Appendix 4 (as supplied by the authors): Supplementary tables

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Supplementary Table S1: Characteristics of Study Populations from Included Primary Studies (Review One and Two)

Author, Year [ref]	Gender Identity	Sample Size	Age (Years) at Study Entry, Mean (SD)	Surgical Procedures, n (%)	CSH Use Details			
					Type of Hormone	Exposed, n (%)	Dose and Delivery	Duration of Use
Brown, 2014 [19]	Trans men	1,579	55.7 (12.9)	NR	Testosterone[1]	218 (17.3%)	NR	950.8 person-years[2]
	Trans women	3,556	55.8 (13.7)	NR	Estrogen[1]	1,112 (80.2%)	NR	NR
Gooren, 2013 [20]	Trans men	795	23.2 (6.5)	NR	Testosterone	795 (100%)	NR	15,974 person-years[2] 8.2% exposed <10 years 53.5% exposed 10–20 years 38.4% exposed ≥20 years
	Trans women	2,307	29.3 (12.7)	NR	Androgen deprivation[3], antiandrogen[3] and/or estrogen	2,307 (100%)	NR	52,370 person-years[2] 21.7% exposed <10 years 51.3% exposed 10–20 years 27.0% exposed ≥20 years
Weyers, 2010 [22]	Trans women	50	43.1 (10.4)	Breast augmentation, 48 (96.0%) Vaginoplasty, 50 (100%)	Estrogen	47 (94.0%)	NR	NR
					Androgen deprivation[4]	2 (4.0%)	10 mg[5]	NR
Kuroda, 2008 [21]	Trans men	186	27.4 (NR)	Mastectomy[6], 186 (100%)	Testosterone	56 (30.1%)	≤125 mg, biweekly, intramuscular injections	11 months[7]

CSH = cross-sex hormone; mg = milligram; NR = not reported; SD = standard deviation

[1] During the 17-year period examined in the study of United States veterans, 1,259 trans men and 1,386 trans women were found to have received at least one prescription for sex hormones (testosterone, estrogen or both hormones) from Veterans Health Administration clinicians during the time they were enrolled for care. Of these individuals, 218 trans men (17.3%) and 1,112 trans women (80.2%) were prescribed CSHs. This review was interested specifically in these two sub-groups of trans people.

[2] Cumulative exposure to CSHs among all participants during study period, as recorded in study sources.

[3] Agent(s) not specified.

[4] Cyproterone acetate.

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[5] Method of hormone delivery not reported.

[6] Type of mastectomy (e.g., total or partial) not specified.

[7] Mean duration of CSH use.

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Supplementary Table S2: Quality Assessment of Included Cohort Studies[1] (Review One)

Author, Year [ref]	Representativeness of Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration that Outcome of Interest was Not Present at Start of Study	Selection (Maximum 4 ★)	Comparability of Cohorts: Controls for Age	Comparability of Cohorts: Controls for Additional Factor	Comparability (Maximum 2 ★)	Assessment of Outcome	Appropriate Duration of Follow-up	Adequacy of Follow-up of Cohorts	Outcome/Exposure (Maximum 3 ★)	Total Score (Maximum 9 ★)	Methodological Quality Rating[2]
Brown, 2014 [19]			★		1	★	★	2	★		★	2	5	Fair
Gooren, 2013 [20]	★		★		2	★	★	2	★	★	★	3	7	Fair
Kuroda, 2008 [21]		★	★		2			0	★		★	2	4	Poor

[1] Assessed using the Newcastle-Ottawa Scale for cohort studies [15].

[2] Scoring algorithm [38] (all domain thresholds must be met for a rating to apply): good = selection ≥3★, comparability ≥2★, outcome ≥2★; fair = selection 2★, comparability ≥1★, outcome ≥2★; poor = selection 0 – 1★, comparability 0★, outcome 0 – 1★.

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Supplementary Table S3: Quality Assessment of the Included Cross-sectional Study (Review Two)

Author, Year [ref]	Risk of Selection Bias	Risk of Information Bias	Methodological Quality Rating
Weyers, 2010 [22]	Unclear[1]	High[2]	Poor[3]

[1] The sample size of this study was small (n = 50); however, 71.4% (50 out of 70 eligible individuals) of the target population agreed to participate in the study. Reasons for study refusal were not reported. The authors reported no statistically significant differences observed in the age, or surgical or psychiatric morbidity between the 50 consenting and 20 non-consenting participants, but as these data were not presented, independent assessment of this interpretation was not possible. Methods of recruitment were not sufficiently described, as such the possibility of these methods impacting study participation could not be assessed.

[2] Pain experienced during breast imagining was assessed using a visual analogue scale (VAS). The validity and reliability of this instrument to assess pain during breast imaging was not described. Of note, participants reported lower pain scores for mammography when the VAS was administered by the radiologist as compared to when it was administered by the study nurse. It is unclear whether this difference is statistically significant, or whether it is a result of measurement error due to validity and reliability issues with the instrument or potential self-reporting or interviewer bias. Although participants were asked to rate their experienced pain during breast imaging, they did not self-administer these surveys. It is possible that participants over- or under-reported their experienced pain to study personnel. Information on the procedures for outcome assessment were also not sufficiently described. For mammography, both the radiologist and a study nurse administered the VAS survey to participants; however, for ultrasonography the study personnel responsible for administering the survey was not reported. Additionally, while the authors state that pain experienced during mammography was assessed post-mammography, it is unclear when the assessment of pain experienced during ultrasonography took place in relation to that of mammography. If pain experienced during each procedure was not assessed immediately after the completion of that procedure, there is a greater risk for recall bias.

[3] This rating was provided due to insufficient information on the characteristics of participants and non-participants, recruitment methods, validity and reliability of the instrument used to assess the outcome and procedures for outcome assessment.

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Supplementary Table S4: Effect of CSH Exposure on Breast Cancer Risk in Trans People (Review One)

		Exposed Group			Comparison Group				
Author, Year [ref]	Case Definition and Data Source(s)	Follow-up Duration (Person-Years)	Number of Cases / Sample Size (%)	Incidence Rate per 100,000 Person-Years (95% CI)	Description	Follow-up Duration (Person-Years)	Number of Cases / Sample Size (%)	Incidence Rate per 100,000 Person-Years (95% CI)	Statistical Significance of Differences
Trans Men									
Brown, 2014 [19]	ICD-9-CM codes from existing VHA records[1] and U.S. population database[2] (i.e., SEER)	NR	1 / 218 (0.5%)	105.2 (3.2, 585.8)[3]	General population of women	NR	3.6[4]	NR	0.3 (0.0, 3.7)[5], NS at $p < 0.05$
Gooren, 2013 [20]	Case definition not provided; data obtained from medical centre database[1] and Dutch population database[2]	17,025[6]	1 / 795 (0.1%)	5.9 (0.5, 27.4)[7]	General population of women	NR	NR	154.7[8] (NR)	NR
Kuroda, 2008 [21]	Pathological diagnosis of epithelial proliferation from surgical institute records	NR	0 / 56 (0%)	NR	Trans men not exposed to male CSHs	NR	1 / 130 (0.8%)	NR	NS, $p = 0.5$
Trans Women									
Brown, 2014 [19]	ICD-9-CM codes from existing VHA records[1] and U.S. population database[2] (i.e., SEER)	NR	0 / 1,112 (0%)	NR	General population of men	NR	0.03[4]	NR	0.0 (0.0, 3.7)[5], NS at $p < 0.05$
Gooren, 2013 [20]	Case definition not provided; data obtained from medical centre database[1] and Dutch population database[2]	49,370[9]	2 / 2,307 (0.1%)	4.1 (0.8, 13.0)[7]	General population of men	NR	NR	1.2[8] (NR)	NR

CI = confidence interval; ICD-9-CM = International Statistical Classification of Diseases, Ninth Revision, Clinical Modification; NR = not reported; NS = not statistically significant; SD = standard deviation; SEER = Surveillance, Epidemiology and End Results; SIR = standardized incidence ratio; U.S. = United States; VHA = Veterans Health Administration

[1] For exposed group (i.e., observed cases).

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[2] For comparison group (i.e., expected cases).

[3] Incidence rate per 100,000 person-years of cross-sex hormone use.

[4] Number of expected cases calculated based on SEER data from 2007 to 2011.

[5] Standardized incidence ratio (95% CI).

[6] Minimum follow-up duration = 6 years; mean (SD) = 20.1 (7.3) years; median (range) = 16.8 (6.0 to 36.0) years.

[7] Observed incidence rate per 100,000 person-years of follow-up.

[8] Expected incidence rate per 100,000, based on Dutch incidence numbers for 2009.

[9] Minimum follow-up duration = 6 years; mean (SD) = 21.4 (8.7) years; median (range) = 17.6 (6.0 to 43.5) years. It should be noted that the upper value of the age range reported in the paper is likely an error, as based on the study dates (i.e., 1975 to 2012) the maximum range should be 38 years.

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Supplementary Table S5: GRADE Evidence Profile for the Effect of CSH Exposure on Breast Cancer Risk in Trans People (Review One)

Quality Assessment							Results	GRADE Certainty Rating
Number of Studies	Design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Other Considerations		
Trans Men – **Breast Cancer Risk** (follow-up: varied from unreported to minimum 6 years post CSH therapy initiation; assessed using: medical records)								
3[1]	observational[2]	serious[3]	serious[4]	not serious[5]	serious[6]	none[7]	fewer observed cases than expected; no statistically significant difference between observed and expected or between CSHs and no CSHs groups[8]	⊕OOO VERY LOW
Trans Women – Breast Cancer Risk (follow-up: varied from unreported to minimum 6 years post CSH therapy initiation; assessed using: medical records)								
2[9]	observational[2]	serious[10]	serious[11]	not serious[12]	serious[13]	none[7]	one study found no cases and no statistically significant difference between observed and expected rates; a second study found two cases (0.09%) and did not report statistical significance of difference between observed and expected[8]	⊕OOO VERY LOW

CSH = cross-sex hormone; very low certainty rating = we have very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

[1] Brown, 2104 [19], Gooren, 2013 [20], Kuroda, 2008 [21].

[2] Assessment began with a low certainty rating due to limitations of observational designs [18]. All studies used retrospective cohort designs.

[3] Using the Newcastle-Ottawa Scale [15] and a scoring algorithm [38], the studies received poor to fair methodological quality ratings. Across studies a main area of concern was related to the selection of participants in terms of the questionable representativeness of the sample for the target population, the reliance on population estimates for risk comparisons in the two larger studies, and the lack of certainty that breast cancer was not present prior to initiating CSH therapy. Given these methodological concerns, this body of evidence was downgraded for risk of bias.

[4] Despite some variability in demographics (e.g., veterans, age at CSH therapy initiation, nationality, surgical procedures), the study participants were all adult trans men which matched the key question. In terms of the interventions, the variability in dose, delivery and duration of CSH therapy was noted but acceptable. The smallest study (n = 186), which was conducted in Japan, was designed to provide evidence from a direct comparison between trans men who were exposed to CSHs and trans men who were not exposed to CSHs. This study, however, did not demonstrate that the intervention and control groups were indeed comparable. However, the two larger studies relied on indirect sources for their comparisons; both used expected breast cancer cases/rates drawn from general

population samples of women. Although there was some variability in descriptions, all three studies were interested in the detection of breast cancer. Given concerns regarding the comparison groups used in the two larger studies, this body of evidence was downgraded for indirectness.

[5] The studies reported similar results for the effect of exposure to CSHs on risk of developing breast cancer in trans men. Any variations could be explained by differences in populations and CSH therapies. This body of evidence was not downgraded for inconsistency.

[6] For assessing the risk of breast cancer, there was uncertainty regarding sufficient sample size to detect a difference between trans men exposed to CSHs and trans men who were not exposed to CSHs or the general population of women. Across studies the total number of cases of breast cancer (n = 3) was low. The confidence intervals across study effect estimates were wide. This body of evidence was downgraded for imprecision.

[7] There was an insufficient number of studies (n < 10) for statistical evaluation of publication bias [18]; the search for studies was comprehensive. No factors (i.e., large effect, dose-response gradient, plausible confounders) were noted that would provide reasons to raise certainty in the evidence.

[8] As per protocol we did not pool the available data; meta-analysis would not have been possible due to study heterogeneity and the lack of counts data for the comparison groups.

[9] Brown, 2014 [19], Gooren, 2013 [20].

[10] Using the Newcastle-Ottawa Scale [15] and a scoring algorithm [38], the studies received fair methodological quality ratings. Across studies a main area of concern was related to the selection of participants who may not be representative of the target population, the reliance on population estimates for risk comparisons and the lack of certainty that breast cancer was not present prior to initiating CSH therapy. Given these methodological concerns, this body of evidence was downgraded for risk of bias.

[11] Despite some variability in demographics (e.g., veterans, age at CSH therapy initiation, nationality), the study participants were all adult trans women which matched the key question. In terms of exposure to CSHs, the variability in dose, delivery and duration of CSH therapy was noted but acceptable. Both studies relied on indirect sources for their comparisons, drawing expected breast cancer cases/rates from general population samples of men. Although there was some variability in descriptions, both studies were interested in the detection of breast cancer. Given concerns regarding the uncertainty around the comparison groups used in both studies, this body of evidence was downgraded for indirectness.

[12] The studies reported similar results for the effect of exposure to CSHs on risk of developing breast cancer in trans women. Any variations could be explained by differences in populations and CSH therapies. This body of evidence was not downgraded for inconsistency.

[13] For assessing the risk of breast cancer, there was uncertainty regarding sufficient sample size to detect a difference between trans women exposed to CSHs and the general population of men. Across studies the total number of cases of breast cancer (n = 2) was low. This body of evidence was downgraded for imprecision.

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Supplementary Table S6: GRADE Evidence Profile for Pain Experienced by Trans Women during Breast Screening (Review Two)

Quality Assessment							Results Mean (SD) Score	GRADE Certainty Rating
Number of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations		
Painfulness of Mammography (assessment point: post-mammography; assessed using: VAS administered by radiologist and study nurse)								
1[1]	cross-sectional[2]	serious[3]	cannot assess[4]	not serious[5]	cannot assess[6]	none[7]	Scores ranged from 1.7 (2.1) to 2.0 (2.3)[8, 9]	⊕OOO VERY LOW
Painfulness of Ultrasonography (assessment point: post-ultrasonography; assessed using: VAS administered by unknown study personnel)								
1[1]	cross-sectional[2]	serious[3]	cannot assess[4]	not serious[5]	cannot assess[6]	none[7]	0.5 (1.2)[9,10]	⊕OOO VERY LOW

SD = standard deviation; VAS = visual analogue scale; very low GRADE certainty rating = we have very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

[1] Weyers, 2010 [22].

[2] Assessment begins with a low certainty rating due to limitations of observational designs [18].

[3] In the absence of a widely accepted tool to assess the methodological quality of cross-sectional studies, a qualitative approach considering the selection of participants and measurement of study variables was used to assess the risk of bias for this cross-sectional study. Given that insufficient information was provided on the characteristics of study participants and non-participants, the validity and reliability of the outcome measure and outcome assessment procedures, this study was considered to be of low methodological quality and downgraded for risk of bias.

[4] Because this was a single study, inconsistency could not be assessed.

[5] Results from this study are based on data for 50 adult (mean age: 43.1 years, SD: 10.4 years) trans women who received two of the screening modalities of interest (mammography and ultrasonography) in a hospital-based setting in Belgium. All 50 participants received sex reassignment surgery (i.e., vaginoplasty) and 48 (96.0%) received breast augmentation. Forty-seven (94.0%) participants were currently taking estrogen replacement therapy and 2 (4.0%) were also taking anti-androgen therapy (i.e., cyproterone acetate). The population characteristics of this study are similar to the criteria specified by the key questions for this review, thus no serious concerns regarding the indirectness of this evidence were noted.

[6] The sample size for this study was small (n = 50). Because no confidence intervals were provided, the precision of the study results could not be assessed.

[7] There was an insufficient number of studies (n < 10) for statistical evaluation of publication bias [18]; the search for studies was comprehensive. No factors (i.e., large effect, dose-response gradient, plausible confounders) were noted that would provide reasons to raise certainty in the evidence.

[8] Two post-mammography assessments of participant-experienced pain were conducted. One assessment was administered by a radiologist and the other by a study nurse. The mean (SD) pain scores from the assessments administered by the radiologist and study nurse were 1.7 (2.0) and 2.0 (2.3) points, respectively.

[9] Data for this body of evidence were not statistically combined due to an insufficient number of studies.

[10] The study personnel responsible for administering the post-ultrasonography assessment of experienced pain was not reported.

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