Sex differences in adverse events following seasonal influenza vaccines: a meta-analysis of randomised controlled trials

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ABSTRACT

Background Despite being a vaccine-preventable disease, influenza remains a major public health threat with vaccine safety concerns reducing vaccine acceptability. Immune responses to vaccines and adverse events may differ between males and females, but most studies do not report results by sex. Using data from clinical trials, we explored sex differences in adverse events following seasonal influenza vaccines.

Methods We obtained data for phase III randomised controlled trials identified through a systematic review and clinical trials registries, and performed a two-stage meta-analysis. Risk ratios (RR) and 95% confidence intervals (95% CI) comparing solicited reactions in females *versus* males were pooled using the Mantel-Haenszel method and a random-effects model. We used the ROBINS-I tool to assess risk of bias and the I^2 statistic for heterogeneity. Main analysis was stratified by age: 18–64 years and ≥65 years.

Results The dataset for this analysis included 34 343 adults from 18 studies (12 with individual-level data and 6 with aggregate data). There was a higher risk of injection site reactions in females compared with males for both younger and older participants, with RRs of 1.29 (95% CI 1.21 to 1.37) and 1.43 (95% CI 1.28 to 1.60), respectively. Higher risk in females was also observed for systemic reactions, with RRs of 1.25 (95% CI 1.20 to 1.31) and 1.27 (95% CI 1.20 to 1.34) for younger and older participants, respectively. We also observed elevated risks of severe reactions in females, with a higher RR in younger *versus* older participants for systemic reactions (RRs 2.12 and 1.48, p=0.03, I^2=79.7%). RRs were not found to vary between quadrivalent and trivalent vaccines.

Conclusion This meta-analysis suggested a higher risk of solicited reactions following influenza vaccines for females compared with males, irrespective of age and vaccine type. Transparent communication of this risk could increase the trust in vaccines and limit vaccine hesitancy. Future studies should report results stratified by sex and explore the role of gender in the occurrence of adverse events.

INTRODUCTION

Seasonal influenza causes significant morbidity and mortality worldwide despite being a vaccine-preventable disease.[1–3] The US Centers for Disease Control and Prevention estimated that influenza infections led to 140 000 to 710 000 hospitalisations and 12 000 to 52 000 deaths annually from 2010 to 2020.[1] In Canada, it was estimated that about 12 000 influenza-related hospitalisations and 3500 influenza-attributable deaths occur annually.[4 5] Influenza vaccination helps to reduce the burden of illness, hospitalisation and death. This is particularly important in the context of the ongoing COVID-19 activity and its impact on the healthcare system.[1 6] Although there are variations in influenza immunisation strategies, the WHO recommends that vaccine programmes target people at higher risk of complications, such as those with chronic health conditions and older adults.[3] Given the need for yearly vaccination and variable vaccine effectiveness, achieving high vaccination coverage remains a challenge.[7–9]

Genetic and hormonal differences between females and males influence both innate and adaptive immune responses to infections; males usually exhibit a lower immune response and higher susceptibility to infectious diseases, including higher incidence and hospitalisations from seasonal influenza infections.[10 11] Sex differences in infectious disease epidemiology varies according to age. Some

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Females and males often differ in their responses to some vaccines and for the risk of adverse events following immunisation.
⇒ The evidence is somewhat limited as vaccination outcomes are generally not stratified and reported by sex.

WHAT THIS STUDY ADDS

⇒ This meta-analysis suggests an elevated risk of injection site reactions and systemic reactions following influenza vaccines in females compared with males, irrespective of age.
⇒ The absolute risk increase was estimated to be 115 additional cases of injection site reactions in females compared with males per 1000 vaccinees and 74 additional cases of systemic reactions.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A better awareness of the relative role of gender *versus* the biological sex for the risk of adverse events following immunisation would be valuable in this matter.

differences are observed throughout the entire lifespan, while others are seen only after puberty and before immunosenescence.[10 12 13] Sex differences have also been observed in response to some vaccines, including influenza vaccine. Females usually develop higher antibody titres following vaccination and could experience a higher incidence and severity of adverse events following immunisation (AEFIs).[2 11 13 14] However, the evidence is somewhat limited as vaccination outcomes in published studies are generally not stratified and reported by sex, even though the information regarding participants' sex is usually available in the original study data.[13 15] In addition to biological differences between females and males, differential health-seeking behaviours have been documented, which could limit the investigation of sex differences if based only on data reported to vaccine surveillance systems.[13] Clinical trials, for which a systematic assessment of AEFIs and an active surveillance of symptoms are undertaken, could minimise this risk of bias in reporting.

Concerns regarding vaccine safety are associated with vaccine hesitancy, with some studies reporting that females were less likely than males to accept the influenza vaccine.[16–19] Because women are overrepresented in healthcare occupations, where vaccination is recommended to decrease transmission to vulnerable patients, these concerns should be addressed. Sex differences are usually not considered in influenza vaccine policies and recommendations. A greater understanding of these differences in AEFIs may support targeted recommendations and communication strategies to address vaccine hesitancy and to improve vaccination uptake. In this study, we therefore explored sex differences in the risk of adverse events following seasonal influenza vaccine in healthy adults, through meta-analysis of data from randomised controlled trials (RCTs) that were not previously analysed to detect these differences.

METHODS
We performed a meta-analysis of RCT data and presented the results according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[20 21] The protocol has been registered in Prospero (CRD42018112260) (online supplemental appendix A).

Search strategy and study selection
To identify RCTs with individual-level participant data available for inclusion, we adapted a search strategy that was developed in collaboration with a research librarian for a previous systematic review[15] (online supplemental appendix B). We searched for RCTs in CINAHL, Embase, PubMed and Web of Science databases. Unique citations were screened at level 1 (title and/or abstract) and at level 2 (full-text) using DistillerSR (version 2.35 DistillerSR Inc 2018, accessed date: October 2018–April 2019). We restricted the search to studies in French or English for which full-text were available. We also searched for RCTs from the following clinical trials databases: ClinicalTrials.gov, Clinical Study Data Request (CSDR), European Organisation for Research and Treatment of Cancer Clinical Trials Database, European Union Clinical Trials Register, the WHO international Clinical Registry Platform, and Health Canada's Clinical Trials Database. The final search was done on 3 October 2018 in all databases, with all data made available by 28 January 2022. All records were assessed for eligibility by two independent reviewers (FT, AA) and discrepancies were resolved through discussion.

Eligibility criteria
We included data from phase III RCTs conducted from 2010 and completed by September 2018. The study population included healthy males and females aged 18 years and older. All seasonal influenza vaccines were considered, for all routes of administration, dosages and formulations, but we excluded the pandemic 2009/2010 A(H1N1) influenza vaccine. Main outcomes were solicited injection site reactions (ISR) and systemic reactions assessed within 7 days after vaccination, as well as specific solicited reactions available for each included study (ie, pain, redness, fever, headache and myalgia). Solicited reactions refer to adverse events that are prelisted and collected within 7 days following vaccination using a diary card. We also qualitatively evaluated related unsolicited adverse events assessed from 21 to 28 days following vaccination and serious adverse events (SAEs) reported during the entire study period.

Data collection process
After removing duplicates from both sources (ie, searches from literature and from clinical trials registries), individual-level data were requested from clinical trials registries or by contacting the corresponding author of the publication. We asked authors to re-analyse the data when individual-level data were not available. For each included study, data on sex, age, number of participants (randomised and included in the safety evaluation), vaccine type (quadrivalent or trivalent influenza vaccine), route of administration (intramuscular or intradermal), influenza season, country/region, underlying medical conditions and previous influenza vaccination were extracted when available. Aggregate-level data for these characteristics among randomised participants were requested from the investigators when individual-level data were not available. For some studies, participant-level data on race, ethnicity and previous influenza illness were also available. For each outcome, we extracted the number of participants reporting at least one AEFI during the assessment period and the number of participants with available data, according to sex, age and vaccine type. Investigators were contacted for further details about the study or for additional data when needed.

Quality assessment
For each included study, the risk of bias was assessed in duplicate by two independent assessors (MK, FT) using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) assessment tool.[22] We used a tool for non-randomised studies as we conducted a secondary analysis of RCTs that were not originally intended for evaluating the effect of sex on AEFIs. Discrepancies were resolved by consensus. Evaluation focused on the following domains: confounding, selection, classification of interventions, missing data, and measurement of outcomes. Quality of evidence for overall ISR and systemic reactions were assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) ()system.[23 24]

Statistical analysis
We performed a two-stage meta-analysis using individual-level and aggregate data.[25] Study-specific unadjusted risk ratios (RR) and 95% confidence intervals (95% CI), comparing proportions of AEFIs in females *versus* males, were estimated and then pooled using the Mantel-Haenszel
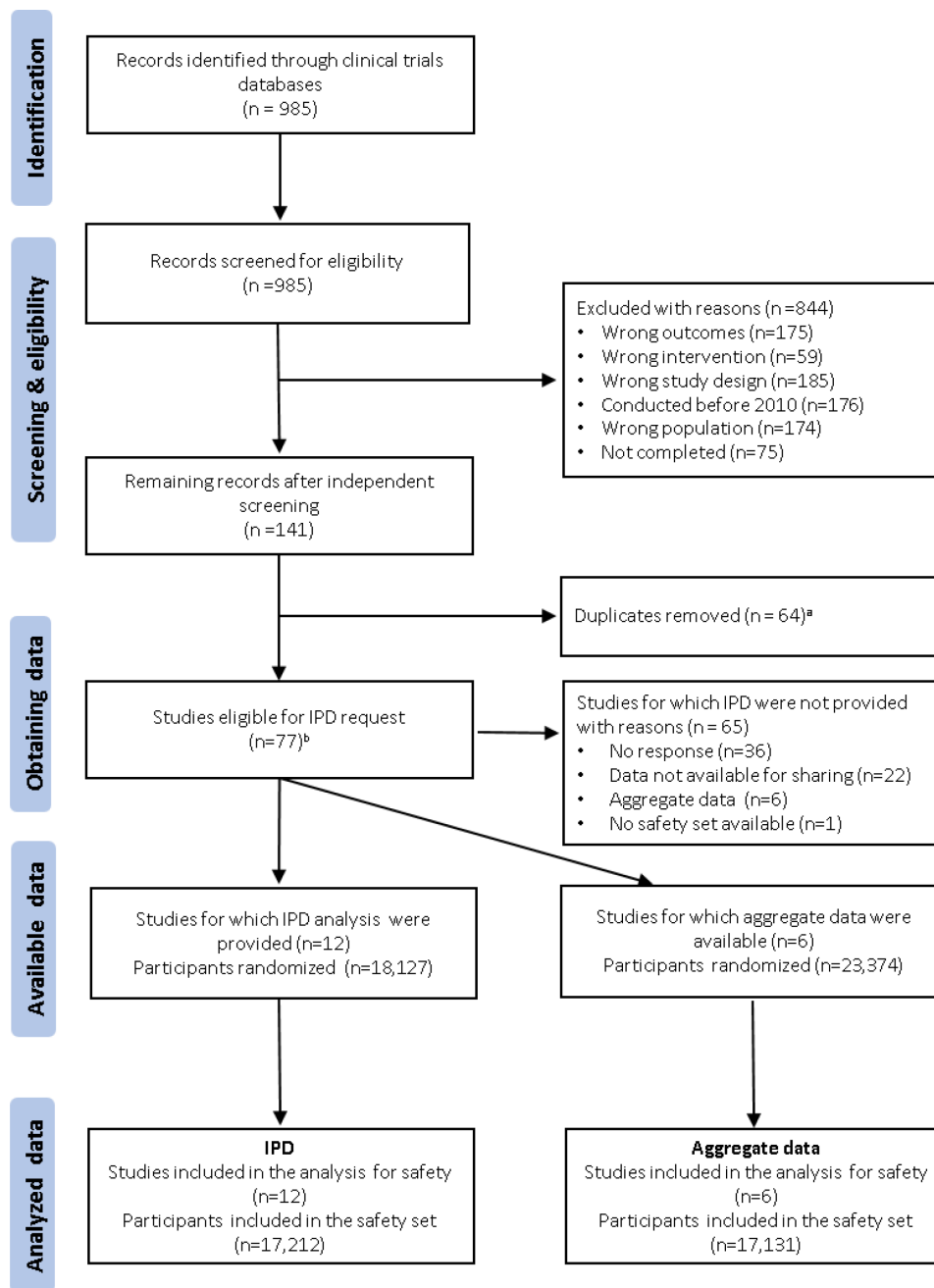
Figure 1 Study selection flowchart from clinical trials databases. [a]Duplicates removed after comparison with studies found through literature search (online supplemental appendix D). [b]Including the 40 studies found through literature search (online supplemental appendix D). IPD, individual-level participant data

method and a random-effects model to allow for between-study heterogeneity.[26] An RR >1 indicates increased risk for females compared with males. As the effect of sex on AEFIs could vary with age,[14 27] the main analysis was stratified by age into younger (18–64 years) and older (≥65 years) participants. Due to data anonymisation procedures imposed by one manufacturer, data on participants' age were grouped in quartiles for both females and males for all trials sponsored by this manufacturer. For these trials, participants in the first two quartiles were classified as younger participants and those in the third and fourth quartiles were classified as older participants. Pre-existing medical conditions should

not impact our results as we only included healthy adults in our study, and participants who are enrolled in RCTs are usually medically stable and not severely immunocompromised (online supplemental appendix C). Considering that sex is a non-manipulable state and that the evidence for the association between other covariates (eg, ethnicity and previous history of vaccination) and the risk of AEFIs was not conclusive, these covariates were not deemed as potential confounders for the association between sex and AEFIs.[28–32] For solicited reactions, we analysed those with complete information, which included over 99% of participants who received one of the study vaccines.

Table 1 Characteristics of included studies (n=18)

Study ID, first author, year	Influenza season	Country / region	N randomised	Included in the overall safety set* N (%)	Vaccines (route of administration)¶	Females N (%)	Median age (range)/ age groups (in years)**	Risk of bias (ROBINS-I)
			41 501	34 343 (82.8%)				
Sanofi Pasteur								
GQM01 Pepin, 2013[35]	NH 2011–2012	Western or Eastern Europe	1568	1565 (99.8%)	IIV4/IIV3 (IM)	916 (58.4%)	F: 59 y (18–89) M: 62 y (18–91)	Serious
GQM04 Cadorna-Carlos, 2015[36]	NH 2011–2012	Australia, Philippines	1566	1565 (99.8%)	IIV4/IIV3 (IM)	918 (58.6%)	F: >36–47y, N=306 F: >47–61 y, N=306 M: 19–28 y, N=216 M: >28–44y, N=216 M: >44–61y, N=216	Serious
GQM07 Choi, 2017	NH 2015–2016	Korea	300	300 (100.0%)	IIV4/IIV3 (IM)	221 (73.7%)	F: 36 y (20–60) M: 34 y (19–60)	Serious
GQM11 Sesay, 2018[38]	NH 2014–2015	Western or Eastern Europe	2225	2222 (99.9%)	IIV4/IIV3 (IM)	1204 (54.1%)	F: 58 y (18–91) M: 62 y (18–88)	Serious
QID01 Gorse, 2015[31]	NH 2012–2013	USA	3360	3355 (99.9%)	QIV/TIV (ID)	2059 (61.3%)	F: 18–49 y, N=1345 F: 50–64 y, N=710 M: 18–49 y, N=888 M: 50–64 y, N=412	Low
QIV03 Not published	NH 2010–2011	USA	739	739 (100.0%)	IIV4/IIV3 (IM)	403 (54.5%)	F: 71 y (30–92) M: 71 y (18–95)	Serious
QIV06 Not published	SH 2015	India	100	100 (100.0%)	IIV4 (IM)	34 (34.0%)	F: 18–64 y, N=22 F: 65 y+, N=12 M: 18–64 y, N=48 M: 65 y+, N=18	Serious
RPV03C Not published	NH 2010–2011	France, Germany	954	472 (49.5%†)	IIV3/REPEVAX (IM)	537 (56.3%)	F: 67 y (60–92) M: 67 y (60–88)	Serious
GlaxoSmithKline								
112963 Tinico, 2014	NH 2010–2011	USA, Mexico, Canada	1707	1703 (99.8%)	IIV4/IIV3 (IM)	1046 (61.3%)	F: 49 y (18–89) M: 53 y (18–88)	Low
201251 Claeys, 2018[40]	NH 2014–2015	Germany	120	120 (100.0%)	IIV4 (IM)	76 (63.3%)	F: 28 y (19–49) M: 29 y (18–49)	Low
114269 Kieninger, 2013[41]	NH 2010–2011	USA, Korea, Germany, Romania, Spain, Taiwan	4659	4656 (99.9%)	IIV4/IIV3 (IM)	2638 (56.6%)	F: 62 y (18–89) M: 66 y (18–89)	Low
117036 Schwarz, 2017[42]	NH 2013–2014	USA, Germany, Canada	829	415 (50.0%‡)	IIV4/HZ/su (IM)	429 (51.8%)	F: 63 y (50–87) M: 61 y (50–88)	Low
CSL Seqirus								
CSLCT-QIV-13–01 Treanor, 2017[43]	NH 2014–2015	USA	3484	3449 (99.0%)	IIV4/IIV3 (IM)	1992 (57.8%)	F: 18–49 y, N=612 F: 50–64 y, N=406 F: 65 y+, N=974 M: 18–49 y, N=408 M: 50–64 y, N=315 M: 65 y+, N=869	Low
V118-18 Not published	NH 2016–2017, SH 2017	Bulgaria, Colombia, Czech Republic, Estonia, Latvia, Lithuania, Malaysia, Philippines, Poland, Romania, Thailand, Turkey	6790	665 (9.8%§)	aQIV/Boostrix (IM)	2089 (61.5%)	F: 65 y+, N=4194 M: 65 y+, N=2596	Low

Continued

Table 1 Continued

Study ID, first author/ year	Influenza season	Country/ region	N randomised	Included in the overall safety set*	Vaccines (route of administration)¶	Females	Median age (range/ age groups (in years)**	Risk of bias (ROBINS-I)
V58-23 Not published	NH 2014–2015	USA	1560	1560 (100.0%)	TIVc/TIVf (IM)	940 (60.3%)	F: 18–49 y, N=940; M: 18–49 y, N=620	Low
V70-27 Frey, 2014[44]	NH 2010–2011	USA	7082	7019 (99.0%)	aTIV/TIV (IM)	4554 (64.3%)	F: 65 y+, N=4616; M: 65 y+, N=2468	Low
V118-20 Beran, 2021[45]	NH 2017–2018	USA	1778	1776 (99.9%)	aQIV/aTIV (IM)	1007 (56.6%)	F: 65 y+, N=1007; M: 65 y+, N=771	Low
V130-01 Bart, 2016[30]	NH 2013–2014	USA	2680	2662 (99.3%)	QIVc/TIVc (IM)	1516 (56.6%)	F: 18–49 y, N=495; F: 50–64 y, N=272; F: 65 y+, N=749; M: 18–49 y, N=368; M: 50–64 y, N=205; M: 65 y+, N=591	Low

*Corresponds to participants who received one of the study vaccines (total vaccinated cohort for analysis of safety). The number of participants with solicited data available may vary.
†Only data from group 2 (influenza vaccine alone at visit 1 followed by REPEVAX at visit 2) post visit 1 were used for the safety evaluation. Data for solicited reactions were not available.
‡Only data from the control group (influenza vaccine alone at visit 1 followed by HZ/su vaccine at month 2 and at month 4) post visit 1 were used for the safety evaluation, except for injection site reactions for which we used reactions related to influenza vaccine for each group (ie, the co-administration group: Influenza+HZ/su vaccine at visit 1 followed by HZ/su vaccine at month 2 and the control group).
§Solicited safety set included a randomly selected sample of subjects (subset) and we included only data for influenza vaccine in our analysis.
¶IIV4: quadrivalent split-virion inactivated influenza vaccine (egg-derived). IIV3: trivalent split-virion inactivated influenza vaccines (egg-derived). QIV ID: quadrivalent influenza intradermal vaccine (zonal purified subvirion). TIV ID: trivalent influenza intradermal vaccine (zonal purified subvirion). REPEVAX: diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine. HZ/su: adjuvanted herpes zoster subunit vaccine. PPV23: 23-valent pneumococcal polysaccharide vaccine. aQIV: adjuvanted quadrivalent influenza vaccine (egg-derived). Boostrix: diphtheria, tetanus and pertussis (acellular, component). TIVc: cell-derived trivalent influenza vaccine. TIVf: egg-derived trivalent influenza vaccine. aTIV: adjuvanted trivalent influenza vaccine. For GlaxoSmithKline's studies, subject age was set to blank over 89 y. For Seqirus's studies, data were available by age groups (aggregated).
**According to anonymisation standards, data on age were only available in quartiles for females and males for Sanofi's studies.
F, females; ID, intradermal; IM, intramuscular; M, males; NA, not available; NH, Northern hemisphere; QIV, quadrivalent vaccine; ROBINS-I, Risk of Bias in Non-Randomized Studies of Interventions ; SH, Southern hemisphere; TIV, trivalent vaccine; y, years.

Heterogeneity was assessed by p value of the χ^2 statistic and the I^2 statistic, which describes the percentage of variability due to heterogeneity rather than to chance. As defined by the Cochrane collaboration, we considered an $I^2 < 40\%$ as negligible heterogeneity, $\geq 40\%$ to 75% as moderate heterogeneity, and >75% as considerable heterogeneity.[26] Analyses were performed with Statistical Analysis System (SAS Institute Inc, Cary, NC, version 9.4) and Review Manager (RevMan version 5.4), with statistical significance set at $p < 0.05$ for most analyses but at $p < 0.10$ for subgroup difference tests.[33] Corrections for multiple comparisons were done using the Holm method.[34]

Subgroup analyses were performed according to vaccination type (quadrivalent vaccine (QIV) *versus* trivalent vaccine (TIV)) and the risk of bias (low/moderate *versus* serious/critical). A sensitivity analysis was conducted to investigate the impact of using the following alternative age groups: 18–49 years, 50–64 years; ≥65 years. We excluded studies for which data were not available for these age groups. We also explored whether results differed after excluding one study that investigated intradermal rather than intramuscular influenza vaccine. To assess the robustness of findings, we performed generalised linear-mixed models with ISR and systemic reactions as the outcomes and sex and age as fixed effects, using the individual-level data from one manufacturer because the exact participants' age was available. The SAS GLIMMIX procedure was used with a Poisson distribution, a log link and a random effect for sex per study to allow that the effect of sex could vary between studies.
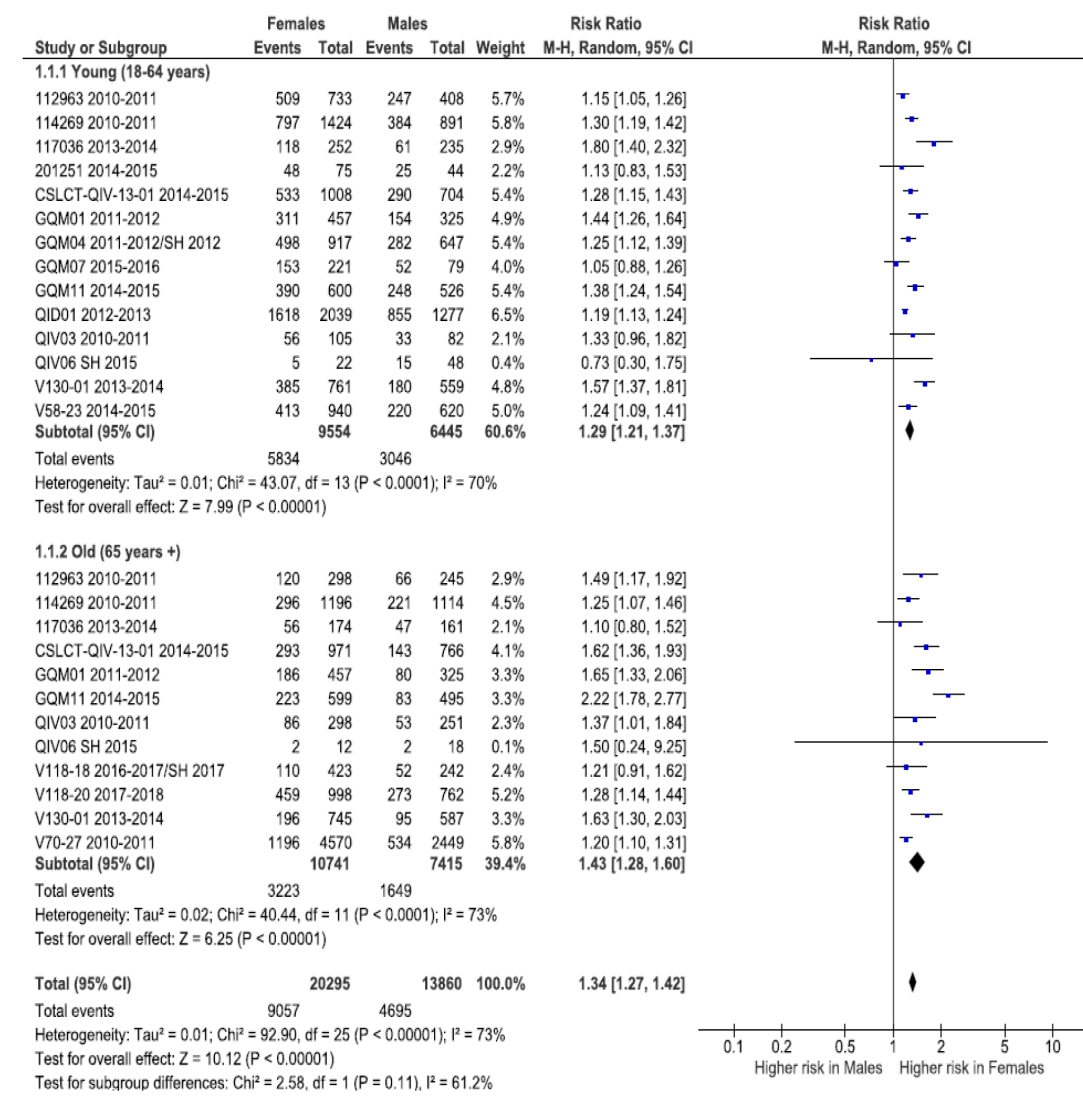
RESULTS

A total of 77 eligible studies were identified from the 985 records found through clinical trials databases (figure 1), including 40 studies identified from the 4629 unique citations found through the literature search (online supplemental appendix D). Eighteen studies had available data, including 12 with individual-level data and six with aggregate data, yielding a total of 34 343 participants that were included in the analysis. For one study (n=472), solicited data for influenza vaccine were not available, and it was therefore excluded from the solicited reactions analysis.

Study characteristics

Characteristics of the 18 included studies are presented in table 1 and in online supplemental appendix C. Eight studies were conducted by Sanofi Pasteur, four by GlaxoSmithKline and six by CSL Seqirus.[30 31 35–45] About half (54%) of participants were females and 10 of 18 studies included participants from the USA. Studies were conducted from the 2010–11 to the 2017–18 Northern influenza season and from the 2012 to the 2017 Southern influenza season. Vaccines investigated were QIV and TIV administered by intramuscular injection, except for one study that evaluated intradermal vaccines. The list of AEFIs assessed and definitions used varied by study (online supplemental appendix E).

Quality assessment

Quality assessment of included studies is presented in online supplemental appendix F and was done in the context of the association between sex and AEFIs. Overall, 11 studies were deemed at low risk of bias and seven at serious risk of bias. Studies for which we were not able to stratify results according to our pre-specified age groups of interest (ie, 18–49 years;

Study or Subgroup	Females Events	Total	Males Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Young (18-64 years)						
112963 2010-2011	509	733	247	408	5.7%	1.15 [1.05, 1.26]
114269 2010-2011	797	1424	384	891	5.8%	1.30 [1.19, 1.42]
117036 2013-2014	118	252	61	235	2.9%	1.80 [1.40, 2.32]
201251 2014-2015	48	75	25	44	2.2%	1.13 [0.83, 1.53]
CSLCT-QIV-13-01 2014-2015	533	1008	290	704	5.4%	1.28 [1.15, 1.43]
GQM01 2011-2012	311	457	154	325	4.9%	1.44 [1.26, 1.64]
GQM04 2011-2012/SH 2012	498	917	282	647	5.4%	1.25 [1.12, 1.39]
GQM07 2015-2016	153	221	52	79	4.0%	1.05 [0.88, 1.26]
GQM11 2014-2015	390	600	248	526	5.4%	1.38 [1.24, 1.54]
QID01 2012-2013	1618	2039	855	1277	6.5%	1.19 [1.13, 1.24]
QIV03 2010-2011	56	105	33	82	2.1%	1.33 [0.96, 1.82]
QIV06 SH 2015	5	22	15	48	0.4%	0.73 [0.30, 1.75]
V130-01 2013-2014	385	761	180	559	4.8%	1.57 [1.37, 1.81]
V58-23 2014-2015	413	940	220	620	5.0%	1.24 [1.09, 1.41]
Subtotal (95% CI)		9554		6445	60.6%	1.29 [1.21, 1.37]
Total events	5834		3046			

Heterogeneity: Tau² = 0.01; Chi² = 43.07, df = 13 (P < 0.0001); I² = 70%
Test for overall effect: Z = 7.99 (P < 0.00001)

Study or Subgroup	Females Events	Total	Males Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.2 Old (65 years +)						
112963 2010-2011	120	298	66	245	2.9%	1.49 [1.17, 1.92]
114269 2010-2011	296	1196	221	1114	4.5%	1.25 [1.07, 1.46]
117036 2013-2014	56	174	47	161	2.1%	1.10 [0.80, 1.52]
CSLCT-QIV-13-01 2014-2015	293	971	143	766	4.1%	1.62 [1.36, 1.93]
GQM01 2011-2012	186	457	80	325	3.3%	1.65 [1.33, 2.06]
GQM11 2014-2015	223	599	83	495	3.3%	2.22 [1.78, 2.77]
QIV03 2010-2011	86	298	53	251	2.3%	1.37 [1.01, 1.84]
QIV06 SH 2015	2	12	2	18	0.1%	1.50 [0.24, 9.25]
V118-18 2016-2017/SH 2017	110	423	52	242	2.4%	1.21 [0.91, 1.62]
V118-20 2017-2018	459	998	273	762	5.2%	1.28 [1.14, 1.44]
V130-01 2013-2014	196	745	95	587	4.0%	1.63 [1.30, 2.03]
V70-27 2010-2011	1196	4570	534	2449	5.8%	1.20 [1.10, 1.31]
Subtotal (95% CI)		10741		7415	39.4%	1.43 [1.28, 1.60]
Total events	3223		1649			

Heterogeneity: Tau² = 0.02; Chi² = 40.44, df = 11 (P < 0.0001); I² = 73%
Test for overall effect: Z = 6.25 (P < 0.00001)

	Females	Total	Males	Total	Weight	Risk Ratio
Total (95% CI)		20295		13860	100.0%	1.34 [1.27, 1.42]
Total events	9057		4695			

Heterogeneity: Tau² = 0.01; Chi² = 92.90, df = 25 (P < 0.00001); I² = 73%
Test for overall effect: Z = 10.12 (P < 0.00001)
Test for subgroup differences: Chi² = 2.58, df = 1 (P = 0.11), I² = 61.2%

Risk Ratio M-H, Random, 95% CI — scale: 0.1 0.2 0.5 1 2 5 10 — Higher risk in Males / Higher risk in Females

Figure 2 Risk ratio for the association of sex with injection site reactions (ISR) following influenza vaccines (solicited period) among younger and older participants Young subgroup includes participants aged 18-64 years and old subgroup includes participants aged 65 years and over. ID used for each study refers to the clinical trial number followed by the Northern hemisphere influenza season; SH denotes Southern Hemisphere influenza season if applicable. Injection site reactions have been collected within 7 days following vaccination. Events: Number of participants reporting at least one solicited local reaction during the period. Total: Number of participants with available data for solicited symptoms. See online supplemental appendix E for the list of ISR collected in each study and the criteria used.

50–59 years; ≥65 years) were considered at serious risk of bias. These studies were nevertheless included in the meta-analysis and this limitation was addressed during subgroup/sensitivity analysis. Outcomes assessed were self-reported and most were subjective measures that may have less validity compared with objective measures. However, due to rigorous methods of outcome assessment used in RCTs, which were comparable for females and males, we considered that the risk of differential misclassification of outcomes should be low. All included studies were deemed at low risk of bias for the other domains (ie, selection, classification of interventions and missing data).

Main and additional outcomes

Among included studies, pain was the most frequently reported solicited ISR and headache and myalgia were commonly reported solicited systemic reactions by both females and males. Pooled results showed a higher risk of ISR in females compared with males for both younger and older participants, with RRs of 1.29 (95% CI 1.21 to 1.37) and 1.43 (95% CI 1.28 to 1.60), respectively (figure 2). While the magnitude of the relative risk is higher for older participants, the test for subgroup differences did not reach statistical significance (p for heterogeneity among subgroups=0.11, I²=61.2%). Moderate heterogeneity existed within both groups (p<0.001, I²=70% and p<0.001, I²=73%). When we only looked at severe ISR, with similar definitions used across studies, the RRs were 1.70 (95% CI 1.19 to 2.43) for younger participants and 1.51 (95% CI 0.87 to 2.63) for older participants, with no evidence of heterogeneity within either group or between groups (figure 3). Elevated risks in females were also observed for specific ISR (ie, pain and redness) with no heterogeneity between younger and older participants (data not shown). However, we noticed considerable heterogeneity within younger participants and moderate heterogeneity within older participants for these outcomes (data not shown).
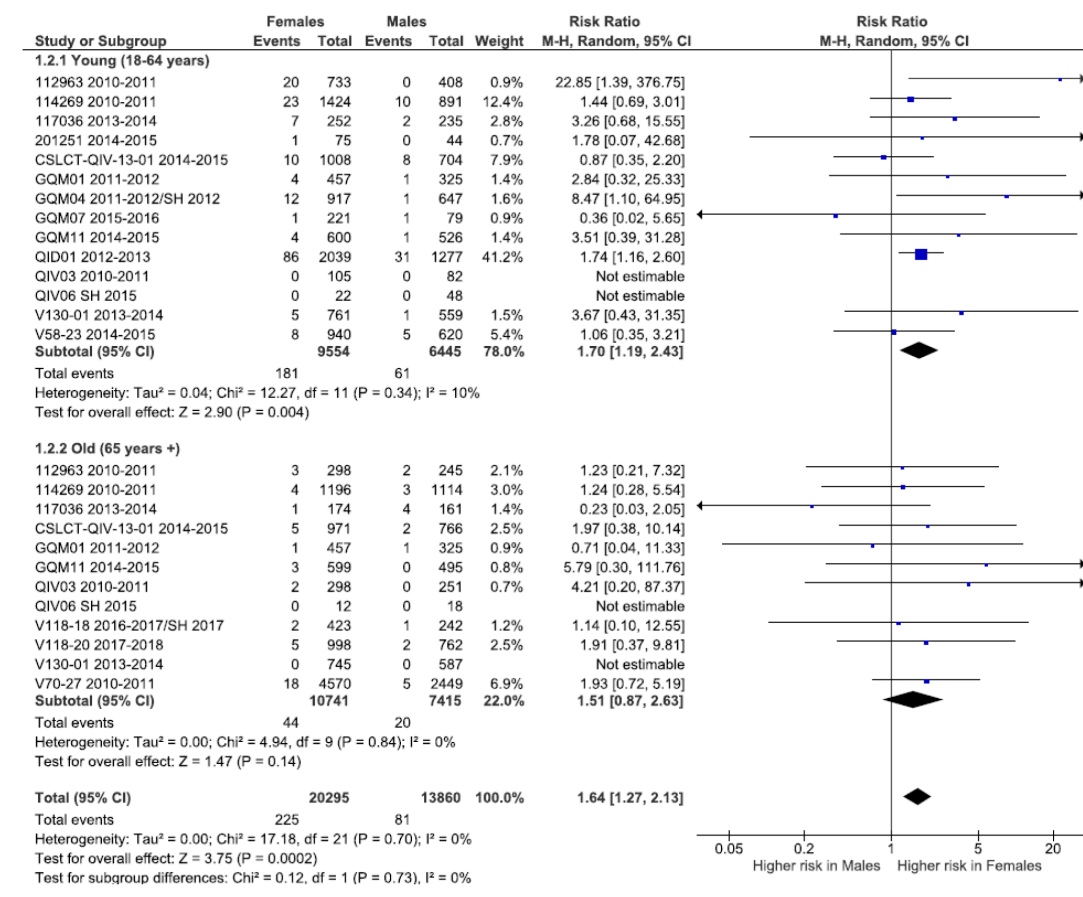
Figure 3 Risk ratio for the association of sex with severe (Grade 3) injection site reactions (ISR) following influenza vaccines (solicited period) among younger and older participants Young subgroup includes participants aged 18-64 years and old subgroup includes participants aged 65 years and over. ID used for each study refers to the clinical trial number followed by the Northern hemisphere influenza season; SH denotes Southern Hemisphere influenza season if applicable. ISR have been collected within 7 days following vaccination. Events: Number of participants reporting at least one grade 3 ISR during the period. Total: Number of participants with available data for solicited symptoms. See online supplemental appendix E for the list of ISR collected in each study and the criteria used for severe ISR.

Higher risk for systemic reactions was also observed in females compared with males, with similar estimates between younger (RR 1.25, 95% CI 1.20 to 1.31) and older participants (RR 1.27, 95% CI 1.20 to 1.34) and no evidence of heterogeneity in both groups (figure 4). For severe systemic reactions, RR among younger participants was greater than the RR among older participants (2.12, 95% CI 1.71 to 2.62 *versus* 1.48, 95% CI 1.17 to 1.87, p for heterogeneity among subgroups=0.03, I^2=79.7%) (figure 5). Elevated risks in females were found for specific systemic reactions (ie, fever, headache and myalgia), with no heterogeneity between younger and older participants (data not shown).

Using data from 13 studies, we found that related unsolicited adverse events ranged from 0.9% to 23% in females and from 0 to 11% in males. None of the SAEs were considered to be vaccine-related by the investigator in 11 studies. For the others, data were not available to explore the risk by sex (data not shown).

Subgroup and sensitivity analyses

Subgroup analysis was done to explore heterogeneity for ISR. Among younger and older participants, the RRs were not found to vary between vaccine types (QIV *versus* TIV). For older participants only, the magnitude of the RR was reduced to 1.33 (95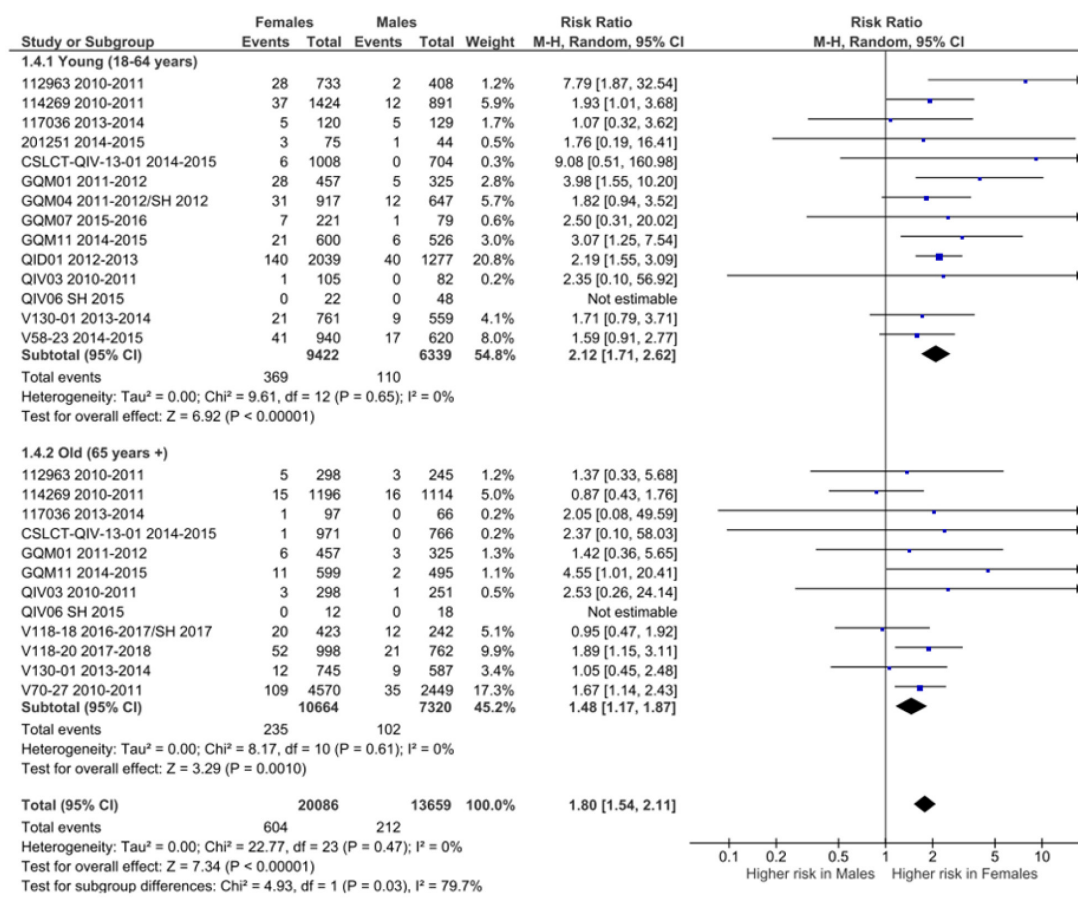% CI 1.21 to 1.46, p for heterogeneity among subgroups=0.05, I^2=73.7%) when only studies at low risk of bias were included (online supplemental appendix G).

In a sensitivity analysis using the data from 12 studies, modifying age groups to be more reflective of hormonal changes through the life course did not change the interpretation of findings. However, we noticed that heterogeneity was reduced in participants aged 18–49 years old for ISR (p=0.12, I^2=40%) (online supplemental appendix H). Results were unchanged after excluding the study with an intradermal influenza vaccine. Finally, the main findings remained robust after analysing data from GlaxoSmithKline only, which included 7315 participants from four studies, using generalised linear-mixed models as well as after corrections for the multiple testing (online supplemental appendix I).

Certainty of evidence

We assessed the certainty of evidence for each main outcome (ISR and systemic reactions) using the GRADE approach guidelines. As we used the ROBINS-I tool to assess the risk of bias, the initial level of certainty was high.[24 46] After the rating process, the certainty of evidence was low for ISR, due to the risk of confounding and inconsistency, and moderate for systemic reactions, due to the risk of confounding (online supplemental appendix F).
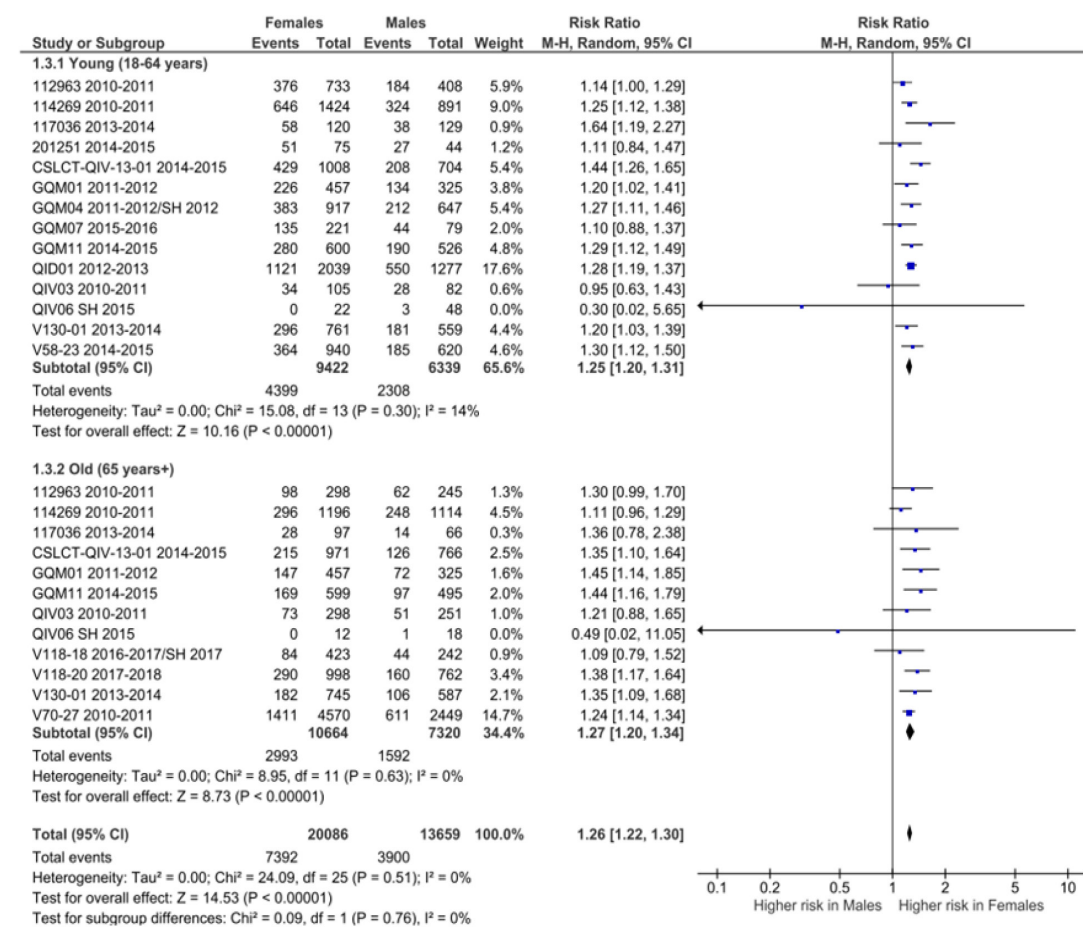
Figure 4 Risk ratio for the association of sex with systemic reactions following influenza vaccines (solicited period) among younger participants and older participants. Young subgroup includes participants aged 18-64 years and old subgroup includes participants aged 65 years and over. ID used for each study refers to the clinical trial number followed by the Northern hemisphere influenza season; SH denotes Southern Hemisphere influenza season if applicable. Systemic reactions have been collected within 7 days following vaccination. Events: Number of participants reporting at least one systemic reaction during the period. Total: Number of participants with available data for solicited symptoms. See online supplemental appendix E for the list of systemic reactions collected in each study and the criteria used.

DISCUSSION

In this meta-analysis of 18 RCTs that included over 34 000 participants, we found that females have, on average, an increased risk of adverse events following influenza vaccines compared with males. This association was observed for different outcomes and across different subgroup and sensitivity analyses. Our results suggest an absolute risk increase of 115 additional cases of ISR in females compared with males per 1000 vaccinees, and 74 additional cases of systemic reactions among females per 1000 vaccinees (online supplemental appendix F). For this secondary analysis of RCTs, the quality of evidence was deemed low for ISR and moderate for systemic reactions. Surprisingly, there was no interaction on the multiplicative scale between sex and age in most of our analyses, although the risk of AEFIs decreased with age in both females and males. This was also confirmed in subgroup and sensitivity analyses. We observed large heterogeneity for overall ISR that was reduced by using severe ISR as the main outcome. This suggests that severe ISR could be a more appropriate outcome, as similar definitions were used across studies. For severe ISR, the test for subgroup difference does not suggest any heterogeneity between younger and older participants, but we noticed that the magnitude of the RR was higher in the younger group. We also observed that the higher risk of severe reactions in younger participants was more pronounced for systemic reactions compared with ISR, with a test for subgroup differences that was

statistically significant in the main analysis, but not after correcting for multiple testing. The heterogeneity for ISR was also reduced when we looked at different age groups, but only for those aged 18–49 years old.

The higher risk of AEFIs in females compared with males observed in this study is consistent with results from other published studies.[11 13 15] Regarding the interaction between age and sex, in a meta-analysis published in 1996, Beyer et al also found no meaningful differences in the young (<60 years) and the elderly (≥60 years) for local and systemic reactions reported during the 48 hour period following influenza vaccination.[47] Similar to our results, they observed a higher risk for females compared with males for all reactions and in all age groups. A different conclusion was found in a recent study published by Bohn-Goldman et al using data from active surveillance of over 300 000 participants.[48] They noticed a complex interaction between age and sex, with a higher OR of AEFIs in females, which was more pronounced for those between 30 and 70 years of age. Although small differences may exist in the frequency of ISR between the QIV and the TIV vaccine,[49] we did not find heterogeneity between vaccine types for both younger and older participants. Subgroup analysis according to study quality suggests a possible overestimation of the effect in studies deemed at serious risk of bias for the older participants. Studies at serious risk of bias were those for which it was impossible to account adequately for

Study or Subgroup	Females Events	Total	Males Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Young (18-64 years)						
112963 2010-2011	28	733	2	408	1.2%	7.79 [1.87, 32.54]
114269 2010-2011	37	1424	12	891	5.9%	1.93 [1.01, 3.68]
117036 2013-2014	5	120	5	129	1.7%	1.07 [0.32, 3.62]
201251 2014-2015	3	75	1	44	0.5%	1.76 [0.19, 16.41]
CSLCT-QIV-13-01 2014-2015	6	1008	0	704	0.3%	9.08 [0.51, 160.98]
GQM01 2011-2012	28	457	5	325	2.8%	3.98 [1.55, 10.20]
GQM04 2011-2012/SH 2012	31	917	12	647	5.7%	1.82 [0.94, 3.52]
GQM07 2015-2016	7	221	1	79	0.6%	2.50 [0.31, 20.02]
GQM11 2014-2015	21	600	6	526	3.0%	3.07 [1.25, 7.54]
QID01 2012-2013	140	2039	40	1277	20.8%	2.19 [1.55, 3.09]
QIV03 2010-2011	1	105	0	82	0.2%	2.35 [0.10, 56.92]
QIV06 SH 2015	0	22	0	48		Not estimable
V130-01 2013-2014	21	761	9	559	4.1%	1.71 [0.79, 3.71]
V58-23 2014-2015	41	940	17	620	8.0%	1.59 [0.91, 2.77]
Subtotal (95% CI)		9422		6339	54.8%	2.12 [1.71, 2.62]
Total events	369		110			

Heterogeneity: Tau² = 0.00; Chi² = 9.61, df = 12 (P = 0.65); I² = 0%
Test for overall effect: Z = 6.92 (P < 0.00001)

Study or Subgroup	Females Events	Total	Males Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.2 Old (65 years +)						
112963 2010-2011	5	298	3	245	1.2%	1.37 [0.33, 5.68]
114269 2010-2011	15	1196	16	1114	5.0%	0.87 [0.43, 1.76]
117036 2013-2014	1	97	0	66	0.2%	2.05 [0.08, 49.59]
CSLCT-QIV-13-01 2014-2015	1	971	0	766	0.2%	2.37 [0.10, 58.03]
GQM01 2011-2012	6	457	3	325	1.3%	1.42 [0.36, 5.65]
GQM11 2014-2015	11	599	2	495	1.1%	4.55 [1.01, 20.41]
QIV03 2010-2011	3	298	1	251	0.5%	2.53 [0.26, 24.14]
QIV06 SH 2015	0	12	0	18		Not estimable
V118-18 2016-2017/SH 2017	20	423	12	242	5.1%	0.95 [0.47, 1.92]
V118-20 2017-2018	52	998	21	762	9.9%	1.89 [1.15, 3.11]
V130-01 2013-2014	12	745	9	587	3.4%	1.05 [0.45, 2.48]
V70-27 2010-2011	109	4570	35	2449	17.3%	1.67 [1.14, 2.43]
Subtotal (95% CI)		10664		7320	45.2%	1.48 [1.17, 1.87]
Total events	235		102			

Heterogeneity: Tau² = 0.00; Chi² = 8.17, df = 10 (P = 0.61); I² = 0%
Test for overall effect: Z = 3.29 (P = 0.0010)

Total (95% CI)		20086		13659	100.0%	1.80 [1.54, 2.11]
Total events	604		212			

Heterogeneity: Tau² = 0.00; Chi² = 22.77, df = 23 (P = 0.47); I² = 0%
Test for overall effect: Z = 7.34 (P < 0.00001)
Test for subgroup differences: Chi² = 4.93, df = 1 (P = 0.03), I² = 79.7%

Risk Ratio M-H, Random, 95% CI
0.1 0.2 0.5 1 2 5 10
Higher risk in Males   Higher risk in Females

Figure 5 Risk ratio for the association of sex and severe (grade 3) systemic reactions following influenza vaccines (solicited period) among younger participants and older participants. Young subgroup includes participants aged 18-64 years and old subgroup includes participants aged 65 years and over. ID used for each study refers to the clinical trial number followed by the Northern hemisphere influenza season; SH denotes Southern Hemisphere influenza season if applicable. Systemic reactions have been collected within 7 days following vaccination. Events: Number of participants reporting at least one systemic reaction during the period. Total: Number of participants with available data for solicited symptoms. See online supplemental appendix E for the list of systemic reactions collected in each study and the criteria used for severe systemic reactions.

the effect of age. For some of these studies, some younger participants were included in the older group, which are potentially at higher risk of ISR. In addition, the age categories used for the analysis varied between females and males for some studies, resulting in a larger proportion of younger females included in the older group. Excluding these studies from the main analysis for ISR reduced the effect estimate and the heterogeneity among older participants.

There are limitations in this study. It should be noted that most safety outcomes were self-reported by vaccinees and that the experience of AEFIs reflects both sex and gender differences. While sex refers to biological and physiological characteristics of males and females, gender is associated with roles, behaviour activities, and attributes considered appropriate for men and women.[10] Although the systematic assessment in clinical trials should limit bias, gender differences could have had an impact on the reporting of adverse events, resulting in a higher apparent risk among women who are generally more likely to report health events.[13] The use of objective measures, such as fever, could help to disentangle the role of sex and gender, but no clear trend was observed in our data. Another limitation is related to data sharing. Of the 77 eligible studies for which individual-level data were requested, we were only able to access 12 for inclusion in our meta-analysis. Six additional studies with aggregate data were provided. We have no reason to believe that studies that were shared would have different findings about the

effect of interest than those that were not shared, and so this should not systematically bias our study's findings. Individual-level participant data meta-analysis has many advantages over the traditional approach with aggregate data from published literature, including the possibility to adjust for potential confounders.[50] Better access to individual-level data from clinical trials is needed to maximise the benefits of clinical research for clinicians, patients, and the overall scientific community.

In the current study, we were limited in our capacity to adequately account for the effect of age. This limitation, combined with differences in the study design and the age distribution of participants, could explain why Bohn-Goldman et al[48] found an age by sex interaction for AEFI reporting that was not seen in our analysis. We performed analyses stratified by age, but we pooled unadjusted RRs from each study. Although sex differences in AEFIs could be related to differences in the distribution of other factors, there was no large imbalance in the distribution of other covariates between males and females in our study and adjustment for these covariates in sensitivity analysis did not change the conclusions. This is consistent with prior knowledge in this domain. In addition, the presence or absence of an association between some characteristics (eg, ethnicity) and the occurrence of solicited reactions in univariate analyses was generally similar between males and females. Other drivers of sex differences should be explored in future work. Finally, we performed

many subgroup and sensitivity analyses to explore possible causes for the observed heterogeneity for the outcome ISR and provided some explanations. Other sources of heterogeneity included the fact that studies were conducted in different countries or regions, during different influenza seasons, and with variability in previous exposure to infection or influenza vaccines among participants. To account for unexplained heterogeneity among studies, we used a random-effects model to estimate an average effect of sex on AEFIs.[51]

Despite these limitations, this meta-analysis helps fill the knowledge gap in the literature regarding the association of sex with AEFIs for influenza vaccines, while addressing some pitfalls from previous studies. Although initial randomisation could not be considered when interpreting results, RCTs are less prone to bias compared with observational studies based on passive surveillance systems. With regard to the generalisation of results, it is known that participants included in RCTs have different characteristics compared with the general population. However, given the biologic plausibility of the effect observed, that was also found in other studies, we think that our findings should apply to other adult populations.[11 47 48] By considering variations in the effects being estimated in the different studies, the random-effects model allows a broader generalisation than does a fixed-effect model. Although there are variations between studies, with a prediction interval ranging from 1.07 to 1.67 for ISR and from 1.22 to 1.30 for systemic reactions, we would expect that for at least 95% of individual studies the true RRs would fall between these values.

Data from RCTs suggest that most reactions following influenza vaccinations are mild, self-limited and rarely serious. However, as the experience of an adverse event could be a barrier for subsequent vaccinations,[8] limiting the impact of safety concerns on vaccination programme success is critical, especially for the influenza vaccine which is needed annually. Transparent communication regarding the increased risk for females would potentially help sustain long-term trust in health authorities and vaccines.[52] Finally, as gender attributes could influence health-seeking behaviours and individual's experience following vaccination, a better awareness of the relative roles of both sex and gender would be valuable in this matter.[53 54]

CONCLUSION

We found a higher risk of solicited reactions following influenza vaccines in females compared with males. Transparent disclosure of this risk could increase the trust in public health authorities and limit vaccine hesitancy. Future studies should report safety outcomes stratified by sex and age and also explore the interaction between sex and gender in the occurrence and reporting of adverse events. Facilitating access to individual-level data will maximise the benefits of clinical research.

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