Sex Differences in Symptom Presentation in Acute Coronary Syndromes: A Systematic Review and Meta-analysis

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Background—Timely recognition of patients with acute coronary syndromes (ACS) is important for successful treatment. Previous research has suggested that women with ACS present with different symptoms compared with men. This review assessed the extent of sex differences in symptom presentation in patients with confirmed ACS.

Methods and Results—A systematic literature search was conducted in PubMed, Embase, and Cochrane up to June 2019. Two reviewers independently screened title-abstracts and full-texts according to predefined inclusion and exclusion criteria. Methodological quality was assessed using the Newcastle-Ottawa Scale. Pooled odds ratios (OR) with 95% CI of a symptom being present were calculated using aggregated and cumulative meta-analyses as well as sex-specific pooled prevalences for each symptom. Twenty-seven studies were included. Compared with men, women with ACS had higher odds of presenting with pain between the shoulder blades (OR 2.15; 95% CI, 1.95–2.37), nausea or vomiting (OR 1.64; 95% CI, 1.48–1.82) and shortness of breath (OR 1.34; 95% CI, 1.21–1.48). Women had lower odds of presenting with chest pain (OR 0.70; 95% CI, 0.63–0.78) and diaphoresis (OR 0.84; 95% CI, 0.76–0.94). Both sexes presented most often with chest pain (pooled prevalences, men 79%; 95% CI, 72–85, pooled prevalences, women 74%; 95% CI, 72–85). Other symptoms also showed substantial overlap in prevalence. The presence of sex differences has been established since the early 2000s. Newer studies did not materially change cumulative findings.

Conclusions—Women with ACS do have different symptoms at presentation than men with ACS, but there is also considerable overlap. Since these differences have been shown for years, symptoms should no longer be labeled as “atypical” or “typical.” **(*J Am Heart Assoc.* 2020;9:e014733. DOI: 10.1161/JAHA.119.014733.)**

Key Words: acute coronary syndrome • diagnosis • meta-analysis • sex differences • symptoms • systematic review

Ischemic heart disease (IHD) is the world’s leading cause of eath accounting for an estimated 9 million deaths in 2015.[1,2] Acute coronary syndrome (ACS) is an umbrella term for unstable angina (UA), non–ST-segment–elevation myocardial infarction (NSTEMI) or ST-segment–elevation myocardial infarction (STEMI) and is a substantial component of IHD.[3] In recent decades ACS mortality has decreased, because of advancements in treatment, lifestyle changes, and a focus on primary prevention, but rates remain high.[1,4]

Effective treatment of ACS is available with reperfusion therapies, preferably with percutaneous coronary intervention and if not available thrombolysis or coronary artery bypass grafting.[3] The efficacy of ACS treatment depends on timely initiation of the required treatment to minimize myocardial damage.[3] Delayed symptom recognition, both

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Accompanying Datas S1, S2, Tables S1 through S5, and Figures S1 through S41 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014733

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Clinical Perspective

What Is New?

- Symptoms experienced by men and women with confirmed acute coronary syndromes show substantial overlap.
- Yet some sex differences in symptoms exist as women have higher odds of experiencing pain between the shoulder blades, nausea or vomiting and shortness of breath, and lower odds of experiencing chest pain or diaphoresis.
- These differences and similarities between women and men with confirmed acute coronary syndromes in symptoms experienced have been established in literature for more than a decade.

What Are the Clinical Implications?

- Symptoms of acute coronary syndromes should no longer be labeled as "typical" or "atypical" for women and/or men.
- Attention for sex differences in symptoms of acute coronary syndromes should be proportional to the large overlap in symptoms of acute coronary syndromes between women and men.

by patients and medical professionals, is an important contributor to delay in treatment and subsequent ACS mortality.[5] Despite several awareness campaigns, referral delay in women with ACS has persisted over time.[6,7]

Previous studies, but not all, have reported that women with ACS experience different symptoms compared with men with ACS.[8–10] Additionally, other studies emphasize the overlap in symptoms between men and women with ACS.[11] Symptoms experienced by women with ACS are often labeled as "atypical" if these are different to those experienced by men. Previous systematic reviews of sex differences in symptoms of patients with ACS have been inconsistent, with varying in- and exclusion criteria and studies lacking standardized data collection.[12,13] Recent studies have attempted to solve these issues, with the development of standardized data collection surveys.[11,14]

The purpose of this systematic review and meta-analysis is to assess the presence and extent of sex differences in symptom presentation in patients with confirmed ACS. It updates and extends earlier meta-analyses on this topic.[12,15] Furthermore, through cumulative meta-analyses in which studies are added to the pooled findings in order of publication date, we aim to determine for how long evidence, where it exists, has been established in the literature. As much has been published on this topic, we hypothesize that recent studies have mainly been confirmatory. Throughout this review, "sex" will be used when referring to differences between men and women. "Gender" is not used, as social and cultural differences are not examined.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files.

Search Strategy

A systematic literature search was performed in PubMed, EMBASE, and the Cochrane Library up to June 2019. A combination of the search terms *symptom*, *presentation*, *gender*, *sex*, *acute coronary syndrome*, *myocardial infarction* and *unstable angina* and synonyms of these terms were used (Data S1). Duplicates were removed using Mendeley Reference Manager. Titles and abstracts and, subsequently, the full-texts of the articles were screened. Screening and study selection were done by 2 independent reviewers (RO and AB) according to predefined inclusion and exclusion criteria and discrepancies were resolved through discussion between these 2 reviewers. In addition, references of included articles and previous reviews on symptom presentation in patients with ACS were checked, and citation tracking was performed on the included studies.

Inclusion and Exclusion Criteria

We included all studies that reported on symptom presentation in both women and men with confirmed ACS. ACS was defined as either myocardial infarction (STEMI or NSTEMI) or UA, in accordance with American Heart Association (AHA) clinical guidelines.[16] ACS is diagnosed by the presence of symptoms of myocardial infarction, new ECG changes and elevated levels of cardiac enzymes. Studies were excluded if they reported on patients with other cardiac conditions or if specific symptoms were required for inclusion in the study. Further exclusion criteria were full texts being unavailable, other publication type such as conference abstracts or reviews, and articles published in languages other than English, Dutch, French, or German. If 2 studies examined the same study population, the study with the largest sample size was included.

Quality Assessment

An adapted version of the Newcastle-Ottawa Scale was used to assess the quality of the included studies. The scoring system is based on 3 components, namely Selection, Comparability, and Outcome.[17] Studies using random or consecutive patient selection were allocated 4 stars for Selection. Studies adjusting for multiple covariables, including age, were allocated 2 stars for Comparability. Studies that independently assessed the symptoms experienced were allocated 1 star for Outcome (Data S2). Studies with a high

risk of selection bias, defined as all other ways of population selection except a random or consecutive approach, were excluded.

Data Collection and Extraction

The study design, method of data collection, patient population, sample size, demographic characteristics and covariable adjustments were extracted for all included studies and reviewed by 2 authors (RO and AB). All reported symptoms were derived from the studies. An overview of the symptoms reported in the individual studies can be found in Table S1. The following symptoms were combined: dizziness or lightheadedness, left arm and left shoulder pain, nausea or vomiting, right arm and right shoulder pain, and stomach or epigastric pain. In 1 study,[18] the presence of symptoms was categorized as present, unknown, or absent. In this case, the unknown symptoms were treated as if the symptom was absent. The outcomes of interest were the symptoms experienced when presenting with ACS. This was summarized as the odds ratio (OR) of the symptom being present in women relative to men and, if available, the OR adjusted for at least age. If the OR was not provided by a study, it was calculated using the provided data.

Statistical Analysis

Aggregated and cumulative meta-analyses were performed for both the crude and adjusted OR using a random effects model with inverse variance weighting. To assess when a possible significant observed sex difference was established in literature, cumulative meta-analysis was performed for symptoms that showed a significant sex difference in the aggregated meta-analysis. For the cumulative meta-analysis, we identified the year after which the pooled OR was statistically significant and did not notably change by adding later studies. Sex-specific prevalence for all symptoms and its variance was calculated for each study. Meta-analysis for the prevalence was performed with a random effects model with inverse variance weighting, 2 separate models were fitted for men and women. Heterogeneity was assessed by visual inspection and using the I^2 statistics. I^2 values <40% were considered to represent low heterogeneity, 30% to 60% moderate heterogeneity, 50% to 90% substantial heterogeneity and >75% as considerable heterogeneity.[19] To explore possible heterogeneity by age, random effects meta-regression was performed for symptoms reported by ≥10 studies. Analyses were performed by mean age of the participants (≤65 years and >65 years). Details of subgroup division are provided in Table S2. A P value of $P<0.05$ is considered statistically significant. Publication bias was assessed using funnel plots if ≥10 studies were available for an individual symptom. All statistical analyses were performed using the "Metafor" package in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Selection and Quality Assessment

The systematic search yielded 3750 unique articles. After title-abstract, full-text screening, and citation tracking 31 studies remained. Results of the quality assessment can be found in Table S3. The majority of studies scored between 5 and 6 out of 7 stars. Four studies[20–23] were excluded after quality assessment because of a high risk of selection bias attributable to the use of convenience sampling. Thus, 27 studies were included in the review (Figure 1). The funnel plots for most symptoms were fairly symmetric, indicating a low risk of publication bias (Figures S1–S10). Diaphoresis was an exception, where there seems to be an overrepresentation of smaller studies with a higher odds for women to present with diaphoresis (Figure S11).

Characteristics of Included Studies

Baseline characteristics of the 27 included studies are summarized in Table 1.[3,8–10,18,24–45] The majority of studies were conducted in Europe or the United States with study years ranging between 1985 and 2017. Data on symptom presentation were collected via the review of medical records (n=10), questionnaires/surveys/checklists (n=9), patient interviews (n=4), voice recordings (n=2), or a combination of a questionnaire and interview (n=2). The sample sizes of studies ranged from 82 to 1 143 513 patients and total sample size was 1 226 163. The mean age of patients ranged from 47 to 78 years in women and from 47 to 69 years in men. Twelve studies adjusted for covariables, with 4 studies adjusting for age only and 8 for other factors in addition to age.

Characteristics of Patient Population

Ten studies included a patient population with ACS (either myocardial infarction [STEMI or NSTEMI] or UA), and 17 studies included patients with myocardial infarction (STEMI or NSTEMI) only. Most studies (n=25) included more men than women, in total 60% and 40%, respectively, and women were generally older than men when presenting with ACS. In most studies women more often had comorbidities such as diabetes mellitus or hypertension at presentation, and less often smoked compared with men.

Symptoms

Figure 2 and Table 2 provide the pooled crude and adjusted odds ratios for sex differences in each examined symptom of

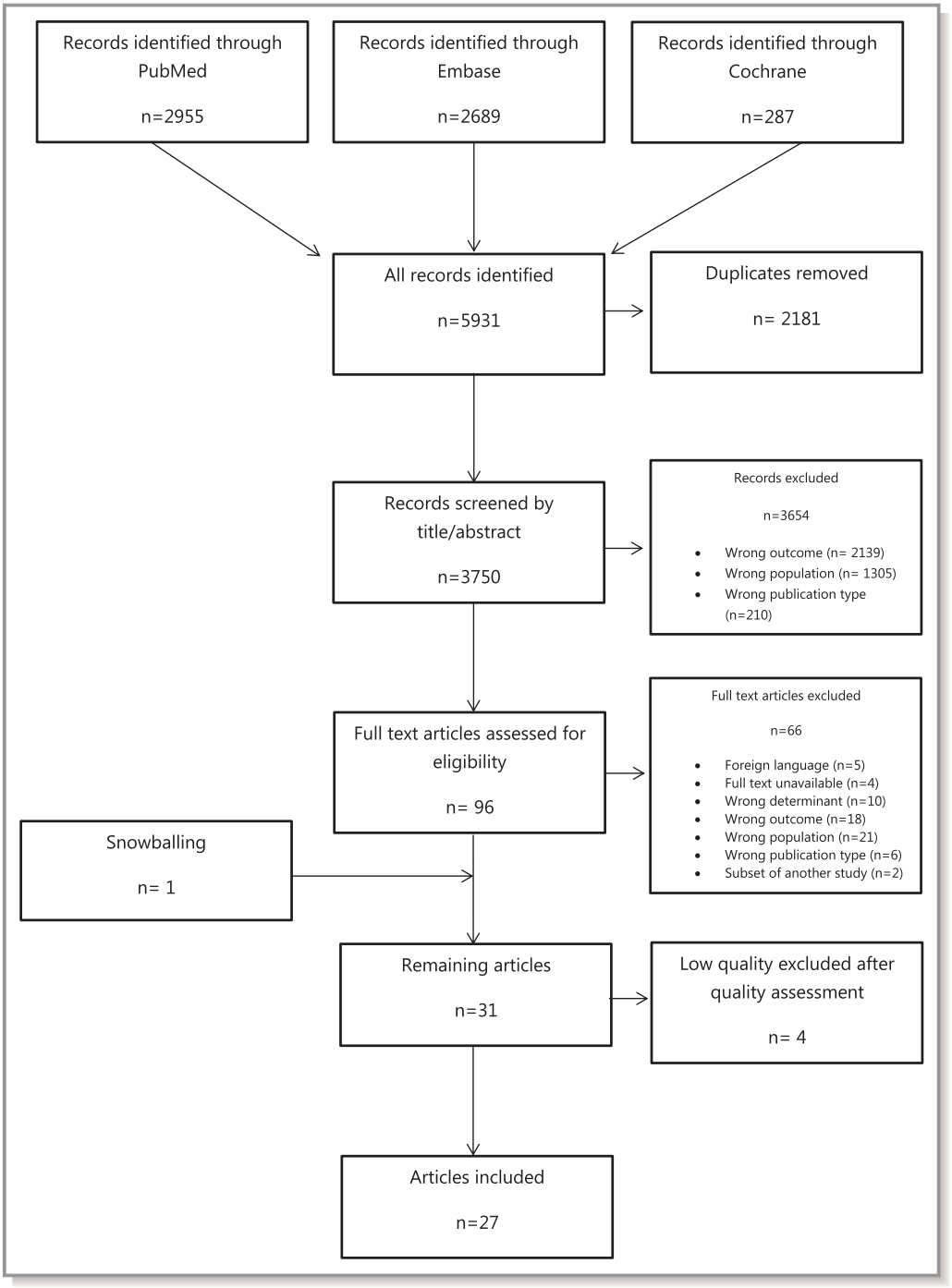

Figure 1. Flow diagram of search results and study selection.

patients with confirmed ACS. Study-specific results are provided in Table S4. Forest plots for all symptoms from the aggregated meta-analysis and the cumulative meta-analysis can be found in Figures S12–S26 and S27–S41, respectively.

Chest pain

Women with ACS had lower odds of presenting with chest pain compared with men with ACS (OR 0.70; CI, 0.63–0.78, I^2=84.5%). This OR remained virtually unchanged from 2006 onwards (Figure 3[3,8–10,18,24–35,37–45]) and was similar for studies that provided adjusted results (OR 0.67; CI, 0.62–0.79, I^2=72%).

Pain between the shoulder blades

Women with ACS had higher odds of presenting with pain between the shoulder blades compared with men with ACS (2.15 [1.95–2.37], I^2=0%). This OR remained virtually unchanged from the early 2000s and was similar for studies that provided adjusted results (1.89 [1.27–2.82], I^2=0%).

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Table 1. Baseline Characteristics of the Included Studies

Study	Country	Study Design	Data Collection	Population	Establishment of ACS	Study, y	Sample Size (Men/Women)	Mean Age Men/ Women, y	Inclusion Criteria	Exclusion Criteria	Adjustments
Tunstall-Pedoe et al. 1996[18]	Scotland	Cross-sectional	Medical records	MI	ECG changes and cardiac enzyme levels exceeding twice the upper limit of normal	1985–1991	5541 (3991/1551)	55.5/57.0	–25 to 64 years old		None
Meischke et al, 1998[24]	United States	Cross-sectional	Medical records	MI	ECG changes or enzyme elevation	1991–1993	4497 (2970/1527)	Median: 64/73	– Clinically stable	– Missing symptom information	None
Goldberg et al, 1998[25]	United States	Cross-sectional	Medical records	MI	≥2 of the following: clinical history of chest pain, elevated serum levels of CK or LDH and ECG changes	1986–1988	1360 (810/550)	64.7/72.1		– MI developed during surgery	Age, medical history
Milner et al, 1999[26]	United States	Cross-sectional	Patient interview	ACI or MI	ACI: ECG changes and lack of cardiac enzyme elevation MI: ECG changes and cardiac enzyme elevation	1995–1997	217 (127/90)	63.0/68.8	– Diagnosis of ACI or MI – >45 years old –18–44 years included with DM or 2 or more cardiac risk factors		Age, DM
Culic et al, 2002[8]	Croatia	Cross-sectional	Questionnaire	MI	≥2 of the following: ECG changes suggestive of MI, symptoms indicating MI, increase in 1 or more cardiac enzymes	1990–1995	1996 (1395/601)	57/63	– First-time MI	– Previous infarction Unable to answer questions	Age, risk factors, cardiac enzyme level
Grace et al, 2003[27]	Canada	Cross-sectional	Patient survey	MI	Diagnosis of MI at CCU	Not described	482 (347/135)	59.2/66.3	– 18 years or older	– Too ill or confused to give informed consent	None
Løvlien, Schei and Gjengedal, 2006[28]	Norway	Cross-sectional	Questionnaire	MI	Diagnosis of MI at CCU	March–October 1999	82 (44/38)	Divided into age groups	–Patients up to age 65 –First time MI		None
Hirakawa et al, 2006[29]	Japan	Cross-sectional	Medical records	MI	Diagnosis of MI in medical chart	2001–2003	2221 (1712/509)	Divided into absence/presence of chest pain		– Presence or absence of chest pain unknown	None
Arslanian-Engoren et al, 2006[30]	United States	Cross-sectional	Medical records	ACS	≥2 of the following: ECG changes, increases in serum enzymes or documentation of coronary artery disease	1999– 2004	1941 (1238/683)	61/67	– Admitted to hospital alive	– Non-ACS presentation	Age
Løvlien, Schei and Hole, 2006[9]	Norway	Cross-sectional	Questionnaire	MI	Elevated cardiac troponin, ECG changes and the presence of clinically appropriate symptoms	2003–2004	533 (384/149)	58.5/61.2	–2 weeks after hospital discharge –First time MI –<76 years old	- Hospitalized patients	Age
Dey et al, 2008[31]	Multinational (14 countries)	Cross-sectional	Medical records	ACS	Clinical history of ACS accompanied by at least 1 of the following: ECG changes, increase in biochemical markers or documented coronary artery disease	1999–2006	a. 43 393 (29 213/ 14 180) b. 1026 (682/344)	Divided into age groups	Chest pain No chest pain	– Non-cardiovascular cause for ACS (trauma, surgery)	None
Kirchberger et al, 2011[32]	Germany	Cross-sectional	Patient interview	MI	According to criteria of the ESC and American College of Cardiology	2001–2006	2278 (1710/568)	59.2/62.9	–Age 25-74 years –Survived >24 hours with MI –First time MI		Age, hypertension, DM, comorbidity
Angerud et al, 2011[33]	Sweden	Cross-sectional	Medical records	MI	Typical chest pain and biomarkers. If only one of the 2 parameters was positive, ECG analysis was used.	2000–2006	4028 (2805/1223)	Divided into age groups	– Age 25–74 years	- Previous MI - Patients who were dead by the time they reached medical help	None
Canto et al, 2012[34]	United States	Cross-sectional	Medical records	MI	Clinical presentation (ischemic symptoms) and elevated cardiac biomarker level, ECG evidence or autopsy evidence	1994–2006	1 143 513 (661 932/ 481 581)	Divided into age groups		- Secondary diagnosis of MI - Patients with missing information on age, sex or symptoms	Age
Pelter et al, 2012[35]	Multinational (United States, Australia, New Zealand)	Cross-sectional	Patient interview	ACS	Discharge diagnosis of ACS in medical record	2001–2004	331 (211/110)	Divided into age groups	–Prior diagnosis of coronary artery disease	- Serious comorbidity -Untreated malignancy or neurologic disorder -Major hearing loss	None

Continued

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Table 1. Continued

Study	Country	Study Design	Data Collection	Population	Establishment of ACS	Study, y	Sample Size (Men/Women)	Mean Age Men/ Women, y	Inclusion Criteria	Exclusion Criteria	Adjustments
O'Donnell et al, 2012[36]	Ireland	Cross-sectional	ACS response to symptoms index	ACS	Discharge diagnosis of ACS	2007–2009	1947 (1402/545)	Divided into age groups	–Admitted through ED –Clinically stable	– Cognitive impairment	Age, BMI, DM, comorbidity, smoking
Zevallos et al, 2012[37]	Puerto Rico	Cross-sectional	Medical records	MI	Clinical history suggestive of AMI, serum enzyme elevations, and serial ECG findings during hospitalization.	2007	1415 (778/637)	63.2/68.6	–Hispanic residents –First time MI	– MI secondary to interventional procedure or surgery	None
Coventry et al, 2013[38]	Australia	Cross-sectional	Voice recordings of emergency telephone calls	MI	As defined by *ICD-10*	January 2008-October 2009	1681 (1060/621)	69.1/77.6	– Arrival at ED by ambulance	– Arrival by private transport or helicopter	Age
Melberg et al, 2013[39]	Norway	Cross-sectional	Voice recordings of emergency telephone calls	STEMI	Documented ST elevation on presenting ECG, ischemic symptoms and a typical rise in serum troponin levels	2004–2007	244 (179/65)	Median: 62/67	– First contact with healthcare system by 113 phone call		None
Khan et al, 2013[40]	Multinational (Canada, United States, Switzerland)	Cross-sectional	McSweeney symptom survey	ACS	1. Signs and symptoms 2. One of the following: a) ECG changes or b) increase in cardiac enzyme levels (troponin I or T, or CK-MB, or CPK)	2009–2012	1015 (710/305)	Median: 49.0/49.0	- 55 years or younger - Admitted to CCU, ICU or cardiology ward		None
Asgar Pour et al, 2015[41]	Iran	Cross-sectional	ACS symptom checklist	ACS	ECG changes (ST-segment and T-wave changes) and cardiac enzyme (CK-MB)	Not mentioned	320 (183/137)	60.92/63.29	– Admitted with at least 1 typical symptom(chest pain/ pressure/heaviness/tightness, diaphoresis, dyspnea, arm pain) or atypical symptom (palpitation, vomiting, dizziness, fatigue, indigestion)	– History of stroke, neurologic disorders, COPD, pneumonia or pulmonary embolism	None
DeVon et al, 2017[42]	United States	Cross-sectional	ACS symptom checklist	ACS	Evidence of ischemia on ECG or elevated troponin level	2011–2014	474 (343/131)	59.5/61.3	– Admitted through ED	– Cognitive impairment	Age, African American race, comorbidity
Lichtman et al, 2018[43]	United States	Cross-sectional	Patient interview	MI	1. Increased cardiac biomarker levels 2. Symptoms of ischemia or ECG changes	2008–2012	2985 (976/2009)	47.2/47.1	– Between 18 and 55 years old –<24 hours since event –2:1 female enrollment		None
Sederholm Lawesson et al, 2018[10]	Sweden	Cross-sectional	Questionnaire	STEMI	ST elevation on ECG and diagnosis of acute MI at discharge	2012–2014	532 (406/126)	64.3/69.7	– Patients with STEMI –Clinically stable –<24 hours since event		Age, level of education, smoking status, comorbidity
Allana et al, 2018[44]	Pakistan	Cross-sectional	Response to Symptoms Questionnaire + interview	ACS	Troponin values and ECG changes	3-mo period	249 (133/116)	56.5/55.8	– Clinically stable – <72 hours since event	– Cognitive or mental impairment	None
An et al, 2018[3]	China	Cross-sectional	McSweeney symptom survey + interview	ACS	As defined by *ICD-10*	2013–2014	806 (323/483)	59.2/63.9	–First ACS event	– Cognitive or mental impairment	Age, DM, smoking
Plaza-Martin et al, 2019[45]	Spain	Cross-sectional	Medical record	ACS	According to ESC guidelines	January–August 2017	1056 (749/307)	64.0/71.0	– Above 18 years of age	– Type 2 or type 4 MI – Evident secondary cause of myocardial ischemia	None

ACS indicates acute coronary syndrome; ACI, acute coronary ischemia; BMI, body mass index; CCU, coronary care unit; CK-MB, creatinine kinase-MB; COPD, chronic obstructive pulmonary disorder; CPK, creatinine phosphokinase; DM, diabetes mellitus; ED, emergency department; ESC, European Society of Cardiology; *ICD-10, International Classification of Diseases, Tenth Revision*; ICU, intensive care unit; LDH, lactate dehydrogenase; AMI, acute myocardial infarction; MI, myocardial infarction; STEMI, ST-segment–elevation myocardial infarction.

Neck pain

Women with ACS had higher odds of presenting with neck pain (1.83 [1.60–2.10], I^2=0%) and this remained in studies that provided adjusted results (1.71 [1.00–2.93], I^2=0%). Studies published after 2003 hardly changed the point estimate.

Palpitations

Women with ACS had higher odds of presenting with palpitations (1.80 [1.44–2.26], I^2=56%), which can be seen from 2015 onwards. The direction of effect remained after adjustment, but the OR became non-significant (1.91 [0.91–4.00], I^2=0%).

Jaw pain

Women had higher odds of presenting with jaw pain (1.75 [1.42–2.17], I^2=56%). This OR has changed minimally since the early 2000s and was similar in studies that provided adjusted results (1.67 [1.01–2.78], I^2=0%).

Nausea or vomiting

Women had higher odds of presenting with nausea or vomiting (1.64 [1.48–1.82], I^2=52%), and this remained in studies that provided adjusted results (1.63 [1.21–2.19], I^2=0%). Studies published after 2011 hardly changed the point estimate.

Fatigue

Women had higher odds of presenting with fatigue (1.36 [1.22–1.52], I^2=23%), which has changed minimally since the early 2000s. The direction of effect remained after adjustment, but the OR became non-significant (1.34 [0.94–1.90], I^2=0%).

Shortness of breath

Women had higher odds of presenting with shortness of breath (1.34 [1.21–1.48], I^2=63%). This OR has changed minimally since 2000 and was similar for studies that provided adjusted results (1.22 [1.01–1.46], I^2=0%).

Indigestion

There was no significant sex difference in presentation with indigestion (1.31 [0.95–1.81]), and this remained non-significant in studies that provided adjusted results (1.55 [0.63–3.83], I^2=0%).

Dizziness or light-headedness

Women had higher odds of presenting with dizziness (1.28 [1.15–1.44], I^2=17%), which has changed minimally since 2003. The direction of effect remained after adjustment, but the OR became non-significant (1.41 [0.96–2.07], I^2=0%).

Syncope

Women had higher odds of presenting with syncope (1.24 [1.09–1.42], I^2=0%), which has changed minimally since the early 2000s. The direction of effect remained after adjustment, but the OR became non-significant (1.08 [0.75–1.56], I^2=0%).

Stomach or epigastric pain

There was no significant sex difference in presentation with stomach or epigastric pain (1.20 [0.94–1.53]), and this remained non-significant in studies that provided adjusted results (0.96 [0.75–1.23], I^2=0%).

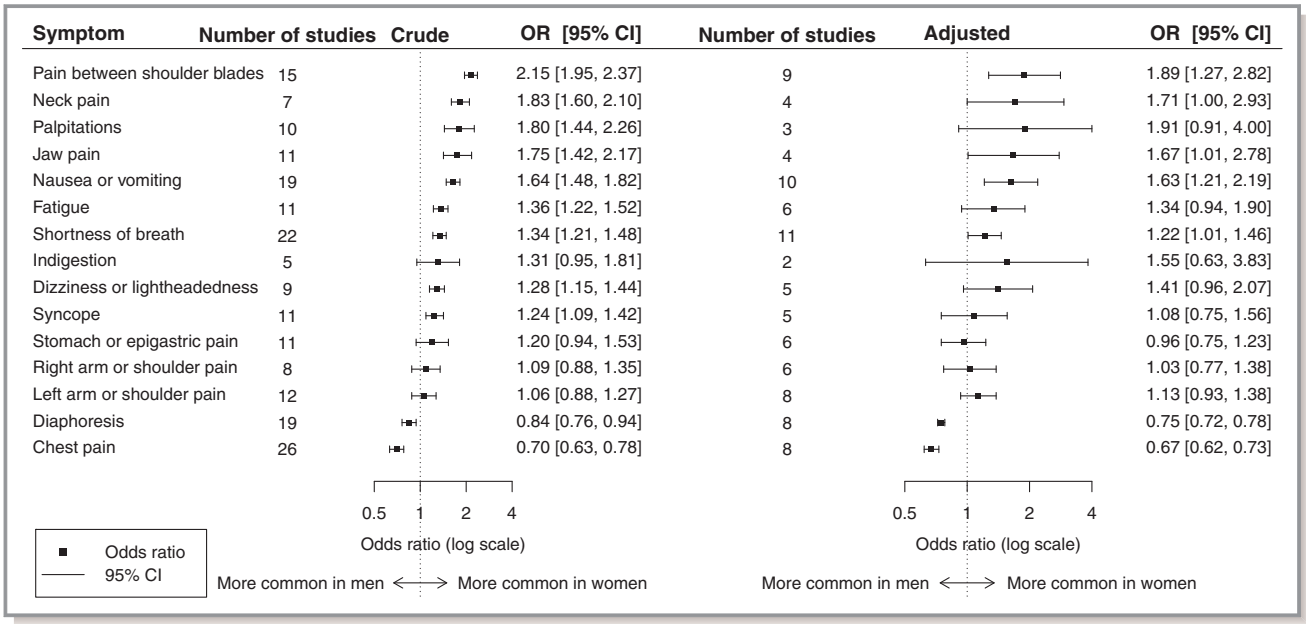

Figure 2. Pooled crude and adjusted odds ratios of symptoms experienced by women relative to men. OR indicates odds ratio.

Table 2. Crude and Adjusted Results of the Aggregated Meta-Analysis for All Symptoms

Symptom	Analysis of Crude Odds Ratio			Stable Results From Cumulative Analysis (y)	Analysis of Adjusted Odds Ratio		
	No. Studies	Pooled Odds Ratio (95% CI)	I^2		No. Studies	Pooled Odds Ratio (95% CI)	I^2
Pain between the shoulder blades	15	2.15 (1.95–2.37)	0%	Early 2000s	9	1.89 (1.27–2.82)	0%
Neck pain	7	1.83 (1.60–2.10)	0%	2003	4	1.71 (1.00–2.93)	0%
Palpitations	10	1.80 (1.44–2.26)	56%	2015	3	1.91 (0.91–4.00)	0%
Jaw pain	11	1.75 (1.42–2.17)	56%	Early 2000s	4	1.67 (1.01–2.78)	0%
Nausea or vomiting	19	1.64 (1.48–1.82)	53%	2011	10	1.63 (1.21–2.19)	0%
Fatigue	11	1.36 (1.22–1.52)	23%	Early 2000s	6	1.34 (0.94–1.90)	0%
Shortness of breath	22	1.34 (1.21–1.48)	63%	Early 2000s	11	1.22 (1.01–1.46)	0%
Indigestion	5	1.31 (0.95–1.81)	37%	NA	2	1.55 (0.63–3.83)	0%
Dizziness or lightheadedness	9	1.28 (1.15–1.44)	17%	2003	5	1.41 (0.96–2.07)	0%
Syncope	11	1.24 (1.09–1.42)	0%	Early 2000s	5	1.08 (0.75–1.56)	0%
Stomach or epigastric pain	11	1.20 (0.94–1.53)	69%	NA	6	0.96 (0.75–1.23)	0%
Right arm or right shoulder pain	8	1.09 (0.88–1.35)	74%	NA	6	1.03 (0.77–1.38)	47%
Left arm or left shoulder pain	12	1.06 (0.88–1.27)	80%	NA	8	1.13 (0.93–1.38)	7%
Diaphoresis	19	0.84 (0.76–0.94)	59%	2003	8	0.75 (0.72–0.78)	28%
Chest pain	26	0.70 (0.63–0.78)	85%	2006	8	0.67 (0.62–0.73)	72%

Right arm or right shoulder pain

There was no significant sex difference in presentation with right arm or shoulder pain (1.09 [0.88–1.35]), and this remained non-significant after adjustment (1.02 [0.77–1.38], I^2=47%).

Left arm or left shoulder pain

There was no significant sex difference in presentation with left arm or shoulder pain (1.06 [0.88–1.27]), and this remained non-significant after adjustment (1.13 [0.93–1.38], I^2=7%).

Diaphoresis

Women with ACS had a lower odds of presenting with diaphoresis than men (0.84 [0.76–0.94], I^2=59%). This OR did not change materially since 2003 and was similar for studies that provided adjusted results (0.75 [0.72–0.78], I^2=28%).

Meta-regression

Differences in symptom presentation between men and women did not differ significantly by the mean age of study participants. Results of the meta-regression analysis are presented in Table S5.

Symptom prevalence

Both men and women with confirmed ACS presented most often with chest pain (pooled prevalence men 79% [72–85]; women 74% [67–81]), diaphoresis (men 47% [38–55]; women 44% [35–53]), shortness of breath (men 40% [35–46]; women 48% [42–53]), left arm and left shoulder pain (men 37% [28–46]; women 38% [27–48]) and nausea or vomiting (men 28% [24–31]; women 39% [33–45]) (Figure 4). Overall, men and women with confirmed ACS showed considerable overlap in symptoms at presentation.

Discussion

This systematic review and meta-analysis of 27 studies including >1 million patients shows that sex differences exist in the symptom presentation in patients with confirmed ACS, while at the same time overlap in symptoms between men and women with confirmed ACS is substantial. Women with ACS have higher odds of presenting with pain between the shoulder blades, nausea or vomiting and shortness of breath compared with men. In contrast, women with ACS have lower odds of presenting with chest pain and diaphoresis compared with their male counterparts. No significant sex differences were found in presentation with left or right arm and shoulder pain, stomach or epigastric pain and indigestion. The cumulative meta-analyses show that more recent studies did not add materially to the available evidence. For both sexes, chest

pain, diaphoresis, shortness of breath, left arm and left shoulder pain, and nausea or vomiting were found to be the most prevalent symptoms.

This present meta-analyses updates and importantly extends earlier systematic reviews of sex differences in ACS symptom presentation,[12,13,15] by including more recently published studies, with larger sample sizes and more standardized methods of data collection such as the McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey[14] and 13-item Acute Coronary Syndrome checklist[11] and by investigating a broader range of symptoms. Through cumulative meta-analyses, we demonstrated that sex differences in symptoms for patients with established ACS have been evident since the early 2000s and hardly changed over time since then. Altogether, our results are consistent with previous systematic reviews, which also concluded that women with ACS are less likely to report chest pain and more likely to report a variety of symptoms than men with ACS.[12,13,15]

Over the past 2 decades, considerable research has been done on sex differences in the pathophysiology, symptom presentation, and outcomes of IHD.[46] Studies have shown that younger women with ACS present more often with type II ACS,[47,48] characterized by coronary artery spasms and vascular dysfunction,[16,47,48] whereas younger men present more often with type I ACS, caused by coronary artery obstruction.[47,48] In addition, at all ages, women with ACS less often have plaque ruptures and present more frequently with plaque erosions than men with ACS.[47,49] Whilst progress in the understanding of sex differences has been made, a recent AHA scientific statement identified several gaps in our understanding of mechanisms for symptoms and pathophysiology of ACS in women.[46] Future research should address these gaps and evaluate sex differences in symptom presentation of type I and type II ACS.

Implications for Future Research and Clinical Practice

This review shows that sex differences in symptoms among patients with confirmed ACS have been established in the literature for more than a decade. To address the remaining uncertainties, such as how sex differences in symptom presentation may differ by age or other patient characteristics, future research should focus on standardized data collection and reporting. Our findings suggest that researchers and medical professionals should refrain from labeling symptoms of ACS as "typical" and "atypical", and, instead, consider the established differences and overlap in symptom presentation between men and women in future studies and clinical practice. Consequently, we need to educate medical professionals more to be familiar with the existing sex differences and overlap. Moreover, studies comparing the symptoms of women and men with a suspicion of ACS, but before the clinical diagnosis, are needed to improve the diagnosis of ACS in routine care. The

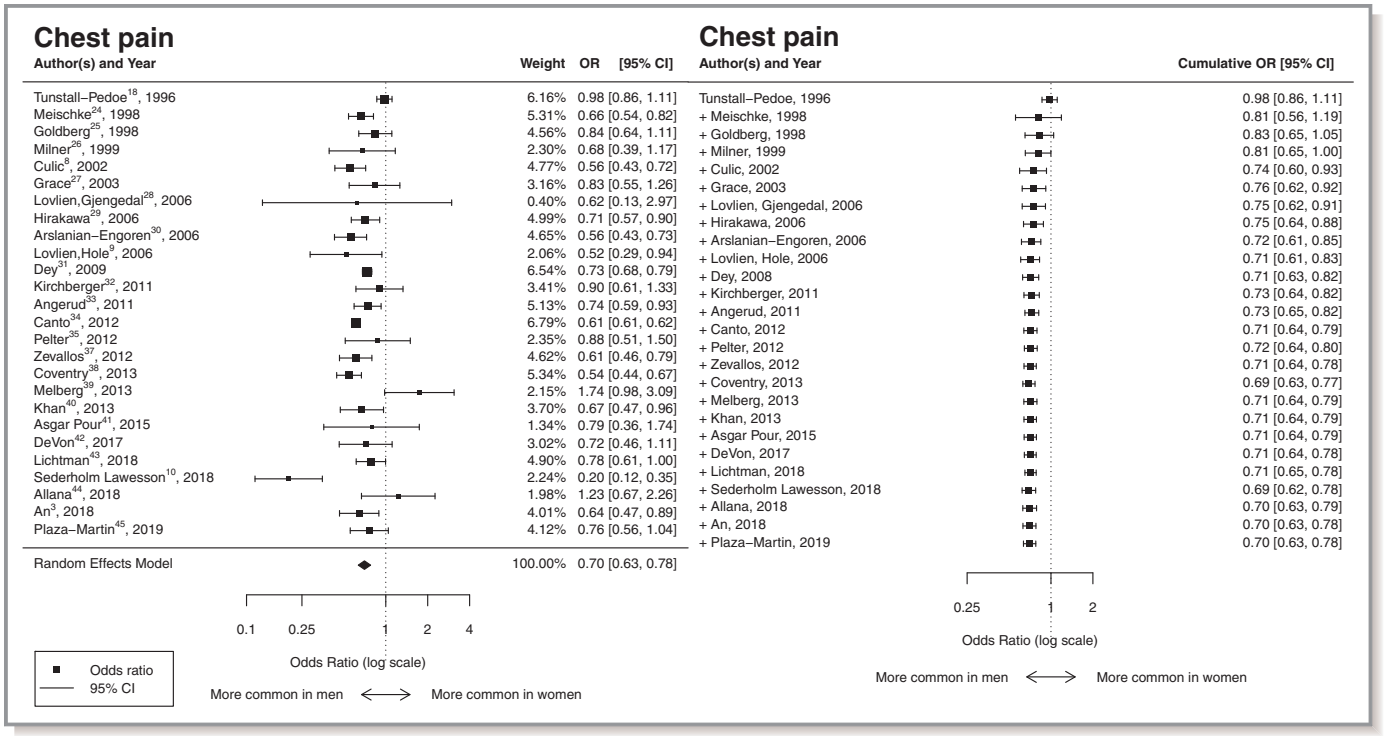

Figure 3. Results of the aggregated and cumulative meta-analysis for chest pain as a symptom of ACS in women relative to men summarized in a forest plot. ACS indicates acute coronary syndromes; OR indicates odds ratio.

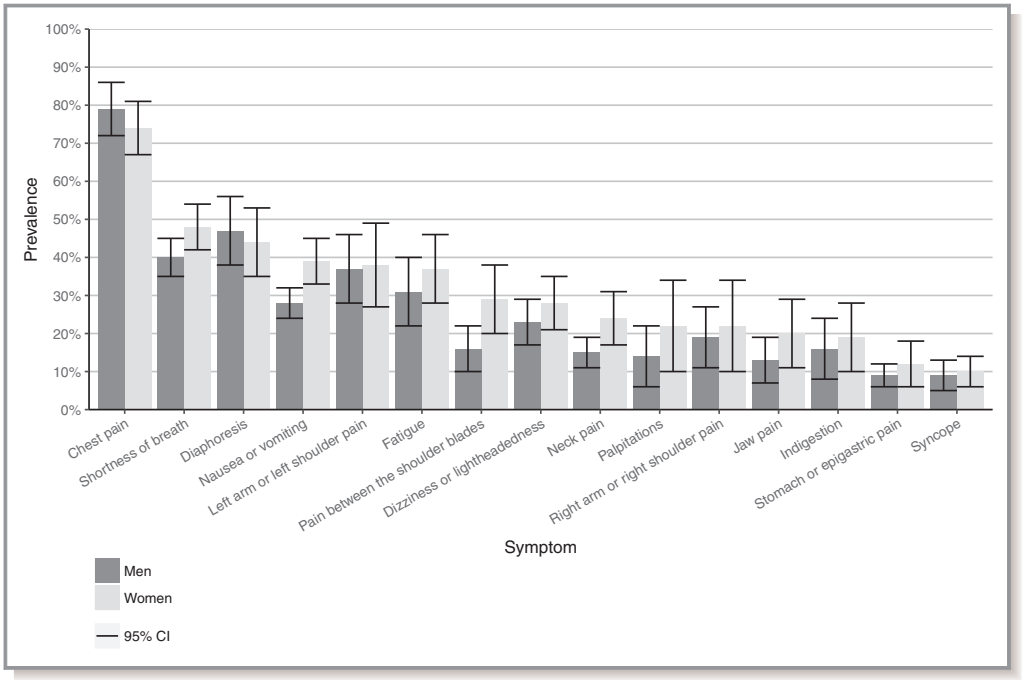

Figure 4. Results of the meta-analysis of the pooled prevalence and corresponding 95% CI for all symptoms for ACS in women and men. ACS indicates acute coronary syndromes.

studies included in the present review were conducted among patients with confirmed ACS. As such, our findings alone cannot be used in the development of diagnostic tools, as a comparison of symptoms among women and men with and without confirmed ACS is required.

Strengths and Limitations

This systematic review has several strengths. A comprehensive and systematic approach of the literature search including the use of multiple databases minimalized the possibility of missing relevant evidence. Quality assessment was performed and studies that required the presence of one specific symptom for the diagnosis of ACS were excluded to limit the risk of selective results. As well as aggregated meta-analysis, cumulative meta-analysis was performed to analyze the direction of the effects over time.

Limitations of this study are inherent to its design and include heterogeneity between studies in terms of sample size, inclusion criteria, data collection methods, and adjustment for covariables. Data collection by medical record retrieval could induce information bias, while the use of patient interviews makes results liable to recall bias, in particular since most studies were conducted in those with confirmed ACS. Although our meta-regression analysis did not imply that the sex differences of symptom presentation were different between studies including relatively younger versus relatively older patients, this should be more thoroughly explored by individual patient data meta-analysis. Statistical heterogeneity for the analyses of chest pain was considerable and sensitivity analyses showed that this was partly driven by the inclusion of 1 large study.[34] In addition, 5 studies were excluded because they were written in Polish or Persian, thus it is possible that potentially relevant studies could have been missed. Moreover, some symptoms had to be combined because of their low prevalence. Finally, the present study was restricted to those with confirmed ACS and did not compare sex differences in symptom presentation of individuals with suspected ACS. The symptoms that women with ACS more often present with than men with ACS are highly common for other conditions and may complicate timely diagnosis. Future research should focus on the development and validation of a diagnostic tool to take sex differences in symptom presentation into account.

Conclusions

This systematic review with meta-analysis shows that there are sex differences in symptom presentation in patients with confirmed ACS. Whilst there is also substantial overlap in symptoms of ACS, women with ACS have higher odds of presenting with pain between the shoulder blades, nausea or vomiting and shortness of breath, and lower odds of presenting with chest pain and diaphoresis compared with men with ACS. Sex differences in symptom presentation seem to be well-established, meaning that the terms “atypical” and “typical” to label symptoms of ACS are outdated.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1. Search string 'Sex Differences in Symptom Presentation in Acute Coronary Syndrome: A Systematic Review and Meta-Analysis'.

Outcome	Determinant	Domain
Symptom* Presentation Presentations	Sex Sex factors (MeSH) Gender	Acute coronary syndrome (MeSH) Acute coronary syndrome* ACS Myocardial infarction (MeSH) Myocardial infarct* Heart attack Heart infarct* Cardiac infarct* MI Unstable angina (MeSH) Unstable angina UA

PubMed/MEDLINE:

(((((symptom*[Title/Abstract]) OR presentation[Title/Abstract]) OR presentations[Title/Abstract])) AND ((((((((((acute coronary syndrome[MeSH Terms]) OR acute coronary syndrome*[Title/Abstract]) OR ACS[Title/Abstract]) OR myocardial infarction[MeSH Terms]) OR myocardial infarct*[Title/Abstract]) OR heart attack[Title/Abstract]) OR heart infarct*[Title/Abstract]) OR cardiac infarct*[Title/Abstract]) OR MI[Title/Abstract]) OR unstable angina[MeSH Terms]) OR unstable angina[Title/Abstract]) OR UA[Title/Abstract])) AND (((sex[Title/Abstract]) OR sex factor[MeSH Terms]) OR gender[Title/Abstract])

Embase:

No.	Query	Results
#7	#5 AND [embase]/lim AND ('article'/it OR 'article in press'/it OR 'review'/it)	**2689**
#5	#1 AND #3 AND #4	**5874**
#4	'symptom'/exp OR 'symptom' OR 'symptom*':ti,ab,kw OR 'presentation':ti,ab,kw OR 'presentations':ti,ab,kw	**2102679**
#3	'sex':ti,ab,kw OR 'sex factor'/exp OR 'sex factor' OR 'gender':ti,ab,kw	**1093115**
#1	'acute coronary syndrome'/exp OR 'acute coronary syndrome' OR 'acute coronary syndrome*':ti,ab,kw OR 'acs':ti,ab,kw OR 'heart infarction'/exp OR 'heart infarction' OR 'myocardial infarct*':ti,ab,kw OR 'mi':ti,ab,kw OR 'heart attack':ti,ab,kw OR 'heart infarct*':ti,ab,kw OR 'cardiac infarct*':ti,ab,kw OR 'unstable angina pectoris'/exp OR 'unstable angina pectoris' OR 'unstable angina':ti,ab,kw OR 'ua':ti,ab,kw	**514604**

Filter: sources as embase or embase + medline, publication types as article, review or article in press

Cochrane:

−	+	#1	MeSH descriptor: [Acute Coronary Syndrome] explode all trees		MeSH	1629
−	+	#2	(acute coronary syndrome*):ti,ab,kw OR (ACS):ti,ab,kw	S	Limits	7609
−	+	#3	MeSH descriptor: [Myocardial Infarction] explode all trees		MeSH	10325
−	+	#4	(myocardial infarct*):ti,ab,kw OR (heart attack):ti,ab,kw OR (heart infarct*):ti,ab,kw OR (cardiac infarct*):ti,ab,kw OR (MI):ti,ab,kw	S	Limits	38922
−	+	#5	MeSH descriptor: [Angina, Unstable] explode all trees		MeSH	1057
−	+	#6	(unstable angina):ti,ab,kw OR (UA):ti,ab,kw	S	Limits	4810
−	+	#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6		Limits	44482
−	+	#8	(symptom*):ti,ab,kw OR (presentation):ti,ab,kw OR (presentations):ti,ab,kw	S	Limits	186850
−	+	#9	MeSH descriptor: [Sex] explode all trees		MeSH	35
−	+	#10	MeSH descriptor: [Sex Factors] explode all trees		MeSH	5719
−	+	#11	(gender):ti,ab,kw	S	Limits	28284
−	+	#12	#9 OR #10 OR #11		Limits	32440
−	+	#13	#8 AND #7 AND #12		Limits	287
−	+	#14	Type a search term or use the S or MeSH buttons to compose	S MeSH	Limits	N/A

Data S2. Adapted Newcastle-Ottawa quality assessment scale(1) (maximum 7 stars).

Selection

1 star per numbered item (maximum 4 stars)

1. Representativeness of exposed*cohort
    a. Truly representative (star)
    b. Somewhat representative (half star)
    c. Selected group
    d. No description
2. Selection of non-exposed cohort
    a. Drawn from same community as exposed (star)
    b. Drawn from different source
    c. No description
3. Ascertainment of exposure
    a. Medical record (star)
    b. Interview (star)
    c. Self-reported
    d. No description
4. Demonstration that outcome of interest was not present at start of study
    a. Yes (star)
    b. No

Comparability

Maximum of 2 stars

1. Comparability of cohorts of basis of design or analysis
    a. Study controls for age (most important factor) (star)
    b. Study controls for comorbidities (star)

Outcome

1 star per numbered item (maximum 1 star)

1. Assessment of outcome
    a. Independent blind assessment (star)
    b. Medical record review (star)
    c. Self-reported (questionnaire or interview)
    d. Not described

*For this review, exposure related to the sex of the patient. When assessing quality of the study using this Newcastle-Ottowa scale, women with ACS were seen as the exposed cohort, and men with ACS as the non-exposed cohort.

Study:

Selection:

1. Representativeness of exposed cohort
    - X star
2. Selection of non-exposed cohort
    - X star
3. Ascertainment of exposure
    - X star
4. Demonstration that outcome of interest was not present at start of study
    - X star

Total: /4

Comparability:

1. Study takes confounder age into account
    - X star
2. Study take confounder comorbidities into account
    - X star

Total: /2

Outcome:

1. Assessment of outcome
    - X star

Total: /1

Cumulative total: /7

Table S1. Reported symptoms in each included study.

Included study	Symptoms reported by study
Tunstall-Pedoe et al., 1996 (2)	Chest pain, syncope
Meischke et al., 1998(3)	Chest pain, diaphoresis, shortness of breath, stomach or epigastric pain, nausea or vomiting, syncope
Goldberg et al., 1998(4)	Pain between shoulder blades, chest pain, diaphoresis, stomach or epigastric pain, jaw pain, left arm pain, nausea, neck pain, right arm pain, shortness of breath, syncope
Milner et al., 1999(5)	Chest pain, pain between shoulder blades, nausea or vomiting, shortness of breath, palpitations, indigestion, fatigue, arm pain, diaphoresis, jaw pain, dizziness, neck pain
Culic et al., 2002(6)	Chest pain, left arm pain, right arm pain, stomach or epigastric pain, neck pain, pain between shoulder blades, jaw pain, headache, diaphoresis, nausea, shortness of breath, belching, cough, dizziness, hiccups, tinnitus
Grace et al., 2003(7)	Chest pain, diaphoresis, shortness of breath, left arm pain, nausea, neck pain, fatigue, dizziness, indigestion, stomach or epigastric pain, syncope
Løvlien, Schei & Gjendal, 2006(8)	Chest pain, left arm pain, jaw pain, pain between shoulder blades, nausea, shortness of breath
Hirakawa et al., 2006(9)	Chest pain
Arslanian-Engoren et al., 2006(10)	Chest pain, shortness of breath, diaphoresis, left arm pain, nausea, right arm pain
Løvlien, Schei & Hole, 2006(11)	Chest pain, diaphoresis, left arm pain, shortness of breath, nausea or vomiting, fatigue, dizziness, palpitations, right arm pain, jaw pain, hot flushes, pain between shoulder blades, stomach or epigastric pain, headache, syncope,
Dey et al., 2008(12)	Chest pain, syncope, shortness of breath, palpitations, jaw pain, nausea or vomiting, diaphoresis
Kirchberger et al., 2011(13)	Chest pain, left arm or shoulder pain, right arm or shoulder pain, jaw pain, stomach or epigastric pain, pain between shoulder blades, nausea, shortness of breath, diaphoresis, fear, dizziness, syncope
Angerud et al., 2011(14)	Chest pain
Canto et al., 2012(15)	Chest pain
Pelter et al., 2012(16)	Chest pain, shortness of breath, arm pain, diaphoresis, stomach or epigastric pain, jaw pain
O'Donnell et al., 2012(17)	Chest pain, shortness of breath, diaphoresis, left arm pain, nausea, fatigue, pain between shoulder blades, palpitations, indigestion, fear
Zevallos et al., 2012(18)	Chest pain, left arm pain, pain between shoulder blades, stomach or epigastric pain
Coventry et al., 2013(19)	Chest pain, left arm pain, right arm pain, diaphoresis, shortness of breath, abdominal or epigastric pain, nausea or vomiting, syncope, fatigue, pain between shoulder blades
Melberg et al., 2013(20)	Chest pain, shortness of breath, syncope, nausea or vomiting, diaphoresis
Khan et al., 2013(21)	Chest pain, fatigue, hot flushes, shortness of breath, diaphoresis, left arm or shoulder pain, pain between shoulder blades, nausea, dizziness, right arm or shoulder pain, neck pain, headache, dizziness, headache, jaw pain,
Asgar Pour et al., 2015(22)	Chest pain, arm pain, diaphoresis, shortness of breath, nausea or vomiting, palpitations, fatigue, indigestion, pain between shoulder blades,
DeVon et al., 2017(23)	Chest pain, shortness of breath, fatigue, dizziness or lightheadedness, nausea, arm pain, sweating, pain between shoulder blades, palpitations, indigestion,
Lichtman et al., 2018(24)	Chest pain, dizziness, palpitations, shortness of breath, sweating, fatigue
Sederholm Lawesson et al., 2018(25)	No chest pain, neck pain, pain between shoulder blades, stomach pain, arm/hands pain, tiredness/fatigue, shortness of breath, syncope, nausea or vomiting, diaphoresis, fear
Allana et al., 2018(26)	Chest pain, shortness of breath, diaphoresis, pain between shoulder blades, nausea or vomiting, stomach or epigastric pain, jaw pain, syncope, palpitations
An et al., 2018(27)	Pain centrally in chest, pain between shoulder blades, left arm or shoulder pain, neck pain, jaw pain, right arm or shoulder pain, diaphoresis, hot flushes,

	fatigue, cough, palpitations, shortness of breath, indigestion, nausea or vomiting, dizziness, headache
Plaza-Martin et al., 2019(28)	Chest pain, shortness of breath, palpitations

Table S2. Subgroups for meta-regression.

Included study	Age: ≤ 65 years or >65 years
Tunstall-Pedoe et al., 1996(2)	≤ 65 years
Meischke et al., 1998(3)	> 65 years
Goldberg et al., 1998(4)	> 65 years
Milner et al., 1999(5)	> 65 years
Culic et al., 2002(6)	≤ 65 years
Grace et al., 2003(7)	≤ 65 years
Løvlien, Schei & Gjendal, 2006(8)	≤ 65 years
Hirakawa et al., 2006(9)	> 65 years
Arslanian-Engoren et al., 2006(10)	> 65 years
Løvlien, Schei & Hole, 2006(11)	≤ 65 years
Dey et al., 2008(12)	> 65 years
Kirchberger et al., 2011(13)	≤ 65 years
Angerud et al., 2011(14)	≤ 65 years
Canto et al., 2012(15)	> 65 years
Pelter et al., 2012(16)	> 65 years
O'Donnell et al., 2012(17)	≤ 65 years
Zevallos et al., 2012(18)	> 65 years
Coventry et al., 2013(19)	> 65 years
Melberg et al., 2013(20)	≤ 65 years
Khan et al., 2013(21)	≤ 65 years
Asgar Pour et al., 2015(22)	≤ 65 years
DeVon et al., 2017(23)	≤ 65 years
Lichtman et al., 2018(24)	≤ 65 years
Sederholm Lawesson et al., 2018(25)	> 65 years
Allana et al., 2018(26)	≤ 65 years
An et al., 2018(27)	≤ 65 years
Plaza-Martin et al., 2019(28)	> 65 years

Table S3. Results of the quality assessment using the Newcastle-Ottawa Scale.

Study	Selection (maximum 4)	Comparability (maximum 2)	Outcome (maximum 1)	Total score (maximum 7)
Plaza-Martin 2019(28)	****		*	5
An 2018 (27)	****	**		6
Allana 2018(26)	****			4
Sederholm Lawesson 2018 (25)	****	**		6
Lichtman 2018(24)	*** and half			3.5
DeVon 2017(23)	****	*	*	6
Asgar Pour 2015(22)	*** and half		*	4.5
Khan 2013 (21)	*** and half			3.5
Melberg 2013 (20)	*** and half		*	4.5
Coventry 2013(19)	*** and half	*	*	5.5
Zevallos 2013 (18)	*** and half		*	4.5
O'Donnell 2012 (17)	****	**		6
Pelter 2012 (16)	*** and half			3.5
Canto 2012 (15)	****	*	*	6
Angerud 2011(14)	** and half		*	3.5
Kirchberger 2011(13)	*** and half	**		5.5
Dey 2008(12)	****		*	5
DeVon 2008(29)	**			2
Løvlien, Schei & Hole, 2006(11)	*** and half	*		4.5
Arslanian-Engoren 2006(10)	****	*	*	6
Hirakawa 2006(9)	****		*	5
Omran 2006(30)	**			2
Løvlien, Schei & Gjendal, 2006(8)	*** and half			3.5
Chen 2005(31)	**	**		4
Grace 2003(7)	****			4
DeVon & Zerwic 2003(32)	**			2
Culic 2002(6)	****	**		6
Milner 1999(5)	*** and half	**		5.5
Goldberg 1998(4)	***	**	*	6
Meischke 1998(3)	****		*	5
Tunstall-Pedoe 1996(2)	*** and half		*	4.5

Table S4. Odds ratios of symptoms experienced when presenting with ACS in women relative to men.

Symptom	Study	Sample size	Crude OR (95% CI)	Adjusted OR (95% CI)
Chest pain	Allana et al (26)	M= 133, F= 116	1.23 (0.67-2.26)	
	An et al(27)	M= 323, F= 483	0.64 (0.47-0.89)	0.63 (0.44-0.91)
	Angerud et al(14)	M=2805, F=1223	0.74 (0.59-0.93)	
	Arslanian-Engoren et al(10)	M= 1258, F=536	0.56 (0.43-0.73)	0.86 (0.63-1.17)
	Asgar Pour et al (22)	M=183, F=137	0.79 (0.36-1.74)	
	Canto et al(15)	M=661,932, F=481,581	0.61 (0.61-0.62)	
	Coventry et al(19)	M= 1060, F=621	0.54 (0.44-0.67)	0.70 (0.57-0.88)
	Culic et al(6)	M=1395, F=601	0.56 (0.43- 0.72)	0.62 (0.48-0.80)
	DeVon et al (23)	M=343, F=131	0.72 (0.46-1.11)	0.70 (0.44-1.12)
	Dey et al (12)	M=29213 F=14180	0.73 (0.68-0.79)	
	Goldberg et al(4)	M=810, F=550	0.84 (0.64-1.11)	0.80 (0.59-1.09)
	Grace et al(7)	M=347, F=135	0.83 (0.55-1.26)	
	Hirakawa et al (9)	M=1712, F=509	0.71 (0.57-0.90)	
	Khan et al(21)	M=710, F=305	0.67 (0.47-0.96)	
	Kirchberger et al(13)	M= 1710, F=568	0.90 (0.61-1.33)	0.83 (0.54-1.28)
	Lichtman et al(24)	M=976, F=2009	0.78 (0.61-1.00)	
	Lovlien, Schei & Hole(11)	M=384, F=149	0.52 (0.29-0.94)	0.53 (0.29-0.97)
	Lovlien, Schei & Gjengedal(8)	M=44, F=38	0.62 (0.13-2.97)	
	Milner et al (5)	M=127, F=90	0.68 (0.39-1.17)	
	Meischke et al (3)	M=2970, F=1527	0.66 (0.54-0.82)	
	Melberg et al (20)	M=179, F=65	1.74 (0.98-3.09)	
	O'Donnell et al (17)	M=1402, F=545	NS: OR not provided	NS: OR not provided
	Pelter et al(16)	M=221, F=110	0.88 (0.51-1.50)	
	Plaza-Martin et al (28)	M=749, F=307	0.76 (0.56-1.04)	
	Sederholm Lawesson et al(25)	M=406, F=126	0.20 (0.12-0.35)	
	Tunstall-Pedoe et al(2)	M=3991, F=1551	0.98 (0.86-1.11)	
	Zevallos et al (18)	M=778, F=637	0.61 (0.46-0.79)	
Left arm or shoulder pain	An et al(27)	M= 323, F= 483	0.94 (0.67-1.33)	2.16 (1.21-3.86)
	Arslanian-Engoren et al(10)	M= 1258, F=536	0.80 (0.64-0.98)	0.93 (0.74-1.16)
	Coventry et al (19)	M=1060, F=621	1.54 (1.14-2.08)	1.26 (0.89-1.80)
	Culic et al(6)	M=1395, F=601	1.28 (1.04-1.57)	1.32 (1.06-1.61)
	Goldberg et al(4)	M=810, F=550	1.00 (0.79-1.27)	1.20 (0.93-1.56)
	Grace et al(7)	M=347, F=135	1.29 (0.87-1.93)	
	Khan et al(21)	M=710, F=305	1.38 (1.05-1.80)	
	Kirchberger et al(13)	M= 1710, F=568	1.26 (1.03-1.52)	1.36 (1.10-1.69)
	Lovlien, Schei & Hole(11)	M=384, F=149	1.16 (0.80-1.70)	1.34 (0.90-1.98)
	Lovlien, Schei & Gjengedal(8)	M=44, F=38	0.57 (0.22-1.46)	
	O'Donnell et al(17)	M=1402, F=545	1.17 (0.95-1.44)	1.27 (1.02-1.58)
	Zevallos et al (18)	M=778, F=637	0.53 (0.41-0.69)	
Right arm or shoulder pain	An et al (27)	M= 323, F= 483	0.66 (0.23-1.91)	NS: OR not provided
	Arslanian-Engoren et al(10)	M= 1258, F=536	0.90 (0.65-1.26)	1.04 (0.74-1.48)
	Coventry et al(19)	M= 1060, F=621	0.57 (0.39-0.83)	0.70 (0.48-1.04)
	Culic et al (6)	M=1395, F=601	1.35 (1.11-1.64)	1.33 (1.09-1.61)
	Goldberg et al(4)	M=810, F=550	1.15 (0.86-1.53)	1.28 (0.93-1.79)
	Khan et al (21)	M=710, F=305	1.45 (1.06-1.99)	
	Kirchberger et al(13)	M= 1710, F=568	1.14 (0.93-1.40)	1.19 (0.95-1.48)
	Lovlien, Schei & Hole(11)	M=384, F=149	1.41 (0.94-2.13)	1.52 (1.00-2.32)
Arm pain	Asgar Pour et al (22)	M=183, F=137	0.84 (0.54-1.31)	
	DeVon et al (23)	M=343, F=131	1.30 (0.87-1.96)	1.28 (0.83-1.98)
	Milner et al (5)	M=127, F=90	1.66 (0.93-2.96)	
	Pelter et al(16)	M=221, F=110	1.50 (0.87-2.59)	
	Sederholm Lawesson et al(25)	M=406, F=126	2.73 (1.72-4.32)	2.55 (1.53-4.25)
Pain between shoulder blades	Allana et al (26)	M= 133, F= 116	3.06 (1.81-5.15)	
	An et al(27)	M= 323, F= 483	1.99 (1.48-2.67)	2.13 (1.53-2.97)
	Asgar Pour et al(22)	M=183, F=137	1.29 (0.81-2.04)	
	Coventry et al(19)	M= 1060, F=621	1.62 (0.96-2.74)	1.62 (0.93-2.81)
	Culic et al (6)	M=1395, F=601	2.16 (1.52-3.06)	1.64 (1.16-2.27)
	DeVon et al(23)	M=343, F=131	2.98 (1.91-4.66)	1.75 (1.21-2.53)
	Goldberg et al (4)	M=810, F=550	2.43 (1.70-3.47)	2.63 (1.79-3.85)
	Khan et al (21)	M=710, F=305	2.03 (1.53-2.69)	
	Kirchberger et al (13)	M= 1710, F=568	2.31 (1.88-2.82)	2.22 (1.78-2.77)

	Lovlien, Schei & Hole (11)	M=384, F=149	1.91 (1.21-3.02)	1.80 (1.12-2.89)
	Lovlien, Schei & Gjengedal(8)	M=44, F=38	3.45 (1.22-9.73)	
	Milner et al(5)	M=127, F=90	9.62 (2.10-44.11)	
	O'Donnell et al(17)	M=1402, F=545	1.62 (1.08-2.42)	1.57 (1.04-2.37)
	Sederholm Lawesson et al(25)	M=406, F=126	3.10 (1.90-5.05)	3.59 (2.09-6.15)
	Zevallos et al (18)	M=778, F=637	1.90 (1.34-2.70)	
Neck pain	An et al(27)	M= 323, F= 483	1.43 (1.01-2.03)	1.54 (1.04-2.27)
	Culic et al(6)	M= 1395, F=601	1.75 (1.33-2.29)	1.56 (1.19-2.04)
	Goldberg et al(4)	M=810, F=550	1.74 (1.26-2.39)	1.92 (1.28-2.86)
	Grace et al(7)	M=347, F=135	2.08 (1.34-3.22)	
	Khan et al(21)	M=710, F=305	2.13 (1.57-2.88)	
	Milner et al (5)	M=127, F=90	1.17 (0.46-2.96)	
	O'Donnell et al(17)	M=1402, F=545	1.71 (1.32-2.21)	1.85 (1.42-2.40)
	Sederholm Lawesson et al(25)	M=406, F= 126	2.40 (1.54-3.76)	2.97 (1.79-4.93)
Jaw pain	Allana et al (26)	M= 133, F= 116	2.33 (1.29-4.22)	
	An et al (27)	M= 323, F= 483	0.70 (0.41-1.21)	NS: OR not provided
	Culic et al (6)	M=1395, F=601	1.72 (1.20-2.47)	1.47 (1.04-2.08)
	Dey et al(12)	M=682, F=344	2.84 (1.69-4.76)	
	Goldberg et al (4)	M=810, F=550	1.90 (1.28-2.82)	2.00 (1.23-3.22)
	Khan et al(21)	M=710, F=305	2.11 (1.50-2.98)	
	Kirchberger et al(13)	M= 1710, F=568	1.73 (1.42- 2.11)	1.78 (1.43-2.21)
	Lovlien, Schei & Hole(11)	M=384, F=149	1.53 (1.01-2.31)	1.66 (1.08-2.55)
	Lovlien, Schei & Gjengedal(8)	M=44, F=38	3.00 (1.18-7.62)	
	Milner et al(5)	M=127, F=90	0.61 (0.18-2.05)	
	Pelter et al(16)	M=221, F=110	1.94 (0.83-4.54)	
Stomach or epigastric pain	Allana et al (26)	M= 133, F=116	2.11 (1.24-3.59)	
	Coventry et al (19)	M=1060, F=621	1.36 (0.74-2.51)	1.02 (0.55-1.91)
	Culic et al (6)	M=1395, F=601	0.80 (0.61-1.05)	0.95 (0.73-1.23)
	Goldberg et al (4)	M=810, F=550	0.73 (0.43-1.22)	0.90 (0.53-1.54)
	Grace et al(7)	M=347, F=135	1.95 (0.93-4.09)	
	Kirchberger et al(13)	M= 1710, F=568	1.37 (1.03-1.83)	1.39 (1.02-1.91)
	Lovlien, Schei & Hole(11)	M=384, F=149	1.29 (0.78-2.14)	1.38 (0.82-2.30)
	Meischke et al (3)	M=2970, F=1527	0.98 (0.80-1.20)	
	Pelter et al(16)	M=221, F=110	1.71 (0.51-5.72)	
	Sederholm Lawesson et al(25)	M=406, F= 126	0.50 (0.21-1.21)	0.55 (0.21-1.42)
	Zevallos et al (18)	M=778, F=637	1.80 (1.20-2.69)	
Shortness of breath	Allana et al (26)	M= 133, F=116	1.74 (1.00-3.05)	
	An et al(27)	M= 323, F= 483	1.88 (1.41-2.51)	2.13 (1.57-2.95)
	Arslanian-Engoren et al(10)	M= 1258, F=536	1.13 (0.94-1.36)	1.10 (0.90-1.34)
	Asgar Pour et al (22)	M=183, F=137	0.81 (0.48-1.34)	
	Coventry et al(19)	M= 1060, F=621	1.14 (0.91-1.42)	1.05 (0.84-1.33)
	Culic et al(6)	M=1395, F=601	1.80 (1.48-2.19)	1.51 (1.23-1.82)
	DeVon et al(23)	M=343, F=131	1.32 (0.88-1.97)	1.45 (0.93-2.26)
	Dey et al (12)	M=682, F=344	1.02 (0.79-1.33)	
	Goldberg et al(4)	M=810, F=550	1.25 (1.00-1.56)	1.16 (0.92-1.49)
	Grace et al(7)	M=347, F=135	1.47 (0.99-2.20)	
	Khan et al(21)	M=710, F=305	0.99 (0.75-1.29)	
	Kirchberger et al(13)	M= 1710, F=568	1.51 (1.25-1.83)	1.45 (1.17-1.78)
	Lichtman et al(24)	M=976, F=2009	1.23 (1.06-1.43)	
	Lovlien, Schei & Hole(11)	M=384, F=149	1.47 (1.00-2.16)	1.63 (1.10-2.42)
	Lovlien, Schei & Gjengedal(8)	M=44, F=38	2.15 (0.88-5.24)	
	Milner et al(5)	M=127, F=90	1.82 (1.05-3.16)	1.68 (0.95-2.96)
	Meischke et al(3)	M=2970, F=1527	1.26 (1.11-1.42)	
	Melberg et al(20)	M=179, F=65	1.17 (0.56-2.46)	
	O'Donnell et al(17)	M=1402, F=545	1.33 (1.09-1.62)	1.33 (1.08-1.63)
	Plaza-Martin et al (28)	M=749, F=307	2.06 (1.53-2.78)	
	Pelter et al(16)	M=221, F=110	1.55 (0.91-2.65)	
	Sederholm Lawesson et al(25)	M=406, F=126	0.98 (0.64-1.50)	1.04 (0.66-1.65)
Diaphoresis	An et al(27)	M= 323, F= 483	1.00 (0.74-1.35)	NS: OR not provided
	Allana et al (26)	M= 133, F= 116	0.85 (0.51-1.41)	
	Arslanian-Engoren et al(10)	M= 1258, F=536	0.67 (0.55-0.82)	0.76 (0.62-0.94)
	Asgar Pour et al(22)	M=183, F=137	0.98 (0.52-1.87)	
	Coventry et al(19)	M= 1060, F=621	0.61 (0.43-0.85)	0.71 (0.50-1.01)
	Culic et al (6)	M=1395, F=601	0.62 (0.52-0.76)	0.73 (0.60-0.88)
	DeVon et al(23)	M=343, F=131	0.94 (0.61-1.43)	0.96 (0.61-1.50)
	Dey et al(12)	M=682, F=344	0.75 (0.56-1.01)	

	Goldberg et al(4)	M=810, F=550	0.79 (0.64-0.98)	0.78 (0.62-1.00)
	Grace et al(7)	M=347, F=135	1.32 (0.88-1.96)	
	Khan et al(21)	M=710, F=305	0.77 (0.59-1.01)	
	Kirchberger et al(13)	M= 1710, F=568	0.91 (0.75-1.10)	0.93 (0.75-1.15)
	Lichtman et al(24)	M=976, F=2009	1.08 (0.74-1.58)	
	Lovlien, Schei & Hole(11)	M=384, F=149	1.08 (0.74-1.58)	1.29 (0.87-1.93)
	Meischke et al(3)	M=2970, F=1527	0.68 (0.60-0.77)	
	Melberg et al (20)	M=179, F=65	0.92 (0.50-1.69)	
	Milner et al (5)	M=127, F=90	1.45 (0.79-2.67)	
	O'Donnell et al(17)	M=1402, F=545	NS: OR not provided	NS: OR not provided
	Pelter et al(16)	M=221, F=110	0.91 (0.43-1.94)	
	Sederholm Lawesson et al(25)	M=406, F=126	1.20 (0.79-1.82)	1.40 (0.88-2.23)
Nausea or vomiting	Allana et al (26)	M= 133, F=116	2.51 (1.50-4.18)	
	An et al (27)	M= 323, F= 483	1.28 (0.93-1.76)	NS: OR not provided
	Arslanian-Engoren et al(10)	M=1258, F=536	1.24 (1.01-1.52)	1.48 (1.19-1.84)
	Asgar Pour et al (22)	M=183, F=137	1.29 (0.81-2.04)	
	Coventry et al(19)	M= 1060, F=621	1.55 (1.03-2.34)	1.57 (1.02-2.41)
	Culic et al (6)	M=1395, F=601	1.94 (1.60-2.36)	1.61 (1.33-1.96)
	DeVon et al(23)	M=343, F=131	1.52 (1.01-2.30)	1.72 (1.21-2.46)
	Dey et al (12)	M=682, F=344	1.63 (1.22-2.18)	
	Goldberg et al(4)	M=810, F=550	1.60 (1.28-2.02)	1.72 (1.33-2.22)
	Grace et al(7)	M=347, F=135	1.81 (1.19-2.73)	
	Khan et al(21)	M=710, F=305	1.85 (1.38-2.49)	
	Kirchberger et al(13)	M= 1710, F=568	1.90 (1.57-2.31)	2.23 (1.67-2.97)
	Lovlien, Schei & Hole(11)	M=384, F=149	2.14 (1.45-3.16)	2.38 (1.59-3.56)
	Lovlien, Schei & Gjengedal(8)	M=44, F=38	3.72 (1.49-9.29)	
	Meischke et al (3)	M=2970, F=1527	1.45 (1.28-1.64)	
	Melberg et al(20)	M=179, F=65	1.32 (0.72-2.43)	
	Milner et al (5)	M=127, F=90	2.29 (1.19-4.42)	2.43 (1.23-4.79)
	O'Donnell et al(17)	M=1402, F=545	1.23 (0.98-1.53)	1.31 (1.04-1.65)
	Sederholm Lawesson et al(25)	M=406, F=126	2.39 (1.59-3.61)	3.04 (1.93-4.78)
Fatigue	An et al(27)	M= 323, F= 483	1.51 (1.14-2.01)	1.39 (1.01-1.91)
	Asgar Pour et al(22)	M=183, F=137	0.85 (0.54-1.35)	
	Coventry et al (19)	M= 1060, F=621	2.13 (1.28-3.56)	
	DeVon et al(23)	M=343, F=131	1.13 (0.75-1.70)	1.04 (0.67-1.62)
	Grace et al(7)	M=347, F=135	1.24 (0.81-1.90)	
	Khan et al(21)	M=710, F=305	1.57 (1.19-2.05)	
	Lichtman et al (24)	M=976, F=2009	1.19 (1.02-1.39)	
	Lovlien, Schei & Hole(11)	M=384, F=149	1.36 (0.93-2.00)	1.43 (0.97-2.11)
	Milner et al (5)	M=127, F=90	2.07 (0.93-4.63)	
	O'Donnell et al(17)	M=1402, F=545	1.49 (1.19-1.87)	1.64 (1.30-2.08)
	Sederholm Lawesson et al(25)	M=406, F=126	1.43 (0.94-2.16)	1.31 (0.84-2.06)
Dizziness or light-headedness	An et al(27)	M= 323, F=483	1.53 (1.14-2.07)	1.83 (1.31-2.58)
	Culic et al (6)	M=1395, F=601	1.39 (0.96-2.03)	1.22 (0.84-1.75)
	DeVon et al(23)	M=343, F=131	1.29 (0.86-1.95)	1.26 (0.81-1.96)
	Grace et al(7)	M=347, F=135	1.70 (1.08-2.67)	
	Lovlien, Schei & Hole(11)	M=384, F=149	1.32 (0.89-1.95)	1.54 (1.03-2.32)
	Lichtman et al(24)	M=976, F=2009	1.09 (0.92-1.29)	
	Khan et al(21)	M=710, F=305	1.17 (0.86-1.58)	
	Kirchberger et al(13)	M= 1710, F=568	1.36 (1.08-1.70)	1.49 (1.16-1.91)
	Milner et al (5)	M=127, F=90	1.21 (0.61-2.38)	
Indigestion	An et al (27)	M= 323, F= 483	1.42 (0.66-3.06)	NS: OR not provided
	Asgar Pour et al(22)	M=183, F=137	0.74 (0.43-1.28)	
	DeVon et al (23)	M=343, F=131	1.51 (0.96-2.38)	1.40 (0.86-2.27)
	Grace et al(7)	M=347, F=135	1.32 (0.82-2.14)	
	Milner et al(5)	M=127, F=90	2.13 (1.03-4.44)	2.13 (1.01-4.53)
	O'Donnell et al(17)	M=1402, F=545	NS: OR not provided	NS: OR not provided
Palpitations	Allana et al(26)	M=133, F=116	2.11 (1.26-3.52)	
	An et al(27)	M= 323, F=483	1.63 (1.11-2.41)	NS: OR not provided
	Asgar Pour et al(22)	M=183, F=137	1.41 (0.85-2.35)	
	DeVon et al(23)	M=343, F=131	1.72 (1.06-2.79)	1.54 (1.05-2.25)
	Dey et al(12)	M=682, F=344	1.46 (0.82-2.61)	
	Lichtman et al(24)	M=976, F=2009	1.61 (1.29-2.01)	
	Lovlien, Schei & Hole(11)	M=384, F=149	2.77 (1.82-4.22)	3.14 (2.02-4.88)
	Milner et al (5)	M=127, F=90	3.42 (1.02-11.47)	
	O'Donnell et al(17)	M=1402, F=545	2.04 (1.25-3.31)	2.18 (1.31-3.63)

	Plaza-Martin et al(28)	M=749, F=307	3.05 (1.52-6.13)	
Fear	Kirchberger et al(13)	M= 1710, F=568	2.03 (1.66-2.49)	2.17 (1.73-2.72)
	O'Donnell et al(17)	M=1402, F=545	1.32 (0.98-1.78)	1.47 (1.08-2.01)
	Sederholm Lawesson et al(25)	M=406, F=126	2.19 (1.39-3.46)	2.65 (1.59-4.41)
Syncope	Allana et al(26)	M=133, F=116	0.95 (0.28-3.21)	
	Coventry et al(19)	M= 1060, F=621	1.41 (0.97-2.05)	1.42 (0.96-2.10)
	Dey et al(12)	M=682, F=344	1.06 (0.77-1.45)	
	Goldberg et al(4)	M=810, F=550	1.27 (0.87-1.86)	0.88 (0.56-1.41)
	Grace et al(7)	M=347, F=135	1.09 (0.46-2.55)	
	Kirchberger et al(13)	M= 1710, F=568	1.41 (0.95-2.09)	1.55 (1.00-2.39)
	Lovlien, Schei & Hole(11)	M=384, F=149	2.04 (1.11-3.77)	2.34 (1.25-4.40)
	Meischke et al (3)	M=2970, F=1527	1.23 (0.85-1.77)	
	Melberg et al(20)	M=179, F=65	0.95 (0.42-2.14)	
	Sederholm Lawesson et al(25)	M=406, F=126	0.98 (0.62-1.54)	0.96 (0.58-1.58)
	Tunstall-Pedoe et al(2)	M=3991, F=1551	1.31 (0.94-1.83)	
Headache	An et al (27)	M= 323, F= 483	1.67 (0.98-2.83)	NS: OR not provided
	Culic et al(6)	M=1395, F=601	2.63 (1.85-3.85)	2.04 (1.45-2.86)
	Khan et al(21)	M=710, F=305	1.54 (1.10-2.15)	
	Lovlien, Schei & Hole(11)	M=384, F=149	1.25 (0.76-2.04)	1.46 (0.88-2.44)
Hot flushes	An et al (27)	M= 323, F= 483	1.14 (0.60-2.14)	NS: OR not provided
	Khan et al(21)	M=710, F=305	1.51 (1.16-1.98)	
	Lovlien, Schei & Hole(11)	M=384, F=149	1.47 (0.95-2.25)	1.63 (1.00-2.54)
Cough	An et al (27)	M= 323, F= 483	0.74 (0.38-1.44)	NS: OR not provided
	Culic et al(6)	M=1395, F=601	2.08 (1.54-2.78)	1.59 (1.19-2.08)

OR: Odds ratio CI: confidence interval, M=male, F=female.

Table S5. Meta-regression showing effects of age on the odds ratio of the symptom being present in women relative to men.

	Age ≤ 65 years	Age > 65 years	p-value
	OR (95%CI)	OR (95%CI)	
Symptom			
Chest pain	0.79 (0.68-0.91)	0.64 (0.55-0.75)	0.06
Diaphoresis	0.90 (0.78-1.05)	0.76 (0.66-0.88)	0.14
Dizziness or lightheadedness*			
Fatigue†	1.32 (1.17-1.48)	1.74 (1.27-2.38)	0.11
Indigestion*			
Jaw pain	1.68 (1.29-2.20)	1.97 (1.37-2.85)	0.57
Left arm or left shoulder pain	1.21 (1.10-1.34)	0.89 (0.58-1.37)	0.10
Nausea or vomiting	1.45 (1.32-1.59)	1.74 (1.53-1.98)	0.49
Neck pain*			
Pain between the shoulder blades	2.12 (1.89-2.37)	2.28 (1.78-2.92)	0.59
Palpitations	1.72 (1.33-2.23)	2.24 (1.25-4.00)	0.42
Shortness of breath	1.40 (1.23-1.59)	1.27 (1.10-1.47)	0.33
Stomach or epigastric pain	1.34 (0.94-1.92)	1.08 (0.75-1.54)	0.40
Syncope	1.35 (1.09-1.68)	1.18 (1.00-1.40)	0.34
Right arm or right shoulder pain*			

*Less than 10 studies reported on this symptom, no meta-regression analysis performed

OR = odds ratio; 95%CI = 95% confidence interval

Figure S1. Funnel plot for pooled odds ratio of chest pain.

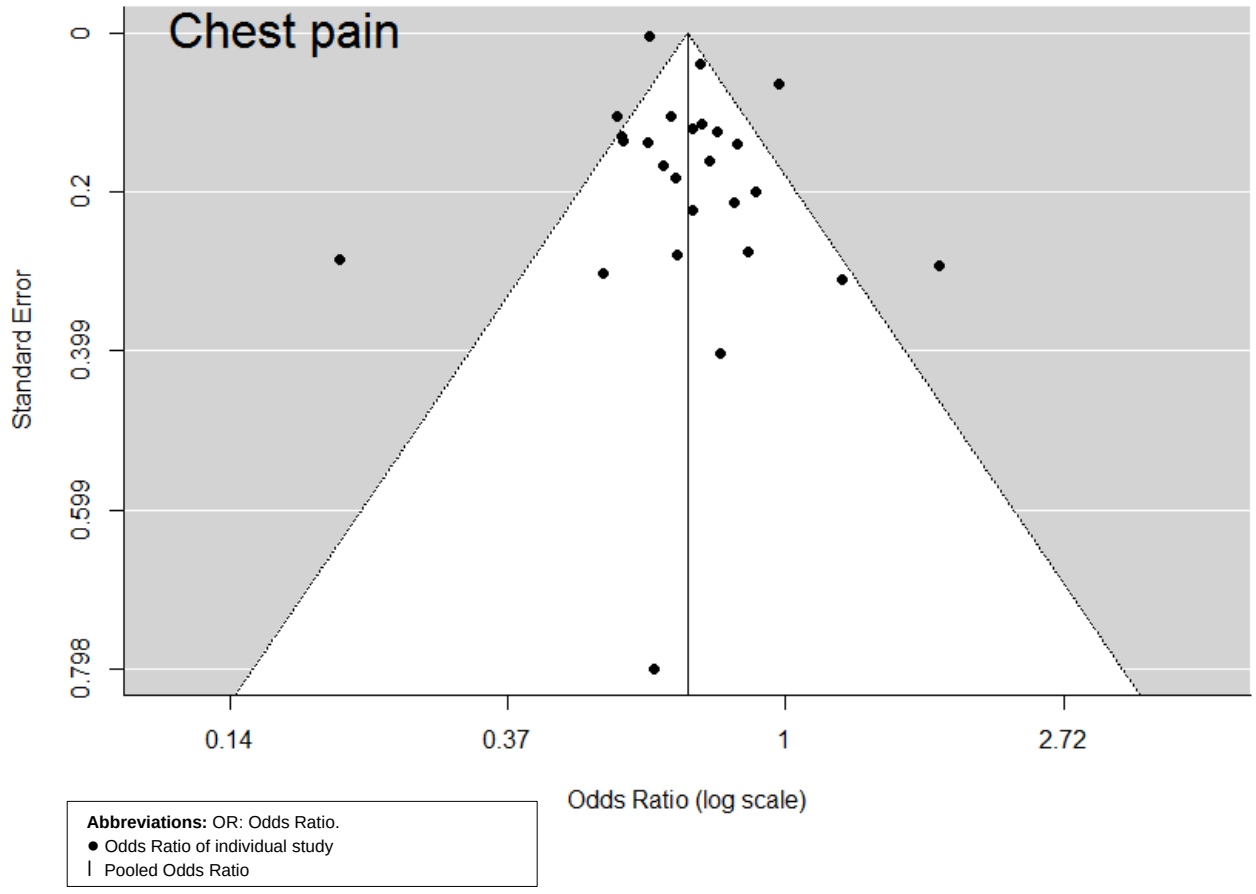


Figure S2. Funnel plot for pooled odds ratio of fatigue.

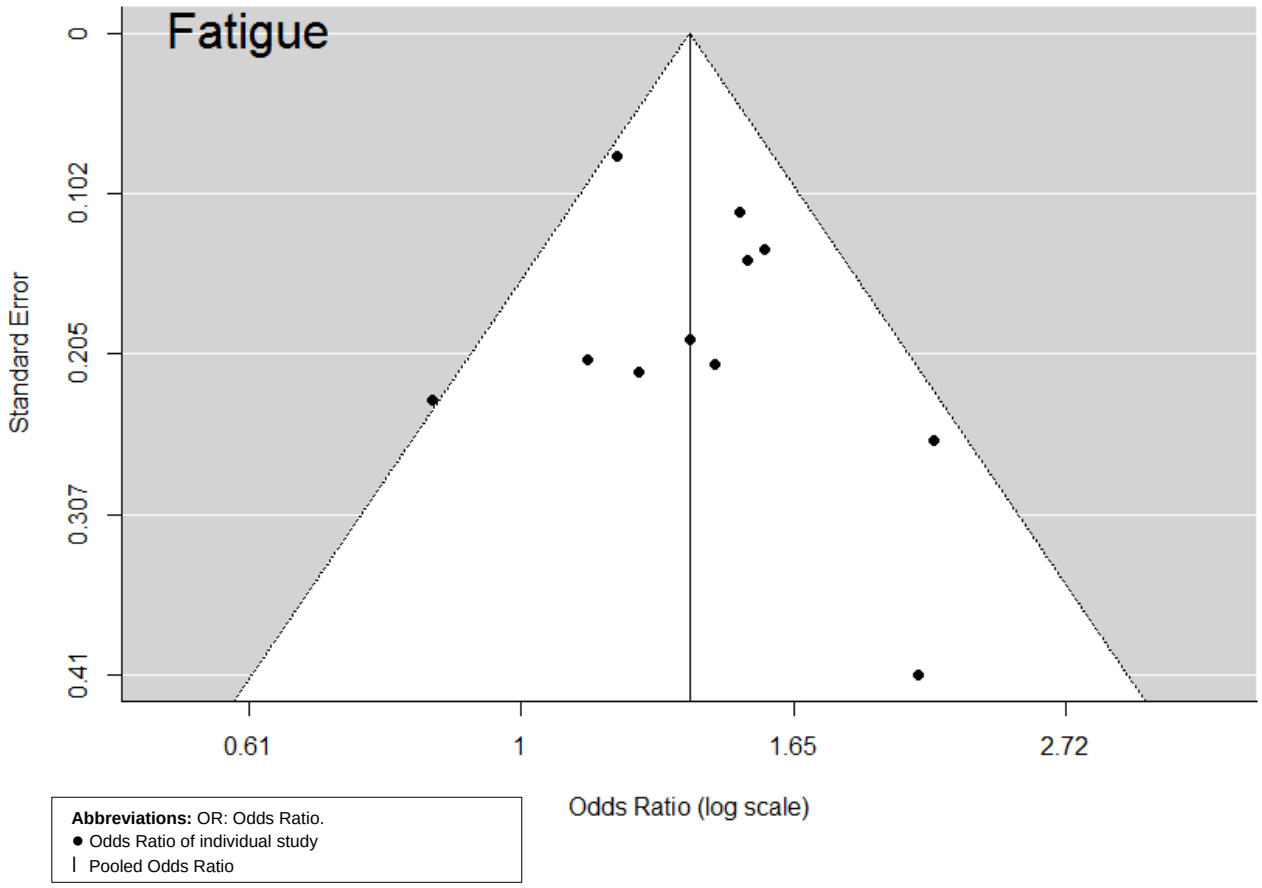


Figure S3. Funnel plot for pooled odds ratio of jaw pain.

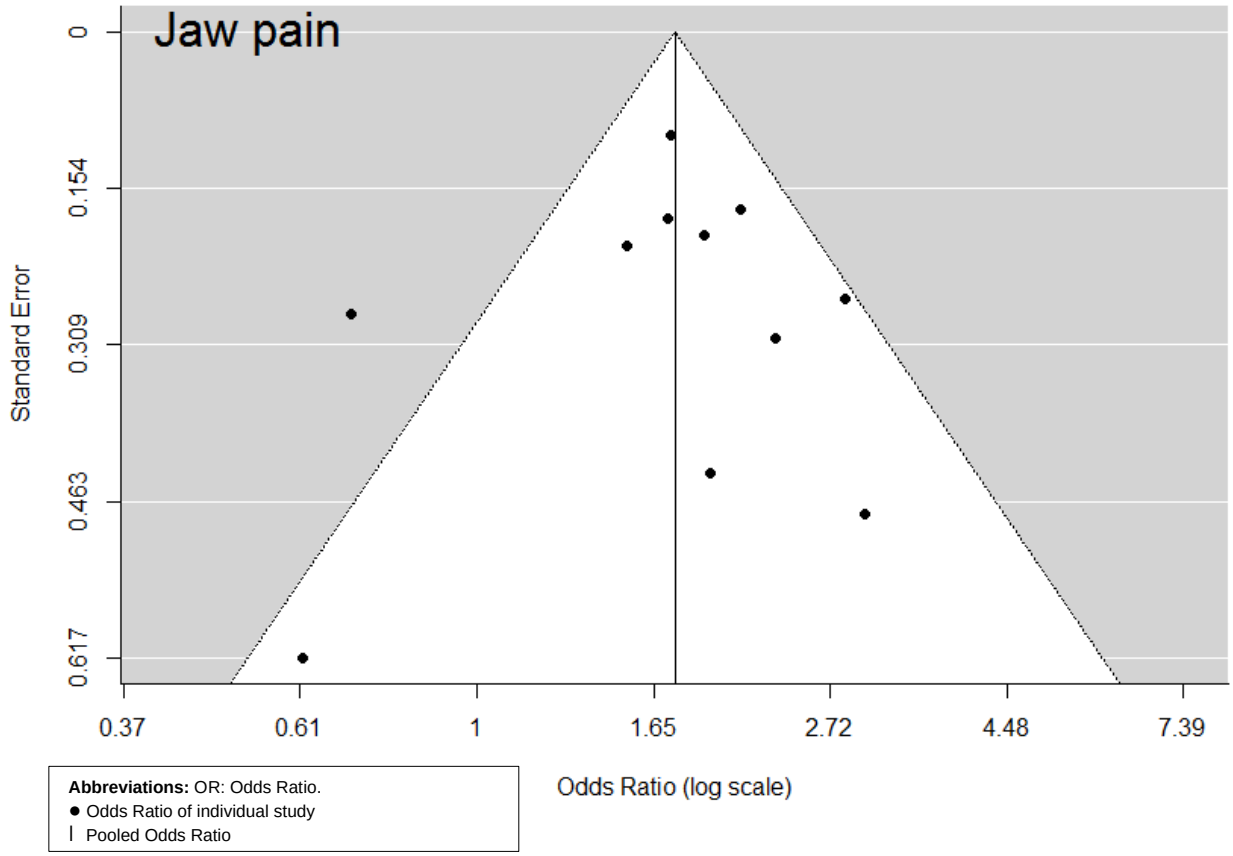


Figure S4. Funnel plot for pooled odds ratio of left arm or left shoulder pain.

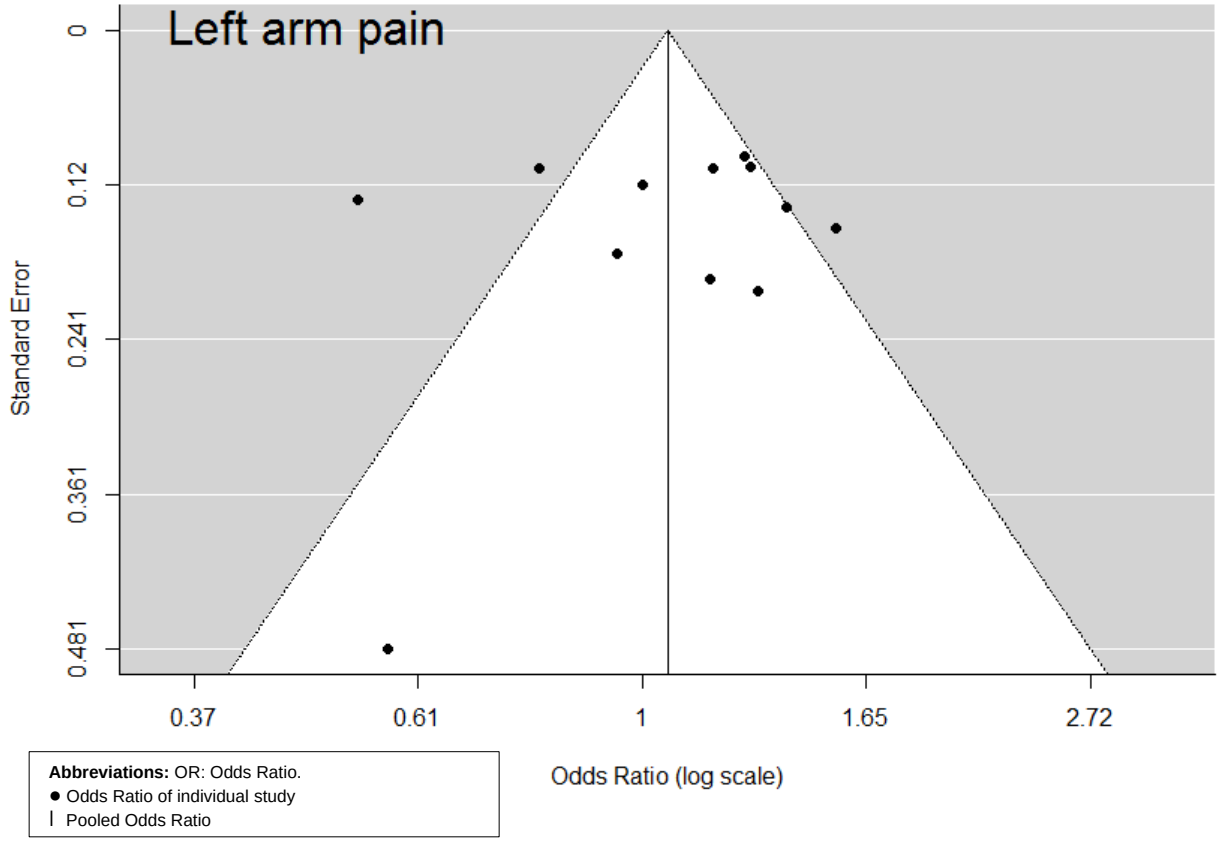


Figure S5. Funnel plot for pooled odds ratio of nausea or vomiting.

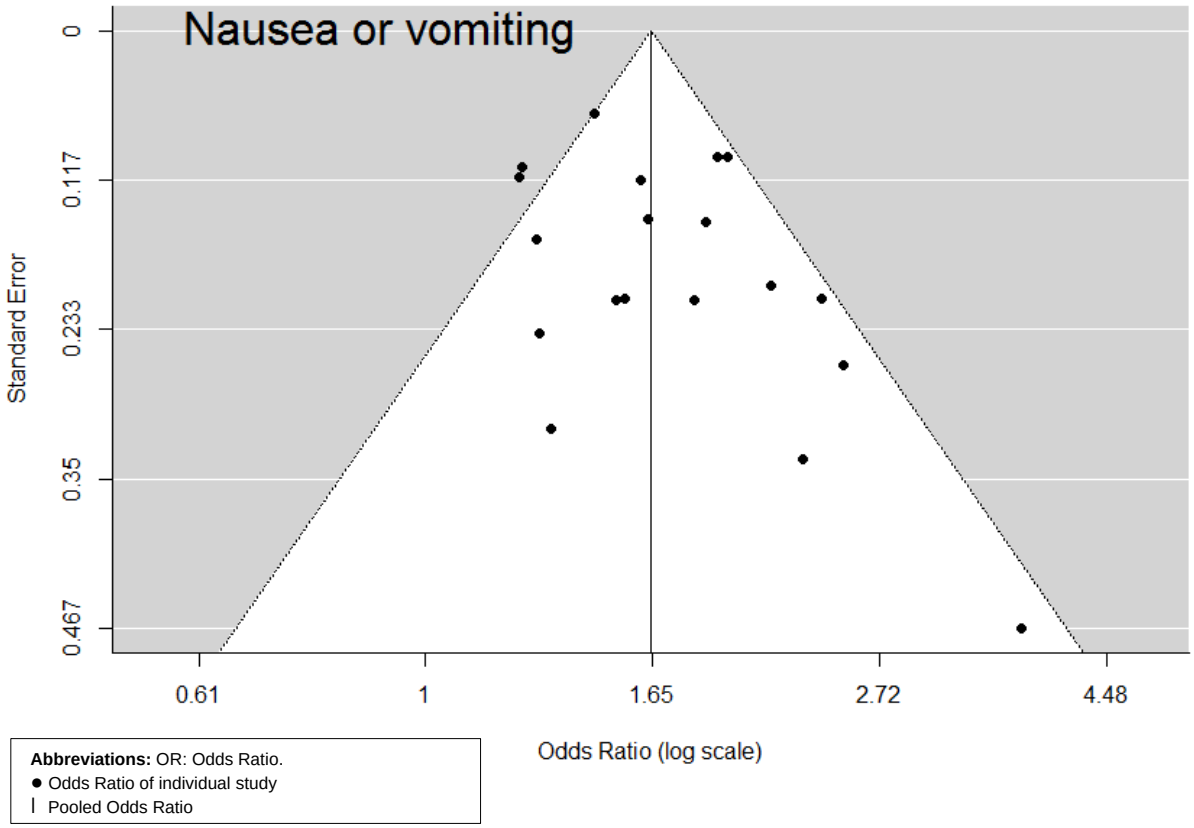


Figure S6. Funnel plot for pooled odds ratio of pain between shoulder blades.

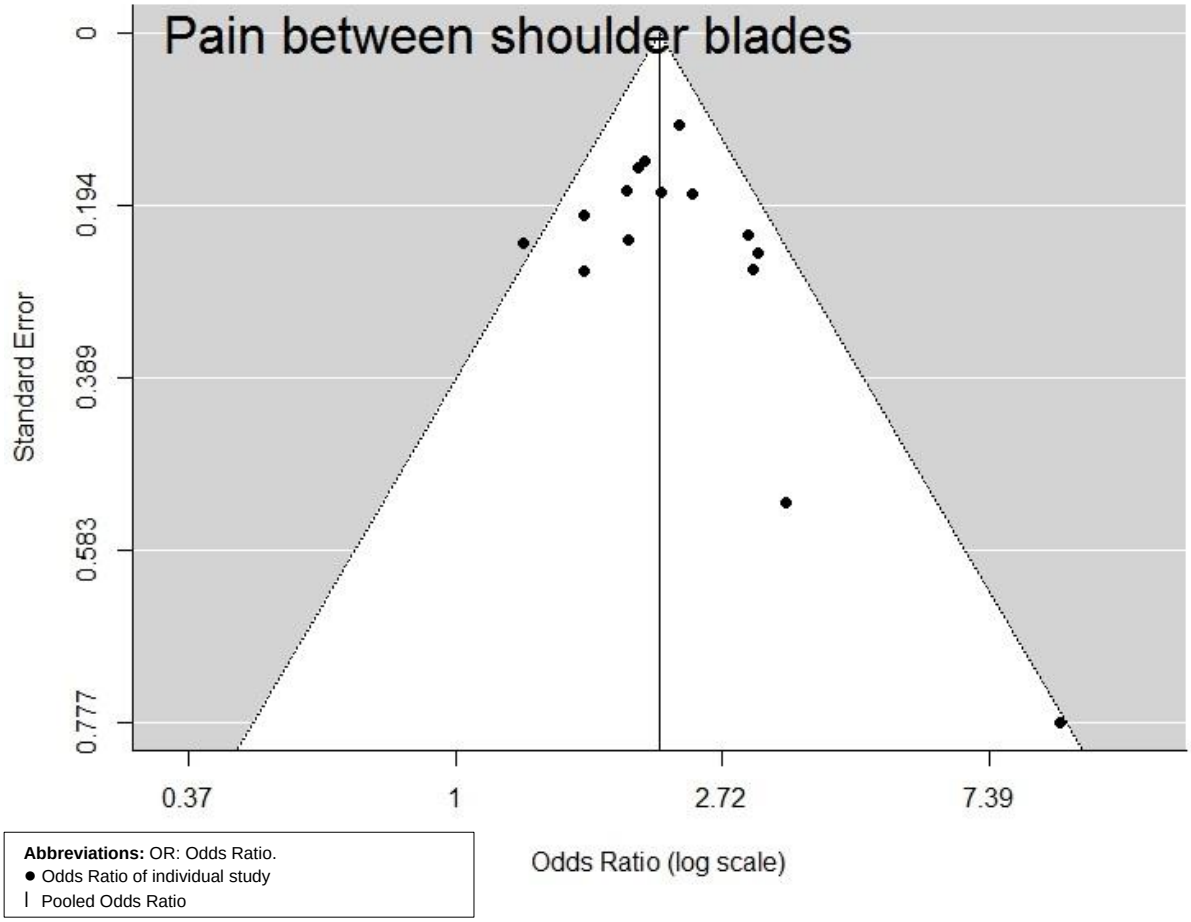


Figure S7. Funnel plot for pooled odds ratio of palpitations.

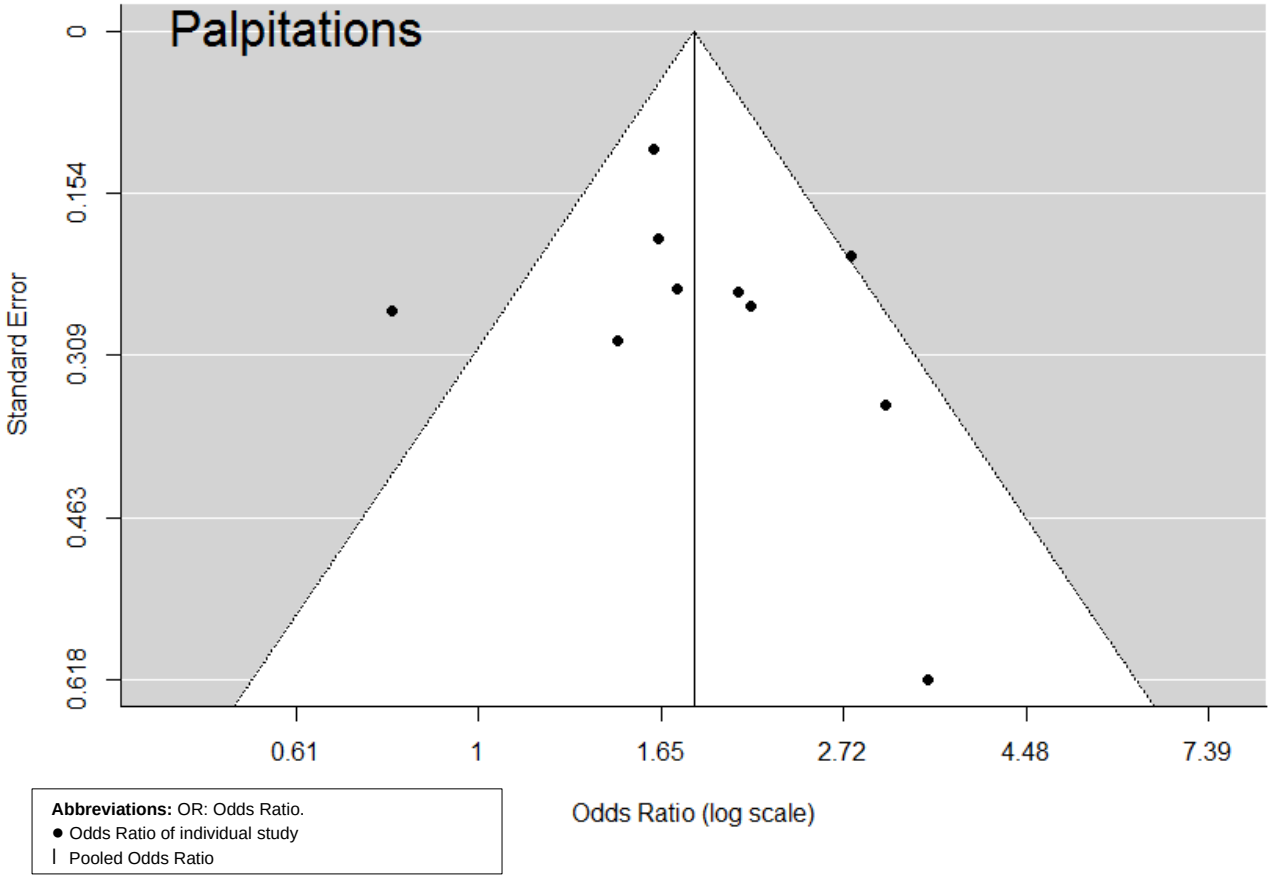


Figure S8. Funnel plot for pooled odds ratio of shortness of breath.

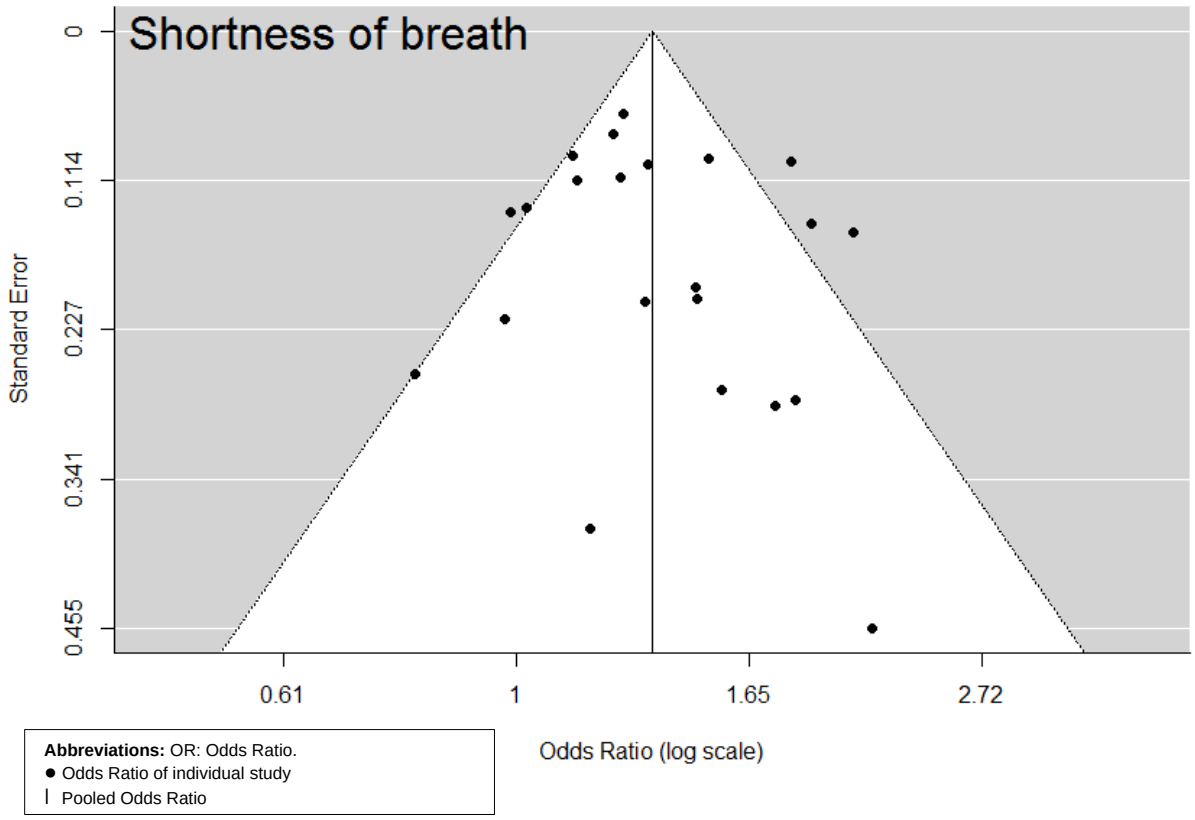


Figure S9. Funnel plot for pooled odds ratio of stomach or epigastric pain.

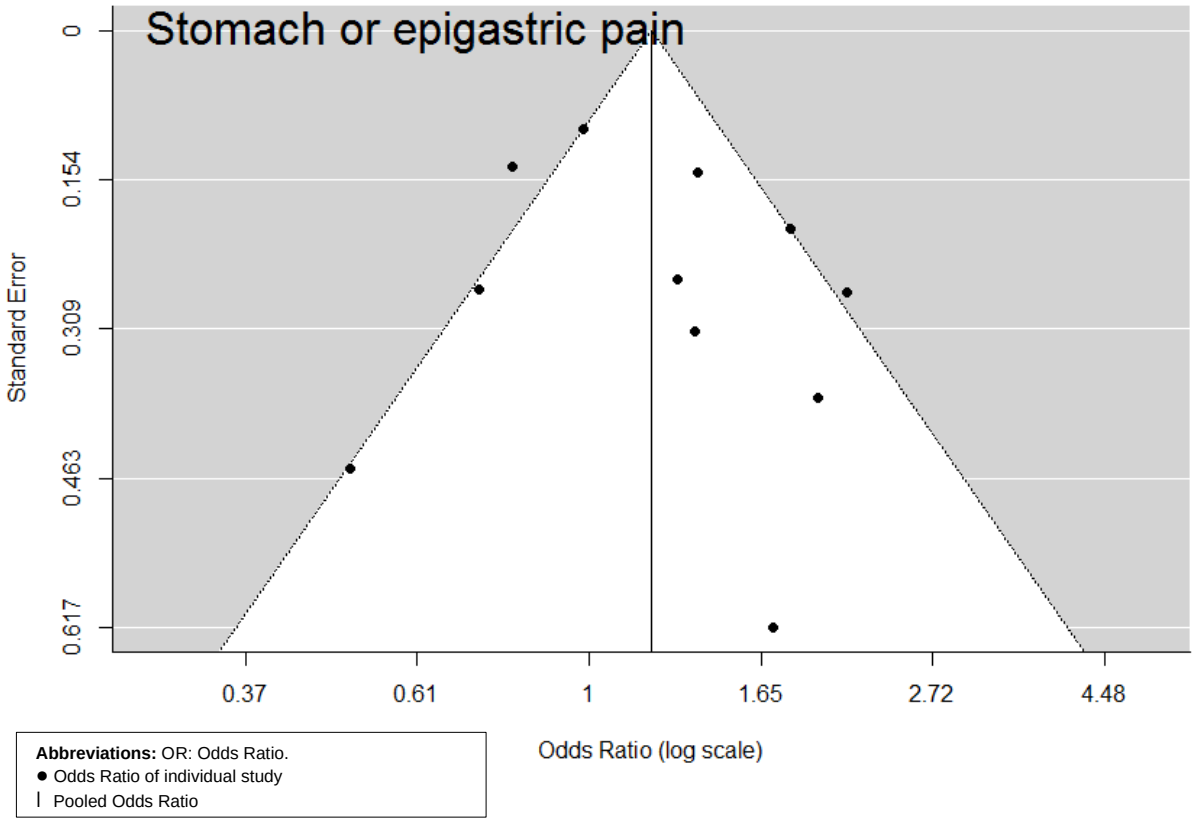


Figure S10. Funnel plot for pooled odds ratio of syncope.

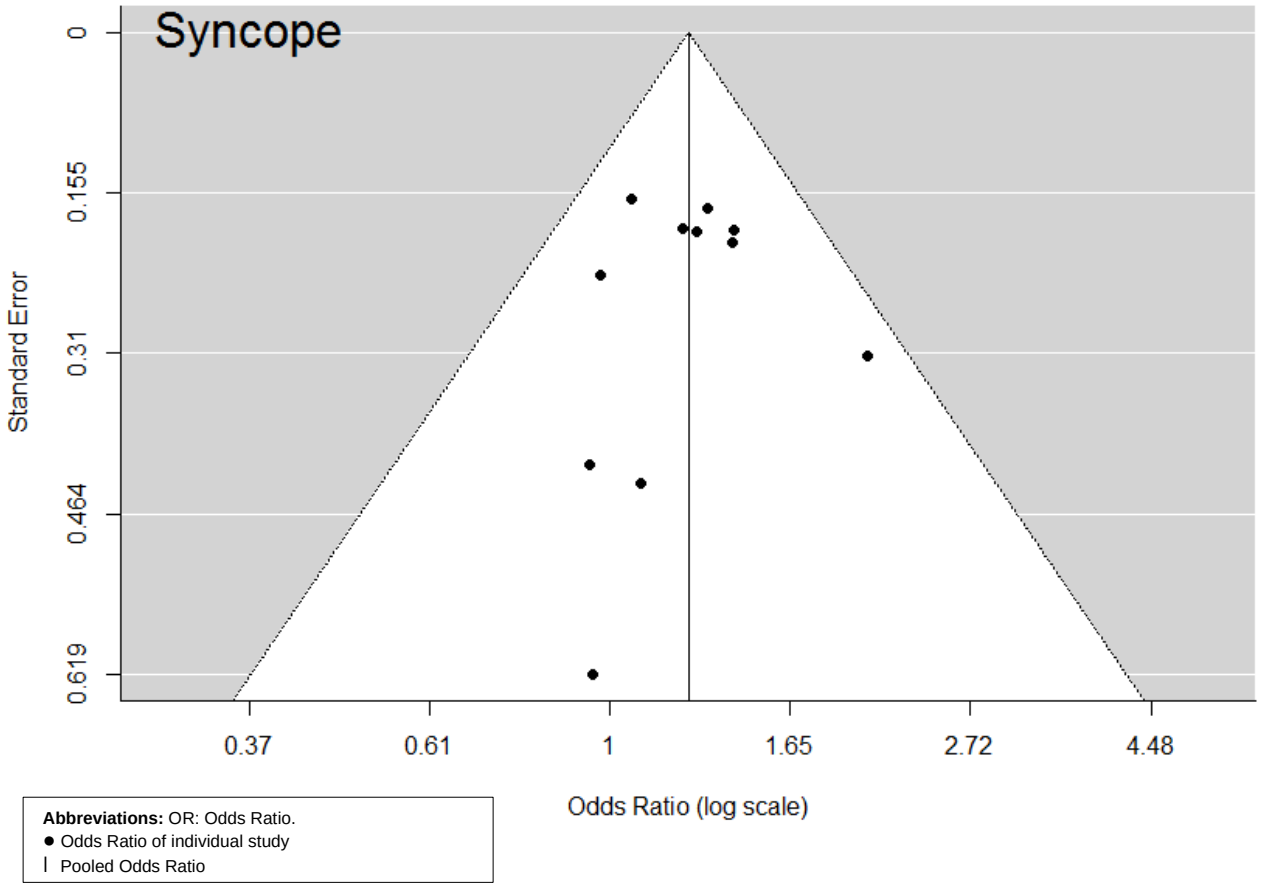


Figure S11. Funnel plot for pooled odds ratio of diaphoresis.

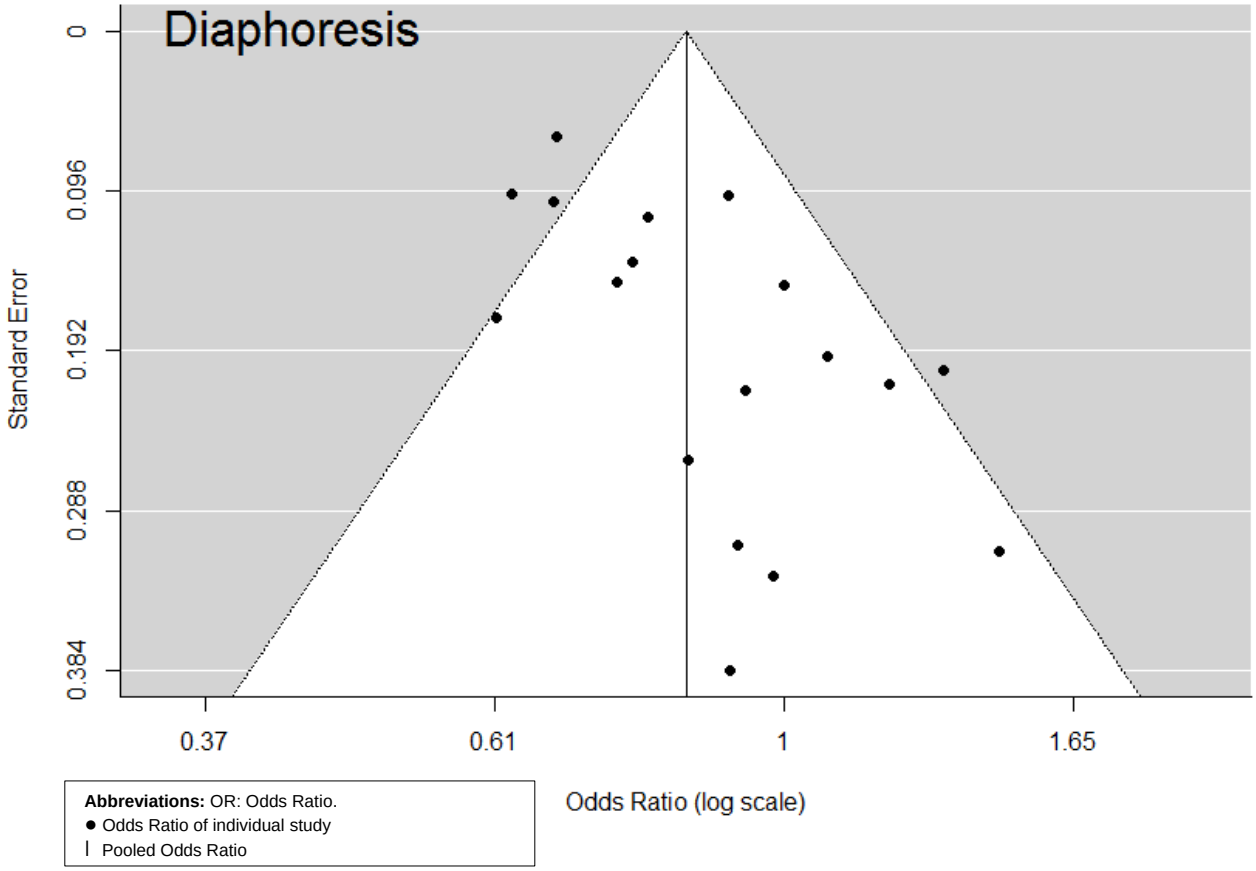


Figure S12. Results of the aggregated meta-analysis for chest pain as a symptom of ACS in women relative to men summarised in a forest plot.

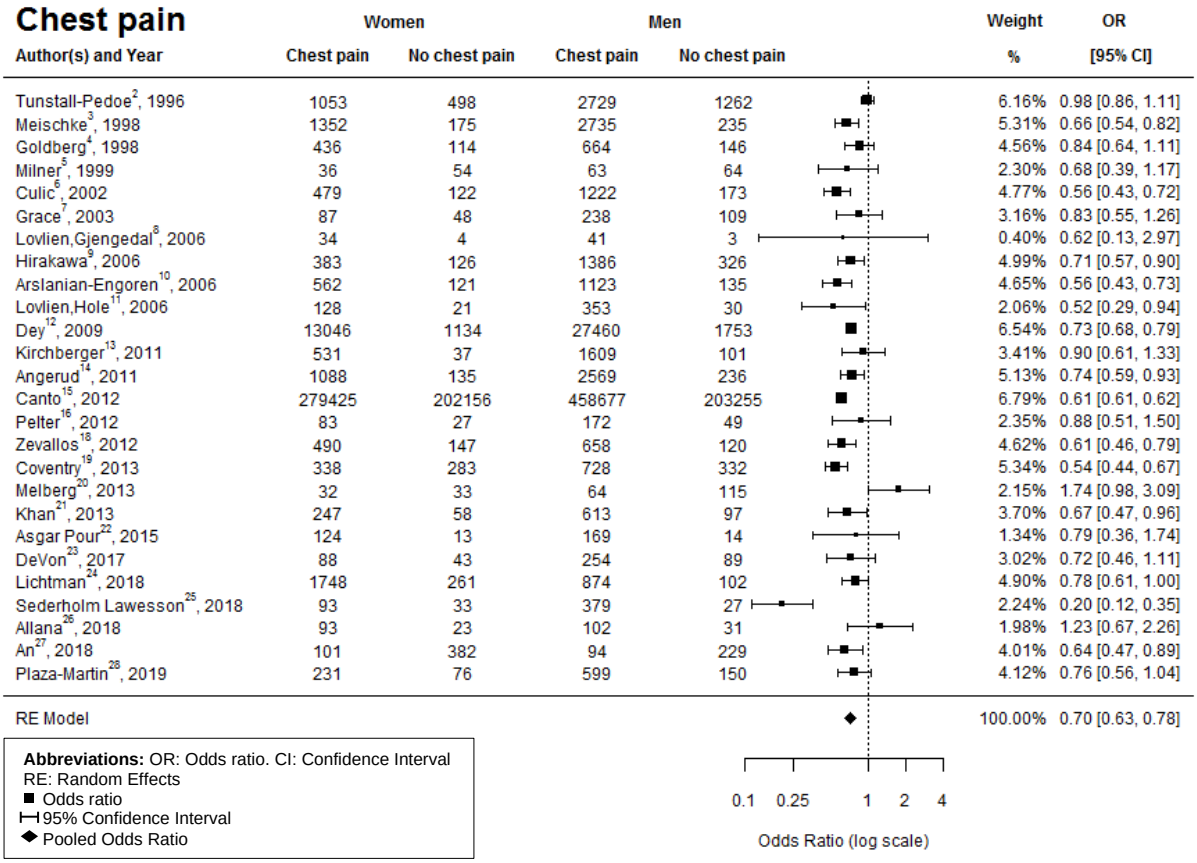


Figure S13. Results of the aggregated meta-analysis for diaphoresis as a symptom of ACS in women relative to men summarised in a forest plot.

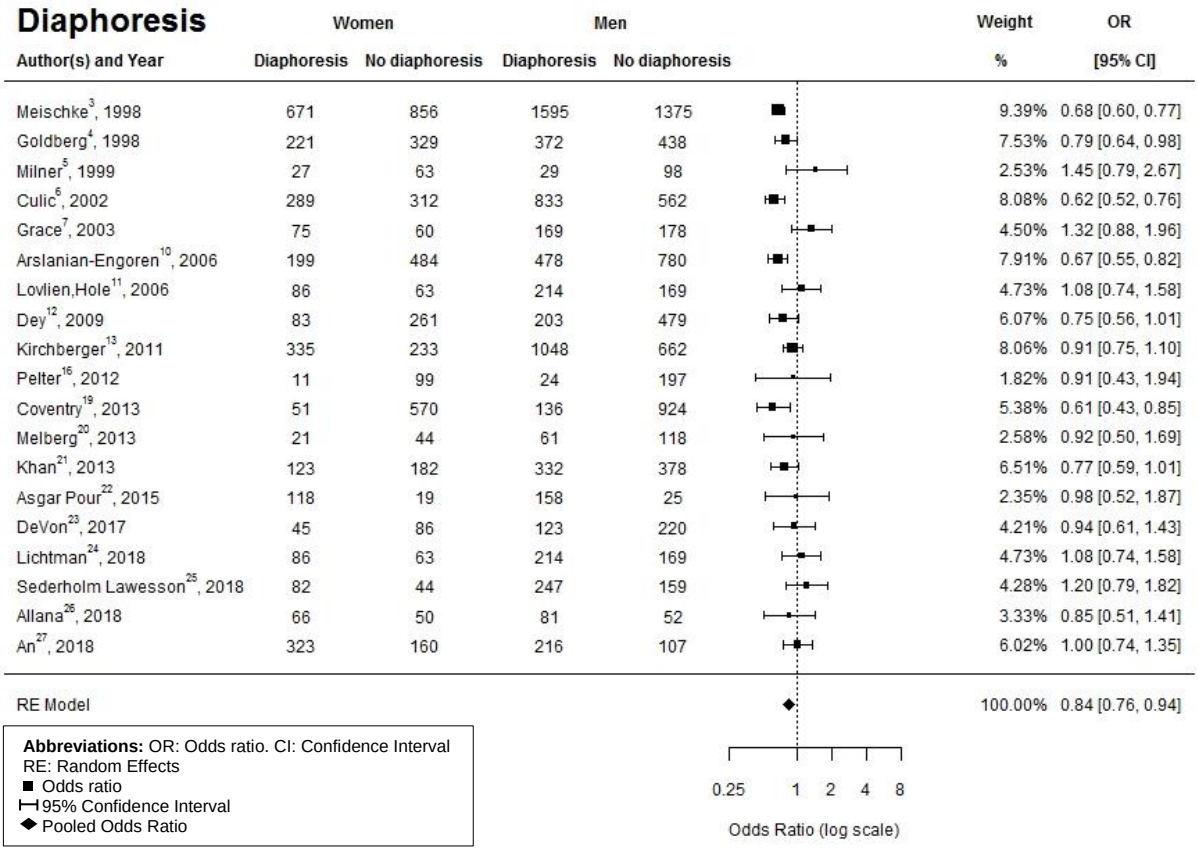


Figure S14. Results of the aggregated meta-analysis for dizziness or light-headedness as a symptom of ACS in women relative to men summarised in a forest plot.

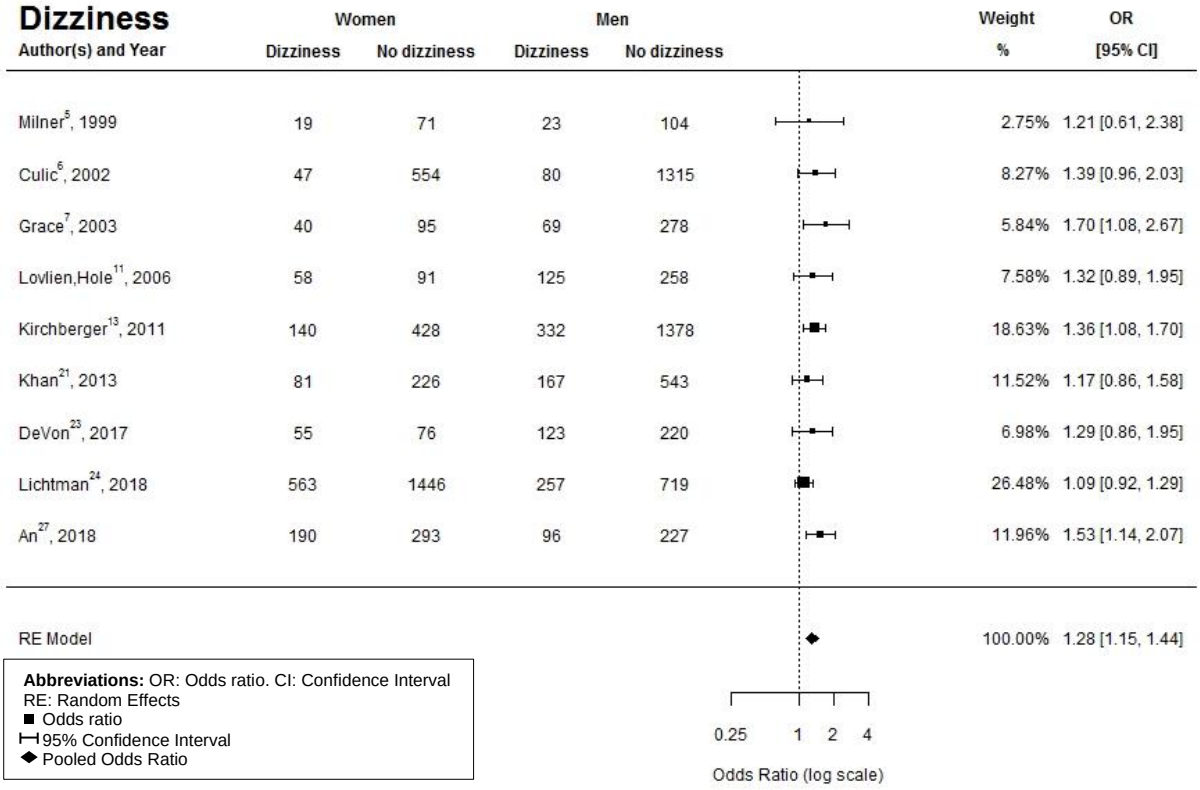


Figure S15. Results of the aggregated meta-analysis for fatigue as a symptom of ACS in women relative to men summarised in a forest plot.

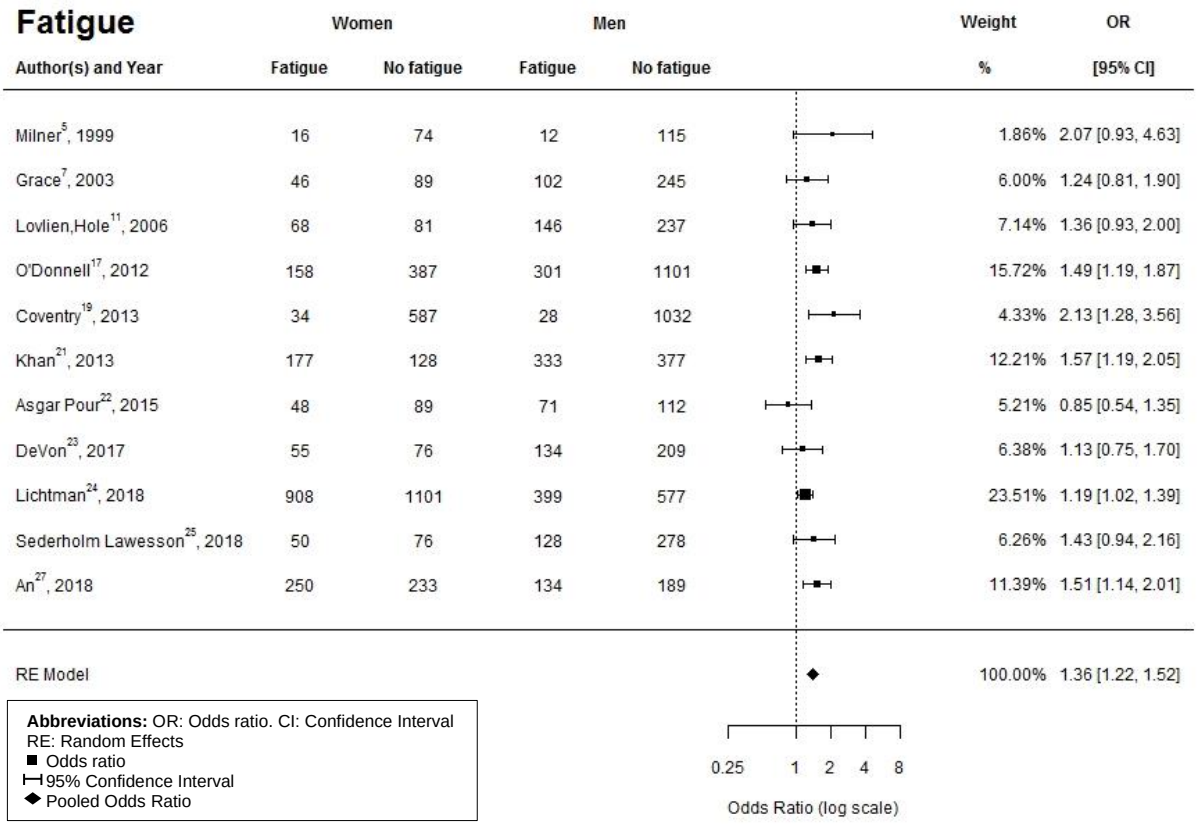


Figure S16. Results of the aggregated meta-analysis for indigestion as a symptom of ACS in women relative to men summarised in a forest plot.

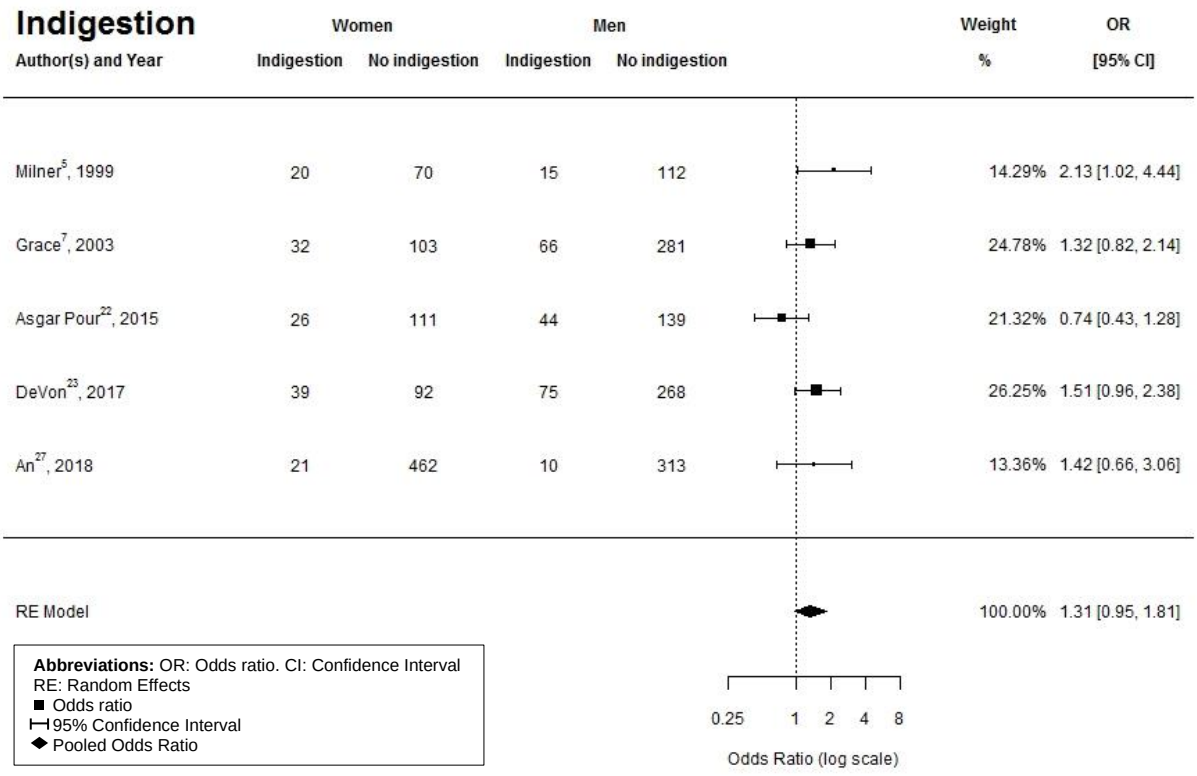


Figure S17. Results of the aggregated meta-analysis for jaw pain as a symptom of ACS in women relative to men summarised in a forest plot.

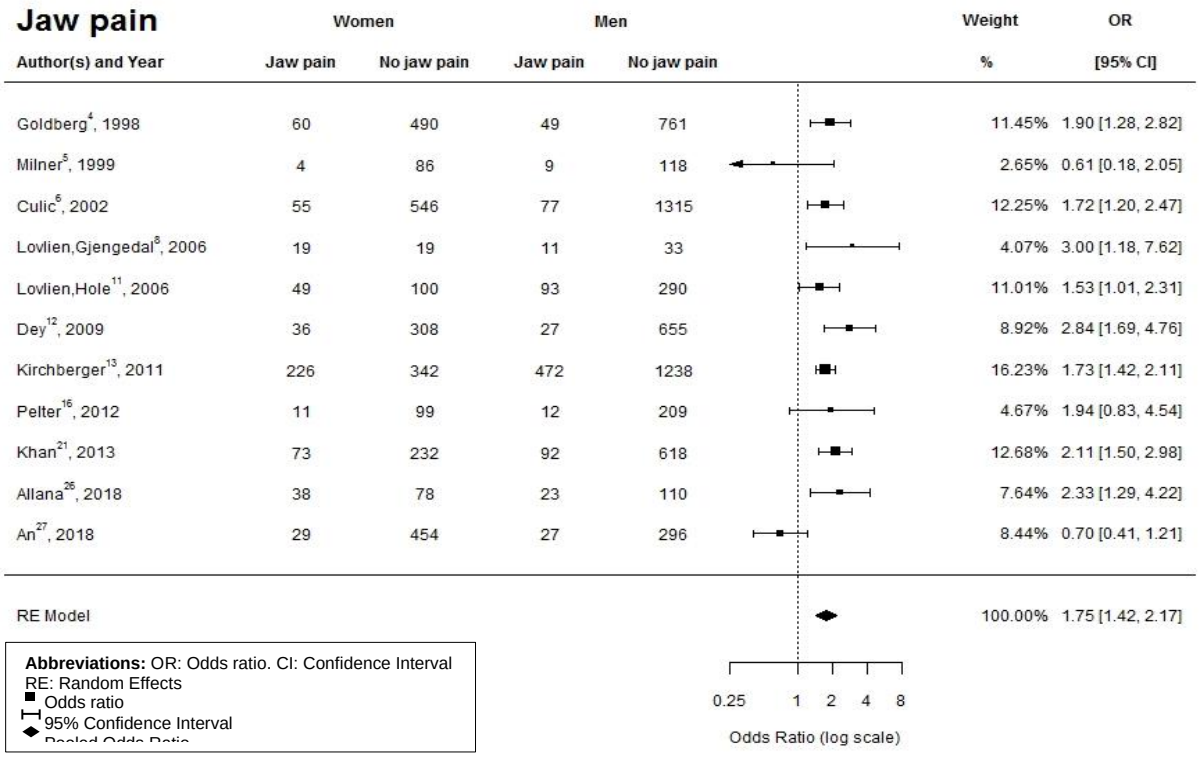


Figure S18. Results of the aggregated meta-analysis for left arm pain or left shoulder pain as a symptom of ACS in women relative to men summarised in a forest plot.

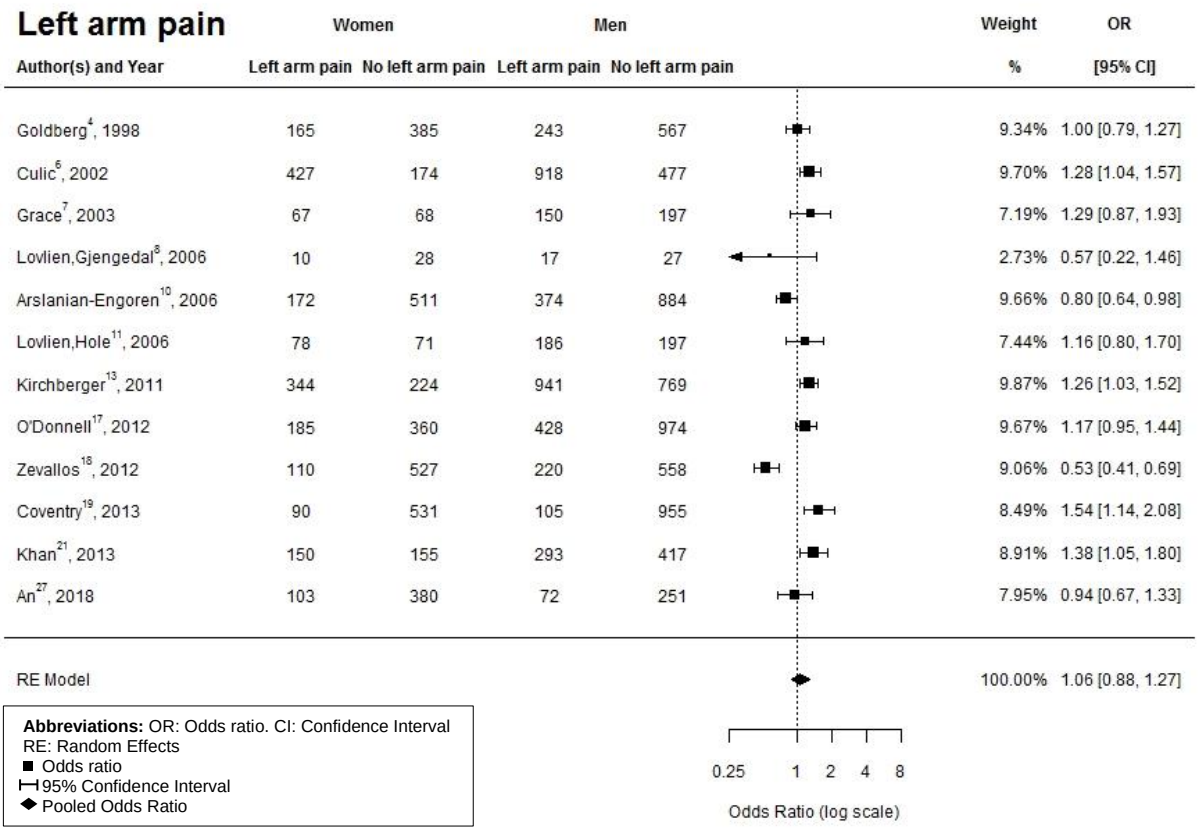


Figure S19. Results of the aggregated meta-analysis for nausea or vomiting as a symptom of ACS in women relative to men summarised in a forest plot.

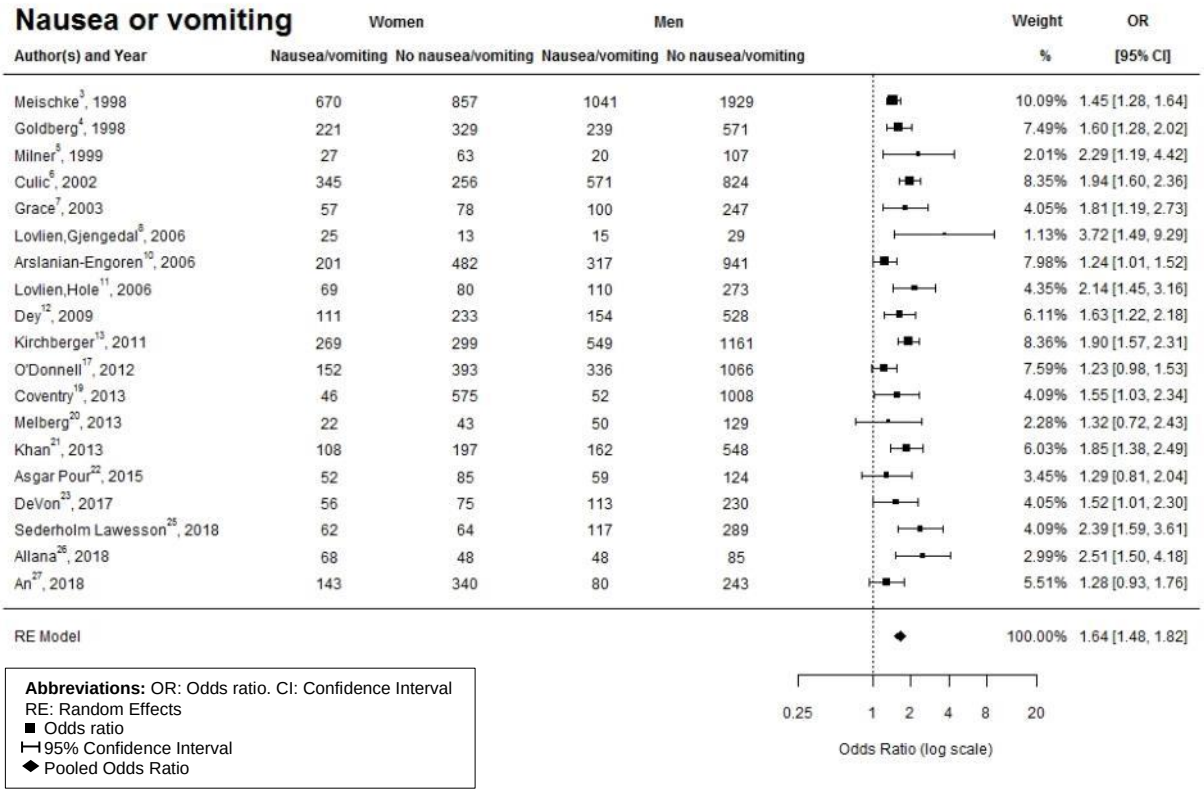


Figure S20. Results of the aggregated meta-analysis for neck pain as a symptom of ACS in women relative to men summarised in a forest plot.

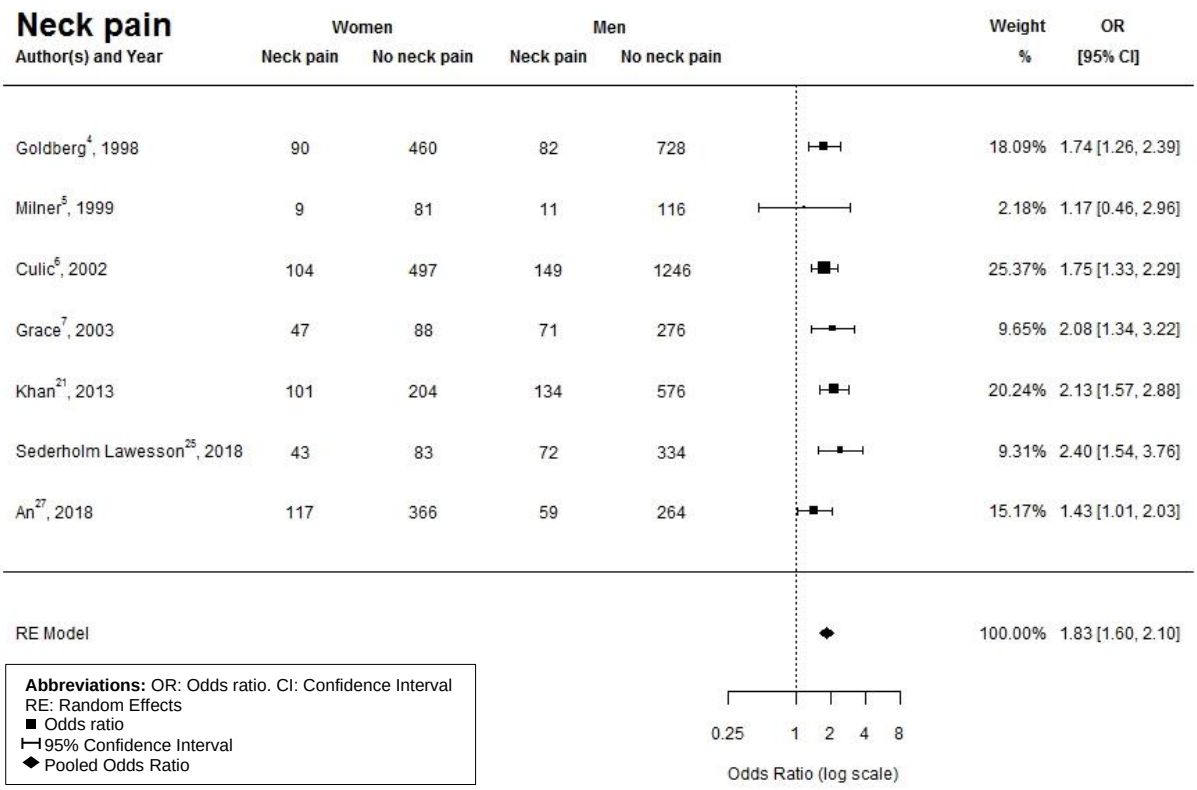


Figure S21. Results of the aggregated meta-analysis for pain between shoulder blades as a symptom of ACS in women relative to men summarised in a forest plot.

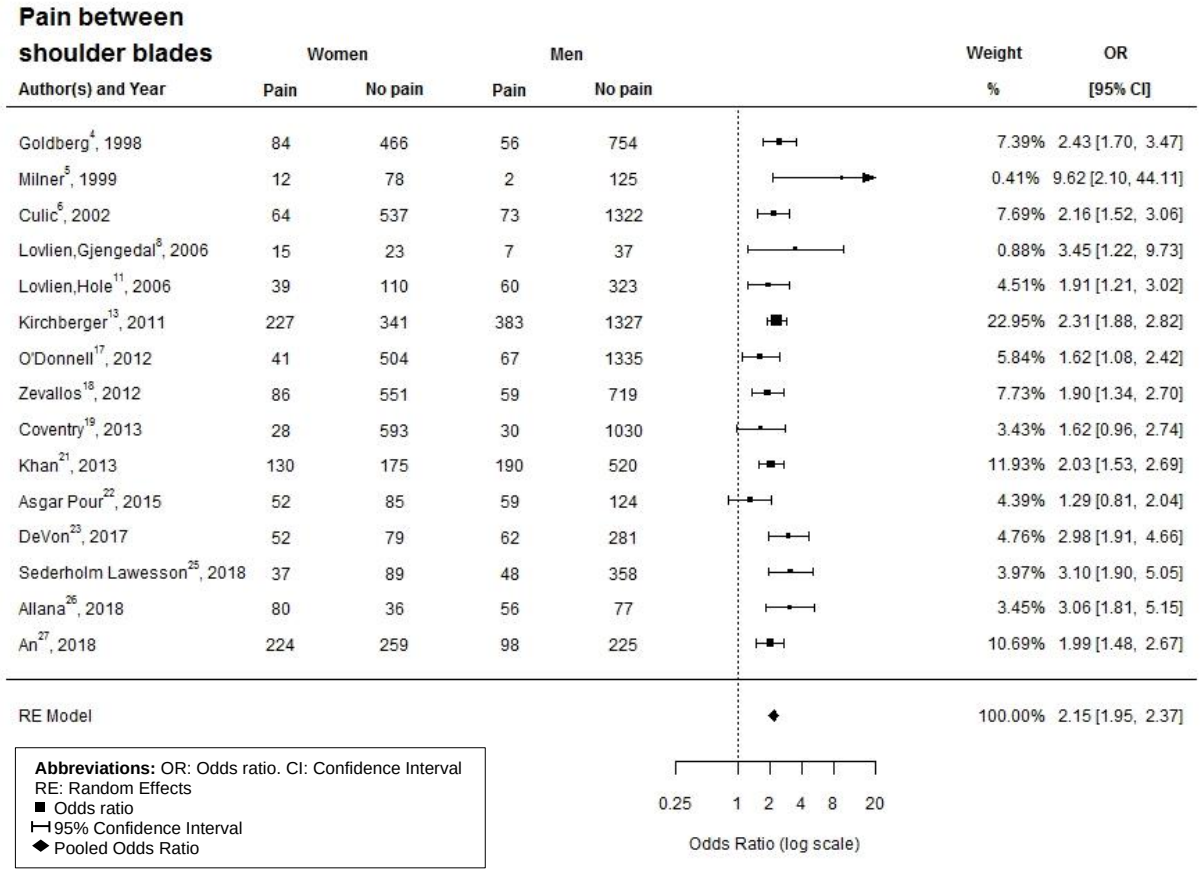


Figure S22. Results of the aggregated meta-analysis for palpitations as a symptom of ACS in women relative to men summarised in a forest plot.

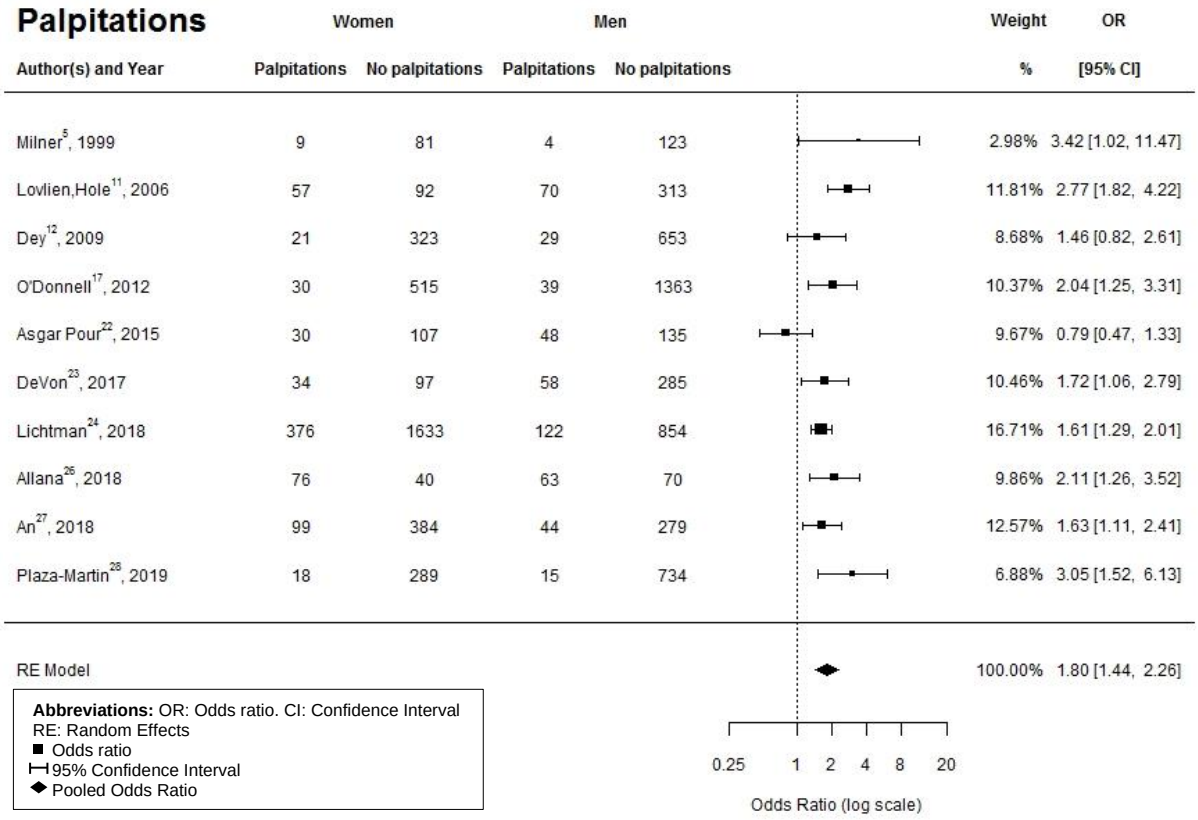


Figure S23. Results of the aggregated meta-analysis for right arm pain or right shoulder pain as a symptom of ACS in women relative to men summarised in a forest plot.

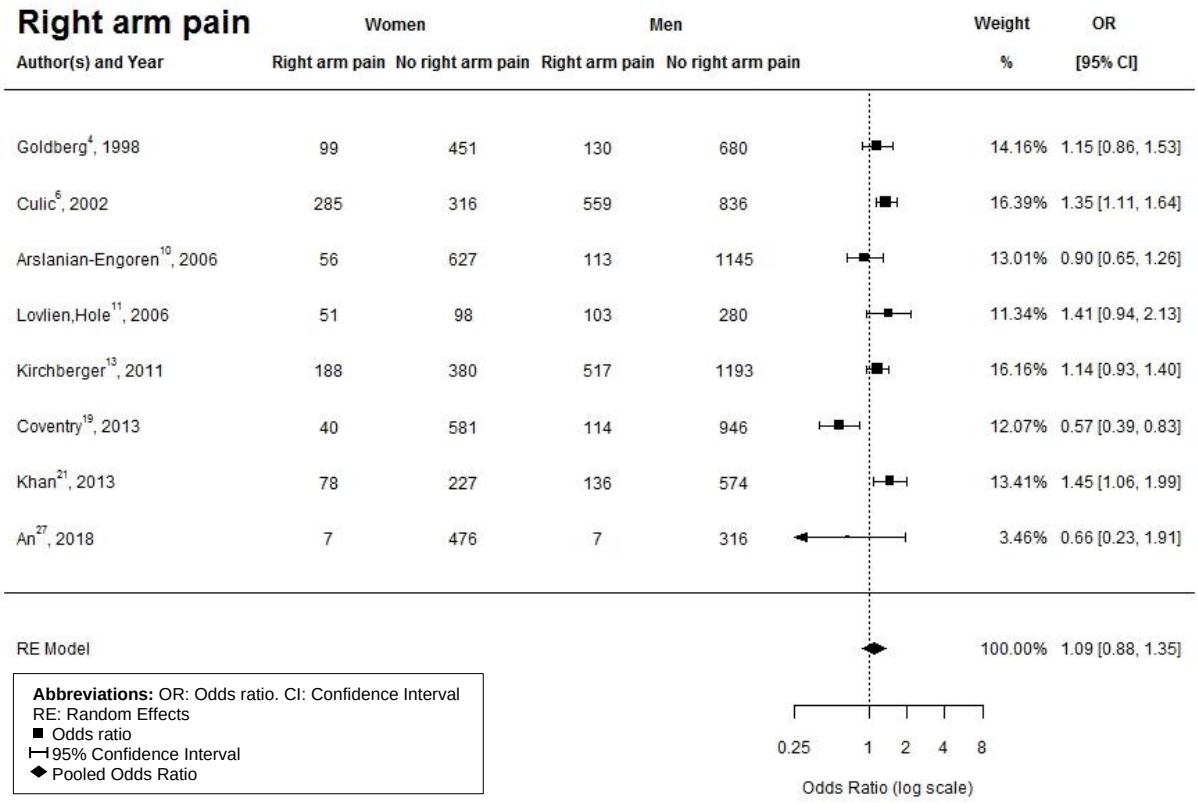


Figure S24. Results of the aggregated meta-analysis for shortness of breath as a symptom of ACS in women relative to men summarised in a forest plot.

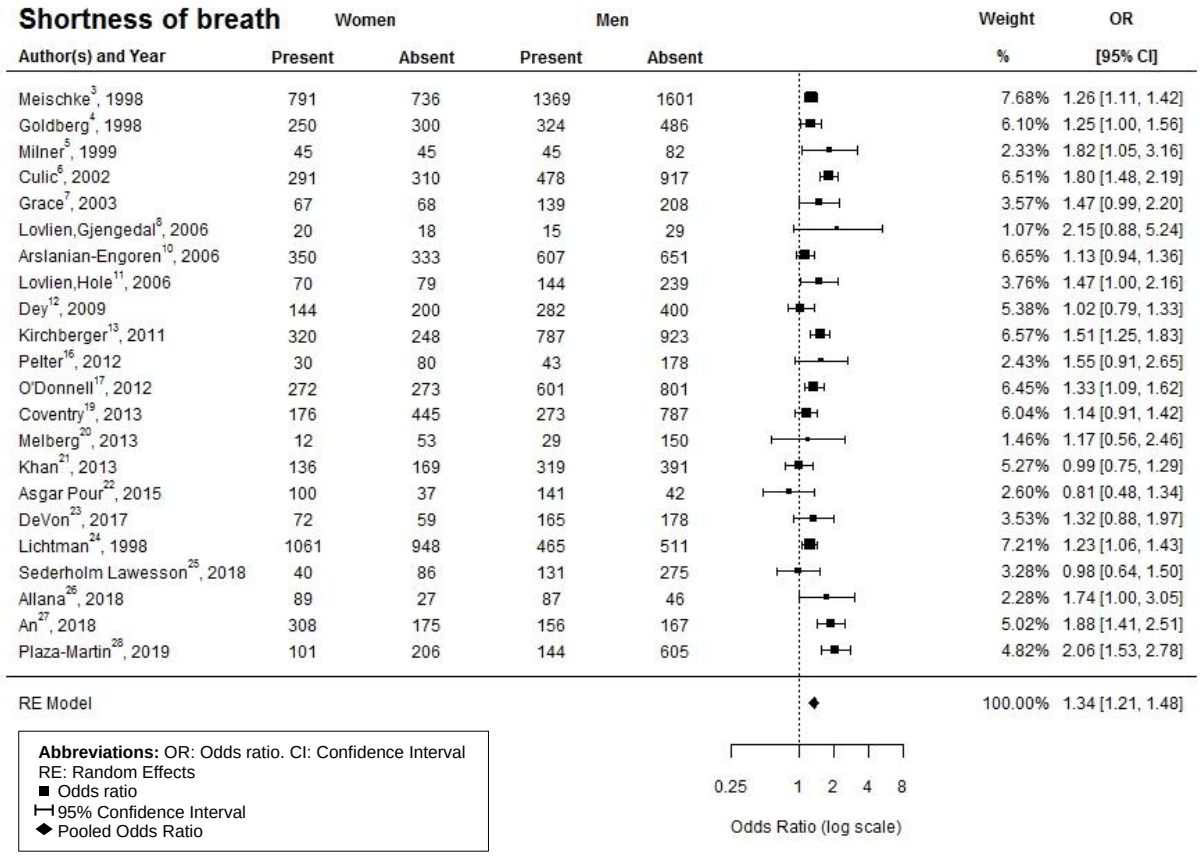


Figure S25. Results of the aggregated meta-analysis for stomach or epigastric pain as a symptom of ACS in women relative to men summarised in a forest plot.

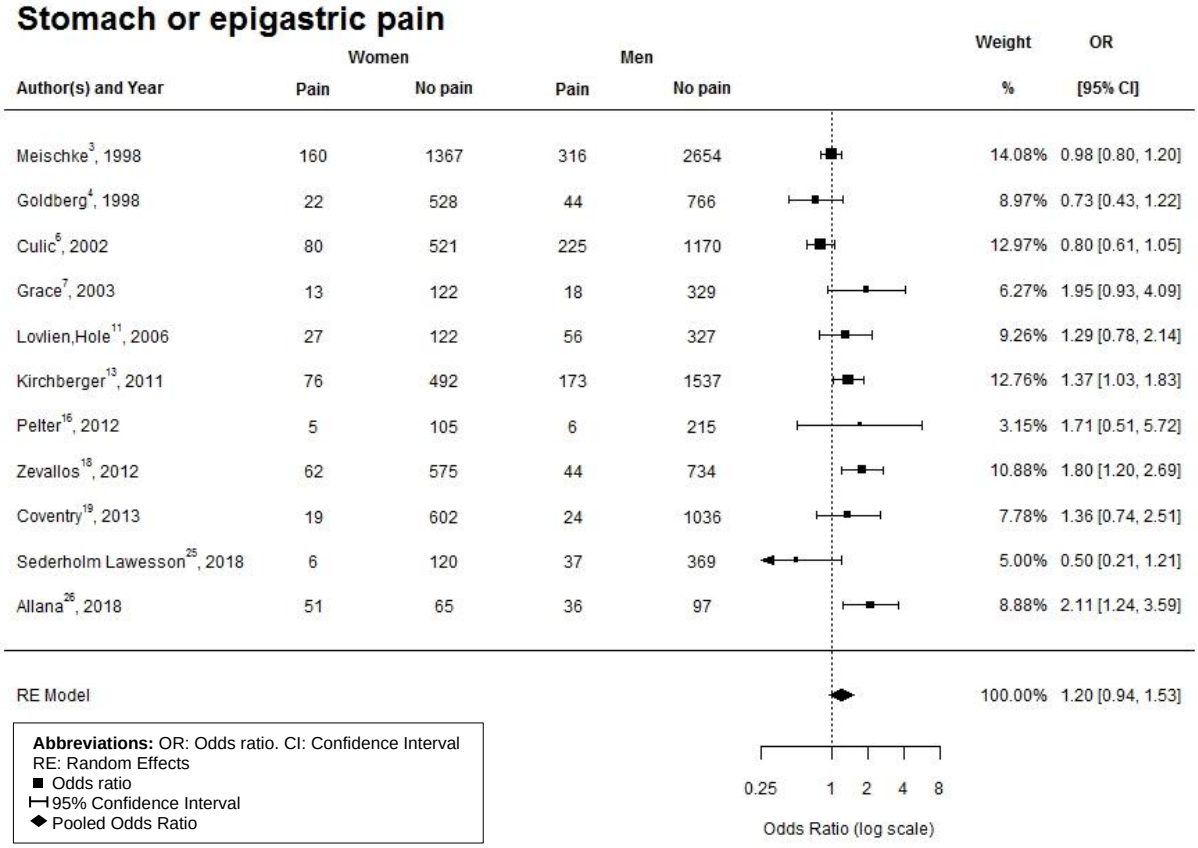


Figure S26. Results of the aggregated meta-analysis for syncope as a symptom of ACS in women relative to men summarised in a forest plot.

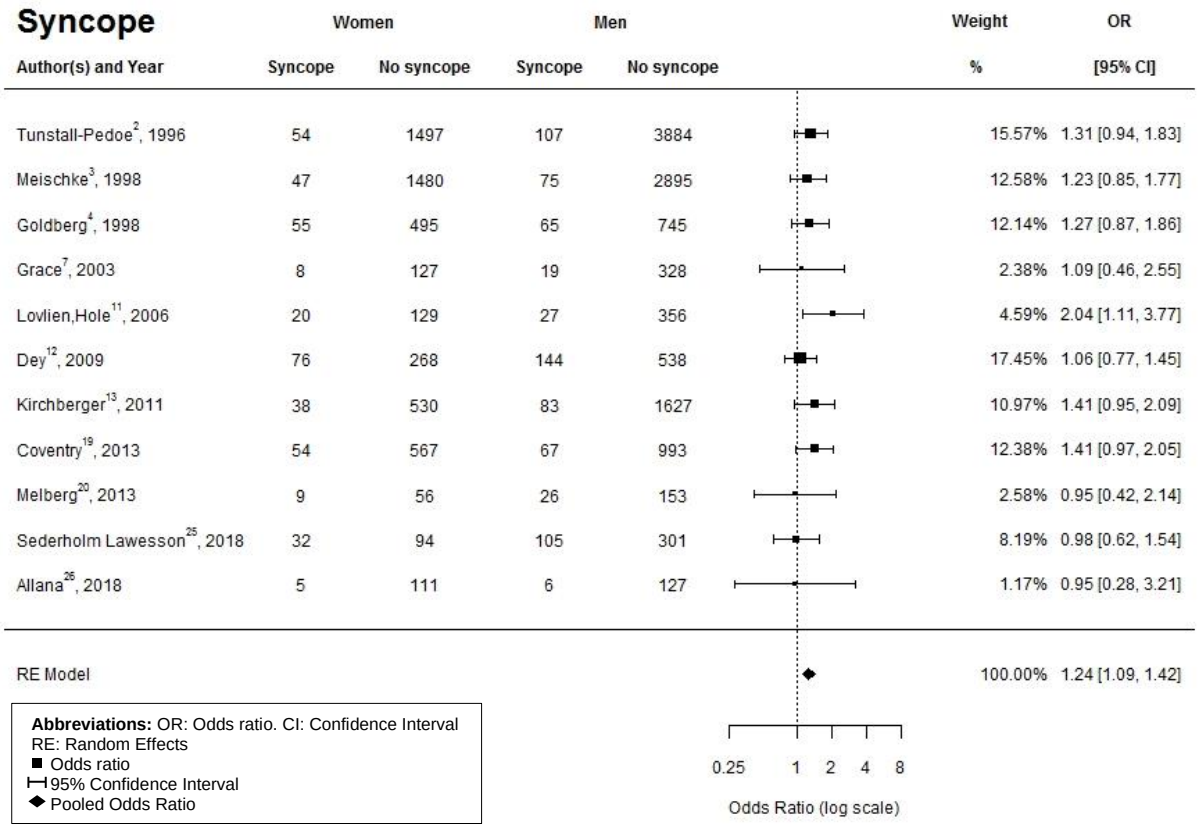


Figure S27. Results of the cumulative meta-analysis for chest pain as a symptom of ACS in women relative to men summarised in a forest plot.

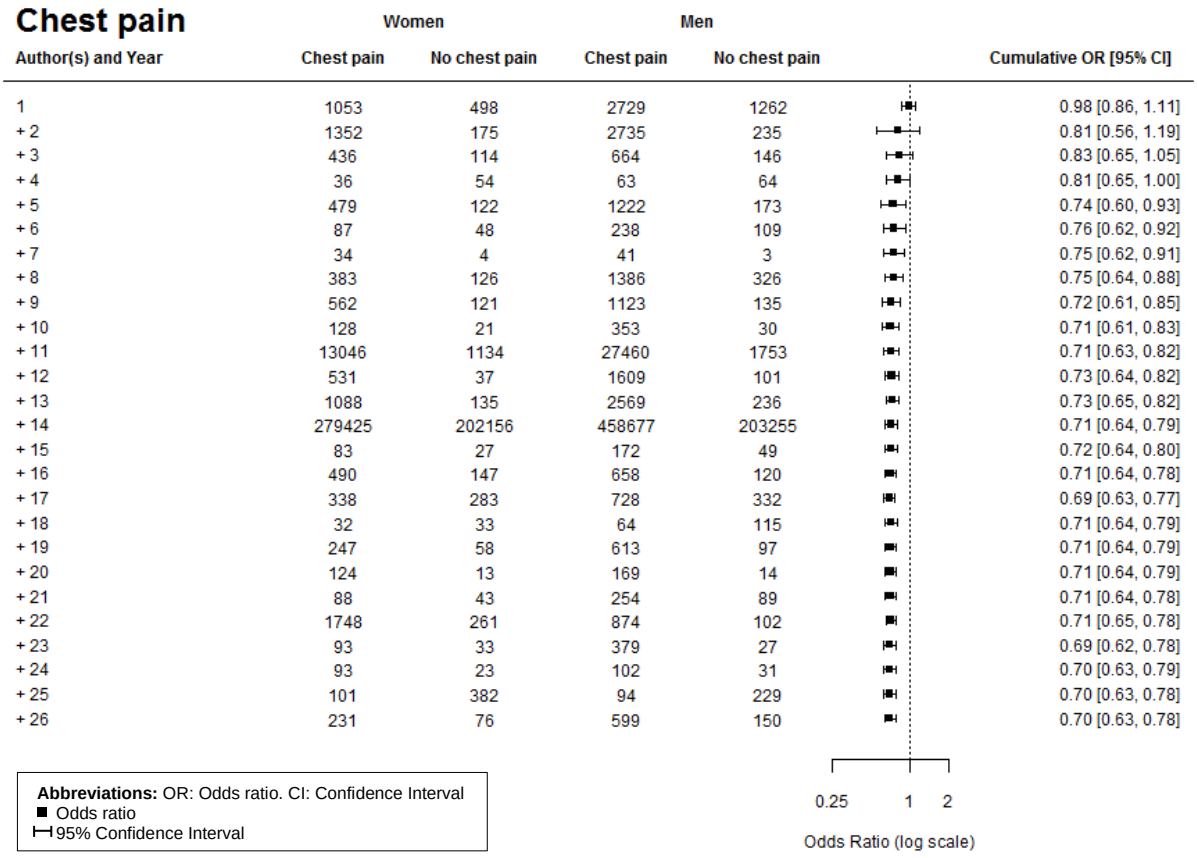


Figure S28. Results of the cumulative meta-analysis for diaphoresis as a symptom of ACS in women relative to men summarised in a forest plot.

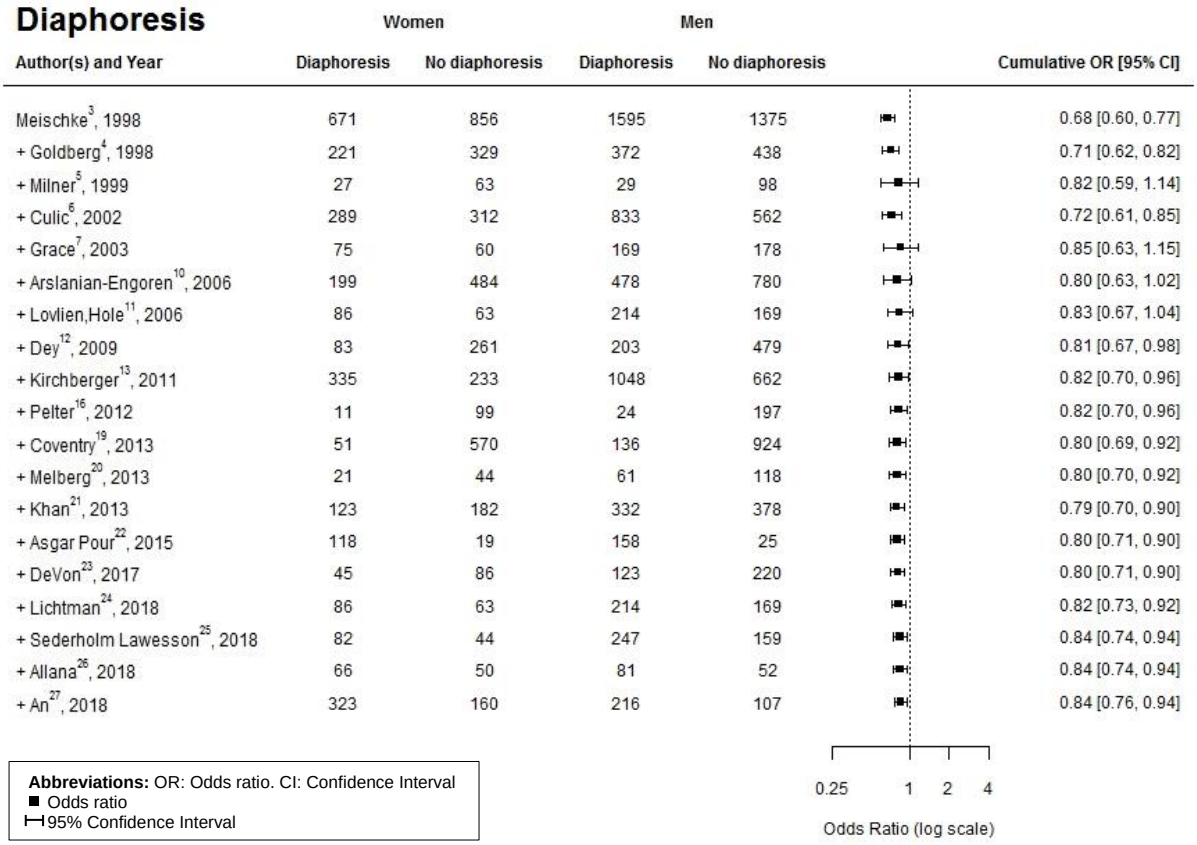


Figure S29. Results of the cumulative meta-analysis for dizziness or light-headedness as a symptom of ACS in women relative to men summarised in a forest plot.

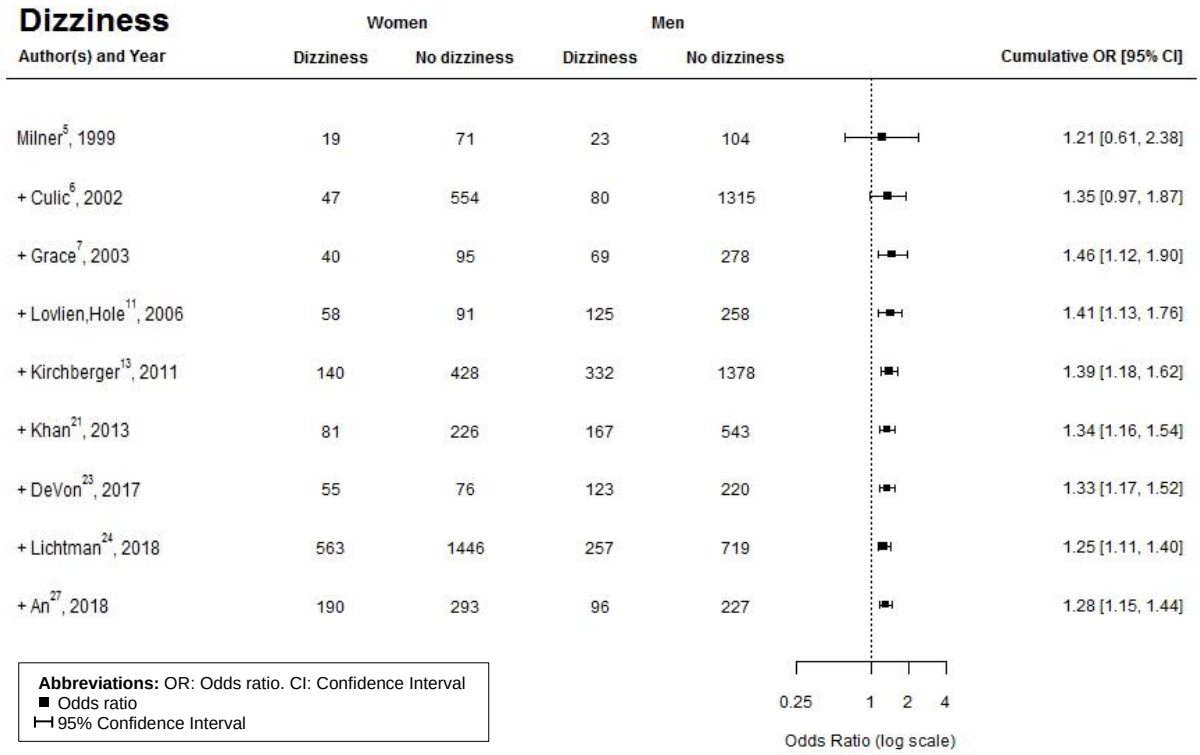


Figure S30. Results of the cumulative meta-analysis for fatigue as a symptom of ACS in women relative to men summarised in a forest plot.

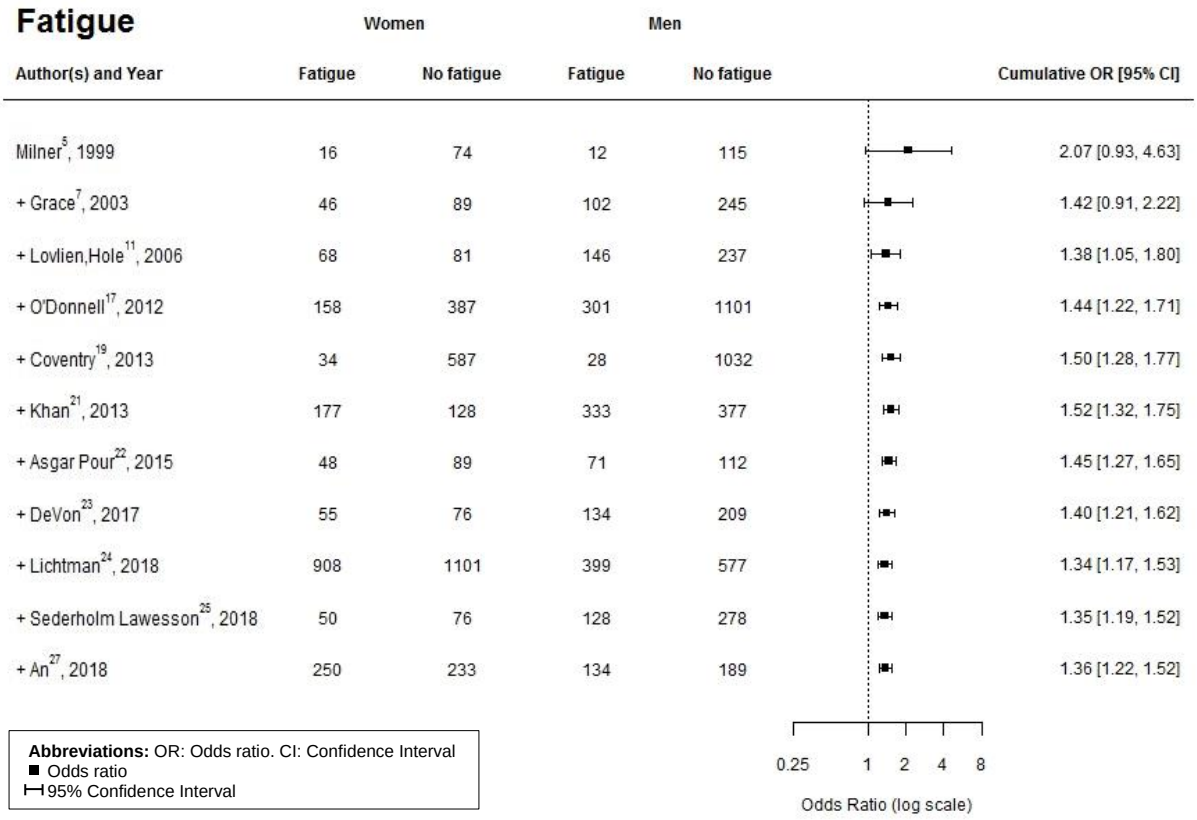


Figure S31. Results of the cumulative meta-analysis for indigestion as a symptom of ACS in women relative to men summarised in a forest plot.

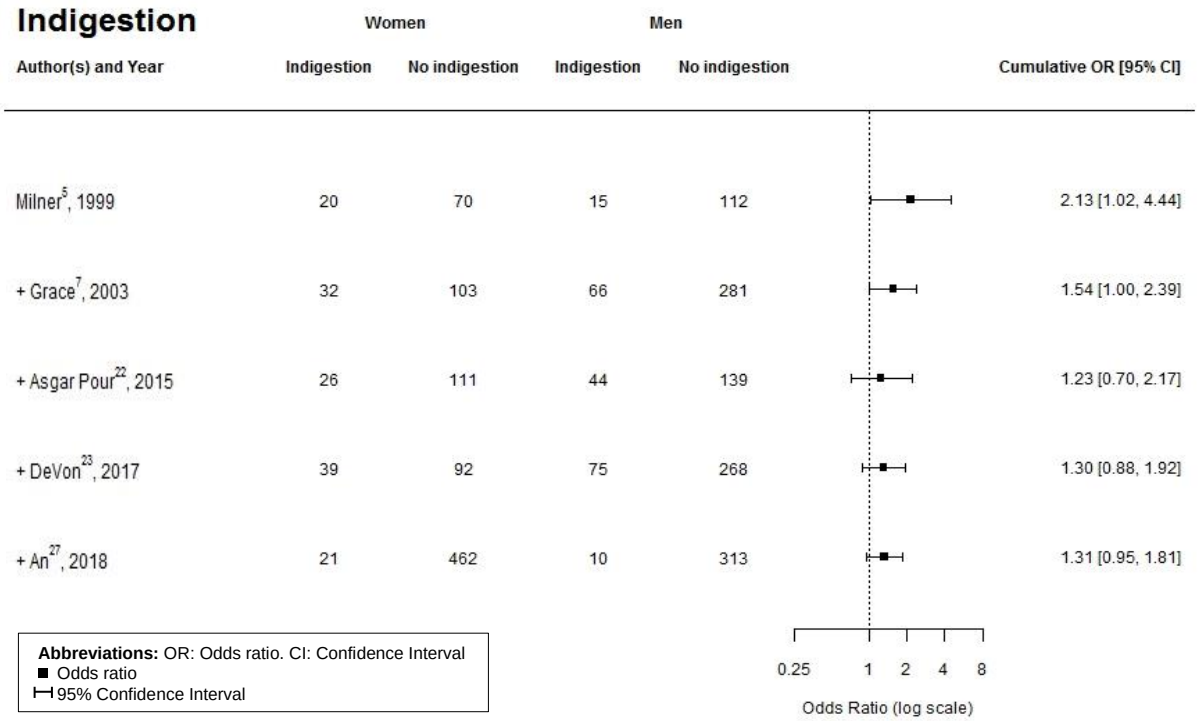


Figure S32. Results of the cumulative meta-analysis for jaw pain as a symptom of ACS in women relative to men summarised in a forest plot.

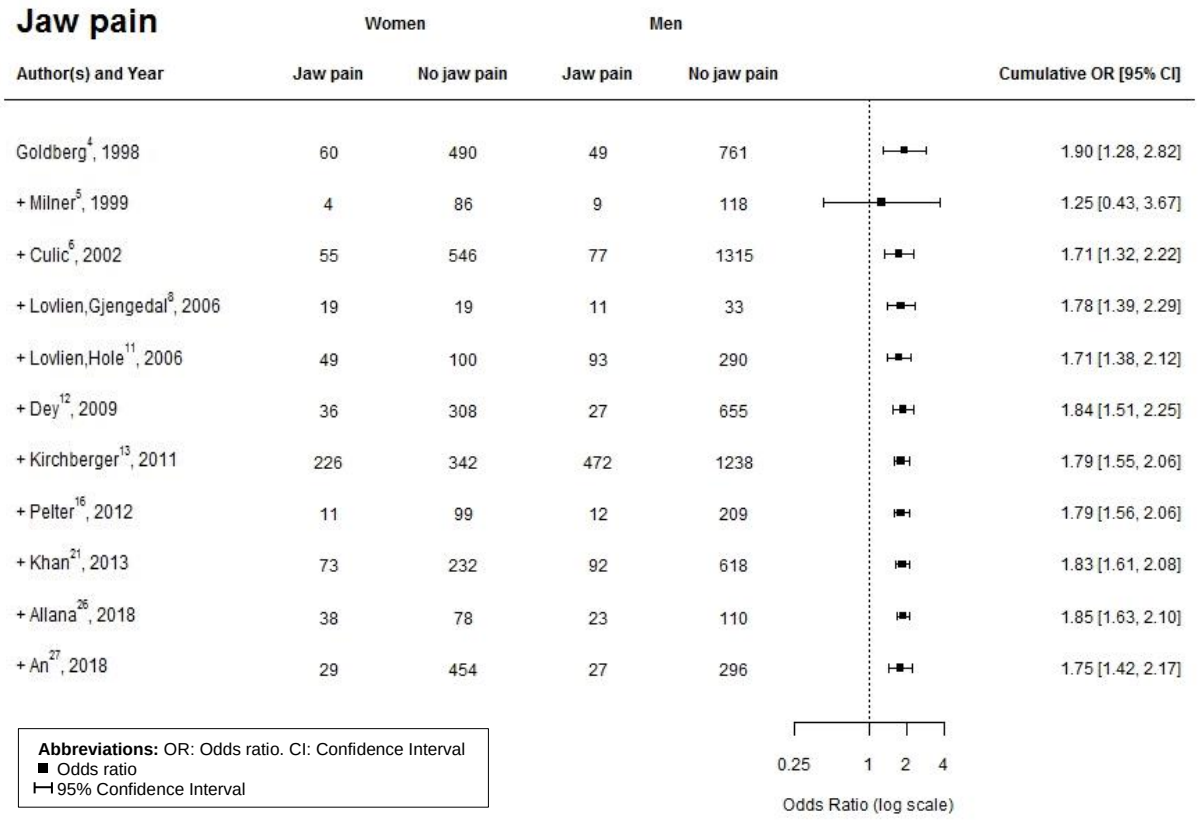


Figure S33. Results of the cumulative meta-analysis for left arm pain or left shoulder pain as a symptom of ACS in women relative to men summarised in a forest plot.

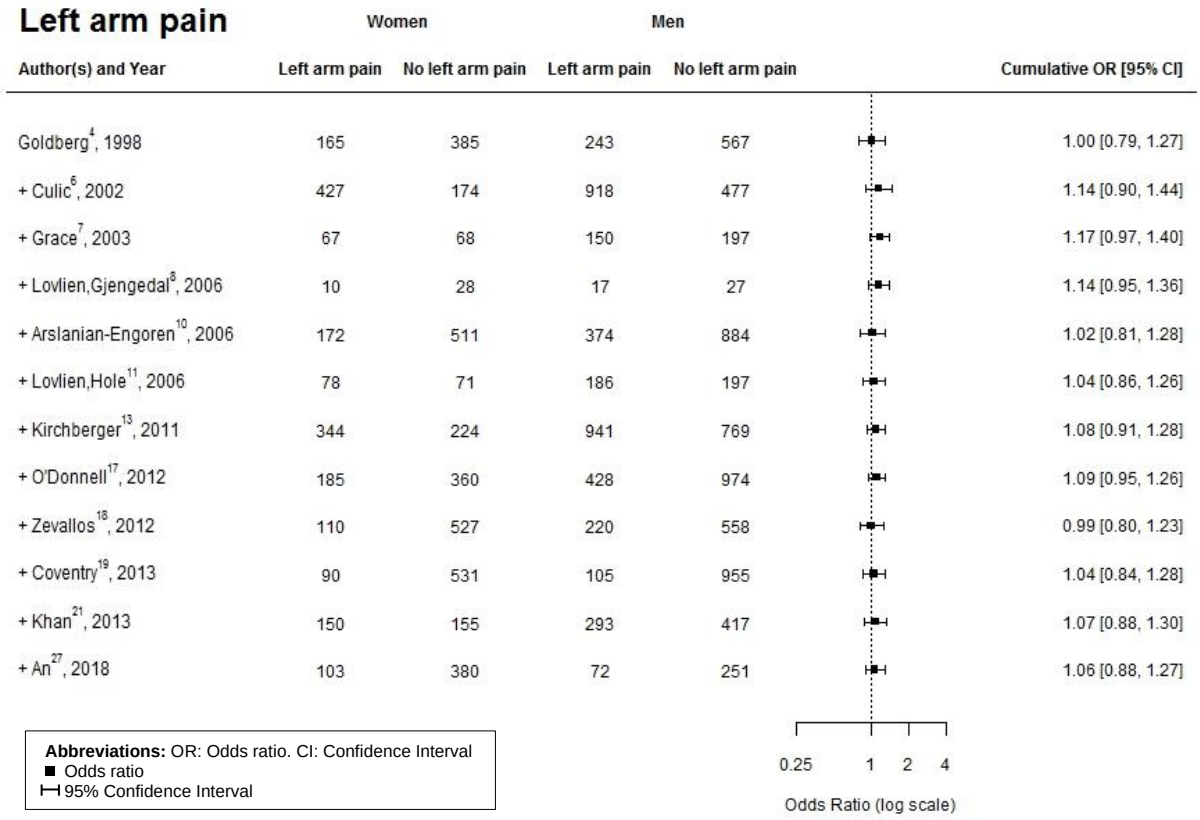


Figure S34. Results of the cumulative meta-analysis for nausea or vomiting as a symptom of ACS in women relative to men summarised in a forest plot.

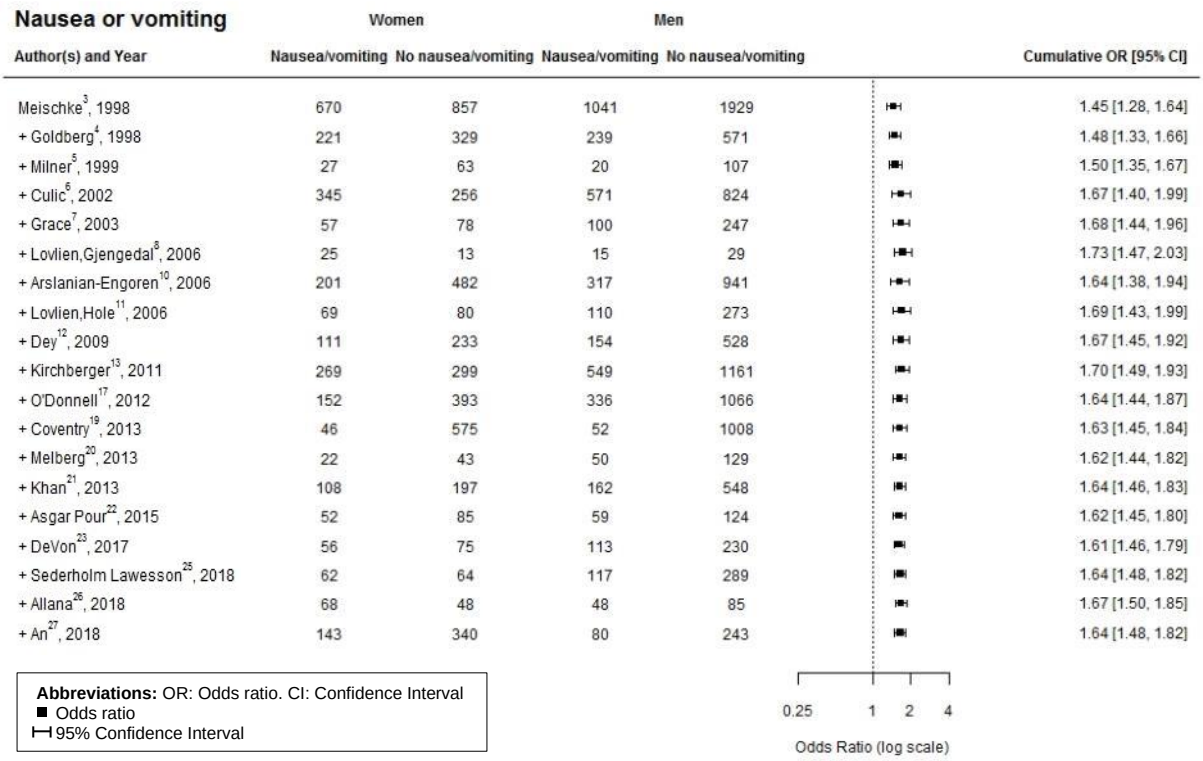


Figure S35. Results of the cumulative meta-analysis for neck pain as a symptom of ACS in women relative to men summarised in a forest plot.

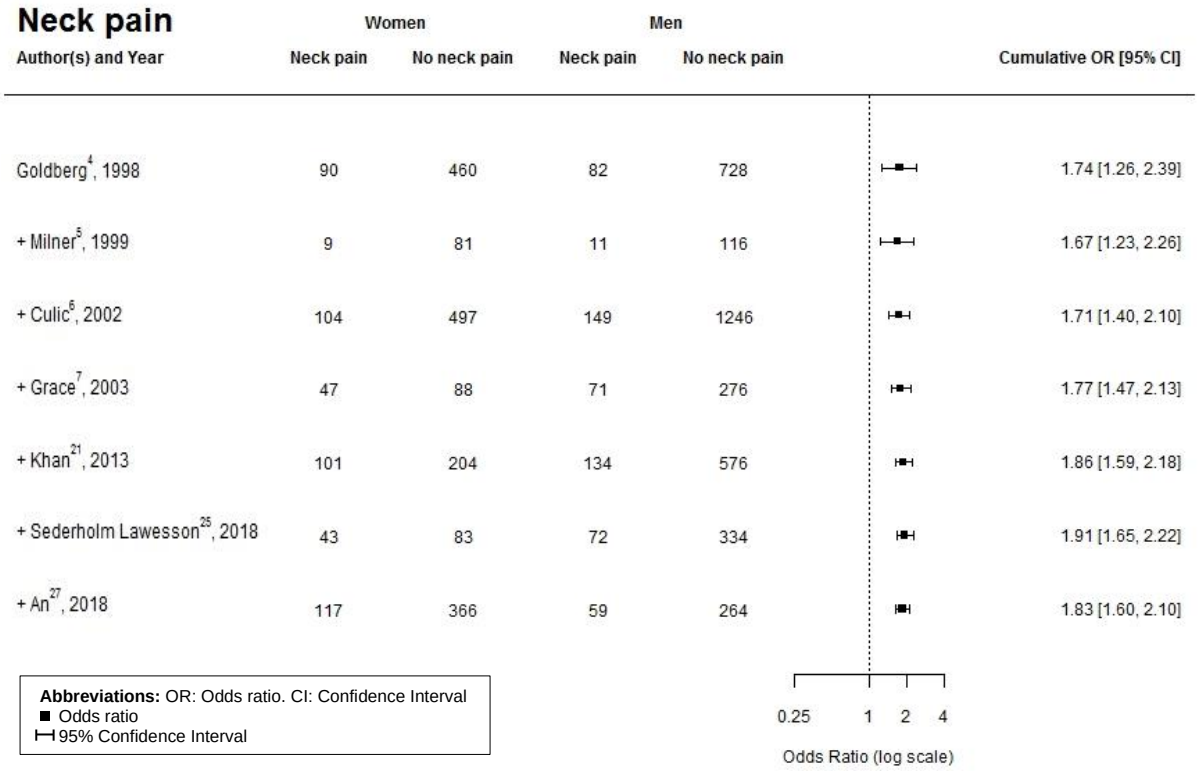


Figure S36. Results of the cumulative meta-analysis for pain between shoulder blades as a symptom of ACS in women relative to men summarised in a forest plot.

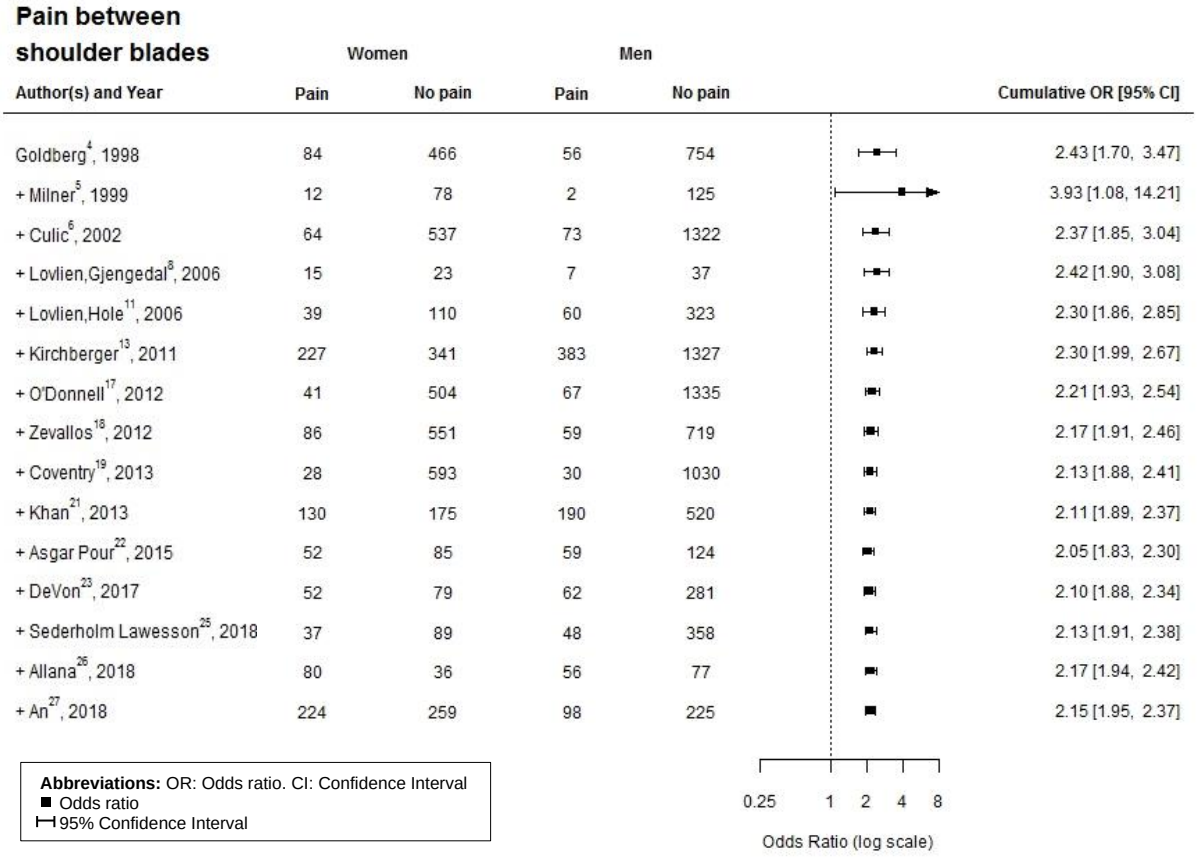


Figure S37. Results of the cumulative meta-analysis for palpitations as a symptom of ACS in women relative to men summarised in a forest plot.

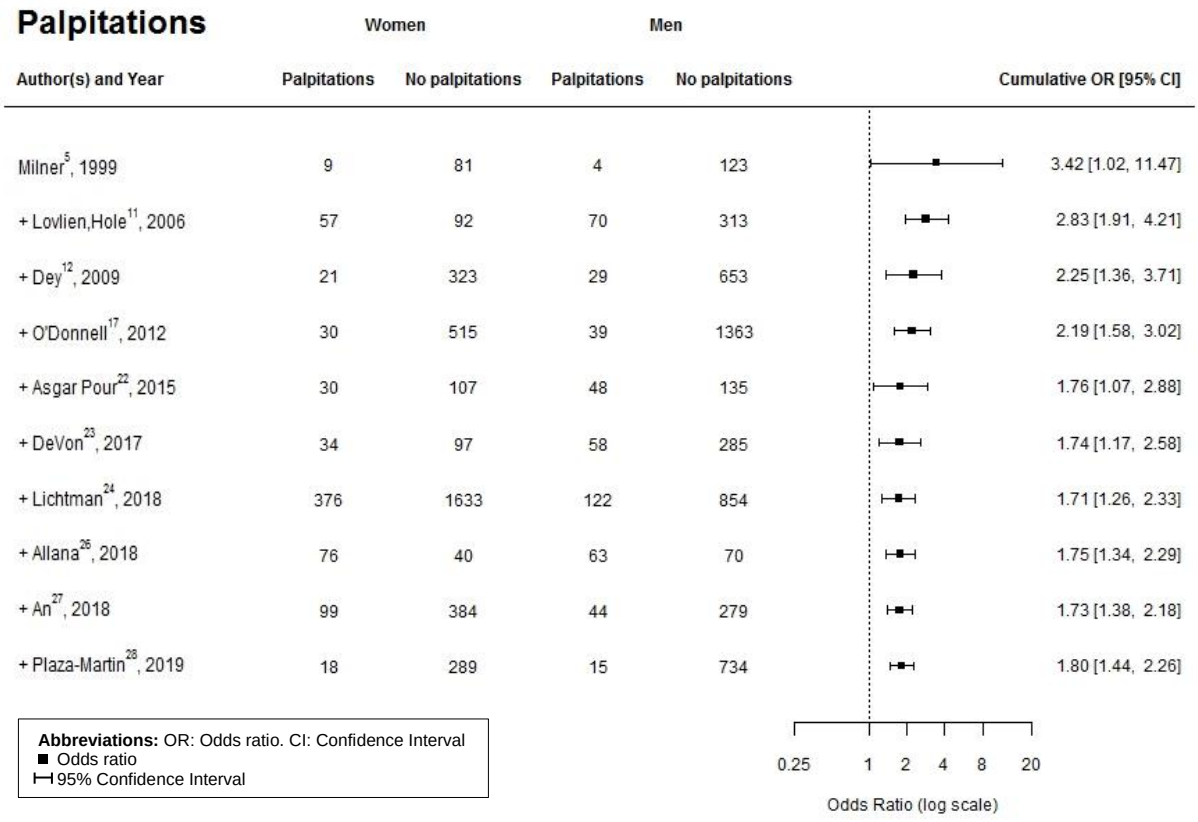


Figure S38. Results of the cumulative meta-analysis for right arm pain or right shoulder pain as a symptom of ACS in women relative to men summarised in a forest plot.

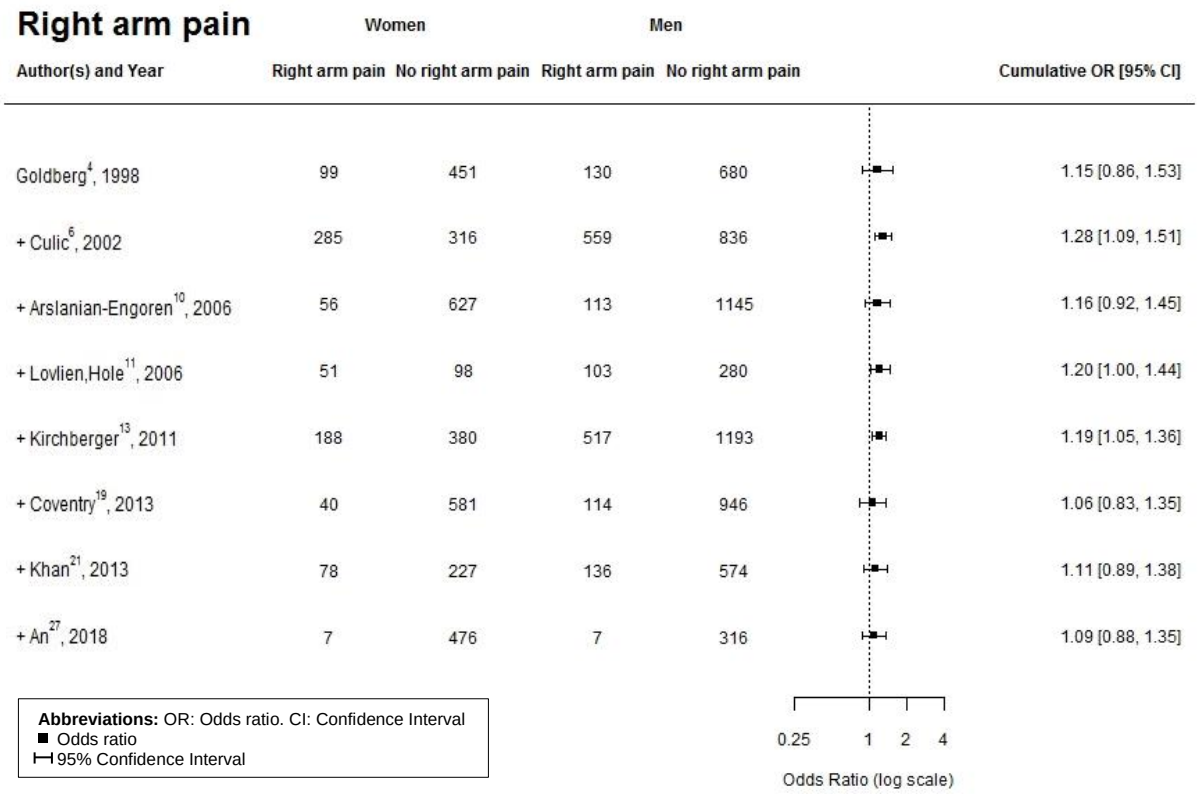


Figure S39. Results of the cumulative meta-analysis for shortness of breath as a symptom of ACS in women relative to men summarised in a forest plot.

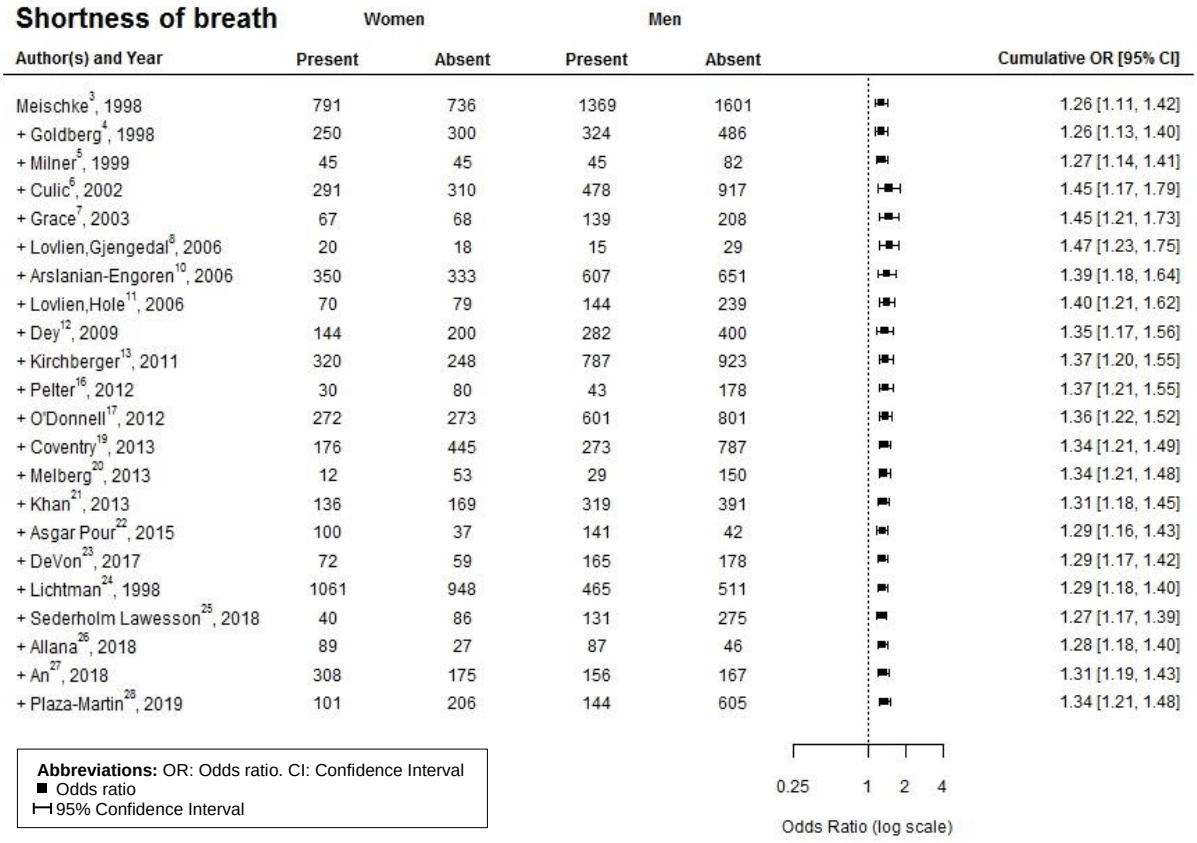


Figure S40. Results of the cumulative meta-analysis for stomach and epigastric pain as a symptom of ACS in women relative to men summarised in a forest plot.

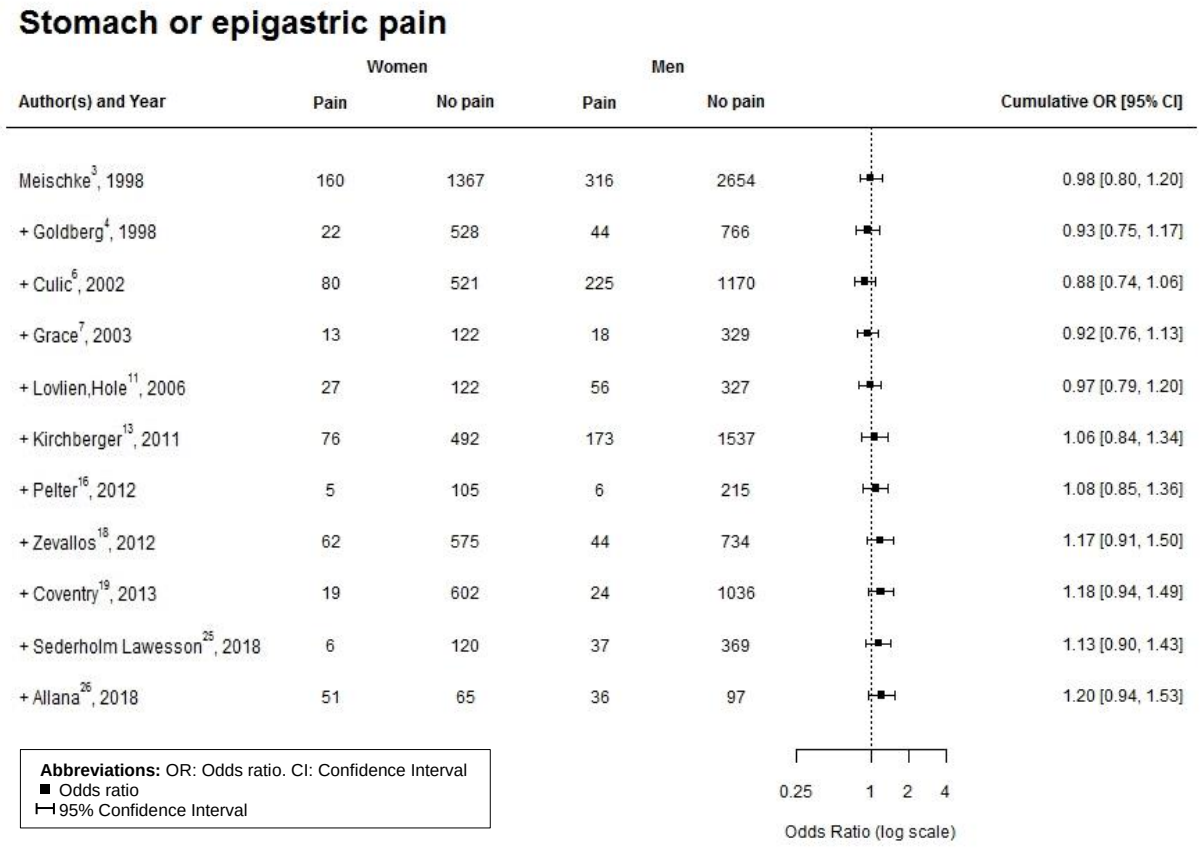
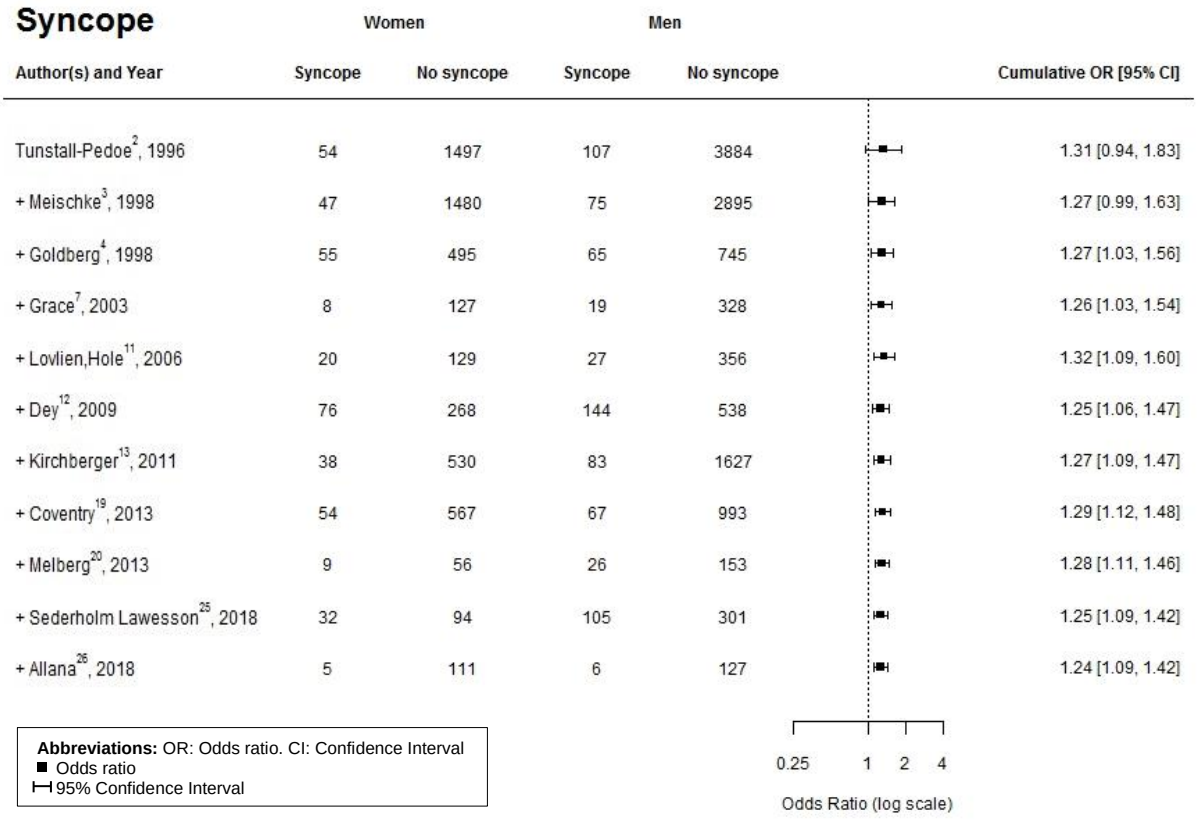


Figure S41. Results of the cumulative meta-analysis for syncope as a symptom of ACS in women relative to men summarised in a forest plot.



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