temporal arteritis and polymyalgia rheumatica (**Table 32**). The study, with ≤84% of women with silicone gel implants, was underpowered for this outcome and had an unadjusted OR of 0.43 (95% CI 0.13, 1.45). In the study, 0.1% (95% CI 0.04, 0.3)of the women with implants had temporal arteritis and polymyalgia rheumatica. The evidence is insufficient to determine if there is an association between breast implants and temporal arteritis and polymyalgia rheumatica.

Note: See "Polymyalgia Rheumatica" and "Temporal Arteritis" sections above.

Undifferentiated Connective Tissue Disease

A single case control study from Michigan and Ohio evaluated undifferentiated CTD with silicone gel implants as a risk factor (**Table 33**). The study was underpowered for this analysis, reporting an adjusted OR of 2.22 (95% CI 0.65, 7.57). The evidence is insufficient to determine if there is an association between breast implants and undifferentiated CTD.

Wegener Granulomatosis

A single Danish study reported on Wegener granulomatosis (**Table 34**). The study, with ≤84% of women with silicone gel implants had no women with the disease. The studies do not provide evidence regarding the association between silicone gel implants and Wegener granulomatosis.

Table 31. Temporal Arteritis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Swedish Inpatient Register[79]	nd	9 y	Br Reduc	1/7442 (0.1%)	0/3353 (0.0%)	ORcalc 1.35 (0.06, 33.20)	
			Gen Pop		--	SHR 0.6 (0, 3.4)	
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=1)					**1.35 (0.06, 33.2)**	
	Any, SIR (n=1)					**0.6 (0, 3.4)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=1)			**0.01% (0.002, 0.10)***			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Exact proportion

Table 32. Temporal Arteritis & Polymyalgia Rheumatica

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Denmark Public-Private[53]	≤84	13 y	Cosm Surg	3/2761 (0.1%)	22/8787 (0.3%)	ORcalc 0.43 (0.13, 1.45)	
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=1)					**0.43 (0.13, 1.45)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=3)			**0.1% (0.04, 0.3)***			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Exact proportion

Table 33. Undifferentiated Connective Tissue Disease

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Michigan/Ohio[73]	100	nd	No implant	3 implants / 205 Undiff CTD (1.5%)	26 implants / 205 No Undiff CTD (13%)	Adj OR 2.22 (0.65, 7.57)	

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation, Undiff CTD = undifferentiated connective tissue disease.

* Case-control study

Table 34. Wegener Granulomatosis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Denmark Public-Private[53]	≤84	13 y	Cosm Surg	0/2761 (0.0%)	0/8787 (0.0%)	No events	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=1)			**0% (0, 0.3)***			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Exact proportion

Symptoms of Connective Tissue, Rheumatologic, and Auto-Immune Diseases

Alopecia

Five studies reported on alopecia, three of which were comparative (**Table 35, Figure 32**). None of the studies provided an adequate definition or description of the type of alopecia being investigated, for example whether temporary or permanent or whether patchy or thinning.

A small, matched German study found no significant association between silicone gel implants and alopecia (described only as "hair loss," by questionnaire). Two additional Scandinavian comparative studies evaluated women with any breast implant. The larger Swedish study found a marginally significant association with alopecia (also described only as "hair loss," by questionnaire), but the other study was imprecise. The study from Copenhagen compared their cohort of women with breast implants to both a cohort of women from the same hospital who had breast reduction surgery and a cohort of women without breast implants from the general population; it evaluated undefined "abnormal hair loss," also by questionnaire. The two adjusted ORs from this study were nearly identical. Across the three studies, the pooled analysis (**Figure 32**) yielded a marginally non-significant ES of 1.32 (95% CI 0.999, 1.74), with no statistical heterogeneity. The meta-analysis is driven largely by the large Swedish study. Two additional studies reported on percentage of women with alopecia in women with silicone gel implants. However, these studies (and the two comparative studies) clearly used different definitions of alopecia (which were not described beyond "hair loss" or "alopecia"). Only one woman in the Allergan cohort (0.1%) reported alopecia, but 15% of women in the Alabama cohort reported persistent hair loss. Given the extreme heterogeneity in reported rates of alopecia, we did not calculate summary estimates of percent of women with the condition.

Overall, the evidence is insufficient to determine if there is an association between breast implants and alopecia. None of the studies adequately defined alopecia and none confirmed the presence of the symptom.

Arthritis Symptoms

Four studies reported on arthritis symptoms (**Table 36, Figure 33**) as an outcome. All studies were comparative; one was restricted to women with silicone gel implants. The studies had a wide range of ES estimates, from 0.43 to 3.01, but each was imprecise. Thus, overall, the summary ES was 1.22 (95% CI 0.77, 1.95), with no heterogeneity (**Figure 33**). Across studies, the percentage of women with arthritis symptoms was 1.7% (95% CI 0.1, 4.7).

The evidence is insufficient to determine if there is an association between breast implants and arthritis symptoms. The summary ES was too imprecise to differentiate between evidence of a small association (ES <2.0) and evidence of no association.

Table 35. Rheumatologic Symptoms: Alopecia

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Munster, Germany[27]	100	nd	No implant	7/32 (22%)	3/32 (9%)	ORcalc 2.71 (0.63, 11.6)	
Copenhagen Deaconess Hospital[28]	77	19 y	Br Reduc†	10/190 (5%)	9/186 (5%)	Adj OR 1.1 (0.4, 2.8)†	**Inad:** A
			No implant†		8/149 (5%) †	Adj OR 1.0 (0.4, 2.8)†	**Inad:** A
Swedish Inpatient Register[52]	nd	nd	Br Reduc	98/1369 (7%)	128/2211 (6%)	Adj RR 1.3 (1.0, 1.8)	**Inad:** A, Y
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	7 y		1/941 (0.1%)			
Birmingham, AL[35]	100	20 y		52/344 (15%)			
Summary Implant vs. No Implant	**100% (n=1)**					**2.71 (0.63, 11.6)**	
	Any, Direct comparisons (n=3)					**1.32 (0.999, 1.74)† P het=0.58, I^2=0%**	
Summary Percent Implant	**100%**			**‡**			
	Any			**‡**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.

† Primary meta-analysis conducted with breast reduction surgery comparison. Alternatively, using no implant comparison: summary OR = 1.31 (0.99, 1.72); P het=0.53, I^2=0%.

‡ Not calculated due to extreme heterogeneity across studies.

Figure 32. Rheumatologic Symptoms: Alopecia

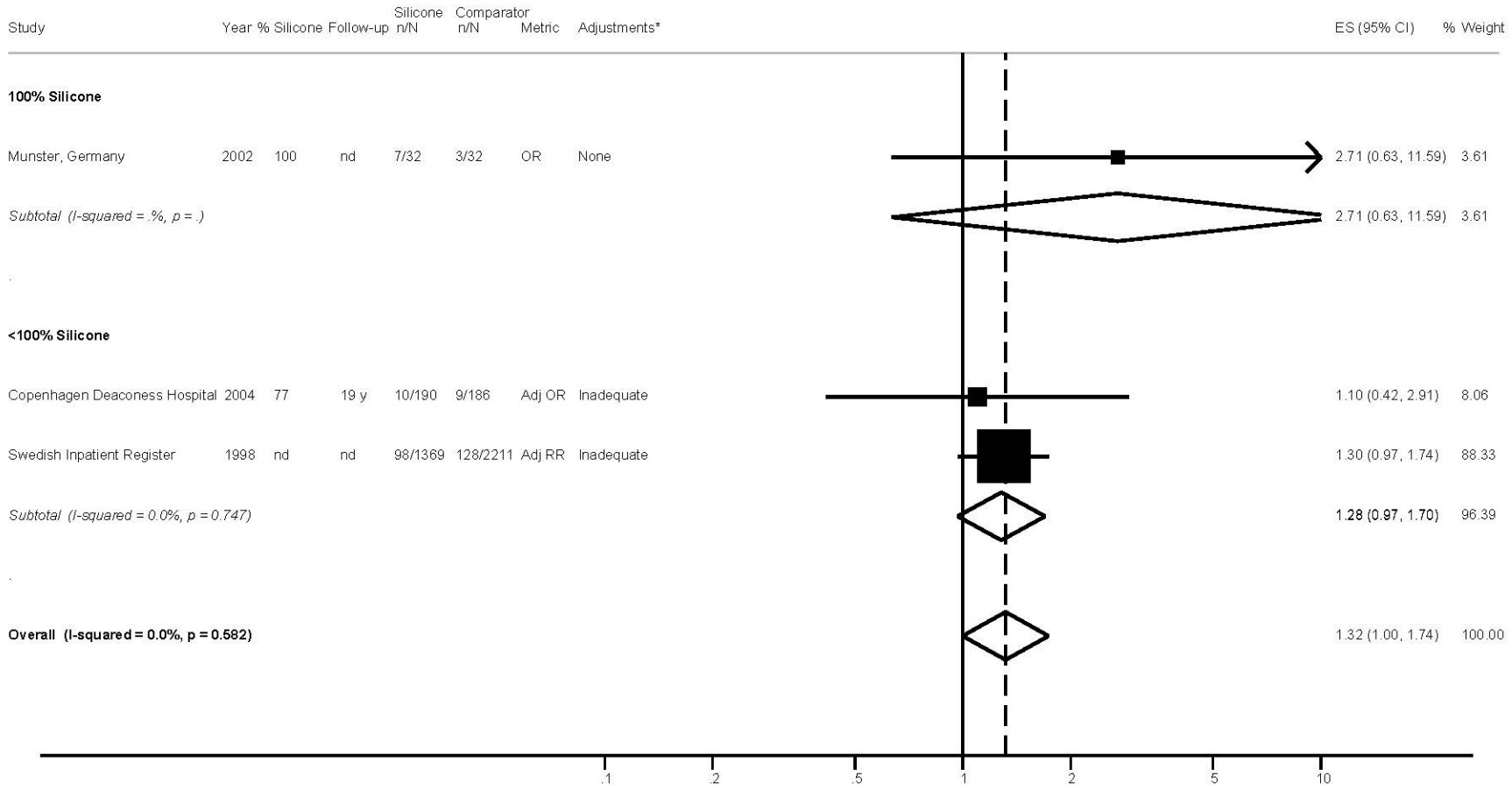


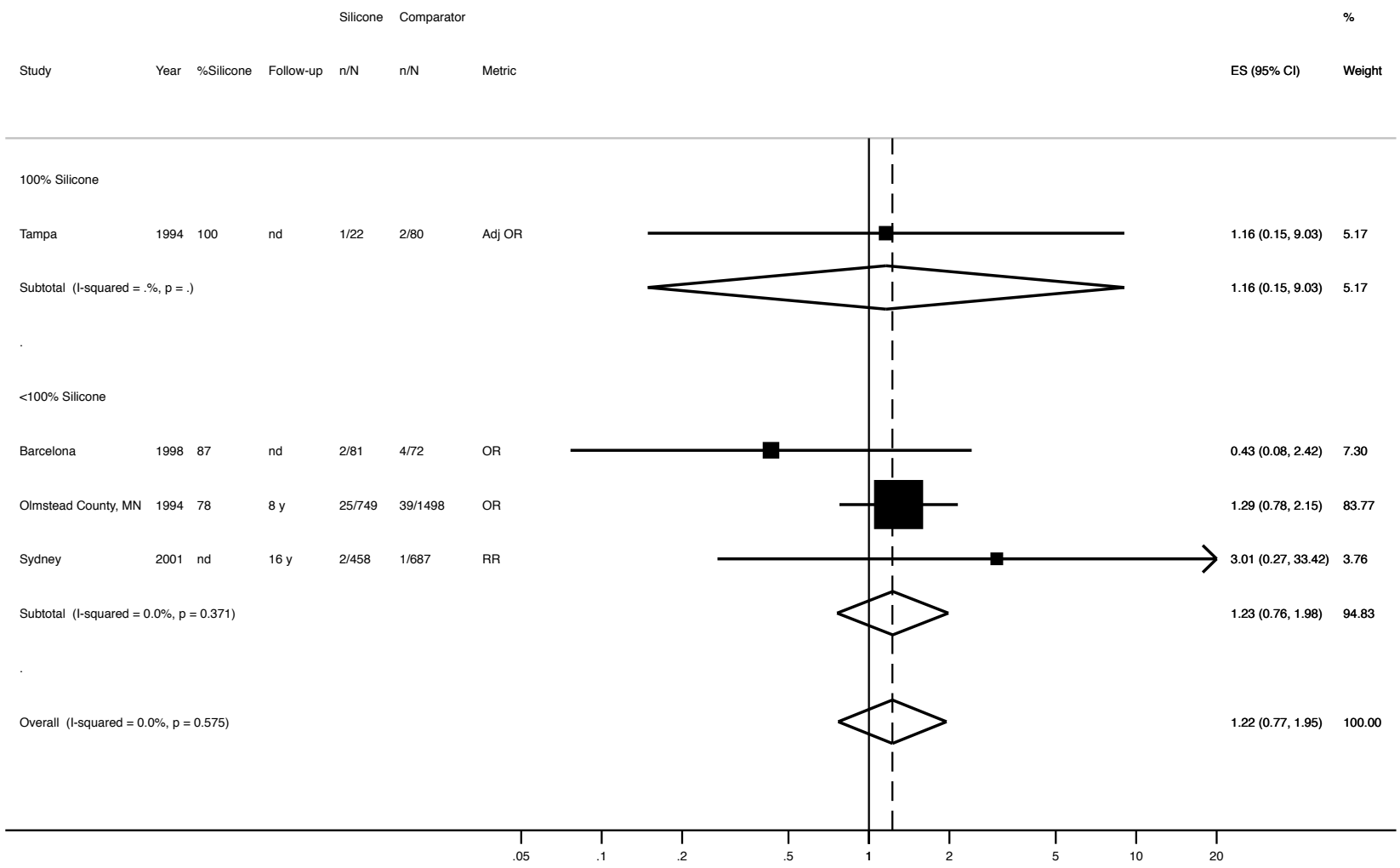
Table 36. Rheumatologic Symptoms: Arthritis Symptoms

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Tampa[96]	100	nd	No implant	1/22 (5%)	2/80 (3%)	Adj OR 1.16 (0.15, 9.03)	**Inad:** A, Y
Barcelona[38]	87	nd	No implant	2/81 (4%)	4/72 (6%)	ORcalc 0.43 (0.08, 2.42)	
Olmstead County, MN[54]	78	8 y	No implant	25/749 (3%)	39/1498 (3%)	ORcalc 1.29 (0.78, 2.15)	
Sydney[47]	nd	16 y	No implant	2/458 (0.4%)	1/687 (0.2%)	RR 3.01 (0.27, 33.3)	
Summary Implant vs. No Implant	**100% (n=1)**					**1.16 (0.15, 9.03)**	
	Any, Direct comparisons (n=4)					**1.22 (0.77, 1.95) P het=0.58, I^2=0%**	
Summary Percent Implant	**100% (n=1)**			**4.5% (0.6, 35)**			
	Any (n=4)			**1.7% (0.1, 4.7)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.

Figure 33. Rheumatologic Symptoms: Arthritis Symptoms



Difficulty Swallowing

Five studies reported on difficulty swallowing (**Table 37, Figure 34**). Among the three comparative studies, the largest study, from Sweden, found a significant association between any breast implant and the symptom. This study drove the pooled ES of 1.48 (95% CI 0.70, 3.11) with little statistical heterogeneity (**Figure 34**). The Denmark Private study compared women with implants to two control groups (women with other cosmetic surgery and general population women with no breast implants). The study adequately adjusted for CTD history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth, and age at implantation. Both comparisons were highly imprecise but the adjusted ORs conflicted (0.7 and 3.7).

Across studies, 1.7% (95% CI 0.3, 4.2) of women with implants complained of difficulty swallowing. In the two studies of women with only silicone gel implants 2.7% (95% CI 0, 17) reported this complaint.

The evidence is insufficient to determine if there is an association between breast implants and difficulty swallowing.

Dry Eyes

Six studies, four of which were comparative, reported on dry eyes (**Table 38, Figure 35**). Among the comparative studies, one small, matched study found no association between silicone gel implants and the complaint of dry eyes. The other comparative studies of women with any implants also found no significant associations, but with a wide range of comparative risk estimates from 0.39 to 1.8. The pooled ES was 1.03 (95% CI 0.63, 1.67) (**Figure 35**). The Denmark Private study compared women with implants to two control groups (women with other cosmetic surgery and general population women with no breast implants) with adequately adjusted analyses. Both comparisons were similar and non-significant (adjusted OR = 1.5 and 1.8).

Across studies 8.9% (95% CI5.9, 12.4) of women with implants complained of dry eyes. In the three studies of women with only silicone gel implants 12.3% (95% CI 7.4, 18.2) reported this complaint.

The evidence is insufficient to determine if there is an association between breast implants and dry eyes. Although all studies were non-significant, they reported inconsistent ESs. The adequately adjusted study had a larger ES than other studies.

Table 37. Rheumatologic Symptoms: Difficulty Swallowing

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
SE Scotland[9]	100	6 y	No implant	2/251 (0.8%)	0/216 (0%)	ORcalc 4.34 (0.21, 90.9)	
Denmark Private[72]	50	nd	Cosm Surg†	nd/423	nd/231	Adj OR 0.7 (0.2, 2.0)†	**Ad:** A, O6
			No implant†		8/149 (5%)	Adj OR 3.7 (0.4, 32.9)†	**Ad:** A, O6
Swedish Inpatient Register[52]	nd	nd	Br Reduc	32/1369 (2.3%)	32/2211 (1.4%)	Adj RR 1.9 (1.1, 3.4)	**Inad:** A, Y
Rotterdam University Hospital 1990-1995[39]	100	nd		0/63 (0%)			
Rotterdam University Hospital 1995-1997[40]	100	1 y		5/57 (9%)			
Summary Implant vs. No Implant	**100% (n=1)**					**4.34 (0.21, 90.9)**	
	Any, Direct comparisons (n=3)					**1.48 (0.70, 3.11)† P het=0.25, I^2=27%**	
	Any, Adequate adjustment (n=1, 2 comparisons)					**0.7 (0.2, 2.0) 3.7 (0.4, 32.9)**	
Summary Percent Implant	**100% (n=3)**			**1.7% (0.01, 7.3)**			
	Any (n=4)			**1.7% (0.3, 4.2)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

† Primary meta-analysis conducted with cosmetic surgery comparison. Alternatively, using no implant comparison: summary OR = 2.03 (1.19, 3.47); P het=0.75, I^2=0%.

Figure 34. Rheumatologic Symptoms: Difficulty Swallowing

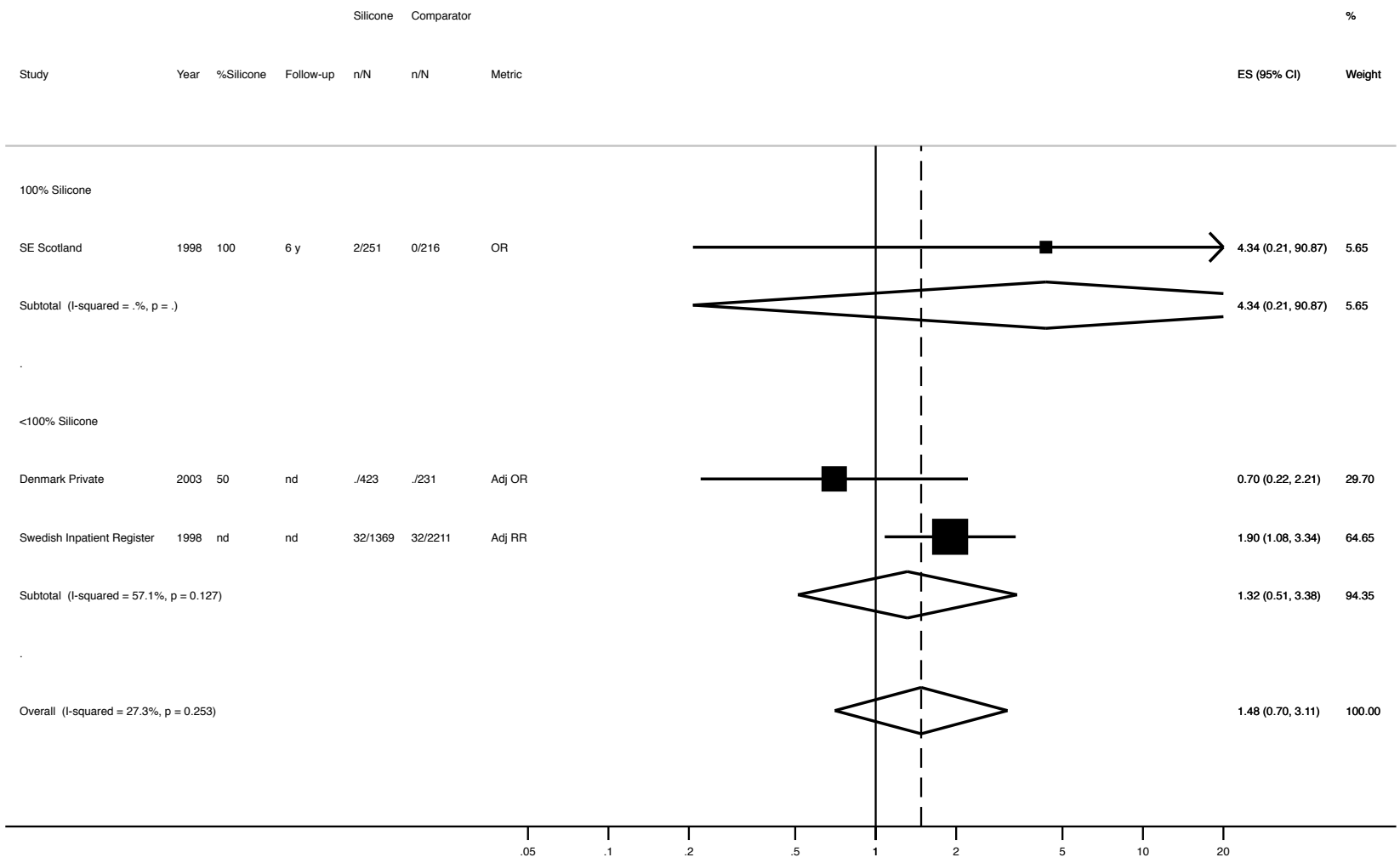


Table 38. Rheumatologic Symptoms: Dry Eyes

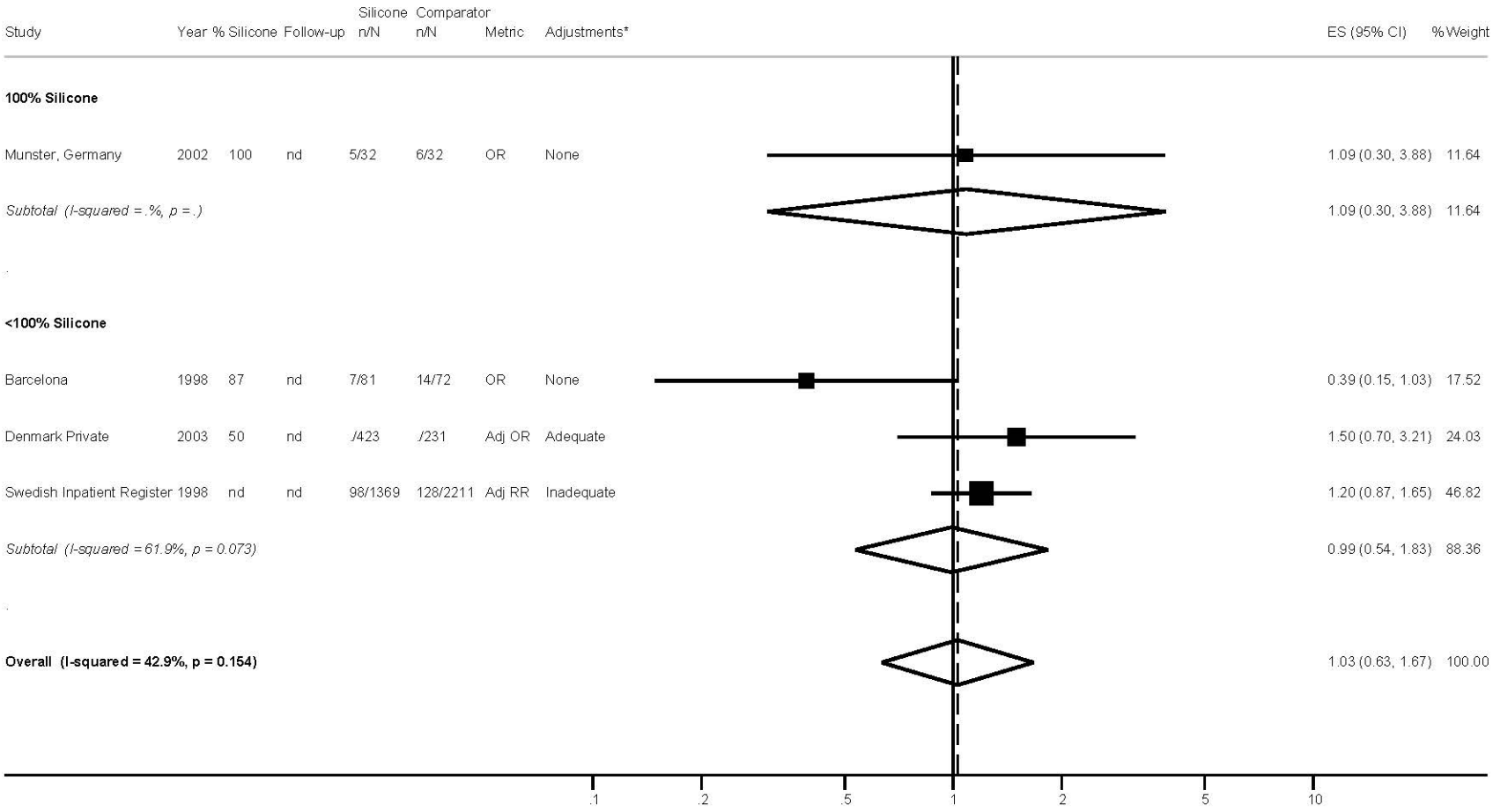
Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Munster, Germany[27]	100	nd	No implant	5/32 (16%)	6/32 (18%)	ORcalc 1.09 (0.30, 3.88)	
Barcelona[38]	87	nd	No implant	7/81 (9%)	14/72 (19%)	ORcalc 0.39 (0.15, 1.03)	
Denmark Private[72]	50	nd	Cosm Surg†	nd/423	nd/231	Adj OR 1.5 (0.7, 3.2)†	**Ad:** A, O6
			No implant†		nd/183	Adj OR 1.8 (0.7, 4.1)†	**Ad:** A, O6
Swedish Inpatient Register[52]	nd	nd	Br Reduc	98/1369 (7%)	128/2211 (6%)	Adj RR 1.2 (0.9, 1.7)	**Inad:** A, Y
Rotterdam University Hospital 1990-1995[39]	100	nd		6/63 (9.5%)			
Rotterdam University Hospital 1995-1997[40]	100	1 y		8/57 (14%)			
Summary Implant vs. No Implant	**100% (n=1)**					**1.09 (0.30, 3.88)**	
	Any, Direct comparisons (n=4)					**1.03 (0.63, 1.67)† P het=0.15, I^2=43%**	
	Any, Adequate adjustment (n=1, 2 comparisons)					**1.5 (0.7, 3.2) 1.8 (0.7, 4.1)**	
Summary Percent Implant	**100% (n=3)**			**12.3% (7.4, 18.2)**			
	Any (n=5)			**8.9% (5.9, 12.4)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

† Primary meta-analysis conducted with cosmetic surgery comparison. Alternatively, using no implant comparison: summary OR = 1.04 (0.60, 1.79); P het=0.12, I^2=48%.

Figure 35. Rheumatologic Symptoms: Dry Eyes



Dry Oropharynx

Six studies, four of which were comparative, reported on dry oropharynx (**Table 39, Figure 36**). A single, small, matched comparative study of German women with silicone gel implants found that more than twice as many women with silicone gel implants complained of dry oropharynx. The other comparative studies of women with any implant had heterogeneous results. Overall, the pooled ES was 1.39 (95% CI 0.85, 2.27) (**Figure 36**). The Denmark Private study that conducted adequate adjustments found conflicting adjusted ORs when different comparator groups were used. It is likely that the definitions of dry oropharynx varied across studies as there was a wide range of percentage of women with the complaint, from 5% and 6% in studies from Sweden and Barcelona to 34% in a study from Germany. The Munster study found a strong association (ES ≥2.0) in women specifically with silicone gel implants, but it was not clear whether the reported symptoms were new since implantation. The Denmark Private study also found a strong association. They conducted an adequately adjusted analysis of only symptoms that arose after implantation, but their cohort included 50% of women with non-silicone gel implants.

Among the three studies of women with only silicone gel implants, 23% (95% CI 14, 33) complained of dry oropharynx. Pooling of all studies was not conducted due to the much lower percentage of women in the remaining studies with the complaint

The evidence is insufficient to determine if there is an association between breast implants and dry oropharynx. The studies provide inconsistent estimates of associations.

Table 39. Rheumatologic Symptoms: Dry Oropharynx

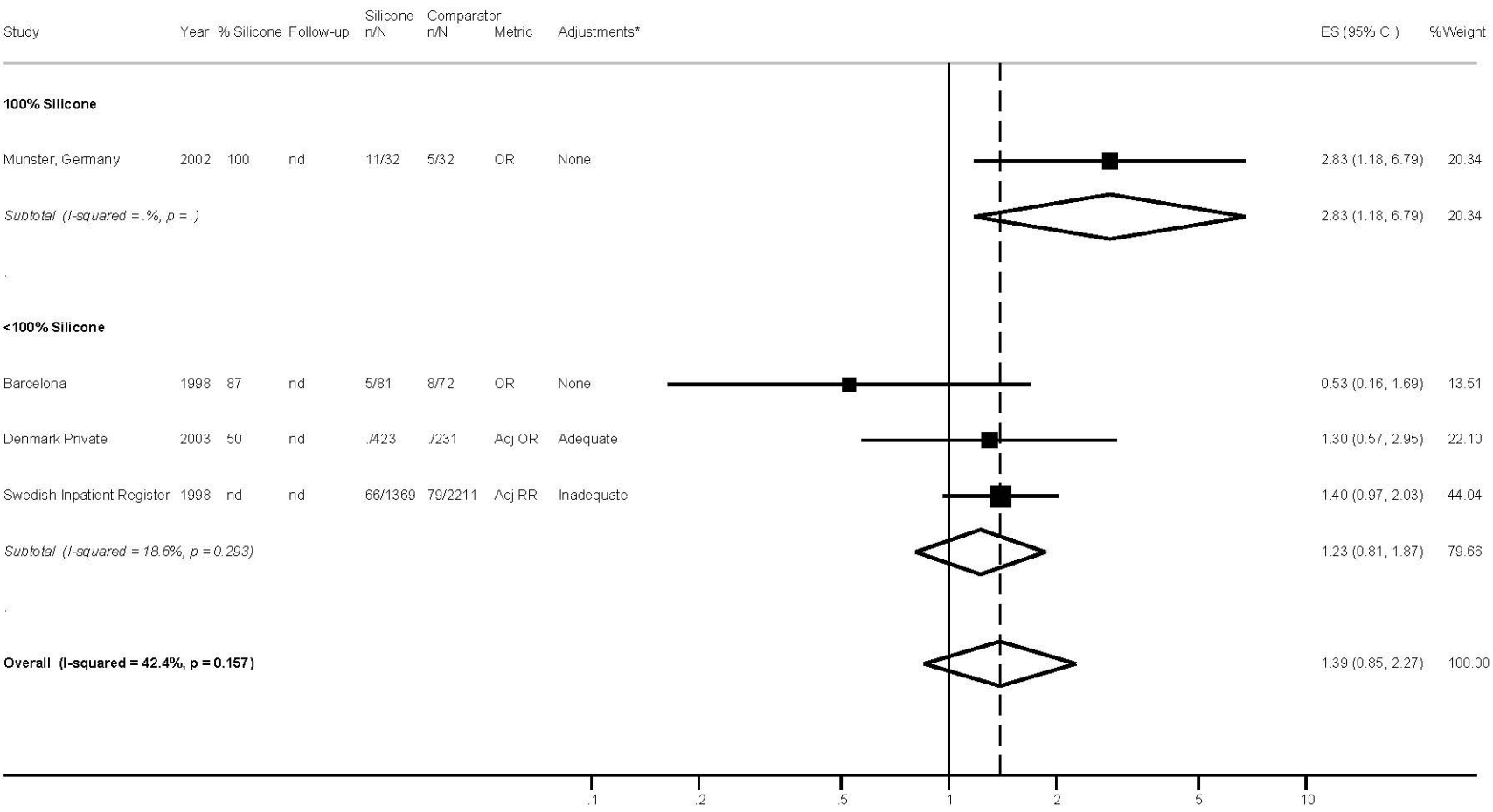
Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Munster, Germany[27]	100	nd	No implant	11/32 (34%)	5/32 (16%)	ORcalc 2.83 (1.18, 6.79)	
Barcelona[38]	87	nd	No implant	5/81 (6%)	8/72 (11%)	ORcalc 0.53 (0.16, 1.69)	
Denmark Private[72]	50	nd	Cosm Surg†	nd/423	nd/231	Adj OR 1.3 (0.6, 3.1)†	**Ad:** A, O6
			No implant†		nd/183	Adj OR 4.5 (1.0, 20.7)†	**Ad:** A, O6
Swedish Inpatient Register[52]	nd	nd	Br Reduc	66/1369 (5%)	79/2211 (4%)	Adj RR 1.4 (1.0, 2.1)	**Inad:** A, Y
Rotterdam University Hospital 1990-1995[39]	100	nd		14/63 (22%)			
Rotterdam University Hospital 1995-1997[40]	100	1 y		9/57 (16%)			
Summary Implant vs. No Implant	**100% (n=1)**					**2.83 (1.18, 6.79)**	
	Any, Direct comparisons (n=4)					**1.39 (0.85, 2.27)† P het=0.16, I^2=42%**	
	Any, Adequate adjustment (n=1, 2 comparisons)					**1.3 (0.6, 3.1) 4.5 (1.0, 20.7)**	
Summary Percent Implant	**100% (n=3)**			**23% (14, 33)**			
	Any			**‡**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

† Primary meta-analysis conducted with cosmetic surgery comparison. Alternatively, using no implant comparison: summary OR = 1.64 (0.82, 3.26); P het=0.064, I^2=59%.
‡ Not calculated due to extreme heterogeneity across studies.

Figure 36. Rheumatologic Symptoms: Dry Oropharynx



Fatigue

Nine studies, all but two of which were comparative, reported on fatigue (**Table 40, Figures 37 & 38**). Four of the studies evaluated only women with silicone implants. Three found non-significant associations. The fourth, the Dutch Silicone Implant Support Group study is particularly biased since it included women who were in a support group, and thus more likely than average to have a concern, symptom, or disease putatively related to silicone gel implants.[93] For this reason, this study is not included in meta-analyses or conclusions. Across the remaining six comparative studies of any breast implants, ESs ranged from 1.0 to 2.6, two of which were statistically significant. The summary OR was 1.39 (95% CI 1.17, 1.65), with no heterogeneity (**Figure 37**). The Denmark Private study that conducted adequate adjustments found discordant non-significant adjusted ORs when different comparator groups were used (1.0 and 1.6), but both analyses were non-significant.[72] Similarly, the Copenhagen Deaconess Hospital study compared women with breast implants to both women with breast reduction surgery and general population women with no implants.[28] This study also had discordant estimates, only one of which was statistically significant (1.3 and 2.6). No difference in association was found across studies based on whether outcomes were clearly incident since implantation (versus possible prevalence at the time of implantation) (P=0.65).

Among the five studies of women with only silicone gel implants, 18% (95% CI 13, 24) complained of fatigue. Across all studies, 17% (14, 21) of women with implants complained of fatigue.

The evidence is insufficient to determine if there is an association between breast implants and fatigue. The adequately adjusted study did not find a consistent association and the remaining studies also did not have consistent results, despite the statistically significant meta-analyzed ES.

Finger Swelling

Two small comparative studies evaluated the complaint of swollen fingers (**Table 41**). The same German study found a significant 3-times higher rate in 32 women with silicone gel implants than the same number of women without implants. The adequately adjusted Denmark Private study found approximately 2-times higher rates in women, half of whom had silicone gel implants, but only one of the analyses was statistically significant.

The Munster study found a strong association (ES $\geq$2.0) in women specifically with silicone gel implants, but it was not clear whether the reported symptoms were new since implantation. The Denmark Private study also found a strong association, but only in one of two analyses. They conducted an adequately adjusted analysis of only symptoms that arose after implantation, but their cohort included 50% of women with non-silicone gel implants.

There is limited evidence of an association between breast implants and finger swelling. Women with breast implants may have two to three times increased risk of the complaint. However, this conclusion is based on one adequately adjusted study that found a significant association in only one of its two analyses, and a second very small study. The studies do not provide sufficient evidence to determine if a true association exists and, therefore, whether silicone gel implants may have a causal link to the symptom.

Table 40. Rheumatologic Symptoms: Fatigue

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Munster, Germany[27]	100	nd	No implant	13/32 (41%)	8/32 (25%)	ORcalc 2.05 (0.87, 4.84)	
SE Scotland[9]	100	6 y	Cosm Surg	27/251 (11%)	23/216 (11%)	ORcalc 1.01 (0.56, 1.82)	
Tampa[96]	100	nd	No implant	33/222 (15%)	9/80 (11%)	Adj OR 1.38 (0.57, 3.31)	**Inad:** A, Y
Dutch Silicone Implant Support Group†[93]	100	nd	No implant	227/319 (71%)†	9/40 (23%)	ORcalc 8.50 (3.89, 18.6)†	
Copenhagen Deaconess Hospital[28]	77	19 y	Br Reduc‡	38/190 (20%)	30/186 (16%)	Adj OR 1.3 (0.8, 2.2)‡	**Inad:** A
			No implant‡		13/149 (9%)	Adj OR 2.6 (1.3, 5.1)‡	**Inad:** A
Denmark Private[72]	50	nd	Cosm Surg‡	nd/423	nd/231	Adj OR 1.6 (0.9, 2.8)‡	**Ad:** A, O6
			No implant‡		nd/183	Adj OR 1.0 (0.6, 1.8)‡	**Ad:** A, O6
Swedish Inpatient Register[52]	nd	nd	Br Reduc	224/1369 (16%)	294/2211 (13%)	Adj RR 1.4 (1.1, 1.7)	**Inad:** A, Y
Birmingham, AL[35]	100	20 y		71/344 (21%)			
Denmark Public-Private Subset[64]	100	nd		41/238 (17%)			
Summary Implant vs. No Implant	**100% (n=3)**					**1.29 (0.85, 1.98) P het=0.41, I^2=0%**	
	Any, Direct comparisons (n=6)					**1.39 (1.17, 1.65)‡ P het=0.82, I^2=0%**	
	Any, Adequate adjustment (n=1, 2 comparisons)					**1.6 (0.9, 2.8) 1.0 (0.6, 1.8)**	
Summary Percent Implant	**100% (n=5)**			**18% (13, 24)**			
	Any (n=7)			**17% (14, 21)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

† Study was of a highly biased sample of women in a silicone breast implant support group. Not included in meta-analyses.
‡ Primary meta-analysis conducted with breast reduction or cosmetic surgery comparison. Alternatively, using no implant comparison: summary OR = 1.40 (1.09, 1.79); P het=0.26, I^2=23%.

Figure 37. Rheumatologic Symptoms: Fatigue

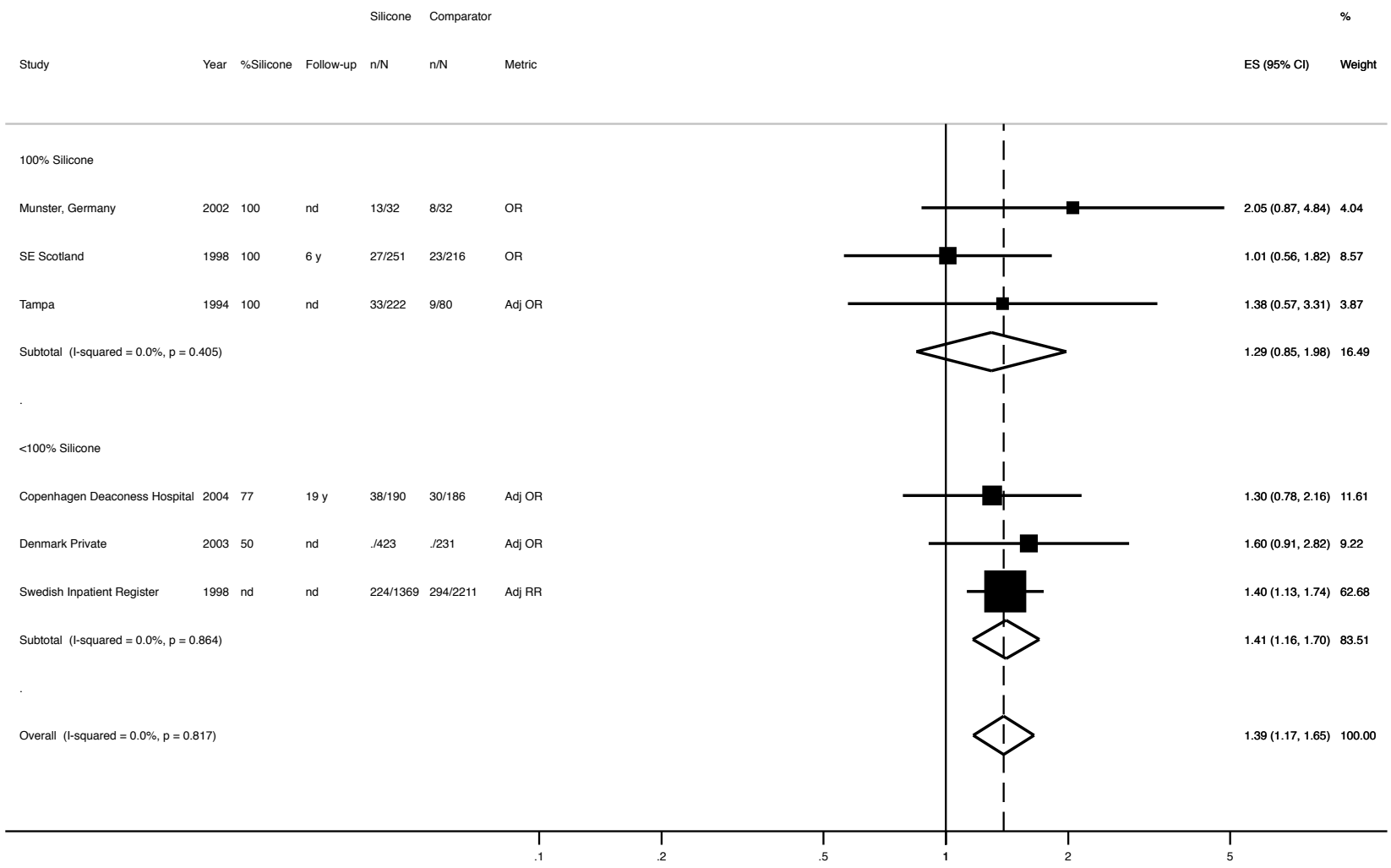


Figure 38. Fatigue: Cumulative Meta-Analysis by End-Entry Date

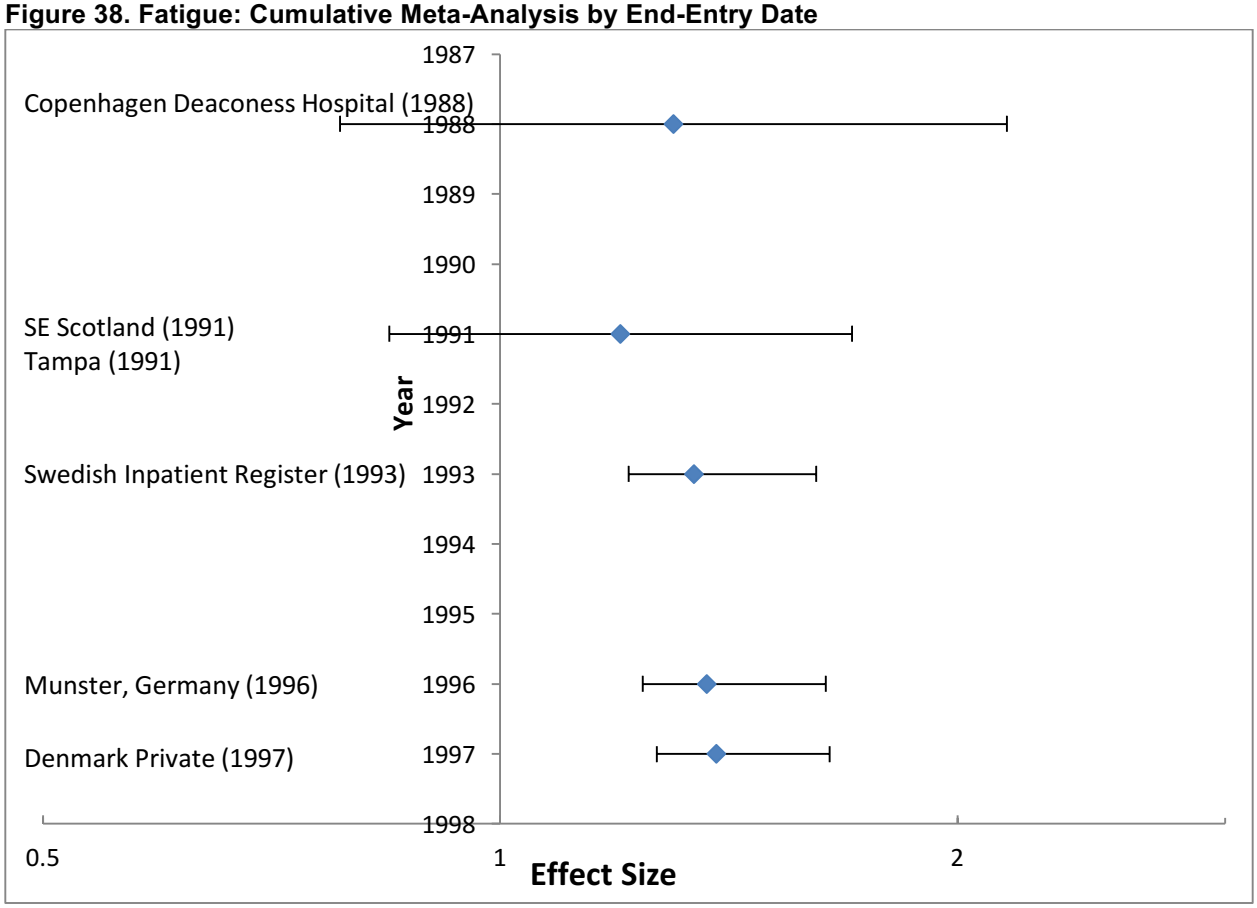


Table 41. Rheumatologic Symptoms: Finger Swelling

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Munster, Germany[27]	100	nd	No implant	10/32 (31%)	4/32 (13%)	ORcalc 3.18 (1.12, 9.05)	
Denmark Private[72]	50	nd	Cosm Surg	nd/423	nd/231	Adj OR 2.4 (1.1, 5.5)	**Ad:** A, O6
			No implant		nd/183	Adj OR 1.8 (0.7, 4.5)	**Ad:** A, O6
Summary Implant vs. No Implant	**100% (n=1)**					**3.18 (1.12, 9.05)**	
	Any, Direct comparisons (vs. no implant; n=2)					**3.18 (1.12, 9.05)** **1.8 (0.7, 4.5)**	
	Any, Adequate adjustment (n=1, 2 comparisons)					**2.4 (1.1, 5.5)** **1.8 (0.7, 4.5)**	
Summary Percent Implant	**100% (n=1)**			**31% (18, 49)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.

A = age, R = race, T = time since surgery, Y = calendar year.

O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

Joint Pain (Arthralgia)

Ten studies reported on arthralgia, eight of which were comparative (**Table 42, Figures 39 & 40**). Five of the comparative studies included women with only silicone gel implants; in the remaining studies, 87% and 50% of the women had silicone gel implants or no data were reported. However, The Dutch Silicone Implant Support Group study, however, included a highly biased sample of women with implants and is not evaluated further here.

The four comparative studies of silicone gel implants had a range of results, from an OR of 1.07 to 2.60, only one of which was statistically significant. By meta-analysis, the summary ES was 1.58 (95% CI 0.96, 2.61). Among the remaining comparative studies the ES ranged from a statistically significant 0.29 to a non-significant 1.92. The one adequately adjusted analysis found no significant association (adjusted OR 1.1, compared with both comparison groups). Thus, the pooled ES was highly heterogeneous (P heterogeneity <0.001, I^2 = 75%), yielding a non-significant association (1.13; 95% CI 0.74, 1.72) (**Figure 39**).

For unclear reasons, the study from Barcelona was an outlier with a statistically significant reduced risk for joint pain in women with breast implants versus women without implants (OR = 0.29; 95% CI 0.15, 0.58). This was the only study to define arthralgia based on physical examination. Removing this study from the meta-analysis yields a statistically significant positive association (increased risk) with reduced heterogeneity: summary OR = 1.36 (95% CI 1.07, 1.72; P heterogeneity = 0.25; I^2 = 25%). The studies had a wide range of percent of women reporting joint pain (11% to 63%, even excluding the Dutch Silicone Implant Support Group study). Meta-regression across the percent of women with the complaint, however, was non-significant (P = 0.74). Likewise, the final recruitment year within each study that women received implants was not a significant factor (P = 0.20). No difference in association was found across studies based on whether outcomes were clearly incident since implantation (versus possible prevalence at the time of implantation) (P=0.13). Cumulative meta-analysis by surgery year, (**Figure 40**) however, shows that the summary ES moved toward the null as studies of women who received implants later in the 1990s were included. Analysis by follow-up time was not possible due to lack of reported data.

As noted, two of the studies had a strong, significant association, but one with an ES >2.0 and one an ES <0.5. The Free University, Amsterdam study, with an ES >2.0, was specific to silicone gel implants; however, it is unclear whether the analyzed symptoms included only those that occurred after implantation. The Barcelona study, with an ES <0.5 was not specific to silicone gel implants and the timing of the symptoms relative to implantation was also unclear.

The evidence is insufficient to determine if there is an association between breast implants and joint pain. The studies had a wide range of inconsistent results including between the two studies of women with only silicone gel implants. Removing an outlier study yielded a statistically significant small association (ES <2.0) with joint pain, but the wide range of percent of women with the complaint (11% to 63%) precludes a definitive conclusion.

Note: See the section Joint Swelling, Stiffness, and Pain", below.

Table 42. Rheumatologic Symptoms: Joint Pain

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Munster, Germany[27]	100	nd	No implant	20/32 (63%)	19/32 (61%)	ORcalc 1.07 (0.39, 2.93)	
Free University, Amsterdam[55]	100	7 y	Cosm Surg	46/235 (20%)	18/210 (9%)	OR 2.60 (1.45, 4.64)	
SE Scotland[9]	100	6 y	Cosm Surg	32/251 (13%)	25/216 (12%)	ORcalc 1.12 (0.64, 1.95)	
Tampa[96]	100	nd	No implant	24/222 (11%)	4/80 (5%)	Adj OR 1.92 (0.52, 7.14)	**Inad:** A, Y
Dutch Silicone Implant Support Group†[93]	100	nd	No implant	247/319 (77%)	7/40 (18%)	ORcalc 16.2 (6.87, 38.1)†	
Barcelona[38]	87	nd	No implant	20/81 (25%)	38/72 (53%)	ORcalc 0.29 (0.15, 0.58)	
Denmark Private[72]	50	nd	Cosm Surg‡	nd/423	nd/231	Adj OR 1.1 (0.7, 1.8)‡	**Ad:** A, O6
			No implant‡		nd/183	Adj OR 1.1 (0.7, 1.9)‡	**Ad:** A, O6
Swedish Inpatient Register[52]	nd	nd	Br Reduc	308/1369 (22%)	432/2211 (20%)	Adj RR 1.3 (1.0, 1.5)	**Inad:** A, Y
Rotterdam University Hospital 1990-1995[39]	100	nd		22/63 (35%)			
Rotterdam University Hospital 1995-1997[40]	100	1 y		19/57(33%)			
Summary Implant vs. No Implant	**100% (n=4)**					**1.58 (0.96, 2.61) P het=0.17, I^2=40%**	
	Any, Direct comparisons (n=7)					**1.13 (0.74, 1.72)‡ P het<0.001, I^2=75%**	
	Any, Adequate adjustment (n=1, 2 comparisons)					**1.1 (0.7, 1.8) 1.1 (0.7, 1.9)**	
Summary Percent Implant	**100%**			**#**			
	Any			**#**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

† Study was of a highly biased sample of women in a silicone breast implant support group. Not included in meta-analyses.
‡ Primary meta-analysis conducted with cosmetic surgery comparison. Alternatively, using no implant comparison: summary OR = 1.13 (0.73, 1.73); P het<0.001, I^2=75%.
# Not calculated due to extreme heterogeneity across studies.

Figure 39. Rheumatologic Symptoms: Joint Pain (Arthralgia)

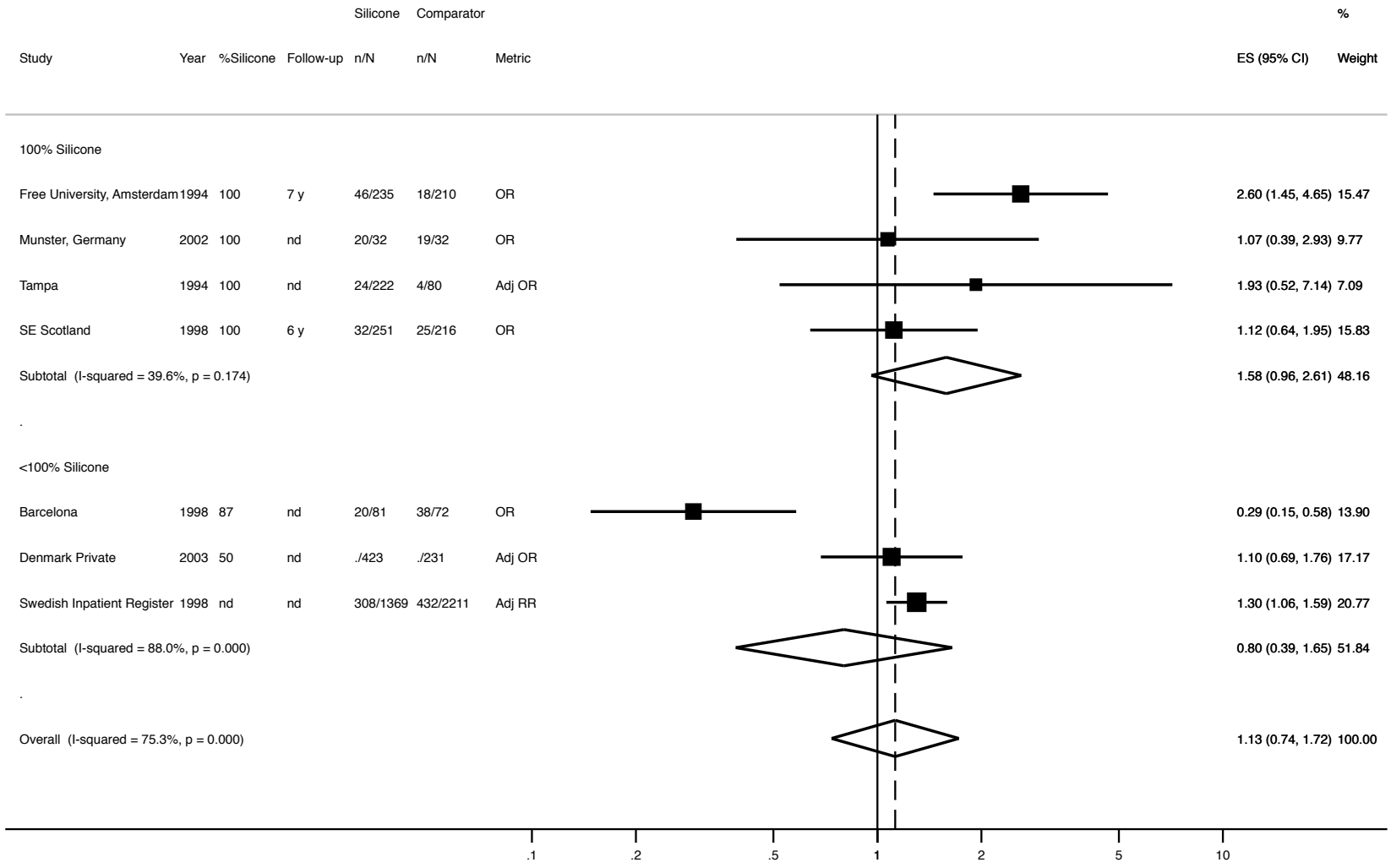
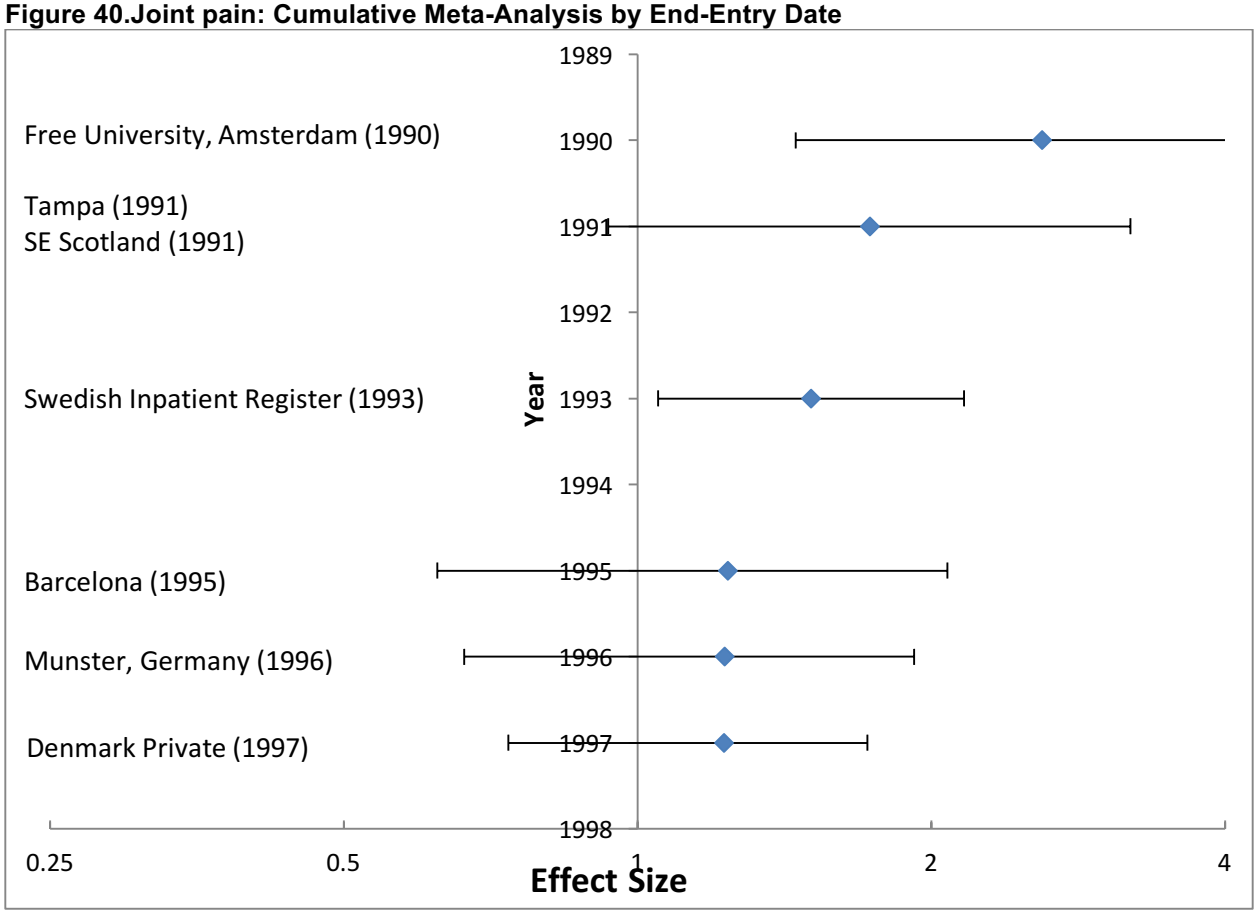


Figure 40.Joint pain: Cumulative Meta-Analysis by End-Entry Date



Joint Stiffness

Five studies reported on joint stiffness (**Table 43, Figure 41**). The three comparative studies included women with any breast implant. Two of the studies found statistically significant higher proportions of women with implants who complained of joint stiffness than women in control groups. This included the one adequately adjusted study that found a significant association in analyses against different control groups. The three studies reported ESs that ranged from a non-significant 0.93 to a significant 2.3. The pooled ES was 1.69 (95% CI 1.11, 2.59), with little heterogeneity (**Figure 41**). However, the percentage of women reporting joint stiffness varied widely, from 4% to 51%, implying that the definition of the condition may have been different across studies.

There is limited or suggestive evidence of an association between breast implants and joint stiffness. Women with breast implants may have about a 70% to 100% increased risk of the complaint. However, this conclusion is based primarily on one adequately adjusted study that found a significant association in only one of its two analyses, and a second very small study.

The Denmark Private study found a strong association (ES ≥2.0) in an adequately adjusted analysis of only symptoms that arose after implantation, but their cohort included 50% of women with non-silicone gel implants.

The evidence is insufficient to determine if there is an association between breast implants and joint stiffness. An adequately adjusted study found a large, significant association, but the lack of consistency among the other two studies and the large range of percentage of women with the complaint preclude a conclusion of a possible association.

Note: See the section, "Joint Swelling, Stiffness, and Pain", below.

Joint Swelling

Six studies evaluated joint swelling (**Table 44, Figure 42**). Two of the four comparative studies found no significant associations between silicone gel implants and joint swelling. The other two comparative studies of any breast implants, had similar findings. The pooled ES was homogeneous with a summary ES of 1.20 (95% CI 0.95, 1.50) (**Figure 42**). The adequately adjusted Denmark Private study found similarly imprecise associations with its two comparator groups.

Across studies, 8.7% (95% CI 4.8, 13.7) of women with implants complained of joint swelling. Among the four studies that included only women with silicone gel implants, 6.8% (95% CI 4.0, 10.2) had the complaint.

The evidence is insufficient to determine if there is an association between breast implants and joint swelling. It is unclear whether a small association (ES <2.0) or no association exists.

Note: See the section "Joint Swelling, Stiffness, and Pain", below.

Table 43. Rheumatologic Symptoms: Joint Stiffness

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Tampa[96]	100	nd	No implant	22/222 (10%)	8/80 (10%)	Adj OR 0.93 (0.38, 2.26)	**Inad:** A, Y
Olmstead County, MN[54]	78	8 y	No implant	30/749 (4%)	35/1498 (2%)	ORcalc 1.74 (1.06, 2.86)	
Denmark Private[72]	50	nd	Cosm Surg†	nd/423	nd/231	Adj OR 2.3 (1.2, 4.3)†	**Ad:** A, O6
			No implant†		nd/183	Adj OR 2.3 (1.1, 4.6)†	**Ad:** A, O6
Rotterdam University Hospital 1990-1995[39]	100	nd		30/63 (48%)			
Rotterdam University Hospital 1995-1997[40]	100	1 y		29/57 (51%)			
Summary Implant vs. No Implant	**100% (n=1)**					0.93 (0.38, 2.26)	
	Any, Direct comparisons (n=3)					**1.69 (1.11, 2.59)† P het=0.27, I^2=24%**	
	Any, Adequate adjustment (n=1, 2 comparisons)					**2.3 (1.2, 1.3) 2.3 (1.1, 4.6)**	
Summary Percent Implant	**100%**			**‡**			
	Any			**‡**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

† Primary meta-analysis conducted with cosmetic surgery comparison. Alternatively, using no implant comparison: summary OR = 1.67 (1.09, 2.55); P het=0.29, I^2=19%.
‡ Not calculated due to extreme heterogeneity across studies.

Figure 41. Rheumatologic Symptoms: Joint Stiffness

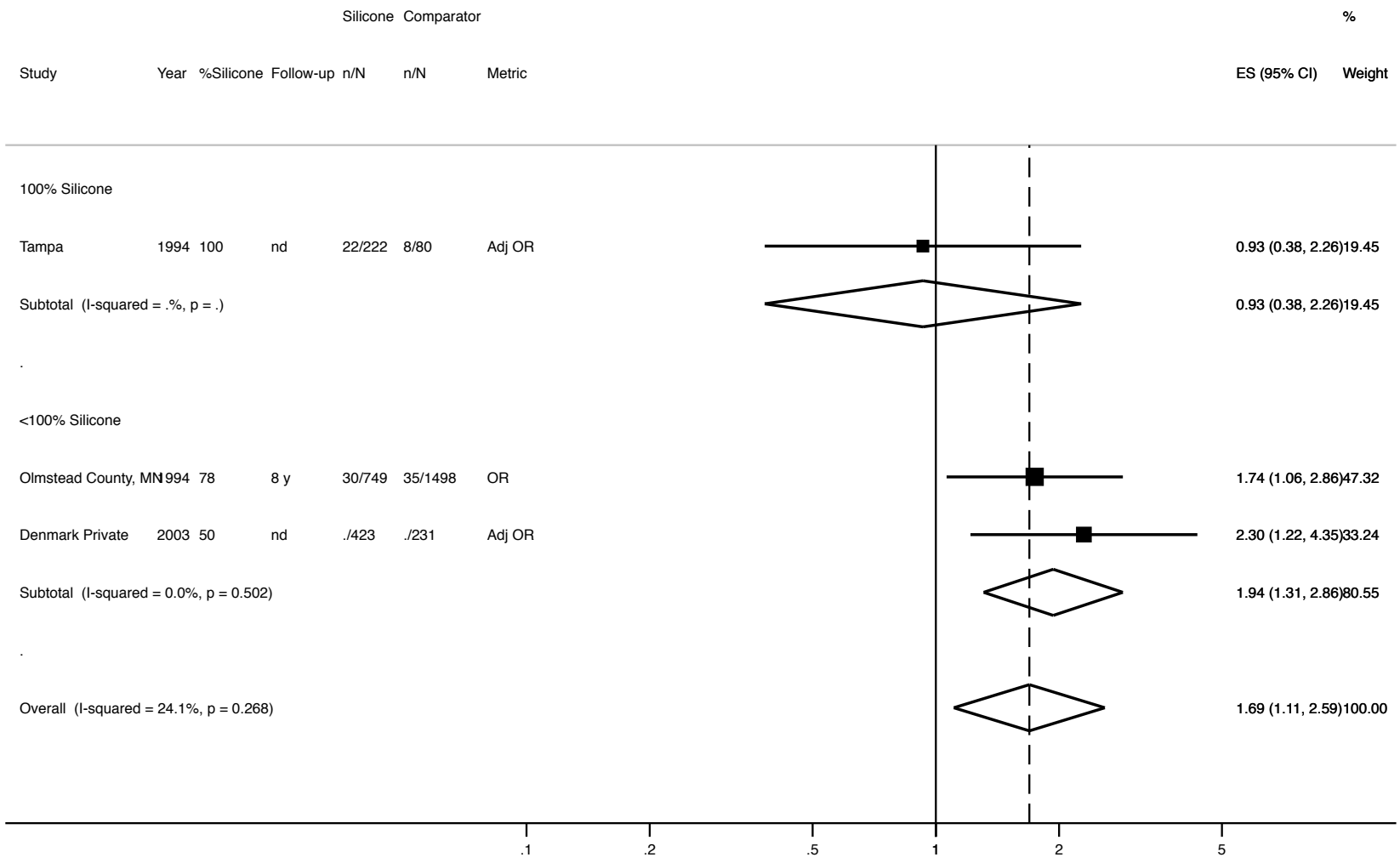


Table 44. Rheumatologic Symptoms: Joint Swelling

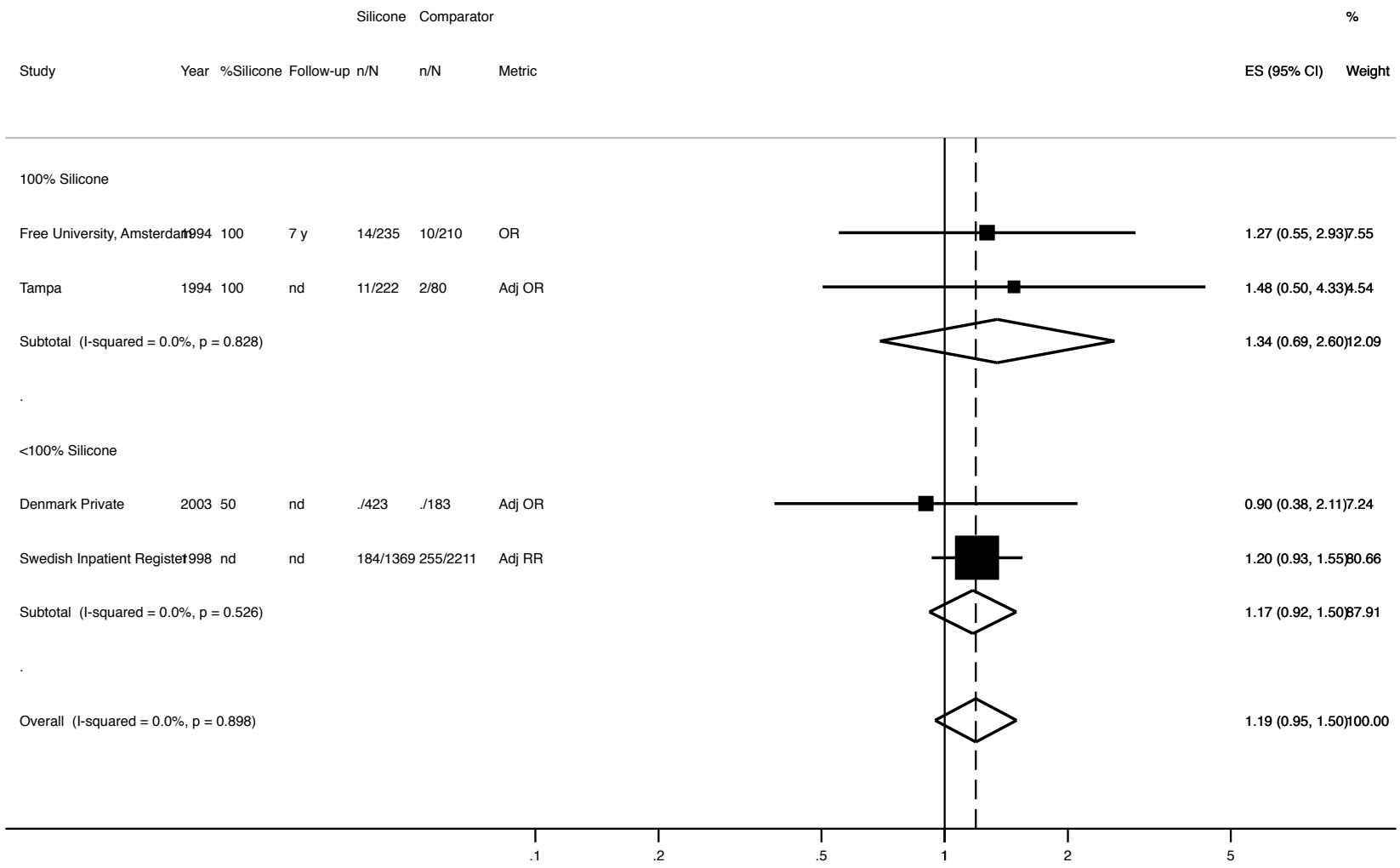
Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Free University, Amsterdam[55]	100	7 y	Cosm Surg	14/235 (6%)	10/210 (5%)	OR 1.27 (0.55, 2.92)	
Tampa[96]	100	nd	No implant	11/211 (5%)	2/80 (3%)	Adj OR 1.48 (0.26, 2.27)	**Inad:** A, Y
Denmark Private[72]	50	nd	Cosm Surg†	nd/423	nd/231	Adj OR 1.0 (0.5, 2.2)†	**Ad:** A, O6
			No implant†		nd/183	Adj OR 0.9 (0.4, 2.2)†	**Ad:** A, O6
Swedish Inpatient Register[52]	nd	nd	Br Reduc	184/1369 (13%)	255/2211 (12%)	Adj RR 1.2 (0.9-1.5)	**Inad:** A, Y
Rotterdam University Hospital 1990-1995[39]	100	nd		5/63 (8%)			
Rotterdam University Hospital 1995-1997[40]	100	1 y		8/57 (14%)			
Summary Implant vs. No Implant	**100% (n=2)**					**1.27 (0.55, 2.92)** **1.48 (0.26, 2.27)**	
	Any, Direct comparisons (n=4)					**1.20 (0.95, 1.50)†** **P het=0.94, I^2=0%**	
	Any, Adequate adjustment (n=1, 2 comparisons)					**1.0 (0.5, 2.2)** **0.9 (0.4, 2.2)**	
Summary Percent Implant	**100% (n=4)**			**6.8% (4.0, 10.2)**			
	Any (n=5)			**8.7% (4.8, 13.7)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

† Primary meta-analysis conducted with cosmetic surgery comparison. Alternatively, using no implant comparison: summary OR = 1.19 (0.95, 1.50); P het=0.90, I^2=0%.

Figure 42. Rheumatologic Symptoms: Joint Swelling



Joint Swelling, Stiffness, and Pain

Three studies evaluated the combined outcome of joint swelling, stiffness, and pain (**Table 45**). Only one of the studies was comparative, evaluating women with any breast implant. It found no difference between women with implants and two different controls (women with breast reduction surgery and women without implants in the general population). The evidence is insufficient to determine if there is an association between breast implants and the combined symptom of joint swelling, stiffness, and pain.

Muscle Pain (Myalgia)

Eight studies reported on myalgia, seven of which were comparative studies (**Table 46, Figures 43 & 44**). The four comparative studies of silicone gel implants had a wide range of rates of complaints of muscle pain in the implant groups (8-76%). One of these, the Dutch Silicone Implant Support Group study had many times more women complaining of myalgia in the implant group than the control group. However, this study is particularly biased since it included women who were in a support group, and thus more likely than average to have a concern, symptom, or disease putatively related to silicone gel implants. For this reason, this study is not included in meta-analyses. The other studies found no significant differences. The comparative studies (of any breast implant) also found no significance in complaints of myalgia. The one adequately adjusted study found somewhat different levels of association with muscle pain depending on which control group (other cosmetic surgery patients or general population without implants) was used. Alternatively using either analysis in meta-analysis yielded a summary ES = 1.28 (95% CI 1.06, 1.55) (**Figure 43**) or summary ES = 1.28 (95% CI 1.26, 1.55), both with no statistical heterogeneity. No differences in association were found between the single study that determined the outcome based on physical examination (Barcelona) versus patient questionnaire (P=0.39) or between studies that explicitly analyzed incident disease (since implantation) versus those that may have included prevalent disease (at the time of implantation) (P=0.59). Cumulative meta-analysis by the final recruitment year within each study that women received implants did not show any trend over time (**Figure 44**). There were insufficient data on follow-up times to allow analysis.

There is limited or suggestive evidence of an association between breast implants and muscle pain. Women with breast implants may have a small increased risk of the complaint of about 20%. However, the adequately adjusted study did not reach this conclusion. The studies do not provide sufficient evidence to determine if a true association exists and, therefore, whether silicone gel implants may have a causal link to the symptom.

Note: See the section “Muscle Weakness and Pain”, below.

Table 45. Rheumatologic Symptoms: Joint Pain, Swelling, Stiffness

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Copenhagen Deaconess Hospital[28]	77	19 y	Br Reduc	72/190 (38%)	66/186 (35%)	Adj OR 1.1 (0.7, 1.9)	**Inad:** A
			No implant		47/149 (32%)	Adj OR 1.3 (0.8, 2.1)	**Inad:** A
Birmingham, AL[35]	100	20 y		140/344 (41%)			
Denmark Public-Private subset[64]	100	nd		62/238 (26%)			
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=1, 2 comparisons)					**1.1 (0.7, 1.9)** **1.3 (0.8, 2.1)**	
Summary Percent Implant	**100% (n=2)**			**33% (20, 48)**			
	Any (n=3)			**35% (26, 44)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.

Table 46. Rheumatologic Symptoms: Muscle Pain

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Munster, Germany[27]	100	nd	No implant	16/32 (50%)	14/32 (44%)	ORcalc 1.29 (0.48, 3.44)	
SE Scotland[9]	100	6 y	Cosm Surg	19/251 (8%)	15/216 (7%)	ORcalc 1.10 (0.54, 2.22)	
Tampa[96]	100	nd	No implant	33/222 (15%)	7/80 (9%)	Adj OR 1.40 (0.54, 3.60)	**Inad:** A, Y
Dutch Silicone Implant Support Group†[93]	100	nd	No implant	243/319 (76%)	6/40 (15%)	ORcalc 18.1 (7.33, 44.8)†	
Barcelona[38]	87	nd	No implant	11/81 (14%)	12/72 (17%)	ORcalc 0.79 (0.32, 1.91)	
Denmark Private[72]	50	nd	Cosm Surg‡	nd/423	nd/231	Adj OR 1.5 (0.9, 2.5)‡	**Ad:** A, O6
			No implant‡		nd/183	Adj OR 1.0 (0.6, 1.6)‡	**Ad:** A, O6
Swedish Inpatient Register[52]	nd	nd	Br Reduc	236/1369 (17%)	324/2211 (15%)	Adj RR 1.3 (1.0, 1.6)	**Inad:** A, Y
Denmark Public-Private subset[64]	100	nd		98/238 (41%)			
Summary Implant vs. No Implant	**100% (n=3)**					**1.22 (0.75, 1.99) P het=0.92, I^2=0%**	
	Any, Direct comparisons (n=6)					**1.28 (1.06, 1.55)‡ P het=0.89, I^2=0%**	
	Any, Adequate adjustment (n=1, 2 comparisons)					**1.5 (0.9, 2.5) 1.0 (0.6, 1.6)**	
Summary Percent Implant	**100%**			**#**			
	Any			**#**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

† Study was of a highly biased sample of women in a silicone breast implant support group. Not included in meta-analyses.
‡ Primary meta-analysis conducted with cosmetic surgery comparison. Alternatively, using no implant comparison: summary OR = 1.21 (1.000, 1.46); P het=0.85, I^2=0%.
# Not calculated due to extreme heterogeneity across studies.

Figure 43. Rheumatologic Symptoms: Muscle Pain

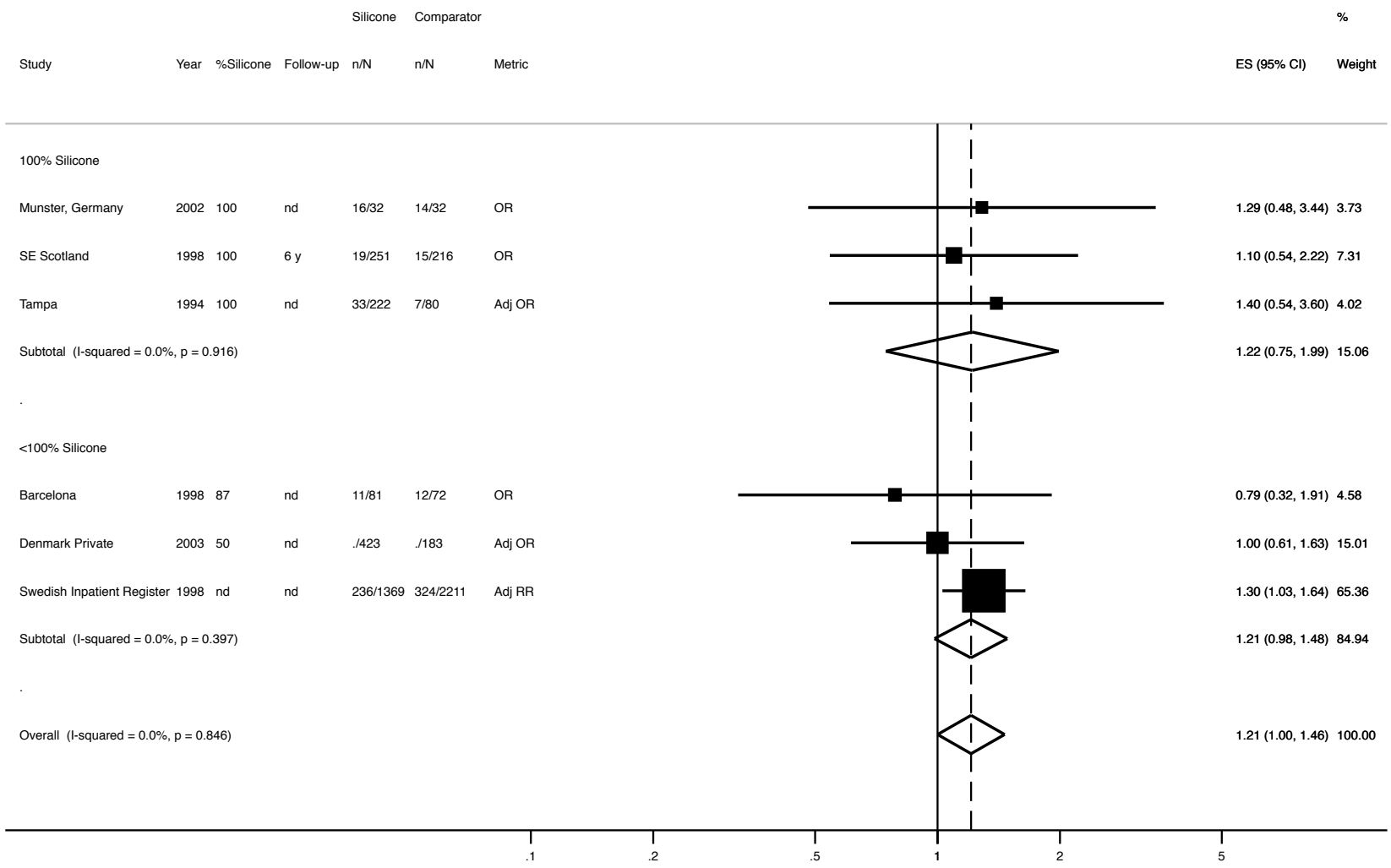
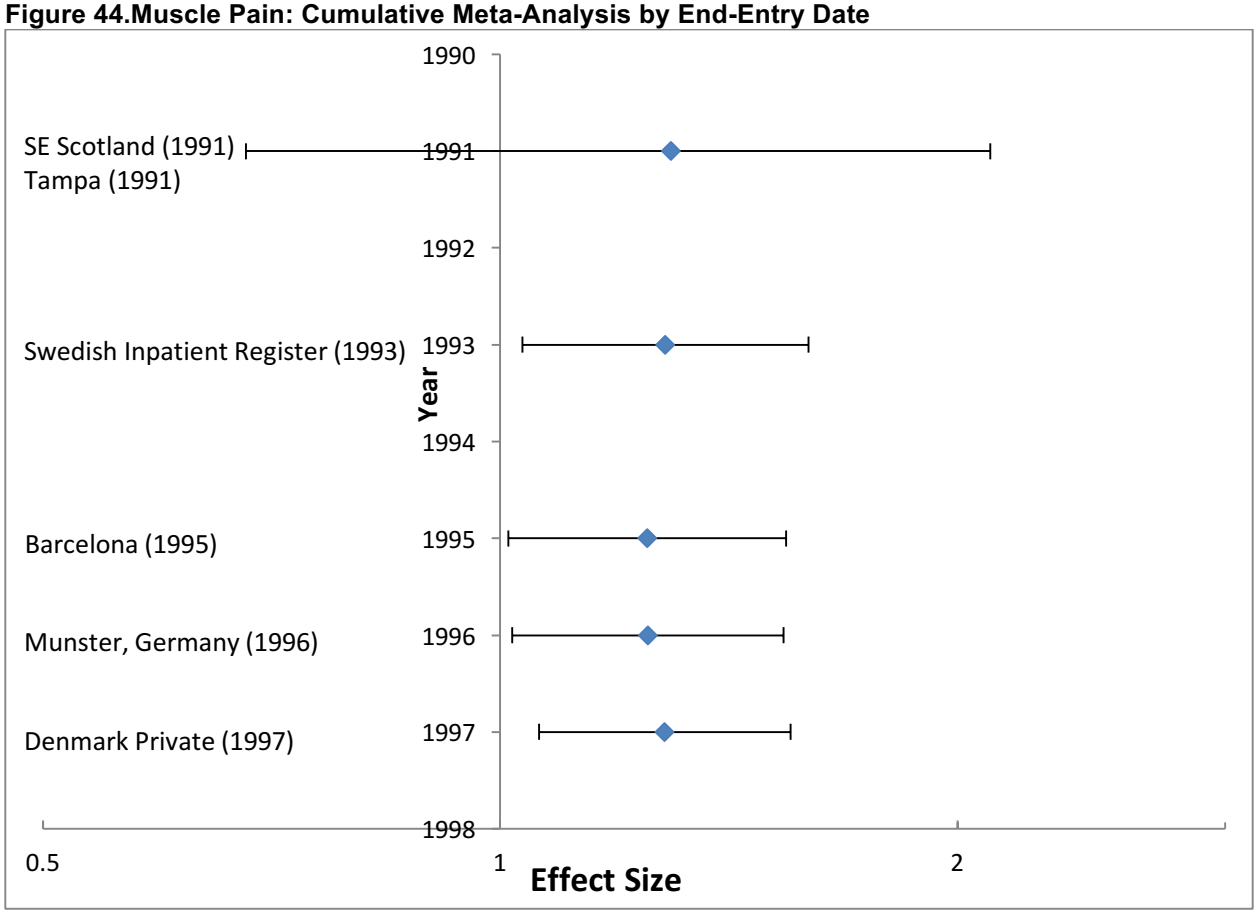


Figure 44.Muscle Pain: Cumulative Meta-Analysis by End-Entry Date



Muscle Weakness

Four studies reported on complaints of muscle weakness (**Table 47, Figure 45**). All were comparative studies evaluating women with any breast implant. The largest study, from Sweden, found a significantly increased risk of muscle weakness in women with breast implants (inadequately adjusted RR = 1.5), but the other three studies found no significant associations, This included the one adequately adjusted study, which found adjusted ORs that were not statistically significant but were similar in magnitude to the Swedish study (adequately adjusted ORs = 1.5 and 1.6 with two different control groups). Two other studies yielded imprecise estimates (wide confidence intervals) that were less than 1.0. Pooling the four studies yielded a statistically significant summary ES of 1.42 (95% CI 1.11, 1.82), with no heterogeneity (**Figure 45**). However, the Swedish study provided 80% of the weight of the meta-analysis, so that the pooled estimate is mostly a recapitulation of the Swedish study.

The evidence is insufficient to determine if there is an association between breast implants and muscle weakness. While a pooled analysis yielded a significant small (ES <2.0) association, this was driven largely by a single study. An adequately adjusted analysis found a similar magnitude of effect but the remaining studies were imprecise with conflicting estimates of association.

Note: See the section “Muscle Pain and Weakness”, below.

Table 47. Rheumatologic Symptoms: Muscle Weakness

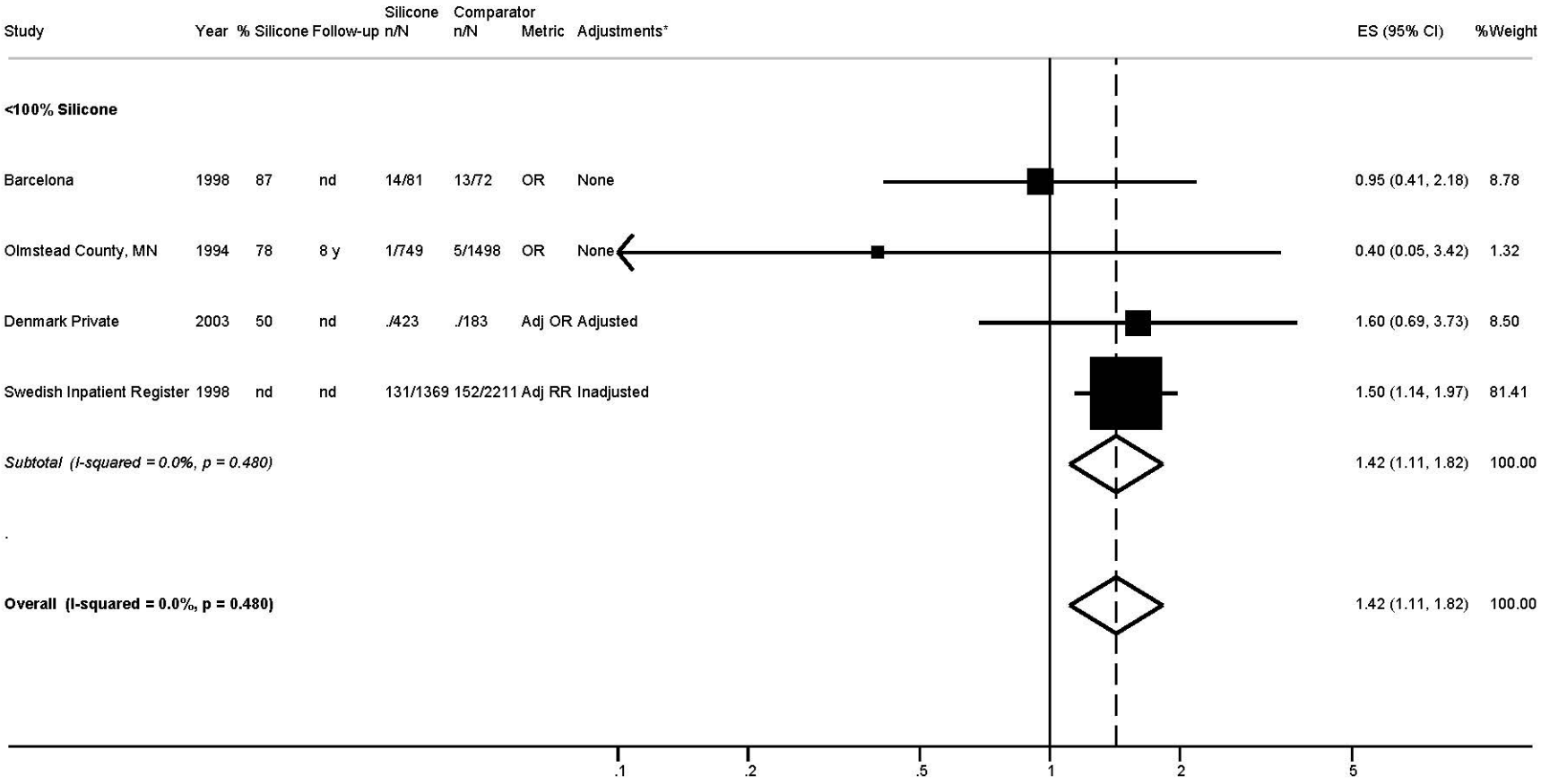
Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Barcelona[38]	87	nd	No implant	14/81 (17%)	13/72 (18%)	ORcalc 0.95 (0.41, 2.18)	
Olmstead County, MN[54]	78	8 y	No implant	1/749 (0.1%)	5/1498 (0.3%)	ORcalc 0.40 (0.05, 3.42)	
Denmark Private[72]	50	nd	Cosm Surg†	nd/423	nd/231	Adj OR 1.5 (0.7, 3.2)†	**Ad:** A, O6
			No implant†		nd/183	Adj OR 1.6 (0.7, 3.8)†	**Ad:** A, O6
Swedish Inpatient Register[52]	nd	nd	Br Reduc	131/1369 (10%)	152/2211 (7%)	Adj RR 1.5 (1.1, 1.9)	**Inad:** A, Y
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=4)					**1.42 (1.11, 1.81)† P het=0.49, I^2=0%**	
	Any, Adequate adjustment (n=1, 2 comparisons)					**1.5 (0.7, 3.2) 1.6 (0.7, 3.8)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any			**‡**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

† Primary meta-analysis conducted with cosmetic surgery comparison. Alternatively, using no implant comparison: summary OR = 1.42 (1.11, 1.82); P het=0.48, I^2=0%.
‡ Not calculated due to extreme heterogeneity across studies.

Figure 45. Rheumatologic Symptoms: Muscle Weakness



Muscle Pain and Weakness

Two Danish studies evaluated the combined outcome of myalgia and muscle weakness (**Table 48**). A single study found no significant association between any breast implant and the combined outcome. The evidence is insufficient to determine if there is an association between breast implants and combined muscle weakness and pain.

Oral Ulcers

Four comparative studies reported on the complaint of oral ulcers (**Table 49, Figure 46**). The single study that evaluated silicone gel implants, from Amsterdam, had few women with the complaint; thus, the study's OR is imprecise at 1.8 (95% CI 0.3, 9.9). Across the four studies, the pooled ES was 0.92 (95% CI 0.55, 1.56) with no statistical heterogeneity (**Figure 45**). The one adequately adjusted analysis reported a highly imprecise association. The evidence is insufficient to determine if there is an association between breast implants and combined muscle weakness and oral ulcers.

Rash That Worsens in Sunlight

Three comparative studies evaluated whether women had rashes that worsened in sunlight (**Table 50, Figure 47**). The one study, from Amsterdam, that examined silicone gel implants found a large, significant increase in risk for women with silicone gel implants, with an OR of 5.05 (95% CI 1.71, 14.9). However, the study reported only raw data and no analysis adjusted for confounders was reported. The study was specific to silicone gel implants but it is unclear whether the analyzed symptoms included only those that occurred after implantation. The two other studies found no association, including the adequately adjusted Denmark Private study that compared women with breast implants to two control groups and found conflicting, but imprecise ESs with its two comparisons (0.8 and 1.2). The overall pooled ES was non-significant with an OR=1.58 (95% CI 0.72, 3.46), but with statistical heterogeneity (P heterogeneity = 0.020, I^2=75%) (**Figure 47**). The evidence is insufficient to determine if there is an association between breast implants and the risk of developing a rash that worsens in sunlight.

Note: See the section "Sun Sensitivity", below.

Rash, Malar

Two comparative studies evaluated the risk of developing a malar rash in women with any breast implant (**Table 51**). The adequately adjusted Danish study found a non-significant increased risk compared with women who had other cosmetic surgeries, but a non-significant decreased risk when compared with the general population. The Swedish study found a significant 80% increased risk in women with breast implants. The evidence is insufficient to determine if there is an association between breast implants and the risk of developing a malar rash.

Table 48. Rheumatologic Symptoms: Muscle Pain, Weakness

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Copenhagen Deaconess Hospital[28]	77	19 y	Br Reduc	60/190 (32%)	54/186 (29%)	Adj OR 1.1 (0.7, 1.7)	**Inad:** A
			No implant		39/149 (26%)	Adj OR 1.3 (0.8, 2.1)	**Inad:** A
Denmark Public-Private subset[64]	100	nd		47/238 (20%)			
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=1, 2 comparisons)					**1.1 (0.7, 1.7)** **1.3 (0.8, 2.1)**	
Summary Percent Implant	**100% (n=1)**			**20% (15, 25)**			
	Any (n=2)			**25% (15, 38)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.

Table 49. Rheumatologic Symptoms: Oral Ulcers

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Free University, Amsterdam[55]	100	7 y	Cosm Surg	4/235 (2%)	2/210 (1%)	OR 1.80 (0.33, 9.93)	
Olmstead County, MN[54]	78	8 y	No implant	7/749 (1%)	21/1498 (1%)	ORcalc 0.66 (0.28 1.56)	
Denmark Private[72]	50	nd	Cosm Surg	nd/423	nd/231	Adj OR 1.73 (0.10, 30.8)	**Ad:** A, O6
Swedish Inpatient Register[52]	nd	nd	Br Reduc	15/1369 (1%)	22/2211 (1%)	Adj RR 1.0 (0.5, 2.2)	**Inad:** A, Y
Summary Implant vs. No Implant	**100% (n=1)**					**1.80 (0.33, 9.93)**	
	Any, Direct comparisons (n=4)					**0.92 (0.55, 1.56)** **P het=71, I^2=0%**	
	Any, Adequate adjustment (n=1)					**1.73 (0.10, 30.8)**	
Summary Percent Implant	**100% (n=1)**			**1.7% (0.6, 4.2)**			
	Any (n=3)			**1.1% (0.6, 1.5)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

Figure 46. Rheumatologic Symptoms: Oral Ulcers

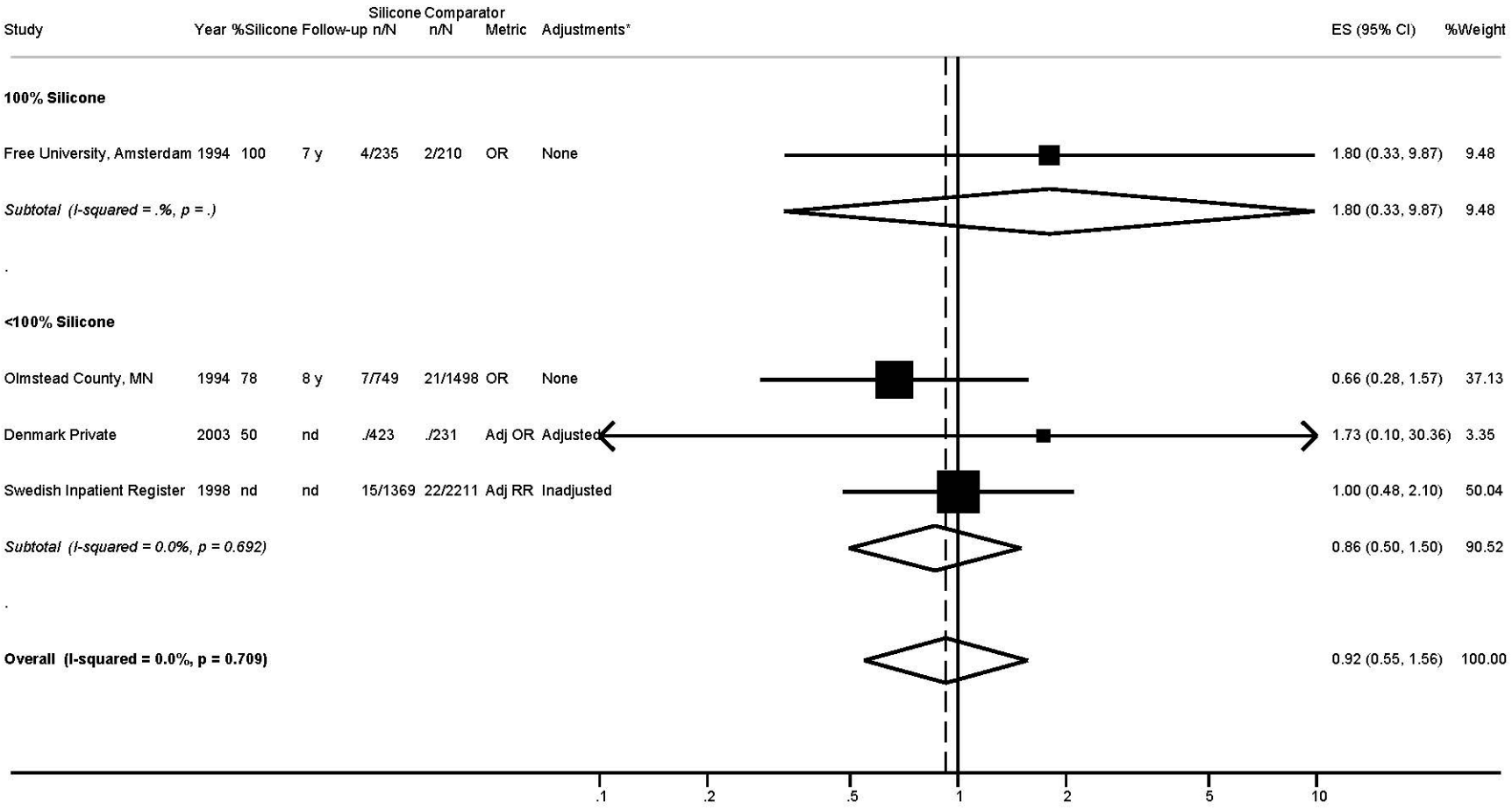


Table 50. Rheumatologic Symptoms: Rash Worsens in Sunlight

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Free University, Amsterdam[55]	100	7 y	Cosm Surg	20/235 (9%)	4/210 (2%)	OR 5.05 (1.71, 14.9)	
Denmark Private[72]	50	nd	Cosm Surg†	nd/423	nd/231	Adj OR 1.2 (0.6, 2.6)†	**Ad:** A, O6
			No implant†		nd/183	Adj OR 0.8 (0.4, 1.6)†	**Ad:** A, O6
Swedish Inpatient Register[52]	nd	nd	Br Reduc	80/1369 (6%)	104/2211 (5%)	Adj RR 1.0 (0.7, 1.4)	**Inad:** A, Y
Summary Implant vs. No Implant	**100% (n=1)**					**5.05 (1.71, 14.9)**	
	Any, Direct comparisons (n=3)					**1.58 (0.72, 3.46)† P het=0.020, I^2=75%**	
	Any, Adequate adjustment (n=1, 2 comparisons)					**1.2 (0.6, 2.6) 0.8 (0.4, 1.6)**	
Summary Percent Implant	**100% (n=1)**			**8.5% (5.6, 12.8)**			
	Any (n=2)			**6.7% (4.3, 9.5)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

† Primary meta-analysis conducted with cosmetic surgery comparison. Alternatively, using no implant comparison: summary OR = 1.39 (0.62, 3.10); P het=0.013, I^2=77%.

Figure 47. Rheumatologic Symptoms: Rash That Worsens in Sunlight

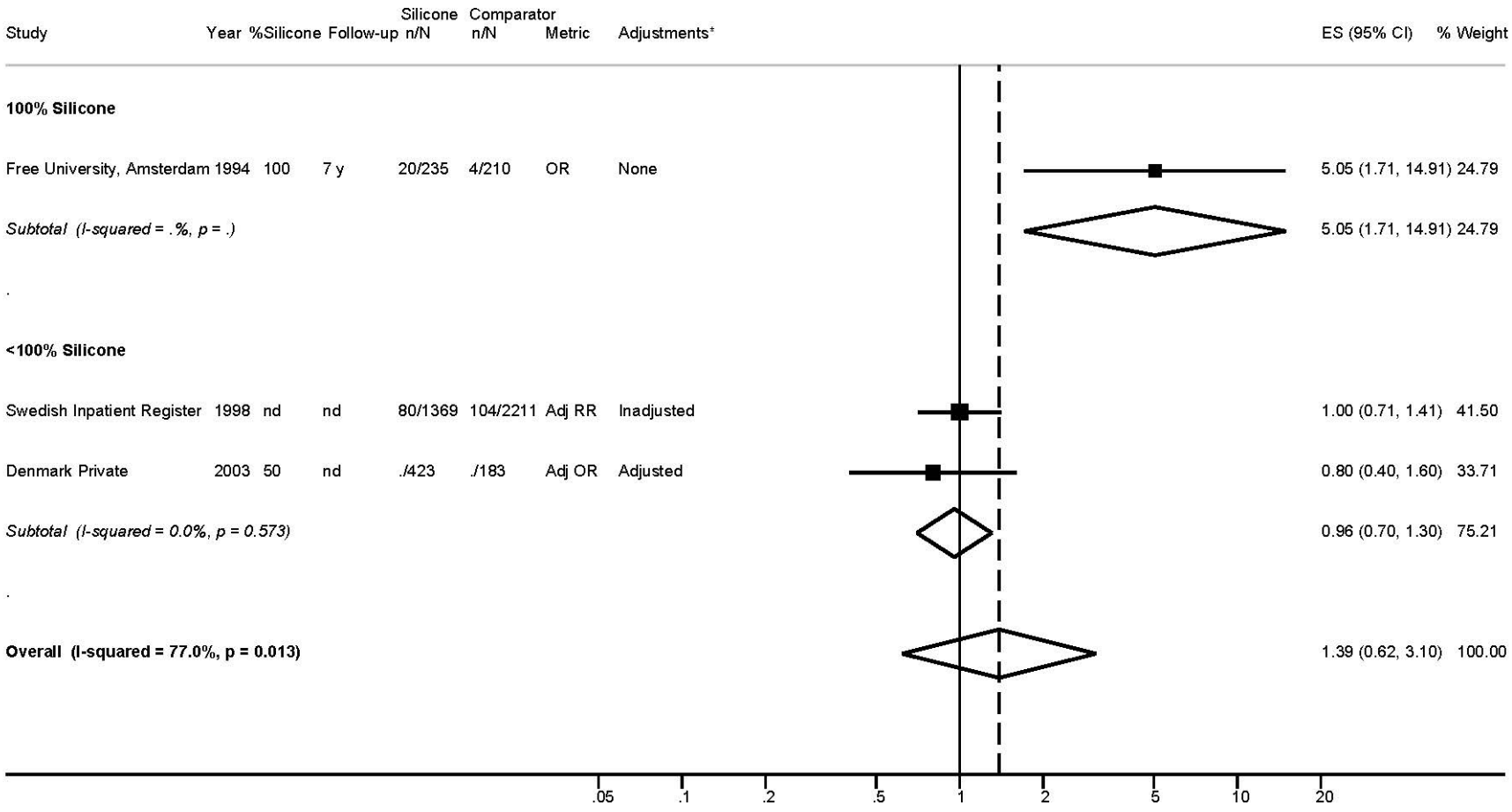


Table 51. Rheumatologic Symptoms: Rash, Malar

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Denmark Private[72]	50	nd	Cosm Surg	nd/423	nd/231	Adj OR 3.2(0.6, 16.0)	**Ad:** A, O6
			No implant		nd/183	Adj OR 0.4 (0.2, 1.0)	**Ad:** A, O6
Swedish Inpatient Register[52]	nd	nd	Br Reduc	50/1369 (4%)	56/2211 (3%)	Adj RR 1.8 (1.2, 2.8)	**Inad:** A, Y
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=2, 3 comparisons)					**3.2(0.6, 16.0) 0.4 (0.2, 1.0) 1.8 (1.2, 2.8)**	
	Any, Adequate adjustment (n=1, 2 comparisons)					**3.2(0.6, 16.0) 0.4 (0.2, 1.0)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=1)			**3.7% (2.8, 4.8)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.

A = age, R = race, T = time since surgery, Y = calendar year.

O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

Raynaud Syndrome

Fifteen studies reported on Raynaud syndrome, eleven of which were comparative studies (**Table 52, Figures 48-52**). Five of the comparative studies included only women with silicone gel implants, but one of these studies had no women complaining of Raynaud syndrome. Four of the remaining comparative studies included between 50% and 87% of women with silicone gel implants and two did not report the data. Follow-up time since surgery ranged from 5 to 19 years among studies that reported the data.

The studies were clearly highly heterogeneous in their definitions of the syndrome as the percentage of women with the condition ranged from 0% to 37%. Even among the comparative studies, the range was 0% to 12% in the groups without silicone implants. One of the two analyzable comparative studies of women with silicone gel implants found 31% of women with implants with the condition but only 3% of women without implants. The other comparative studies of women with silicone gel implants found no significant association. Among the remaining studies, the ESs ranged from 0.29 (with wide confidence intervals) to a statistically significant 2.6. Overall, across 12 analyses (including studies that compared their cohorts of women to two control groups each) seven associations were positive (ES >1.0)—three of which were statistically significant—one study had a null effect (ES = 1.0), and 4 had non-significant inverse associations (ES <1.0). The one adequately adjusted study (Denmark Private) found non-significant associations against its two control groups (adjusted OR= 1.0 and 0.5). The Copenhagen Deaconess Hospital study also compared its cohort of women with breast implants to two control groups, which resulted in conflicting findings (adjusted OR= 1.2 [non-significant] and 2.4 [significant]).

Pooling the studies (using the cosmetic or breast reduction surgery control groups from the two studies with multiple control groups) yielded a heterogeneous summary ES = 1.33 (95% CI 0.97, 2.25) (**Figure 48**). Using the alternative control group analyses yielded similar results: ES = 1.36 (95% CI 0.70, 2.40). Removing the Munster study, which was clearly an outlier, removed the heterogeneity (P = 0.45, I^2 = 0%), but shifted the summary ES somewhat and narrowed the confidence interval such that the ES was statistically significant: summary ES = 1.23 (95% CI 1.01, 1.46). However, if the alternate control group analyses were used in the sensitivity analysis without the Munster study, the summary ES is 1.19 (95% CI 0.81, 1.75) with significant heterogeneity (P = 0.016, I^2 = 58%).

The three studies that determined the diagnosis of Raynaud syndrome on medical records (or physical examination) found a non-significant "protective" association (ES=0.49), in contrast to the eight studies that relied on patient questionnaire (ES=1.49); although, this difference was not statistically significant (P=0.12). Studies that explicitly analyzed incident disease (since implantation) versus those that may have included prevalent disease (at the time of implantation) had similar findings (P=0.96). Cumulative meta-analysis by the final recruitment year within each study that women received implants (**Figure 49**) did not show an evident trend over time. The cumulative meta-analysis by follow-up time suggests that the summary ES stabilized upon 12 years of follow-up (**Figure 50**). A funnel plot of the included studies provides no evidence of publication bias (**Figure 51**).

Three studies found strong associations, but two found a strong positive association (ES ≥2.0) while one found a strong inverse association (ES ≤0.5). Two of the conflicting studies (South 18 Centers and Denmark Private) were adequately adjusted, but the Danish study found the association only in one of its comparisons with different control groups. Only the third study,

the unadjusted Munster study, was specific to silicone gel implants, but in this study it was not clear whether the reported symptoms were new since implantation.

Overall, the evidence is insufficient to determine if there is an association between breast implants and Raynaud syndrome. The two adequately adjusted studies yielded conflicting results and the choice of different control groups led to inconsistent conclusions.

Table 52. Rheumatologic Symptoms: Raynaud Syndrome

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Munster, Germany[27]	100	nd	No implant	10/32 (31%)	1/32 (3%)	ORcalc 14.1 (2.96, 67.2)	
Free University, Amsterdam[55]	100	7 y	Cosm Surg	12/235 (5%)	7/210 (3%)	OR 1.56 (0.60, 4.04)	
Italy[81]	100	5 y	No implant	0/102 (0%)	0/102 (0%)	No events	
SE Scotland[9]	100	6 y	Cosm Surg	6/251 (2%)	8/216 (4%)	OR 0.64 (0.22, 1.86)	
			No implant	5/141 (4%)	5/88 (6%)	OR 0.61 (0.15, 2.52)	
Tampa[96]	100	nd	No implant	2/222 (0.9%)	0/80 (0%)	Adj OR 0.49 (0.02, 12.8)	**Inad:** A, Y
Barcelona[38]	87	nd	No implant	0/81 (0%)	1/72 (1%)	ORcalc 0.29 (0.01, 7.29)	
Copenhagen Deaconess Hospital[28]	77	19 y	Br Reduc†	28/190 (15%)	23/186 (12%)	Adj OR 1.2 (0.8, 2.2)†	**Inad:** A
			No implant†		10/149 (7%)	Adj OR 2.4 (1.1, 5.1)†	**Inad:** A
Denmark Private[72]	50	nd	Cosm Surg†	nd/423	nd/231	Adj OR 1.0 (0.5, 1.9)†	**Ad:** A, O6
			No implant†		nd/183	Adj OR 0.5 (0.3, 1.0)†	**Ad:** A, O6
South 18 Centers[32]	50	12 y	Cosm Surg	97/7234 (1%)	10/2138 (0.5%)	Adj RR 2.6 (1.3, 5.1)	**Ad**: A, R, T, Y, O5
Sydney[47]	nd	16 y	No implant	26/458 (6%)	34/687 (5%)	RR 1.15 (0.70, 1.89)	
Swedish Inpatient Register[52]	nd	nd	Br Reduc	120/1369 (9%)	146/2211 (7%)	Adj RR 1.2 (0.9, 1.6)	**Inad:** A, Y
Allergan (Inamed/Natrelle Round) Cohort[88]	100	10 y		1/715 (0.1%)			
Birmingham, AL[35]	100	20 y		14/344 (4%)			
Rotterdam University Hospital 1990-1995[39]	100	nd		21/63 (33%)			
Rotterdam University Hospital 1995-1997[40]	100	1 y		21/57 (37%)			
Summary Implant vs. No Implant	**100% (n=4, 5 comparisons)**					**1.42 (0.23, 8.74)** **P het=0.020, I^2=66%**	
	Any, Direct comparisons (n=10, 11 comparisons)					**1.33 (0.97, 2.25)†** **P het=0.058, I^2=44%**	
	Augmentation (n=8)					**1.25 (0.67, 2.32)**	**P btw = 0.58**
	Reconstruction (n=3)					**1.86 (0.45, 7.68)**	
	Confirmed diagnosis (n=3)					**0.49 (0.12, 1.98)**	**P btw = 0.12**
	Self-reported diagnosis (n=8)					**1.49 (0.93, 2.38)**	
	Any, Adequate adjustment (n=2, 3 comparisons)					**1.0 (0.5, 1.9)** **0.5 (0.3, 1.0)** **2.6 (1.3, 5.1)**	
Summary Percent Implant	**100%**			**‡**			
	Any			**‡**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O5 = education, family history
O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

† Primary meta-analysis conducted with cosmetic or breast reduction surgery comparisons. Alternatively, using no implant comparisons: summary OR = 1.36 (0.70, 2.48); P het=0.001, I^2=68%.
‡ Not calculated due to extreme heterogeneity across studies.

Figure 48. Rheumatologic Symptoms: Raynaud Syndrome (Direct Comparison)

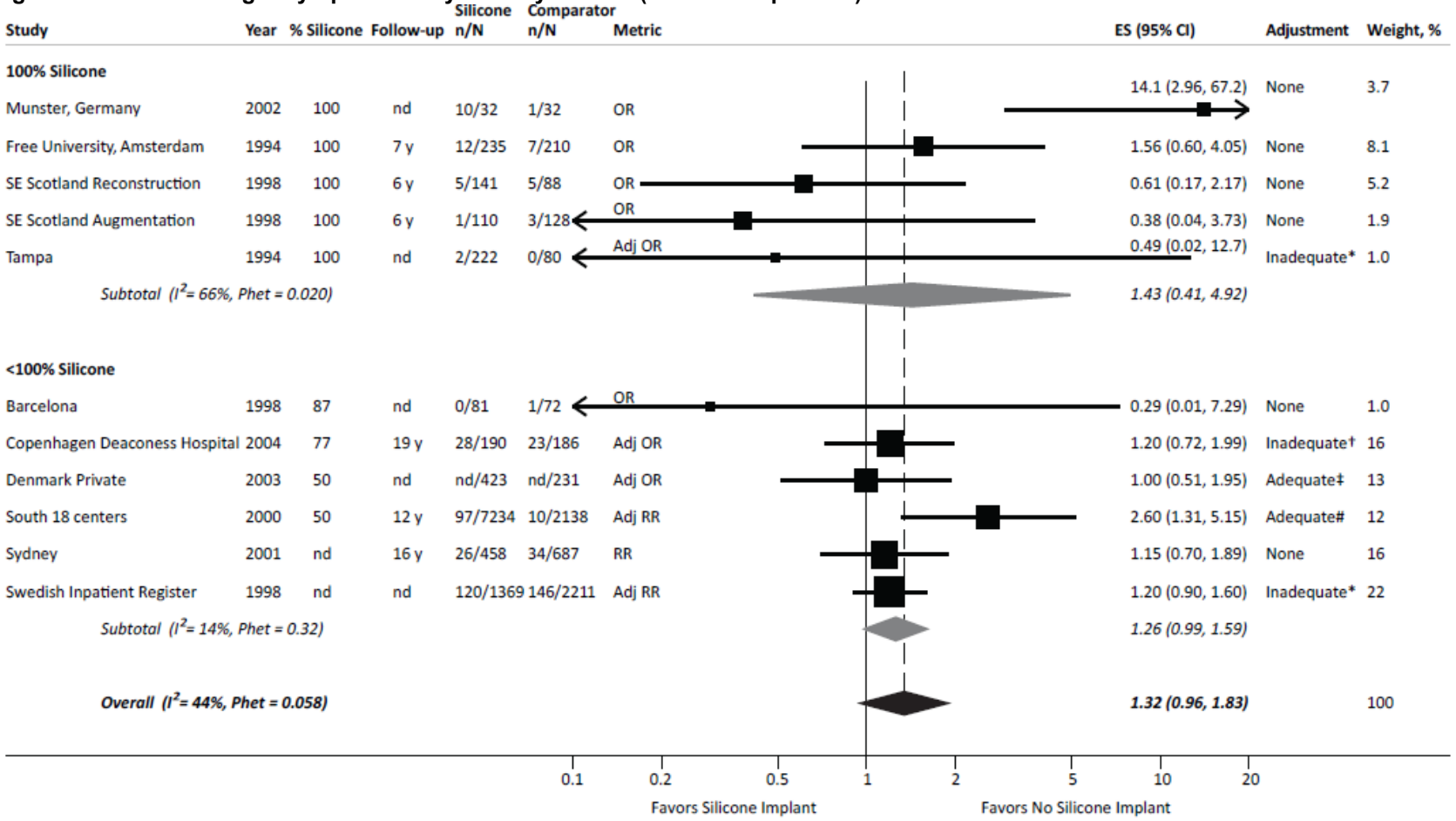


Figure 49. Raynauld Syndrome: Cumulative Meta-Analysis by End-Entry Date

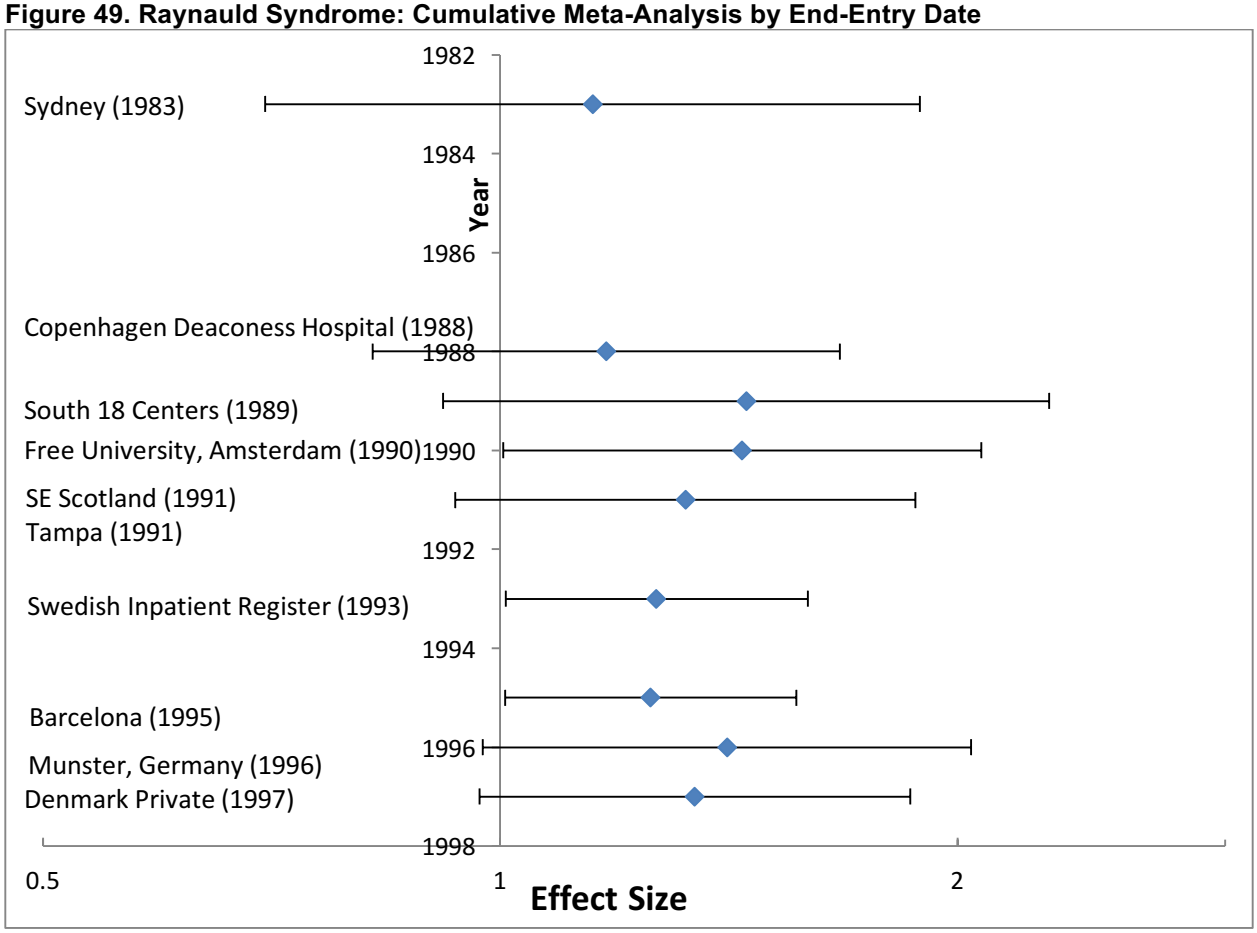


Figure 50. Raynaud Syndrome: Cumulative Meta-Analysis by Follow-Up Duration

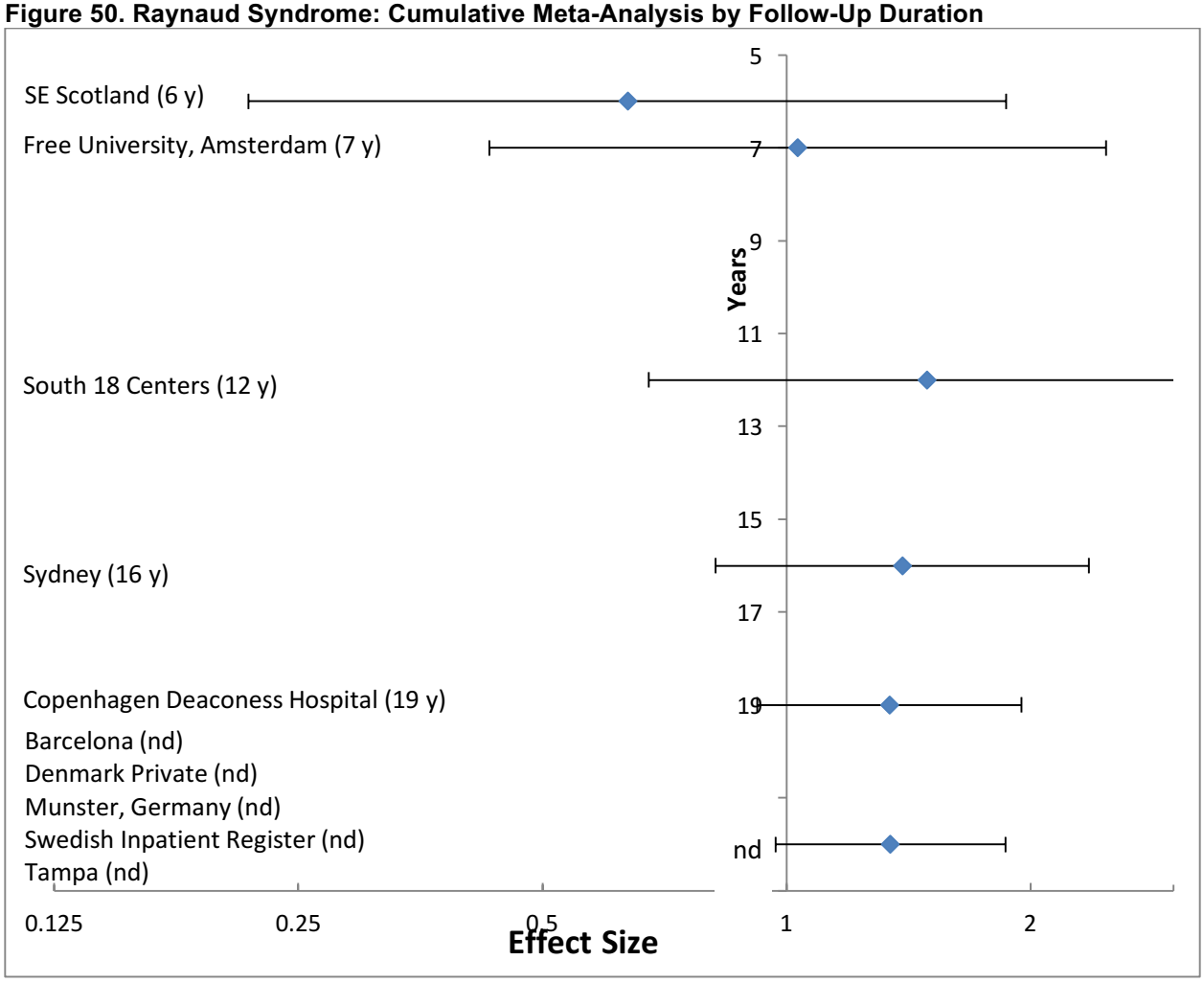
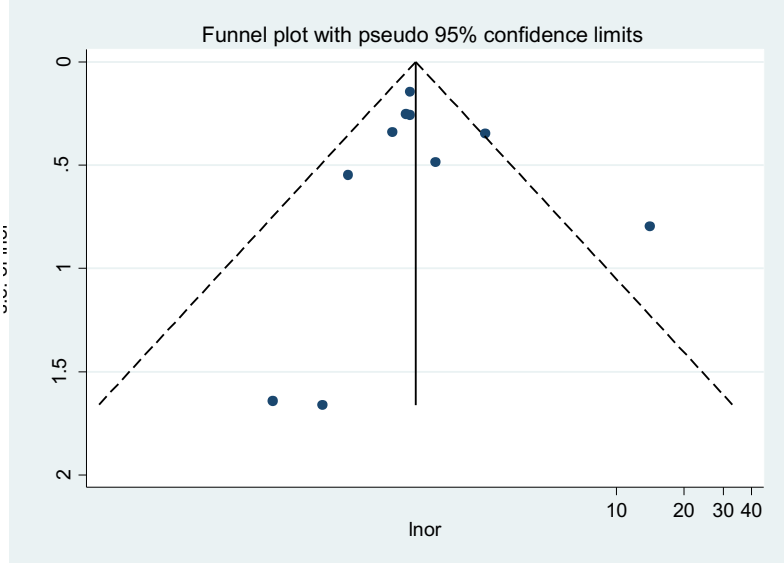


Figure 51. Raynaud Syndrome: Funnel Plot



Egger test: Test of H0: no small-study effects; P = 0.71

Salivary Gland Enlargement

A single comparative study of all women with breast implants found no significant difference in the complaint compared with women without implants (**Table 53**). The evidence is insufficient to determine if there is an association between breast implants and salivary gland enlargement.

Serositis

Three comparative studies evaluated serositis (**Table 54, Figure 52**). A small Dutch study found no significant difference in the proportion of women with silicone gel implants with serositis compared to women without implants, but with wide confidence intervals. Across the three studies, the summary ES was 1.41 (95% CI 0.88, 2.25) with no statistical heterogeneity (**Figure 52**). The adequately adjusted Danish study found non-significant associations. The evidence is insufficient to determine if there is an association between breast implants and serositis.

Sicca

Two comparative studies evaluated sicca in women with any breast implant (**Table 55**). Both found a small (ES <2.0) non-significant association. Neither reported an adjusted analysis. The evidence is insufficient to determine if there is an association between breast implants and sicca.

Skin Thickening

Two small comparative studies reported few events of skin thickening in women with silicone breast implants (**Table 56**). The location of the skin thickening was not defined, but was implied to be generalized and not specific to the breast. The two studies had conflicting OR estimates, but with overlapping confidence intervals. The Tampa study found a strong association (ES ≤0.5) with symptoms that began after implantation, but the study was not specific to silicone gel implants. The evidence is insufficient to determine if there is an association between silicone breast implants and skin thickening.

Skin Tightness

Two small comparative studies reported on skin tightening in women with breast implants (**Table 57**). The location of the skin tightening was not defined, but was implied to be generalized and not specific to the breast. The two studies had similar non-significant findings when compared with the general population of women without breast implants. However, the adequately adjusted Danish study had conflicting adjusted ORs for its two comparison groups (0.8 and 1.6), but with very wide confidence intervals. The evidence is insufficient to determine if there is an association between breast implants and skin tightness.

Table 53. Rheumatologic Symptoms: Salivary Gland Enlargement

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Olmstead County, MN[54]	78	8 y	No implant	2/749 (0.3%)	3/1498 (0.2%)	ORcalc 1.33 (0.22, 8.00)	
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=1)					**1.33 (0.22, 8.00)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=1)			**0.3% (0.1, 0.97)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Table 54. Rheumatologic Symptoms: Serositis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Free University, Amsterdam[55]	100	7 y	Cosm Surg	4/235 (2%)	5/210 (2%)	OR 0.71 (0.18, 2.68)	
Olmstead County, MN[54]	78	8 y	No implant	18/749 (2%)	21/1498 (1.4%)	ORcalc 1.73 (0.92, 3.27)	
Denmark Private[52]	50	nd	Cosm Surg†	nd/423	nd/231	Adj OR 1.3 (0.6, 3.0)†	**Ad:** A, O6
			No implant†		nd/183	Adj OR 1.8 (0.6, 5.0)†	**Ad:** A, O6
Summary Implant vs. No Implant	**100% (n=1)**					**0.71 (0.18, 2.68)**	
	Any, Direct comparisons (n=3)					**1.41 (0.88, 2.25)† P het=0.49, I^2=0%**	
	Any, Adequate adjustment (n=1, 2 comparisons)					**1.2 (0.6, 2.6) 0.8 (0.4, 1.6)**	
Summary Percent Implant	**100% (n=1)**			**1.7% (0.7, 4.3)**			
	Any (n=2)			**2.2% (1.3, 3.2)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

† Primary meta-analysis conducted with cosmetic surgery comparisons. Alternatively, using no implant comparisons: summary OR = 1.54 (0.93, 2.56); P het=0.48, I^2=0%.

Figure 52. Rheumatologic Symptoms: Serositis

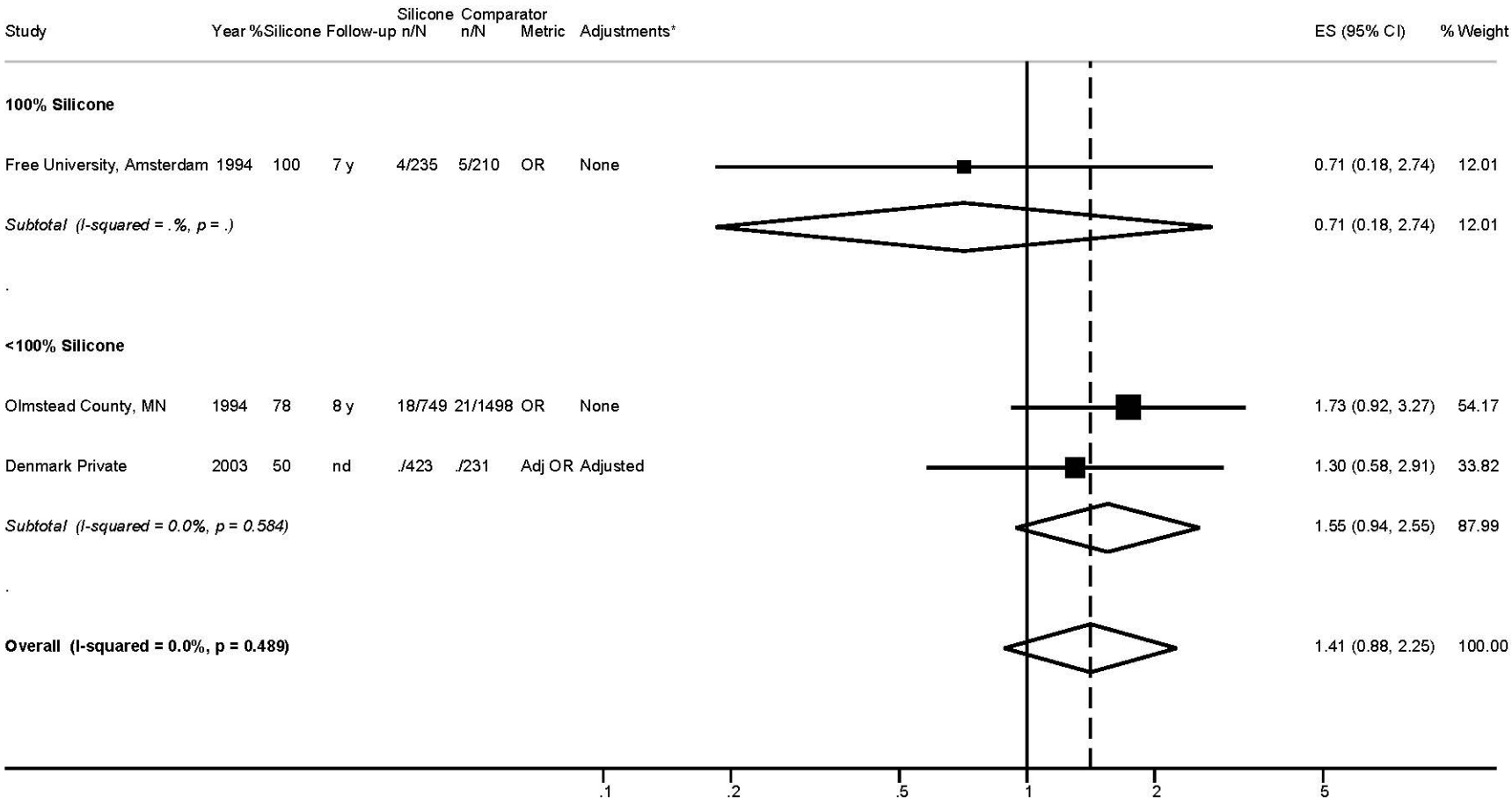


Table 55. Rheumatologic Symptoms: Sicca

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Olmstead County, MN[54]	78	8 y	No implant	33/749 (4.4%)	50/1498 (3.3%)	ORcalc 1.33 (0.85, 2.09)	
Sydney[47]	nd	16 y	No implant	15/458 (3.3%)	18/687 (2.6%)	RR 1.24 (0.63, 2.44)	
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=2)					**1.33 (0.85, 2.09)** **1.24 (0.63, 2.44)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=2)			**4.0% (2.9, 5.1)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Table 56. Rheumatologic Symptoms: Skin Thickening

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
SE Scotland[9]	100	6 y	Cosm Surg	1/251 (0.4%)	0/216 (0%)	ORcalc 2.59 (0.11, 64.0)	
Tampa[96]	100	nd	No implant	nd/222	nd/80	Adj OR 0.21 (0.04, 0.99)	**Inad:** A, Y
Summary Implant vs. No Implant	**100% (n=2)**					**2.59 (0.11, 64.0)** **0.21 (0.04, 0.99)**	
	Any, Direct comparisons (n=2)					**2.59 (0.11, 64.0)** **0.21 (0.04, 0.99)**	
Summary Percent Implant	**100% (n=1)**			**0.4% (0.07, 2.2)**			
	Any (n=1)			**0.4% (0.07, 2.2)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.

* Exact proportion

Table 57. Rheumatologic Symptoms: Skin Tightening

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Tampa[96]	100	nd	No implant	27/222 (12%)	15/80 (19%)	Adj OR 0.58 (0.26, 1.28)	**Inad:** A, Y
Denmark Private[72]	50	nd	Cosm Surg	nd/423	nd/231	Adj OR 1.6 (0.2, 11.9)	**Ad:** A, O6
			No implant		nd/183	Adj OR 0.8 (0.1, 6.0)	**Ad:** A, O6
Summary Implant vs. No Implant	**100% (n=1)**					**0.58 (0.26, 1.28)**	
	Any, Direct comparisons (n=2, 3 comparisons)					**1.6 (0.2, 11.9)** **0.8 (0.1, 6.0)** **0.58 (0.26, 1.28)**	
	Any, Adequate adjustment (n=1, 2 comparisons)					**1.6 (0.2, 11.9)** **0.8 (0.1, 6.0)**	
Summary Percent Implant	**100% (n=1)**			**12% (8.5, 17)**			
	Any (n=1)			**12% (8.5, 17)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.

A = age, R = race, T = time since surgery, Y = calendar year.

O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

Sun Sensitivity

Five comparative studies evaluated sun sensitivity in women with breast implants, but one of the studies, from Barcelona, had no women with the complaint (**Table 58, Figure 53**). Only one of the studies evaluated women specifically with silicone gel implants. All studies mostly found no significant association, with imprecise estimates. The adequately adjusted Danish study found decreased risk of sun sensitivity with breast implants compared with both its control groups, but the analysis with women with other cosmetic surgery was highly non-significant and the comparison with general population women with no implant was highly significant. Across the studies, the pooled ES was 0.97 (95% CI 0.70, 1.36), with no heterogeneity (**Figure 53**). The evidence is insufficient to determine if there is an association between breast implants and sun sensitivity. The summary ES was too imprecise to differentiate between evidence of a small association (ES <2.0) and evidence of no association.

Table 58. Rheumatologic Symptoms: Sun Sensitivity

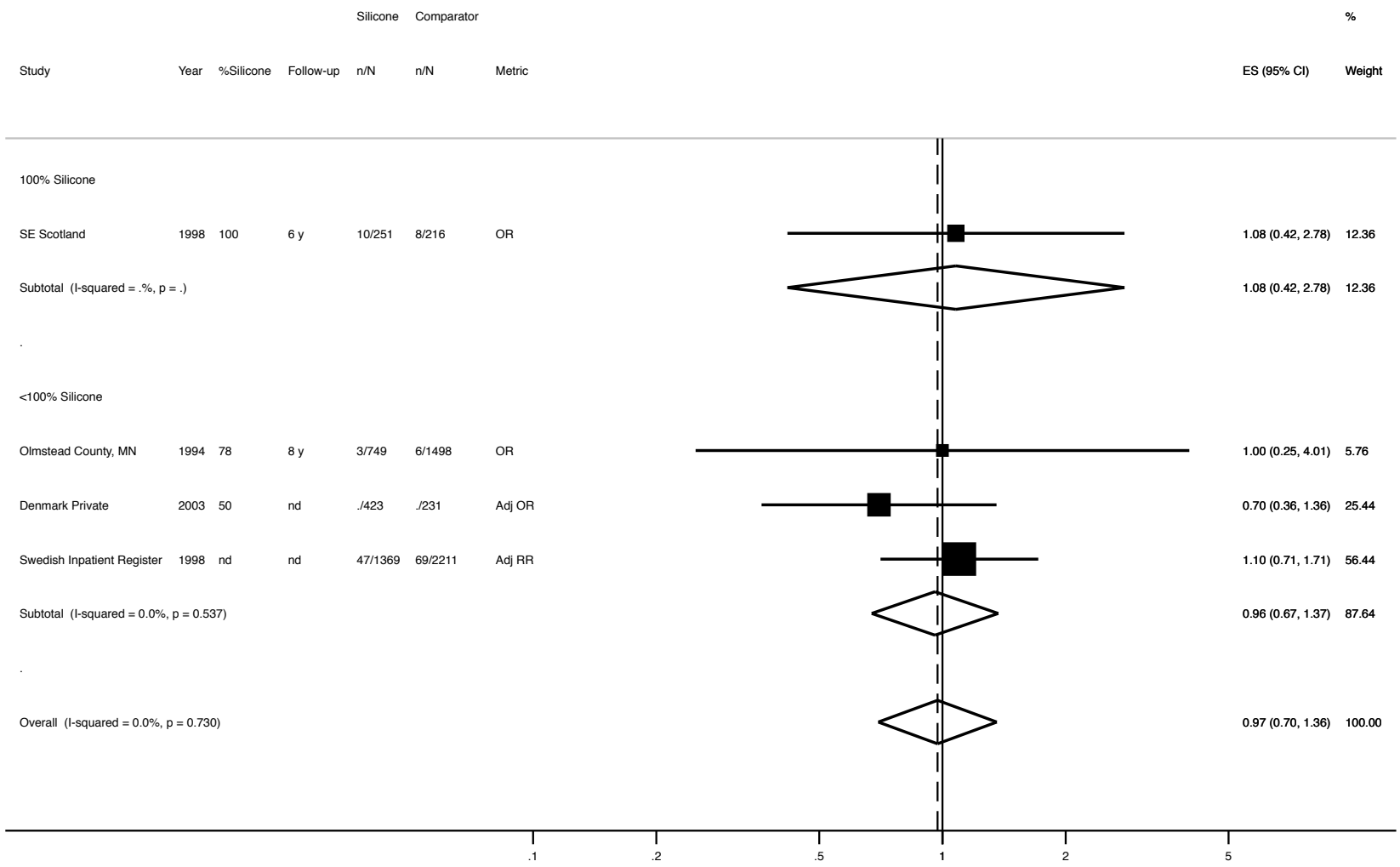
Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
SE Scotland[9]	100	6 y	Cosm Surg	10/251 (4%)	8/216 (4%)	ORcalc 1.08 (0.42, 2.78)	
Barcelona[38]	87	nd	No implant	0/81 (0.0%)	0/72 (0.0%)	No events	
Olmstead County, MN[54]	78	8 y	No implant	3/749 (	6/1498 (0.4%)	ORcalc 1.00 (0.25, 4.01)	
Denmark Private[72]	50	nd	Cosm Surg†	nd/423	nd/231	Adj OR 0.7 (0.4, 1.5)†	**Ad:** A, O6
			No implant†		nd/183	Adj OR 0.4 (0.2, 0.7)†	**Ad:** A, O6
Swedish Inpatient Register[52]	nd	nd	Br Reduc	47/1369 (3%)	69/2211 (3%)	Adj RR 1.1 (0.7, 1.7)	**Inad:** A, Y
Summary Implant vs. No Implant	**100% (n=1)**					**1.08 (0.42, 2.78)**	
	Any, Direct comparisons (n=4)					**0.97 (0.70, 1.36)† P het=0.73, I^2=0%**	
	Any, Adequate adjustment (n=1, 2 comparisons)					**0.7 (0.4, 1.5) 0.4 (0.2, 0.7)**	
Summary Percent Implant	**100% (n=1)**			**4.0% (2.2, 7.8)**			
	Any (n=4)			**1.6% (0.1, 4.2)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O6 = connective tissue disease history, depression, tobacco use, alcohol use, body mass index, parity, age at first birth.

† Primary meta-analysis conducted with cosmetic surgery comparisons. Alternatively, using no implant comparisons: summary OR = 0.80 (0.45, 1.43); P het=0.068, I^2=58%.

Figure 53. Rheumatologic Symptoms: Sun Sensitivity



Neurologic Diseases

Amyotrophic Lateral Sclerosis (ALS)

A single study comparing women with and without breast implants reported on ALS (**Table 59**). No women in the study were given the diagnosis yielding a percentage of 0% (95% CI 0, 0.1). The studies do not provide evidence regarding the association between silicone gel implants and ALS.

Guillian-Barré Syndrome

Only the Swedish Inpatient Register comparing women with and without breast implants reported on Guillian-Barré syndrome (**Table 60**). Only one woman in the study was given the diagnosis, yielding an approximate OR of 1.4 (95% CI 0.1, 3.3). The study found that 0.01% (95% CI 0.002, 0.10) of women with implants had Guillian-Barré syndrome after 9 years of follow-up after breast implantation. The evidence is insufficient to determine if there is an association between breast implants and Guillian-Barré syndrome.

Meniere Disease

Two comparative studies from Sweden and Denmark reported on Meniere disease and compared women with and without any breast implants (**Table 61**). Despite including over 22,000 women, the studies had few events yielding imprecise ESs. One study calculated a SHR, which was likewise imprecise. Across studies, 0.04% (95% CI 0.01, 0.1) of women with breast implants had Meniere disease. The evidence is insufficient to determine if there is an association between breast implants and Meniere disease.

Mononeuritis

The Swedish Inpatient Register comparing women with and without breast implants (with an unreported percentage of silicone gel implants) reported on mononeuritis in both the upper and lower limbs (**Table 62**). About half as many women with implants had upper limb mononeuritis, but with few events the estimate was imprecise, yielding an adjusted OR of 0.5 (95% CI 0.2, 1.03). Similarly, few events of lower limb mononeuritis yielded an imprecise OR of 1.3 (95% CI 0.6, 2.5). The reported SHRs were also non-significant: for upper limb mononeuritis SHR was 1.1 (95% CI 0.5, 2.2) and for lower limb mononeuritis SHR was 2.4 (95% CI 0.95, 4.9). The percentage of women with mononeuritis in the upper limbs were 0.11% (95% CI 0.05, 0.22) and the lower limbs were 0.09% (95% CI 0.05, 0.2), The evidence is insufficient to determine if there is an association between breast implants and mononeuritis.

Table 59. Amyotrophic Lateral Sclerosis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Swedish Inpatient Register[80]	nd	9 y	Br Reduc	0/7429 (0%)	0/3351 (0%)	No events	
			Gen Pop		--	SHR 0 (0, 3.6)	

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Table 60. Guillian-Barré Syndrome

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Swedish Inpatient Register[80]	nd	9 y	Br Reduc	1/7429 (0.01%)	0/3351 (0%)	ORcalc 1.35 (0.06, 33.2)	
			Gen Pop		--	SHR 1.2 (0, 6.6)	

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Table 61. Meniere Disease

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Denmark Public-Private[97]	≤84	13 y	Cosm Surg	1/2761 (0.04%)	4/8787 (0.1%)	ORcalc 0.80 (0.09, 7.12)	
Swedish Inpatient Register[80]	nd	9 y	Br Reduc	3/7429 (0.04%)	1/3351 (0.03%)	Adj RR 0.8 (0.3 2.2)	**Inad:** A, T
			Gen Pop		--	SHR 0.8 (0.2, 2.5)	
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=2)					**0.80 (0.09, 7.12)** **0.8 (0.3 2.2)**	
	Any, SIR (n=1)					**0.8 (0.2, 2.5)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=2)			**0.04% (0.01, 0.10)***			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Exact proportion

Table 62. Mononeuritis

Study	% Silicone	Follow-up	Limb	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Swedish Inpatient Register[80]	nd	9 y	Upper	Br Reduc	8/7429 (0.1%)	8/3351 (0.2%)	Adj RR 0.5 (0.2, 1.03)	**Inad:** A, T
				Gen Pop		--	SHR 1.1 (0.5, 2.2)	
			Lower	Br Reduc	7/7429 (0.1%)	3/3351 (0.1%)	Adj RR 1.3 (0.6, 2.5)	**Inad:** A, T
				Gen Pop		--	SHR 2.4 (0.95, 4.9)	

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Motor Neuropathy

Only the Denmark Public-Private cohort comparing women with and without breast implants of any type reported on motor neuropathy (**Table 63**). Three women in only the no implant arm were given the diagnosis, yielding an approximate OR of 0.45 (95% CI 0.02, 8.80). The study found a percentage of 0% (95% CI 0, 0.3) of women with implants had motor neuropathy. The evidence is insufficient to determine if there is an association between breast implants and motor neuropathy.

Multiple Sclerosis

Five studies reported on multiple sclerosis (**Table 64, Figure 54**). Among the four comparative studies of women with any breast implant, the Danish study found a large statistically significant association between breast implantation and occurrence of multiple sclerosis with a calculated OR of 6.1. However, this analysis was not adjusted for possible confounders. In contrast, the Swedish Inpatient Register study found a strong, significant association in the opposite direction with an (inadequately) adjusted RR of 0.5. The other two studies were consistent with the Swedish study, but with imprecise, wide confidence intervals. Across studies, the pooled ES found no evidence of an association with a summary ES of 1.33 (95% CI 0.18, 9.68), with significant heterogeneity (P = 0.001, I^2 = 82%). Removing the outlier the Danish study yielded a still non-significant summary ES that was in the opposite direction: 0.64 (95% CI 0.27, 1.47; P heterogeneity = 0.93; I^2 = 0%).

Only one non-comparative study was restricted to women with silicone gel implants. In this study the percentage of women with multiple sclerosis was 0.05% (95% CI 0.03, 0.08). The pooled percentage across the five studies was 0.20% (95% CI 0.03, 0.52).

Two of the studies had large ESs, but as noted, in opposite directions. Neither study was adequately adjusted nor specific to silicone gel implants, but in both the disease occurred after implantation.

The evidence is insufficient to determine if there is an association between breast implants and multiple sclerosis.

Myasthenia Gravis

Only the Denmark Public-Private cohort comparing women with and without breast implants of any type reported on myasthenia gravis (**Table 65**). Three women in only the no implant arm were given the diagnosis, yielding an OR of 0.45 (95% CI 0.02, 8.80). The evidence is insufficient to determine if there is an association between breast implants and myasthenia gravis.

Optic Neuritis

Only the Swedish Inpatient Register, comparing women with and without breast implants of any type, reported on optic neuritis (**Table 66**).The studies do not provide evidence regarding the association between silicone gel implants and optic neuritis.

Table 63. Motor Neuropathy

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Denmark Public-Private[97]	≤84	13 y	Cosm Surg	0/2761 (0.0%)	3/8787 (0.03%)	ORcalc 0.45 (0.02, 8.80)	

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Table 64. Multiple Sclerosis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Denmark Public-Private[97]	≤84	13 y	Cosm Surg	23/2761 (0.8%)	12/8787 (0.1%)	ORcalc 6.14 (3.05, 12.4)	
South 18 Centers[32]	50	12 y	No implant	26/7234 (0.4%)	5/2138 (0.2%)	Adj RR 0.7 (0.2, 1.9)	**Inad**: A, R, T
Sydney[47]	nd	16 y	No implant	1/458 (0.2%)	2/687 (0.3%)	RR 0.75 (0.07, 8.29)	
Swedish Inpatient Register[80]	nd	9 y	Br Reduc	3/7433 (0.04%)	4/3351 (0.2%)	Adj RR 0.5 (0.2, 0.9)	**Inad:** A, T
Mentor (MemoryGel/MemoryShape) Post-Approval Study[59]	100	5 y		20/41451 (0.1%)			
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=4)					**1.33 (0.18, 9.68) P het=0.001, I^2=82%**	
Summary Percent Implant	**100% (n=1)**			**0.05% (0.03, 0.08)†**			
	Any (n=5)			**0.2% (0.03, 0.52)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.

†Exact proportion

Figure 54. Multiple Sclerosis

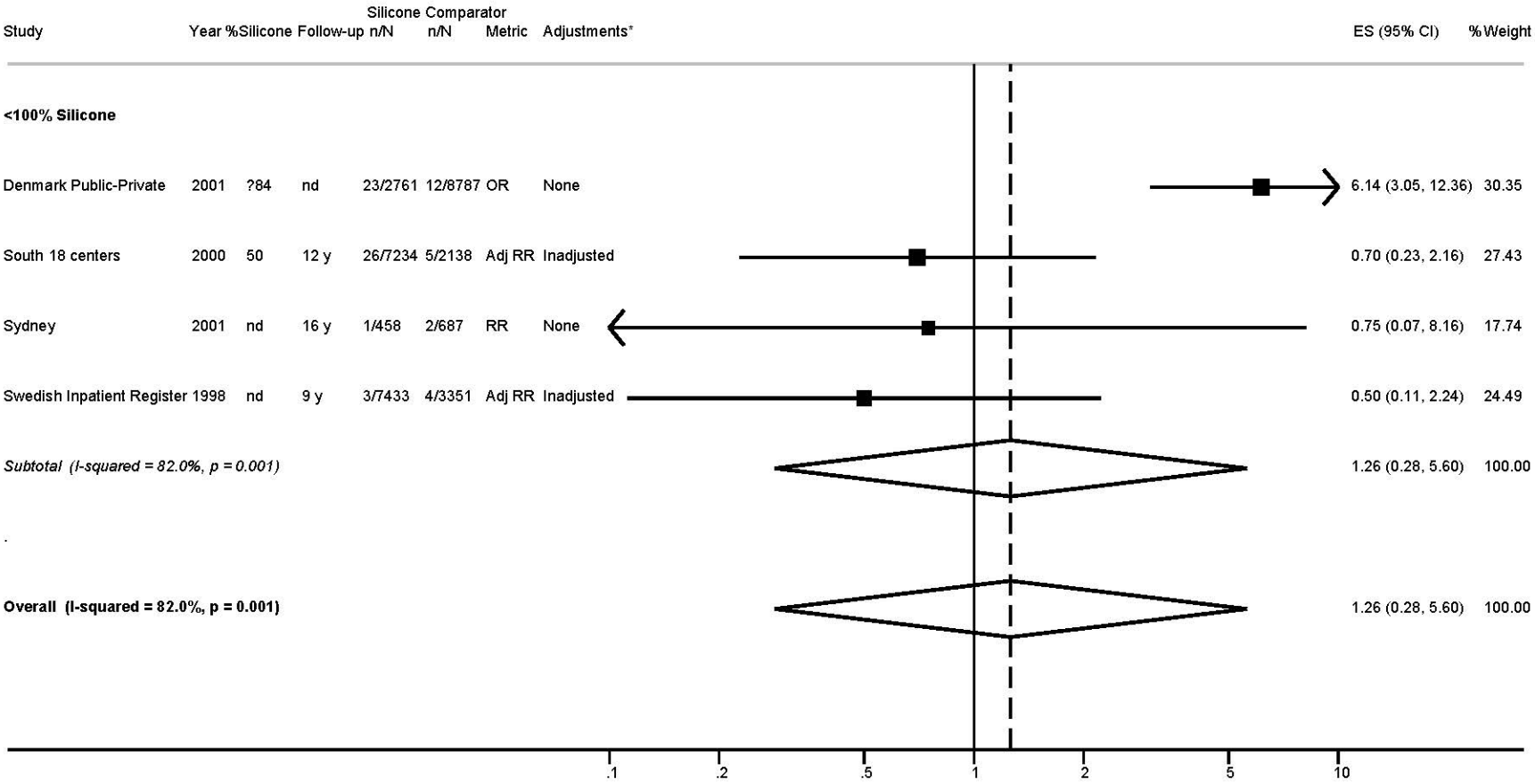


Table 65. Myasthenia Gravis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Denmark Public-Private[97]	≤84	13 y	Cosm Surg	0/2761 (0%)	3/8787 (0.03%)	ORcalc 0.45 (0.02, 8.80)	

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Table 66. Optic Neuritis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Swedish Inpatient Register[80]	nd	9 y	Br Reduc	0/7429 (0%)	0/3351 (0%)	No events	
			Gen Pop		--	SHR 0 (0, 134)	

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Optical Retinopathy and Neuropathy

Only the Denmark Public-Private cohort, comparing women with and without breast implants of any type, reported on optical retinopathy and neuropathy (**Table 67**). Two women in only the no implant arm were given the diagnosis, yielding an estimated OR of 0.64 (95% CI 0.03, 13.3). The evidence is insufficient to determine if there is an association between breast implants and optical retinopathy and neuropathy.

Peripheral Neuropathy

The Denmark Public-Private cohort comparing women with and without breast implants of any type was also the only study to report on peripheral neuropathy (**Table 68**). The study found no significant association, with an OR of 0.78 (95% CI 0.5, 1.3). The study revealed a percentage of 0.7% (95% CI 0.4, 1.1) of women with implants had peripheral neuropathy. The evidence is insufficient to determine if there is an association between breast implants and optical retinopathy and peripheral neuropathy.

Table 67. Optical Retinopathy and Neuropathy

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Denmark Public-Private[97]	≤84	13 y	Cosm Surg	0/2761 (0.0%)	2/8787 (0.02%)	ORcalc 0.64 (0.03,13.3)	

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Table 68. Peripheral Neuropathy

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Denmark Public-Private[97]	≤84	13 y	Cosm Surg	19/2761 (0.7%)	77/8787 (0.9%)	ORcalc 0.78 (0.47, 1.30)	

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Neurologic Symptoms

Cognitive Symptoms

The effect of silicone gel implants on cognitive symptoms was analyzed in three European cohorts (**Table 69**). The Dutch Implant Support Group study assessed self-reported impaired memory or concentration in women with and without silicone gel implants and found a large and significant OR of 3.7 (95% CI 1.8, 7.9). However, this study is particularly biased since it included women who were in a support group, and thus more likely than average to have a concern, symptom, or disease putatively related to silicone gel implants.

The Copenhagen Deaconess Hospital cohort compared an all implant arm versus both a breast reduction arm and the general population for the outcome of impaired memory, problems with traffic orientation, and difficulties in adding numbers. The comparison of implant patients to those undergoing a breast reduction yielded a non-significant OR of 1.2 (95% CI 0.8, 1.8) and an OR of 1.9 (1.2, 3.1) when compared to the general population.

Lastly, the Swedish Impatient Register comparing women with and without implants. It assessed both memory difficulties and difficulty finding words, for which it found no significant associations. For the former outcome, there was an OR of 1.1 (95% CI 0.8, 1.5) and for the latter, an OR of 1.3 (95% CI 1, 1.8).

The various outcomes and lack of nonbiased studies restricted to women with silicone gel implants resulted in the conclusion that the evidence is insufficient to determine if there is an association between breast implants and cognitive symptoms.

Paresthesia

Five studies reported on paresthesia, three of which were comparative (**Table 70, Figure 55**). One of the comparative studies and both non-comparative studies included women with silicone gel implants. Of note, the definitions of paresthesia are likely to have varied across studies as indicated by the high percentage of women with paresthesia in comparative studies (20% to 59%) but low percentage in the two single group studies (0.1% and 0.3%).

The very small comparative study of silicone gel implants found a non-significant increased risk of paresthesia among women with the implants. The adequately adjusted analysis, which controlled for pregnancy history, tobacco and alcohol use, health care, body mass index, age, and time since surgery, found a marginally significant adjusted RR (1.3; 95% CI 1.0, 1.6). The third study found no significant association. The pooled summary ES of all comparative studies was, however, marginally statistically significant at 1.35 (95% CI 1.02, 1.78), with little heterogeneity (**Figure 55**).

The Munster study found a strong association (ES $\geq$2.0) in women specifically with silicone gel implants, but it was not clear whether the reported symptoms were new since implantation.

There is limited or suggestive evidence of an association between breast implants and a complaint of paresthesia. Women with breast implants may have a small increased risk, about 35%, of paresthesia. The studies do not provide sufficient evidence to determine if a true association exists and, therefore, whether silicone gel implants may have a causal link to the symptom.

Table 69. Neurologic Symptoms: Cognitive symptoms

Study	% Silicone	Follow-up	Outcome	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Dutch Silicone Implant Support Group†[93]	100	nd	Impaired memory or concentration	No implant	177/319 (56%)	10/40 (25%)	ORcalc 3.74 (1.77, 7.91)	
Copenhagen Deaconess Hospital[28]	77	19 y	E.g., impaired memory, problems with traffic orientation, difficulties in adding numbers	Breast Reduction	79/190 (42%)	69/186 (37%)	Adj OR 1.2 (0.8, 1.8)	**Inad:** A
				Gen pop		40/149 (27%)	Adj OR 1.9 (1.2, 3.1)	**Inad:** A
Swedish Inpatient Register[79]	nd	nd	Memory difficulties	Br Reduc	112/1369 (8.2%)	151/2211 (6.8%)	Adj RR 1.1 (0.8, 1.5)	**Ad:** A, T, O7
			Hard to find words			146/2211 (6.6%)	Adj RR 1.3 (1, 1.8)	**Ad:** A, T, O7

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O7 = Ever pregnant, Tobacco use, Alcohol use, Health care, Body mass index

Table 70. Neurologic Symptoms: Paresthesia

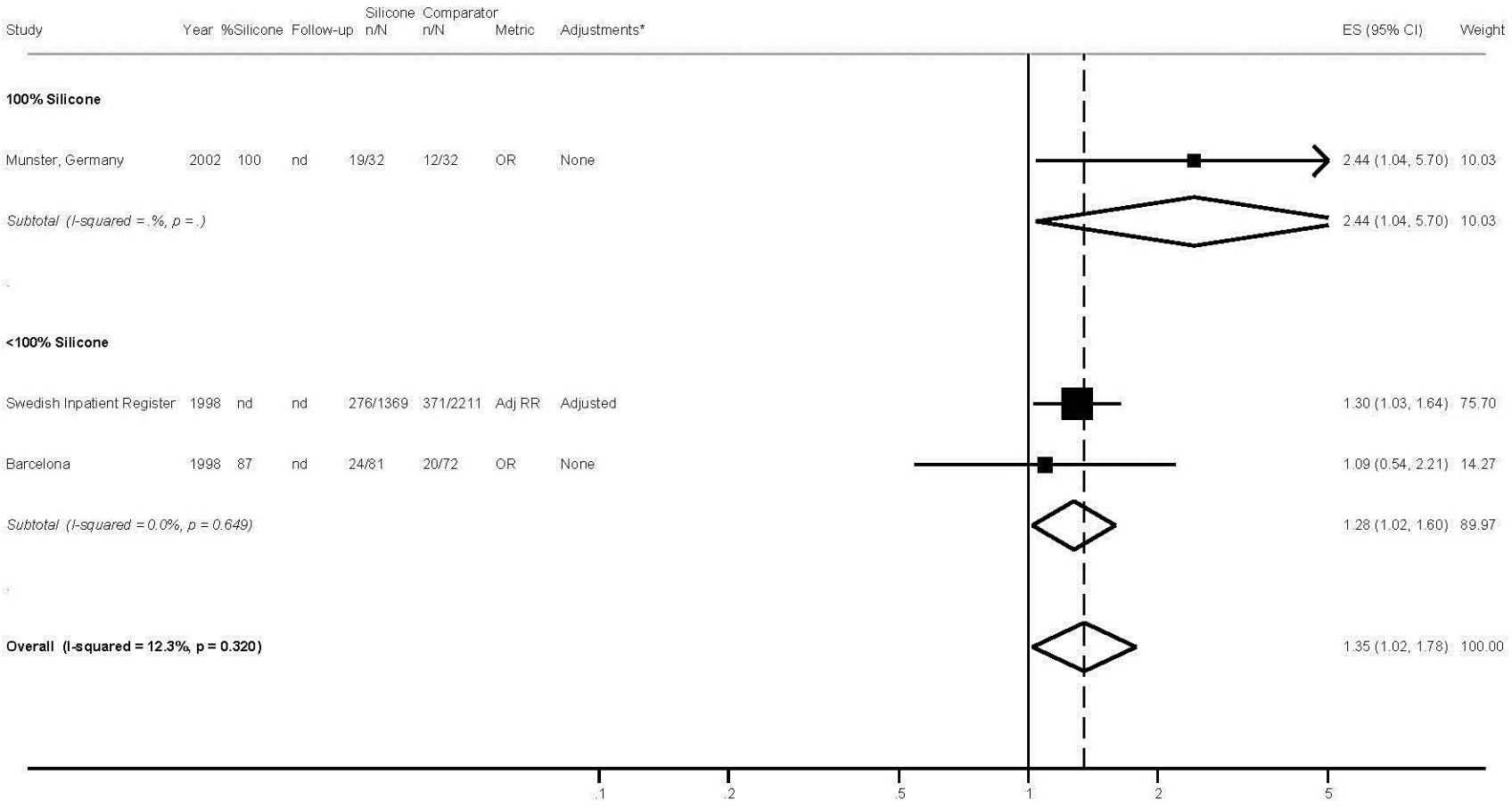
Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Munster, Germany[27]	100	nd	No implant	19/32 (59%)	12/32 (38%)	ORcalc 2.44 (1.04, 5.70)	
Barcelona[38]	87	nd	No implant	24/81 (30%)	20/72 (28%)	ORcalc 1.09 (0.54, 2.21)	
Swedish Inpatient Register[52]	nd	nd	Br Reduc	276/1369 (20%)	371/2211 (17%)	Adj RR 1.3 (1.0, 1.6)	**Ad:** A, T, O7
U Minnesota[42]	100	10 y		1/310 (0.3%)			
Mentor (MemoryGel Round) Cohort[87]	100	3 y		1/1007 (0.1%)			
Summary Implant vs. No Implant	**100% (n=1)**					**2.44 (1.04, 5.70)**	
	Any, Direct comparisons (n=3)					**1.35 (1.02, 1.78) P het=0.32, I^2=12%**	
Summary Percent Implant	**100%**			**†**			
	Any			**†**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O7 = Ever pregnant, Tobacco use, Alcohol use, Health care, Body mass index

† Not calculated due to extreme heterogeneity across studies.

Figure 55. Paresthesia



Vertigo

Only the Munster, Germany cohort, comparing women with and without silicone gel breast implants, reported on vertigo (**Table 71**). In this study of 64 women, there were twice as many events in the silicone gel implant arm than the control, but the estimate was non-significant, yielding an OR of 2.83 (95% CI 0.85, 9.40). The evidence is insufficient to determine if there is an association between breast implants and vertigo.

Table 71. Neurologic Symptoms: Vertigo

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Munster, Germany[27]	100	nd	No implant	11/32 (34%)	5/32 (16%)	ORcalc 2.83 (0.85, 9.40)	

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Reproductive Issues

Any Reproductive Issues

Five studies reported on a combined outcome of any reproductive issues, all in women with silicone gel implants (**Table 72**). None of the studies compared these women to women without implants. They also all combined different specific reproduction-related outcomes, including miscarriage, stillbirth, infertility, and pre-term labor. None of the studies reported that they restricted these analyses to premenopausal women or women who might otherwise expect to be fertile or who were attempting pregnancy. The studies do not provide evidence regarding the association between silicone gel implants and overall problems with reproductive outcomes.

Lactation Issues

Eleven studies with 12 cohorts of women with implants reported on problems with lactation (**Table 73**). Only a single small study from Texas compared women with and with breast implants. Almost 2/3 of women with breast augmentation with implants of any kind who attempted lactation experienced "insufficient lactation", while only 3 of 42 (7%) matched controls had insufficient lactation. This difference was highly significant. The study was not specific to silicone gel implants, nor was it clear how the lactation issues compared with pre-implantation lactation. One study compared women with silicone gel implants to those with saline implants. A similar percentage of women in both groups (15% and 16%) had difficulties with lactation, but there were insufficient data reported for complete analysis.

The 10 other cohorts all evaluated silicone gel implants only, but were not compared with women without implants. Reported difficulties with lactation ranged from 0% to 25% across these studies. It is likely that studies used different criteria to define difficulties with lactation.

The evidence is insufficient to determine if there is an association between breast implants and difficulties with lactation.

Miscarriage

Seven studies evaluated miscarriage (or stillbirth) in women with breast implants (**Table 74**). Three of the studies compared women with and without implants. One study compared women with silicone gel implants to those with saline implants. A similar percentage of women in both groups had a miscarriage (18% and 14%), but there were insufficient data reported for complete analysis. The Danish study found that significantly more women with breast implants of any type had a miscarriage than women with cosmetic surgery (adjusted OR=1.40), but the association was not significant when compared with women in the general population. The Swedish study found similar proportions of women who had miscarriages comparing those with breast implants of any kind and those with breast reduction. Notably, this study had much lower reported rates of miscarriage than the other studies (except Style 410 Europe). Across studies, 17% (95% CI 15, 19) of women with silicone gel implants had a miscarriage. Across all studies, 13% (95% CI 2.3, 30) had a miscarriage.

The evidence is insufficient to determine if there is an association between breast implants and miscarriage.

Table 72. "Reproductive Issues"

Study	% Silicone	Follow-up	Definition	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Allergan (Inamed/Natrelle Round) Cohort[88]	100	10 y	Miscarriage, infertility, possibly others		44/715 (6.2%)			
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	9 y	"Any", most commonly miscarriage / stillbirth		21/941 (2.2%)			
Buenos Aires[78]	100	6 y	Trouble of any kind during pregnancy		0/64 (0%)			
Sientra[89]	100	3 y	Miscarriage, preterm labor, or stillbirth		21/1788 (1.2%)			
Style 410 Stockholm[62]	100	5-9 y	Infertility, miscarriage		6/144 (4.2%)			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Table 73. Lactation Issues

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Allergan Natrelle Breast Implant Follow-up Study[58]	100	1-3 y	Saline	nd (15%)	nd (16%)	RR 0.94 (nd)	
Texas Children's Hospital[65]	nd	nd	No implant	27/42 (64%)	3/42 (7%)	ORcalc 23.4 (6.17, 88.8)	
Allergan (Inamed/Natrelle Round) Cohort[88]	100	4 y		11/65 (17%)			
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	9 y		11/49 (22%)			
Allergan vs. Mentor (Allergan)[67]	100	10 y		0/7 (0%)			
Allergan vs. Mentor (Mentor)[67]	100	10 y		0/6 (0%)			
Buenos Aires[78]	100	6 y		0/7 (0%)			
Mentor (MemoryGel Round) Cohort[87]	100	9 y		15/71 (21%)			
Mentor (MemoryShape/CPG Anatomic) Cohort[91]	100	8 y		6/76 (7.9%)			
Sientra[89]	100	3 y		14/206 (6.8%)			
Style 410 Europe[61]	100	5-11 y		6/27 (22%)			
Style 410 Stockholm[62]	100	5-9 y		5/20 (25%)			
Summary Implant vs. No Implant	**100% (n=1)**					**0.94 (nd) vs. saline**	
	Any, Direct comparisons (n=2)					**0.94 (nd) vs. saline 23.4 (6.17, 88.8)**	
Summary Percent Implant	**100%**			*****			
	Any			*****			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Not calculated due to extreme heterogeneity across studies.

Table 74.Miscarriage

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Allergan Natrelle Breast Implant Follow-up Study[58]	100	1-3 y	Saline	nd (18%)	nd (14%)	RR 1.3 (nd)	
Denmark Private[71]	50	nd	Cosm Surg	110/423 (26%)	47/231 (20%)	Adj OR 1.4 (1.0, 2.1)	**Inad:** A
			No implant		39/183 (21%)	Adj OR 1.3 (0.9, 2.0)	**Inad:** A
Swedish Inpatient Register[86]	nd	8 y	Br Reduc	6/1589 (0.4%)	46/13274 (0.4%)	Adj RR 0.9 (0.4, 2.1)	**Inad:** A, Y, O8
Mentor (MemoryGel/MemoryShape) Post-Approval Study[59]	100	5 y		245/1415 (17%)			
Mentor (MemoryGel Round) Cohort[87]	100	9 y		26/159 (16%)			
Mentor (MemoryShape/CPG Anatomic) Cohort[91]	100	8 y		16/115 (14%)			
Style 410 Europe[61]	100	5-11 y		nd (0.1%)			
Summary Implant vs. No Implant	**100% (n=1)**					**1.3 (nd)**	
	Any, Direct comparisons (n=3, 4 comparisons)					**1.3 (nd)** **1.4 (1.0, 2.1)** **1.3 (0.9, 2.0)** **0.9 (0.4, 2.1)**	
Summary Percent Implant	**100% (n=3)**			**17% (15, 19)**			
	Any (n=5)			**13% (2.3, 30)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.

A = age, R = race, T = time since surgery, Y = calendar year.

O8 = Offspring sex.

Offspring Issues

Cancer

One comparative study from the Swedish Inpatient Register comparing women receiving any implant versus women undergoing a breast reduction and one non-comparative study from Allergan of silicone gel implants provided results on cancer among offspring of women with implants (**Table 75**). In both studies the diagnosis was rare in the implant arms yielding an overall prevalence of 0.1% (95% CI 0, 0.2). Due to the rarity of the outcome, the comparative study of any breast implant was imprecise with an adjusted RR of 0.3 (95% CI 0.0, 2.5). The evidence is insufficient to determine if there is an association between breast implants and cancer among the women's offspring.

Congenital Malformations, Any

Four comparative studies reviewed the risk of congenital malformations in the offspring of women with implants (**Table 76**). Two studies included only women with silicone gel implants. The Allergan study reported a marginally significant adjusted RR of 1.5, but the Mentor study reported (only) that there was no significant difference versus what was apparently a historical control. The other two Scandinavian studies of any implants also found no significant difference. The evidence is insufficient to determine if there is an association between breast implants and congenital malformations among the women's offspring.

Congenital Malformations, Gastrointestinal Organs

Two comparative studies from Scandinavia reported specifically on congenital malformations of gastrointestinal organs (**Table 77**). Both studies included women with any breast implant. Both found no significant association. Overall, 1.1% (95% CI 0.1, 2.8) of women with breast implants had offspring with congenital malformations of gastrointestinal organs. The evidence is insufficient to determine if there is an association between breast implants and congenital malformations of gastrointestinal organs among the women's offspring.

Congenital Malformations, Esophagus

The same two studies from Scandinavia reported on esophageal malformations in offspring. (**Table 78**). Both found no significant association. Overall, 1.2% (95% CI 0.6, 2.0) of women with breast implants had offspring with esophageal malformations. The evidence is insufficient to determine if there is an association between breast implants and esophageal malformations among the women's offspring.

Table 75. Offspring: Cancer

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Swedish Inpatient Register[86]	nd	8 y	Br Reduc	1/1588 (0.1%)	17/13274 (0.1%)	Adj RR 0.3 (0.0, 2.5)	**Inad:** A, Y, O8
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	7 y		1/941 (0.1%)			
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=1)					**0.3 (0.0, 2.5)**	
Summary Percent Implant	**100% (n=1)**			**0.1% (0.02, 0.6)**			
	Any (n=2)			**0.1% (0, 0.2)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O8 = Offspring sex.

Table 76. Offspring: Congenital Malformations

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Allergan Natrelle Breast Implant Follow-up Study[58]	100	1-3 y	Saline	nd (1.5%)	nd (1.0%)	RR 1.5 (nd)	
Mentor (MemoryGel/MemoryShape) Post-Approval Study[59]	100	5 y	Hist Cx	10/674 (1.5%)	nd	Reported P value NS	
Denmark Public-Private[70]	≤84	nd	Cosm surg	53/748 (7.1%)	189/3209 (5.8%)	ORcalc 1.22 (0.89, 1.67)	
Swedish Inpatient Register[86]	nd	8 y	Br Reduc	88/1589 (5.5%)	769/13274 (5.8%)	Adj RR 1.0 (0.6, 1.5)	**Inad:** A, Y, O8
Summary Implant vs. No Implant	**100% (n=2)**					**1.5 (nd)** **NS**	
	Any, Direct comparisons (n=4)					**1.5 (nd)** **NS** **1.22 (0.89, 1.67)** **1.0 (0.6, 1.5)**	
Summary Percent Implant	**100% (n=2)**			**1.5% (0.8, 2.7)**			
	Any (n=4)			**4.4% (1.8, 8.1)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O8 = Offspring sex.

Table 77.Offspring: Congenital Malformations of Gastrointestinal Organs

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Denmark Public-Private[70]	≤84	nd	Cosm surg	14/748 (1.9%)	62/3209 (1.9%)	ORcalc 0.97 (0.54, 1.74)	
Swedish Inpatient Register[86]	nd	8 y	Br Reduc	8/1589 (0.5%)	111/13274 (0.8%)	Adj RR 0.5 (0.2, 1.3)	**Inad:** A, Y, O8
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=2)					**0.97 (0.54, 1.74)** **0.5 (0.2, 1.3)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=4)			**1.1% (0.1, 2.8)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O8 = Offspring sex.

Table 78. Offspring: Esophageal Malformations

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Denmark Public-Private[70]	≤84	nd	Cosm surg	6/748 (1.9%)	32/3209 (1.9%)	ORcalc 0.80 (0.33, 1.93)	
Swedish Inpatient Register[86]	nd	8 y	Br Reduc	24/1589 (0.5%)	194/13274 (0.8%)	Adj RR 1.0 (0.7, 1.6)	**Inad:** A, Y, O8
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=2)					**0.80 (0.33, 1.93)** **1.0 (0.7, 1.6)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=4)			**1.2% (0.6, 2.0)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O8 = Offspring sex.

Low Birth Weight

Two comparative studies reported on low birth weight among the offspring of women with breast implants (**Table 79**). The Mentor study, however, reported only that the percentage of low birth weight children of mothers with silicone gel implants was not significantly different from a historical control. A study from Finland reported several related outcomes, including by weight (1500 and 2500 g) and small for gestational age. For each outcome, there was no significant association (see Table 79).. Between studies, 7.4% (95% CI 6.4, 10) of children born to women with breast implants had low birth weight, using the broadest definition (<2500 g). The evidence is insufficient to determine if there is an association between breast implants and low birth weight among women's offspring.

Neonatal Intensive Care

Only the Mentor Post-Approval Study examined the number of offspring who needed care in the neonatal intensive care unit (**Table 80**). The study reported only that the percent of children of women with silicone gel implants who required intensive care (11%) was not significantly different than a historical control. The evidence is insufficient to determine if there is an association between breast implants and the need for neonatal intensive care among women's offspring.

Perinatal Death

Two comparative studies from Scandinavian studies (**Table 81**) compared perinatal death in the offspring of women with any breast implants to those women receiving no implants (Finland) and those undergoing breast reduction surgery (Sweden). One study conducted an adequate adjustment, controlling for social class, urbanity, marital status, previous births, tobacco use, and age. Nevertheless, the study had an imprecise, non-significant adjusted OR for perinatal death. The other study also found no significant association. The overall prevalence of perinatal death in these studies was 0.6% (95% CI 0.3, 1.0). The evidence is insufficient to determine if there is an association between breast implants and perinatal death among women's offspring.

Preterm Delivery

Two comparative studies evaluated the risk of preterm delivery in women with breast implants (**Table 82**). The Mentor study found no difference between women with silicone breast implants and a historical control The Finnish study found a non-significant adjusted OR of 1.3 (95% CI 0.8, 2.0). The overall risk of preterm delivery among women with breast implants was 10% (95% CI 4, 19). The evidence is insufficient to determine if there is an association between breast implants and preterm delivery.

Table 79. Offspring: Low Birth Weight

Study	% Silicone	Follow-up	Comparator	Definition	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Mentor (MemoryGel/MemoryShape) Post-Approval Study[59]	100	5 y	Hist Cx	nd	57/674 (8.5%)	nd	Reported P value NS	
Finland hospitals[63]	>90	5 y	No implant	<1500 g	5/423 (1.2%)	85/8460 (1.0%)	Adj OR 1.44 (0.58, 3.63)	**Ad:** A, O9
				<2500 g	24/423 (5.7%)	355/8460 (4.2%)	Adj OR 1.43 (0.90, 2.29)	
				SGA†	10/423 (2.4%)	203/8460 (2.4%)	Adj OR 1.01 (0.51, 2.00)	
Summary Implant vs. No Implant	**100% (n=1)**						**NS**	
	Any, Direct comparisons (n=2)						**NS**	
							1.65 (0.98, 2.80)	
Summary Percent Implant	**100% (n=1)**			**8.5% (6.6, 11)**				
	Any (n=2)			**7.4% (6.4, 10.0)**				

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O9 = Class, Urbanity, Marital status, Previous births, Tobacco use.

† Small for gestational age, based on a Finnish national standard.

Table 80. Offspring: Neonatal Intensive Care Admission

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Mentor (MemoryGel/MemoryShape) Post-Approval Study[59]	100	5 y	Hist Cx	73/674 (11%)	nd	Reported P value NS	

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Table 81. Offspring: Perinatal death

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Finland hospitals[63]	>90	5 y	No implant	1/423 (0.2%)	66/8460 (0.8%)	Adj OR 0.33 (0.05, 2.42)	**Ad:** A, O9
Swedish Inpatient Register[86]	nd	8 y	Br Reduc	11/1589 (0.7%)	81/13274 (0.6%)	Adj RR 0.9 (0.5, 1.8)	**Inad:** A, Y, O8
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=2)					**0.33 (0.05, 2.42)** **0.9 (0.5, 1.8)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=2)			**0.6% (0.3, 1.0)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O8 = Offspring sex
O9 = Class, Urbanity, Marital status, Previous births, Tobacco use.

Table 82. Offspring: Preterm

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Mentor (MemoryGel/MemoryShape) Post-Approval Study[59]	100	5 y	Hist Cx	98/674 (15%)	nd	Reported P value NS	
Finland hospitals[63]	>90	5 y	No implant	27/423 (6.4%)	457/8460 (5.4%)	Adj OR 1.28 (0.83, 1.96)	**Ad:** A, O9
Summary Implant vs. No Implant	**100% (n=1)**					**NS**	
	Any, Direct comparisons (n=2)					**NS 1.28 (0.83, 1.96)**	
Summary Percent Implant	**100% (n=1)**			**15% (12, 17)**			
	Any (n=2)			**10% (3.6, 19)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O9 = Class, Urbanity, Marital status, Previous births, Tobacco use.

Pyloric Stenosis

Only the Denmark Public-Private cohort compared the incidence of pyloric stenosis in offspring born of women with any breast implant to those receiving no implant (**Table 83**). The risk of pyloric stenosis was 0.4% (95% CI 0.1, 1.1) with an OR for the comparison of 0.6 (95% CI 0.2, 2.1). The evidence is insufficient to determine if there is an association between breast implants and pyloric stenosis among women's offspring.

Rheumatic Disease

The two Scandinavian comparative studies also reported on rheumatic disease incidence in the offspring born of women with breast implants (**Table 84**). Both included women with any breast implant and found no significant association. Overall, 0.3% (95% CI 0.03, 0.8) of women with breast implants had offspring with rheumatic diseases. The evidence is insufficient to determine if there is an association between breast implants and rheumatic diseases in offspring.

Table 83. Offspring: Pyloric Stenosis

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments
Denmark Public-Private[70]	≤84	nd	No implant	3/748 (0.4%)	21/3209 (0.7%)	ORcalc 0.61 (0.18, 2.05)	

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

Table 84. Offspring: Rheumatic disease

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Denmark Public-Private[70]	≤84	nd	Cosm surg	11/2106 (0.5%)	9/2596 (0.3%)	ORcalc 1.51 (0.62, 3.65)	
Swedish Inpatient Register[86]	nd	8 y	No implant	2/1589 (0.1%)	10/13274 (0.1%)	Adj RR 1.1 (0.2, 5.3)	**Inad:** A, Y, O8
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=2)					**1.51 (0.62, 3.65)** **1.1 (0.2, 5.3)**	
Summary Percent Implant	**100% (n=0)**			**No data**			
	Any (n=2)			**0.3% (0.03, 0.8)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.
O8 = Offspring sex.

Mental Health Issues

Depression

Two studies compared the diagnosis of depression in women with and without breast implants (**Table 85**). In a small matched study about twice as many women with silicone gel implants had depression than those without (34% vs. 19%), though the difference was not statistically significant. A study from Copenhagen compared women with breast implants to those from the general population and also women with breast reduction surgery. About 20% of women in each of the three groups had depression. Between the two studies, 26% (95% CI 15, 38) of women with breast implants had experienced depression. Two additional studies compared women's history of depression before breast implantation and the depression course 6 months or 3 years after surgery. In both studies, a small number of women newly developed depression. In the French study, about half the women who had depression pre-surgery had resolution of their depression, but in the Norwegian study, only one of the four women with depression had resolution. The evidence is insufficient to determine if there is an association between breast implants and the risk of depression.

Table 85. Depression

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Munster, Germany[27]	100	nd	No implant	11/32 (34%)	6/32 (19%)	ORcalc 2.27 (0.85, 6.03)	
Copenhagen Deaconess Hospital[28]	77	19 y	Br Reduc	42/190 (22%)	37/186 (20%)	Adj OR 1.2 (0.7, 1.9)	**Inad:** A
			Gen pop		27/149 (18%)	Adj OR 1.3 (0.8, 2.2)	**Inad:** A
France clinic[99]	nd	0.5 y		35/122 pre-implantation 2/87 new depression 19/35 resolved			
Norway clinic[98]	nd	3 y		4/61 pre-implantation 1/4 worsened 1/4 resolved			
Summary Implant vs. No Implant	**100% (n=1)**					**2.27 (0.85, 6.03)**	
	Any, Direct comparisons (n=2, 3 comparisons)					**2.27 (0.85, 6.03)** **1.2 (0.7, 1.9)** **1.3 (0.8, 2.2)**	
Summary Percent Implant	**100% (n=1)**			**34% (20, 52)**			
	Any (n=2)			**26% (15, 38)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.

Suicide

Thirteen studies reported on suicide, of which six were comparative (**Table 86, Figures 56-59**). None of the comparative studies evaluated silicone gel implants specifically. Two of the studies (Breast Implant Surveillance Study and WHI OS) found large differences in the number of suicides between women with and without implants (OR = 13.1 and 10.6), but neither study adjusted for possible confounders. The remaining three studies found no significant difference. Across the five studies with direct comparisons, there was a large degree of statistical heterogeneity (P = 0.003, I^2 = 76%) with a non-significant pooled ES for suicide of 2.85 (95% CI 0.77, 10.55) (**Figure 56**). Based on the pooled ES and the pooled risk of suicide across studies, the RD between women with and without implants—the absolute percentage of women who would commit suicide associated with their implant (assuming the association is causal)—ranges from 0.03% (95% CI 0.01, 0.04) to 0.19% (95% CI 0.05, 0.25).

As noted, there was a large degree of statistical heterogeneity with a wide spread of ES estimates, but there was no clear outlier study. The Ontario/Quebec study had the effect closest to the null, but it was not clearly different than all but the WHI OS study. Removing it from meta-analysis, yielded a larger, still non-significant summary ES, still with heterogeneity: summary ES = 3.88 (95% CI 0.79, 19.1); P heterogeneity = 0.031; I^2=66%. Likewise, removing the study with the largest ES (Breast Implant Surveillance Study) had only a small effect on the summary estimate: ES = 2.36 (95% 0.52, 10.7); P heterogeneity = 0.005; I^2=77%. Cumulative meta-analyses by the last year women received the implant (**Figure 57**) and by duration of follow-up (**Figure 58**) did not display clear trends over time.

Three studies also reported SMRs. These were all statistically significant and ranged from 1.63 to 3.0. The pooled SMR across the studies was 1.99 (95% CI 0.89, 4.43), but with some heterogeneity (P heterogeneity = 0.066, I^2 = 63%) (**Figure 59**).

Three studies reported subgroup analyses. The Ontario/Quebec study found that the SMR was highest among those who had their implant at a later age (≥40 y: SMR 2.31) compared with other age groups (30-39 y: SMR 1.52; 18-29 y: SMR 1.77), although this potential difference was not statistically analyzed.{Villeneuve, 2006 9 /id} The South 18 Centers study did not find a difference by age at time of implantation.{ Brinton, 2006 26 /id} These two studies also found no difference by calendar year of implant (through 1989 or 1992). All three studies found no difference by time since implant, but the Denmark Public-Private study did note that the highest SMR they found was at 1 to 4 years after implantation.[66]

Six of the seven single group studies reporting on suicide were conducted in women with silicone gel implants only. The range of suicides in these studies was from 0% to 0.4% over 3 to 10 years, with a pooled estimate of 0.05% (95% CI 0, 0.07%). Higher rates of suicide were seen in some of the all breast implant studies, so the overall pooled estimate was 0.2% (95% CI 0.05, 0.3) across all studies.

The evidence is insufficient to determine if there is an association between breast implants and the risk of suicide. Although, not statistically significant, women with breast implants may have a two- to three-times higher risk of committing suicide. However, it is reasonable to conclude that the association is actually between the decision to have breast augmentation and the risk of suicide, rather than between the implant itself and suicide. It is difficult to fully adjust for the psychosocial aspects (psychological, societal, and interpersonal) that may confound the association. None of the studies adjusted for possible confounders beyond age, race, and time since surgery, none of which account for the underlying differences between women who choose

to have breast implants and those who do not. Furthermore, none of the studies investigated the possible causes of suicide among the women.

Table 86: Suicide

Study	% Silicone	Follow-up	Comparator	n/N Implant (%)	n/N Comparator (%)	Comparison ES (95% CI)	Adjustments*
Denmark Public-Private[66]	≤84	nd	Br Reduc	14/2761 (0.05%)	22/7071 (0.3%)	ORcalc 1.63 (0.83, 3.20)	
Breast Implant Surveillance Study[74]	75	12 y	No implant	3/817 (0.4%)	1/3568 (0.03%)	ORcalc 13.1 (1.37, 127)	
WHI OS[84]	67	nd	No implant	3/1257 (0.2%)	20/88686 (0.02%)	ORcalc 10.6 (3.15, 35.7)	
Ontario/Quebec[34]	66	15 y	Cosm surg	58/24558 (0.2%)	33/15893 (0.2%)	Adj RR 1.10 (0.72, 1.69)	**Inad:** A, T
			Gen pop		--	SMR 1.73 (1.31, 2.24)	
South 18 Centers[94]	50	20 y	Cosm surg	29/13488 (0.2%)	4/3936 (0.1%)	Adj RR 2.58 (0.9, 7.8)	**Inad:** A, T, R
			Gen pop		--	SMR 1.63 (1.1, 2.3)	
Swedish Inpatient Register[76]	nd	19 y	Gen pop	24/3527 (0.7%)	--	SMR 3.0 (1.9, 4.5)	
Allergan (Inamed/Natrelle Round) Cohort[88]	100	10 y		3/715 (0.4%)			
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort[90]	100	7 y		0/941 (0%)			
Mentor (MemoryGel/MemoryShape) Post-Approval Study[59]	100	5 y		2/41451 (0.01%)			
Mentor (MemoryGel Round) Cohort[87]	100	9 y		0/1008 (0%)			
Mentor (MemoryShape/CPG Anatomic) Cohort[91]	100	8 y		0/955 (0%)			
Sientra[89]	100	3 y		0/1788 (0%)			
Finland hospitals[63]	>90	10 y		10/1266 (0.8%)			
Summary Implant vs. No Implant	**100% (n=0)**					**No data**	
	Any, Direct comparisons (n=5)					**2.85 (0.77, 10.55) P het=0.003, I^2=76%**	
	Any, With SMR data (n=3)					**1.99 (0.89, 4.43) P het=0.066, I^2=63%**	
Summary Percent Implant	**100% (n=6)**			**0.05% (0, 0.07)**			
	Any (n=13)			**0.2% (0.05 0.3)**			

Abbreviations: Adj RR = adjusted relative risk, Br Reduc = breast reduction, CI = confidence interval, Cosm surg = other cosmetic surgery, ES = effect size, Gen pop = general population, Hist Cx = historical control, I^2 = variation in effect size attributable to heterogeneity, n = number of studies included in meta-analysis, nd = no data, NS = reported as non-significant, ORcalc = calculated odds ratio (based on reported counts, unadjusted), P het = P value of heterogeneity, SHR = standardized hospitalization ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, tubal lig = tubal ligation.

* Ad = adequate adjustment (account for outcome confounders; more than just age, race, time, and year); Inad = inadequate (only age, race, time, or year); Unc = unclear adequacy of adjustment.
A = age, R = race, T = time since surgery, Y = calendar year.

Figure 56. Suicide (Direct Comparison)

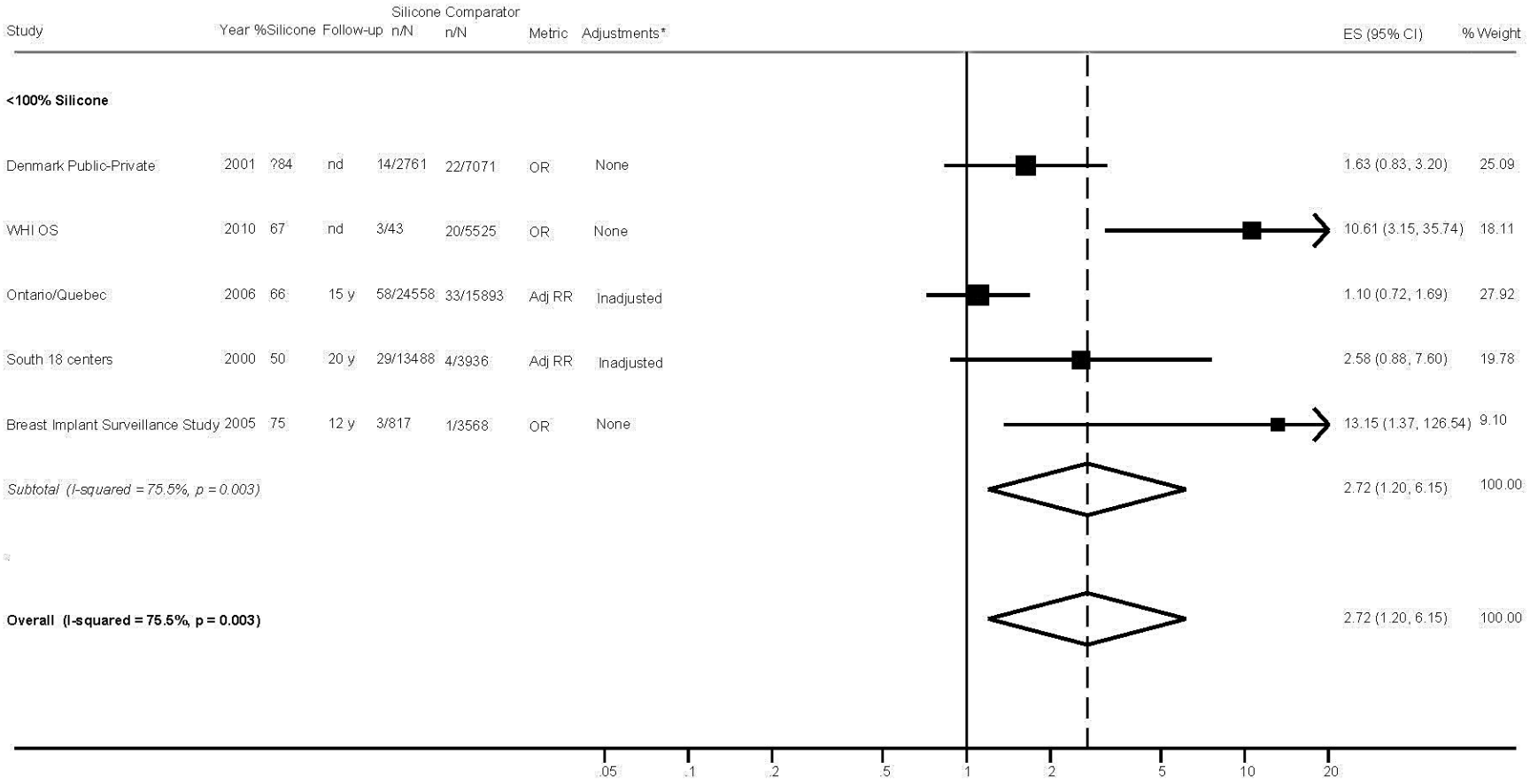


Figure 57.Suicide: Cumulative Meta-Analysis by End-Entry Date

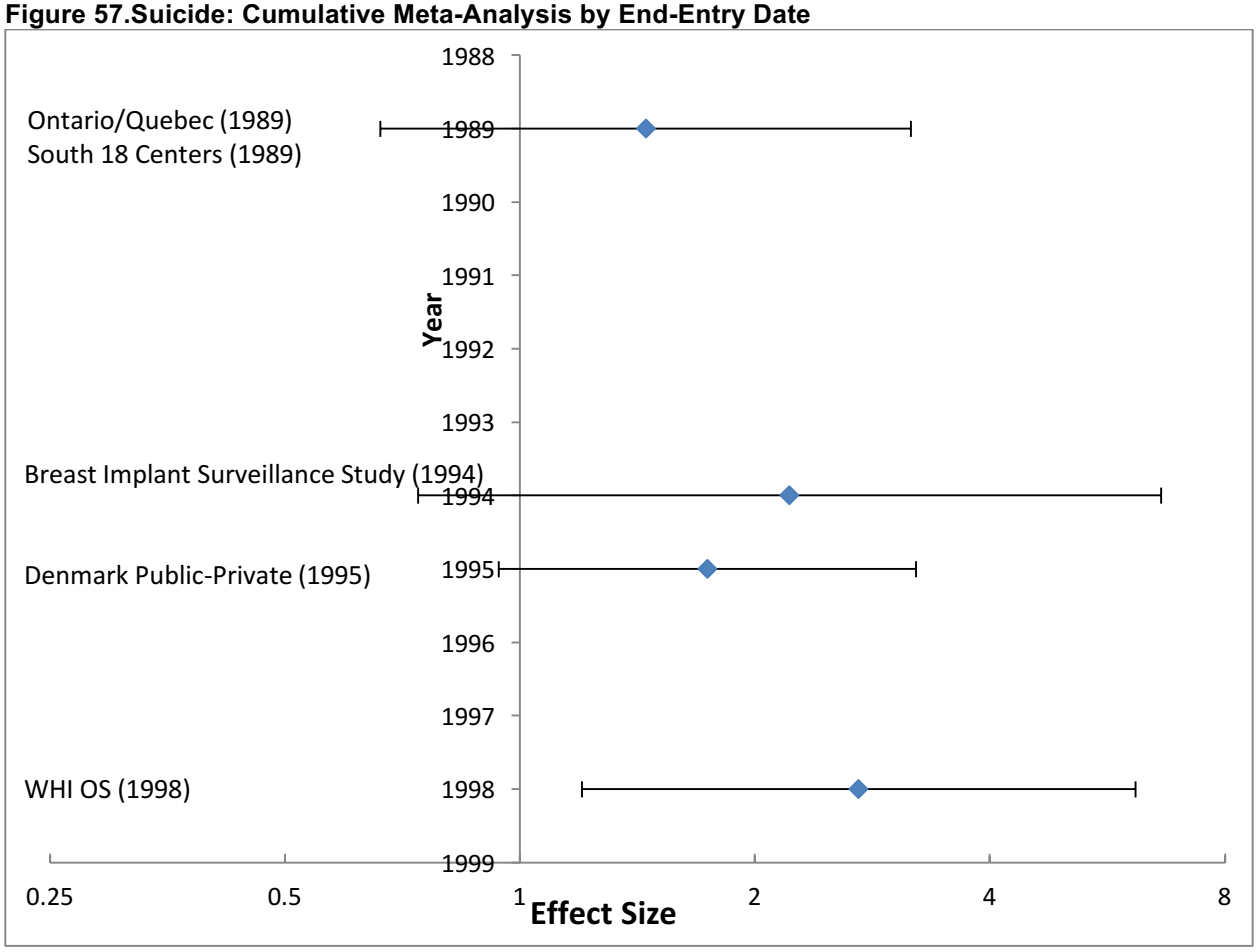


Figure 58.Suicide: Cumulative Meta-Analysis by Follow-Up Duration

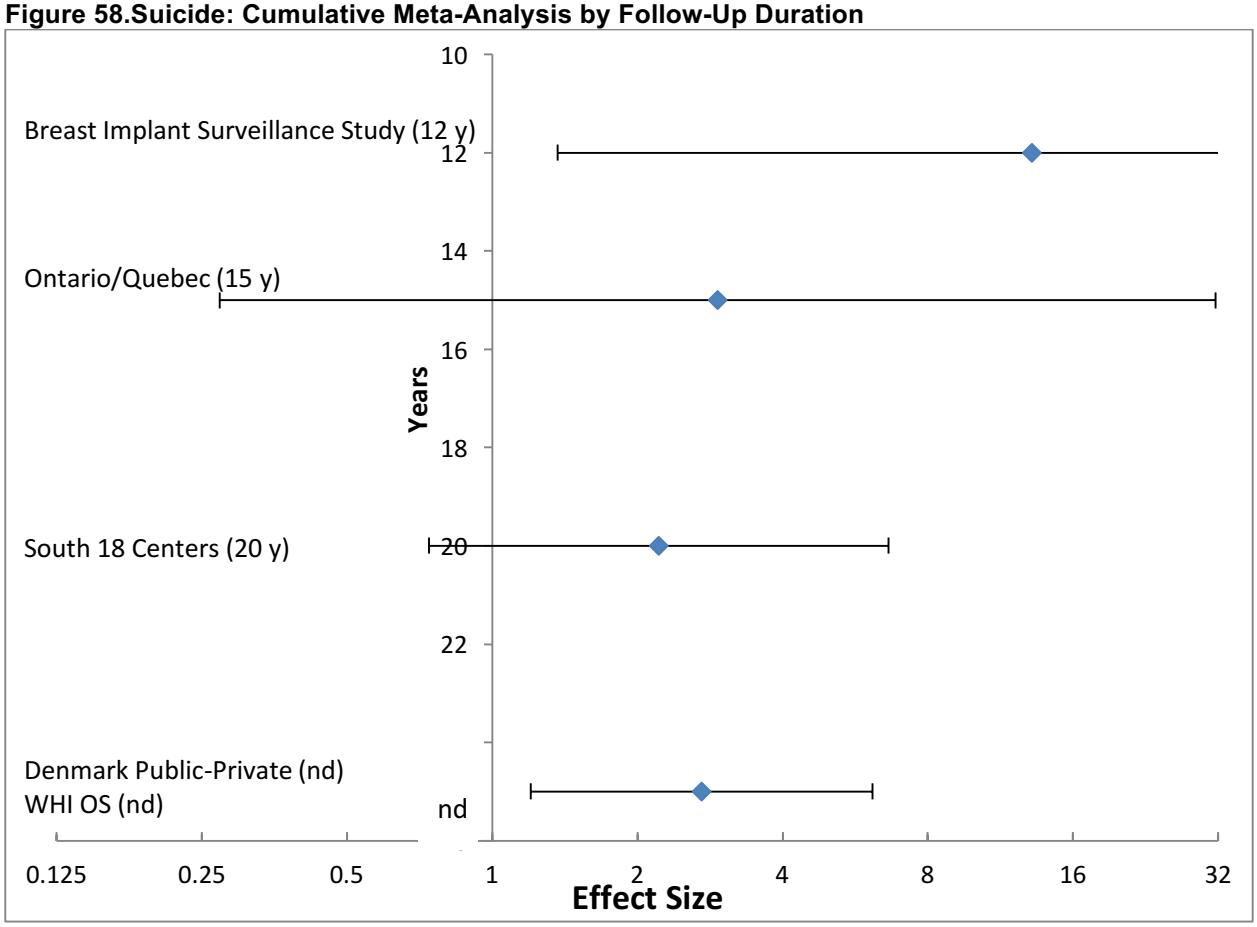
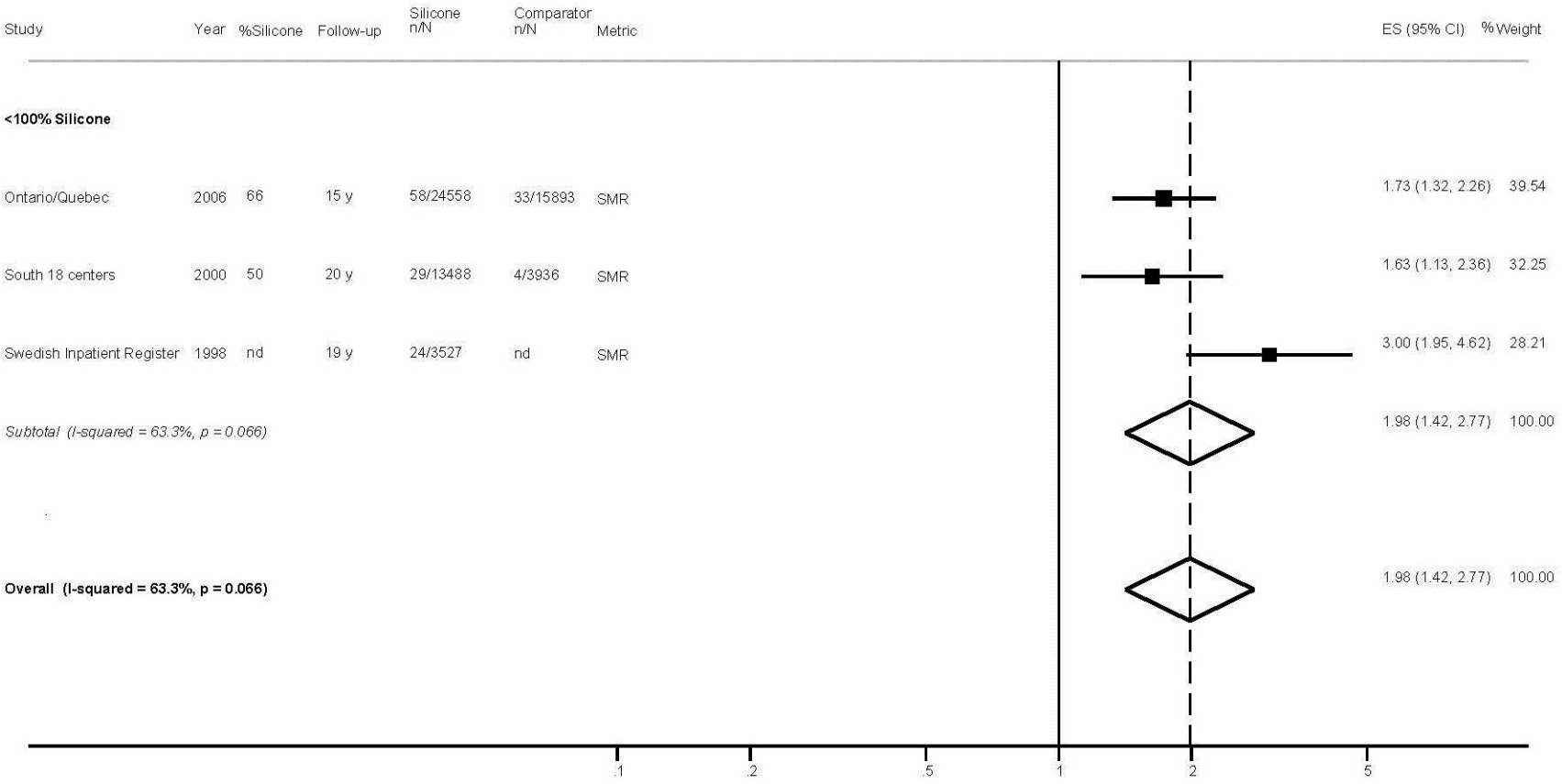


Figure 59.Suicide (Standardized Incidence Ratios)



Discussion

Summary

Despite a large volume of studies reporting on the risk of developing numerous diseases, conditions, and symptoms, the evidence is limited or insufficient regarding the association between silicone gel implants and selected cancers, rheumatologic diseases and symptoms, neurologic diseases and symptoms, reproductive health, harms to offspring, and selected psychiatric conditions (**Table 87**). For none of the outcomes was there sufficient evidence of an association with breast implants or, more specifically, silicone gel implants. No outcome had at least two adequately adjusted studies that yielded consistent estimates of associations. Given the lack of sufficient evidence for associations, based on sparse data, generally weak possible associations, general lack of adequate accounting for possible confounders, and often inconsistency between studies, none of the outcomes had evidence that provided minimally sufficient evidence to support the possibility of causality from silicone gel implants. In particular, none of the studies restricted to women with silicone gel implants provided an adequate adjustment for potential confounders.

For four outcomes the studies were sufficient to conclude that there is limited or suggestive evidence of association between breast implants and the outcome (**Table 87**); though for none of these is the evidence specific to silicone gel implants sufficient to form a conclusion regarding whether the implants are causative of the outcomes. These include primary breast cancer, endometrial cancer, lung cancer, and rheumatoid arthritis. Using an explicit system to categorize the sufficiency of evidence, we determined that for none of the outcomes was the evidence sufficient to make a definitive conclusion. Therefore, by definition, there were important deficiencies to the evidence. These included items such as a lack of sufficient studies free of major bias and confounding (i.e., fully and adequately adjusted) that found a strong association (i.e., ES $\geq$2.0 or $\leq$0.5, commonly used thresholds to decide whether an association found in an observational study is likely to be valid). For most of the outcomes with limited or suggestive evidence, there was only a single adequately adjusted study which was consistent with the overall finding across studies, but was not itself statistically significant. All these outcomes require further investigation, either by the existing studies or in new studies, to determine whether a true association exists. Also important to note is that for none of the outcomes do the studies provide sufficient evidence to support causality between silicone gel implants and the outcome.

Ten comparative studies evaluated primary **breast cancer** in women who had breast implants for augmentation. The studies included both direct comparisons with control groups and SIR estimates. One study conducted an adequate adjustment, although which specific confounders were controlled for was unclear as they reported controlling for "predictors of cancer" in addition to age, race, and follow-up time. A second study conducted a less clear adjustment, controlling for "extraneous variables." All studies found that women with implants were at *lower* risk of developing breast cancer. Meta-analysis of five studies with direct comparisons yielded a homogeneous, statistically significant summary ES of 0.63. Meta-analysis of six of the seven studies that reported SIR estimates was consistent with a statistically significant summary SIR of 0.77. Neither of these summary estimates of the association between breast implants and primary breast cancer reach the commonly accepted threshold of a doubling (or halving) of risk in

association studies to be considered evidence that a true association exists. In addition, these studies were statistically heterogeneous. The single comparative study restricted to women with silicone gel implants had a consistent, but non-significant association. The two adequate or unclearly adjusted studies were also consistent, but non-significant. Five of the studies reported no evidence of significant differences in associations in subgroups based on age at implantation, follow-up time, calendar year of implant, bra cup size pre-implant, polyurethane coating, or fill volume. One study found no evidence of a difference in association between silicone gel and saline implants. Several possible explanations for the reduced risk of primary breast cancer have been proposed by authors of the primary studies. Women who choose to undergo breast implantation have different characteristics than the general population, including lower body mass index, increased exercise, better physical health, higher use of oral contraceptives, higher parity and younger age at first birth, but also higher smoking rates and alcohol consumption.[71,103-106] However, studies that attempted to control for these factors continued to find decreased risk after adjustment.[34] Women who undergo breast implantation (for augmentation) are more similar to women who undergo other cosmetic surgeries than to the general population.[103] As noted by the Ontario/Quebec study,[34] they found a weaker, though still statistically significant, association when breast implant patients were compared with other cosmetic surgery patients than the general population. Another possibility raised by the Ontario/Quebec study researchers is that women with a family history of breast cancer may have elected not to receive breast implants; although the impact of this possible selection bias is unclear. Nevertheless, several biological mechanisms have also been proposed for how the implant itself may reduce breast cancer risk, including immune system enhancement due to the implant or the surgery, compression of glandular tissue resulting in a decreased blood supply that may reduce the rate of cell proliferation, and a long-term reduction in the metabolic rate resulting from lower temperature of the breast tissue.[107]

Two comparative studies evaluated **endometrial cancer** with a direct comparison in one study and SIR estimates in both. Neither study provided an adequate adjustment for potential confounders and both were conducted in women with any breast implant. One study found a strong, statistically significant association by both direct comparison (adjusted RR = 0.55) and SIR estimate (0.44). The second study found a non-significant association that was consistent in direction with the first study (SIR = 0.73). One study found no evidence of a difference by age at implant, time since implant, calendar year of implant (through 1989), or between those with silicone gel and saline implants, polyurethane-coating, or by fill volume. While the association found in the studies was strong, the evidence base is small, consisting of only two comparative studies in which only 63 women with breast cancer had endometrial cancer. Of note, the possible inadequately adjusted-for confounders that might explain the inverse association between breast implants and primary breast cancer may also apply to endometrial cancer, which share many of the same risk factors.

Six comparative studies evaluated **lung cancer** with both direct comparisons and SIR estimates. Only one of the studies provided a (possibly) adequate adjustment in an analysis restricted to women with silicone gel implants, although which specific confounders were controlled for was unclear as they reported controlling for "predictors of cancer" (which likely, though not definitively, includes smoking, a highly likely confounder) in addition to age, race, and follow-up time. The conclusion of a possible association with lung cancer was based primarily on SIR data, which when meta-analyzed, found a homogeneous, statistically significant but small (ES <2.0) 80% increased risk in women with breast implants compared with the

general population. Direct comparisons within studies were each non-significant, but were consistent in the magnitude of the association with the SIR meta-analysis. In particular, the adequately adjusted study of silicone gel implants (assuming smoking was adjusted for) found a non-significant adjusted RR of 2.6. This study also reported an apparent trend related to years since implant with larger associations with greater follow-up time; however, the trend was not analyzed statistically. Two other studies, though, found no significant difference in association by follow-up time. Two studies found no interaction with women's age at implant, calendar year of implant (through 1988 or 1989), or type of implant (vs. saline). One of studies found no interaction with polyurethane coating or fill volume. The lack (or sparseness) of studies that clearly accounted for important confounders of lung cancer—including smoking, second-hand smoke, urban residence (air pollution exposure), among others—and the weak (or lack of) association among the studies with direct comparisons call into question whether the suggested association is valid.

Ten comparative studies evaluated **rheumatoid arthritis**, mostly with direct comparisons. Two of the studies provided adequate adjustments for body mass index, tobacco use, hormone replacement therapy, history of breast cancer, and age in one study and education, family history, age, race, time since implantation, and year of implantation in the other. The studies were statistically heterogeneous, but by meta-analysis, there was a small (ES <2.0) statistically significant 38% increased risk of rheumatoid arthritis in women with breast implants compared with women without implants or who had other cosmetic surgery. All studies, except one which was highly imprecise, had estimates of association greater than 1.0. The two adequately adjusted studies were consistent, but only one had a statistically significant association. No clear cause of the statistical heterogeneity across studies was found. One study reported no difference in association by age at implant, time since implant, or calendar year of implant (through 1992). The small association, heterogeneity of associations found across studies, and the sparseness across studies of adequate adjustment warrant caution in interpreting the likelihood that the association between silicone gel implants and rheumatoid arthritis is real.

Also, notably, six comparative studies evaluated **suicide**, with both direct comparisons and estimates of SMR. Meta-analyses of the five direct comparisons and the three SMR estimates yielded non-significant, but large, associations (2.7 and 2.0, respectively); though both meta-analyses were statistically heterogeneous. All studies found a positive association with suicide, ranging from a non-significant adjusted RR of 1.1 to a significant OR of 13.1. None of the analyses were adequately adjusted. While it is difficult to fully adjust for the psychosocial aspects (psychological, societal, and interpersonal) that may confound the association, none of the studies adjusted for possible confounders beyond age, race, and time since surgery, none of which account for the underlying differences between women who choose to have breast implants and those who do not. Women who have breast augmentation are, almost by definition, more likely to be dissatisfied with their bodies. The WHI OS study found that women with breast implants were less optimistic and had poorer quality of life than women without implants, suggesting psychological differences that may make them more prone to suicide.[84] In another population with potential body image issues, the WHI OS study found a similar persistent increased risk of suicide among morbidly obese women who had bariatric surgery.[108] Furthermore, none of the studies investigated the possible causes of suicide among the women. One study found that the SMR was highest among those who had their implant at a later age (≥40 years old), but this potential interaction was not statistically analyzed. A second study found no difference by age at time of implantation. These two studies also found no difference

by calendar year of implant (through 1989 or 1992). Three studies found no difference by time since implant. No clear explanation of the statistical heterogeneity across studies was found. It is reasonable to conclude that the association is actually between the decision to have breast augmentation and the risk of suicide, rather than between the implant itself and suicide.

Table 87. Summary of Conclusions, by Outcome*

Outcome	Silicone Implants Summary ES (95% CI) [n Studies]	All Implants Summary ES (95% CI) [n Studies]	Conclusion
Limited/Suggestive Evidence of an Association			
Cancer, Breast, primary	0.67 (0.20, 2.17) [1 study]	0.63 (0.54, 0.73) [6 studies] Ad Adj: 0.84 (0.62, 1.14) 0.64 (0.4, 1.0) [2 studies] SIR: 0.76 (0.64, 0.91) & 0.54 (P<0.05) [7 studies]	There is suggestive evidence of an association between breast implants and primary breast cancer. The evidence suggests that women with breast implants may have a small (about 15% to 35%) decreased risk of developing primary breast cancer compared with women without breast implants. The evidence is insufficient regarding the association specifically with silicone gel implants, per se, but a single study is consistent with the studies of all breast implants. The weak strength of the association (<50% reduction in risk) and questions about whether the studies have (or can) sufficiently adjust for important confounders related to how women who choose to undergo breast augmentation differ from the general population in terms of overall health status and family history of breast cancer yield an evidence base that does not provide sufficient evidence to support causality between silicone gel implants and reduced risk of primary breast cancer.

Outcome	Silicone Implants Summary ES (95% CI) [n Studies]	All Implants Summary ES (95% CI) [n Studies]	Conclusion
Cancer, Endometrium	No data	0.55 (0.38, 0.78) [1 study] SIR: 0.44 (P<0.05) 0.73 (0.36, 1.30) [2 studies]	There is limited or suggestive evidence of an association between breast implants and endometrial cancer; however this conclusion is based on only two studies, only one of which provided an inadequately adjusted direct comparison. Women with breast implants may have a large (about 50%) decreased risk of developing endometrial cancer than women without breast implants. The evidence is insufficient regarding the association specifically with silicone gel implants, per se. While the association found in the studies was strong, the evidence base is small, consisting of only two comparative studies in which only 63 women with breast cancer had endometrial cancer and the studies failed to adjust for important possible confounders between the decision to undergo breast implantation and endometrial cancer. The studies do not provide sufficient evidence to determine if a true association exists and, therefore, whether silicone gel implants may have a causal link to endometrial cancer.
Cancer, Lung	1.50 (0.21, 10.7) 2.6 (NS) [2 studies]	1.50 (0.21, 10.7) 2.6 (NS) 1.18 (0.97, 1.44) [3 studies] Ad Adj: 2.6 (NS) SIR: 1.82 (1.37, 2.42) & 1.04 (NS) 0.2 [7 studies]	There is limited or suggestive evidence of an association between breast implants and lung cancer. The evidence suggests that women with breast implants may have about a small (ES <2.0) 80% increased risk of developing lung cancer compared with women without breast implants. However, this conclusion is based largely on SIR data and the only study with an adequate adjustment (probably including smoking status) found a non-significant association (in women with only silicone gel implants). The studies do not provide sufficient evidence to determine if a true association exists and, therefore, whether silicone gel implants may have a causal link to lung cancer.

Outcome	Silicone Implants Summary ES (95% CI) [n Studies]	All Implants Summary ES (95% CI) [n Studies]	Conclusion
CTD, Rheumatoid arthritis	1.42(1.04, 1.95) [3 studies]	1.38 (1.06, 1.80) [11 studies] Ad Adj: 1.3 (0.56, 3.04) 1.9 (1.4, 2.7) [2 studies] SIR: 1.0 (0.6, 1.5) [1 study]	In summary, there is limited or suggestive evidence of an association between breast implants and rheumatoid arthritis. Women with breast implants may have an about 40% increased risk of developing rheumatoid arthritis than women without breast implants, but this summary association is small (ES <2.0) and heterogeneous, warranting a cautious interpretation. The evidence is insufficient regarding the association specifically with silicone gel implants, but these studies are consistent with the studies of all breast implants. The studies do not provide sufficient evidence to determine if a true association exists and, therefore, whether silicone gel implants may have a causal link to rheumatoid arthritis.

Outcome	Silicone Implants Summary ES (95% CI) [n Studies]	All Implants Summary ES (95% CI) [n Studies]	Conclusion
Insufficient Evidence			
Cancer, Brain	0.21 (0.01, 4.15) Ad Adj: 2.9 (0.34, 24.8) [2 studies]	0.76 (0.11, 5.34) [3 studies] Ad Adj: 2.9 (0.34, 24.8) [1 study] SIR: 1.41 (0.91, 2.19) & 0.73 (NS) 0.6 [7 studies]	There is insufficient evidence to determine whether an association exists between breast implants and brain cancer. The associations across studies are not consistent in direction or statistical significance.
Cancer, Cervix	0.16 (0.01, 3.09) [1 study]	1.04 (0.18, 6.00) [3 studies] Ad Adj: 1.78 (0.7, 4.8) [1 study] SIR: 1.58 (0.74, 3.35) & 0.83 (NS) [6 studies]	There is insufficient evidence to determine whether an association exists between breast implants and cervical cancer. The studies were imprecise and found inconsistent associations. Meta-analyses did not yield precise, homogeneous estimates of associations.
Cancer, Hodgkin lymphoma	No data	Ad Adj: 0.11 (0.01,1.21) [1 study] SIR: 1.15 (0.15, 4.16) 0.46 (NS) [2 studies]	There is insufficient evidence to determine whether an association exists between breast implants and Hodgkin lymphoma. The studies found imprecise, inconsistent associations.
Cancer, Leukemia	1.66 (0.28, 9.94) [1 study]	1.66 (0.28, 9.94) 1.34 (0.72, 2.51) [2 studies] Ad Adj: 1.66 (0.28, 9.94) [1 study] SIR: 1.54 (0.45, 4.22) & 0 (0, 7.8) 0.75 (NS) [5 studies]	There is insufficient evidence to determine whether an association exists between breast implants and leukemia. The studies found imprecise, inconsistent associations.
Cancer, Multiple myeloma	No data	0.10 (0.004, 2.4) [1 study] SIR: 0.46 (0.09, 1.33) 0 (NS)	There is insufficient evidence to determine whether an association exists between breast implants and multiple myeloma.

Outcome	Silicone Implants Summary ES (95% CI) [n Studies]	All Implants Summary ES (95% CI) [n Studies]	Conclusion
Cancer, Non-Hodgkin lymphoma	No data	1.03 (0.70, 1.52) 0.55 (0.16, 1.95) [2 studies] Ad Adj: 0.97 (0.53, 1.76) [1 study] SIR: 1.30 (0.63, 2.71) & 0.84 (NS) 0.72 (NS) [6 studies]	There is insufficient evidence to determine whether an association exists between breast implants and non-Hodgkin lymphoma.
Cancer, Uterus	0.2 (0.01, 3.1) [1 study]	0.2 (0.01, 3.1) 0.9 (0.39, 2.09) [2 studies] Ad Adj: 0.9 (0.39, 2.09) [1 study] SIR: 0.74 (0.35, 1.36) 1.15 (NS) [2 studies]	There is insufficient evidence to determine whether an association exists between breast implants and uterine cancer.
Cancer, Vulva	No data	1.24 (0.15, 10.3) [1 study] SIR: 2.51 (1.2, 3.9) 3.14 (1.50, 5.77) [2 studies]	While the two SIR analyses found significant associations, the single direct comparison, which was adequately adjusted found no significant association. Thus, overall, there is insufficient evidence to determine whether an association exists between breast implants and vulvar cancer.
CTD, Amyloidosis	No data	No data	The studies do not provide evidence regarding the association between silicone gel implants and amyloidosis.
CTD, Ankylosing spondylitis	No data	0.63 (0.07, 5.45) 3.16 (0.16, 61.2) [2 studies] SIR: 0.74 (0.35, 1.36) [1 study]	There is insufficient evidence to determine whether an association exists between breast implants and ankylosing spondylitis.
CTD, Chronic fatigue syndrome	No data	2.4 (1.6, 3.6) [1 study]	There is insufficient evidence to determine whether an association exists between breast implants and chronic fatigue syndrome. While a single study found a strong association after adequate adjustment, there are no confirmatory studies.
CTD, Dermatomyositis	No data	1.4 (0.1, 33.2) [1 study] SIR: 3.4 (0.1, 19.1) [1 study]	There is insufficient evidence to determine whether an association exists between breast implants and dermatomyositis.

Outcome	Silicone Implants Summary ES (95% CI) [n Studies]	All Implants Summary ES (95% CI) [n Studies]	Conclusion
CTD, Dermatomyositis & polymyositis	No data	1.97 (0.08, 15.3) [3 studies]	There is insufficient evidence to determine whether an association exists between breast implants and combined dermatomyositis and polymyositis.
CTD, Fibromyalgia	1.08 (0.7, 1.6) [1 study]	1.20 (0.83, 1.72) [4 studies] Ad Adj: 1.3 (0.9, 1.7) [1 study] SIR: 1.6 (0.9, 2.7) [1 study]	There is insufficient evidence to determine whether an association exists between breast implants and fibromyalgia. The studies consistently found small (ES <2.0) non-significant associations, but there is insufficient evidence to distinguish between a real, small association and no association.
CTD, Hashimoto thyroiditis	No data	0.64 (0.03, 13.3) 0.95 (0.45, 2.03) [2 studies]	There is insufficient evidence to determine whether an association exists between breast implants and Hashimoto thyroiditis. The rarity of the outcome resulted in imprecise estimates of any association.
CTD, Mixed CTD	No data	No data	The studies do not provide evidence regarding the association between silicone gel implants and mixed CTD.
CTD, MGUS	0.9 (0.1, 5.5) [1 study]	No data	There is insufficient evidence to determine whether an association exists between breast implants and MGUS.
CTD, Polyarteritis nodosa	No data	0.35 (0.02, 6.57) 1.35 (0.06, 33.2) [2 studies] SIR: 3.1 (0.1, 17.3) [1 study]	There is insufficient evidence to determine whether an association exists between breast implants and polyarteritis nodosa.
CTD, Polymyalgia rheumatica	4.0 (0.2, 98)	3.99 (0.16, 98.2) 2.70 (0.33, 22.5) [2 studies] SIR: 1.4 (0.5, 3.1) [1 study]	There is insufficient evidence to determine whether an association exists between breast implants and polymyalgia rheumatica.
CTD, Polymyositis	No data	1.35 (0.06, 33.2) [1 study]	There is insufficient evidence to determine whether an association exists between breast implants and polymyositis.
CTD, Psoriatic arthritis	No data	0.29 (0.04, 2.24) 0.10 (0.005, 1.99) [2 studies] SIR: 0 (0, 3.2) [1 study]	There is insufficient evidence to determine whether an association exists between breast implants and psoriatic arthritis.
CTD Symptoms, Raynaud syndrome	14.1 (2.96, 67.2) 1.56 (0.60, 4.04) [2 studies]	1.34 (0.97, 1.86) [10 studies] Ad Adj: 1.6 (0.9, 2.8) 1.0 (0.6, 1.8) [1 study; 2 comparisons]	There is insufficient evidence to determine if there is an association between breast implants and Raynaud syndrome. The two adequately adjusted studies yielded conflicting results and the choice of different control groups led to inconsistent conclusions.

Outcome	Silicone Implants Summary ES (95% CI) [n Studies]	All Implants Summary ES (95% CI) [n Studies]	Conclusion
CTD, Sarcoidosis	No data	0.34 (0.02, 5.56) [3 studies] SIR: 0.6 (0.1, 2.1) [1 study]	There is insufficient evidence to determine whether an association exists between breast implants and sarcoidosis. The studies were consistent but imprecise and the meta-analysis did not yield a sufficiently precise estimate to provide sufficient evidence.
CTD, Scleroderma	NS†	1.38 (0.60, 3.17) [9 studies] Ad Adj: 3.0 (0.8, 10.9) [1 study] SIR: 0.8 (0, 4.4) [1 study]	There is insufficient evidence to determine if there is an association between breast implants and scleroderma, particularly silicone gel implants. Studies were inconsistent with each other, but largely imprecise. Meta-analysis failed to provide a sufficiently precise estimate to allow a conclusion of association or lack thereof.
CTD, Sjögren syndrome	6.64 (2.01, 21.9) [1 study]	2.92 (1.01, 8.47) [7 studies] Ad Adj: 11.7 (2.5, 54.9) [1 study] SIR: 1.8 (0.4, 5.4) [1 study]	Overall, there is insufficient evidence to determine if there is an association between breast implants and Sjögren syndrome. While one adequately adjusted study found a large (ES >2.0), significant association, it (and the other study with a strong association) determined outcome based on questionnaire, which may result in bias if women with implants are more likely to incorrectly self-diagnose with Sjögren syndrome than women without implants. Overall, the studies were inconsistent with each other. Meta-analysis of studies based on confirmed diagnoses of scleroderma was imprecise.
CTD, Systemic lupus erythematosus	1.02 (0.82, 1.27) [1 study]	1.28 (0.76, 2.14) [9 studies] Ad Adj: 2.1 (1.1, 4.2) [1 study] SIR: 1.8 (0.7, 3.7) [1 study]	There is insufficient evidence to determine if there is an association between breast implants and SLE, particularly silicone gel implants. While two large studies found a significant doubling of risk, overall the summary estimate is non-significant and these studies were outliers also in having only two-thirds or fewer women with silicone gel implants and also having SLE prevalence rates about 10-times higher than other studies. Furthermore, the higher the percentage of women in the study who had silicone gel implants, the smaller the association between implants and SLE.
CTD, Temporal arteritis	No data	1.4 (0.1, 33) [1 study] SIR: 0.6 (0, 3.4) [1 study]	There is insufficient evidence to determine if there is an association between breast implants and temporal arteritis.

Outcome	Silicone Implants Summary ES (95% CI) [n Studies]	All Implants Summary ES (95% CI) [n Studies]	Conclusion
CTD, Temporal arteritis & polymyalgia rheumatica	No data	0.4 (0.1, 1.4) [1 study]	There is insufficient evidence to determine if there is an association between breast implants and temporal arteritis & polymyalgia rheumatica.
CTD, Undifferentiated CTD	Adj: 2.2 (0.6, 7.6) [1 study]	No data	There is insufficient evidence to determine if there is an association between breast implants and undifferentiated CTD .
CTD, Wegener granulomatosis	No data	No data	The studies do not provide evidence regarding the association between silicone gel implants and Wegener granulomatosis.
Neurologic, Amyotrophic Lateral Sclerosis	No data	No data	The studies do not provide evidence regarding the association between silicone gel implants and amyotrophic lateral sclerosis.
Neurologic, Guillian-Barré Syndrome	No data	1.4 (0.1, 3.3) [1 study]	There is insufficient evidence to determine if there is an association between breast implants and Guillian-Barré syndrome.
Neurologic, Meniere disease	No data	0.80 (0.09, 7.12) 0.8 (0.3 2.2) [2 studies] SIR: 0.8 (0.2, 2.5) [1 study]	There is insufficient evidence to determine if there is an association between breast implants and Meniere disease.
Neurologic, Mononeuritis	No data	NS†	There is insufficient evidence to determine if there is an association between breast implants and mononeuritis.
Neurologic, Motor neuropathy	No data	0.5 (0.02, 8.8) [1 study]	There is insufficient evidence to determine if there is an association between breast implants and motor neuropathy.
Neurologic, Multiple sclerosis	No data	1.33 (0.18, 9.68) [4 studies]	There is insufficient evidence to determine if there is an association between breast implants and multiple sclerosis.
Neurologic, Myasthenia gravis	No data	0.5 (0.02, 8.8) [1 study]	There is insufficient evidence to determine if there is an association between breast implants and myasthenia gravis.
Neurologic, Optic neuritis	No data	No data	The studies do not provide evidence regarding the association between silicone gel implants and optic neuritis.
Neurologic, Optical retinopathy and neuropathy	No data	0.6 (0.03, 13) [1 study]	There is insufficient evidence to determine if there is an association between breast implants and optical retinopathy and optical retinopathy and neuropathy.
Neurologic, Peripheral neuropathy	No data	0. 8 (0.5, 1.3) [1 study]	There is insufficient evidence to determine if there is an association between breast implants and optical retinopathy and peripheral neuropathy.
Offspring, Cancer	No data	0.3 (0.04, 2.5) [3 studies]	There is insufficient evidence to determine if there is an association between breast implants and cancer among the women's offspring.

Outcome	Silicone Implants Summary ES (95% CI) [n Studies]	All Implants Summary ES (95% CI) [n Studies]	Conclusion
Offspring, Congenital malformations, Any	1.5 (nd) NS [2 studies]	1.5 (nd) NS 1.22 (0.89, 1.67) 1.0 (0.6, 1.5) [4 studies]	There is insufficient evidence to determine if there is an association between breast implants and congenital malformations among the women's offspring.
Offspring, Congenital malformations, gastrointestinal Organs	No data	0.97 (0.54, 1.74) 0.5 (0.2, 1.3) [2 studies]	There is insufficient evidence to determine if there is an association between breast implants and congenital malformations of gastrointestinal organs among the women's offspring.
Offspring, Esophageal malformations	No data	0.80 (0.33, 1.93) 1.0 (0.7, 1.6) [2 studies]	There is insufficient evidence to determine if there is an association between breast implants and esophageal malformations among the women's offspring.
Offspring, Low birth weight	No data	NS (1 study) 3 definitions (1 study): 1.44 (0.58, 3.63)‡ 1.43 (0.90, 2.29)§ 1.01 (0.51, 2.00)|| [2 studies]	There is insufficient evidence to determine if there is an association between breast implants and low birth weight among women's offspring.
Offspring, NICU Admission	No data	NS [1 study]	There is insufficient evidence to determine if there is an association between breast implants and the need for neonatal intensive care among women's offspring.
Offspring, Perinatal death	No data	0.33 (0.05, 2.42) 0.9 (0.5, 1.8) [2 studies]	There is insufficient evidence to determine if there is an association between breast implants and perinatal death among women's offspring.
Offspring, Preterm	No data	NS 1.28 (0.83, 1.96) [2 studies]	There is insufficient evidence to determine if there is an association between breast implants and preterm delivery.
Offspring, Pyloric stenosis	No data	0.6 (0.2, 2.1) [1 study]	There is insufficient evidence to determine if there is an association between breast implants and pyloric stenosis among women's offspring.
Offspring, Rheumatic disease	No data	1.51 (0.62, 3.65) 1.1 (0.2, 5.3) [2 studies]	There is insufficient evidence to determine if there is an association between breast implants and rheumatic diseases in offspring.
Psychiatric, Depression	2.3 (0.9, 6.0) [1 study]	2.27 (0.85, 6.03) 1.2 (0.7, 1.9) 1.3 (0.8, 2.2) [2 studies, 3 comparisons]	There is insufficient evidence to determine if there is an association between breast implants and the risk of depression.

Outcome	Silicone Implants Summary ES (95% CI) [n Studies]	All Implants Summary ES (95% CI) [n Studies]	Conclusion
Psychiatric, Suicide	No data	2.85 (0.77, 10.55) [5 studies] SMR: 1.99 (0.89, 4.43) [3 studies]	There is insufficient evidence to determine if there is an association between breast implants and the risk of suicide. Women with breast implants may have a two- to three-times higher risk of committing suicide. However, it is reasonable to conclude that the association is actually between the decision to have breast augmentation and the risk of suicide, rather than between the implant itself and suicide. It is difficult to fully adjust for the psychosocial aspects (psychological, societal, and interpersonal) that may confound the association. None of the studies adjusted for possible confounders beyond age, race, and time since surgery, none of which account for the underlying differences between women who choose to have breast implants and those who do not. Furthermore, none of the studies investigated the possible causes of suicide among the women.
Reproduction, Any Issues	No data	No data	The studies do not provide evidence regarding the association between silicone gel implants and overall problems with reproductive outcomes.
Reproduction, Lactation	0.94 (nd) vs. saline [1 study]	0.94 (nd) vs. saline 23.4 (6.17, 88.8)	The evidence is insufficient to determine if there is an association between breast implants and difficulties with lactation.
Reproduction, Miscarriage	1.3 (nd) [1 study]	1.3 (nd) 1.4 (1.0, 2.1) 1.3 (0.9, 2.0) 0.9 (0.4, 2.1) [3 studies, 4 comparisons]	The evidence is insufficient to determine if there is an association between breast implants and miscarriage.

Abbreviations: ; Ad Adj = studies with adequate adjustment (findings not noted to have adequate adjustment were based on either unadjusted or inadequately adjusted associations); CI = confidence interval; CTD = connective tissue disease; ES = effect size (e.g., odds ratio); MGUS =monoclonal gammopathy of undetermined significance; NICU =neonatal intensive care unit; NS = non-significant; SIR = standardized incidence (or mortality or hospitalization) ratio.

* Symptoms of CTD, rheumatologic, and auto-immune diseases and neurologic symptoms omitted, except for Raynaud syndrome
† Non-significant. See Scleroderma and Mononeuritis results tables.
‡ <1500 g
§<2500 g
|| Small for gestational age

Lack of Adequate Adjustment

The non-significant, but strong association (ES >2) between breast implants and suicide may highlight a fundamental flaw in the evidence for the risks of silicone gel implants, and breast implants, in general. It is highly likely that women who choose to have breast implants, particularly for augmentation, are fundamentally different than women without implants. Several researchers, including those who conducted the larger, better analyzed studies included in this review, have shown that women who choose to undergo breast implantation (either for cosmetic augmentation or for breast reconstruction) are different in many ways from women who do not have breast implants. Four examples include the Swedish Inpatient Register,[105] the Denmark Private study,[71] the South 18 Centers study,[103] and the Atlanta/Seattle/NJ study (together with other data from Washington State).[104] The studies consistently found that women with breast implants were thinner and more likely to have had induced abortions than women without implants (either general population or who had undergone other cosmetic surgery). Individual studies found that women with implants were more likely to be white, to have been screened for breast cancer, to have used hair dyes, and to have more sexual partners. Some studies found associations that others failed to find, including increased tobacco and alcohol use, more live births, younger age at first birth, hormone use, lower education level, or never married. Regardless of the specific differences between women with and without breast implants, it appears clear that women who undergo breast implantation have underlying differences from the rest of the population that may put them at increased (or possibly decreased) risk for all the outcomes of interest. Some of these differences may be difficult to measure, for example, whether there may be personality, psychological, or social support differences that may explain the association of breast implants with suicide, an outcome for which it is particularly unlikely that silicone causes suicidal ideation. One study comparing breast augmentation candidates with physically similar women not interested in breast augmentation found that those who wanted implants had greater distress about their appearance in a variety of situations, more frequent teasing about their appearance, and more frequent use of psychotherapy in the year before the operation.[109]

In theory, randomized controlled trials could balance out the non-implant related differences, but these studies are neither ethical nor feasible, as women would not submit to receiving or withholding an implant based on randomization. Observational studies, though, need to be analyzed appropriately for their conclusions to be valid. However, for most outcomes, a large proportion of the studies reported only raw counts of events (e.g., 3 of 817 women committed suicide) or unadjusted RRs or ORs, which do not account for any possible confounders. The suicide outcome provides a good example of this problem. Of the six comparative studies, three reported only unadjusted results. The two studies of direct comparisons with a control group that adjusted their findings and the three that estimated SMRs all adjusted for age alone (the SMR estimates), or age, time since implantation, and in one study race, and one study province of residence. None of the studies adjusted for a wide range of likely more important confounders between breast implantation and suicide, including those found to differ within the same studies being analyzed for suicide. Therefore, for all studies, it is reasonable to conclude that the nearly tripled risk of suicide among women with breast implants could be explained by the possibility that women who choose to have an implant may inherently be at higher risk of suicide than women who do not get implants and, thus, that the association with implants, per se, is spurious,

or at least not due to the implant itself. Unfortunately, the evidence does not allow a valid estimate of the true association one way or the other.

Similarly, none of the studies of cancer, and for lung cancer in particular, explicitly adjusted for tobacco use or family history of cancer (though two studies reported adjusting for "predictors of cancer" or "extraneous variables"). As noted above, women with breast implants are more likely to smoke, may be at higher risk of cancer for other reasons, and may be less likely to have a family history of breast cancer (due to self-selection and the perceived difficulties with diagnosing breast cancer). These deficiencies are fundamental flaws in the analyses of associations in non-randomized, observational studies.

Only nine of the comparative studies adjusted for possible confounders beyond basic data such as age, time since implantation, and sometimes race. However, even these mostly considered only a small number of potential confounders or poorly reported what factors were adjusted for (e.g., "predictors of cancer).

Assessment of the Possibility of Causality

In 1965, Sir Austin Bradford Hill proposed criteria as considerations to best determine whether associations found in observational studies are likely to describe causation.[19] These included assessments of the strength, consistency, specificity (between factor and effect), temporality (the effect occurring after the exposure, with a reasonable delay), biological gradient, plausibility, coherence (between epidemiological and laboratory findings), experiment (if possible), and analogy (with other exposure risks) of the association between the exposure and the effect. We addressed the first five criteria, for which observational studies of humans can provide evidence. We evaluated these considerations both within individual studies and across studies for each outcome. Neither within studies nor across studies was evidence reported to allow an assessment of "biological gradient" as either "dose" of exposure based on implant size (and silicone gel volume) or as a within-women change in exposure (and risk of outcome) after removal of implants. Few studies directly evaluated consistency by comparing effects in different groups of women. In evaluating consistency across studies, where we found statistical homogeneity (i.e., consistency in effect) across studies, this usually could be explained more by the imprecision of the estimates and resulting large 95% CIs than by consistency in the actual estimates of effect. As discussed, most studies did not provide sufficient evidence for specificity since most evaluated women with any breast implant with as few as 50% of them being made of silicone gel. Temporality was also a concern for a number of outcomes, particularly CTD and CTD symptoms, where some studies did not clearly analyze new diagnoses from the time since implantation, rather than prevalent diagnoses, regardless of when the diagnosis was made. However, by meta-regression, no differences were found among studies that clearly included only incidence outcomes (since the time of implantation) and those that may have also included outcomes that were prevalent at the time of implantation. Only one study, the Mentor Post-Approval Study, in its finding for Sjögren syndrome found a strong association for a new diagnosis in women who all had silicone gel implants.[59] However, this finding is flawed in relation to providing evidence for causality as it is based on an unadjusted comparison with a historical control for which no information is provided (including outcome risk) and the outcome was derived from a patient questionnaire.

Within-Study Subgroup Analyses

Six studies reported subgroup analyses or interactions between the association of breast implant and outcomes and patient characteristics. These included the South 18 Centers study (for cancers, rheumatologic diseases, and suicide),[31,32,94] the Ontario/Quebec study (for cancers and suicide),[34,100] the Sweden/Denmark Public-Private study (for cancers),[77] the Atlanta/Seattle/NJ and Finland Hospital studies (for breast cancer),[29,63] and the Denmark Public Private study (for suicide).[66] In addition, the Allergan, Mentor, and Sientra reports to the U.S. FDA and Health Canada provide event counts by women having primary augmentation, revision augmentation, primary reconstruction, and revision reconstruction. However, no analyses across these groups were reported.

The studies reporting subgroup analyses evaluated, in order of frequency, age at implantation, year of implantation, and duration of follow-up; implant type, polyurethane vs. silicone coating, fill volume; and in one analysis bra cup size pre-implantation and body mass index. For almost all subgroup analyses, no evidence for a difference in association based on the subgroup characteristic was found. For lung cancer, one study found an apparent trend related to years since implantation (higher association after longer follow-up), but the interaction was non-significant and two other studies found no evidence of an interaction. Similarly, for suicide, one study found that the SMR was highest among women who had their implants when they were 40 years old or older, but the potential difference was not statistically analyzed and a second study found no interaction by age.

The studies did not provide sufficient data to allow meaningful evaluations of differences in association based on whether implants are currently FDA approved, whether implants were used for reconstruction or augmentation, whether implants were revised or removed and not replaced, type of gel, smooth versus textured shell surfaces, anatomic versus round shells, or manufacturer or brand.

Across-Study Subgroup Analyses

In general, across-study subgroup analyses (including meta-regression and cumulative meta-analysis) need to be interpreted with caution. These analyses look for statistical differences in results between studies with different characteristics and then hypothesize that the differences found are related to the factor being analyzed, even though the studies may differ from each other in numerous ways including underlying differences in study eligibility criteria and setting (resulting in both implicit and explicit differences in populations), differences in exposure (e.g., the details of the the breast implants and surgical techniques used), how the outcomes were assessed (e.g., by questionnaire, examination, or medical record; blinded or unblended), and how analyses were conducted (whether adjusted, which factors were adjusted for, and what metrics and models were used). When there are few studies to analyze, and especially when only one or two studies have a given subgroup feature (such as questionnaire versus registry outcome data), ascribing any difference found between subgroups to the factor being analyzed may be particularly prone to misinterpretation. Another important caveat to analyzing subgroups of studies is that one can only meaningfully analyze study level characteristics. Evaluating patient-level characteristics (e.g., age, bra cup size, smoking status) across studies is inappropriate and can result in ecological fallacy, where differences in mean characteristics (e.g., mean age) across studies are erroneously ascribed to individual people.[110]

Since most comparative studies evaluated all women with breast implants (or occasionally with silicone gel implants, specifically) within their cohort, regardless of specific type of implant, implant material, other implant characteristics, or patient characteristics, there were very few study features that could be analyzed across studies (or across reported subgroups from within studies). No features specific to the implants or to the women could be appropriately analyzed.

Cumulative meta-analysis suggests that any association of an increased risk for Raynaud syndrome that may exist might may stabilize at about 12 years after implantation. However, since the evidence overall is not sufficient to conclude that an association exists, interpretation of this finding is difficult. Similarly, cumulative meta-analysis of joint pain (arthralgia) suggests that the symptom was less common in cohorts of women who had their implants more recently (in the later 1990s), but again the evidence overall was insufficient for this outcome.

Meta-regression did not find significant differences in associations for any outcome in regards to duration of follow-up, year of last implantation (within a cohort), or whether outcomes were clearly incident (to the time of implantation) or may have included prevalent disease or symptoms (at the time of implantation). This latter factor was of particular concern for some connective tissue diseases and for symptoms which often relied on questionnaire data for outcomes. For three outcomes, significant differences (or trends; i.e., $P<0.10$) were found between studies that ascertained their outcomes by registry, medical record data, or physical examination versus outcomes derived from patient questionnaires. These included scleroderma, Sjögren syndrome, and joint pain (arthralgia). In all cases, the studies that used questionnaire data found larger (stronger) associations. This is what would be expected if there is a concern that women with breast implants, who may be concerned about the health implications of the implants, are more likely to self-diagnose conditions or be bothered by symptoms that they may ascribe to the implants.

Comparison with Previous Systematic Reviews

To put our findings into context, we searched MEDLINE for recent existing reviews on this topic. Our review findings mostly concur with existing systematic reviews that focused on association between any breast implantation and clinical outcomes. However, in this review, use of the more inclusive category or "limited or suggestive evidence of an association" resulted in conclusions somewhat more favorable toward possible associations. In addition, where this review generally concluded that there is insufficient evidence to determine whether associations exist, the previous systematic reviews that found no significant associations generally concluded that there is no association. This review considered that conclusion only when there was convincing evidence of no association; which was not found for any outcome.

Our review findings mostly concur with those of existing systematic reviews that focused on associations between any breast implantation and health outcomes. A 2004 systematic review of brain cancer by McLaughlin et al.[111] concluded that the evidence did not support an association between breast implants and brain cancer incidence. Our review included twice as many brain cancer studies, including from North America, but similarly found a lack of evidence to support an association. In 2011, Lipworth et al.[112] firmly concluded that there is no association with increased occurrence of CTDs. This review did not report tabulated data, did not conduct statistical analyses, and largely relied on the statistical significance of individual studies.

The 2011 FDA review is the most recent comprehensive review before ours, but it reported on a narrower range of cancer types and CTDs, did not conduct meta-analyses or other statistical analyses across studies, and largely reviewed the evidence in a narrative fashion.[13] We have also added more recently reported studies and analyses. Similar to our findings, the FDA review found that women who received silicone gel implants for augmentation may be at lower risk for breast cancer, but the review did not report on endometrial cancer. It cautiously concluded that the evidence did not support an association between silicone gel implants and CTD, but did not report on specific diseases. In our disease-specific analysis, we conclude that there may be suggestive evidence of associations with rheumatoid arthritis. It concluded that there was no significant evidence to suggest harms by silicone gel implants on pregnancy or fertility or a causal relationship with adverse health outcomes in children born to women with implants, but this was based primarily on only four disparate studies and studies of silicon concentrations in breast milk; we did not find sufficient studies to form a conclusion.

The FDA review also found that studies consistently suggest an increased rate of suicide among women with breast implants compared with the general population.[13] Although our review does not disagree, our meta-analysis does not support a significant association.

Potential Future Analyses

Re-analyses of existing or ongoing studies could overcome many of the flaws in the current evidence base. In particular, the evidence is very weak for associations specific to women with silicone gel implants, since few comparative studies have been restricted to this implant type. Larger, well-established studies that evaluated all breast implants should be re-analyzed specifically for those women with silicone gel implants, either standard silicone gel implants or double lumen implants (where the silicone gel implant is within a saline implant). If a sufficient number of women in the study have double lumen implants, subgroup analyses by implant type would be appropriate. The Scandinavian studies (particularly from Denmark and Sweden, which mostly had about 84% of women with silicone gel implants) and the South 18 Center study (with 50% silicone gel implants) are large datasets with long-term follow-up and apparently detailed information about the enrolled women and their clinical outcomes. Re-analyses of these studies, in particular, would be of great value. Better would be the possibility of conducting an individual participant-level meta-analysis of these large datasets (and maybe others). This type of analysis would require the participant-level data from each study but would allow more complex analyses than is feasible by standard meta-analysis, such as consistent adjustment for possible confounders and participant-level subgroup analyses (such as by participant age or weight).

Even if participant-level meta-analysis is not feasible, re-analyses of existing data and new analyses of ongoing and future studies need to conduct more appropriate adjustment for possible confounders than has been done to date. The list of possible confounders included in analyses should be as complete as the data allow. The analyses should account for both the underlying differences between women who choose to have breast implants (whether for augmentation or reconstruction) and women who do not have implants, such as age, race, weight, smoking, socioeconomic factors, and psychosocial and interpersonal relationship features. They should also account for predictors of each outcome, such as family history of disease, cancer risk factors, or predictors of specific (or general) rheumatologic conditions. They should not be restricted, as has been the case to date, to age, geographic location, year of implant, and race.

While these may be confounders for some outcomes, there are numerous other factors that could be important confounders.

Other Limitations

Beyond the concerns regarding the evidence already discussed, there were additional limitations to the systematic review and our ability to adequately analyze the data. Studies, particularly older publications, very commonly provided only limited descriptions of the implants that women received, including information related to implant type (silicone gel, double lumen, saline, etc.), silicone gel implant generation, implant manufacturer or brand, shell type (textured, smooth, polyurethane-coated, etc.), shape (round or anatomic), etc. There were generally only limited or difficult-to-interpret data describing the women; however, based on where the studies were conducted and how women were enrolled, the bulk of the evidence appears to be applicable to women in the U.S. and northern Europe. The applicability, though, may not extend well to African American women or women of Asian ancestry since few such women were included in studies and none of the studies were conducted in Asia. In addition, to determine whether the current evidence is applicable to the current generation of silicone gel implants, we will need to wait for longer-term follow-up results from the post-approval comparative studies of approved silicone gel implants from Allergan, Mentor, and Sientra. It may be that the older generations of implants may be more prone to leakage and rupture, which may suggest that the current evidence provides a worst-case scenario for positive associations with outcomes compared with newly placed implants. Most of the data from large studies currently is based on implants put in before the mid-1990s. We believe that our inclusion criteria and search were comprehensive and that we included all published observational studies of women with breast implants and outcomes of interest. However, there are likely to be other important data that are not publicly available from implant manufacturers or possibly known to the FDA and other national regulatory agencies.

Our review is the most comprehensive to date, but it has several review-specific limitations. First, because of differences across studies in how data were analyzed, we could not meta-analyze a standard metric (such as an adjusted hazard ratio) but instead had to combine metrics into an ES. We decided that quantitative estimates of summary effects would provide better insights regarding the likelihood of a true association than only recapitulating the individual studies.

Second, while our review included a broad range of health outcomes, we restricted it to silicone gel breast implants. We excluded the Poly Implant Prothèse implant, which was manufactured with industrial-grade, not medical-grade, silicone, and was recalled. We also did not consider injectable silicone, which can migrate systemically and is not FDA approved. Findings of adverse health effects from defective implants or from injectable silicone would not be clearly applicable to the determination of possible health outcomes related to silicone breast implants.

Third, on the basis of discussions with our advisory panel, we did not evaluate ALCL, an extremely rare type of non-Hodgkin lymphoma. As of 2011, the FDA was aware of about 60 cases of ALCL among 5 to 10 million women with breast implants worldwide.[113] However, only about 3 in 100 million women per year are diagnosed with ALCL in the breast per year.[114] Largely on the basis of this comparison, the FDA concluded there is a possible association between breast implants and ALCL. Because of the rarity of the disease, the FDA concluded that

a study would need to collect data on hundreds of thousands of women for more than 10 years to confirm an association.[113] In part with this goal in mind, the FDA is collaborating with the ASPS to establish a national breast implant registry for post-market surveillance of all breast implants, with a particular interest in ALCL.[15]

Finally, our review would ideally have been restricted to studies of only silicone gel implants, but as noted, few studies evaluated only women with these implants; most did combined analyses with saline-filled implants. Thus, any findings of associations are most applicable to women with breast implants in general, not specifically with silicone gel implants. However, all implants expose women to silicone because they are usually made with silicone elastomer shells. We were interested in possible differences in health outcomes between silicone gel and saline implants (which also have silicone elastomer shells), but only a single study reported this comparison, for reproductive and offspring outcomes only.[58]

Conclusion

Originally, concerns about cancer and connective tissue disorder arose from studies conducted in animals.[6-8] Despite concerns that the silicone gel implant or leaking silicone implants can lead to a variety of health problems, including cancers, autoimmune diseases, connective tissue disorders, and neurological diseases,[4,5] it was recognized that there were limited data on rare events and there was no evidence that silicone breast implants caused systemic health effects such as cancer or autoimmune disease.[3]

The current systematic review finds that, to date, the body of evidence on breast implants does not provide strong, conclusive evidence regarding whether silicone gel implants affect the risk of developing any of the outcomes analyzed in this review. For none of the outcomes was there sufficient evidence of an association. Furthermore, none of the studies provide sufficient evidence to support causality between silicone gel implants and any of the analyzed diseases, conditions, or symptoms. In brief, for most outcomes there were no studies that adequately adjusted for potential confounders between having breast implantation and the outcomes (such as psychosocial factors or risk factors for the outcomes) beyond age, time since implantation, and the like. For several outcomes there was a single adequately adjusted study, which usually had a non-significant association. Only for primary breast cancer and rheumatoid arthritis, were there two adequately adjusted studies. No study found a strong association (ES $\geq$2.0 or $\leq$0.5) in a population specific to silicone gel implants for an outcome that definitively newly occurred after implantation. None of the studies restricted to women with silicone gel implants were adequately adjusted.

For four outcomes, we concluded that the studies were sufficient to conclude that there is (only) limited or suggestive evidence of association between breast implants and the outcome. These include lung cancer, for which there may be about a 50% to 80% increased risk compared with the general population, and rheumatoid arthritis, for which there may be about a 40% increased risk; and primary breast cancer and endometrial cancer, for which there may be a inverse association (ES <1.0). However, there were flaws in the studies or sufficient inconsistencies among studies that all these outcomes require further investigation, either by the existing studies or in new studies, to determine whether a true association exists.

For all outcomes, better evidence is needed. It is likely that existing large studies can be re-analyzed to clarify the strength of associations between silicone gel implants and outcomes. These re-analyses should focus exclusively on silicone gel implants (and double lumen

implants), account for differences in implant type (e.g., generation), and most importantly, adequately and fully adjust for important possible confounders between receiving a breast implant and the outcome. Future analyses of the ongoing comparative studies in North America by the major implant manufacturers should also analyze and report their results fully and appropriately.

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APPENDIX A. Literature Searches

Searches conducted in OVID Medline, Cochrane Central, and Ovid HealthStar on 9/17/2013

Connective Tissue Diseases, Rheumatologic, Auto-Immune, Neurologic Diseases and Symptoms

#	Searches
1	exp breast implants/ or exp breast implantation/ or (breast adj3 implant$).af.
2	(breast and (augment$ or reconstruct$ or remov$ or revis$ or replant$ or replace$ or lift or enlarge$)).af.
3	(*breast/ and surgery, plastic/) or breast/su
4	exp mammaplasty/ or mammaplasty.af. or mammoplasty.af.
5	implants, artificial/ or prosthesis/
6	(2 or 3 or 4) and 5
7	exp silicones/ or (silicone$ and gel).af. or silicone$.af. or silicone-filled.tw. or gel-filled.tw.
8	breast/ or breast$.af.
9	(Natrelle or MemoryGel or MemoryShape or Sientra).tw.
10	(7 and 8) or (7 and 9)
11	1 or 6 or 10
12	autoimmune.af. or exp lupus/ or lupus.af.
13	exp connective tissue diseases/ or connective tissue.af.
14	exp cartilage diseases/
15	exp collagen diseases/
16	(cutis laxa or dupuytren's contracture or homocystinuria or marfan or mixed connective or mucinoses or noonan or osteopoikilosis or pseudoxanthoma or mctd or sclerosis-like or scleroderma or arthralgia or polyarthralgia or myalgia).af.
17	exp irritable bowel syndrome/ or irritable bowel.af.
18	(Rheumatological or rheumato$).af.
19	exp raynaud disease/ or raynaud.af.
20	exp arthritis, rheumatoid/
21	(rheumatic or fatigue or fibromyalgia or sjogren).af.
22	exp fibromyalgia/
23	exp chronic fatigue syndrome/
24	(polymyalgia or pain or myalg$ or fibrositis or polychondritis or angitis or vasculitis or arteritis or phlebitis or behcet$ or churg-strauss or wegener$ or mucocutaneous lymph).af.
25	(thrombophlebitis or thromboangiitis).af.
26	exp inflammatory bowel diseases/
27	(crohn$ or colitis or ileitis or enteritis or rectocolitis or proctocolitis or inflammatory bowel).af.
28	or/12-27
29	exp nervous system diseases/ or (nerv$ or neur$).af.
30	exp amyotrophic lateral sclerosis/ or amyotrophic.af.
31	lou gehrig's disease.af.
32	exp multiple sclerosis/ or (multiple adj sclerosis).af.
33	exp myasthenia gravis/ or (myasthenia and gravis).af.
34	exp polyradiculoneuropathy, chronic inflammatory demyelinating/
35	exp guillain-barre syndrome/ or guillain-barre.af.
36	exp neuritis/ or (motor and neuropathy).af.

#	Searches
37	exp myositis/ or myositis.af.
38	exp polymyositis/ or polymyositis.af.
39	exp dermatomyositis/ or dermatomyositis.af.
40	exp myositis, inclusion body/ or (myositis and inclusion).af.
41	exp headache/ or headach$.af.
42	or/29-41
43	(exp skin/ or skin.af.) and nodule$.af.
44	(limited and (mobility or function$)).af.
45	exp anorexia/ or anorexia.af. or (loss and appetite).af.
46	(exp spasm/ or (spasm$ or tight$).af.) and muscle.af.
47	exp photophobia/ or (photophobia or (sensitivity and light)).af.
48	exp hydrarthrosis/ or (hydrarthrosis or (joint and effusion)).af.
49	exp pharyngitis/ or pharyngitis.af.
50	(sore and throat).af.
51	(vertigo or dizziness or (balance and problem)).af.
52	(tingling or burning).af.
53	attention deficit.af.
54	exp insomnia/ or (insomnia or sleep).af.
55	or/43-54
56	exp neck/ or (neck or cervical).af.
57	exp lymphatic diseases/ or (lymphatic or lymphadenopathy).af.
58	56 and 57
59	exp joints/ or joint$.af.
60	exp edema/ or (edema$ or tender$ or swelling or swollen or redness or warm$ or stiff$).af.
61	59 and 60
62	28 or 42 or 55 or 58 or 61
63	11 and 62
64	exp breast implants/ or exp breast implantation/ or (breast adj3 implant$).af.
65	(breast and (augment$ or reconstruct$ or remov$ or revis$ or replant$ or replace$ or lift or enlarge$)).af.
66	exp mammaplasty/ or mammaplasty.af. or mammoplasty.af.
67	(*breast/ and surgery, plastic/) or breast/su
68	implants, artificial/ or prosthesis/
69	(65 or 66 or 67) and 68
70	exp silicones/ or (silicone$ and gel).af. or silicone$.af. or silicone-filled.tw. or gel-filled.tw.
71	breast/ or breast$.af.
72	(Natrelle or MemoryGel or MemoryShape or Sientra).tw.
73	(70 and 71) or (70 and 72)
74	64 or 69 or 73
75	exp carcinoma/ or carcinoma.tw.
76	exp neoplasm/ or cancer.tw.
77	exp brain neoplasms/
78	(brain and tumor).tw.
79	exp astrocytoma/ or astrocytoma.tw.
80	exp gliobastoma/ or glioblastoma.tw. or glioma.tw.

#	Searches
81	exp oligodendroglioma/ or oligodendroglioma.tw.
82	exp meningioma/ or meningioma.tw.
83	exp ependymoma/ or ependymoma.tw.
84	exp lung neoplasms/ or (lung adj2 cancer).tw.
85	exp carcinoma, bronchogenic/
86	exp lymphoma/ or lymphoma.tw.
87	exp hodgkin disease/ or hodgkin.tw.
88	exp uterine cervical neoplasms/ or (uterine and cervical and neoplasm$).tw.
89	exp vulvar neoplasms/ or (vulvar or neoplasm$).tw. or (vulvar and cancer).tw.
90	((gynecolog$ or gynaecolog$) and (neoplasm$ or cancer)).tw.
91	exp lymphatic vessels/ and (neoplasm$ or cancer).tw.
92	or/75-91
93	((breast and feed$) or breastfeed$ or (breast and fed) or breastfed).af.
94	((breast adj2 fed) or (breast adj2 feed)).tw.
95	exp lactation/ or lactat$.af.
96	exp mastitis/ or mastitis.af.
97	93 or 94 or 95 or 96
98	exp pregnancy/ or pregnancy.af.
99	exp gravidity/ or gravid$.af. or (pregnant or pregnan$).af.
100	exp abortion, spontaneous/ or miscarriage.af.
101	(gestation$ or ectopic).af. or exp pregnancy, ectopic/
102	exp parturition/ or exp premature, birth/ or preterm.af. or premature.af.
103	exp stillbirth/ or stillbirth.af. or stillborn.af.
104	exp reproduction/ or reproduction.af.
105	exp eclampsia/ or eclampsia.af. or exp pre-eclampsia/ or (pre adj1 eclampsia).tw.
106	exp hypertension, pregnancy-induced/ or (hypertension and pregnancy-induced).mp. or (gestational and hypertension).af. or gestational hypertension.af.
107	or/98-106
108	exp congenital abnormalities/ or (congenital and abnormalities).af.
109	exp cleft lip/ or exp cleft palate/ or (cleft and palate).af. or (cleft and lip).af.
110	exp down syndrome/ or (down and syndrome).af.
111	exp heart defects, congenital/ or (heart and defects).af. or congenital heart defect$.af.
112	exp anencephaly/ or anencephaly.af.
113	(exp heart/ or heart.af. or cardiac.af.) and defect$.af.
114	exp spinal dysraphism/ or (spinal and dysraphism).af. or (spinal and bifida).af.
115	or/108-114
116	adverse effect$.sh. or complication$.af.
117	exp suicide/ or suicide.af.
118	(suicide and ideation).af. or exp suicidal ideation/ or (suicidal and tendency).af.
119	((suicid$ and ideation) or (suicid$ and tendency)).af.
120	exp depressive disorder/ or exp depression/ or (depressi$ and disorder).af. or depression.af.
121	or/116-120
122	74 and (92 or 97 or 107 or 115 or 121)
123	63 not 122
124	remove duplicates from 123

Searches conducted in OVID Medline, Cochrane Central, and Ovid HealthStar on 9/3/2013

Cancer, Reproduction, Offspring, Mental Health

#	Searches
1	exp breast implants/ or exp breast implantation/ or (breast adj3 implant$).af.
2	(breast and (augment$ or reconstruct$ or remov$ or revis$ or replant$ or replace$ or lift or enlarge$)).af.
3	exp mammaplasty/ or mammaplasty.af. or mammoplasty.af.
4	(*breast/ and surgery, plastic/) or breast/su
5	implants, artificial/ or prosthesis/
6	(2 or 3 or 4) and 5
7	exp silicones/ or (silicone$ and gel).af. or silicone$.af. or silicone-filled.tw. or gel-filled.tw.
8	breast/ or breast$.af.
9	(Natrelle or MemoryGel or MemoryShape or Sientra).tw.
10	(7 and 8) or (7 and 9)
11	1 or 6 or 10
12	exp carcinoma/ or carcinoma.tw.
13	exp neoplasm/ or cancer.tw.
14	exp brain neoplasms/
15	(brain and tumor).tw.
16	exp astrocytoma/ or astrocytoma.tw.
17	exp gliobastoma/ or glioblastoma.tw. or glioma.tw.
18	exp oligodendroglioma/ or oligodendroglioma.tw.
19	exp meningioma/ or meningioma.tw.
20	exp ependymoma/ or ependymoma.tw.
21	exp lung neoplasms/ or (lung adj2 cancer).tw.
22	exp carcinoma, bronchogenic/
23	exp lymphoma/ or lymphoma.tw.
24	exp hodgkin disease/ or hodgkin.tw.
25	exp uterine cervical neoplasms/ or (uterine and cervical and neoplasm$).tw.
26	exp vulvar neoplasms/ or (vulvar or neoplasm$).tw. or (vulvar and cancer).tw.
27	((gynecolog$ or gynaecolog$) and (neoplasm$ or cancer)).tw.
28	exp lymphatic vessels/ and (neoplasm$ or cancer).tw.
29	or/12-28
30	((breast and feed$) or breastfeed$ or (breast and fed) or breastfed).af.
31	((breast adj2 fed) or (breast adj2 feed)).tw.
32	exp lactation/ or lactat$.af.
33	exp mastitis/ or mastitis.af.
34	30 or 31 or 32 or 33
35	exp pregnancy/ or pregnancy.af.
36	exp gravidity/ or gravid$.af. or (pregnant or pregnan$).af.
37	exp abortion, spontaneous/ or miscarriage.af.
38	(gestation$ or ectopic).af. or exp pregnancy, ectopic/
39	exp parturition/ or exp premature, birth/ or preterm.af. or premature.af.
40	exp stillbirth/ or stillbirth.af. or stillborn.af.

#	Searches
41	exp reproduction/ or reproduction.af.
42	exp eclampsia/ or eclampsia.af. or exp pre-eclampsia/ or (pre adj1 eclampsia).tw.
43	exp hypertension, pregnancy-induced/ or (hypertension and pregnancy-induced).mp. or (gestational and hypertension).af. or gestational hypertension.af. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, sh, kw]
44	or/35-43
45	exp congenital abnormalities/ or (congenital and abnormalities).af.
46	exp cleft lip/ or exp cleft palate/ or (cleft and palate).af. or (cleft and lip).af.
47	exp down syndrome/ or (down and syndrome).af.
48	exp heart defects, congenital/ or (heart and defects).af. or congenital heart defect$.af.
49	exp anencephaly/ or anencephaly.af.
50	(exp heart/ or heart.af. or cardiac.af.) and defect$.af.
51	exp spinal dysraphism/ or (spinal and dysraphism).af. or (spinal and bifida).af.
52	or/45-51
53	adverse effect$.sh. or complication$.af.
54	exp suicide/ or suicide.af.
55	(suicide and ideation).af. or exp suicidal ideation/ or (suicidal and tendency).af.
56	((suicid$ and ideation) or (suicid$ and tendency)).af.
57	exp depressive disorder/ or exp depression/ or (depressi$ and disorder).af. or depression.af.
58	or/53-57
59	11 and (29 or 34 or 44 or 52 or 58)
60	remove duplicates from 59

Search conducted in EMBASE on 10/1/2013

#	Query
1	'breast'/exp/mj OR breast AND ('implantation'/exp/mj OR implantation)
2	'breast'/exp/mj OR breast AND implant$
3	'breast'/exp/mj OR breast AND (augment$ OR reconstruct$ OR remov$ OR revis$ OR replant$ OR replace$ OR 'lift'/exp/mj OR lift OR enlarge$)
4	'mammaplasty'/exp/mj OR mammaplasty OR 'mammoplasty'/exp/mj OR mammoplasty
5	'breast'/exp/mj OR breast AND ('plastic'/exp/mj OR plastic) AND ('surgery'/exp/mj OR surgery)
6	'breast'/exp/mj OR breast AND ('cosmetic'/exp/mj OR cosmetic) AND ('surgery'/exp/mj OR surgery)
7	'breast'/exp/mj OR breast AND artificial OR ('breast'/exp/mj OR breast AND ('prosthesis'/exp/mj OR prosthesis))
8	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
10	natrelle OR memorygel OR memoryshape OR sientra AND ('breast'/exp/mj OR breast)
11	'silicones'/exp/mj OR silicones OR (silicone$ AND ('gel'/exp/mj OR gel)) OR 'silicone'/exp/mj OR silicone OR 'silicone filled' OR 'gel filled'
12	8 AND 11
13	10 OR 12
14	'carcinoma'/exp/mj OR carcinoma OR 'cancer'/exp/mj OR cancer OR 'neoplasm'/exp/mj OR neoplasm OR cancer$ OR neoplas$
15	'tumor'/exp OR 'tumour'/exp
16	14 OR 15
17	'brain'/exp/mj OR brain OR 'lung'/exp/mj OR lung OR 'bronchus'/exp/mj OR bronchus OR bronchogenic OR 'lymph'/exp/mj OR lymph OR 'uterus'/exp/mj OR uterus OR 'uterine'/exp/mj OR uterine OR 'cervix'/exp/mj OR cervix OR cervical OR 'vulva'/exp/mj OR vulva OR vulvar OR gynaecol$ OR gynecol$
18	16 AND 17
19	'lymphoma'/exp/mj OR lymphoma OR hodgkin OR 'astrocytoma'/exp/mj OR astrocytoma OR 'glioma'/exp/mj OR glioma OR 'glioblastoma'/exp/mj OR glioblastoma OR 'ependymoma'/exp/mj OR ependymoma OR 'meningioma'/exp/mj OR meningioma OR 'oligodendroglioma'/exp/mj OR oligodendroglioma OR 'oligoastrocytoma'/exp/mj OR oligoastrocytoma
20	18 OR 19
21	13 AND 20
22	'breast'/exp/mj OR breast AND (feed OR fed OR 'feeding'/exp/mj OR feeding)
23	'lactation'/exp/mj OR lactation OR 'lactate'/exp/mj OR lactate OR lactating
24	22 OR 23
25	13 AND 24
26	'pregnancy'/exp/mj OR pregnancy OR pregnant OR gravid OR gravid$ OR pregnan$ OR 'abortion'/exp/mj OR abortion OR 'miscarriage'/exp/mj OR miscarriage OR (ectopic AND pregnan$) OR (ectopic AND gravid$) OR gestation$ OR 'parturition'/exp/mj OR parturition OR preterm OR reprodu$ OR 'stillbirth'/exp/mj OR stillbirth OR stillbirths OR birth$ OR stillborn OR 'eclampsia'/exp/mj OR eclampsia OR 'preeclampsia'/exp/mj OR preeclampsia OR 'pre eclampsia'/exp/mj OR 'pre eclampsia' OR (pregnancy AND ('hypertension'/exp/mj OR hypertension)) OR (gestation$ AND ('hypertension'/exp/mj OR hypertension))
27	13 AND 26

#	Query
28	cleft AND ('lip'/exp/mj OR lip) OR cleft AND ('palate'/exp/mj OR palate) OR down AND ('syndrome'/exp/mj OR syndrome) OR (congenital AND ('abnormalities'/exp/mj OR abnormalities)) OR 'heart'/exp/mj OR heart AND defect OR 'heart'/exp/mj OR heart AND defects OR cardiac AND defect OR cardiac AND defects OR 'anencephaly'/exp/mj OR anencephaly OR spina AND bifida OR spina AND ('dysraphism'/exp/mj OR dysraphism) OR congenital
29	13 AND 28
30	'suicide'/exp/mj OR suicide OR suicidal OR 'depression'/exp/mj OR depression OR depressive OR (suicid$ AND idea$)
31	13 AND 30
32	autoimmune OR 'lupus'/exp/mj OR lupus OR (connective AND ('tissue'/exp/mj OR tissue)) OR ctd OR ('cartilage'/exp/mj OR cartilage AND disease$) OR ('collagen'/exp/mj OR collagen AND disease$) OR 'cutis'/exp/mj OR cutis AND laxa OR dupuytren AND ('contracture'/exp/mj OR contracture) OR 'homocystinuria'/exp/mj OR homocystinuria OR marfan OR mixed AND connective OR 'mucinoses'/exp/mj OR mucinoses OR noonan OR 'osteopoikilosis'/exp/mj OR osteopoikilosis OR pseudoxanthoma OR 'mctd'/exp/mj OR mctd OR 'sclerosis like' OR 'scleroderma'/exp/mj OR scleroderma OR 'arthralgia'/exp/mj OR arthralgia OR 'polyarthralgia'/exp/mj OR polyarthralgia OR 'myalgia'/exp/mj OR myalgia OR irritable AND ('bowel'/exp/mj OR bowel) OR ibd OR rheumatol$ OR rheumatoid OR 'arthritis'/exp/mj OR arthritis OR rheumatic OR 'fatigue'/exp/mj OR fatigue OR 'fibromyalgia'/exp/mj OR fibromyalgia OR sjogren OR (chronic AND ('fatigue'/exp/mj OR fatigue)) OR polymyalgia OR 'pain'/exp/mj OR pain OR myalg$ OR 'fibrositis'/exp/mj OR fibrositis OR 'polychondritis'/exp/mj OR polychondritis OR 'angitis'/exp/mj OR angitis OR 'vasculitis'/exp/mj OR vasculitis OR 'arteritis'/exp/mj OR arteritis OR 'phlebitis'/exp/mj OR phlebitis OR behcet$ OR 'churg strauss'/exp/mj OR 'churg strauss' OR wegener$ OR (mucocutaneous AND lymph$) OR 'thrombophlebitis'/exp/mj OR thrombophlebitis OR thromboangiitis OR (inflammatory AND ('bowel'/exp/mj OR bowel) AND disease$) OR crohn$ OR 'colitis'/exp/mj OR colitis OR 'ileitis'/exp/mj OR ileitis OR 'enteritis'/exp/mj OR enteritis OR 'rectocolitis'/exp/mj OR rectocolitis OR 'proctocolitis'/exp/mj OR proctocolitis
33	13 AND 32
34	amyotrophic AND lateral AND ('sclerosis'/exp/mj OR sclerosis) OR lou AND gehrig OR multiple AND ('sclerosis'/exp/mj OR sclerosis) OR 'myasthenia'/exp/mj OR myasthenia AND gravis OR 'polyradiculoneuropathy'/exp/mj OR polyradiculoneuropathy OR 'guillain barre'/exp/mj OR 'guillain barre' OR (guillain AND barre) OR 'neuritis'/exp/mj OR neuritis OR (motor AND ('neuropathy'/exp/mj OR neuropathy)) OR 'myositis'/exp/mj OR myositis OR 'polymyositis'/exp/mj OR polymyositis OR 'dermatomyositis'/exp/mj OR dermatomyositis OR 'headache'/exp/mj OR headache OR 'migraine'/exp/mj OR migraine OR nervous AND system AND ('diseases'/exp/mj OR diseases) OR 'neuropathy'/exp/mj OR neuropathy
35	13 AND 34

#	Query
36	'anorexia'/exp/mj OR anorexia OR loss AND ('appetite'/exp/mj OR appetite) OR mobility OR function OR 'spasm'/exp/mj OR spasm OR tightness OR 'photophobia'/exp/mj OR photophobia OR 'hydrarthrosis'/exp/mj OR hydrarthrosis OR swollen AND ('joint'/exp/mj OR joint) OR 'joint'/exp/mj OR joint AND ('effusion'/exp/mj OR effusion) OR 'skin'/exp/mj OR skin AND nodule OR 'pharyngitis'/exp/mj OR pharyngitis OR sore AND ('throat'/exp/mj OR throat) OR 'vertigo'/exp/mj OR vertigo OR 'dizziness'/exp/mj OR dizziness OR tingling OR 'burning'/exp/mj OR burning OR 'attention'/exp/mj OR attention AND deficit OR 'insomnia'/exp/mj OR insomnia OR 'sleep'/exp/mj OR sleep AND ('disorder'/exp/mj OR disorder) OR 'edema'/exp/mj OR edema OR 'pain'/exp/mj OR pain OR 'lymphadenopathy'/exp/mj OR lymphadenopathy OR stiff AND ('joint'/exp/mj OR joint) OR 'stiffness'/exp/mj OR stiffness OR tingling OR 'burning'/exp/mj OR burning
37	13 AND 36
38	21 OR 25 OR 27 OR 29 OR 31 OR 33 OR 35 OR 37

Appendix B: Excluded Studies

Akali AU, McArthur P. Complications of breast implants associated with pregnancy. Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS 2008 Nov;61(11):1413-15. *Reason for Exclusion: Case Report*

Bartel DR. Sclerodermalike esophageal disease in children of mothers with silicone breast implants.[Erratum appears in JAMA 1995 Feb 15;273(7):524]. JAMA 1994 Sep 14;272(10):767-70. *Reason for Exclusion: Letter*

Bengtsson AA, Rylander L, Hagmar L, et al. Risk factors for developing systemic lupus erythematosus: a case-control study in southern Sweden. Rheumatology 2002 May;41(5):563-71. *Reason for Exclusion: No Data*

Berkel H, Birdsell DC, Jenkins H. Breast augmentation: a risk factor for breast cancer? New England Journal of Medicine 1992 Jun 18;326(25):1649-53. *Reason for Exclusion: Reanalyzed in Bryant PMID 7739707*

Berlin CM, Jr. Silicone breast implants and breast-feeding. Pediatrics 1994 Oct;94(4:Pt 1):t-9. *Reason for Exclusion: Review*

Bowers DG, Jr., Radlauer CB. Breast cancer after prophylactic subcutaneous mastectomies and reconstructionwith silastic prostheses. Plastic & Reconstructive Surgery 1969 Dec;44(6):541-44. *Reason for Exclusion: Case Report*

Brinton LA, Brown SL, Colton T, et al. Characteristics of a population of women with breast implants compared with women seeking other types of plastic surgery. Plastic & Reconstructive Surgery 928 Sep;105(3):919-27. *Reason for Exclusion: No outcome of interest*

Brinton LA, Lubin JH, Burich MC, et al. Mortality among augmentation mammoplasty patients. Epidemiology 2001 May;12(3):321-26. *Reason for Exclusion: No outcome of interest*

Brody GS, Conway DP, Deapen DM, et al. Consensus statement on the relationship of breast implants to connective-tissue disorders. [Review] [42 refs]. Plastic & Reconstructive Surgery 1992 Dec;90(6):1102-05. *Reason for Exclusion: Task Force Recommendation*

Brown MH, Shenker R, Silver SA. Cohesive silicone gel breast implants in aesthetic and reconstructive breast surgery. Plastic & Reconstructive Surgery 780 Jan;116(3):768-79. *Reason for Exclusion: No outcome of interest*

Caputy GG, Flowers RS. Copious lactation following augmentation mammaplasty: an uncommon but not rare condition. [Review] [5 refs]. Aesthetic Plastic Surgery 1994;18(4):393-97. *Reason for Exclusion: No outcome of interest*

Coleman E, Lemon S, Rudick J, et al. Rheumatic Disease Among 1167 Women Reporting Local Implant and Systemic Problems After Breast Implant Surgery. Journal of Women's Health 2009;3(3):165-77. *Reason for Exclusion: Not population of interest*

Cook LS, Daling JR, Voigt LF, et al. Characteristics of women with and without breast augmentation. JAMA 1997 May 28;277(20):1612-17. *Reason for Exclusion: Letter*

Cook RR, Klein PJ, Perkins LL, et al. Epidemiology and causation: the breast implant controversy. Plastic & Reconstructive Surgery 1998 Sep;102(3):921-23. *Reason for Exclusion: Comment*

Cuellar ML, Gluck O, Molina JF, et al. Silicone breast implant--associated musculoskeletal manifestations. Clinical Rheumatology 1995 Nov;14(6):667-72. *Reason for Exclusion: Not population of interest*

De CT. Augmentation mammaplasty. Survey of complications in 10,941 patients by 265 surgeons. Plastic & Reconstructive Surgery 1970 Jun;45(6):573-77. *Reason for Exclusion: Uninterpretable results*

Deapen DM, Pike MC, Casagrande JT, et al. The relationship between breast cancer and augmentation mammaplasty: an epidemiologic study. Plastic & Reconstructive Surgery 1986 Mar;77(3):361-68. *Reason for Exclusion: Early data only*

Deapen DM, Bernstein L, Brody GS. Are breast implants anticarcinogenic? A 14-year follow-up of the Los Angeles Study. Plastic & Reconstructive Surgery 1997 Apr;99(5):1346-53. *Reason for Exclusion: Early data only*

Dewey KG, Nommsen-Rivers LA, Heinig MJ, et al. Risk factors for suboptimal infant breastfeeding behavior, delayed onset of lactation, and excess neonatal weight loss. Pediatrics 2003 Sep;112(3:Pt 1):t-19. *Reason for Exclusion: Not implant study*

Engel A, Lamm SH, Lai SH. Human breast sarcoma and human breast implantation: a time trend analysis based on SEER data (1973-1990). Journal of Clinical Epidemiology 1995 Apr;48(4):539-44. *Reason for Exclusion: Not analysis of implants*

Englert H, Morris D, March L. Scleroderma and silicone gel breast prostheses--the Sydney study revisited. Australian & New Zealand Journal of Medicine 1996 Jun;26(3):349-55. *Reason for Exclusion: Case report*

Englert HJ, Brooks P. Scleroderma and augmentation mammoplasty--a causal relationship? Australian & New Zealand Journal of Medicine 1994 Feb;24(1):74-80. *Reason for Exclusion: Case report*

Ericsson A. Syndromes Associated with Silicone Breast Implants: A Clinical Study and Review. Journal of Nutritional and Environmental Medicine 1998;8(1):35-51. *Reason for Exclusion: Review*

Ferguson JH. Silicone breast implants and neurologic disorders. Report of the Practice Committee of the American Academy of Neurology. [Review] [16 refs]. Neurology 1997 Jun;48(6):1504-07. *Reason for Exclusion: Review*

Field T, Bridges AJ. Clinical and laboratory features of patients with scleroderma and silicone implants. Current Topics in Microbiology & Immunology 1996;210:283-90. *Reason for Exclusion: Case Series*

Flick JA. Silicone implants and esophageal dysmotility. Are breast-fed infants at risk? JAMA 1994 Jan 19;271(3):240-41. *Reason for Exclusion: Not Primary Study*

Freundlich B, Altman C, Snadorfi N, et al. A profile of symptomatic patients with silicone breast implants: a Sjogrens-like syndrome. Seminars in Arthritis & Rheumatism 1994 Aug;24(1:Suppl 1):Suppl-53. *Reason for Exclusion: Only referred patients*

Friis S, McLaughlin JK, Mellemkjaer L, et al. Breast implants and cancer risk in Denmark. International Journal of Cancer 1997 Jun 11;71(6):956-58. *Reason for Exclusion: Superceded by Lipworth PMID 19003966*

Garland LL, Ballester OF, Vasey FB, et al. Multiple myeloma in women with silicone breast implants. Serum immunoglobulin and interleukin-6 studies in women at risk. Current Topics in Microbiology & Immunology 1996;210:361-66. *Reason for Exclusion: Case Series*

Georgiade GS, Riefkohl R, Cox E, et al. Long-term clinical outcome of immediate reconstruction after mastectomy. Plastic & Reconstructive Surgery 1985 Sep;76(3):415-20. *Reason for Exclusion: Breast reconstruction with and without implants*

Goldman JA, Greenblatt J, Joines R, et al. Breast implants, rheumatoid arthritis, and connective tissue diseases in a clinical practice. Journal of Clinical Epidemiology 1995 Apr;48(4):571-82. *Reason for Exclusion: Rheumatology clinic patients*

Greenland S, Finkle WD. A retrospective cohort study of implanted medical devices and selected chronic diseases in Medicare claims data. Annals of Epidemiology 2000 May;10(4):205-13. *Reason for Exclusion: Conducted during US Moratorium (thus few silicone)*

Handel N, Jensen JA, Black Q, et al. The fate of breast implants: a critical analysis of complications and outcomes. Plastic & Reconstructive Surgery 1995 Dec;96(7):1521-33. *Reason for Exclusion: Not outcome of interest*

Handel N. The effect of silicone implants on the diagnosis, prognosis, and treatment of breast cancer. [Review] [64 refs]. Plastic & Reconstructive Surgery 2007 Dec;120(7:Suppl 1):Suppl-93S. *Reason for Exclusion: Not outcome of interest*

Harris HI. Survey of breast implants from the point of view of carcinogenesis. Plastic & Reconstructive Surgery & the Transplantation Bulletin 1961 Jul;28:81-83. *Reason for Exclusion: Not Silicone Implants*

Hennekens CH, Lee IM, Cook NR, et al. Self-reported breast implants and connective-tissue diseases in female health professionals. A retrospective cohort study.[Erratum appears in JAMA 1998 Jan 21;279(3):198]. JAMA 1996 Feb 28;275(8):616-21. *Reason for Exclusion: More complete subsequent analysis in Lee PMID 20943932)*

Hochberg MC, Perlmutter DL, Medsger TA, Jr., et al. Lack of association between augmentation mammoplasty and systemic sclerosis (scleroderma). Arthritis & Rheumatism 1996 Jul;39(7):1125-31. *Reason for Exclusion: Case Series*

Holmich LR, Mellemkjaer L, Gunnarsdottir KA, et al. Stage of breast cancer at diagnosis among women with cosmetic breast implants. British Journal of Cancer 2003 Mar 24;88(6):832-38. *Reason for Exclusion: Not outcome of interest*

Jakub JW, Ebert MD, Cantor A, et al. Breast cancer in patients with prior augmentation: presentation, stage, and lymphatic mapping. Plastic & Reconstructive Surgery 2004 Dec;114(7):1737-42. *Reason for Exclusion: Case Series*

Janowsky E, Kupper L, Hulka B. Silicone breast implants do not increase the risk for connective tissue diseases. Evid -Based Med 2000;5:189. *Reason for Exclusion: Abstract of Systematic Review*

Jensen B, Bliddal H, Kjoller K, et al. Rheumatic manifestations in danish women with silicone breast implants. Clinical Rheumatology 2001;20(5):345-52. *Reason for Exclusion: Case Series*

Jensen B, Hechmann WI, Friis S, et al. Self-reported symptoms among Danish women following cosmetic breast implant surgery. Clinical Rheumatology 2002 Feb;21(1):35-42. *Reason for Exclusion: Case Series*

Jensen B, Wiik A, Hechmann W, I, et al. Silicate antibodies in Danish women with silicone breast implants. Rheumatology 2003 Sep;42(9):1032-35. *Reason for Exclusion: Not outcome of interest*

Jensen B, Wittrup IH, Wiik A, et al. Antipolymer antibodies in Danish women with silicone breast implants. Journal of Long-Term Effects of Medical Implants 2004;14(2):73-80. *Reason for Exclusion: Not outcome of interest*

Joiner TE, Jr. Does breast augmentation confer risk of or protection from suicide? Aesthetic Surgery Journal 2003 Sep;23(5):370-75. *Reason for Exclusion: Not primary study*

Karlson EW, Lee IM, Cook NR, et al. Comparison of self-reported diagnosis of connective tissue disease with medical records in female health professionals: the Women's Health Cohort Study. American Journal of Epidemiology 1999 Sep 15;150(6):652-60. *Reason for Exclusion: More complete subsequent analysis in Lee PMID 20943932*

Kim DW, Harris JP. Risk of progressive sensorineural hearing loss and Meniere's disease after breast implantation. Otolaryngology - Head & Neck Surgery 1998 Jun;118(6):747-50. *Reason for Exclusion: No outcome of interest*

Kjoller K, McLaughlin JK, Friis S, et al. Health outcomes in offspring of mothers with breast implants. Pediatrics 1998 Nov;102(5):1112-15. *Reason for Exclusion: Literature Review*

Kjoller K, Friis S, Mellemkjaer L, et al. Connective tissue disease and other rheumatic conditions following cosmetic breast implantation in Denmark. Archives of Internal Medicine 2001 Apr 9;161(7):973-79. *Reason for Exclusion: Superceded by Fryzek 2007 17321754*

Kjoller K, Friis S, Lipworth L, et al. Adverse health outcomes in offspring of mothers with cosmetic breast implants: a review. [Review] [25 refs]. Plastic & Reconstructive Surgery 2007 Dec;120(7:Suppl 1):Suppl-134S. *Reason for Exclusion: Superceded by Kjoller 2002 11862026*

Koot VC, Peeters PH, Granath F, et al. Total and cause specific mortality among Swedish women with cosmetic breast implants: prospective study. BMJ 2003 Mar 8;326(7388):527-28. *Reason for Exclusion: Superceded by Lipworth 2007 17667401*

Lai S, Goldman JA, Child AH, et al. Fibromyalgia, hypermobility, and breast implants. Journal of Rheumatology 2000 Sep;27(9):2237-41. *Reason for Exclusion: Rheumatology clinic patients*

Levine JJ, Ilowite NT. Sclerodermalike esophageal disease in children breast-fed by mothers with silicone breast implants.[Erratum appears in JAMA 1994 Sep 14;272(10):770]. JAMA 1994 Jan 19;271(3):213-16. *Reason for Exclusion: Only referred patients*

Levine JJ, Trachtman H, Gold DM, et al. Esophageal dysmotility in children breast-fed by mothers with silicone breast implants. Long-term follow-up and response to treatment. Digestive Diseases & Sciences 1996 Aug;41(8):1600-03. *Reason for Exclusion: Only referred patients*

Lipworth L, Kjoller K, Holmich LR, et al. Psychological characteristics of Danish women with cosmetic breast implants. Annals of Plastic Surgery 2009 Jul;63(1):11-14. *Reason for Exclusion: No outcome of interest*

MacDonald KL, Osterholm MT, LeDell KH, et al. A case-control study to assess possible triggers and cofactors in chronic fatigue syndrome. American Journal of Medicine 1996 May;100(5):548-54. *Reason for Exclusion: Not implant study*

McCarthy E, Merkatz R, Bagley G. A Descriptive Analysis of Physical Complaints From Women With Silicone Breast Implants. J Women's Health 2009;2(2) *Reason for Exclusion: Based on letters, not questioner*

McLaughlin JK, Fraumeni JF, Jr., Nyren O, et al. Silicone breast implants and risk of cancer? JAMA 1995 Jan 11;273(2):116. *Reason for Exclusion: Letter*

McLaughlin JK, Nyren O, Blot WJ, et al. Cancer risk among women with cosmetic breast implants: a population-based cohort study in Sweden. Journal of the National Cancer Institute 1998 Jan 21;90(2):156-58. *Reason for Exclusion: Subset of Lipworth 2009 19003966*

McLaughlin JK. Do cosmetic breast implants cause suicide? Plastic & Reconstructive Surgery 2003 Nov;112(6):1721-23. *Reason for Exclusion: Review*

McLaughlin JK, Lipworth L. Brain cancer and cosmetic breast implants: a review of the epidemiologic evidence. Annals of Plastic Surgery 2004 Feb;52(2):115-17. *Reason for Exclusion: Review*

McLaughlin JK, Lipworth L, Fryzek JP, et al. Long-term cancer risk among Swedish women with cosmetic breast implants: an update of a nationwide study. Journal of the National Cancer Institute 2006 Apr 19;98(8):557-60. *Reason for Exclusion: Subset of Lipworth 2009 19003966*

Mellemkjaer L, Kjoller K, Friis S, et al. Cancer occurrence after cosmetic breast implantation in Denmark. International Journal of Cancer 2000 Oct 15;88(2):301-06. *Reason for Exclusion: Superceded by Lipworth 2008 19003966*

Merida N, Estrada R, Graham S, et al. Cystic adenomatoid malformations of lung. Are those associated to inhaled environmental pollutants? Rev Mex Pediatr 2010;77(6) *Reason for Exclusion: Case Series*

Meyer L, Ringberg A. Augmentation mammaplasty--psychiatric and psychosocial characteristics and outcome in a group of Swedish women. Scandinavian Journal of Plastic &

Reconstructive Surgery & Hand Surgery 1987;21(2):199-208. *Reason for Exclusion: No outcomes of interest*

Michalopoulos K. The effects of breast augmentation surgery on future ability to lactate. Breast Journal 2007 Jan;13(1):62-67. *Reason for Exclusion: Review*

Miller AS, III, Willard V, Kline K, et al. Absence of longitudinal changes in rheumatologic parameters after silicone breast implantation: a prospective 13-year study. Plastic & Reconstructive Surgery 1998 Dec;102(7):2299-303. *Reason for Exclusion: Laboratory findings*

Morgan E. Suicide after breast augmentation. Epidemiology 2008 May;19(3):520-21. *Reason for Exclusion: Letter*

Morrison B, Mickelson WP. Silicone-gel-filled breast implants: how they interface with breast cancer. The Working Group on Guidelines for Silicone Gel-Filled Breast Implants. Cancer Prevention & Control 1997;1(1):61-65. *Reason for Exclusion: Review*

Munhoz AM, Gemperli R, Filassi JR. Immediate reconstruction with implants in women with invasive breast cancer does not affect oncological safety in a matched cohort study. Breast Cancer Research & Treatment 2011 Aug;129(1):287-89. *Reason for Exclusion: Letter*

Neifert M, DeMarzo S, Seacat J, et al. The influence of breast surgery, breast appearance, and pregnancy-induced breast changes on lactation sufficiency as measured by infant weight gain. Birth 1990 Mar;17(1):31-38. *Reason for Exclusion: Not implant study*

O'Hanlon T, Koneru B, Bayat E, et al. Immunogenetic differences between Caucasian women with and those without silicone implants in whom myositis develops. Arthritis & Rheumatism 2004 Nov;50(11):3646-50. *Reason for Exclusion: No outcomes of interest*

Panjari M, Bell RJ, Fradkin P, et al. Cosmetic surgery prior to diagnosis of breast cancer. Climacteric 2012 Apr;15(2):195-99. *Reason for Exclusion: Case series*

Peters W, Smith D, Fornasier V, et al. An outcome analysis of 100 women after explantation of silicone gel breast implants. Annals of Plastic Surgery 1997 Jul;39(1):9-19. *Reason for Exclusion: Explants only*

Petit JY, Le MG, Mouriesse H, et al. Can breast reconstruction with gel-filled silicone implants increase the risk of death and second primary cancer in patients treated by mastectomy for breast cancer? Plastic & Reconstructive Surgery 1994 Jul;94(1):115-19. *Reason for Exclusion:*

Petit JY, Rietjens M, Le M, et al. [Carcinologic risk of silicone gel breast prostheses in women treated for breast cancer]. [French]. Annales de Chirurgie Plastique et Esthetique 1994 Dec;38(6):801-03. *Reason for Exclusion: Duplicate publication*

Petit JY, Rietjens M, Le MG, et al. [Silicone breast implants and breast cancer]. [French]. Annales de Chirurgie Plastique et Esthetique 1997 Apr;42(2):107-09. *Reason for Exclusion: Duplicate publication*

Petit JY, Le M, Rietjens M, et al. Does long-term exposure to gel-filled silicone implants increase the risk of relapse after breast cancer? Tumori 1998 Sep;84(5):525-28. *Reason for Exclusion: No outcome of interest*

Polednak AP. Suicide among breast cancer patients who have had reconstructive surgery: a population-based study. Psychosomatics 2007 Mar;48(2):178-79. *Reason for Exclusion: No outcome of interest*

Press RI, Peebles CL, Kumagai Y, et al. Antinuclear autoantibodies in women with silicone breast implants. Lancet 1992 Nov 28;340(8831):1304-07. *Reason for Exclusion: Rheumatology clinic patients*

Puskas JE, Luebbers MT. Breast implants: the good, the bad and the ugly. Can nanotechnology improve implants?. [Review]. Wiley interdisciplinary reviews 2012 Mar;Nanomedicine(2):153-68. *Reason for Exclusion: Narrative Review*

Rabkin CS, Silverman S, Tricot G, et al. The National Cancer Institute Silicone Implant/Multiple Myeloma Registry. Current Topics in Microbiology & Immunology 1996;210:385-87. *Reason for Exclusion: Case Series*

Sandelin K, Billgren AM, Wickman M. Management, morbidity, and oncologic aspects in 100 consecutive patients with immediate breast reconstruction. Annals of Surgical Oncology 1998 Mar;5(2):159-65. *Reason for Exclusion: No outcomes of interest*

Sarwer DB, Brown GK, Evans DL. Cosmetic breast augmentation and suicide. [Review] [47 refs]. American Journal of Psychiatry 2007 Jul;164(7):1006-13. *Reason for Exclusion: Narrative review*

Silverstein MJ, Gierson ED, Gamagami P, et al. Breast cancer diagnosis and prognosis in women augmented with silicone gel-filled implants. Cancer 1990 Jul 1;66(1):97-101. *Reason for Exclusion: No outcome of interest*

Silverstein MJ, Handel N, Gamagami P, et al. Breast cancer diagnosis and prognosis in women following augmentation with silicone gel-filled prostheses. European Journal of Cancer 1992;28(2-3):635-40. *Reason for Exclusion: No outcome of interest*

Solomon G. A clinical and laboratory profile of symptomatic women with silicone breast implants. Seminars in Arthritis & Rheumatism 1994 Aug;24(1:Suppl 1):Suppl-37. *Reason for Exclusion: Only referred patients*

Spear SL, Heden P. Allergan's silicone gel breast implants. [Review] [48 refs]. Expert Review of Medical Devices 2007 Sep;4(5):699-708. *Reason for Exclusion: Narrative review*

Spendel S, Hintringer T, Pilz S, et al. Clinical and laboratory investigation of women with intact and women with ruptured silicone gel breast implants. European Journal of Plastic Surgery 1998;21(7):338-43. *Reason for Exclusion: Rupture study*

Story SK, Schowalter MK, Geskin LJ. Breast implant-associated ALCL: a unique entity in the spectrum of CD30+ lymphoproliferative disorders. Oncologist 2013;18(3):301-07. *Reason for Exclusion: No outcomes of interest.*

Strom BL, Reidenberg MM, Freundlich B, et al. Breast silicone implants and risk of systemic lupus erythematosus. Journal of Clinical Epidemiology 1994 Oct;47(10):1211-14. *Reason for Exclusion: Case control with only 1 breast implant*

Tricot GJ, Naucke S, Vaught L, et al. Is the risk of multiple myeloma increased in patients with silicone implants? Current Topics in Microbiology & Immunology 1996;210:357-59. *Reason for Exclusion: Case Series*

Vasey FB, Havice DL, Bocanegra TS, et al. Clinical findings in symptomatic women with silicone breast implants. Seminars in Arthritis & Rheumatism 1994 Aug;24(1:Suppl 1):Suppl-8. *Reason for Exclusion: Rheumatology clinic patients*

Vasey FB, Seleznick M, Wells AF, et al. Rheumatic disease symptoms and silicone breast implants: comment on the article by Cook et al and the article by Sanchez-Guerrero et al. Arthritis & Rheumatism 1995 May;38(5):719-21. *Reason for Exclusion: Letter*

Walden JL, Panagopoulous G, Shrader SW. Contemporary decision making and perception in patients undergoing cosmetic breast augmentation. Aesthetic Surgery Journal 2010 May;30(3):395-403. *Reason for Exclusion: No outcomes of interest*

Walden KJ, Thompson JK, Wells KE. Body image and psychological sequelae of silicone breast explantation: preliminary findings. Plastic & Reconstructive Surgery 1997 Oct;100(5):1299-306. *Reason for Exclusion: Explants only*

Wallace DJ, Basbug E, Schwartz E, et al. A Comparison of Systemic Lupus Erythematosus and Scleroderma Patients with and without Silicone Breast Implants. JCR: Journal of Clinical Rheumatology 1996 Oct;2(5):257-61. *Reason for Exclusion: Only referred patients*

Weinzweig J, Schnur PL, McConnell JP, et al. Silicon analysis of breast and capsular tissue from patients with saline or silicone gel breast implants: II. Correlation with connective-tissue disease. Plastic & Reconstructive Surgery 1998 Jun;101(7):1836-41. *Reason for Exclusion: Tissue study*

Wells KE, Roberts C, Daniels SM, et al. Comparison of psychological symptoms of women requesting removal of breast implants with those of breast cancer patients and healthy controls. Plastic & Reconstructive Surgery 1997 Mar;99(3):680-85. *Reason for Exclusion: No outcomes of interest*

Williams AF. Silicone breast implants, breastfeeding, and scleroderma. Lancet 1994 Apr 23;343(8904):1043-44. *Reason for Exclusion: Letter*

Williams HJ, Weisman MH, Berry CC. Breast implants in patients with differentiated and undifferentiated connective tissue disease. Arthritis & Rheumatism 1997 Mar;40(3):437-40. *Reason for Exclusion: Inappropriate study design*

Winther JF, Bach FW, Friis S, et al. Neurologic disease among women with breast implants. Neurology 1998 Apr;50(4):951-55. *Reason for Exclusion: Superceded by Winther PMID 11227138*

Wolfe F, Anderson J. Silicone filled breast implants and the risk of fibromyalgia and rheumatoid arthritis.[Erratum appears in J Rheumatol 2000 Mar;27(3):825]. Journal of Rheumatology 1999 Sep;26(9):2025-28. *Reason for Exclusion: Only referred patients*

Xie L, Brisson J, Holowaty EJ, et al. The influence of cosmetic breast augmentation on the stage distribution and prognosis of women subsequently diagnosed with breast cancer. International Journal of Cancer 2010 May 1;126(9):2182-90. *Reason for Exclusion: Not outcome of interest*

Young VL, Watson ME, Boswell CB, et al. Initial results from an online breast augmentation survey. Aesthetic Surgery Journal 2004 Mar;24(2):117-35. *Reason for Exclusion: Too few silicone implants*

Zuckerman D. Mortality in Swedish women with cosmetic breast implants: study found increased risk of suicides and cancer deaths. BMJ 2003 Jun 7;326(7401):1266. *Reason for Exclusion: Comment*

Appendix C.1. Study Characteristics

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Allergan (Inamed/Natrelle Round) Cohort	US Allergan (Inamed/Natrelle Round) Cohort 2006 No PMID[47,80]	Allergan Yes	Single arm, prospective, observational	nd nd Industry-organized cohort	Primary augmentation, Primary reconstruction, Replacement/revision augmentation, Replacement/revision reconstruction, Specific implant type: Allergan Inamed (aka Natrelle) round	NA	nd
Allergan Natrelle Breast Implant Follow-up Study	US (mostly), Canada, and maybe others Allergan Natrelle Breast Implant Follow-up Study 2011 No PMID[46,47]	Allergan Yes	Comparative, prospective, observational	nd nd nd	Only silicone gel implants, Primary augmentation, Primary reconstruction, Replacement/revision augmentation, Replacement/revision reconstruction, Specific implant type: Allergan Inamed (aka Natrelle) round or anatomic	Saline-filled breast implants	nd

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort	US Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort 2013 No PMID[48,65]	Allergan Yes	Single arm, prospective, observational	2001-2002 1 y Industry-organized cohort	Primary augmentation, Primary reconstruction, Replacement/revision augmentation, Replacement/revision reconstruction, Specific implant type: Allergan Natrelle 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implants, ≥18 years old; Exclusions: History of premalignant or malignant breast disease without mastectomy, contraindications to surgery, breast tissue incompatible with mammoplasty, psychological characteristics such as body dysmorphic disorder	NA	nd
Munster, Germany	Germany Berner 2002 12039092[16]	German Research Foundation No	Comparative, retrospective, observational	nd nd Medical records	Only silicone gel implants; Breast cancer patients; Exclusions: patients with metastatic disease	Breast cancer patients without implants	From women, Questionnaire, Clinical/Physical examination

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Copenhagen Deaconess Hospital	Denmark Breiting 2004 15220596[17]	International Epidemiology Institute, which received funds from the Dow Corning Corporation, and by the Danish Cancer Society Indirect, to funding institution	Comparative, matched, retrospective, observational	1997 nd Medical records, multiple center	All implants allowed, Augmentation only	1st control group: women who had undergone breast reduction surgery at the same hospital or clinic as the breast implant patients; 2nd control group: women from the general population identified through the files of the Central Population Register	Medical records, From women, Questionnaire, Clinical/Physical examination

Cohort name	**Country** **Author, Year, PMID (see report reference list for references)**	**Funding** **Industry funded?**	**Study design**	**Recruitment: years** **duration** **setting**	**Inclusion/exclusion criteria for implant**	**Inclusion/exclusion criteria for controls**	**How were results obtained?**
Atlanta/Seattle/New Jersey	US Brinton 1996 8559808[18]	National Cancer Institute, Fred Hutchinson Cancer Research Center, Department of Epidemiology, Rollins School of Public Health at Emory University, and Special Epidemiology Program at the New Jersey State Department of Health. No	Case-control, retrospective	1990-1992 2.5 y Registry, medical records	Augmentation only, All implants allowed, Restrictive population (Age <45 y (New Jersey, Seattle), Age <55 y (Atlanta)	Random digit dialing, matched to geographic area and age, no breast cancer	Medical records, From women, Questionnaire
South 18 centers	US Brinton 2000 11075871[19]; Brinton 2001 11306343[20]; Brinton 2004 15383405[21]; Brinton 2006 16477256[22]	US governmental funds allocated to the intramural budget of the National Cancer Institute. No	Comparative, retrospective, observational	nd nd Medical records, multiple centers	Primary augmentation at 1 of 18 plastic surgery practices prior to 1989; Exclusions: History of breast cancer	Similarly-aged subject who had some other type of plastic surgery (not involving silicone) during the same time period in all but 1 practice	Medical records, From women, Questionnaire, Death certificates

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Ontario/Quebec	Canada Brisson 2006 16381020[23]; Villeneuve 2006 16777929[85]	Public Health Agency of Canada, formerly in Health Canada No	Comparative, matched, retrospective, observational	nd nd Medical records	Augmentation only, ≥18 years old, who were residents of either Ontario or Quebec, underwent mammoplasty between January 1, 1974-December 31, 1989; Exclusions: women who had undergone any previous major breast surgery, including reduction mammoplasty, breast lift and breast cancer surgery, women who had a male genotype, or who had a history of cancer (excluding non-melanoma skin cancer), women whose index bilateral breast augmentation surgery involved different implants for the left and right breasts.	Women who received other common elective cosmetic surgeries matched to the breast implant recipients by year of entry into the cohort, and by surgeon. Exclusions: women who had undergone any previous major breast surgery, including reduction mammoplasty, breast lift and breast cancer surgery, or received other types of silicone or artificial implants.	Registry
Birmingham, AL	US Brown 2001 11361228[24]	FDA, NIH, and the US Department of Health and Human Services No	Comparative, matched, cross-sectional	1980-1995 15 y Medical records	All implants allowed, Reconstruction only	Women who had undergone mastectomy for breast cancer but who had not received and implant (without reconstruction or with reconstruction done with autologous tissue)	Clinical/Physical examination, Laboratory tests

Cohort name	**Country** **Author, Year, PMID (see report reference list for references)**	**Funding** **Industry funded?**	**Study design**	**Recruitment: years** **duration** **setting**	**Inclusion/exclusion criteria for implant**	**Inclusion/exclusion criteria for controls**	**How were results obtained?**
Alberta Health Care Data	Canada Bryant 1995 7739707[25]	nd No	Comparative, matched, retrospective, observational	1973 or 1974-1986 12 or 13 y Registry	Augmentation only, 20-64 years old; Exclusions: received implants outside of the study period, unilateral first implantation, women who had surgery during a gap in their Alberta Health Care coverage of ≥1 year	No control group (1973 vs. 1974 cohorts)	Registry
Michigan	US Burns 1996 8923364[26]	Dow Corning Corporation Yes	Case-control, retrospective	mid-1990s once Medical records, multiple centers, specialty clinic: rheumatologists, United Scleroderma Foundation	Only silicone gel implants, Scleroderma diagnosed between 1985-1991, Exclusions: date of scleroderma diagnosis unknown	Random digit dialing, No scleroderma, Matched controls by age and geographic region	Medical records

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Barcelona	Spain Collado 1998 No PMID[27]	nd nd	Comparative, matched, cross-sectional	1980-1995 15 y	All implants allowed, Reconstruction only, The case group was limited to those women who had undergone mastectomy for breast cancer and were reconstructed in our service with implants. Besides silicone gel-filled implants, we decided that saline implant cases should not be discarded because after all, their envelope consists of a silicone elastomer; Exclusions: None reported	The control group was integrated by women who had undergone mastectomy for breast cancer but who had not received and implant (without reconstruction or with reconstruction done with autologous tissue)	Clinical/Physical examination, Laboratory tests
Rotterdam University Hospital 1990-1995	The Netherlands Contant 2000 11147756[28]	nd No	Single arm, prospective, observational	1990-1995 5 y Single surgeon	Only silicone gel implants, Reconstruction only, Exclusions: incomplete data or lost to f/u	NA	From women, Questionnaire, Clinical/Physical examination
Rotterdam University Hospital 1995-1997	The Netherlands Contant 2002 12111627[29]	nd No	Single arm, prospective, observational	1995-1997 2 y Medical records, single surgeon	Only silicone gel implants, Reconstruction only	NA	From women, Questionnaire, Clinical/Physical examination
Puerto Rico	US (Puerto Rico) Cruz 1992 1388458[30]	nd No	Single arm, retrospective, observational	~1991 nd Survey of plastic surgeons, multiple centers	Only silicone gel implants, Primary augmentation, Primary reconstruction	NA	nd (implied from plastic surgeon survey)

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
U Minnesota	US Cunningham 2007 18090810[31]	Inamed and Mentor Core Gel Studies. Indirect, to funding institution etc.	Comparative, prospective, observational	nd nd nd	Primary augmentation, Primary reconstruction, Replacement/revision augmentation, Replacement/revision reconstruction	4 groups: primary augmentation, primary reconstruction, revision augmentation, revision reconstruction	From women, Questionnaire, Clinical/Physical examination
Los Angeles	US Deapen 2007 17519689[33]; Deapen 1992 1546077[32]	NIH and Dow Corning Corporation, Cooper Surgical, McGhan Medical Corporation, Mentor Indirect, to funding institution	Single arm observational with pro- and retrospective features	nd nd Medical records	Augmentation only, Caucasian women who received cosmetic breast implants and resided in LA County, Exclusions: history of breast carcinoma, prophylactic subcutaneous mastectomy before implantation; non-Caucasian or Spanish-surnamed women	NA	Medical records
Mayo Clinic	US Duffy 1994 8041820[34]	nd No	Single arm, retrospective, observational	1993 nd Medical records, single surgeon	Replacement/revision augmentation, Replacement/revision reconstruction, All have replacement/revision, All implants, but implied that all were silicone	NA	Clinical/Physical examination
Alberta Health Registry	Canada Edworthy 1998 9489816[35]	Medical Research Council of Canada No	Comparative, matched, retrospective, observational	1978-1986 8 y Registry	Augmentation only, Exclusion: reconstruction implants	Women with non-silicone related cosmetic surgery	From women, Questionnaire, Clinical/Physical examination, Serology specimen

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Sydney	Australia Englert 2001 11480483[36]	Dow Corning, USA Indirect, to funding institution	Comparative, matched, retrospective, observational,	1979-1983 ~5 y Multiple centers	Only silicone gel implants, Primary augmentation, Surgery for non-malignancy related reasons, Residence within Sydney at the time of surgery for ≥6 months prior to study participation within a defined geographical area centered around Sydney and bounded by Wyong (north), Katoomba (west) and Wollongong (south). Partial participation involved completion of the Women's Health questionnaire by telephone interview; Exclusions: history of known diagnosis of connective tissue diseases prior to index plastic surgery, index plastic surgery secondary to underlying malignancy, exposure to silicone-containing prostheses either prior to or subsequent to index plastic surgery	Undergoing non-silicone types of plastic surgeries. The status of full participation was accorded to patients who completed a standardized Women's Health after Plastic Surgery questionnaire, a standardized clinical examination, nail fold capillaroscopy photography and, where permitted, serological assessment. Partial participation involved completion of the Women's Health questionnaire by telephone interview	From women, Questionnaire, Clinical/Physical examination

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Tuscon	US Fajardo 1995 7862991[37]	nd No	Single arm, retrospective, observational	1985-1992 7 y Medical records, mammogram records	All implants allowed, Had mammogram	NA	Medical records
Massachusetts General Hospital	US Fiala 1993 8368775[38]	nd No	Single arm, prospective, observational	nd nd Survey of women	Augmentation only, Exclusions: Reconstruction implants	NA	Medical records, From women, Questionnaire, Self-examination leading to the Self-Assessed Baker (SAB) score
Denmark Reconstruction	Denmark Friis 1997 9229085[39]	nd No	Comparative, retrospective, observational	~1996 nd Registry, multiple center, National hospital discharge register	All implants allowed, Reconstruction only; Exclusions: Non-Danish residents or invalid identification numbers	Breast cancer but no implant match on age, extent of disease, and calendar time [implicitly since time of surgery]	Registry
Olmstead Country, MN	US Gabriel 1994 8190133[43]	Plastic Surgery Foundation and NIH No	Retrospective, observational, population-based	1964-1991 27 y Medical records, multiple centers	All implants allowed, Primary augmentation, Primary reconstruction, Replacement/revision augmentation, Replacement/revision reconstruction, All implants had silicone envelope	Controls who had a medical evaluation within 2 years of the date matched for age, county on the index date	Medical records

Cohort name	**Country** **Author, Year, PMID (see report reference list for references)**	**Funding** **Industry funded?**	**Study design**	**Recruitment: years** **duration** **setting**	**Inclusion/exclusion criteria for implant**	**Inclusion/exclusion criteria for controls**	**How were results obtained?**
Free University, Amsterdam	The Netherlands Giltay 1994 8154939[44]	nd No	Comparative, matched, retrospective, observational	1978-1990 12 y Survey of women, single center	Only silicone gel implants, Primary augmentation, Exclusions: polyurethane shell, died since operation, lost to follow-up, or family practitioner advised not to send questionnaire	Matched control of same age with an operation but without use of silicone; operated in the same year and same department	From women, Questionnaire
Style 410 Europe	Europe Heden 2009 19437071[50]	Allergan Yes	Single arm, prospective, observational	1995-2001 6 y Existing population-based study, multiple centers	Only silicone gel implants, Primary augmentation, Primary reconstruction, Replacement/revision augmentation, Style 410 implant type, Willing and eligible to undergo MRI scan	NA	Clinical/Physical examination
Style 410 Stockholm	Sweden Heden 2006 17051096[51]	Inamed Corporation Yes	Single arm, retrospective, observational	1995-1999 4 y Medical records, single center	Only silicone gel implants, Replacement/revision augmentation, Augmentation only, Undergone implantation from a single private hospital in Stockholm and Style 410 was not removed; Exclusions: pregnant, breast-feeding, claustrophobia, implanted metal-screw, refused follow-up, not signing informed consent	NA	Medical records, From women, Questionnaire, Clinical/Physical examination

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Finland hospitals	Finland Hemminki 2004 15548145[52]; Pukkala 2002 12627789[74]; Pukkala 2003 14520056[73]	nd No	Comparative, retrospective, observational	~2000-2003 ~2y Registry, medical records, multiple centers	All implants allowed; Augmentation only, In Pukkala: cosmetic breast operation from 1970-1999; In Hemminki: 1st child born after implant (born 1987-1999); Exclusions: breast cancer diagnosed before the implant	In Hemminki: 20 infants of nonexposed women born in the same year	Registry
Denmark Public-Private subset	Denmark Holmich 2003 12560693[53]	International Epidemiology Institute, which in turn received funding from the Dow Corning Corporation, and the Danish Cancer Society. Indirect, to funding institution	Single arm, retrospective, observational	1997-1999 2 y Medical records, multiple centers	Only silicone gel implants, Augmentation only, Women receiving implants at 3 private plastic surgery clinics and 1 public hospital in Denmark from 1973-1998; Exclusions: women who had received Biogel or saline implants, implants for breast reconstruction, and women who had received implants in 1997 or later	NA	Medical records, From women, Questionnaire, Clinical/Physical examination
Texas Children's Hospital	US Hurst 1996 8532261[54]	nd No	Comparative, matched, retrospective observational	1990-1995 ~5 y Medical records	Augmentation only	Control group had no augmentation	Medical records

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Allergan vs. Mentor	US Jewell 2010 20442075[56]	None No	Comparative, prospective, observational	Allergan: 2001-2007 Mentor: 2002-2008 6 y Existing population-based study, single surgeon	Primary augmentation, Primary reconstruction, Replacement/revision augmentation, Replacement/revision reconstruction, Women ≥18 years of age; Exclusions: Allergan: History of advanced fibrocystic disease, existing carcinoma, active infection, and disease including DM with HbA1C>8%, pregnant or nursing, tissue incompatible with mammaplasty, condition causing an unwarranted surgical risk, psychologically incompatible with surgery, wiling to undergo further surgery for revision; Mentor CPG: history of rheumatic diseases or syndromes or inflammatory arthritic condition, advanced cancer, infection or abscess, premalignant breast disease, breast malignancy, HIV, individuals with ptosis of a severity that would require a mastopexy, pregnant or nursing, history of nursing within 3 mo of study enrollment, presence of any other silicone implant other than a breast implant, condition that would	nd	Clinical/Physical examination

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Connecticut	US Kern 1997 9283576[58]	McGhan Medical Corporation Indirect, to funding institution	Comparative, historical cohort, registry-linked, retrospective, observational	Implant: 1980-1993; Control: 1985-1993 Implant: 13 y; Control: 8 y Registry, medical records	Only silicone gel implants, Primary augmentation, Received implants, later developed primary breast cancer or other systemic malignancies; Exclusions: history of breast or nonbreast cancer	Historical cohort, registry-linked approach	Registry
Denmark Private	Denmark Kjoller 2003 12545102[60]; Kjoller 2004 14676691[61]	International Epidemiology Institute, which in turn received funding from the Dow Corning Corporation, and the Danish Cancer Society. Indirect, to funding institution	Comparative, retrospective, observational	1998 nd Registry, medical records	Primary augmentation, Replacement/revision augmentation, Augmentation only, Women receiving implants at 2 private plastic surgery clinics between January 1, 1977-December 31, 1997.	1st group: women who had undergone other forms of cosmetic surgery at the same study clinics as the breast implant patients matched by age and calendar year at procedure; 2nd group: women from the general population matched to the women with implants based on sex, age, and current residence.	From women, Questionnaire

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Michigan/Ohio	US Laing 2001 11581094[62]	Dow Corning Corporation and NIH Indirect, to funding institution	Comparative, prospective, observational	1992-1995 3 y Survey of women	All implants allowed, Female health professionals with or without implants, 18 to 99 years old who returned completed questionnaires in response to the invitational mailing of the Women's Health Study; Exclusions: women declining to participate, missing updated information on breast implant history on the baseline questionnaire, reporting a CTD diagnosis, or missing information on a CTD, diagnosis of a CTD, but unable to obtain a date of diagnosis from the participant or their physicians	Female health professionals without implants, 18 to 99 years who returned completed questionnaires in response to the invitational mailing of the Women's Health Study	Medical records, From women, Questionnaire
Breast Implant Surveillance Study	US Le 2005 15743498[63]	National Cancer Institute, NIH No	Comparative, retrospective, observational	1993-1994 1 y Registry	All implants allowed, Primary reconstruction, Reconstruction only, Breast cancer diagnosed age <65 y, early stage or unstaged first primary breast cancer in 1983, 1985, 1987, or 1989, treated with mastectomy; Exclusions: discordant types of implants in two breasts; implant data unavailable	Breast cancer diagnosed age <65 y, early stage or unstaged first primary breast cancer in 1983, 1985, 1987, or 1989, treated with mastectomy, No implant	Registry

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Women's Health Cohort Study	US Lee 2011 20943932[64]	National Institute of Health	Comparative, prospective, observational	1992-1995 3 y Survey of women	All implants allowed, Female health professionals, with or without implants 18 to 99 years who returned completed questionnaires in response to the invitational mailing of the Women's Health Study; Exclusions: Women declining to participate from the beginning; those missing updated information on breast implant history on the baseline questionnaire, 2001; those reporting a CTD diagnosis occurring before baseline, or were missing information on a CTD; those subsequently declining participation after enrolling; and those providing a subsequent diagnosis of a CTD, but we were unable to obtain a date of diagnosis from the participant or their physicians	Female health professionals without implants, 18 to 99 years who returned completed questionnaires in response to the invitational mailing of the Women's Health Study	Medical records, From women, Questionnaire

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Sweden/Denmark Public-Private	Sweden, Denmark Lipworth 2009 19003966[67]; Friis 2006 16152592[40]	Dow Corning Corporation, International Epidemiology Institute, and Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center Indirect, to funding institution etc.	Single arm, prospective, observational	nd nd Medical record, multiple center	All implants allowed. Augmentation only, Swedish women who underwent implantation for the first time between 1965- 1993, Danish women who underwent implantation at public hospitals between 1977-1992 or at 8 private clinics of plastic surgery between 1973-1995; Exclusions: implants for reconstruction	NA	Medical records
Mentor (MemoryGel Round) Cohort	US (mostly) Mentor (MemoryGel Round) Cohort 2005 No PMID[49,79]	Mentor Yes	Single arm, prospective, observational	nd nd Industry-organized cohort	Primary augmentation, Primary reconstruction, Replacement/revision augmentation, Replacement/revision reconstruction, Specific implant type: Mentor MemoryGel (Silicone Gel-Filled Breast Implants, Round)	NA	nd
Mentor (MemoryGel/ MemoryShape) Post-Approval Study	US Mentor (MemoryGel/ MemoryShape) Post-Approval Study 2014 No PMID[48,49]	Mentor Yes	Comparative, prospective, observational	nd nd Industry-organized cohort	Primary augmentation, Primary reconstruction, Augmentation only, Reconstruction only; Specific implant type: Mentor MemoryGel	Saline implants	nd

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Mentor (MemoryShape/CPG Anatomic) Cohort	US Mentor (MemoryShape/CPG Anatomic) Cohort 2013 No PMID[48,82]; Hammond 2012 22327894[45]	Mentor Yes	Single arm, prospective, observational	2002-2004 2 y Industry-organized cohort	Primary augmentation, Primary reconstruction, Replacement/revision augmentation, Replacement/revision reconstruction, Specific implant type: Mentor MemoryShape/CPG Anatomic, ≥18 years old; Exclusions: pregnant or recent nursing, diagnosed rheumatic disease, cancer (in augmentation arm), high surgical risk	NA	nd

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Swedish Inpatient Register	Sweden Nyren 1998 9492663[70]; Nyren 1998 9566378[69]; Signorello 2001 11293521[78]; Fryzek 2001 11176625[41]; Lipworth 2007 17667401[66]	International Epidemiology Institute, which in turn received funds from the Dow Corning Corporation Indirect, to funding institution etc.	Comparative, matched, retrospective, observational	nd nd Medical records	All implants allowed, augmentation or reconstruction; Exclusions: National registration numbers that could not be found in any of the three registers, date of death or of emigration before date of admittance, no operation confirmed, or inconsistent gender code, definite connective tissue disease diagnosed before or within 1 mo of the first hospital admission for breast augmentation, entered the study <30 days before the end of follow up (December, 31 1993), and emigrated between the operation and the start of follow up	Women with breast reduction surgery between 1965-1993; Exclusions: same as for implant group, matched for hospital, age and calendar year at operation.	Medical records, Registry, From women, Questionnaire
Italy	Italy Oberto 1993 No PMID[71]	nd No	Comparative, retrospective, observational	~1992 nd Single center	Only silicone gel implants, Reconstruction only, >2 years since surgery, Exclusions: Deceased, signs of symptoms of cancer	>2 years since surgery. Random sample of clinic patients post-mastectomy, no implant, free of cancer signs or symptoms	Clinical/Physical examination

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
SE Scotland	Scotland Park 1998 9462756[72]	nd No	Comparative, matched, retrospective, observational	1982-1991 nd Medical records	Only silicone gel implants, Primary augmentation, Primary reconstruction, Survived for 1 year following their operation, Breast augmentation for reasons other than reconstruction following mastectomy for cancer between 1982-1991; Breast reconstruction for reconstruction following mastectomy for breast cancer over the same 10-year period; Exclusions: History of locally advanced or metastatic disease at the time of initial treatment; <1 year survival after initial breast implant operation	Women matched with women who had undergone mastectomy for breast cancer without reconstruction, matched for age, stage of disease at diagnosis, and time of operation.	From women, Questionnaire, Clinical/Physical examination, Laboratory examinations
WHI OS	US Rubin 2010 20195108[75]	National Heart, Lung and Blood Institute, NIH, U.S. Department of Health and Human Services No	Comparative, prospective, observational	1993-1998 5 y Multiple centers	All implants allowed, Postmenopausal women 50-79 years old with implants; Exclusions: History of breast cancer	Postmenopausal women 50-79 years old without implants	From women, Questionnaire

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Nurses Health Study	US Sanchez-Guerrero 1995 7760867[76]; Karlson 2001 11268230[57]	NIH No	Comparative, matched, retrospective, observational	1976-1990 14 y Survey of female nurses age 30-55 at enrollment	All implants allowed, Sanchez: from May 1990 or earlier; Karlson: women who reported having implants for cosmetic or prophylactic purposes; Exclusions: Sanchez: Women for whom information was missing or whose connective-tissue disease was diagnosed before 1976 or after May 1990; Karlson: women without a blood sample, and who reported any condition potentially associated with hypergammaglobulinemia or monoclonal gammopathy, connective tissue disease, and breast implant surgery after breast cancer surgery before the time of the blood collection (exclusions not mutually exclusive).	Sanchez: women without implants in the Nurses' Health Study cohort; Karlson: identical exclusion criteria, women without breast implants were potential controls, matched to the exposed group by year of birth and the date the blood sample was returned.	Medical records, From women, Questionnaire

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Houston	US Schusterman 1993 8395164[77]	nd No	Comparative, prospective, observational	1986-1992 6 y Registry	Only silicone gel implants, Reconstruction only	Women with autogenous tissue reduction	Registry, Medical records, From women, Questionnaire, Clinical/Physical examination, Laboratory examination
Sientra	US Sientra 2012 No PMID[81]	Sientra Yes	Single arm, prospective, observational	2002-2007 5 y Industry-organized cohort	Primary augmentation, Primary reconstruction, Replacement/revision augmentation, Replacement/revision reconstruction, Specific implant type: Sientra Silicone Gel Breast Implants, ≥18 years old; Exclusions: CTD, premalignant or malignant breast disease without mastectomy, pregnant or lactating, contraindications to surgery	NA	nd
Dutch Silicone Implant Support Group	The Netherlands Vermeulen 2003 14528527[84]	nd No	Comparative, retrospective, observational	1998 nd Survey of women	Only silicone gel implants, Replacement/revision, Exclusions: received information from the surgeon about the integrity of the removed implant	Patients attending the clinic for chronic pain and fatigue, female coworkers from the Center and others.	From women, Questionnaire

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
San Diego	US Weisman 1988 3420184[86]	Arthritis Foundation Clinical Center, NIH Rheumatic Disease Training Program, UCSD General Clinical Research Center, National Institutes of Health/Division of Research Resources No	Single arm, retrospective, observational	~1986 1 mailing Medical records, single center	Only silicone gel implants, Augmentation only	NA	From women, Questionnaire
Tampa	US Wells 1994 8134482[87]	nd No	Comparative, retrospective, observational	1990-1991 1 y Survey of women, Single surgeon	Only silicone gel implants, Primary augmentation, Primary reconstruction, 20-60 years old, Exclusions: silicone chin or nose implant or collagen injections	Undergone blepharoplasty, liposuction, or rhinoplasty, Exclusions: undergone breast implantation	From women, Questionnaire

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Denmark Public-Private	Denmark Winther 2001 11227138[88]; Kjoller 2002 11862026[59]; Jacobsen 2004 15596635[55]; Fryzek 2007 17321754[42]	International Epidemiology Institute and The Danish Cancer Society No	Comparative, matched, retrospective, observational	nd nd Medical records	All implants allowed, Augmentation only, Women who received cosmetic breast implants between 1973- 1995 (Winther 2001 11227138); Women who receive breast implant surgery at public hospitals between 1977- 1992 and at 8 private clinics between 1973- 1995 (Fryzek 2007 17321754); Exclusions: children born outside of Denmark or before January 1, 1977, were excluded (Kjoller 2010 11862026).)	Women undergoing another type of cosmetic treatment matched on age and calendar year from procedure/consultation, (Winther 2001 11227138); 1st control group: women who underwent breast reduction surgery at Danish public hospitals between 1977- 1992 (n=7,071); 2nd control group: women who attended the private clinics for reasons other than breast implantation (breast reduction and mastopexia, facial surgery, skin excisions, liposuction, other types of plastic surgery, and consultation only, matched on clinic, age, and calendar year of procedure or consultation to women who underwent breast augmentation. (Fryzek 2007 17321754, Jacobsen 2004 15596635, Kjoller 2010 11862026)	Medical records

Cohort name	Country Author, Year, PMID (see report reference list for references)	Funding Industry funded?	Study design	Recruitment: years duration setting	Inclusion/exclusion criteria for implant	Inclusion/exclusion criteria for controls	How were results obtained?
Buenos Aires	Marchioni 1994 No PMID	nd nd	Single arm, retrospective, observational	1993- nd Medical records	nd	NA	NA
Chambrey-Les-Tours, France	Penaud 2013 23122532	nd nd	Single arm, prospective, observational	2009-2011 nd Survey of women, selected surgeons	Women who were examined by 1 of 15 participating plastic surgeons who wanted a breast augmentation.	NA	From women, Questionnaire
Oslo, Norway	Kalaaji 2013 23324358	nd nd	Single arm, retrospective, observational	nd nd Survey of women, Single surgeon	Patients treated by senior author between 2005-2008 who were reachable through email and who answered the survey.	NA	From women, Questionnaire

Abbreviations: DM, diabetes; FDA, Food and Drug Administration; mo, months; NIH, National Institute of Health; y, year

Appendix C.2. Details of Implant Arms

Study Cohort	Women [Implants] N eligible N enrolled	Women [Implants] Primary implant Explanted	Women [Implants] Replacement Concomitant surgery Other	Augmentation	Reconstruction	Implant Shape Size Surface	Implant Brand Manufacturer Years	Type of silicone Type of shell	% Silicone % Saline % Double lumen % Other
Allergan (Inamed/Natrelle Round) Cohort	nd 715	553/715 [1035/1348] nd	162/715 [313/1348] nd nd	602/715	113/715	Round nd Smooth (55%), Textured 45%	Inamed Round (Natrelle round) Allergan unclear	Base and Crosslinker; platinum cure Diphenyl silicone elastomer dispersion (textured: MED-6400 silicone elastomer)	100 0 0 0
Allergan Natrelle Breast Implant Follow-up Study	nd 41,405 nd 15.643	84% nd 94% nd	16% nd nd 7% nd nd	nd nd	nd nd	Round 300-399 cm2 43% Smooth: 93% Round 300-399 cm2 43%	nd nd	nd nd	100% 0 0 0 0 100% 0 0

Study Cohort	**Women [Implants] N eligible** **N enrolled**	**Women [Implants] Primary implant** **Explanted**	**Women [Implants] Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant Shape** **Size** **Surface**	**Implant Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort	nd 941	717/941 nd	224/941 nd nd	648/941	293/941	Anatomic nd Textured	Natrelle 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implant Allergan 2001-2002	Highly cohesive silicone gel Biocell elastomer surface shell	100 0 0 0
Munster, Germany	nd 32	nd	nd	0	32/32 (100%) [assumed]	nd	nd	nd	100 0 0 0
Copenhagen Deaconess Hospital	368 190 [354]	114/190 (60%) 19/190 (10%) [38/354 (11%)]	74/190 (30%) nd nd	190/190 (100%)	0	nd	nd nd 1963-1987	nd	77 2 2 3% (Unknown 6%; No current 11%)

Study Cohort	**Women [Implants] N eligible** **N enrolled**	**Women [Implants] Primary implant** **Explanted**	**Women [Implants] Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant Shape** **Size** **Surface**	**Implant Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
Atlanta/Seattle/ New Jersey	Case: 2551 2174 [36] Control: 2571 2009 [44]	36/2174 (2%) nd 44/2009 (2%) nd	nd nd nd nd nd nd	36/2174 44/2009	nd nd	nd nd	nd nd	nd nd	nd nd
South 18 Centers	13488 7447	7447/7447 (100%) 0	0 0 0	7447/7447 (100%)	0	nd	nd nd 1962-1988	nd	50% 12% 34% 0.1% (4% Unknown)
Ontario/Quebec	24897 24558	nd	nd	15893/15893 (100%)	0	nd <175->225cc nd	nd	nd 11% polyurethane; 65% other; 25% unknown	66% 4% nd Saline & silicone 15% (Unknown 16%)

Study Cohort	**Women [Implants] N eligible** **N enrolled**	**Women [Implants] Primary implant** **Explanted**	**Women [Implants] Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant Shape** **Size** **Surface**	**Implant Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
Birmingham, AL	445 344 [687]	344/344 (100%) [687/687 (100%)] 0	0 0 0	344/344 (100%)	0	nd	nd Surgitek, Cox-Uphoff International, Dow Corning, Mentor or Heyer-Schulte, and McGhan or 3M/McGhan before or during 1970-1988	nd	100 0 17 nd
Alberta Health Care Data	10,835 10,835 10,368 10,368	10,835/10,835 (100%) 0 10,368/10,368 (100%) 0	0 0 0 0 0 0	10,835/10,835 (100%) 10,368/10,368 (100%)	0 0	nd nd	nd nd 1973-1986 nd nd 1974-1986	nd nd	nd nd
Michigan	Case: nd 274	nd	nd	nd	nd	nd	nd	nd	nd

Study Cohort	**Women [Implants]** **N eligible** **N enrolled**	**Women [Implants]** **Primary implant** **Explanted**	**Women [Implants]** **Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant** **Shape** **Size** **Surface**	**Implant** **Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
	Control: 1200 1184	nd	nd	nd	nd	nd	nd	nd	nd
Barcelona	225 81 [93]	60/81 (69%) nd	19/81 (22%) nd 3 implants in 5 breast (6%) and 4 implants in 1 breast (1%). In 2 cases (2%), we don't know if the implant was changed at some time	0	81/81 (100%)	nd	nd nd 1980-1995	nd	87% 5% 2% nd (Unknown 6%)
Rotterdam University Hospital 1990-1995	102 63	nd	nd	0	63/63 (100%)	nd	nd nd 1990-1995	nd	100% 0 0 0
Rotterdam University Hospital 1995-1997	57 57	nd	nd	0	57/57 (100%)	nd	nd Laboratoires Eurosilicone, Apt, France 1995-1997	nd	100 0 0 0

Study Cohort	**Women [Implants] N eligible** **N enrolled**	**Women [Implants] Primary implant** **Explanted**	**Women [Implants] Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant Shape** **Size** **Surface**	**Implant Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
Puerto Rico	~2474 1682	nd	nd	1379/1682 (92%)	303/1682 (18%)	nd	nd	nd Polyurethane (n=8, 0.5%)	100 0 0 0
U Minnesota	251 251 59 59	251/251 (100%) nd nd nd	nd nd nd 59/59 (100%) nd nd	0 0	251/251 (100%) 59/59 (100%)	Round 150-775cc Smooth or textured Round 150-775cc Smooth or textured	MemoryGel Mentor nd MemoryGel Mentor nd	Cohesive gel Silicone Cohesive gel Silicone	100 0 0 0 100 0 0 0
Los Angeles	nd 3500	nd nd	nd nd nd	3139/3139 (100%)	0	nd	nd nd 1953-1980	nd	nd 9% nd (or Unknown) 14%

Study Cohort	**Women [Implants] N eligible** **N enrolled**	**Women [Implants] Primary implant** **Explanted**	**Women [Implants] Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant Shape** **Size** **Surface**	**Implant Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
Mayo Clinic	2033 200 [681]	0 0	100% 0 0	27/200 (14%)	173/200 (87%)	nd	nd	nd	100% 0 0 0
Alberta Health Registry	9200 1112	nd nd	nd nd nd	1112/1112 (100%)	0	nd	nd nd 1978-1986	nd	100% 0 0 0
Sydney	528 458	458/528 (87%) nd	nd nd nd	458/528 (87%)	nd	nd	nd nd 1979-1983	nd	100% 0 0 0
Tuscon	1968 1968	nd 0/1968 (0%)	nd nd nd	1968/1968 (100%)	0	nd	nd	nd	nd

Study Cohort	**Women [Implants] N eligible** **N enrolled**	**Women [Implants] Primary implant** **Explanted**	**Women [Implants] Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant Shape** **Size** **Surface**	**Implant Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
Massachusetts General Hospital	304 106	nd	nd	106/106 (100%)	0	nd Mean 246.9 mL (120-600 mL) Smooth and textured	nd nd 1973-1991	Gel Silicone and polyurethane	73% nd nd Polyurethane-coated 27%
Denmark Reconstruction	1439 1435	nd	nd	nd	nd	nd	nd nd 1977-1993	nd	nd
Olmstead County, MN	749 [1840] 749 [1840]	572/749 (76%) nd	177/749 (24%) nd nd	534/749 (71%)	215/749 (29%)	nd	Becker expanders, bilumen implants, or both nd 1964-1991	nd Silicone	78% 5% nd 17% (10% polyurethane; 7% were a combination of silicone and saline)

Study Cohort	**Women [Implants] N eligible** **N enrolled**	**Women [Implants] Primary implant** **Explanted**	**Women [Implants] Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant Shape** **Size** **Surface**	**Implant Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
Free University, Amsterdam	374 235 [392]	235/235 (100%) 0	0 0 0	nd	nd	nd	nd nd 1978-1990	nd	100% 0 0 0
Style 410 Europe	163 [300] 163 [300]	137/163 (85%) nd	nd nd 25/163 (15%) Both reconstruction and revision	112/163 (70%)	25/163 (15%)	Round nd Textured/cohesive	Style 410 Allergan 1995-2001	nd Biocell texturing	100% 0 0 0
Style 410 Stockholm	302 144 [286]	124/144 (86%) nd	nd nd 20/144 (14%) Revision of previous implantation	124/144 (86%)	nd	nd 190 to 475 cc; median 280 cc nd	Style 410 Inamed 1995-1999	Cohesive nd	100% 0 0 0

Study Cohort	**Women [Implants] N eligible** **N enrolled**	**Women [Implants] Primary implant** **Explanted**	**Women [Implants] Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant Shape** **Size** **Surface**	**Implant Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
Finland Hospitals	423 423	nd	nd	100%	0	nd	nd nd 1967-1999	nd	>90% (estimated) 0 0 0
Denmark Private-Public subset	630 271 [533]	nd	nd	271/271 (100%)	0	nd	nd nd 1973-1998	nd	100% 0 0 0
Texas Children's Hospital	nd 42	nd	nd	42/42 (100%)	0	nd	nd	nd	nd
Allergan vs. Mentor	119 [238] 118	nd	nd	nd	nd	Anatomic 140 cc to 740 cc Textured	Natrelle 410 Allergan nd	Highly cohesive Silicone	100% 0 0 0

Study Cohort	**Women [Implants] N eligible** **N enrolled**	**Women [Implants] Primary implant** **Explanted**	**Women [Implants] Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant Shape** **Size** **Surface**	**Implant Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
	118 [236] 117	nd	nd	nd	nd	Anatomic 120 cc to 775 cc Textured	321 CPG, 321, 332, 322 Mentor ns	Cohesive III™ MemoryGel™ Silicone	100 0 0 0
Connecticut	4179 680	nd	nd	680/680 (100%)	0	nd	nd nd 1980-1993	nd	100% 0 0 0
Denmark Private	754 423	717/754 (95%) nd	37/754 (5%) nd nd	423/423 (100%)	0	nd nd Textured	nd nd 1977-1997	nd nd	50% 0 34% 16%
Michigan/Ohio	Case: 212 205 Control: 2258 2095	nd nd	nd nd	nd nd	nd nd	nd nd	nd nd	nd nd	nd nd

Study Cohort	**Women [Implants] N eligible** **N enrolled**	**Women [Implants] Primary implant** **Explanted**	**Women [Implants] Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant Shape** **Size** **Surface**	**Implant Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
Breast Implant Surveillance Study	5862 1018 [866]	100% [289/866]	[237/866]	0	100%	nd	nd	nd	38% 17% 36% 4% (Unknown 4%)
Women's Health Cohort Study	nd 3950	nd	nd	1866/3950 (49%)	1202/3950 (32%)	nd	nd nd after 1962	nd	70% 37% nd 14% (Both)
Sweden/Denmark Public-Private	6274 6222	nd	nd	6222/6222 (100%)	0	nd	nd nd 1965-1995	nd	80% nd nd nd

Study Cohort	**Women [Implants] N eligible** **N enrolled**	**Women [Implants] Primary implant** **Explanted**	**Women [Implants] Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant Shape** **Size** **Surface**	**Implant Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
Buenos Aires	91 64	nd	nd	100%	0	nd nd Smooth 48%; Textured 31%; Polyurethane 21%	nd nd 1987-1991	nd Silicone 79%; polyurethane 21%	100% 0 0 0
Mentor (MemoryGel Round) Cohort	nd 1008 [1898]	803/1008 nd	205/1008 nd nd	697/1008	311/1008	Round nd Smooth 70%, Textured 30%	MemoryGel Mentor nd	Base and Crosslinker; platinum cure Diphenyl Silicone Elastomer Dispersion	100% 0 0 0
Mentor (MemoryGel/ MemoryShape) Post-Approval Study	nd 41,451	31,195/41,338 nd	10,143/41,338 nd nd	34,554/41,338	6784/41,338	Round and anatomic nd Smooth and Textured	MemoryGel & MemoryShape Mentor nd	Base and Crosslinker; platinum cure Diphenyl Silicone Elastomer Dispersion	100% 0 0 0

Study Cohort	Women [Implants] N eligible N enrolled	Women [Implants] Primary implant Explanted	Women [Implants] Replacement Concomitant surgery Other	Augmentation	Reconstruction	Implant Shape Size Surface	Implant Brand Manufacturer Years	Type of silicone Type of shell	% Silicone % Saline % Double lumen % Other
	nd 1039	952/1036 nd	84/1036 nd nd	1012/1036	24/1036	nd	nd	nd	0 100% 0 0
Mentor (MemoryShape/CPG Anatomic	nd 955 [1831]	763/955 nd	192/955 nd nd	696/955	259/955	Anatomic nd Smooth and Textured	MemoryShape /CPG Anatomic Mentor 2002-2004	High Purity Silicone Gel Diphenyl Silicone Elastomer / High Consistency, High Tear Strength Silicone Elastomer	100% 0 0 0
Swedish Impatient Register	7632 7442	nd	nd	3500/7442 (47%)	3942/7442 (53%)	nd	nd nd 1965-1993	nd	nd

Study Cohort	**Women [Implants] N eligible** **N enrolled**	**Women [Implants] Primary implant** **Explanted**	**Women [Implants] Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant Shape** **Size** **Surface**	**Implant Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
Italy	165 102	nd	nd	0	100%	nd	nd	nd	100% 0 0 0
SE Scotland	186 110 289 207	nd nd	nd nd	110/110 (100%) 0	0 207/207 (100%)	nd 258 mL nd 258 mL nd	nd nd	nd nd	nd nd
WHI OS	93,676 (both arms) 1,257	nd	nd	nd	nd	nd	nd	nd	67% 17% nd 5% (12% Unknown)

Study Cohort	**Women [Implants] N eligible** **N enrolled**	**Women [Implants] Primary implant** **Explanted**	**Women [Implants] Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant Shape** **Size** **Surface**	**Implant Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
Nurses Health Study	1864 1183	nd	nd	587/1183 (50%)	387/1183 (33%)	nd	nd nd 1976-1990	nd	74% 14% 6% Polyurethane-coated 1% (Unknown 5%)
Houston	250 [308] 250 [308]	nd	nd	0	250/250 (100%)	nd	nd nd 1986-1992	nd	100% 0 0 0
Sientra	nd 1788 [3506]	1344/1755 nd	444/1788 nd nd	1477/1788	311/1788	Round 88% nd Smooth 58%, Textured 42%	Sientra Silicone Gel Breast Implants Sientra 2002-2007	High-strength silicone gel High-strength silicone elastomer	100% 0 0 0

Study Cohort	**Women [Implants] N eligible** **N enrolled**	**Women [Implants] Primary implant** **Explanted**	**Women [Implants] Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant Shape** **Size** **Surface**	**Implant Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
Dutch Silicone Implant Support Group	500 319	0 nd	nd nd nd	nd	nd	nd	nd	nd	100% 0 0 0
San Diego	463 378	nd	nd	378/378 (100%)	0	nd	nd Dow-Corning, Heyer-Schulte, McGhan, Cox-Uphoff 1970-1981	nd Silicone elastomeric shell	100% 0 nd 0
Tampa	nd 222	nd	nd	nd	nd	nd	nd nd Median 1986±0.48	nd	100% 0 0 0

Study Cohort	**Women [Implants] N eligible** **N enrolled**	**Women [Implants] Primary implant** **Explanted**	**Women [Implants] Replacement** **Concomitant surgery** **Other**	**Augmentation**	**Reconstruction**	**Implant Shape** **Size** **Surface**	**Implant Brand** **Manufacturer** **Years**	**Type of silicone** **Type of shell**	**% Silicone** **% Saline** **% Double lumen** **% Other**
Denmark Public-Private	2761 2761	nd	nd	2761/2761 (100%)	0	nd	nd nd 1973-1995	nd	≤84% nd nd nd (Unknown 16%)
Buenos Aires	91 64	nd	nd	100%	0	nd nd Smooth 48%, Textured 31%, Polyrethane 21%	nd nd 1987-1991	nd Silicone 79%; Polyurethane 21%	100% nd nd nd
Chambrey-Les-Tours, France	270 122	122 (100%) nd	nd	122/122 (100%)	0	nd	nd	nd	nd
Oslo, Norway	121 61	61 (100%) nd	nd	61/61 (100%)	0	nd	nd	nd	nd

Abbreviations: nd, not documented

Appendix C.3. Baseline Characteristics

Study Cohort	Mean age at 1st implant (SD), y	Mean age at time of study (SD), y	Implant duration, y	Race/Ethnicity	History of breast cancer	Other comorbidities
Allergan (Inamed/Natrelle Round) Cohort	38 Primary aug: 34 Rev-aug: 42 Primary recon: 50 Rev-recon: 56	nd	4, 10y	W: 86% B: <1% H: 5% A: 3% Other: 5%	nd	nd
Allergan Natrelle Breast Implant Follow-up Study	All arms: 36 [median]	nd	nd	nd	nd	nd
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort	41 [median]	nd	nd	W: 91.5% B: 1.5% H: 3.0% A: 2.3% Other: 1.3%	nd	nd
Munster, Germany	nd	Silicone: 53 (9.5)	nd	nd	T1N0M0 40.6% T2N0M0 28% T1N1M0 12.5% T2N1M0 9.3% T3N1M0 6.2% T4N1M0 3.4% Radiation therapy: 25% Chemotherapy: 28% Time passed since surgery: 6.9 (4.6) y Modified mastectomy 69.9% Skin sparing Mastectomy 25% Tylectomy 3.1%	nd

Study Cohort	Mean age at 1st implant (SD), y	Mean age at time of study (SD), y	Implant duration, y	Race/Ethnicity	History of breast cancer	Other comorbidities
Copenhagen Deaconess Hospital	31 (17-57)	52 (33-81)	19 (5-35)	nd	nd	Current smoker: 45% BMI ≥25: 24% Alcohol ≥7 drinks/wk: 39% Alcohol <1 drink/wk: 24%
Atlanta/Seattle/New Jersey	<30: 10 (28%) 30-34: 11 (31%) ≥35: 15 (42%)	nd	<5 y: 12 (33%) 5-9 y: 12 (33%) ≥10 y: 12 (33%)	nd	nd	nd
South 18 Centers	nd	34.8	12.9 (mean years of follow-up)	nd	Age at breast cancer: 48.0	nd
Ontario/Quebec	31.3 (18-≥45) [median]	nd	nd	nd	nd	nd
Birmingham, AL	34.1 (7.9)	51.4 (8.4)	nd	nd	nd	nd
Alberta Health Care Data	nd	nd	nd	nd	nd	nd
Michigan	nd	nd	8.8 (1-28) [median]	nd	nd	nd
Barcelona	nd	49.6 (8.95) (32-72)	4.36 (2.87) (1-13) [mean silicone exposure]	nd	100% mastectomy	nd
Rotterdam University Hospital 1990-1995	46 (9) 46 (25-71) [median]	nd	nd	nd	The indications for mastectomy were breast cancer (n=42).	Mastectomy for DCIS: 21% Mastectomy for prophylactic reasons: 8% Pagat: 3%

Study Cohort	Mean age at 1st implant (SD), y	Mean age at time of study (SD), y	Implant duration, y	Race/Ethnicity	History of breast cancer	Other comorbidities
Rotterdam University Hospital 1995-1997	43 (26-58)	nd	nd	nd	Primary occurrence: 26% Recurrence: 7% The indications for breast cancer (n=15) and recurrence of breast cancer after breast-conserving therapy (n=4)	Mastecomy for prophylactic reasons: n=56 Mastectomy for extensive ductal carcinoma in situ: n=12
Puerto Rico	nd	nd	nd	nd	nd	nd
U Minnesota	45	nd	nd	Total participants: W: 90% B: 2% A: 2% Other: 6%	nd	nd
Los Angeles	For 11y data: 34.1	Assumed: 32	nd	W: 100%	nd	nd
Mayo Clinic	14-75	nd	4.1 (0.5) [median]	nd	nd	nd
Alberta Health Registry	30 (26-35)	42 (37-48)	12 (calculated)	nd	nd	Years education: 12 (12-14) Married: 80% Single: 5% Divorced, windowed: 15%
Sydney	32.47	nd	nd	nd	nd	nd
Tuscon	42.8 (calculated)	52.1 (43-69)	9.3 (1.1-17)	nd	nd	nd
Massachusetts General Hospital	32.4 (15-56)	nd	6.7 (0.6-18.5)	nd	nd	nd
Denmark Reconstruction	45 (15-78) [median]	nd	7.2	nd	nd	nd
Olmstead County, MN	34.4 (10.5)	nd	7.8 (5.5) (0-25.8)	W: 96.8%	nd	nd

Study Cohort	Mean age at 1st implant (SD), y	Mean age at time of study (SD), y	Implant duration, y	Race/Ethnicity	History of breast cancer	Other comorbidities
Free University, Amsterdam	nd	43 (19-73)	6.5 (2-14)	W: 100% (probably)	Primary occurrence: 24%	nd
Style 410 Europe	43 (25-83) [median]	nd	nd	W: 98.2% B: 0.6% H: 0% A: 0.6% Other: 0.6%	nd	nd
Style 410 Stockholm	39 (25-65) [median]	nd	6 [5-9]	W: 95.8%	nd	nd
Finland Hospitals	nd	30.5 (5.0) [mean age at first birth after implant]	4.7 (3.1)	nd	nd	No previous births: 49.9% No previous pregnancies: 35.2% Smoking during pregnancy: 17.9% >20 antenatal visits: 11.6% Antenatal hospital stay: 19.4% Cesarean section: 18.4%
Denmark Private-Public subset	31.3	nd	nd	nd	nd	Smoking: never: 29% Smoking: past: 19% Smoking: current: 51% Alcohol: 0-56 drinks/y: 23% Alcohol: 57-173 drinks/y: 23% Alcohol: 174-416 drinks/y: 22%

Study Cohort	Mean age at 1st implant (SD), y	Mean age at time of study (SD), y	Implant duration, y	Race/Ethnicity	History of breast cancer	Other comorbidities
Texas Children's Hospital	nd	30.8 (4.3) (22-39)	nd	W: 86% B: 2% H: 12%	nd	Smoking: 10% Cesarean delivery: 38% Parity: Primiparous: 64% Previous breast-feeding experience: 26% Late breast-feeding initiation: 57%
Allergan vs. Mentor	nd	nd	nd	nd	nd	nd
Connecticut	34 (10) (assumed)	nd	nd	nd	nd	nd
Denmark Private	32 (17-61)	42 (8)	year of operation: 1990	nd	nd	Smoking: current: 55% Smoking: former: 19% Alcohol: <1 drink/wk: 24% Alcohol: 1-2.9 drinks/wk: 23% Alcohol: 3-6.9 drinks/wk: 24% Alcohol: 7+drinks/wk: 29%
Michigan/Ohio	nd	nd	nd	nd	nd	nd
Breast Implant Surveillance Study	46.7	nd	nd	W: 94.2% B: 1.3% H: 2.0% A: 1.6%	In situ: 19.6% Localized 59.0% Regional 20.7% Radiation therapy: 4.7%	nd

Study Cohort	Mean age at 1st implant (SD), y	Mean age at time of study (SD), y	Implant duration, y	Race/Ethnicity	History of breast cancer	Other comorbidities
Women's Health Cohort Study	nd	57.0 (8.4)	17.1 (12.7-23.0) [median]	nd	History of breast cancer: 28.2%	Smoking: never: 52.4% Smoking: past: 38.0% Smoking: current: 9.6% Mean BMI: 24.7 Mean alcohol consumption g/d: 5.5 Post-menopausal hormone use: never: 32.8% Post-menopausal hormone use: past: 14.8% Post-menopausal hormone use: current: 52.4%
Sweden/Denmark Public-Private	32 (6.6)	nd	18.4 (0.1-37.8)	nd	nd	nd
Buenos Aires	32 (17-47)	nd	nd	nd	nd	nd
Mentor (MemoryGel Round) Cohort	39	42 (implicit)	3	nd	nd	nd
Mentor (MemoryGel/MemoryShape) Post-Approval Study	≥30: 79.3%	nd	nd	W: 79.4%	nd	nd
Mentor (MemoryShape/CPG Anatomic	25-40: 42% 40 (18->70) [median]	nd	nd	W: 92% B: 1.7% A: 1.7%	nd	nd
Swedish Impatient Register	nd	nd	nd	nd	nd	nd
Italy	42 (19-60)	48.5 (33-67)	5 (2-17)	nd	nd	nd

Study Cohort	Mean age at 1st implant (SD), y	Mean age at time of study (SD), y	Implant duration, y	Race/Ethnicity	History of breast cancer	Other comorbidities
SE Scotland	17-60	34.1	5.25	nd	nd	nd
WHI OS	<30-≥55	50-79	nd	W: 1.5% B: 0.5% H: 1.7% A: 1.7% Native American: 1.5% Other: 2.0%	nd	College education: 1.5% <College education: 1.7% Hormone use: never: 0.7% Hormone use: past: 1.3% Hormone use: current: 2.1% Current smoker: 2.1%
Nurses Health Study	nd	51.7 [at time of blood collection]	12.13	nd	33% described cancer as an indication for implants	nd
Houston	nd	46.3	nd	nd	Benign, T1, T2 Recurrence: 0.7% Radiation therapy: 7% Chemotherapy: 12%	nd
Sientra	39 [median]	nd	nd	W: 91.5% B: 1.5% H: 3.1% A: 2.1% Indian: 0.1%	nd	nd
Dutch Silicone Implant Support Group	nd	nd	nd	nd	nd	nd
San Diego	42	nd	6.8	nd	nd	nd

Study Cohort	Mean age at 1st implant (SD), y	Mean age at time of study (SD), y	Implant duration, y	Race/Ethnicity	History of breast cancer	Other comorbidities
Tampa	37 (0.67) [median]	nd	nd	W: 98%	nd	Prevalence of allergies: 38% History of cancer: 5%
Denmark Public-Private	nd	31 (13-64) [median]	nd	nd	nd	nd
Buenos Aires	32	nd	nd	nd	nd	nd
Chambrey-Les-Tours, France	34.3 (8.5)	nd	0.6	nd	nd	nd
Oslo, Norway	nd	nd	2.8	nd	nd	nd

Abbreviations: A, Asian; aug, augmentation; B, Black; DCIS, ductal carcinoma in situ; H, Hispanic; nd, no data; recon, reconstruction; rev, revision; W, White; wk, week; y, year

Appendix C.4. Results

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Allergan (Inamed/Natrelle Round) Cohort Implants: 715 women	100% [Inamed Round (aka Natrelle round)]	NA	Brain cancer	All participants	4 y	0.14% (1/715) [100%]	NA	NA
			Breast cancer, primary	All participants	4 y	0.17% (1/602) [84%]	NA	NA
					10 y	1.2% (7/602) [84%]	NA	NA
				Primary augmentation	10 y	0.88% (4/455)	NA	NA
				Revision augmentation	10 y	2.4% (3/127)	NA	NA
			Cervical cancer	All participants	4 y	0.14% (1/715) [100%]	NA	NA
			Lung cancer	All participants	4 y	0% (0/715) [100%]	NA	NA
			Vulvar cancer	All participants	4 y	0% (0/715) [100%]	NA	NA
			Lactation issues	All participants	4 y	18.5% (12/65) [100%]	NA	NA
				Primary augmentation	4 y	17.6% (9/51)	NA	NA
					10 y	18/nd	NA	NA
				Revision augmentation	4 y	15.4% (2/13)	NA	NA
					10 y	6/nd	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
				Primary reconstruction	4 y	0% (0/1)	NA	NA
					10 y	0% (0/nd)	NA	NA
				Revision reconstruction	4 y	0% (0/0)	NA	NA
					10 y	0% (0/nd)	NA	NA
			Reproductive issues	All participants	4 y	3.6% (26/715) [100%]	NA	NA
					10 y	6.2% (44/715) [100%]	NA	NA
				Primary augmentation	4 y	4.2% (19/455)	NA	NA
					10 y	7.9% (36/455)	NA	NA
				Revision augmentation	4 y	3.4% (5/147)	NA	NA
					10 y	4.1% (6/147)	NA	NA
				Primary reconstruction	4 y	2% (2/98)	NA	NA
					10 y	2% (2/98)	NA	NA
				Revision reconstruction	4 y	0% (0/15)	NA	NA
					10 y	0% (0/15)	NA	NA
			Raynaud's	All participants	10 y	0.14% (1/715) [100%]	NA	NA
				Primary augmentation	10 y	0.22% (1/455)	NA	NA
			Fibromyalgia	All participants	4 y	0.14% (1/715) [100%]	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
					10 y	1.3% (3/715) [100%]	NA	NA
				Primary augmentation	4 y	0% (0/455)	NA	NA
					10 y	0.44% (2/455)	NA	NA
				Revision augmentation	4 y	0.68% (1/147)	NA	NA
					10 y	0.68% (1/147)	NA	NA
				Primary reconstruction	4 y	0% (0/98)	NA	NA
					10 y	0% (0/98)	NA	NA
				Revision reconstruction	4 y	0% (0/15)	NA	NA
					10 y	0% (0/15)	NA	NA
			Rheumatoid arthritis	All participants	4 y	0.28% (2/715) [100%]	NA	NA
					10 y	0.56% (4/715) [100%]	NA	NA
				Primary augmentation	4 y	0.44% (2/455)	NA	NA
					10 y	0.44% (2/455)	NA	NA
				Revision augmentation	4 y	0% (0/147)	NA	NA
					10 y	0.68% (1/147)	NA	NA
				Primary reconstruction	4 y	0% (0/98)	NA	NA
					10 y	1% (1/98)	NA	NA
				Revision reconstruction	4 y	0% (0/15)	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
					10 y	0% (0/15)	NA	NA
			Scleroderma	All participants	4 y	0.14% (1/715) [100%]	NA	NA
				Primary augmentation	4 y	0% (0/455)	NA	NA
				Revision augmentation	4 y	0% (0/147)	NA	NA
				Primary reconstruction	4 y	1% (1/98)	NA	NA
				Revision reconstruction	4 y	0% (0/15)	NA	NA
			Suicide	All participants	4 y	0.28% (2/715) [100%]	NA	NA
					10 y	0.42% (3/715) [100%]	NA	NA
Allergan Natrelle Breast Implant Follow-up Study	100% (Natrelle Round)	Saline implant	Lactation issues	All participants	1-3 y	14.7% [nd]	15.7%	nd
			Offspring issues	All participants	1-3 y	Incidence rate: 0.74 [nd]	Incidence rate: 1.17	nd
Silicone implants: 41,405 women			Offspring issues: Congenital malformations	All participants	1-3 y	1.5% [nd]	1.0%	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Saline implants: 15,643 women			Reproductive issues: Miscarriage	All participants	1-3 y	18.4% [nd]	14.4%	nd
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort Implants: 941 women	100% (Natrelle 410 Highly Cohesive Anatomically Shaped Silicone-Filled Breast Implant)	NA	Brain cancer	All participants	7 y	0% (0/941) [100%]	NA	NA
			Breast cancer, primary	All participants	7 y	0.62% (4/648) [69%]	NA	NA
				Primary augmentation	7 y	0.38% (3/492)	NA	NA
					9 y	1.0% (5/492)	NA	NA
				Revision augmentation	7 y	0.64% (1/156)	NA	NA
					9 y	0.64% (1/156)	NA	NA
			Cervical cancer	All participants	7 y	0% (0/941) [100%]	NA	NA
			Lung cancer	All participants	7 y	0% (0/941) [100%]	NA	NA
			Multiple myeloma	All participants	7 y	0.11% (1/941) [100%]	NA	NA
			Cancer: Non-Hodgkins lymphoma	All participants	7 y	0.11% (1/941) [100%]	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Uterine cancer	All participants	7 y	0.11% (1/941) [100%]	NA	NA
			Vulvar cancer	All participants	7 y	0% (0/941) [100%]	NA	NA
			Lactation issues	All participants	9 y	22.4% (11/49) [100%]	NA	NA
				Primary augmentation	9 y	22.7% (10/44)	NA	NA
				Revision augmentation	9 y	33.3% (1/3)	NA	NA
				Primary reconstruction	9 y	0% (0/2)	NA	NA
				Revision reconstruction	9 y	0% (0/0)	NA	NA
			Offspring issues: Cancer	All participants	7 y	0.11% (1/941) [100%]	NA	NA
			Reproductive issues	All participants	9 y	2.2% (21/941) [100%]	NA	NA
				Primary augmentation	9 y	3.5% (17/492)	NA	NA
				Revision augmentation	9 y	1.3% (2/156)	NA	NA
				Primary reconstruction	9 y	0.4% (1/225)	NA	NA
				Revision reconstruction	9 y	1.5% (1/68)	NA	NA
			Alopecia	All participants	7 y	0.11% (1/941) [100%]	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Fibromyalgia	All participants	7 y	0.21% (2/941) [100%]	NA	NA
			Hashimoto's thyroiditis	All participants	7 y	0.11% (1/941) [100%]	NA	NA
			Rheumatoid arthritis	All participants	7 y	0.11% (1/941) [100%]	NA	NA
			Scleroderma	All participants	7 y	0.11% (1/941) [100%]	NA	NA
			Suicide	All participants	7 y	0% (0/941) [100%]	NA	NA
Munster, Germany	100% (nd)	No implant	Depression	All participants	nd	34.4% N analyzed 32 [100%]	20.4% N analyzed 32	p=0.1
			Paresthesia	All participants	nd	59.4% [100%]	37.5%	p-0.04
Implants: 32 women				Patients with prosthesis defect	nd	44.4%	84.6%	p=0.02
No implants: 32 women			Vertigo	All participants	nd	34.4% [100%]	14.1%	p=0.01
				Patients with prosthesis defect	nd	27.8%	46.2%	p=NS
			Alopecia	All participants	nd	21.9%	9.4%	NA
				Patients with prosthesis defect	nd	27.8%	15.4%	p=NS

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Arthralgia	Patients with prosthesis defect	nd	61.1%	69.2%	p=NS
			Dry eyes	All participants	nd	15.6	17.5	NA
				Patients with prosthesis defect	nd	11.1%	23.1%	p=NS
			Dry oropharynx	All participants	nd	34.4% [100%]	14.1%	p=0.02
				Patients with prosthesis defect	nd	27.8%	46.2%	p=NS
			Fatigue	All participants	nd	40.6% [100%]	25.0%	p=0.1
			Finger swelling	All participants	nd	31.3% [100%]	12.5%	p=0.03
				Patients with prosthesis defect	nd	33.3%	30.8%	p=NS
			Myalgia	Patients with prosthesis defect	nd	50.0%	43.8%	p=NS
Copenhagen Deaconess Hospital	77%	Breast reduction	Depression	All participants	19 y	22% (42/190) [100%]	20% (37/186)	Adj OR 1.2 (0.7; 1.9)[1]
		General population		All participants		22% (42/190) [100%]	18% (27/149)	Adj OR 1.3 (0.8, 2.2) [2]

[1] Adjusted for age
[2] Adjusted for age

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Silicone Implants: 190 women		Breast reduction	Cognitive symptoms	All participants	19 y	42% (79/190) [100%]	37% (69/186)	Adj OR 1.2 (0.8; 1.8)[3]
General population: 149 women		General population		All participants		42% (79/190) [100%]	27% (40/149)	Adj OR 1.9 (1.2, 3.1)[4]
Breast reduction: 186 women		Breast reduction	Alopecia	All participants	19 y	5% (10/190) [100%]	5% (9/186)	Adj OR 1.1 (0.4, 2.8)[5]
		General population		All participants		5% (10/190) [100%]	5% (8/149)	Adj OR 1.0 (0.4, 2.8)[6]
		Breast reduction	Fatigue	All participants	19 y	20% (38/190) [100%]	16% (30/186)	Adj OR 1.3 (0.8, 2.2)[7]
		General population		All participants		20% (38/190) [100%]	9% (13/149)	Adj OR 2.6 (1.3, 5.1)[8]
		Breast reduction	Joint pain, swelling or stiffness	All participants	19 y	38% (72/190) [100%]	35% (66/186)	Adj OR 1.1 (0.7, 1.7)[9]
		General population		All participants		38% (72/190) [100%]	32% (47/149)	Adj OR 1.3 (0.8, 2.1)[10]
		Breast reduction	Muscle pain, weakness	All participants	19 y	32% (60/190) [100%]	29% (54/186)	Adj OR 1.1 (0.7, 1.7)[11]

[3] Adjusted for age
[4] Adjusted for age
[5] Adjusted for age
[6] Adjusted for age
[7] Adjusted for age
[8] Adjusted for age
[9] Adjusted for age
[10] Adjusted for age

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
		General population		All participants		32% (60/190) [100%]	26% (39/149)	Adj OR 1.3 (0.8, 2.1) [12]
		Breast reduction	Raynaud's	All participants	19 y	15% (28/190) [100%]	12% (23/186)	Adj OR 1.2 (0.8, 2.2) [13]
		General population		All participants		15% (28/190) [100%]	7% (10/149)	Adj OR 2.4 (1.1, 5.1) [14]
South 18 Centers	49.7% (nd)	No implant	Brain cancer	All participants	12 y	0.15% N observed: 11 N analyzed: 7447 [100%]	0.04% N observed: 1 N analyzed: 2203	RR 2.83
Implants: 7447 women			Breast cancer, primary	All participants	12 y	1.8% (136/7447) N observed: 124 [100%]	2.7% (60/2203) N observed: 50	RR 0.84
No Implants: 2203 women			Cervical cancer	All participants	12 y	N observed: 40 N analyzed: 7447 [100%]	N observed: 5 N analyzed: 2203	RR 1.78

[11] Adjusted for age
[12] Adjusted for age
[13] Adjusted for age
[14] Adjusted for age

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Hodgkin's lymphoma	All participants	12 y	N observed: 6 N analyzed: 7447 [100%]	N observed: 1 N analyzed: 2203	RR 1.24
			Leukemia	All participants	12 y	N observed: 8 N analyzed: 7447	N observed: 2 N analyzed: 2203	RR 1.83
			Lung cancer	All participants	12 y	N observed: 33 N analyzed: 7447 [100%]	N observed: 13 N analyzed: 2203	RR 2.23
			Multiple myeloma	All participants	12 y	N observed: 0 N analyzed: 7447	N observed: 1 N analyzed: 2203	RR 0.00
			Non-Hodgkin's lymphoma	All participants	12 y	N observed: 6 N analyzed: 7447 [100%]	N observed: 4 N analyzed: 2203	RR 0.55
			Uterine cancer	All participants	12 y	N observed: 17 N analyzed: 7447 [100%]	N observed: 8 N analyzed: 2203	RR 0.90
			Vulvar cancer	All participants	12 y	N observed: 6 N analyzed: 7447 [100%]	N observed: 1 N analyzed: 2203	RR 1.24

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Multiple sclerosis	All participants	12 y	0.4% (26/7234) [97%]	0.2% (5/2138)	Adj RR 0.7 (0.2, 1.9)[15]
			Raynaud's	All participants	12 y	1.3% (97/7234) [97%]	0.5% (10/2138)	Adj RR 2.6 (1.3, 5.1)[16]
			Chronic fatigue	All participants	12 y	3.4% (246/7234) [97%]	1.3% (27/2138)	Adj RR 2.4 (1.6, 3.6)[17]
			Fibromyalgia	All participants	12 y	4.3% (311/7234) [97%]	2.7% (57/2138)	Adj RR 1.3 (0.9, 1.7)[18]
			Rheumatoid arthritis	All participants	12 y	3.6% (258/7234) [97%]	23.3% (499/2138)	Adj RR 1.9 (1.4, 2.7)[19]
			Scleroderma	All participants	12 y	0.32% (23/7234) [97%]	0.14% (3/2138)	Adj RR 3.0 (0.8, 10.9)[20]

[15] Adjusted for age at follow-up (5-year intervals through age 85 years), calendar period of follow-up (1960– 1964, …, 1990–1994, 1995–1996), and race (White or Black)

[16] Adjusted for age at follow-up (5-year intervals through age 85 years), calendar period of follow-up (1960– 1964, …, 1990–1994, 1995–1996), and race (White or Black)

[17] Adjusted for age at follow-up (5-year intervals through age 85 years), calendar period of follow-up (1960– 1964, …, 1990–1994, 1995–1996), and race (White or Black)

[18] Adjusted for age at follow-up (5-year intervals through age 85 years), calendar period of follow-up (1960– 1964, …, 1990–1994, 1995–1996), and race (White or Black)

[19] Adjusted for age at follow-up (5-year intervals through age 85 years), calendar period of follow-up (1960– 1964, …, 1990–1994, 1995–1996), and race (White or Black)

[20] Adjusted for age at follow-up (5-year intervals through age 85 years), calendar period of follow-up (1960– 1964, …, 1990–1994, 1995–1996), and race (White or Black)

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Sjogren's	All participants	12 y	0.6% (43/7234) [97%]	0.1% (2/2138)	Adj RR 11.7 (2.5, 54.9)[21]
			SLE (lupus)	All participants	12 y	1.0% (72/7234) [97%]	0.5% (10/2138)	Adj RR 2.1 (1.1, 4.2)[22]
			Suicide	All participants	20 y	29/nd SMR 1.63 (1.1, 2.3) Age standardized death/100,000 person-years: 0.06 [nd]	29/nd SMR 0.85 (0.3, 2.3) Age standardized death/100,000 person-years: 0.03	Adj RR 2.58 (0.9, 7.8)[23]
Ontario/Quebec	65.6% (nd)	No implant	Breast cancer, primary	All participants	15 y	nd/24558 N observed/N expected: 188/331.6 SRR 0.57 [100%]	nd/15893 N observed/N expected: 206/237.3 SRR 0.87	RR 0.64 (0.53, 0.79)

[21] Adjusted for age at follow-up (5-year intervals through age 85 years), calendar period of follow-up (1960– 1964, …, 1990–1994, 1995–1996), and race (White or Black)

[22] Adjusted for age at follow-up (5-year intervals through age 85 years), calendar period of follow-up (1960– 1964, …, 1990–1994, 1995–1996), and race (White or Black)

[23] Adjusted for age at follow-up (5-year intervals through age 85 years), calendar period of follow-up (1960– 1964, …, 1990–1994, 1995–1996), and race (White or Black)

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Implants: 24558 women No implants: 15893 women			Cervical cancer	All participants	15 y	nd/24558 N observed/N expected: 46/48.0 SRR 0.96 [100%]	nd/15893 N observed/N expected: 28/30.7 SRR 0.91	RR 1.00 (0.62, 1.61)
			Endometrium cancer	All participants	15 y	nd/24558 N observed/N expected: 23/43.7 SRR 0.53 [100%]	nd/15893 N observed/N expected: 32/37.1 SRR 0.86	RR 0.63 (0.37, 1.09)
			Leukemia	All participants	15 y	nd/24558 N observed/N expected: 12/17.6 SIR 0.68 [100%]	nd/15893 N observed/N expected: 9/13.7 SIR 0.66	RR 0.94 (0.39, 2.25)
			Lung cancer	All participants	15 y	nd/24558 N observed/N expected: 96/87.9 SRR 1.07 [100%]	nd/15893 N observed/N expected: 81/73.1 SRR 1.11	RR 0.93 (0.69, 1.26)
			Non-Hodgkin's lymphoma	All participants	15 y	nd/24558 N observed/N expected: 25/33.5 SRR 0.75 [100%]	nd/15893 N observed/N expected: 20/25.6 SRR 0.78	RR 0.97 (0.53, 1.76)

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Suicide	All participants	15 y	0.2% (58/24558) N observed/N expected: 58/33.5 SMR 1.73 (1.31, 2.24) [100%]	0.2% (33/15893) N observed/N expected: nd SMR nd	Adj RR 1.10 (0.72, 1.69)[24]
Birmingham, AL	100% (nd)	NA	Alopecia	All participants	20 y	15.1% (52/344) [100%]	NA	NA
			Fatigue	All participants	20 y	20.6% (71/344) [100%]	NA	NA
Implants: 344 women			Joint pain, swelling, stiffness	All participants	20 y	40.6% (140/344) [100%]	NA	NA
			Raynaud's	All participants	20 y	4.1% (14/344) [100%]	NA	NA
			Chronic fatigue	All participants	20 y	9.0% (31/344) [100%]	NA	NA
			Fibromyalgia	All participants	20 y	13.6% (47/344) [100%]	NA	NA
			Scleroderma	All participants	20 y	0.9% (3/344) [100%]	NA	NA
			Sjogren's	All participants	20 y	0.9% (3/344) [100%]	NA	NA

[24] Adjusted for age and province of residence

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			SLE (lupus)	All participants	20 y	2.3% (8/344) [100%]	NA	NA
Alberta Health Care Data	nd (nd)	NA	Breast cancer, primary	Implants from 1973	0 y	(nd/10835) SIR 0.76 (0.55, 1.02) [100%]	NA	NA
	nd (nd)	NA		Implants from 1974		(nd/10368) SIR 0.72 (0.51, 0.99) [100%]	NA	NA
Pre-1973: 10835 women From 1974: 10368 women	nd (nd)	NA		Implants from 1973	1 y	(nd/10835) SIR 0.81 (0.59, 1.08)	NA	NA
	nd (nd)	NA		Implants from 1974		(nd/10368) SIR 0.77 (0.55, 1.05)	NA	NA
	nd (nd)	NA		Implants from 1973	5 y	(nd/10835) SIR 0.85 (0.58, 1.19)	NA	NA
	nd (nd)	NA		Implants from 1974		(nd/10368) SIR 0.81 (0.53, 1.18)	NA	NA
	nd (nd)	NA		Implants from 1973	10 y	(nd/10835) SIR 0.68 (0.32, 1.25)	NA	NA
	nd (nd)	NA		Implants from 1974		(nd/10368) SIR 0.51 (0.19, 1.12)	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Barcelona	87.4% (nd)	No implant	Paresthesia	All participants	nd	29.6% (24/81) [100%]	27.8% (20/72)	nd
			Arthralgia	All participants	nd	24.7% (20/81) [100%]	52.8% (38/72)	p<0.001
Implants: 81 women			Arthritis symptoms	All participants	nd	2.5% (2/81) [100%]	5.6% (4/72)	nd
No Implants: 72 women			Dry eyes	All participants	nd	88% (7/81) [100%]	2.8% (14/72)	nd
			Dry oropharynx	All participants	nd	2.5% (5/81) [100%]	11.1% (8/72)	nd
			Muscle weakness	All participants	nd	17.3% (14/81) [100%]	18.1% (13/72)	nd
			Myalgia	All participants	nd	13.6% (11/81) [100%]	16.7% (12/72)	nd
			Raynaud's	All participants	nd	0% (0/81) [100%]	1.4% (1/72)	nd
			Sun sensitivity	All participants	nd	0% (0/81) [100%]	0% (0/72)	nd
Rotterdam University Hospital 1990-1995	100% (nd)	NA	Arthralgia	All participants	nd	35% (nd/63) [100%]	NA	NA
			Difficulty swallowing	All participants	nd	0% (0/63) [100%]	NA	NA
Implants: 63 women			Dry eyes	All participants	nd	11% (nd/63) [100%]	NA	NA
			Dry oropharynx	All participants	nd	22% (nd/63) [100%]	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Joint stiffness	All participants	nd	48% (nd/63) [100%]	NA	NA
			Joint swelling	All participants	nd	8% (nd/63) [100%]	NA	NA
			Raynaud's	All participants	nd	33% (nd/63) [100%]	NA	NA
Rotterdam University Hospital 1995-1997	100% (nd)	NA	Arthralgia	All participants	0 y (preop)	22.8% (nd/57) [100%]	NA	NA
					1 y (postop)	33.3% (nd/57) [100%]	NA	NA
Implants: 57 women			Difficulty swallowing	All participants	0 y (preop)	5.3% (nd/57) [100%]	NA	NA
					1 y (postop)	8.8% (nd/57) [100%]	NA	NA
			Dry eyes	All participants	0 y (preop)	10.5% (nd/57) [100%]	NA	NA
					1 y (postop)	14.0% (nd/57) [100%]	NA	NA
			Dry oropharynx	All participants	0 y (preop)	15.8% (nd/57) [100%]	NA	NA
					1 y (postop)	15.8% (nd/57) [100%]	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Joint stiffness	All participants	0 y (preop)	31.6% (nd/57) [100%]	NA	NA
					1 y (postop)	50.9% (nd/57)[25] [100%]	NA	NA
			Joint swelling	All participants	0 y (preop)	10.5% (nd/57) [100%]	NA	NA
					1 y (postop)	14.0% (nd/57) [100%]	NA	NA
			Raynaud's	All participants	0 y (preop)	36.8% (nd/57) [100%]	NA	NA
					1 y (postop)	36.8% (nd/57) [100%]	NA	NA
Puerto Rico Implants: 1682 women	nd (nd)	NA	Breast cancer, primary	All participants	nd	0.24% (4/1682) [100%]	NA	NA
U Minnesota	100% (MemoryGel)	NA	Breast cancer, primary	Primary reconstruction	10 y	0% (0/251) [100%]	NA	NA
	100% (MemoryGel)	NA		Revision-reconstruction		1.7% (nd/59) [100%]	NA	NA
Primary reconstruction : 251 women	100% (MemoryGel)	NA	Paresthesia	Primary reconstruction	10 y	0% (0/251) [100%]	NA	NA

[25] Within-arm p-value from year 0 to year 1 was 0.04

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Revision-reconstruction: 59 women	100% (MemoryGel)	NA		Revision-reconstruction		1.7% (nd/59) [100%]	NA	NA
Los Angeles Implants: 3500 women	nd (nd)	NA	Brain cancer	All participants	16 y	0.1% (2/3139) N expected 1.7 SIR 1.16 (0.13, 4.19) [63%]	NA	NA
			Breast cancer, primary	All participants	11 y	0.7% (21/3112) N expected 31.7 SIR 66% (41%, 101%) [89%]	NA	NA
					16 y	1.4% (43/3139) N expected 62.6 SIR 0.69 (0.50, 0.93) [63%]	NA	NA
			Cervical cancer	All participants	11 y	0.1% (4/3112) N expected 2.9 SIR 137.9 (37.6, 353.2) [89%]	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
					16 y	0.2% (6/3139) N expected 5.3 SIR 1.13 (0.41, 2.46) [63%]	NA	NA
			Endometrium cancer	All participants	16 y	0.3% (9/3139) N expected 9.2 SIR 0.98 (0.45, 1.86) [63%]	NA	NA
			Lung cancer	All participants	11 y	0.4% (12/3112) N expected 5.7 SIR 211.6 (109.4, 369.7) [89%]	NA	NA
					16 y	0.9% (28/3139) N expected 13.1 SIR 2.14 (1.42, 3.09) [63%]	NA	NA
			Non-Hodgkin's lymphoma	All participants	16 y	0.2% (5/3139) N expected 3.9 SIR 1.29 (0.42, 3.01) [63%]	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Vulvar cancer	All participants	11 y	0.2% (5/3112) N expected 1.0 SIR 526.3 (170.9, 1228.2) [89%]	NA	NA
					16 y	0.2% (7/3139) N expected 2.0 SIR 3.47 (1.39, 7.16) [63%]	NA	NA
Mayo Clinic Implants: 200 women	100% (nd)	NA	Brain cancer	All participants	4 y	0.5% (1/200) [100%]	NA	NA
			Breast cancer, primary	All participants	4 y	1% (2/200) [100%]	NA	NA
			Hodgkin's lymphoma	All participants	4 y	0.5% (1/200) [100%]	NA	NA
			Non-Hodgkin's lymphoma	All participants	4 y	0.5% (1/200) [100%]	NA	NA
Alberta Health Registry	nd (nd)	No implant	Rheumatoid arthritis	All participants	nd	1.0% (11/1112) Incidence rate/10,000 person-years 8.39 [100%]	0.8% (6/727) Incidence rate/10,000 person-years 7.07	Adj RR 1.44 (0.50, 4.15)[26]

[26] Adjusted for age

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Implants: 1112 women No implants: 727 women			Scleroderma	All participants	nd	0% (0/1112) Incidence rate/10,000 person-years 0.00 [100%]	0.4% (3/727) Incidence rate/10,000 person-years 3.53	nd
			Sjogren's	All participants	nd	0.4% (5/1112) Incidence rate/10,000 person-years 3.8 [100%]	0.6% (4/727) Incidence rate/10,000 person-years 4.7	Adj RR 0.99 (0.17, 5.94)[27]
			SLE (lupus)	All participants	nd	0.4% (3/1112) Incidence rate/10,000 person-years 2.28 [100%]	0.4% (3/727) Incidence rate/10,000 person-years 3.52	Adj RR 0.94 (0.17, 5.23)[28]
Sydney	nd (nd)	No implant	Breast cancer, primary	All participants	16 y	0.4% (2/458) [100%]	0.9% (6/687)	RR 0.50 (0.10, 2.48)
			Multiple sclerosis	All participants	16 y	0.2% (1/458) [100%]	0.2% (2/687)	RR 0.75, 0.07, 8.29)
Implants: 458 women			Arthritis symptoms	All participants	16 y	0.4% (2/458) [100%]	0.1% (1/687)	RR 3.01 (0.27, 33.28)
No implants: 687 women			Raynaud's	All participants	16 y	5.7% (26/458) [100%]	4.9% (34/687)	RR 1.15 (0.70, 1.89)

[27] Adjusted for age
[28] Adjusted for age

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Sicca	All participants	16 y	3.3% (15/458) [100%]	2.6% (18/687)	RR 1.24 (0.63, 2.44)
			Dermatomyositis & polymyositis	All participants	16 y	0% (0/458) [100%]	0% (0/687)	nd
			Scleroderma	All participants	16 y	0.2% (1/458) [100%]	0.2% (1/687)	RR 1.50 (0.09, 24.0)
			SLE (lupus)	All participants	16 y	0% (0/458) [100%]	0.4% (3/587)	nd
Tuscon Implants: 1968 women	nd (nd)	NA	Breast cancer, primary	All participants	9 y	0.9% (18/1968) [100%]	NA	NA
Massachusetts General Hospital Implants: 106 women	73% (nd)	NA	Breast cancer, primary	All participants	7 y	0% (0/106) [100%]	NA	NA
Denmark Reconstruction	≥84% (nd)	No implant	Dermatomyositis & polymyositis	All participants	7 y	0% (0/1435) N expected 0.2 Observed/Expected 0 (0, 24) [100%]	0.02% (1/3952) N expected 0.3 Observed/Expected 3.0 (0.1, 16.6)	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Implants: 1435 women No implants: 3952 women			Rheumatoid arthritis	All participants	7 y	0.3% (4/1435) N expected 4.3 Observed/Expected 0.9 (0.3, 2.4) [100%]	0.1% (2/3952) N expected 9.3 Observed/Expected 0.2 (0, 0.8)	nd
			Scleroderma	All participants	7 y	0.1% (1/1435) N expected 0.2 Observed/Expected 4.1 (0.1, 22.7) [100%]	0.02% (1/3952) N expected 0.5 Observed/Expected 1.9 (0, 10.6)	nd
			Sjogren's	All participants	7 y	0.1% (1/1435) N expected 0.3 Observed/Expected 3.1 (0.1, 17.4) [100%]	0.02% (1/3952) N expected 0.4 Observed/Expected 1.4 (0, 7.8)	nd
			SLE (lupus)	All participants	7 y	0.1% (1/1435) N expected 0.5 Observed/Expected 1.9 (0, 10.7) [100%]	0.1% (2/3952) N expected 1.1 Observed/Expected 1.9 (0.2, 6.7)	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Olmstead County, MN	78.3% (Becker expanders, bilumen implants or both)	No implant	Arthritis symptoms	All participants	8 y	0.3% (25/749) Rate ratio 1.35 (0.81, 2.23) Incidence rate/10,000 person-years 42.8 [100%]	2.6% (39/1498) Rate ratio NA Incidence rate/10,000 person-years 31.6	nd
Implants: 749 women No implants: 1498 women			Joint stiffness	All participants	8 y	4% (30/749) Rate ratio 1.81 (1.11, 2.95) Incidence rate/10,000 person-years 30.8 [100%]	2.3% (35/1498) Rate ratio NA Incidence rate/10,000 person-years 28.3	nd
			Muscle weakness	All participants	8 y	0.1% (1/749) Rate ratio 0.43 (0.04, 1.7) Incidence rate/10,000 person-years 2.67 [100%]	0.3% (5/1498) Rate ratio NA Incidence rate/10,000 person-years 4.0	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Oral ulcers	All participants	8 y	0.9% (7/749) Rate ratio 0.71 (0.29, 1.59) Incidence rate/10,000 person-years 12.0 [100%]	1.4% (21/1498) Rate ratio NA Incidence rate/10,000 person-years 4.9	nd
			Salivary gland enlargement	All participants	8 y	0.3% (2/749) Rate ratio 1.42 (0.22, 7.98) Incidence rate/10,000 person-years 3.4 [100%]	0.2% (3/1498) Rate ratio NA Incidence rate/10,000 person-years 2.4	nd
			Serositis	All participants	8 y	2.4% (18/749) Rate ratio 1.81 (0.96, 3.39) Incidence rate/10,000 person-years 30.8 [100%]	1.4% (21/1498) Rate ratio NA Incidence rate/10,000 person-years 17.0	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Sicca	All participants	8 y	4.4% (33/749) Rate ratio 1.39 (0.89, 2.16) Incidence rate/10,000 person-years 56.4 [100%]	3.3% (50/1498) Rate ratio NA Incidence rate/10,000 person-years 40.5	nd
			Sun sensitivity	All participants	8 y	0.4% (3/749) Rate ratio 1.04 (0.25, 3.96) Incidence rate/10,000 person-years 5.1 [100%]	0.4% (6/1498) Rate ratio NA Incidence rate/10,000 person-years 4.9	nd
			Hashimoto's thyroiditis	All participants	8 y	1.3% (10/749) Rate ratio 1.01 (0.46, 2.09) Incidence rate/10,000 person-years 17.1 [100%]	1.4% (21/1498) Rate ratio NA Incidence rate/10,000 person-years 17.0	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Sarcoidosis	All participants	8 y	0% (0/749) Rate ratio 0 (0, 4.23) Incidence rate/10,000 person-years 0 [100%]	0.1% (2/1498) Rate ratio NA Incidence rate/10,000 person-years 1.6	nd
Free University, Amsterdam	100 (nd)	No implant	Arthralgia	All participants	7 y	19.6% (46/235) [100%]	88% (18/210)	OR 2.6 (1.45, 4.64) p-value <0.001
			Joint swelling	All participants	7 y	6.0% (14/235)	4.8% (10/210)	OR 1.27 (0.55, 2.92) p-value NS
Implants: 235 women			Oral ulcers	All participants	7 y	1.7% (4/235) [100%]	1.0% (2/210)	OR 1.8 (0.33, 9.93) p-value NS
No implants: 210 women			Rash that worsens in the sun	All participants	7 y	8.9% (20/235) [100%]	1.9% (4/210)	OR 5.05 (1.71, 14.91) p-value <0.001
			Raynaud's	All participants	7 y	5.1% (12/235) [100%]	3.3% (7/210)	OR 1.56 (0.60, 4.04) p-value NS
			Serositis	All participants	7 y	1.7% (4/235) [100%]	2.4% (5/210)	OR 0.71 (0.18, 2.68) p-value NS
Style 410 Europe	nd (Allergan Style 410)	NA	Lactation issues	Before implant	0 y	36.2% (34/94)	NA	NA
				After implant	5-11 y	22.2% (6/27)	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Implants: 163 women			Miscarriage	Before implant	0 y	25.8% (nd)	NA	NA
				After implant	5-11 years	88% (nd)	NA	NA
Style 410 Stockholm	100% (Inamed Style 410)	NA	Lactation issues	Before implant	0 y	17.2% (16/93)	NA	NA
				After implant	5-9 y	25% (5/20)	NA	NA
Implants: 144 women			Reproductive issues	Before implant	0 y	10.4% (15/144)	NA	NA
				After implant	5-9 y	4.2% (6/144)	NA	NA
Finland Hospitals	>90% (nd)	No implant	Brain cancer	All participants	8 y	N analyzed 2171 N observed 2 N expected 2.0 SIR 1.0 (0.1, 3.5) [97%]	nd	nd
			Breast cancer, primary	All participants	8 y	N analyzed 2171 N observed 7 N expected 13.9 SIR 0.5 (0.2, 1.0) [97%]	nd	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Implants: 2236 women No implants: 8460 women			Cervical cancer	All participants	8 y	N analyzed 2171 N observed 1 N expected 1.0 SIR 1.0 (0.0, 5.6) [97%]	nd	nd
			Hodgkin's lymphoma	All participants	8 y	N analyzed 2171 N observed 0 N expected 0.5 SIR 0.0 (0.0, 7.8) [97%]	nd	nd
			Leukemia	All participants	8 y	N analyzed 2171 N observed 0 N expected 0.5 SIR 0.0 (0.0, 7.8) [97%]	nd	nd
			Lung cancer	All participants	8 y	N analyzed 2171 N observed 1 N expected 0.8 SIR 1.3 (0.0, 7.0) [97%]	nd	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Multiple myeloma	All participants	8 y	N analyzed 2171 N observed 0 N expected 0.2 SIR 0.0 (0.0, 19.0) [97%]	nd	nd
			Non-Hodgkin's lymphoma	All participants	8 y	N analyzed 2171 N observed 3 N expected 0.8 SIR 3.7 (0.8, 10.7) [97%]	nd	nd
			Uterine cancer	All participants	8 y	N analyzed 2171 N observed 1 N expected 1.4 SIR 0.7 (0.0, 4.0) [97%]	nd	nd
			Offspring issues: Low birth weight	All participants	5 y	3.8% N analyzed 423 [19%]	2.6% N analyzed 8460	Adj OR 1.65 (0.98, 2.80) [29]

[29] Adjusted for age, social class, urbanity, marital status, previous births, smoking; controls

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Offspring issues: Perinatal mortality	All participants	5 y	0.24% N analyzed 423 [19%]	0.78% N analyzed 8460	Adj OR 0.33 (0.05, 2.42) [30]
			Offspring issues: Preterm	All participants	5 y	6.4% N analyzed 423 [19%]	5.4% N analyzed 8460	Adj OR 1.28 (0.83, 1.96) [31]
			Offspring issues: Small for gestational age	All participants	5 y	2.4% N analyzed 423 [19%]	2.4% N analyzed 8460	Adj OR 1.01 (0.51, 2.00) [32]
Denmark Private-Public subset	100% (nd)	NA	Fatigue	All participants	nd	17% (41/238) [88%]	NA	NA
			Joint pain, swelling, or stiffness	All participants	nd	26% (62/238) [88%]	NA	NA
Implants: 271 women			Muscle paint, weakness	All participants	nd	20% (47/238) [88%]	NA	NA
			Myalgia	All participants	nd	41% (98/238) [88%]	NA	NA

[30] Adjusted for age, social class, urbanity, marital status, previous births, smoking; controls
[31] Adjusted for age, social class, urbanity, marital status, previous births, smoking; controls
[32] Adjusted for age, social class, urbanity, marital status, previous births, smoking; controls

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Texas Children's Hospital Implants: 42 women No implants: 42 women	nd (nd)	No implant	Lactation issues	All participants	nd	64% (27/42) [100%]	7% (3/42)	p-value<0.001
Allergan vs. Mentor	100% (Allergan Natrelle 410)	NA	Breast cancer, primary	Allergan 410	10 y	0% (0/118) [100%]	NA	NA
	100% (Mentor 321 CPG, 321, 332, 322)	NA		Mentor CPG	10 y	2.6% (3/117) [100%]	NA	NA
Allergan 410 Implants: 118 women	100% (Allergan Natrelle 410)	NA	Lactation issues	Allergan 410	10 y	0% (0/7) [100%]	NA	NA
Mentor CPG: 117 women	100% (Mentor 321 CPG, 321, 332, 322)	NA		Mentor CPG	10 y	0% (0/6) [100%]	NA	NA
Connecticut	100% (nd)	No implant	Brain cancer	All participants	4 y	0% (0/680) [100%]	0.29% (3/1022)	nd
			Breast cancer, primary	All participants	4 y	0.59% (4/680) [100%]	0.88% (9/1022)	RR 0.67 (0.20, 2.17) p-value 0.35
Implants: 680 women			Cervical cancer	All participants	4 y	0% (0/680) [100%]	0.39% (4/1022)	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
No Implants: 1022 women			Lung cancer	All participants	4 y	0.29% (2/680) [100%]	0.19% (2/1022)	nd
			Uterine cancer	All participants	4 y	0% (0/680) [100%]	0.39% (4/1022)	nd
Denmark Private Implants: 423 women	50% (nd)	Other cosmetic surgery	Miscarriage	All participants	nd	26% (110/423) [100%]	20% (47/231)	Adj OR 1.4 (1.0, 2.1)[33]
		General population		All participants	nd	26% (110/423) [100%]	21% (39/183)	Adj OR 1.3 (0.9, 2.0)[34]
Other surgeries: 231 women		Other cosmetic surgery	Arthralgia	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 1.1 (0.7, 1.8)[35]
General Population: 183 women		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 1.1 (0.7, 1.9)[36]
		Other cosmetic surgery	Difficulty swallowing	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 0.7 (0.2, 2.0)[37]
		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 3.7 (0.4, 32.9)[38]
		Other cosmetic surgery	Dry eyes	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 1.5 (0.7, 3.2)[39]

[33] Adjusted for age
[34] Adjusted for age
[35] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[36] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[37] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[38] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 1.8 (0.7, 4.1)[40]
		Other cosmetic surgery	Dry oropharynx	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 1.3 (0.6, 3.1)[41]
		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 4.5 (1.0, 20.7)[42]
		Other cosmetic surgery	Fatigue	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 1.6 (0.9, 2.8)[43]
		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 1.0 (0.6, 1.8)[44]
		Other cosmetic surgery	Finger swelling	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 2.4 (1.1, 5.5)[45]
		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 1.8 (0.7, 4.5)[46]
		Other cosmetic surgery	Joint stiffness	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 2.3 (1.2, 4.3)[47]

[39] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[40] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[41] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[42] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[43] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[44] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[45] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[46] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[47] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 2.3 (1.1, 4.6)[48]
		Other cosmetic surgery	Joint swelling	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 1.0 (0.5, 2.2)[49]
		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 0.9 (0.4, 2.2)[50]
		Other cosmetic surgery	Muscle weakness	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 1.5 (0.7, 3.2)[51]
		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 1.6 (0.7, 3.8)[52]
		Other cosmetic surgery	Myalgia	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 1.5 (0.9, 2.5)[53]
		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 1.0 (0.6, 1.6)[54]
		Other cosmetic surgery	Oral ulcers	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 1.73 (0.1, 30.8)[55]
		General population		All participants	nd	(nd/423)	(--/183)	NA--

[48] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[49] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[50] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[51] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth

[53] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[54] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[55] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
		Other cosmetic surgery	Rash, malar	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 3.2 (0.6, 16.0)[56]
		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 0.4 (0.2, 1.0)[57]
		Other cosmetic surgery	Rash that worsens in the sun	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 1.2 (0.6, 2.6)[58]
		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 0.8 (0.4, 1.6)[59]
		Other cosmetic surgery	Raynaud's	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 1.0 (0.5, 1.9)[60]
		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 0.5 (0.3, 1.0)[61]
		Other cosmetic surgery	Serositis	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 1.3 (0.6, 3.0)[62]
		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 1.8 (0.6, 5.0)[63]

[56] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[57] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[58] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[59] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[60] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[61] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[62] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[63] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
		Other cosmetic surgery	Skin tightness	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 1.6 (0.2, 11.9)[64]
		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 0.8 (0.1, 6.0)[65]
		Other cosmetic surgery	Sun sensitivity	All participants	nd	(nd/423) [100%]	(nd/231)	Adj OR 0.7 (0.4, 1.5)[66]
		General population		All participants	nd	(nd/423) [100%]	(nd/183)	Adj OR 0.4 (0.2, 0.7)[67]
Breast Implant Surveillance Study Implants: 1018 women No implants: 3950 women	75% (nd)	No implant	Suicide	All participants	12 y	0.36% (3/817) [80%]	0.03% (1/3568)	p-value 0.02
Women's Health Cohort Study	69.5% (nd)	No implant	Dermatomyositis & polymyositis	All participants	4 y	0% (0/3950) [100%]	0.001% (1/19897)	nd
			Rheumatoid arthritis	All participants	4 y	0.30% (12/3950) [100%]	0.16% (32/19897)	Adj RR 1.30 (0.56, 3.04)[68]

[64] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[65] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[66] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[67] Adjusted for age, history of CTD, depression, cigarette smoking, alcohol use, body mass index, education, parity, and age at first birth
[68] Adjusted for age, BMI, smoking, and post-menopausal hormone use

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Implants: 3950 women No implants: 19897 women			Scleroderma	All participants	4 y	0.03% (1/3950) [100%]	0.02% (4/19897)	nd
			Sjogren's	All participants	4 y	0% (0/3950) [100%]	0.03% (6/19897)	nd
			SLE (lupus)	All participants	4 y	0.05% (2/3950) [100%]	0.01% (2/19897)	nd
Sweden/Denmark Public-Private	nd (nd)	NA	Brian cancer	Combined Swedish & Danish cohort	17 y	N analyzed 6222 Observed/Expected 17/14.12 SIR 1.20 (0.70, 1.93) [100%]	NA	NA
Implants: 6222 women		NA	Breast cancer, primary	Combined Swedish & Danish cohort	17 y	N analyzed 6222 Observed/Expected 84/115.62 SIR 0.73 (0.58, 0.73)	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
		NA	Cervical cancer	Combined Swedish & Danish cohort	17 y	N analyzed 6222 Observed/Expected 19/18.48 SIR 1.03 (0.62, 1.61)	NA	NA
		NA	Hodgkins lymphoma	Combined Swedish & Danish cohort	17 y	N analyzed 6222 Observed/Expected 2/1.74 SIR 1.15 (0.14, 4.16)	NA	NA
		NA	Leukemia	Combined Swedish & Danish cohort	17 y	N analyzed 6222 Observed/Expected 4/4.89 SIR 0.82 (0.22, 2.09)		
		NA	Lung cancer	Combined Swedish & Danish cohort	17 y	N analyzed 6222 Observed/Expected 29/17.64 SIR 1.64 (1.10, 2.36)	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
		NA	Non-Hodgkins lymphoma	Combined Swedish & Danish cohort	17 y	N analyzed 6222 Observed/Expected 9/7.36 SIR 1.22 (0.56, 2.32)	NA	NA
		NA	Uterine cancer	Combined Swedish & Danish cohort	17 y	N analyzed 6222 Observed/Expected 10/13.56 SIR 0.74 (0.35, 1.36)	NA	NA
Buenos Aires	100% (nd)	NA	Lactation issues	All participants	6 y	0% (0/7) [100%]	NA	NA
Implants: 64 women			Reproductive issues	All participants	6 y	0% (0/64) [100%]	NA	NA
Mentor (MemoryGel Round) Cohort	100% (MemoryGel)	NA	Brain cancer	All participants	3 y	0% (0/1007) [100%]	NA	NA
Implants: 1008 women			Breast cancer, primary	All augmentations	3 y	0% (0/697) [100%]	NA	NA
					9 y	0.29% (2/697) [100%]	NA	NA
			Cervical cancer	All participants	3 y	0% (0/1007) [100%]	NA	NA
			Lung cancer	All participants	3 y	0% (0/1007) [100%]	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Uterine cancer	All participants	3 y	0% (0/1007) [100%]	NA	NA
			Vulvar cancer	All participants	3 y	0% (0/1007) [100%]	NA	NA
			Lactation issues	All participants	3 y	88% (3/35) [100%]	NA	NA
					9 y	21.1% (15/71) [100%]	NA	NA
				Primary augmentation	3 y	8% (2/25) [100%]	NA	NA
				Revision augmentation	3 y	14.3% (1/7) [100%]	NA	NA
				Primary reconstruction	3 y	0% (0/3) [100%]	NA	NA
				Revision reconstruction	3 y	0% (0/0) [100%]	NA	NA
			Paresthesia	All participants	3 y	0.10% (1/1007) [100%]	NA	NA
			Miscarriage	All participants	3 y	1% (10/1007) [100%]	NA	NA
					9 y	16.4% (26/159) [100%]	NA	NA
			Chronic fatigue	All participants	3 y	0% (0/1007) [100%]	NA	NA
					9 y	0.40% (4/1008) [100%]	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Fibromyalgia	All participants	3 y	0.20% (2/1007) [100%]	NA	NA
					9 y	0.70% (7/1008) [100%]	NA	NA
			Hashimoto's thyroiditis	All participants	3 y	0.1% (1/1007) [100%]	NA	NA
					9 y	0.1% (1/1008) [100%]	NA	NA
			Rheumatoid arthritis	All participants	3 y	0.2% (2/1007) [100%]	NA	NA
					9 y	0.3% (3/1008) [100%]	NA	NA
			Scleroderma	All participants	3 y	0% (0/1007) [100%]	NA	NA
					9 y	0.1% (1/1008) [100%]	NA	NA
			Sjogren's	All participants	3 y	0% (0/1007) [100%]	NA	NA
					9 y	0.2% (2/108) [100%]	NA	NA
			SLE (lupus)	All participants	3 y	0% (0/1007) [100%]	NA	NA
					9 y	0.1% (1/1008) [100%]	NA	NA
			Suicide	All participants	3 y	0% (0/1007) [100%]	NA	NA
					9 y	0% (0/1008) [100%]	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Mentor (MemoryGel/ MemoryShape) Post-approval Study Silicone implants: 41451 women Saline implants: 1039 women	100% (MemoryGel & MemoryShape)	Saline implant	Brain cancer	All participants	5 y	0.002% (1/41451) Incidence rate/10,000 person-years 0.3 [100%]	(nd/1039)	Standard morbidity ratio 0.6
			Lung cancer	All participants	5 y	0.007% (3/41451) Incidence rate/10,000 person-years 0.8 [100%]	(nd/1039)	Standard morbidity ratio 0.2
			Multiple sclerosis	All participants	5 y	0.05% (20/41451) Incidence rate/10,000 person-years 3.7 [100%]	(nd/1039)	nd
		"Historical control"	Offspring issues: Congenital malformations (all types)	All offspring	5 y	1.5% (10/674 [100%]	nd	p-value NS
			Off spring issues: Low birth weight	All offspring	5 y	8.5% (57/674) [100%]	nd	p-value NS

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Offspring issues: Neonatal intensive care	All offspring	5 y	10.8% (73/674) [100%]	nd	p-value NS
			Offspring issues: Preterm	All offspring	5 y	14.5% (98/674) [100%]	nd	p-value NS
		Saline implant	Miscarriage	All participants	5 y	17.3% (245/1415) [100%]	nd	nd
		"Historical control"	Fibromyalgia	All participants	5 y	0.3% (137/41451) Incidence rate/10,000 person-years 25.9 [100%]	(nd/1039)	RR 1.08 p-value 0.70
			Rheumatoid arthritis	All participants	5 y	0.4% (160/41451) Incidence rate/10,000 person-years 30.1 [100%]	(nd/1039)	RR 1.46 p-value 0.02

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Scleroderma	All participants	5 y	0.05% (20/41451) Incidence rate/10,000 person-years 3.7 [100%]	(nd/1039)	RR 2.95 p-value 0.09
			Sjogren's	All participants	5 y	0.05% (30/41451) Incidence rate/10,000 person-years 5.6 [100%]	(nd/1039)	RR 6.64 p-value <0.002
			SLE (lupus)	All participants	5 y	0.06% (23/41451) Incidence rate/10,000 person-years 4.3 [100%]	(nd/1039)	RR 1.02 p-value 0.57 (one-sided)
		Saline implant	Suicide	All participants	5 y	0.004% (2/41451) [100%]	nd	nd
Mentor (MemoryShape/CPG Anatomic) Cohort	100% (MemoryShape/CPG Anatomic)	Na	Brain cancer	All participants	6 y	0% (0/955) [100%]	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Implants: 955 women			Breast cancer, primary	All participants	6 y	0.62% (5/696) [73%]	NA	NA
					8 y	1.0% (7/696) [73%]	NA	NA
				Primary augmentation	6 y	0.7% (4/572)	NA	NA
					8 y	1.0% (6/572)	NA	NA
				Revision augmentation	6 y	0.8% (1/124)	NA	NA
					8 y	0.8% (1/124)	NA	NA
			Cervical cancer	All participants	6 y	0% (0/955) [100%]	NA	NA
			Lung cancer	All participants	6 y	0% (0/955) [100%]	NA	NA
			Vulvar cancer	All participants	6 y	0% (0/955) [100%]	NA	NA
			Lactation issues	All participants	6 y	8.3% (4/48) [100%]	NA	NA
					8 y	7.9% (6/76) [100%]	NA	NA
				Primary augmentation	6 y	9.1% (4/44)	NA	NA
				Revision augmentation	6 y	0% (0/4)	NA	NA
			Miscarriage	All participants	8 y	13.9% (16/115) [12%]	NA	NA
			Fibromyalgia	All participants	6 y	0.3% (3/955) [100%]	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
					8 y	0.2% (2/955) [100%]	NA	NA
			Rheumatoid arthritis	All participants	6 y	0.2% (2/955) [100%]	NA	NA
					8 y	0.3% (3/955) [100%]	NA	NA
			Sjogren's	All participants	6 y	0.2% (2/955) [100%]	NA	NA
					8 y	0.2% (2/955) [100%]	NA	NA
			SLE (lupus)	All participants	6 y	0.3%(3/955) [100%]	NA	NA
					8 y	0.4% (4/955) [100%]	NA	NA
			Suicide	All participants	6 y	0% (0/955) [100%]	NA	NA
					8 y	0% (0/955) [100%]	NA	NA
Swedish Inpatient Registry	nd (nd)	No implant	Hard to find words	All participants	nd	8.8% (120/1369) [100%]	6.6% (146/2211)	Adj RR 1.3 (1.0, 1.8)[69] p-value significant
			Memory difficulties	All participants	nd	8.2% (112/1369) [100%]	6.8% (151/2211)	Adj RR 1.1 (0.8, 1.5)[70]

[69] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI
[70] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Implants: 7632 women No implants: 3351 women			Paresthesia	All participants	nd	20.2% (276/1369) [100%]	16.8% (371/2211)	Adj RR 1.3 (1.0, 1.6)[71] p-value significant
			Amyotrophic lateral sclerosis	All participants	9 y	0% (0/7433) SHR 0 (0, 3.6) [97%]	0% (0/3351) SHR 0 (0, 12.9)	nd
				Augmented patients	9 y	0% (0/3502) SHR 0 (0, 12.7)	NA	NA
				Reconstructio n patients	9 y	0% (0/3931) SHR 0 (0, 5.1)	NA	NA
			Guillain-Barre syndrome	All participants	9 y	0.01% (1/7433) SHR 1.2 (0, 6.6) [97%]	0% (0/3351) SHR 0 (0, 6.8)	nd
				Augmented patients	9 y	0% (0/3502) SHR 0 (0, 6.5)	NA	NA
				Reconstructio n patients	9 y	0.03% (1/3931) SHR 2.6 (0.1, 14.3)	NA	NA
			Meniere disease	All participants	9 y	0.04% (3/7433) SHR 0.8 (0.2, 2.5) [97%]	0.03% (1/3351) SHR 0.7 (0, 3.7)	nd

[71] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
				Augmented patients	9 y	0.09% (3/3502) SHR 1.8 (0.4, 5.4)	NA	NA
				Reconstructio n patients	9 y	0% (0/3931) SHR 0 (0, 1.6)	NA	NA
			Mononeuritis: upper limb	All participants	9 y	0.11% (8/7433) SHR 1.1 (0.5, 2.2) [97%]	0.24% (8/3351) SHR 2.1 (0.9, 4.2)	nd
				Augmented patients	9 y	0.11% (4/3502) SHR 1.0 (0.3, 2.5)	NA	NA
				Reconstructio n patients	9 y	0.10% (4/3931) SHR 1.3 (0.4, 3.3)	NA	NA
			Mononeuritis: lower limb	All participants	9 y	0.09% (7/7433) SHR 2.4 (0.95, 4.9) [97%]	0.09% (3/3351) SHR 2.4 (0.5, 7.0)	nd
				Augmented patients	9 y	0.17% (6/3502) SHR 4.5 (1.6, 9.7)	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
				Reconstructio n patients	9 y	0.03% (1/3931) SHR 0.6 (0, 3.4)	NA	NA
			Multiple sclerosis	All participants	9 y	0.13% (10/7433) SHR 1.5 (0.7, 2.8) [97%]	0.15% (5/3351) SHR 1.4 (0.5, 3.4)	nd
				Augmented patients	9 y	0.17% (6/3502) SHR 1.6 (0.6, 3.4)	NA	NA
				Reconstructio n patients	9 y	0.10% (4/3931) SHR 1.5 (0.4, 3.9)	NA	NA
			Optic nerve neuritis	All participants	9 y	0% (0/7431) SHR 0 (0, 134) [97%]	0% (0/3351) SHR 0 (0, 219)	nd
				Augmented patients	9 y	0% (0/3502) SHR 0 (0, 197)	NA	NA
				Reconstructio n patients	9 y	0% (0/3931) SHR 0 (0, 416)	NA	NA
			Cognitive symptoms	All participants	nd	0.87% (12/1369)	6.6% (146/2211)	RR 1.3 (1.0, 1.8)
			Paresthesia	All participants	nd	20.16% (276/1369)	16.78% (371/2211)	RR 1.3 (1.0, 1.6)

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
		Offspring of reduction mothers born after index operation	Offspring issues: Cancer	Offspring of implant mothers born after index operation	8 y	0.06% (1/1589) Incidence rate per 100,000 person-years 7.1 Person-years 14092	0.13% (17/13274) Incidence rate per 100,000 person-years 19.81 Person-years 85975	Adj RR 0.3 (0.0, 2.5)[72]
			Offspring issues: Congenital malformations (all)	Offspring of implant mothers born after index operation	8 y	5.5% (88/1589) Incidence rate per 100,000 person-years 5.54%	5.78% (769/13274) Incidence rate per 100,000 person-years 5.79%	Adj RR 1.0 (0.6, 1.5)[73]
			Offspring issues: Congenital malformations of digestive organs	Offspring of implant mothers born after index operation	8 y	0.50% (8/1589) Incidence rate per 100,000 person-years 0.50%	0.84% (111/13274) Incidence rate per 100,000 person-years 0.84%	Adj RR 0.5 (0.2, 1.3)[74]

[72] Adjusted for offspring sex, maternal age, and calendar year of birth
[73] Adjusted for offspring sex, maternal age, and calendar year of birth and follow-up time
[74] Adjusted for offspring sex, maternal age, and calendar year of birth and follow-up time

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Offspring issues: Esophageal disorder	Offspring of implant mothers born after index operation	8 y	1.5% (24/1589) Incidence rate per 100,000 person-years 172.2 Person-years 13940	1.5% (194/13274) Incidence rate per 100,000 person-years 228.0 Person-years 85075	Adj RR 1.0 (0.7, 1.6)[75]
			Perinatal mortality	Offspring of implant mothers born after index operation	8 y	0.69% (11/1589) Incidence rate per 100,000 person-years 0.69%	0.61% (81/13274) Incidence rate per 100,000 person-years 0.61%	Adj RR 0.9 (0.5, 1.8)[76]
			Rheumatic diseases	Offspring of implant mothers born after index operation	8 y	0.13 (2/1589) Incidence rate per 100,000 person-years 14.2%	0.07% (10/13274) Incidence rate per 100,000 person-years 11.6%	

[75] Adjusted for offspring sex, maternal age, and calendar year of birth
[76] Adjusted for offspring sex, maternal age, and calendar year of birth

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Miscarriage	Offspring of implant mothers born after index operation	8 y	0.38% (6/1589) Incidence rate per 100,000 person-years 0.38%	0.35% (46/13274) Incidence rate per 100,000 person-years 0.35%	Adj RR 0.9 (0.2, 2.1)[77]
		No implant	Alopecia	All participants	nd	7.2% (98/1369) [18%]	5.8% (128/2211)	Adj RR 1.3 (1.0, 1.8)[78] p-value significant
			Arthralgia	All participants	nd	22.5% (308/1369) [18%]	19.5% (432/2211)	Adj RR 1.3 (1.0, 1.5)[79] p-value significant
			Difficulty swallowing	All participants	nd	2.3% (32/1369) [18%]	1.4% (32/2211)	Adj RR 1.9 (1.1, 3.4)[80] p-value significant
			Dry eyes	All participants	nd	7.2% (98/1369) [18%]	5.8% (128/2211)	Adj RR 1.2 (0.9, 1.7)[81]

[77] Adjusted for offspring sex, maternal age, and calendar year of birth
[78] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI
[79] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI
[80] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI
[81] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Dry oropharynx	All participants	nd	4.8% (66/1369) [18%]	3.6% (79/2211)	Adj RR 1.4 (1.0, 2.1)[82] p-value significant
			Fatigue	All participants	nd	16.4% (224/1369) [18%]	13.3% (294/2211)	Adj RR 1.4 (1.1, 1.7)[83] p-value significant
			Joint swelling	All participants	nd	13.4% (184/1369) [18%]	11.5% (255/2211)	Adj RR 1.2 (0.9, 1.5)[84]
			Muscle weakness	All participants	nd	9.6% (131/1369) [18%]	6.9% (152/2211)	Adj RR 1.5 (1.1, 1.9)[85] p-value significant
			Myalgia	All participants	nd	17.2% (236/1369) [18%]	14.6% (324/2211)	Adj RR 1.3 (1.0, 1.6)[86] p-value significant
			Oral ulcers	All participants	nd	1.1% (15/1369) [18%]	1.0% (22/2211)	Adj RR 1.0 (0.5, 2.2)[87]

[82] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI
[83] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI
[84] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI
[85] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI
[86] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI
[87] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Rash, malar	All participants	nd	3.7% (50/1369) [18%]	2.5% (56/2211)	Adj RR 1.8 (1.2, 2.8)[88] p-value significant
			Rash that worsens in sun	All participants	nd	5.8% (80/1369) [18%]	4.7% (104/2211)	Adj RR 1.0 (0.7, 1.4)[89]
			Raynaud's	All participants	nd	8.8% (120/1369) [18%]	6.6% (146/2211)	Adj RR 1.2 (0.9, 1.6)[90]
			Sun sensitivity	All participants	nd	3.4% (47/1369) [18%]	3.1% (69/2211)	Adj RR 1.1 (0.7, 1.7)[91]
			Ankylosing spondylitis	All participants	9 y	0.04% (3/7431) SHR 1.4 (0.3, 4.2) [97%]	0% (0/3351) SHR 1 (1, 2.5)	nd
			Dermatomyositis	All participants	9 y	0.01% (1/7433) SHR 3.4 (0.1, 19.1) [97%]	0% (0/3353) SHR 0 (0, 23.5)	nd

[88] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI
[89] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI
[90] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI
[91] Adjusted for age, ever pregnancy, ever smoking, ever use of university-related health care, current alcohol drinking, time since operation, and BMI

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
				Augmented patients	9 y	0.03% (1/3500) SHR 1.3 (0.2, 40.5)	NA	NA
				Reconstructio n patients	9 y	0% (0/3942) SHR 0 (0, 19.5)	NA	NA
			Fibromyalgia	All participants	9 y	0.19% (14/7442) SHR 1.6 (0.9, 2.7) [97%]	0.15% (5/3353) SHR 1.3 (0.4, 3.0)	nd
			Polyarteritis nodosa	All participants	9 y	0.01% (1/7442) SHR 3.1 (0.1, 17.3) [97%]	0% (0/3353) SHR 0 (0, 22.9)	nd
			Polymyalgia rheumatica	All participants	9 y	0.08% (6/7442) SHR 1.4 (0.5, 3.1) [97%]	0.03% (1/3353) SHR 1 (0, 5.6)	nd
			Polymyositis	All participants	9 y	0.01% (1/7442) SHR 1.7 (0, 9.4) [97%]	0.03% (1/3353) SHR 1 (1, 12.7)	nd
			Psoriatic arthritis	All participants	9 y	0% (0/7442) SHR 0 (0, 3.2) [97%]	0.06% (2/3353) SHR 1.3 (0.5, 15.4)	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Rheumatoid arthritis	All participants	9 y	0.26% (19/7442) SHR 1.0 (0.6, 1.5) [97%]	0.30% (10/3353) SHR 1.3 (0.6, 2.4)	nd
				Augmented patients	9 y	0.31% (11/3500) SHR 1.3 (0.7, 2.4)	NA	NA
				Reconstructio n patients	9 y	0.20% (8/3942) SHR 0.7 (0.3, 1.4)	NA	NA
				Definite RA	9 y	0.1% (11/7442)	0.1% (5/3353)	RR 1.3 (0.7, 2.5)
			Sarcoidosis	All participants	9 y	0.02% (2/7442) SHR 0.6 (0.1, 2.1) [97%]	0.06% (2/3353) SHR 1.2 (0.1, 4.2)	nd
			Scleroderma	All participants	9 y	0.01% (1/7442) SHR 0.8 (0.0, 4.4) [97%]	0.09% (3/3353) SHR 5.0 (1.0, 14.7)	nd
				Augmented patients	9 y	0% (0/3500) SHR 1 (7, 4.6)	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
				Reconstructio n patients	9 y	0.03% (1/3942) SHR 1.6 (0.0, 9.0)	NA	NA
			Sjogren's	All participants	9 y	0.04% (3/7442) SHR 1.8 (0.4, 5.4) [97%]	0% (0/3353) SHR 0 (0, 5.3)	nd
				Augmented patients	9 y	0.08% (3/3500) SHR 5.0 (1, 14.5)	NA	NA
				Reconstructio n patients	9 y	0% (0/3942) SHR 0 (0, 2.9)	NA	NA
			SLE (lupus)	All participants	9 y	0.09% (7/7442) SHR 1.8 (0.7, 3.7) [97%]	0.09% (3/3353) SHR 1.5 (0.3, 4.3)	nd
				Augmented patients	9 y	0.14% (5/3500) SHR 2.3 (0.7, 5.3)	NA	NA
				Reconstructio n patients	9 y	0.05% (2/3942) SHR 1.2 (0.1, 4.2)	NA	NA
				Definite SLE	9 y	0.04%(3/7442)	0.09% (3/3353)	RR 0.7 (0.3, 1.6)

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Temporal arteritis	All participants	9 y	0.01% (1/7442) SHR 0.6 (0.0, 3.4) [97%]	0% (0/3353) SHR 0 (0, 8.0)	nd
		NA	Suicide	All participants	19 y	N Analyzed 3527 N observed 24 N expected 8.0 SMR 3.0 (1.9, 4.5) [46%]	NA	NA
Italy	100% (nd)	No implant	Raynaud's	All participants	5 y	0% (0/102) [100%]	0% (0/102)	nd
Implants: 102 women			Rheumatoid arthritis	All participants	5 y	2.0% (2/102) [100%]	2.0% (2/102)	nd
No Implants: 102 women			Scleroderma	All participants	5 y	0% (0/102) [100%]	0% (0/102)	nd
SE Scotland	100% (nd)	Control for augmented patients	Arthralgia	Augmented patients	6 y	10% (11/110) [100%]	9.4% (12/128)	OR 1.07 (0.42, 2.76) p-value NS
		Control for reconstruction patients		Reconstructio n patients	6 y	14.9% (21/141) [100%]	14.8% (13/88)	OR 1.01 (0.45, 2.28) p-value NS
Augmented: 110 Women		Control for augmented patients	Difficulty swallowing	Augmented patients	6 y	1.8% (2/110) [100%]	0% (0/128)	OR infinity

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Reconstructio n: 141 Women		Control for reconstruction patients		Reconstructio n patients	6 y	0% (0/141) [100%]	0% (0/88)	OR infinity
		Control for augmented patients	Fatigue	Augmented patients	6 y	11.8% (13/110) [100%]	6.3% (8/128)	OR 2.01 (0.74, 5.56) p-value NS
		Control for reconstruction patients		Reconstructio n patients	6 y	9.9% (14/141) [100%]	17.1% (15/88)	OR 0.54 (0.23, 1.25) p-value NS
		Control for augmented patients	Myalgia	Augmented patients	6 y	6.4% (7/110) [100%]	9.4% (12/128)	OR 1.17 (0.36, 3.88) p-value NS
		Control for reconstruction patients		Reconstructio n patients	6 y	8.5% (12/141) [100%]	3.4% (3/88)	OR 2.64 (0.67, 12.15) p-value NS
		Control for augmented patients	Raynaud's	Augmented patients	6 y	0.9% (1/110) [100%]	2.34% (3/128)	OR 0.38 (0.02, 4.19) p-value NS
		Control for reconstruction patients		Reconstructio n patients	6 y	3.6% (5/141) [100%]	5.8% (5/88)	OR 0.61 (0.15, 2.52) p-value NS
		Control for augmented patients	Skin thickening	Augmented patients	6 y	0% (0/110) [100%]	0% (0/128)	OR infinity
		Control for reconstruction patients		Reconstructio n patients	6 y	0.7% (1/141) [100%]	0% (0/88)	OR infinity

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
		Control for augmented patients	Sun sensitivity	Augmented patients	6 y	4.6% (5/110) [100%]	2.3% (3/128)	OR 1.98 (0.40, 10.75) p-value NS
		Control for reconstruction patients		Reconstructio n patients	6 y	3.6% (5/141) [100%]	5.7% (5/88)	OR 0.61 (0.15, 2.52) p-value NS
		Control for augmented patients	Rheumatoid arthritis	Augmented patients	6 y	nd (nd/110) [100%]	nd (nd/128)	nd
		Control for reconstruction patients		Reconstructio n patients	6 y	0.7% (1/141) [100%]	1.14% (1/88)	OR 0.62 (0.02, 23.05) p-value NS
WHI OS Implants: 1257 women No implants: 86,686 women	67% (nd)	No implant	Breast cancer, primary	All participants	nd	2.1% (30/1250) Mortality rate per 10,000 31.3 (21.9, 44.8) Adjusted mortality rate per 10,000 35.0 (17.8, 71.8) [99%]	4.1% (3524/86208) Mortality rate per 10,000 54.5 (52.7, 56.3) Adjusted mortality rate per 10,000 54.7 (51.6, 57.8)	Adj p-value 0.015[92]
			Rheumatoid arthritis	All participants	nd	5.4% (67/1241) [99%]	5.3% (4545/86208)	p-value 0.909 Adj p-value 0.364[93]

[92] Adjusted for age, body mass index, education and total metabolic equivalent of tasks (METs) per week
[93] Adjusted for age

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			SLE (lupus)	All participants	nd	1.2% (15/1220) [97%]	0.5% (462/85127)	p-value 0.001
			Suicide	Total deaths	nd	0.2% (3/1257) [100%]	0.02% (20/88686)	nd
Nurses Health Study Implants: 1183 women No Implants: 86,318 women	74% (nd)	No implant	Dermatomyositis & polymyositis	Total cohort	nd	0.01% (12/87501) Incidence rate per 100,000 person-years 1.0 [100%]	NA	NA
			Mixed CTD	Total cohort	nd	0% (0/87501) [100%]	NA	NA
			Monoclonal gammopathy of undetermined significance (MGUS)	All participants	nd	1.4% (4/288) [100%]	1.7% (5/288)	OR 1.25 (0.27, 6.39) p-value >0.99 Adj OR 1.23 (0.32, 4.66)[94] Adj p-value 0.76
				Silicone implant	nd	1.3% (3/235) [100%]	NA	OR 0.92 (0.13, 5.49)

[94] Adjusted for age

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Rheumatoid arthritis	Total cohort	nd	0.45% (392/87501) Incidence rate per 100,000 person-years 33.2 [100%]	NA	NA
			Scleroderma	Total cohort	nd	0.02% (14/87501) Incidence rate per 100,000 person-years 1.2 [100%]	NA	NA
			Sjogren's	Total cohort	nd	0.002% (2/87501) [100%]	NA	NA
			SLE (lupus)	Total cohort	nd	0.11% (96/87501) Incidence rate per 100,000 person-years 8.1 [100%]	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Houston Implants: 250 women/308 Implants No Implants: 408 women	100% (nd)	No implant	Polymyalgia rheumatica	All participants	nd	0.32% (1/308) incidence rate per 1000 person-years 1.62 Person-years 615.81 [100%]	0% (0/408) incidence rate per 1000 person-years 0 Person-years 633.41	nd
Sientra Implants: 1788 women	100% (Sientra Silicone Gel Breast Implants)	NA	Breast cancer, primary	All participants	3 y	0.2% (3/1477) [83%]	NA	NA
			Lactation issues	Women with live births	3 y	6.8% (14/206) [100%]	NA	NA
				Primary augmentation	3 y	8% (12/150)	NA	NA
				Revision augmentation	3 y	5.1% (2/39)	NA	NA
				Primary reconstruction	3 y	0% (0/16)	NA	NA
				Revision reconstruction	3 y	0% (0/1)	NA	NA
			Reproductive issues	All participants	3 y	1.2% (21/1788) [100%]	NA	NA
				Primary augmentation	3 y	1.3% (15/1115)	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
				Revision augmentation	3 y	1.1% (4/362)	NA	NA
				Primary reconstruction	3 y	0.8% (2/229)	NA	NA
				Revision reconstruction	3 y	0% (0/82)	NA	NA
			Fibromyalgia	All participants	3 y	0.11% (2/1788) [100%] [100%]	NA	NA
			Rheumatoid arthritis	All participants	3 y	0.05% (1/1788) [100%]	NA	NA
			Scleroderma	All participants	3 y	0% (0/1788) [100%]	NA	NA
			SLE (lupus)	All participants	3 y	0% (0/1788) [100%]	NA	NA
			Suicide	All participants	3 y	0% (0/1788) [100%]	NA	NA
Dutch Silicone Implant Support Group	100% (nd)	No implant	Cognitive symptoms	All participants	nd	56% (177/319) [100%]	25% (10/40)	nd
				Women with chronic fatigue complaints	nd	92% (92/100)	NA	NA
Implants: 319 women			Arthralgia	All participants	nd	77% (247/319) [100%]	18% (7/40)	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
No Implant: 40 women				Women with chronic fatigue complaints	nd	61% (61/100)	NA	NA
			Fatigue	All participants	nd	227/319 (71%) [100%]	9/40 (23%)	nd
			Myalgia	All participants	nd	76% (243/319) [100%]	15% (6/40)	nd
				Women with chronic fatigue complaints	nd	73% (73/100)	NA	NA
San Diego	100% (nd)	NA	Fibromyalgia	All participants	7 y	2.4% (3/125) [33%]	NA	NA
			Polymyositis	All participants	7 y	0% (0/125) [33%]	NA	NA
Implants: 378 women			Rheumatoid arthritis	All participants	7 y	0% (0/125) [33%]	NA	NA
			Scleroderma	All participants	7 y	0% (0/125) [33%]	NA	NA
			Sjogren's	All participants	7 y	0% (0/125) [33%]	NA	NA
			SLE (lupus)	All participants	7 y	0% (0/125) [33%]	NA	NA
Tampa	100 (nd)	No implant	Arthralgia	All participants	nd	11% (nd/222) [100%]	5% (nd/80)	Adj OR 1.029 (0.521, 7.142)[95] Adj p-value NS

[95] Adjusted for differences in age and year of cosmetic surgery

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Arthritis symptoms	All participants	nd	5% (nd/222) [100%]	3% (nd/80)	Adj OR 1.159 (0.149, 9.040)[96] Adj p-value NS
Implants: 222 women			Fatigue	All participants	nd	15% (nd/222) [100%]	11% (nd/80)	Adj OR 1.379 (0.574, 3.310)[97] Adj p-value NS
No Implants: 80 women			Joint stiffness	All participants	nd	10% (nd/222) [100%]	10% (nd/80)	Adj OR 0.930 (0.382, 2.265)[98] Adj p-value NS
			Joint swelling	All participants	nd	5% (nd/222) [100%]	3% (nd/80)	Adj OR 1.477 (0.263, 8.291)[99] Adj p-value NS
			Myalgia	All participants	nd	15% (nd/222) [100%]	9% (nd/80)	Adj OR 1.396 (0.541, 3.600)[100] Adj p-value NS
			Raynaud's	All participants	nd	1% (nd/222) [100%]	0% (0/80)	Adj OR 0.488 (0.019, 12.803)[101] Adj p-value NS

[96] Adjusted for differences in age and year of cosmetic surgery
[97] Adjusted for differences in age and year of cosmetic surgery
[98] Adjusted for differences in age and year of cosmetic surgery
[99] Adjusted for differences in age and year of cosmetic surgery
[100] Adjusted for differences in age and year of cosmetic surgery

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Skin thickening	All participants	nd	2% (nd/222) [100%]	7% (nd/80)	Adj OR 0.206 (0.0431, 0.992)[102] Adj p-value <0.05
			Skin tightness	All participants	nd	12% (nd/222) [100%]	19% (nd/80)	Adj OR 0.582 (0.264, 1.284)[103] Adj p-value NS
			Scleroderma	All participants	nd	0% (0/222) [100%]	0% (0/80)	nd
			SLE (lupus)	All participants	nd	0% (0/222) [100%]	0% (0/80)	nd
Denmark Public-Private	≤84%	No implant	Meniere disease	All participants	nd	N analyzed 2761 N observed 1 N expected 0.4 Observed/Expected 2.6 (0.0, 14.4) [100%]	N analyzed 8787 N observed 4 N expected 1.7 Observed/Expected 2.4 (0.7, 6.2)	nd

[101] Adjusted for differences in age and year of cosmetic surgery
[102] Adjusted for differences in age and year of cosmetic surgery
[103] Adjusted for differences in age and year of cosmetic surgery

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Implants: 2761 women No implants: 8807 women			Motor neuropathy	All participants	nd	N analyzed 2761 N observed 0 N expected 0.2 Observed/Expected 0 (0.0, 17.2) [100%]	N analyzed 8787 N observed 3 N expected 1.3 Observed/Expected 2.2 (0.5, 6.6)	nd
			Multiple sclerosis	All participants	nd	N analyzed 2761 N observed 23 N expected 3.6 Observed/Expected 1.3 (0.8, 1.9) [100%]	N analyzed 8787 N observed 12 N expected 10.9 Observed/Expected 1.1 (0.6, 1.9)	nd
			Myasthenia gravis	All participants	nd	N analyzed 2761 N observed 0 N expected 0.2 Observed/Expected 0 (0.0, 16.8) [100%]	N analyzed 8787 N observed 3 N expected 0.8 Observed/Expected 3.6 (0.7, 10.4)	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Optical retino- & neuropathy	All participants	nd	N analyzed 2761 N observed 0 N expected 0.4 Observed/Expected 0 (0.0, 8.5) [100%]	N analyzed 8787 N observed 2 N expected 1.4 Observed/Expected 1.4 (0.2, 5.0)	nd
			Peripheral neuropathy	All participants	nd	N analyzed 2761 N observed 19 N expected 12.8 Observed/Expected 1.5 (0.9, 2.3) [100%]	N analyzed 8787 N observed 77 N expected 44.3 Observed/Expected 1.7 (1.4, 2.2)	nd
		Children of the combined control cohort	Congenital malformations (any type)	Children of the combined implant cohort born before surgery	nd	N analyzed 2106 N observed 202 N expected 158.1 Observed/Expected 1.3 (1.1, 1.5)	N analyzed 2596 N observed 223 N expected 200.3 Observed/Expected 1.1 (1.0, 1.3)	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
				Children of the combined implant cohort born after surgery	nd	N analyzed 748 N observed 53 N expected 45.4 Observed/Expected 1.2 (0.9, 1.5)	N analyzed 3209 N observed 189 N expected 197.7 Observed/Expected 1.0 (0.8, 1.1)	nd
			Congenital malformations of the digestive organs	Children of the combined implant cohort born before surgery	nd	N analyzed 2106 N observed 36 N expected 26.9 Observed/Expected 1.3 (0.9, 1.9)	N analyzed 2596 N observed 40 N expected 34.1 Observed/Expected 1.2 (0.8, 1.6)	nd
				Children of the combined implant cohort born after surgery	nd	N analyzed 748 N observed 14 N expected 7.7 Observed/Expected 1.8 (1.0, 3.1)	N analyzed 3209 N observed 62 N expected 33.6 Observed/Expected 1.9 (1.4, 2.4)	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Esophageal disorders	Children of the combined implant cohort born before surgery	nd	N analyzed 2106 N observed 29 N expected 14.9 Observed/Expected 2.0 (1.3, 2.8)	N analyzed 2596 N observed 38 N expected 18.4 Observed/Expected 2.1 (1.5, 2.8)	nd
				Children of the combined implant cohort born after surgery	nd	N analyzed 748 N observed 6 N expected 4.5 Observed/Expected 1.3 (0.5, 2.9)	N analyzed 3209 N observed 32 N expected 20.0 Observed/Expected 1.6 (1.1, 2.3)	nd
			Pyloric stenosis	Children of the combined implant cohort born before surgery	nd	N analyzed 2106 N observed 10 N expected 6.1 Observed/Expected 1.6 (0.8, 3.0)	N analyzed 2596 N observed 9 N expected 7.8 Observed/Expected 1.1 (0.5, 2.2)	nd
				Children of the combined implant cohort born after surgery	nd	N analyzed 748 N observed 3 N expected 1.6 Observed/Expected 1.9 (0.4, 5.5)	N analyzed 3209 N observed 21 N expected 6.9 Observed/Expected 3.0 (1.9, 4.7)	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Rheumatic diseases	Children of the combined implant cohort born before surgery	nd	N analyzed 2106 N observed 11 N expected 7.6 Observed/Expected 1.4 (0.7, 2.6)	N analyzed 2596 N observed 9 N expected 10.1 Observed/Expected 0.9 (0.4, 1.7)	nd
				Children of the combined implant cohort born after surgery	nd	N analyzed 748 N observed 2 N expected 1.5 Observed/Expected 1.4 (0.2, 5.0)	N analyzed 3209 N observed 9 N expected 6.2 Observed/Expected 1.5 (0.7, 2.8)	nd
		No implant	Amyloidosis	All participants	13 y	N analyzed 2761 N observed 0 SRR 0.0 (0.0, 20.7) [100%]	N analyzed 8807 N observed 0 SRR 0.0 (0.0, 4.7)	nd
			Ankylosing spondylitis	All participants	13 y	N analyzed 2761 N observed 1 SRR 0.9 (0.0, 4.8) [100%]	N analyzed 8807 N observed 5 SRR 1.5 (0.5, 3.4)	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Dermatoyositis & polymyositis	All participants	13 y	N analyzed 2761 N observed 2 SRR 4.4 (0.5, 15.8) [100%]	N analyzed 8787 N observed 4 SRR 2.5 (0.7, 6.4)	nd
			Dermatoyositis & polymyositis	With verified diagnosis of conditions	13 y	N analyzed nd N observed 2	N analyzed nd N observed 3	HR 3.0 (0.4, 22.5) Adj HR 2.8 (0.4, 20.4)[104]
			Fibromyalgia	With verified diagnosis of conditions	13 y	N analyzed nd N observed 17	N analyzed nd N observed 37	HR 1.2 (0.6, 2.1) Adj HR 1.2 (0.6, 2.1)[105]
			Hashimoto's thyroiditis	All participants	13 y	N analyzed 2761 N observed 0 SRR 0.0 (0.0, 1.9) [100%]	N analyzed 8807 N observed 2 SRR 0.3 (0.0, 1.2)	nd
			Polyarteritis nodosa	All participants	13 y	N analyzed 2761 N observed 0 SRR 0.0 (0.0, 15.2) [100%]	N analyzed 8807 N observed 4 SRR 3.5 (0.9, 9.0)	nd

[104] Adjusted for calendar year and time since operation or consultation
[105] Adjusted for calendar year and time since operation or consultation

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Psoriatic arthritis	All participants	13 y	N analyzed 2761 N observed 1 SRR 0.4 (0.0, 2.0) [100%]	N analyzed 8807 N observed 11 SRR 1.3 (0.6, 2.3)	nd
			Rheumatoid arthritis	All participants	13 y	N analyzed 2761 N observed 17 SRR 1.3 (0.8, 2.2) [100%]	N analyzed 8787 N observed 53 SRR 1.1 (0.8, 1.4)	nd
			Rheumatoid arthritis	With verified diagnosis of conditions	13 y	N analyzed nd N observed 15	N analyzed nd N observed 49	HR 1.4 (0.8, 2.6) Adj HR 1.3 (0.7, 2.5)
			Sarcoidosis	All participants	13 y	N analyzed 2761 N observed 1 SRR 0.3 (0.0, 1.6) [100%]	N analyzed 8807 N observed 14 SRR 1.1 (0.6, 1.9)	nd
			Scleroderma	All participants	13 y	N analyzed 2761 N observed 30 SRR 2.9 (0.6, 8.3) [100%]	N analyzed 8787 N observed 5 SRR 1.4 (0.5, 3.3)	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Scleroderma	With verified diagnosis of conditions	13 y	N analyzed nd N observed 3	N analyzed nd N observed 5	HR 1.8 (0.4, 8.1) Adj HR 1.7 (0.4, 7.7)
			Sjogren's	All participants	13 y	N analyzed 2761 N observed 2 SRR 1.0 (0.1, 3.5) [100%]	N analyzed 8787 N observed 9 SRR 1.2 (0.6, 2.3)	nd
			Sjogren's	With verified diagnosis of conditions	13 y	N analyzed nd N observed 2	N analyzed nd N observed 6	HR 1.6 (0.3, 8.7) Adj HR 1.3 (0.9, 1.9)
			SLE (lupus)	All participants	13 y	N analyzed 2761 N observed 2 SRR 0.8 (0.1, 2.9) [100%]	N analyzed 8807 N observed 13 SRR 1.6 (0.9, 2.8)	nd
			Temporal arteritis and polymyalgia rheumatica	All participants	13 y	N analyzed 2761 N observed 3 SRR 1.5 (0.3, 4.4) [100%]	N analyzed 8807 N observed 22 SRR 1.1 (0.7, 1.7)	nd

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
			Wegener's granulomatosis	All participants	13 y	N analyzed 2761 N observed 0 SRR 0.0 (0.0, 13.6)	N analyzed 8807 N observed 0 SRR 0.0 (0.0, 3.2)	nd
			Suicide	All participants	nd	N analyzed 2761 N observed 14 N expected 4.5 SRR 3.1 (1.7, 5.2) [100%]	nd	nd
		Breast reduction: Public hospital		Implant: Public hospital	nd	N analyzed 1135 N observed 7 N expected 2.5 SRR 2.8 (1.1, 5.7)	N analyzed 7071 N observed 22 N expected nd SRR 1.6 (1.0, 2.5)	nd
				Implant: Private hospital	nd	N analyzed 16553 N observed 7 N expected 2.0 SRR 3.5 (1.4, 7.1)	N analyzed 7071 N observed 22 N expected nd SRR 1.6 (1.0, 2.5)	nd
Chambrey-Les-Tours, France Implants: 181 Women	nd (nd)	NA	Depression	All participants	1 y	100% (122/122) [67%]	NA	NA

Study, Year, PMID N Enrolled	% Silicone (or Brand)	Comparator	Outcome Detail	Subpopulation	Time From Implant	%* (n/N) Implant [% Follow-up]	%* (n/N) Comparator	Btw-Arm (95% CI)
Oslo, Norway Implants: 61 Women	nd (nd)	NA	Depression	All participants	3 y	100% (61/61) [100%]	NA	NA

Abbreviations: BMI, body mass index; CTD, connective tissue disease; NS, not significant; SHR, standardized hospitalization ratio; SIR, standardized incidence ratio; SLE, systemic lupus erythematosus; SMR, standardized mortality ratio; SRR, standardized risk ratio

Results of case-control studies examining the harms of silicone breast implants

Study, Year	% Silicone, of Those with Implant	Implant Comparator	Outcome Detail	Subpopulation	Time From Implant	n Implant / N Disease	n Implant / N No Disease	Btw-Arm Disease vs. No Disease (95% CI)
Atlanta/Seattle/New Jersey	nd	No breast enlargement	Primary breast cancer	All participants	Median ~7 y	36/2174	44/2009	Adj RR 0.64 (0.4, 1.0)[106]
Michigan	100%	No silicone implant	Scleroderma	All participants	nd	2/274	272/1183	Adj OR 1.30 (0.27, 6.23)[107]
Michigan/Ohio	100%	No silicone implant	Undifferentiated CTD	All participants	nd	3/205	202/2095	Adj OR 2.22 (0.65, 7.57)[108]

[106] Adjusted for study site, age, race, breast cancer in a mother or sister, BMI, history of a mammogram within 1 year.
[107] Adjusted for age, race, and date of birth
[108] Adjusted for age and year of birth

Appendix C.5. Study Quality

Study, Year, PMID	Representativeness of exposed	Selection of nonexposed	Exposure ascertainment	Outcome not present at start	Outcome assessment	Confounders	Clear reporting	Clear eligibility	Harms pre-defined	Active collection	Passive collection	Number of withdrawals	Other risks of bias
Allergan (Inamed/Natrelle Round) Cohort	yes	NA	secure record	yes	nd	NA	yes	no	no	yes	no	yes	no
Allergan Natrelle Breast Implant Follow-up Study	yes	yes	nd	yes	nd	nd	no	no	yes	yes	no	yes	no
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort	yes	nd	secure record	yes	nd	NA	yes	no	no	yes	no	yes	no
Munster, Germany	yes	yes	secure record	no	self-report	nd	yes	yes	no	no	yes	yes	no
Copenhagen Deaconess Hospital	yes	yes	secure record	no	self-report	yes	yes	yes	no	yes	yes	yes	no
South 18 Centers	yes	yes	secure record	yes	record linkage	yes	yes	yes	yes	yes	no	yes	yes, RRs were adjusted for baseline characteristics not presented in the article
Ontario/Quebec	yes	yes	secure record	no	record linkage	nd	yes	yes	yes	yes	no	yes	no
Birmingham, AL	no	NA	secure record	no	self-report	nd	yes	yes	no	no	yes	yes	no
Alberta Health Care Data	yes	no	secure record	yes	record linkage	no	no	yes	yes	yes	no	yes	no
Barcelona	yes	yes	secure record	yes	independent blind assessment	no	yes	yes	yes	yes	no	yes	no
Rotterdam University Hospital 1990-1995	yes	NA	secure record	no	self-report	NA	yes	yes	yes	yes	no	yes	no
Rotterdam University Hospital 1995-1997	yes	NA	secure record	no	self-report	no	yes	yes	yes	yes	no	yes	no

Study, Year, PMID	Representativeness of exposed	Selection of nonexposed	Exposure ascertainment	Outcome not present at start	Outcome assessment	Confounders	Clear reporting	Clear eligibility	Harms pre-defined	Active collection	Passive collection	Number of withdrawals	Other risks of bias
Puerto Rico	yes	NA	nd	no	nd	NA	yes	yes	no	yes	no	NA	yes, Unclear how outcomes were determined. Appear to be from survey to plastic surgeons. Unclear whether breast cancer outcome is independent of original breast cancer in relevant women.
U Minnesota	yes	yes	nd	no	self-report	no	yes	no	no	yes	no	no	no
Los Angeles	yes	NA	secure record	yes, for breast cancer only	record linkage	nd	yes	yes	yes	yes	no	yes	yes, poor description of baseline population data and characteristics in primary study, sparse data on implants
Mayo Clinic	no	nd	secure record	yes	clinical exam (not blind or independent)	NA	yes	yes	yes	yes	no	yes	no
Alberta Health Registry	yes	yes	secure record	no	independent blind assessment	yes	yes	yes	yes	yes	yes	yes	no

Study, Year, PMID	Representativeness of exposed	Selection of nonexposed	Exposure ascertainment	Outcome not present at start	Outcome assessment	Confounders	Clear reporting	Clear eligibility	Harms pre-defined	Active collection	Passive collection	Number of withdrawals	Other risks of bias
Sydney	yes	yes	secure record	yes	self-report	no	yes	yes	yes	no	yes	yes	no
Tuscon	yes	NA	secure record	yes	record linkage	NA	yes	yes	yes	yes	no	yes	yes, Does not include women without mammograms
Massachusetts General Hospital	yes	NA	secure record	no	self-report	no	yes	yes	yes	yes	yes	yes	no
Denmark Reconstruction	yes	yes	secure record	no	record linkage	no	yes	yes	yes	yes	no	yes	no
Olmstead County, MN	no	yes	secure record	no	self-report	no	yes	yes	yes	no	yes	yes	no
Free University, Amsterdam	yes	yes	secure record	no	self-report	no	yes	yes	no	no	yes	yes	no
Style 410 Europe	no	nd	secure record	no	self-report	no	yes	yes	yes	no	yes	yes	no
Style 410 Stockholm	yes	nd	secure record	no	self-report	no	yes	yes	yes	no	yes	yes	no
Finland Hospitals	yes	yes	secure record	yes	record linkage	yes	yes	yes	yes	yes	no	yes	no
Denmark Private-Public subset	yes	NA	secure record	no	record linkage	nd	yes	yes	no	yes	yes	yes	no
Texas Children's Hospital	yes	yes	secure record	no	record linkage	NA	yes	no	yes	yes	no	no	no
Allergan vs. Mentor	yes	yes	secure record	yes	nd	no	yes	yes	yes	no	yes	no	yes, no baseline data; not much data on implants; unclear % silicone
Connecticut	yes	yes	secure record	yes	record linkage	nd	yes	yes	yes	yes	no	yes	no
Denmark Private	no	yes	secure record	no	self-report	yes	yes	yes	no	yes	no	yes	no

Study, Year, PMID	Representativeness of exposed	Selection of nonexposed	Exposure ascertainment	Outcome not present at start	Outcome assessment	Confounders	Clear reporting	Clear eligibility	Harms pre-defined	Active collection	Passive collection	Number of withdrawals	Other risks of bias
Breast Implant Surveillance Study	yes	yes	secure record	yes	record linkage	no	yes	yes	yes	yes	no	yes	no
Women's Health Cohort Study	yes	yes	written self-report	yes	record linkage	yes	yes	yes	yes	yes	no	yes	no
Sweden/Denmark Public-Private	no	NA	secure record	yes	record linkage	no	yes	yes	no	yes	no	yes	no
Buenos Aires	no	NA	written self-report	no	nd	NA	yes	yes	no	yes	no	yes	no
Mentor (MemoryGel Round) Cohort	yes	NA	secure record	yes	nd	NA	yes	no	no	yes	no	no	no
Mentor (MemoryGel/MemoryShape) Post-Approval Study	yes	no	secure record	yes	independent blind assessment	no	no	no	yes	yes	no	no	no
Mentor (MemoryShape/CPG Anatomic	yes	no	secure record	yes	independent blind assessment	NA	yes	yes	yes	yes	no	no	no
Swedish Impatient Register	yes	yes	secure record	yes	record linkage	yes	yes	yes	yes	yes	no	yes	no
Italy	yes	yes	secure record	no	clinical exam and lab tests	no	yes	yes	no	yes	no	yes	no
SE Scotland	no	yes	secure record	no	self-report	no	yes	yes	yes	no	yes	yes	no
WHI OS	yes	yes	written self-report	no	self-report	yes	yes	yes	no	no	yes	no	no
Nurses Health Study	yes	yes	secure record	no	record linkage	no	yes	yes	no	no	yes	yes	yes
Houston	yes	yes	secure record	no	record linkage	no	yes	yes	yes	yes	yes	yes	no
Sientra	yes	NA	secure record	yes	nd	NA	yes	yes	yes	yes	no	yes	no
Dutch Silicone Implant Support Group	yes	yes	written self-report	no	self-report	no	yes	yes	yes	yes	no	yes	yes
San Diego	yes	NA	secure record	no	physical examination	NA	yes	yes	yes	yes	no	yes	no

Study, Year, PMID	Representativeness of exposed	Selection of nonexposed	Exposure ascertainment	Outcome not present at start	Outcome assessment	Confounders	Clear reporting	Clear eligibility	Harms pre-defined	Active collection	Passive collection	Number of withdrawals	Other risks of bias
Tampa	yes	yes	secure record	yes	self-report	yes	yes	yes	yes	yes	no	yes	no
Denmark Public-Private	yes	yes	secure record	no	independent blind assessment	no	yes	yes	no	yes	no	yes	no
Buenos Aires	yes	NA	written self-report	no	self-report	NA	yes	yes	no	yes	no	yes	no
Chambrey-Les-Tours, France	yes	NA	written self-report	yes	self-report	no	yes	yes	yes	yes	no	Yes	yes
Oslo, Norway	no	NA	written self-report	yes	self-report	no	yes	yes	yes	yes	no	yes	yes

Questions:

Q1: Is the exposed cohort truly representative of the population of interest?

Q2: Is the nonexposed cohort drawn from the same community as the exposed cohort?

Q3: Ascertainment of exposure

Q4: Demonstration that outcome of interest was not present at start of study

Q5: Assessment of outcome

Q6: Were potential confounders properly accounted for?

Q7: Clear reporting with no discrepancies?

Q8: Were eligibility criteria clear?

Q9: Were harms pre-defined using standardized or precise definitions?

Q10: Was the mode of harms collections specified as active?

Q11: Was the mode of harms collection specified as passive?

Q12: Was the number of participants that withdrew or were lost to follow-up specified for each study group?

Q13: Are there other risks of bias?

Study Quality: Case-Control Studies

Study, Year, PMID	Adequate case definition	Consecutive cases	Control from same community	Definition of controls	Exposure ascertainment	Same for controls	Non-exposure rate	Confounders	Clear reporting	Clear eligibility	Harms pre-defined	Active collection	Passive collection	Number of withdrawals	Other risks of bias
Atlanta/Seattle/New Jersey	yes	yes	yes	no history of disease	nd	yes	yes	yes	no	yes	yes	yes	no	yes	no
Michigan	yes	yes	yes	no history of disease	interview not blinded case-control status	yes	yes	yes	yes	yes	yes	yes	no	yes	no
Michigan/Ohio	yes	yes	yes	no history of disease	structured interview where blind to case/control status	yes	no	yes	yes	yes	yes	yes	no	yes	no

Questions:

Q1: Is the case definition adequate?

Q2: Were the cases consecutive or an obviously representative series?

Q3: Were the controls drawn from the same community as the exposed cohort?

Q4: Definition of controls

Q5: Ascertainment of exposure

Q6: Same method of ascertainment for cases and controls?

Q7: Was the non-response rate the same for both groups?

Q8: Were potential confounders properly accounted for?

Q9: Clear reporting with no discrepancies?

Q10: Were eligibility criteria clear?

Q11: Were harms pre-defined using standardized or precise definitions?

Q12: Was the mode of harms collections specified as active?

Q13: Was the mode of harms collection specified as passive?

Q14: Was the number of participants that withdrew or were lost to follow-up specified for each study group?

Q15: Are there other risks of bias?

Appendix C.6. Bradford Hill Considerations, By Study

Study	Strength Is an association measured and is it large (eg, RR≥2.0)	Consistency Is consistency across different groups evaluated within the study and are findings consistent?	Specificity Is the association evaluated specifically for silicone gel implants?	Temporality Did the events definitely occur after implantation and was there adequate delay between implantation and outcome?	Biological Gradient Is evidence provided that associations differ based on implant size or that events decrease after removal of implant?
Comparative Studies					
Alberta Health Registry	No	No	No	No	No
Allergan Natrelle Breast Implant Follow-up Study	No	No	**Yes**	**Yes**	No
Barcelona	No	No	No	**Yes**	No
Breast Implant Surveillance Study	**Yes**	No	No	**Yes**	No
Connecticut	No	No	No	**Yes**	No
Copenhagen Deaconess Hospital	No	No	No	No	No
Denmark Private	No	No	No	No	No
Denmark Public-Private	No	No	No	No	No
Denmark Reconstruction	No	No	No	No	No
Dutch Silicone Implant Support Group	No	No	**Yes**	No	No
Finland Hospitals	No	No	No	**Yes**	No
Free University, Amsterdam	**Yes**	No	**Yes**	**Yes**	No
Houston	No	No	**Yes**	No	No
Italy	No	No	**Yes**	No	No
Mentor (MemoryGel/MemoryShape) Post-Approval Study	**Yes**	No	**Yes**	**Yes**	No
Munster, Germany	No	No	**Yes**	No	No
Nurses Health Study	No	No	No	No	No
Olmstead County, MN	No	No	No	**Yes**	No
Ontario/Quebec	No	No	No	**Yes**	No
SE Scotland	No	No	No	No	No
South 18 Centers	No	No	No	**Yes**	No
Swedish Impatient Register	No	No	No	**Yes**	No
Sydney	**Yes**	No	No	**Yes**	No
Tampa	No	No	No	**Yes**	No
Texas Children's Hospital	No	No	No	No	No
WHI OS	No	No	No	No	No
Women's Health Cohort Study	**Yes**	No	No	**Yes**	No

Study	Strength Is an association measured and is it large (eg, RR≥2.0)	Consistency Is consistency across different groups evaluated within the study and are findings consistent?	Specificity Is the association evaluated specifically for silicone gel implants?	Temporality Did the events definitely occur after implantation and was there adequate delay between implantation and outcome?	Biological Gradient Is evidence provided that associations differ based on implant size or that events decrease after removal of implant?
Case-Control Studies					
Atlanta/Seattle/New Jersey	No	No	No	**Yes**	No
Michigan	No	No	**Yes**	**Yes**	No
Michigan/Ohio	**Yes**	No	**Yes**	No	No
Single Group Studies					
Alberta Health Care Data	No	No	No	**Yes**	No
Allergan (Inamed/Natrelle Round) Cohort	No	**Yes**	**Yes**	**Yes**	No
Allergan (Natrelle Anatomic/410 Highly Cohesive) Cohort	No	**Yes**	**Yes**	**Yes**	No
Allergan vs. Mentor	No	No	No	No	No
Birmingham, AL	No	No	**Yes**	No	No
Buenos Aires	No	No	**Yes**	No	No
Denmark Private-Public subset	No	No	**Yes**	No	No
Los Angeles	No	No	No	**Yes**	No
Massachusetts General Hospital	No	No	No	No	No
Mayo Clinic	No	No	**Yes**	**Yes**	No
Mentor (MemoryGel Round) Cohort	No	**Yes**	**Yes**	**Yes**	No
Mentor (MemoryShape/CPG Anatomic	No	**Yes**	**Yes**	**Yes**	No
Puerto Rico	No	No	No	No	No
Rotterdam University Hospital 1990-1995	No	No	**Yes**	No	No
Rotterdam University Hospital 1995-1997	No	No	**Yes**	No	No
San Diego	No	No	**Yes**	**Yes**	No
Sientra	No	**Yes**	**Yes**	**Yes**	No
Style 410 Europe	No	No	No	No	No
Style 410 Stockholm	No	No	No	No	No
Sweden/Denmark Public-Private	No	No	No	No	No
Tuscon	No	No	No	**Yes**	No
U Minnesota	No	No	**Yes**	No	No
Buenos Aires	No	No	**Yes**	No	No

Study	Strength Is an association measured and is it large (eg, RR≥2.0)	Consistency Is consistency across different groups evaluated within the study and are findings consistent?	Specificity Is the association evaluated specifically for silicone gel implants?	Temporality Did the events definitely occur after implantation and was there adequate delay between implantation and outcome?	Biological Gradient Is evidence provided that associations differ based on implant size or that events decrease after removal of implant?
Chambrey-Les-Tours, France	No	No	No	**Yes**	No
Oslo, Norway	No	No	No	**Yes**	No

Appendix D. Incidence and Prevalence of Diseases in the General Population

Population	Site/Disease	Source	Estimated year	Result
Among US women, Incidence of Cancer Conditions†				
	Brain	SEER registries	1975-2010	**Age-adjusted 5.52**
	Breast	SEER registries	1975-2010	**Age-adjusted 125.48**
	Cancer	SEER registries	1975-2010	**Age-adjusted 9.32**
	Hodgkin's lymphoma	SEER registries	1975-2010	**Age-adjusted 2.9**
	Leukemia	SEER registries	1975-2010	**Age-adjusted 10.13**
	Lung cancer	SEER registries	1975-2010	**Age-adjusted 46.05**
	Multiple myeloma	SEER registries	1975-2010	**Age-adjusted 4.68**
	Non-Hodgkin's Lymphoma	SEER registries	1975-2010	**Age-adjusted 14.83**
	Corpus uteri	SEER registries	1975-2010	**Age-adjusted 26.25**
	Vulva	SEER registries	1975-2010	**NR**
	Endometrium	SEER registries	1975-2010	**NR**
Among US women, Prevalence of Cancer Conditions‡				
	Brain	SEER registries	2010	**Age-adjusted 0.02%**
	Breast	SEER registries	2010	**Age-adjusted 1.08%**
	Cancer	SEER registries	2010	**Age-adjusted 0.07%**
	Hodgkin's lymphoma	SEER registries	2010	**Age-adjusted 0.03%**
	Leukemia	SEER registries	2010	**Age-adjusted 0.05%**
	Lung cancer	SEER registries	2010	**Age-adjusted 0.09%**
	Multiple myeloma	SEER registries	2010	**Age-adjusted 0.02%**
	Non-Hodgkin's Lymphoma	SEER registries	2010	**Age-adjusted 0.10%**
	Corpus uteri cancer	SEER registries	2010	**Age-adjusted 0.2%**
	Cancer vulva	SEER registries	2010	**NR**
	Endometrium	SEER registries	1975-2010	**NR**

†Age-adjusted (to the 2000 US standard population) SEER incidence rates per 100,000 person-years

‡Prevalence counts are based on 2010 cancer prevalence proportions and 1/1/2010 US population estimates based on the average of population estimates from the US Bureau of the Census. Prevalence was calculated using the First Malignant Primary Only for a person.

(table continued)

Population	Site/Disease	Source/Reference	Result
Among US Adults, Prevalence and Incidence of Non-Cancer Conditions			
Prevalence among US adults (Both men and women)	**Amyloidosis**	**1**	**1 in 90,666**
Incidence each year among US adults (Both men and women)	**Amyloidosis**	**1**	**9 per million**
Prevalence among US adults (Both men and women)	**Ankylosing Spondylitis**	**2**	**0.1% to 1.4%**
Lifetime risk among US women (Both men and women)	**Ankylosing Spondylitis**	**3**	**0.08%**
Prevalence among US adults (Women only)	**Chronic Fatigue Syndrome**	**4**	0.37%
Incidence each year among US adults (Women only)	**Chronic Fatigue Syndrome**	**4**	180 cases per 100,000 women
Prevalence among US adults (Both men and women)	**Dermatomyositis**	**5**	**0.21%**
Incidence each year among US adults (Both men and women)	**Dermatomyositis**	**5**	**9.6 per 100,000**
Prevalence among US adults (Women only)	**Fibromyalgia**	2	3.4%
Incidence each year among US adults (Women only)	**Fibromyalgia**	**6**	11.3 per 1000 person-years
Prevalence among US adults (Women only)	**Monoclonal Gammopathy of Undetermined Significance**	**7**	2.7%
Incidence each year among US adults (Women only)	**Monoclonal Gammopathy of Undetermined Significance**	8	60 per 100,000 persons at the age of 50 years; 370 per 100,000 at the age of 90 years‡
Prevalence among US adults (Women only)	**Polyarteritis Nodosa**	**9**	**0.34%**
Incidence each year among US adults (Women only)	**Polyarteritis Nodosa**		**No data**
Prevalence among US adults (Women only)	polymyalgia rheumatic	**9**	0.9%*
Incidence each year among US adults (Women only)	polymyalgia rheumatic	**10**	69.8 per 100,000 per year among ≥50 years of age‡
Prevalence among US adults (Both men and women)	**Psoriatic Arthritis**	**11**	0.25%
Incidence each year among US	**Psoriatic**	**12**	**6.59 per 100,000**

Population	Site/Disease	Source/Reference	Result
adults (Both men and women)	**Arthritis**[3]		**0.46%#**
Lifetime risk among US adults (Women only)	**Rheumatoid arthritis**	**3**	**3.6%**
Prevalence among US adults (Women only)	**Sarcoidosis**	**13**	**0.05%**
Incidence each year among US adults (Women only)	**Sarcoidosis**	**14**	164 per 100,000¶ to 330 per 100,000*
Prevalence among US adults (Both men and women)	**Scleroderma**	**15,16**	0.002% to 0.02%
Incidence each year among US adults (Both men and women)	**Scleroderma**	**15,17**	13.9 to 19 per million per year
Prevalence among US adults (Women only)	**Sjogren's**		**0.2% to 1.4%**
Lifetime risk among US adults (Women only)	**Sjogren's**	**3**	0.75%
Prevalence among US adults (Both men and women)	**Systemic Lupus Erythematosus**	**9**	**0.05%**
Incidence each year among US adults (Both men and women)	**Systemic Lupus Erythematosus**	**18**	1.8 to 7.6 cases per 100,000

† Age- and sex-adjusted

‡ Age-adjusted prevalence data among women

#Life-time risk of developing psoriatic arthritis among US women

¶ In the year 1995 (sarcoidosis)

* In the year 2010 (sarcoidosis)

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