

## 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% Cl 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% Cl, 1.95–2.37), nausea or vomiting (OR 1.64; 95% Cl, 1.48–1.82) and shortness of breath (OR 1.34; 95% Cl, 1.21–1.48). Women had lower odds of presenting with chest pain (OR 0.70; 95% Cl, 0.63–0.78) and diaphoresis (OR 0.84; 95% Cl, 0.76–0.94). Both sexes presented most often with chest pain (pooled prevalences, men 79%; 95% Cl, 72–85, pooled prevalences, women 74%; 95% Cl, 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

**I** schemic heart disease (IHD) is the world's leading cause of eath accounting for an estimated 9 million deaths in 2015.<sup>1,2</sup> 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.<sup>3</sup> In recent decades ACS mortality has decreased, because of advancements in treatment, lifestyle changes, and a focus on primary prevention, but rates remain high.<sup>1,4</sup>

Effective treatment of ACS is available with reperfusion therapies, preferably with percutaneous coronary intervention and if not available thrombolysis or coronary artery bypass grafting.<sup>3</sup> The efficacy of ACS treatment depends on timely initiation of the required treatment to minimize myocardial damage.<sup>3</sup> 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.<sup>5</sup> Despite several awareness campaigns, referral delay in women with ACS has persisted over time.<sup>6,7</sup>

Previous studies, but not all, have reported that women with ACS experience different symptoms compared with men with ACS.<sup>8–10</sup> Additionally, other studies emphasize the overlap in symptoms between men and women with ACS.<sup>11</sup> 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.<sup>12,13</sup> Recent studies have attempted to solve these issues, with the development of standardized data collection surveys.<sup>11,14</sup>

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.<sup>12,15</sup> 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.<sup>16</sup> 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.<sup>17</sup> 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,<sup>18</sup> 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. Sexspecific 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  $l^2$  statistics.  $l^2$  values <40% were considered to represent low heterogeneity, 30% to 60% moderate heterogeneity, 50% to 90% substantial heterogeneity and >75% as considerable heterogeneity.<sup>19</sup> To explore possible heterogeneity by age, random effects meta-regression was performed for symptoms reported by  $\geq 10$  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  $\geq$ 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 titleabstract, 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<sup>20–23</sup> 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.<sup>3,8–10,18,24–45</sup> 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; Cl, 0.63–0.78,  $l^2$ =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<sup>2</sup>=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],  $l^2=0\%$ ). This OR remained virtually unchanged from the early 2000s and was similar for studies that provided adjusted results (1.89 [1.27–2.82],  $l^2=0\%$ ).

Adjustments	None	None	Age, medical history	Age, DM	Age, risk factors, cardiac enzyme level	None	None	None	Age	Age	None	Age, hypertension, DM, comorbidity	None	Age	None
Exclusion Criteria		<ul> <li>Missing symptom information</li> </ul>	<ul> <li>MI developed during surgery</li> </ul>		<ul> <li>Previous infarction Unable to answer questions</li> </ul>	<ul> <li>Too ill or confused to give informed consent</li> </ul>		<ul> <li>Presence or absence of chest pain unknown</li> </ul>	- Non-ACS presentation	- Hospitalized patients	<ul> <li>Non-cardiovascular cause for ACS (trauma, surgery)</li> </ul>		<ul> <li>Previous MI</li> <li>Patients who were dead by the time they reached medical help</li> </ul>	<ul> <li>Secondary diagnosis of MI</li> <li>Patients with missing information on age, sex or symptoms</li> </ul>	<ul> <li>Serious comorbidity</li> <li>-Untreated malignancy or neurologic disorder</li> <li>-Major hearing loss</li> </ul>
Inclusion Criteria	-25 to 64 years old	<ul> <li>Clinically stable</li> </ul>		<ul> <li>Diagnosis of ACI or MI</li> <li>&gt;45 years old</li> <li>-18-44 years included with DM or 2 or more cardiac risk factors</li> </ul>	- First-time MI	- 18 years or older	<ul> <li>Patients up to age 65</li> <li>First time MI</li> </ul>		<ul> <li>Admitted to hospital alive</li> </ul>	<ul> <li>2 weeks after hospital discharge</li> <li>First time MI</li> <li>-&lt;76 years old</li> </ul>	Chest pain No chest pain	<ul> <li>Age 25-74 years</li> <li>Survived &gt;24 hours with MI</li> <li>First time MI</li> </ul>	– Age 25–74 years		Prior diagnosis of coronary artery disease
Mean Age Men/ Women, y	55.5/57.0	Median: 64/73	64.7/72.1	63.0/68.8	57/63	59.2/66.3	Divided into age groups	Divided into absence/presence of chest pain	61/67	58.5/61.2	Divided into age groups	59.2/62.9	Divided into age groups	Divided into age groups	Divided into age groups
Sample Size (Men/Women)	5541 (3991/1551)	4497 (2970/1527)	1360 (810/550)	217 (127/90)	1996 (1395/601)	482 (347/135)	82 (44/38)	2221 (1712/509)	1941 (1238/683)	533 (384/149)	a. 43 393 (29 213/ 14 180) b. 1026 (682/344)	2278 (1710/568)	4028 (2805/1223)	1 143 513 (661 932/ 481 581)	331 (211/110)
Study, y	1985–1991	1991–1993	1986–1988	1995–1997	1990–1995	Not described	March-October 1999	2001–2003	1999- 2004	2003-2004	1999–2006	2001–2006	2000-2006	1994–2006	2001-2004
Establishment of ACS	ECG changes and cardiac enzyme levels exceeding twice the upper limit of normal	ECG changes or enzyme elevation	≥2 of the following: clinical history of chest pain, elevated serum levels of CK or LDH and ECG changes	ACI: ECG changes and lack of cardiac enzyme elevation MI: ECG changes and cardiac enzyme elevation	≥2 of the following: ECG charges suggestive of MI, symptoms indicating MI, increase in 1 or more cardiac enzymes	Diagnosis of MI at CCU	Diagnosis of MI at CCU	Diagnosis of MI in medical chart	≥2 of the following: ECG changes, increases in serum enzymes or documentation of coronary artery disease	Elevated cardiac troponin, ECG changes and the presence of clinically appropriate symptoms	Clinical history of ACS accompanied by at least 1 of the following: ECG changes, increase in biochemical markers or documented coronary artery disease	According to criteria of the ESC and American College of Cardiology	Typical chest pain and biomarkers. If only one of the 2 parameters was positive, ECG analysis was used.	Clinical presentation (ischemic symptoms) and elevated cardiac biomarker level, ECG evidence or autopsy evidence	Discharge diagnosis of ACS in medical record
Population	W	¥	ē	ACI or MI	W	¥	₽	W	ACS	¥	ACS	W	ē	¥	ACS
Data Collection	Medical records	Medical records	Medical records	Patient interview	Questionnaire	Patient survey	Questionnaire	Medical records	Medical records	Questionnaire	Medical records	Patient interview	Medical records	Medical records	Patient interview
Study Design	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional
Country	Scotland	United States	United States	United States	Croatia	Canada	Norway	Japan	United States	Norway	Multinational (14 countries)	Germany	Sweden	United States	Multinational (United States, Australia, New Zealand)
Study	Tunstall-Pedoe et al. 1996 <sup>18</sup>	Meischke et al, 1998 <sup>24</sup>	Goldberg et al, 1998 <sup>25</sup>	Milner et al, 1999 <sup>26</sup>	Culic et al, 2002 <sup>6</sup>	Grace et al, 2003 <sup>27</sup>	Løvlien, Schei and Gjengedal, 2006 <sup>28</sup>	Hirakawa et al, 2006 <sup>29</sup>	Arslanian-Engoren et al, 2006 <sup>30</sup>	Løvlien, Schei and Hole, 2006 <sup>9</sup>	Dey et al, 2008 <sup>31</sup>	Kirchberger et al, 2011 <sup>32</sup>	Angerud et al, 2011 <sup>33</sup>	Canto et al, 2012 <sup>34</sup>	Petter et al, 2012 <sup>35</sup>

Continued

Table 1. Baseline Characteristics of the Included Studies

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Adjustments	Age, BMI, DM, comorbidity, smoking	None	Age	None	None	None	Age, African American race, comorbidity	None	Age, level of education, smoking status, comorbidity	None	Age, DM, smoking	None
Exclusion Criteria	<ul> <li>Cognitive impairment</li> </ul>	<ul> <li>MI secondary to interventional procedure or surgery</li> </ul>	<ul> <li>Arrival by private transport or helicopter</li> </ul>			– History of stroke, neurologic disorders, COPD, pneurnonia or pulmonary embolism	<ul> <li>Cognitive impairment</li> </ul>			<ul> <li>Cognitive or mental impairment</li> </ul>	<ul> <li>Cognitive or mental impairment</li> </ul>	<ul> <li>Type 2 or type 4 MI</li> <li>Evident secondary cause of myocardial ischemia</li> </ul>
Inclusion Criteria	<ul> <li>Admitted through ED</li> <li>Clinically stable</li> </ul>	-Hispanic residents First time MI	<ul> <li>Arrival at ED by ambulance</li> </ul>	<ul> <li>First contact with healthcare system by 113 phone call</li> </ul>	- 55 years or younger - Admitted to CCU, ICU or cardiology ward	<ul> <li>Admitted with at least 1 typical symptom(chest pain/ pressure/heaviness/fightness, disploresis, dyspnea, arm pain) or atypical symptom (pablatidon, vomitting, dizziness, fatigue, indigestion)</li> </ul>	<ul> <li>Admitted through ED</li> </ul>	<ul> <li>Between 18 and 55 years old</li> <li>-&lt;24 hours since event</li> <li>-2:1 female enrollment</li> </ul>	<ul> <li>Patients with STEMI</li> <li>Clinically stable</li> <li>&lt;24 hours since event</li> </ul>	<ul> <li>Clinically stable</li> <li>&lt;72 hours since event</li> </ul>	-First ACS event	- Above 18 years of age
Mean Age Men/ Women, y	Divided into age groups	63.2/68.6	69.1/77.6	Median: 62/67	Median: 49.0/49.0	60.92/63.29	59.5/61.3	47.2/47.1	64.3/69.7	56.5/55.8	59.2/63.9	64.0/71.0
Sample Size (Men/Women)	1947 (1402/545)	1415 (778/637)	1681 (1060/621)	244 (179/65)	1015 (710/305)	320 (183/137)	474 (343/131)	2985 (976/2009)	532 (406/126)	249 (133/116)	806 (323/483)	1056 (749/307)
Study, y	2007–2009	2007	January 2008- October 2009	2004-2007	2009-2012	Not mentioned	2011-2014	2008-2012	2012-2014	3-mo period	2013-2014	January-August 2017
Establishment of ACS	Discharge diagnosis of ACS	Clinical history suggestive of AM, serum enzyme elevations, and serial ECG findings during hospitalization.	As defined by ICD-10	Documented ST elevation on presenting ECG, ischemic symptoms and a typical rise in serum troponin levels	<ol> <li>Signs and symptoms</li> <li>One of the following: a) ECG changes or b) increase in cardiac enzyme levels (tropoint   or T, or CK-MB, or CPN)</li> </ol>	ECG changes (ST-segment and T-wave changes) and cardiac erzyme (CK-MB)	Evidence of ischemia on ECG or elevated troponin level	<ol> <li>Increased cardiac biomarker levels</li> <li>Symptoms of ischemia or ECG changes</li> </ol>	ST elevation on ECG and diagnosis of acute MI at discharge	Troponin values and ECG changes	As defined by ICD-10	According to ESC guidelines
Population	ACS	¥	Ē	STEMI	ACS	ACS	ACS	W	STEMI	ACS	ACS	ACS
Data Collection	ACS response to symptoms index	Medical records	Voice recordings of emergency telephone calls	Voice recordings of emergency telephone calls	McSweeney symptom survey	ACS symptom checklist	ACS symptom checklist	Patient interview	Questionnaire	Response to Symptoms Questionnaire + interview	McSweeney symptom survey + interview	Medical record
Study Design	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional
Country	Ireland	Puerto Rico	Australia	Norway	Multinational (Canada, United States, Switzerland)	Itan	United States	United States	Sweden	Pakistan	China	Spain
Study	0'Donnell et al, $2012^{36}$	Zevallos et al, 2012 <sup>37</sup>	Coventry et al, 2013 <sup>38</sup>	Melberg et al, 2013 <sup>39</sup>	Khan et al, 2013 <sup>40</sup>	Asgar Pour et al, 2015 <sup>41</sup>	DeVon et al, 2017 <sup>42</sup>	Lichtman et al, 2018 <sup>43</sup>	Sederholm Lawesson et al, 2018 <sup>10</sup>	Allana et al, 2018 <sup>44</sup>	An et al, 2018 <sup>3</sup>	Plaza-Martin et al, 2019 <sup>45</sup>

www inucates acute coronary synorome; AU, 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; MI, 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.

#### Neck pain

Women with ACS had higher odds of presenting with neck pain (1.83 [1.60–2.10],  $l^2=0\%$ ) and this remained in studies that provided adjusted results (1.71 [1.00–2.93],  $l^2=0\%$ ). 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],  $l^2=56\%$ ), 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],  $l^2=0\%$ ).

#### 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],  $l^2=52\%$ ), and this remained in studies that provided adjusted results (1.63 [1.21–2.19],  $l^2=0\%$ ). 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],  $l^2=63\%$ ). This OR has changed minimally since 2000 and was similar for studies that provided adjusted results (1.22 [1.01–1.46],  $l^2=0\%$ ).

#### 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],  $l^2=0\%$ ).

#### Dizziness or light-headedness

Women had higher odds of presenting with dizziness (1.28 [1.15–1.44],  $l^2=17\%$ ), 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],  $l^2=0\%$ ).

#### Syncope

Women had higher odds of presenting with syncope (1.24 [1.09–1.42],  $l^2=0\%$ ), 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],  $l^2=0\%$ ).

#### 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],  $l^2=0\%$ ).

Symptom	Number of stu	idies Crude	OR [95% CI]	Number of studies	Adjusted	OR [95% CI]
Pain between shoul	der blades 15	H	2.15 [1.95, 2.37]	9	<b>⊢_</b> ∎	1.89 [1.27, 2.82]
Neck pain	7	H <b>H</b> H	1.83 [1.60, 2.10]	4		1.71 [1.00, 2.93]
Palpitations	10	<b>⊢</b> ∎-4	1.80 [1.44, 2.26]	3	F	1.91 [0.91, 4.00]
Jaw pain	11	⊢∎→	1.75 [1.42, 2.17]	4		1.67 [1.01, 2.78]
Nausea or vomiting	19	Hel	1.64 [1.48, 1.82]	10	<b>⊢</b> ∎—1	1.63 [1.21, 2.19]
Fatigue	11	HeH	1.36 [1.22, 1.52]	6		1.34 [0.94, 1.90]
Shortness of breath	22	Heri	1.34 [1.21, 1.48]	11		1.22 [1.01, 1.46]
Indigestion	5	<b>⊨</b> I	1.31 [0.95, 1.81]	2		— 1.55 [0.63, 3.83]
Dizziness or lighthe	adedness 9	HEH	1.28 [1.15, 1.44]	5		1.41 [0.96, 2.07]
Syncope	11	H∎H	1.24 [1.09, 1.42]	5	<b>⊢</b> ∎−−−1	1.08 [0.75, 1.56]
Stomach or epigasti	ric pain 11		1.20 [0.94, 1.53]	6	<b>⊢</b> ∎→	0.96 [0.75, 1.23]
Right arm or should	er pain 8	⊢■→	1.09 [0.88, 1.35]	6		1.03 [0.77, 1.38]
Left arm or shoulder	r pain 12	⊢≡⊣	1.06 [0.88, 1.27]	8	<b>⊢</b> ∎−-1	1.13 [0.93, 1.38]
Diaphoresis	19	HeH	0.84 [0.76, 0.94]	8	-	0.75 [0.72, 0.78]
Chest pain	26	Heri	0.70 [0.63, 0.78]	8	HBH	0.67 [0.62, 0.73]
		0.5 1 2	4		0.5 1 2	4
<ul> <li>Odds ratio</li> </ul>		Odds ratio (log	scale)		Odds ratio (log scal	e)
95% CI	More common	in men $\longleftrightarrow$ Mo	ore common in women	More common in	men $\longleftrightarrow$ More co	mmon in women

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

Table	2.	Crude a	and A	djusted	Results	of the	Aggregated	Meta-Analy	vsis for	All S	ymptoms

	Analysis of Cru	ıde Odds Ratio		Analysis of Adjusted Odds Ratio			
Symptom	No. Studies	Pooled Odds Ratio (95% Cl)	l <sup>2</sup>	Stable Results From Cumulative Analysis (y)	No. Studies	Pooled Odds Ratio (95% CI)	l <sup>2</sup>
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],  $l^2=47\%$ ).

#### 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],  $l^2=7\%$ ).

#### Diaphoresis

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

#### 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,<sup>12,13,15</sup> 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<sup>14</sup> and 13-item Acute Coronary Syndrome checklist<sup>11</sup> 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.<sup>12,13,15</sup>

Over the past 2 decades, considerable research has been done on sex differences in the pathophysiology, symptom presentation, and outcomes of IHD.<sup>46</sup> Studies have shown that younger women with ACS present more often with type II ACS,<sup>47,48</sup> characterized by coronary artery spasms and vascular dysfunction,<sup>16,47,48</sup> whereas younger men present more often with type I ACS, caused by coronary artery obstruction.<sup>47,48</sup> In addition, at all ages, women with ACS less often have plaque ruptures and present more frequently with plaque erosions than men with ACS.<sup>47,49</sup> 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.<sup>46</sup> 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

Chest pain Author(s) and Year	Weight OR [95% CI]	Chest pain Author(s) and Year	Cumulative OR [95% CI]
Tunstall-Pedoe <sup>18</sup> , 1996       Image: Constraint of the second seco	$  \begin{array}{ccccccccccccccccccccccccccccccccccc$	Tunstall-Pedoe, 1996       Implementation         + Mileschke, 1998       Implementation         + Goldberg, 1998       Implementation         + Milner, 1999       Implementation         + Culic, 2002       Implementation         + Culic, 2002       Implementation         + Lovlien, Gjengedal, 2006       Implementation         + Hirakawa, 2006       Implementation         + Arskalnan-Engoren, 2006       Implementation         + Lovlien, Hole, 2006       Implementation         + Lovlien, Hole, 2006       Implementation         + Kirchberger, 2011       Implementation         + Kirchberger, 2011       Implementation         + Kana, 2012       Implementation         + Pelter, 2012       Implementation         + Petter, 2012       Implementation         + Zoventry, 2013       Implementation         + Korchberger, 2013       Implementation         + Korchberger, 2013       Implementation         + Coventry, 2013       Implementation         + Korchberger, 2013       Implementation         + Korchberger, 2015       Implementation         + Korchberger, 2015       Implementation         + Sederholm Lawesson, 2018       Implementation         + Allana, 2018	$\begin{array}{c} 0.98 & [0.86, 1.11]\\ 0.81 & [0.56, 1.19]\\ 0.83 & [0.65, 1.06]\\ 0.83 & [0.65, 1.06]\\ 0.74 & [0.60, 0.93]\\ 0.76 & [0.62, 0.92]\\ 0.75 & [0.64, 0.88]\\ 0.72 & [0.61, 0.85]\\ 0.71 & [0.61, 0.83]\\ 0.71 & [0.64, 0.82]\\ 0.73 & [0.64, 0.82]\\ 0.73 & [0.64, 0.82]\\ 0.71 & [0.64, 0.78]\\ 0.69 & [0.63, 0.77]\\ 0.71 & [0.64, 0.78]\\ 0.69 & [0.63, 0.77]\\ 0.71 & [0.64, 0.79]\\ 0.71 & [0.64, 0.79]\\ 0.71 & [0.64, 0.79]\\ 0.71 & [0.64, 0.78]\\ 0.71 & [0.64, 0.78]\\ 0.71 & [0.64, 0.78]\\ 0.71 & [0.64, 0.78]\\ 0.71 & [0.64, 0.78]\\ 0.71 & [0.64, 0.78]\\ 0.71 & [0.64, 0.78]\\ 0.71 & [0.64, 0.78]\\ 0.70 & [0.63, 0.78]\\ 0.$
Odds ratio     95% CI     More common in men ←→ Me	4 ore common in women	0.25 1 2 ⊖ Odds Ratio (log scale) More common in men ←→ Mor	e common in women

**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.<sup>34</sup> 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*	Sex	Acute coronary syndrome (MeSH)
Presentation	Sex factors (MeSH)	Acute coronary syndrome*
Presentations	Gender	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
Filte	r: sources as embase or embase + medline, publication types as article, review or ar	ticle in

press

## Cochrane:

-	+	#1	MeSH descriptor: [Acute Coronary Syndrome] explode all trees		MeSH <b>▼</b>	1629		
-	+	#2	(acute coronary syndrome*):ti,ab,kw OR (ACS):ti,ab,kw S					
-	+	#3	MeSH descriptor: [Myocardial Infarction] explode all trees					
-	+	#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 OR (MI)					
-	+	#5	MeSH descriptor: [Angina, Unstable] explode all trees					
-	+	#6	(unstable angina):ti,ab,kw OR (UA);ti,ab,kw S					
-	+	#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6					
-	+	#8	(symptom*):ti,ab,kw OR (presentation):ti,ab,kw OR (presentations):ti,ab,kw					
-	+	#9	MeSH descriptor: [Sex] explode all trees					
-	+	#10	MeSH descriptor: [Sex Factors] explode all trees		MeSH 🔻	5719		
-	+	#11	(gender):ti,ab,kw S▼					
-	+	#12	#9 OR #10 OR #11					
-	+	#13	#8 AND #7 AND #12					
-	+	#14	Type a search term or use the S or MeSH buttons to compose S	▼ MeSH	<ul> <li>Limits</li> </ul>	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. Reporte	d symptoms in each	included study.
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Included study	Symptoms reported by study
I UNSTAIL-PEODE 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
O'Donnell et al. 2012(17)	Chest pain, shortness of breath diaphoresis left arm pain, pausea, fatigue
	nain between shoulder blades nalpitations 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
	snoulder pain, neck pain, neadache, dizziness, neadache, jaw pain,
Asgar Pour et al., 2015(22)	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

Та	able	9 8	52	Subgroups for meta-regress	ion.	
-				-	-	

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	Comparability	Outcome	Total score
	(maximum 4)	(maximum 2)	(maximum 1)	(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)
	Dev 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	An et al (27)	M= 323, F= 483	0.66 (0.23-1.91)	NS: OR not provided
pain	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)	0.55 (4.50, 4.05)
Dein between start	Sederholm Lawesson et al(25)	IVI=406, F=126	2.73 (1.72-4.32)	2.55 (1.53-4.25)
Pain between shoulder	Aliana et al (26)	IVI= 133, F= 116	3.06 (1.81-5.15)	0.40./4.50.0.07\
Diades	An et al(27)	IVI= 323, F= 483	1.99 (1.48-2.67)	2.13 (1.53-2.97)
	Asgar Pour et al(22)	IVI=183, F=137	1.29 (0.81-2.04)	1 62 (0 02 2 94)
	Coventry et al (19)	IVI= 1000, F=021	1.02 (0.90-2.74)	1.02 (0.93-2.81)
	CullC et al (b) $D_{0}/(c_{0})$ of $c_{1}/(c_{0})$	IVI=1395, F=601 M-242 E-124	2.10 (1.52-3.06)	1.04 (1.10-2.27)
	$\frac{DeVOII et al(23)}{Coldborg of ol (4)}$	IVI=343, F=131 M_910 E_550	2.30 (1.91-4.00)	1.70 (1.21-2.03)
	Khop et al (21)	IVI=010, F=000	2.43 (1.70-3.47)	2.03 (1.19-3.83)
	Kirabbargar at al (21)	IVI=710, F=305	2.03 (1.53-2.69)	2 22 (1 79 2 77)
	Kirchberger et al (13)	IVI= 1710, F=568	2.31 (1.00-2.82)	2.22 (1.10-2.11)

	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	Allana et al (26)	M= 133, F=116	2.11 (1.24-3.59)	
pain	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)	IVI=/49, F=30/	2.06 (1.53-2.78)	
		IVI=221, F=110	1.55 (0.91-2.65)	
Dianhanasis	Sedernoim Lawesson et al(25)	IVI=406, F=126	0.98 (0.64-1.50)	1.04 (0.66-1.65)
Jiapnoresis	An et al(27)	IVI= 323, F= 483	1.00 (0.74-1.35)	INS: UK not provided
	Allana et al (26)	IVI= 133, F= 116		0.76 (0.60.0.04)
	Arsianian-Engoren et al(10)	IVI= 1200, F=530	0.07 (0.55-0.82)	0.76 (0.62-0.94)
	Asgar Pour et al(22)	IVI=183, F=137	0.98 (0.52-1.87)	0.74 (0.50.4.04)
	Coventry et al(19)	IVI= 1000, F=021		
		IVI=1395, F=601	0.02(0.52-0.76)	
	Devon et al(23)	IVI=343, F=131	0.94 (0.01-1.43)	0.90 (0.01-1.50)
	Dev et al(12)	IVI=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)	ľ
	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)
	Dev 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 & Giengedal(8)	M=44 F=38	3 72 (1 49-9 29)	2.00 (1.00 0.00)
	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)
	$\Omega^{2}$	M=127,1 = 50 M=1402 E=545	1 23 (0 98-1 53)	1 31 (1 04-1 65)
	Sederbolm Lawesson et al(25)	M=406 F=126	2 39 (1 59-3 61)	3 04 (1 93-4 78)
Fatique	An et al(27)	M = 323 F= 483	1.51 (1.14-2.01)	1 39 (1 01-1 91)
i diguo	Asgar Pour et al(22)	M=183 F=137	0.85 (0.54-1.35)	
	Coventry et al (19)	M = 1060 E=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)	1.04 (0.07 1.02)
	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)	1.10 (0.07 2.11)
	$\Omega^{2}$	M=1402 E=545	1 49 (1 19-1 87)	1 64 (1 30-2 08)
	Sederbolm Lawesson et al(25)	M=406 F=126	1 43 (0 94-2 16)	1 31 (0.84-2.06)
Dizziness or light-	An et al(27)	M= 323 F=483	1 53 (1 14-2 07)	1.83 (1.31-2.58)
headedness	Culic et al (6)	M=1395 E=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)	1.20 (0.01 1.00)
	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)	1.10 (0.00 2.27)
	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)
	Dev 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.

	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 <sup>+</sup>	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*			

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

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

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












































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.

Chest pain	Wo	omen	Ν	len		Weight	OR
Author(s) and Year	Chest pain	No chest pain	Chest pain	No chest pain	i i i i i i i i i i i i i i i i i i i	%	[95% CI]
Tunstall-Pedoe <sup>2</sup> , 1996	1053	498	2729	1262		6.16%	0.98 [0.86, 1.11]
Meischke <sup>3</sup> , 1998	1352	175	2735	235	H■H	5.31%	0.66 [0.54, 0.82]
Goldberg <sup>4</sup> , 1998	436	114	664	146	<b>⊢∎</b> ii	4.56%	0.84 [0.64, 1.11]
Milner <sup>5</sup> , 1999	36	54	63	64	⊢∎∔I	2.30%	0.68 [0.39, 1.17]
Culic <sup>6</sup> , 2002	479	122	1222	173	H <b>B</b> H	4.77%	0.56 [0.43, 0.72]
Grace <sup>7</sup> , 2003	87	48	238	109	⊢∎∔	3.16%	0.83 [0.55, 1.26]
Lovlien,Gjengedal <sup>8</sup> , 2006	34	4	41	3 ⊢		0.40%	0.62 [0.13, 2.97]
Hirakawa <sup>9</sup> , 2006	383	126	1386	326	⊢∎⊣	4.99%	0.71 [0.57, 0.90]
Arslanian-Engoren <sup>10</sup> , 2006	562	121	1123	135	⊢∎⊣	4.65%	0.56 [0.43, 0.73]
Lovlien,Hole <sup>11</sup> , 2006	128	21	353	30	<b>⊢_</b> ∎;	2.06%	0.52 [0.29, 0.94]
Dey <sup>12</sup> , 2009	13046	1134	27460	1753	•	6.54%	0.73 [0.68, 0.79]
Kirchberger <sup>13</sup> , 2011	531	37	1609	101	⊢	3.41%	0.90 [0.61, 1.33]
Angerud <sup>14</sup> , 2011	1088	135	2569	236	HEH	5.13%	0.74 [0.59, 0.93]
Canto <sup>15</sup> , 2012	279425	202156	458677	203255		6.79%	0.61 [0.61, 0.62]
Pelter <sup>16</sup> , 2012	83	27	172	49	<b>⊢</b> ∎ <u>−</u> 1	2.35%	0.88 [0.51, 1.50]
Zevallos <sup>18</sup> , 2012	490	147	658	120	⊢∎⊣	4.62%	0.61 [0.46, 0.79]
Coventry <sup>19</sup> , 2013	338	283	728	332	H∎H	5.34%	0.54 [0.44, 0.67]
Melberg <sup>20</sup> , 2013	32	33	64	115	<b>├_</b> ∎	2.15%	1.74 [0.98, 3.09]
Khan <sup>21</sup> , 2013	247	58	613	97	⊢∎⊸į	3.70%	0.67 [0.47, 0.96]
Asgar Pour <sup>22</sup> , 2015	124	13	169	14	⊢ <b>−</b> ++−+	1.34%	0.79 [0.36, 1.74]
DeVon <sup>23</sup> , 2017	88	43	254	89	⊢■∔	3.02%	0.72 [0.46, 1.11]
Lichtman <sup>24</sup> , 2018	1748	261	874	102	⊢∎⊣	4.90%	0.78 [0.61, 1.00]
Sederholm Lawesson <sup>25</sup> , 2018	93	33	379	27 ⊢-•		2.24%	0.20 [0.12, 0.35]
Allana <sup>25</sup> , 2018	93	23	102	31	⊢	1.98%	1.23 [0.67, 2.26]
An <sup>27</sup> , 2018	101	382	94	229	⊢∎⊣	4.01%	0.64 [0.47, 0.89]
Plaza-Martin <sup>28</sup> , 2019	231	76	599	150	<b>⊢</b> ∎_1	4.12%	0.76 [0.56, 1.04]
RE Model					•	100.00%	0.70 [0.63, 0.78]
Abbreviations: OR: Odds ratio RE: Random Effects	. CI: Confidence	e Interval		Γ			
Odds ratio				0.1 0	.25 1 2 4		
H95% Confidence Interval							
<ul> <li>Pooled Odds Ratio</li> </ul>				Odd	ds Ratio (log scale)		

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.

Diaphoresis	We	omen	N	<b>Nen</b>		Weight	OR
Author(s) and Year	Diaphoresis	No diaphoresis	Diaphoresis	No diaphoresis	8	%	[95% CI]
Meischke <sup>3</sup> , 1998	671	856	1595	1375	•	9.39%	0.68 [0.60, 0.77]
Goldberg <sup>4</sup> , 1998	221	329	372	438	H <b>B</b> -1	7.53%	0.79 [0.64, 0.98]
Milner <sup>5</sup> , 1999	27	63	29	98	<b></b>	2.53%	1.45 [0.79, 2.67]
Culic <sup>6</sup> , 2002	289	312	833	562	HEH	8.08%	0.62 [0.52, 0.76]
Grace <sup>7</sup> , 2003	75	60	169	178	1 <b></b>	4.50%	1.32 [0.88, 1.96]
Arslanian-Engoren <sup>10</sup> , 2006	199	484	478	780	HEH	7.91%	0.67 [0.55, 0.82]
Lovlien, Hole <sup>11</sup> , 2006	86	63	214	169	<b></b>	4.73%	1.08 [0.74, 1.58]
Dey <sup>12</sup> , 2009	83	261	203	479	⊦∎-1	6.07%	0.75 [0.56, 1.01]
Kirchberger <sup>13</sup> , 2011	335	233	1048	662	H <b>al</b> i	8.06%	0.91 [0.75, 1.10]
Pelter <sup>16</sup> , 2012	11	99	24	197	<b></b>	1.82%	0.91 [0.43, 1.94]
Coventry <sup>19</sup> , 2013	51	570	136	924	H <b></b> 1	5.38%	0.61 [0.43, 0.85]
Melberg <sup>20</sup> , 2013	21	44	61	118	<b>⊢</b> ∎ <mark>∔</mark> −1	2.58%	0.92 [0.50, 1.69]
Khan <sup>21</sup> , 2013	123	182	332	378	⊦∎→	6.51%	0.77 [0.59, 1.01]
Asgar Pour <sup>22</sup> , 2015	118	19	158	25	F	2.35%	0.98 [0.52, 1.87]
DeVon <sup>23</sup> , 2017	45	86	123	220	ب_ف_	4.21%	0.94 [0.61, 1.43]
Lichtman <sup>24</sup> , 2018	86	63	214	169	H H	4.73%	1.08 [0.74, 1.58]
Sederholm Lawesson <sup>25</sup> , 2018	82	44	247	159	H.	4.28%	1.20 [0.79, 1.82]
Allana <sup>26</sup> , 2018	66	50	81	52	<b>⊢</b> ∎ <u>∔</u> - I	3.33%	0.85 [0.51, 1.41]
An <sup>27</sup> , 2018	323	160	216	107	<b>⊢</b> ≢⊣	6.02%	1.00 [0.74, 1.35]

RE Model

Abbreviations: OR: Odds ratio. CI: Confidence Interval



100.00% 0.84 [0.76, 0.94]

RE: Random Effects ■ Odds ratio → 95% Confidence Interval ◆ Pooled Odds Ratio

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.

Dizziness	We	omen	N	len		Weight	OR
Author(s) and Year	Dizziness	No dizziness	Dizziness	No dizziness	10	%	[95% CI]
Milner⁵, 1999	19	71	23	104	J	2.75%	1.21 [0.61, 2.38]
Culic <sup>6</sup> , 2002	47	554	80	1315	<b>⊨</b> ∎_	8.27%	1.39 [0.96, 2.03]
Grace <sup>7</sup> , 2003	40	95	69	278	<b></b> -1	5.84%	1.70 [1.08, 2.67]
Lovlien,Hole <sup>11</sup> , 2006	58	91	125	258	H	7.58%	1.32 [0.89, 1.95]
Kirchberger <sup>13</sup> , 2011	140	428	332	1378	⊦∎⊣	18.63%	1.36 [1.08, 1.70]
Khan <sup>21</sup> , 2013	81	226	167	543	H <b>a</b> -1	11.52%	1.17 [0.86, 1.58]
DeVon <sup>23</sup> , 2017	55	76	123	220	<b>⊢</b> •-4	6.98%	1.29 [0.86, 1.95]
Lichtman <sup>24</sup> , 2018	563	1446	257	719	1 <b>8</b> -1	26.48%	1.09 [0.92, 1.29]
An <sup>27</sup> , 2018	190	293	96	227	<b></b> 1	11.96%	1.53 [1.14, 2.07]
RE Model					•	100.00%	1.28 [1.15, 1.44]
Abbreviations: OR: Odd RE: Random Effects ■ Odds ratio H 95% Confidence Interv	ls ratio. CI: Confide ral	ence Interval		Г 0.2	25 1 2 4		
				Od	ds Ratio (log scale)		

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.

Fatigue	We	omen	Ν	1en		Weight	OR
Author(s) and Year	Fatigue	No fatigue	Fatigue	No fatigue		%	[95% CI]
Milner <sup>5</sup> , 1999	16	74	12	115	· · · · ·	1.86%	2.07 [0.93, 4.63]
Grace <sup>7</sup> , 2003	46	89	102	245	<b>La</b> - 1	6.00%	1.24 [0.81, 1.90]
Lovlien,Hole <sup>11</sup> , 2006	68	81	146	237	<b>H-</b>	7.14%	1.36 [0.93, 2.00]
O'Donnell <sup>17</sup> , 2012	158	387	301	1101	⊦∎⊣	15.72%	1.49 [1.19, 1.87]
Coventry <sup>19</sup> , 2013	34	587	28	1032	<b>⊢</b> i	4.33%	2.13 [1.28, 3.56]
Khan <sup>21</sup> , 2013	177	128	333	377	<b>⊢=</b> -1	12.21%	1.57 [1.19, 2.05]
Asgar Pour <sup>22</sup> , 2015	48	89	71	112	<b>⊢_∎_</b> -1	5.21%	0.85 [0.54, 1.35]
DeVon <sup>23</sup> , 2017	55	76	134	209	<b>⊢</b> ,∎_,1	6.38%	1.13 [0.75, 1.70]
Lichtman <sup>24</sup> , 2018	908	1101	399	577	3 <b>22</b> 4	23.51%	1.19 [1.02, 1.39]
Sederholm Lawesson <sup>25</sup> , 2018	50	76	128	278	· · · · ·	6.26%	1.43 [0.94, 2.16]
An <sup>27</sup> , 2018	250	233	134	189	<b>⊢</b> ∎-1	11.39%	1.51 [1.14, 2.01]

RE Model

- Abbreviations: OR: Odds ratio. CI: Confidence Interval RE: Random Effects
- Odds ratio
- Odds ratio
   95% Confidence Interval
   ◆ Pooled Odds Ratio



100.00% 1.36 [1.22, 1.52]

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.

Indigestion	We	omen	N	len		Weight	OR
Author(s) and Year	Indigestion	No indigestion	Indigestion	No indigestion		%	[95% CI]
Milner <sup>5</sup> , 1999	20	70	15	112	<b></b>	14.29%	2.13 [1.02, 4.4 <mark>4</mark> ]
Grace <sup>7</sup> , 2003	32	103	66	281	<b>⊨</b> ₩-3	24.78%	1.32 [0.82, 2.14]
Asgar Pour <sup>22</sup> , 2015	26	111	44	139	<b></b>	21.32%	0.74 [0.43, 1.28]
DeVon <sup>23</sup> , 2017	39	92	75	268	₽₽₽	26.25%	1.51 [0.96, 2.38]
An <sup>27</sup> , 2018	21	462	10	313	i i i i i i i i i i i i i i i i i i i	13.36%	1.42 [0.66, 3.06]
RE Model					•	100.00%	1.31 [0.95, 1.81]
Abbreviations: OR: Odd RE: Random Effects ■ Odds ratio H 95% Confidence Intern ◆ Pooled Odds Ratio	ds ratio. CI: Confi val	dence Interval		Г 0.2 с	5 1 2 4 8 Ddds Ratio (log scale)		

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.

Jaw pain	We	omen	N	len		Weight	OR
Author(s) and Year	Jaw pain	No jaw pain	Jaw pain	No jaw pain		%	[95% CI]
Goldberg <sup>4</sup> , 1998	60	490	49	761	<b>⊢</b> ∎→1	11.45%	1.90 [1.28, 2.82]
Milner <sup>5</sup> , 1999	4	86	9	118 🚽		2.65%	0.61 [0.18, 2.05]
Culic <sup>6</sup> , 2002	55	546	77	1315	<b>⊢</b> ∎i	12.25%	1.72 [1.20, 2.47]
Lovlien,Gjengedal <sup>8</sup> , 2006	19	19	11	33	·	4.07%	3.00 [1.18, 7.62]
Lovlien,Hole <sup>11</sup> , 2006	49	100	93	290	} <b>∎</b> (	11.01%	1.53 [1.01, 2.31]
Dey <sup>12</sup> , 2009	36	308	27	655	<b></b> 12	8.92%	2.84 [1.69, 4.76]
Kirchberger <sup>13</sup> , 2011	226	342	472	1238	HEH	16.23%	1.73 [1.42, 2.11]
Pelter <sup>16</sup> , 2012	11	99	12	209	F	4.67%	1.9 <mark>4</mark> [0.83, 4.54]
Khan <sup>21</sup> , 2013	73	232	92	618	<b>⊢</b> ∎1	12.68%	2.11 [1.50, 2.98]
Allana <sup>26</sup> , 2018	38	78	23	110	F	7.64%	2.33 [1.29, 4.22]
An <sup>27</sup> , 2018	29	454	27	296 F		8.44%	0.70 [0.41, 1.21]
RE Model					•	100.00%	1.75 [1.42, 2.17]

Abbreviations: OR: Odds ratio. CI: Confidence Interval RE: Random Effects Odds ratio 95% Confidence Interval



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.

Left arm pain	We	omen	N	len		Weight	OR
Author(s) and Year	Left arm pain	No left arm pain	Left arm pain	No left arm pain		%	[95% CI]
Goldberg <sup>4</sup> , 1998	165	385	243	567	H <b>#</b> H	9.34%	1.00 [0.79, 1.27]
Culic <sup>6</sup> , 2002	427	174	918	477	₩	9.70%	1.28 [1.04, 1.57]
Grace <sup>7</sup> , 2003	67	68	150	197	ı <b>∔∎</b> 1	7.19%	1.29 [0.87, 1.93]
Lovlien,Gjengedal <sup>8</sup> , 2006	10	28	17	27 •	• • •	2.73%	0.57 [0.22, 1.46]
Arslanian-Engoren <sup>10</sup> , 2006	172	511	374	884	H <b>B</b> -1	9.66%	0.80 [0.64, 0.98]
Lovlien,Hole <sup>11</sup> , 2006	78	71	186	197	<b>⊢</b> ∎-1	7.44%	1.16 [0.80, 1.70]
Kirchberger <sup>13</sup> , 2011	344	224	941	769	-	9.87%	1.26 [1.03, 1.52]
O'Donnell <sup>17</sup> , 2012	185	360	428	974	k∰-i	9.67%	1.17 [0.95, 1.44]
Zevallos <sup>18</sup> , 2012	110	527	220	558	H∎→I	9.06%	0.53 [0.41, 0.69]
Coventry <sup>19</sup> , 2013	90	531	105	955	⊦∎→	8.49%	1.54 [1.14, 2.08]
Khan <sup>21</sup> , 2013	150	155	293	417	⊨∎⊣	8.91%	1.38 [1.05, 1.80]
An <sup>27</sup> , 2018	103	380	72	251	H <b>H</b> -1	7.95%	0.94 [0.67, 1.33]

RE Model

- Abbreviations: OR: Odds ratio. Cl: Confidence Interval RE: Random Effects ■ Odds ratio H95% Confidence Interval
- Pooled Odds Ratio

Г Т ٦ 0.25 1 2 4 8 Odds Ratio (log scale)

100.00% 1.06 [0.88, 1.27]

## 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.

Nausea or vomit	ting w	omen		Men		Weight	OR
Author(s) and Year	Nausea/vomiting	No nausea/vomiting	Nausea/vomiting	No nausea/vomiting		%	[95% CI]
Meischke <sup>3</sup> , 1998	670	857	1041	1929	-	10.09%	1.45 [1.28, 1.64]
Goldberg <sup>4</sup> , 1998	221	329	239	571	H <b>B</b> -1	7.49%	1.60 [1.28, 2.02]
Milner <sup>5</sup> , 1999	27	63	20	107	·	2.01%	2.29 [1.19, 4.42]
Culic <sup>6</sup> , 2002	345	256	571	824	HEH	8.35%	1.94 [1.60, 2.36]
Grace <sup>7</sup> , 2003	57	78	100	247	<b>⊢</b> ∎i	4.05%	1.81 [1.19, 2.73]
Lovlien, Gjengedal <sup>8</sup> , 2006	25	13	15	29	· · · ·	1.13%	3.72 [1.49, 9.29]
Arslanian-Engoren <sup>10</sup> , 2006	201	482	317	941	⊨∎-i	7.98%	1.24 [1.01, 1.52]
Lovlien, Hole11, 2006	69	80	110	273	<b>⊢</b> ∎→I	4.35%	2.14 [1.45, 3.16]
Dey <sup>12</sup> , 2009	111	233	154	528		6.11%	1.63 [1.22, 2.18]
Kirchberger <sup>13</sup> , 2011	269	299	549	1161	HEH	8.36%	1.90 [1.57, 2.31]
O'Donnell <sup>17</sup> , 2012	152	393	336	1066	<b>⊨</b> ∎-(	7.59%	1.23 [0.98, 1.53]
Coventry <sup>19</sup> , 2013	46	575	52	1008		4.09%	1.55 [1.03, 2.34]
Melberg <sup>20</sup> , 2013	22	43	50	129	ц.	2.28%	1.32 [0.72, 2.43]
Khan <sup>21</sup> , 2013	108	197	162	548	⊢∎⊣	6.03%	1.85 [1.38, 2.49]
Asgar Pour <sup>22</sup> , 2015	52	85	59	124	i i i i i i i i i i i i i i i i i i i	3.45%	1.29 [0.81, 2.04]
DeVon <sup>23</sup> , 2017	56	75	113	230	i⊥∎i	4.05%	1.52 [1.01, 2.30]
Sederholm Lawesson <sup>25</sup> , 2018	62	64	117	289	<b>⊢</b> •−-1	4.09%	2.39 [1.59, 3.61]
Allana <sup>26</sup> , 2018	68	48	48	85		2.99%	2.51 [1.50, 4.18]
An <sup>27</sup> , 2018	143	340	80	243	⊨■→	5.51%	1.28 [0.93, 1.76]
RE Model					•	100.00%	1.64 [1.48, 1.82]

- Abbreviations: OR: Odds ratio. CI: Confidence Interval

   RE: Random Effects

   Odds ratio

   H 95% Confidence Interval

   ◆ Pooled Odds Ratio



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.

Neck pain	We	omen	N	<b>Nen</b>		Weight	OR
Author(s) and Year	Neck pain	No neck pain	Neck pain	No neck pair	1	%	[95% CI]
							· · · · · · · · · · · · · · · · · · ·
Goldberg <sup>4</sup> , 1998	90	460	82	728	<b>⊢</b> ∎–1	18.09%	1.74 [1.26, 2.39]
Milner <sup>5</sup> , 1999	9	81	11	116	<u> </u>	<mark>2.18%</mark>	1.17 [0.46, 2.96]
Culic <sup>6</sup> , 2002	104	497	149	1246	<b>⊨</b> ∎∔	25.37%	1.75 [1.33, 2.29]
Grace <sup>7</sup> , 2003	47	88	71	276	<b>⊢</b> ∎-1	9.65%	2.08 [1.34, 3.22]
Khan <sup>21</sup> , 2013	101	204	134	576	H <b>H</b> H	20.24%	2.13 [1.57, 2.88]
Sederholm Lawesson <sup>25</sup> , 2018	43	83	72	334	F-8-4	9.31%	2.40 [1.54, 3.76]
An <sup>27</sup> , 2018	117	366	59	264		15.17%	1.43 [1.01, 2.03]
							ž
RE Model					•	100.00%	1.83 [1.60, 2.10]
Abbreviations: OR: Odds rati RE: Random Effects	o. CI: Confid	ence Interval			r +		
Odds ratio Odds ratio 95% Confidence Interval				C	0.25 1 2 4 8		
<ul> <li>Pooled Odds Ratio</li> </ul>					Odds Ratio (log scale)		

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.

Pain between							
shoulder blades	We	omen	I	/len		Weight	OR
Author(s) and Year	Pain	No pain	Pain	No pain		%	[95% CI]
Goldberg <sup>4</sup> , 1998	84	466	56	754	- <b></b> -	7.39%	2.43 [1.70, 3.47]
Milner <sup>5</sup> , 1999	12	78	2	125	<b>⊢−−</b> +	0.41%	9.62 [2.10, 44.11]
Culic <sup>6</sup> , 2002	64	537	73	1322	⊢⊷⊣	7.69%	2.16 [1.52, 3.06]
Lovlien,Gjengedal <sup>8</sup> , 2006	15	23	7	37	<b></b>	0.88%	3.45 [1.22, 9.73]
Lovlien,Hole <sup>11</sup> , 2006	39	110	60	323	<b>⊢</b> •1	4.5 <mark>1%</mark>	1.91 [1.21, 3.02]
Kirchberger <sup>13</sup> , 2011	227	341	383	1327	H <b>E</b> H	22.95%	2.31 [1.88, 2.82]
O'Donnell <sup>17</sup> , 2012	41	504	67	1335	⊢	5.84%	1.62 [1.08, 2.42]
Zevallos <sup>18</sup> , 2012	86	551	59	719	<b>⊢</b> ∎1	7.73%	1.90 [1.34, 2.70]
Coventry <sup>19</sup> , 2013	28	593	30	1030	<b>—</b>	3.43%	1.62 [0.96, 2.74]
Khan <sup>21</sup> , 2013	130	175	190	520	F=-1	11.93%	2.03 [1.53, 2.69]
Asgar Pour <sup>22</sup> , 2015	52	85	59	124	i <b>⊢a</b> -i	4.39%	1.29 [0.81, 2.04]
DeVon <sup>23</sup> , 2017	52	79	62	281	⊢	4.76%	2.98 [1.91, 4.66]
Sederholm Lawesson <sup>25</sup> , 2018	37	89	48	358	<b></b>	3.97%	3.10 [1.90, 5.05]
Allana <sup>26</sup> , 2018	80	36	56	77	<b>⊢</b> •1	3.45%	3.06 [1.81, 5.15]
An <sup>27</sup> , 2018	224	259	98	225	+ <b>-</b> -1	10.69%	1.99 [1.48, 2.67]
RE Model					•	100.00%	2.15 [1.95, 2.37]

Abbreviations: OR: Odds ratio. CI: Confidence Interval RE: Random Effects Odds ratio

➡ 95% Confidence Interval
 ◆ Pooled Odds Ratio

0.25 1 2 4 8 20 Odds Ratio (log scale)

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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.

Palpitations	We	omen	N	1en		Weight	OR
Author(s) and Year	Palpitations	No palpitations	Palpitations	No palpitations		%	[95% CI]
Milner <sup>5</sup> , 1999	9	81	4	123		2.98%	3.42 [1.02, 11.47]
Lovlien,Hole <sup>11</sup> , 2006	57	92	70	313		11.81%	2.77 [1.82, 4.22]
Dey <sup>12</sup> , 2009	21	323	29	653	F	8.68%	1.46 [0.82, 2.61]
O'Donnell <sup>17</sup> , 2012	30	515	39	1363	<b>⊢</b> ∎1	10.37%	2.04 [1.25, 3.31]
Asgar Pour <sup>22</sup> , 2015	30	107	48	135	L	9.67%	0.79 [0.47, 1.33]
DeVon <sup>23</sup> , 2017	34	97	58	285	<b></b> 1	10.46%	1.72 [1.06, 2.79]
Lichtman <sup>24</sup> , 2018	376	1633	122	854	HE	16.71%	1.61 [1.29, 2.01]
Allana <sup>26</sup> , 2018	76	40	63	70	<b></b>	9.86%	2.11 [1.26, 3.52]
An <sup>27</sup> , 2018	99	384	44	279	<b>⊢</b> ∎_1	12.57%	1.63 [1.11, 2.41]
Plaza-Martin <sup>28</sup> , 2019	18	289	15	734	<b>⊢</b> •−•	6.88%	3.05 [1.52, 6.13]

RE Model

Abbreviations: OR: Odds ratio. CI: Confidence Interval RE: Random Effects Odds ratio

➡ 95% Confidence Interval
 ➡ Pooled Odds Ratio



100.00% 1.80 [1.44, 2.26]

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.

<b>Right arm pain</b>	Wo	omen	I	<b>Nen</b>		Weight	OR
Author(s) and Year	Right arm pain	No right arm pain	Right arm pain	No right arm p	ain	%	[95% CI]
Goldberg <sup>4</sup> , 1998	99	451	130	680	₽₩	14.16%	1.15 [0.86, 1.53]
Culic <sup>6</sup> , 2002	285	316	559	836	H <b>a</b> ri	16.39%	1.35 [1.11, 1.64]
Arslanian-Engoren <sup>10</sup> , 2006	56	627	113	1145	<b>⊢∎</b> -1	13.01%	0.90 [0.65, 1.26]
Lovlien,Hole <sup>11</sup> , 2006	51	98	103	280	<b></b> 1	11.34%	1.41 [0.94, 2.13]
Kirchberger <sup>13</sup> , 2011	188	380	517	1193	# <b>#</b> -1	16.16%	1.14 [0.93, 1.40]
Coventry <sup>19</sup> , 2013	40	581	114	<mark>946</mark>	<b>⊢∎</b> →	12.07%	0.57 [0.39, 0.83]
Khan <sup>21</sup> , 2013	78	227	136	574	⊨∎⊣	13.41%	1.45 [1.06, 1.99]
An <sup>27</sup> , 2018	7	476	7	316		3.46%	0.66 [0.23, 1.91]
RE Model					•	100.00%	1.09 [0.88, 1.35]
Abbreviations: OR: Odds rat RE: Random Effects Odds ratio H95% Confidence Interval Pooled Odds Ratio	io. CI: Confidenc	e Interval			0.25 1 2 4	8	

### 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.

Shortness of brea	th wo	men	Me	en		Weight	OR
Author(s) and Year	Present	Absent	Present	Absent	97	%	[95% CI]
Meischke <sup>3</sup> , 1998	791	736	1369	1601	-	7.68%	1.26 [1.11, 1.42]
Goldberg <sup>4</sup> , 1998	250	300	324	486	} <b></b> ⊦	6.10%	1.25 [1.00, 1.56]
Milner <sup>5</sup> , 1999	45	45	45	82	<b>—</b>	2.33%	1.82 [1.05, 3.16]
Culic <sup>6</sup> , 2002	291	310	478	917	HEH	6.51%	1.80 [1.48, 2.19]
Grace <sup>7</sup> , 2003	67	68	139	208		3.57%	1.47 [0.99, 2.20]
Lovlien,Gjengedal <sup>8</sup> , 2006	20	18	15	29	·	1.07%	2.15 [0.88, 5.24]
Arslanian-Engoren <sup>10</sup> , 2006	350	333	607	651	1 <b>2</b> -1	6.65%	1.13 [0.94, 1.36]
Lovlien,Hole <sup>11</sup> , 2006	70	79	144	239	<b></b>	3.76%	1.47 [1.00, 2.16]
Dey <sup>12</sup> , 2009	144	200	282	400	⊨ <b>∔</b> -4	5.38%	1.02 [0.79, 1.33]
Kirchberger <sup>13</sup> , 2011	320	248	787	923	HEH	6.57%	1.51 [1.25, 1.83]
Pelter <sup>16</sup> , 2012	30	80	43	178	· · · · · · · · · · · · · · · · · · ·	2.43%	1.55 [0.91, 2.65]
O'Donnell <sup>17</sup> , 2012	272	273	601	801	H	6.45%	1.33 [1.09, 1.62]
Coventry <sup>19</sup> , 2013	176	445	273	787	0 <b>--</b>	6.04%	1.14 [0.91, 1.42]
Melberg <sup>20</sup> , 2013	12	53	29	150	⊢ i e − i	1.46%	1.17 [0.56, 2.46]
Khan <sup>21</sup> , 2013	136	169	319	391	H <b>a</b> H	5.27%	0.99 [0.75, 1.29]
Asgar Pour <sup>22</sup> , 2015	100	37	141	42		2.60%	0.81 [0.48, 1.34]
DeVon <sup>23</sup> , 2017	72	59	165	178	ı <b>⊨</b> ∎—ı	3.53%	1.32 [0.88, 1.97]
Lichtman <sup>24</sup> , 1998	1061	948	465	511		7.21%	1.23 [1.06, 1.43]
Sederholm Lawesson <sup>25</sup> , 2018	40	86	131	275	H-	3.28%	0.98 [0.64, 1.50]
Allana <sup>26</sup> , 2018	89	27	87	46	┝━━┥	2.28%	1.74 [1.00, 3.05]
An <sup>27</sup> , 2018	308	175	156	167	H <b>B</b> -1	5.02%	1.88 [1.41, 2.51]
Plaza-Martin <sup>28</sup> , 2019	101	206	144	605	H	4.82%	2.06 [1.53, 2.78]

#### RE Model

Abbreviations: OR: Odds ratio. CI: Confidence Interval

RE: Random Effects ■ Odds ratio H 95% Confidence Interval ◆ Pooled Odds Ratio

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100.00% 1.34 [1.21, 1.48]

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.

#### Stomach or epigastric pain

erenaen er epig	W	omen	N	len		Weight	OR
Author(s) and Year	Pain	No pain	Pain	No pain		%	[95% CI]
Meischke <sup>3</sup> , 1998	160	1367	316	2654	H <b>a</b> ri	14.08%	0.98 [0.80, 1.20]
Goldberg <sup>4</sup> , 1998	22	528	44	766	<b></b>	8.97%	0.73 [0.43, 1.22]
Culic <sup>6</sup> , 2002	80	521	225	1170	<b>⊢</b> ∰-1	12.97%	0.80 [0.61, 1.05]
Grace <sup>7</sup> , 2003	13	122	18	329	· • • • •	6.27%	1.95 [0.93, 4.09]
Lovlien,Hole <sup>11</sup> , 2006	27	122	56	327	<b></b>	9.26%	1.29 [0.78, 2.14]
Kirchberger <sup>13</sup> , 2011	76	492	173	1537		12.76%	1.37 [1.03, 1.83]
Pelter <sup>16</sup> , 2012	5	105	6	215	<b></b> 1	3.15%	1.71 [0.51, 5.72]
Zevallos <sup>18</sup> , 2012	62	575	44	734	F- <b>B</b> 1	10.88%	1.80 [1.20, 2.69]
Coventry <sup>19</sup> , 2013	19	602	24	1036	1 <b></b> 1	7.78%	1.36 [0.74, 2.51]
Sederholm Lawesson <sup>25</sup> , 2018	6	120	37	369	• <b>•</b> ••••	5.00%	0.50 [0.21, 1.21]
Allana <sup>26</sup> , 2018	51	65	36	97	F	8.88%	2.11 [1.24, 3.59]

RE Model

Abbreviations: OR: Odds ratio. CI: Confidence Interval RE: Random Effects ■ Odds ratio H 95% Confidence Interval ◆ Pooled Odds Ratio



100.00% 1.20 [0.94, 1.53]

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.

Syncope	We	omen	A	len		Weight	OR
Author(s) and Year	Syncope	No syncope	Syncope	No syncope		%	[95% CI]
Tunstall-Pedoe <sup>2</sup> , 1996	54	1497	107	3884	<b>₩</b> ₩-1	15.57%	1.31 [0.94, 1.83]
Meischke <sup>3</sup> , 1998	47	1480	75	2895	i <b>∔</b> ∎−4	12.58%	1.23 [0.85, 1.77]
Goldberg <sup>4</sup> , 1998	55	495	65	745	<b>⊬æ</b> .⊣	12.14%	1.27 [0.87, 1.86]
Grace <sup>7</sup> , 2003	8	127	19	328	i i	2.38%	1.09 [0.46, 2.55]
Lovlien, Hole <sup>11</sup> , 2006	20	129	27	356	<b>⊢</b> •−-1	4.59%	2.04 [1.11, 3.77]
Dey <sup>12</sup> , 2009	76	268	144	538	⊦₩	17.45%	1.06 [0.77, 1.45]
Kirchberger <sup>13</sup> , 2011	38	530	83	1627	u <b>⊢</b> ∎−4	10.97%	1.41 [0.95, 2.09]
Coventry <sup>19</sup> , 2013	54	567	67	993	t-=-1	12.38%	1.41 [0.97, 2.05]
Melberg <sup>20</sup> , 2013	9	56	26	153	<b>F</b>	2.58%	0.95 [0.42, 2.14]
Sederholm Lawesson <sup>25</sup> , 2018	32	94	105	301	<b>⊢</b> ∎-1	8.19%	0.98 [0.62, 1.54]
Allana <sup>26</sup> , 2018	5	111	6	127	r1	1.17%	0.95 [0.28, 3.21]
PE Model						100 00%	1 24 [1 00 1 42]

Abbreviations: OR: Odds ratio. CI: Confidence Interval RE: Random Effects Odds ratio 95% Confidence Interval Pooled Odds Ratio

٦ Г Т Т Т 0.25 1 2 4 8 Odds Ratio (log scale)

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.

Chest pain	We	omen	Ν	/len		
Author(s) and Year	Chest pain	No chest pain	Chest pain	No chest pain		Cumulative OR [95% CI]
1	1053	498	2729	1262	H <b>e</b> l	0.98 [0.86, 1.11]
+2	1352	175	2735	235	⊢∎∔∣	0.81 [0.56, 1.19]
+3	436	114	664	146	⊢∎÷	0.83 [0.65, 1.05]
+ 4	36	54	63	64	⊢∎-į	0.81 [0.65, 1.00]
+ 5	479	122	1222	173	⊢■⊣	0.74 [0.60, 0.93]
+ 6	87	48	238	109	⊢∎⊣	0.76 [0.62, 0.92]
+7	34	4	41	3	⊢∎⊣	0.75 [0.62, 0.91]
+ 8	383	126	1386	326	HEH	0.75 [0.64, 0.88]
+ 9	562	121	1123	135	HEH	0.72 [0.61, 0.85]
+ 10	128	21	353	30	HEH	0.71 [0.61, 0.83]
+ 11	13046	1134	27460	1753	HEH	0.71 [0.63, 0.82]
+ 12	531	37	1609	101	HEH	0.73 [0.64, 0.82]
+ 13	1088	135	2569	236	184	0.73 [0.65, 0.82]
+ 14	279425	202156	458677	203255	H <b>e</b> H	0.71 [0.64, 0.79]
+ 15	83	27	172	49	H <b>B</b> 4	0.72 [0.64, 0.80]
+ 16	490	147	658	120	<b>-</b>	0.71 [0.64, 0.78]
+ 17	338	283	728	332	HEH	0.69 [0.63, 0.77]
+ 18	32	33	64	115	184	0.71 [0.64, 0.79]
+ 19	247	58	613	97	=	0.71 [0.64, 0.79]
+ 20	124	13	169	14	<b>F</b> I	0.71 [0.64, 0.79]
+ 21	88	43	254	89	<b></b>	0.71 [0.64, 0.78]
+ 22	1748	261	874	102	<b>F</b> I	0.71 [0.65, 0.78]
+ 23	93	33	379	27	H#H	0.69 [0.62, 0.78]
+ 24	93	23	102	31	HEH	0.70 [0.63, 0.79]
+ 25	101	382	94	229	HEH	0.70 [0.63, 0.78]
+ 26	231	76	599	150	<b>F</b> 1	0.70 [0.63, 0.78]
				Г		
Abbreviations: OR: Odds Odds ratio	ratio. CI: Confidence	Interval		0.25	1 2	
- 95% Confidence Interva	I			Odds	Ratio (log sca	ale)

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.

Diaphoresis	We	omen	I	Aen		
Author(s) and Year	Diaphoresis	No diaphoresis	Diaphoresis	No diaphoresis		Cumulative OR [95% CI]
Meischke <sup>3</sup> , 1998	671	856	1595	1375	H <b>a</b> ri	0.68 [0.60, 0.77]
+ Goldberg <sup>4</sup> , 1998	221	329	372	438	HEH	0.71 [0.62, 0.82]
+ Milner <sup>5</sup> , 1999	27	63	29	98		0.82 [0.59, 1.14]
+ Culic <sup>6</sup> , 2002	289	312	833	562	H <b>=</b> 1	0.72 [0.61, 0.85]
+ Grace <sup>7</sup> , 2003	75	60	169	178	F-	0.85 [0.63, 1.15]
+ Arslanian-Engoren <sup>10</sup> , 2006	199	484	478	780	⊢∎→	0.80 [0.63, 1.02]
+ Lovlien, Hole <sup>11</sup> , 2006	86	63	214	169	H <b>B</b> - 1	0.83 [0.67, 1.04]
+ Dey <sup>12</sup> , 2009	83	261	203	479	H <b></b> -4	0.81 [0.67, 0.98]
+ Kirchberger <sup>13</sup> , 2011	335	233	1048	662	H <b></b> -4	0.82 [0.70, 0.96]
+ Pelter <sup>16</sup> , 2012	11	99	24	197	H <b>H</b> HC	0.82 [0.70, 0.96]
+ Coventry <sup>19</sup> , 2013	51	570	136	924	HEH	0.80 [0.69, 0.92]
+ Melberg <sup>20</sup> , 2013	21	44	61	118	HEH	0.80 [0.70, 0.92]
+ Khan <sup>21</sup> , 2013	123	182	332	378	HE-H	0.79 [0.70, 0.90]
+ Asgar Pour <sup>22</sup> , 2015	118	19	158	25	HEH	0.80 [0.71, 0.90]
+ DeVon <sup>23</sup> , 2017	45	86	123	220	HEH	0.80 [0.71, 0.90]
+ Lichtman <sup>24</sup> , 2018	86	63	214	169	( HEH	0.82 [0.73, 0.92]
+ Sederholm Lawesson <sup>25</sup> , 2018	82	44	247	159	8 <b>11</b> 1	0.84 [0.74, 0.94]
+ Allana <sup>26</sup> , 2018	66	50	81	52	HEH:	0.84 [0.74, 0.94]
+ An <sup>27</sup> , 2018	323	160	216	107	HEH.	0.84 [0.76, 0.94]
Abbreviations: OR: Odds ratio.	. CI: Confidence I	nterval				
<ul> <li>Odds ratio</li> </ul>				0.25	1 2	4

H95% Confidence Interval

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.

Dizziness	Wo	omen	I	<b>Nen</b>		
Author(s) and Year	Dizziness	No dizziness	Dizziness	No dizziness		Cumulative OR [95% CI]
Milner <sup>5</sup> , 1999	19	71	23	104	ii	1.21 [0.61, 2.38]
+ Culic <sup>6</sup> , 2002	47	554	80	1315	<b>⊨</b> =-1	1.35 [0.97, 1.87]
+ Grace <sup>7</sup> , 2003	40	95	69	278	<b>⊢</b> ∎-)	1.46 [1.12, 1.90]
+ Lovlien,Hole <sup>11</sup> , 2006	58	91	125	258		1.41 [1.13, 1.76]
+ Kirchberger <sup>13</sup> , 2011	<mark>14</mark> 0	428	332	1378	HEH	1.39 [1.18, 1.62]
+ Khan <sup>21</sup> , 2013	81	226	167	543	<b> #</b> -	1.34 [1.16, 1.54]
+ DeVon <sup>23</sup> , 2017	55	76	123	220	H <b>a</b> n I	1.33 [1.17, 1.52]
+ Lichtman <sup>24</sup> , 2018	563	1 <mark>4</mark> 46	257	719	<b>B</b> H	1.25 [1.11, 1.40]
+ An <sup>27</sup> , 2018	190	293	96	227	i#i	1.28 [1.15, 1.44]
Abbreviations: OR: Odds rat ■ Odds ratio H 95% Confidence Interval	tio. CI: Confident	ce Interval		0.25 Odds	1 2 4 s Ratio (log scale)	

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.

Fatigue	Women		Men			
Author(s) and Year	Fatigue	No fatigue	Fatigue	No fatigue		Cumulative OR [95% CI]
Milner <sup>5</sup> , 1999	16	74	12	<mark>115</mark>	<b>—</b> —	2.07 [0.93, 4.63]
+ Grace <sup>7</sup> , 2003	46	89	102	245	⊨∎⊸≀	1.42 [0.91, 2.22]
+ Lovlien,Hole <sup>11</sup> , 2006	68	81	146	237	⊨∎⊣	1.38 [1.05, 1.80]
+ O'Donnell <sup>17</sup> , 2012	158	387	301	1101	H∎H	1.44 [1.22, 1.71]
+ Coventry <sup>19</sup> , 2013	34	587	28	1032	+=+	1.50 [1.28, 1.77]
+ Khan <sup>21</sup> , 2013	177	128	333	377	HEH	1.52 [1.32, 1.75]
+ Asgar Pour <sup>22</sup> , 2015	48	89	71	112	<b>i≡</b> i	1.45 [1.27, 1.65]
+ DeVon <sup>23</sup> , 2017	55	76	134	209	H <b>a</b> H	1.40 [1.21, 1.62]
+ Lichtman <sup>24</sup> , 2018	908	1101	399	577	<b>I</b>	1.34 [1.17, 1.53]
+ Sederholm Lawesson <sup>25</sup> , 2018	50	76	128	278	<b>H</b>	1.35 [1.19, 1.52]
+ An <sup>27</sup> , 2018	250	233	134	189	<b>I</b>	1.36 [1.22, 1.52]
Abbreviations: OR: Odds ratio. ■ Odds ratio H95% Confidence Interval	CI: Confidenc	e Interval		0.25	1 2 4 8	

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.

Indigestion	Wo	omen	I	/len		
Author(s) and Year	Indigestion	No indigestion	Indigestion	No indigestion		Cumulative OR [95% CI]
						2
Milner <sup>5</sup> , 1999	20	70	15	112	<b></b> 1	2.13 [1.02, 4.44]
+ Grace <sup>7</sup> , 2003	32	103	66	281	<b>⊢</b> ∎-1	1.54 [1.00, 2.39]
+ Asgar Pour <sup>22</sup> , 2015	26	111	44	139	)- <b></b> -1	1.23 [0.70, 2.17]
+ DeVon <sup>23</sup> , 2017	39	92	75	268	<b>+•</b> -1	1.30 [0.88, 1.92]
+ An <sup>27</sup> , 2018	21	462	10	313	<b></b> -1	1.31 [0.95, 1.81]
Abbreviations: OR: Odds ■ Odds ratio H 95% Confidence Interva	ratio. CI: Confiden	ce Interval		0.1	25 1 2 4 Odds Ratio (log scale)	1 8

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.

Jaw <mark>pain</mark>	Women		N	len		
Author(s) and Year	Jaw pain	No jaw pain	Jaw pain	No jaw pain		Cumulative OR [95% CI]
Goldberg <sup>4</sup> , 1998	60	490	49	761	<b></b>	1.90 [1.28, 2.82]
+ Milner <sup>5</sup> , 1999	4	86	9	118	┝──┼╋───┤	1.25 [0.43, 3.67]
+ Culic <sup>6</sup> , 2002	55	546	77	1315	⊢∎⊣	1.71 [1.32, 2.22]
+ Lovlien,Gjengedal <sup>8</sup> , 2006	19	19	11	33	+=-1	1.78 [1.39, 2.29]
+ Lovlien,Hole <sup>11</sup> , 2006	49	100	93	290	<b>⊢</b> ∎⊣	1.71 [1.38, 2.12
+ Dey <sup>12</sup> , 2009	36	308	27	655	HEH	1.84 [1.51, 2.25]
+ Kirchberger <sup>13</sup> , 2011	226	342	472	1238	<b>i≡</b> -i	1.79 [1.55, 2.06]
+ Pelter <sup>16</sup> , 2012	11	99	12	209	HE-1	1.79 [1.56, 2.06]
+ Khan <sup>21</sup> , 2013	73	232	92	618	I=I	1.83 [1.61, 2.08]
+ Allana <sup>26</sup> , 2018	38	78	23	110	H#4	1.85 [1.63, 2.10]
+ An <sup>27</sup> , 2018	29	<mark>4</mark> 54	27	296	⊦∎⊣	1.75 [1.42, 2.17]
Abbreviations: OR: Odds ra ■ Odds ratio H 95% Confidence Interval	atio. CI: Confidenc	ce Interval		0.25	1 2 4	

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.

Left arm pain	Women		N	1en		
Author(s) and Year	Left arm pain	No left arm pain	Left arm pain	No left arm pain		Cumulative OR [95% CI]
Goldberg <sup>4</sup> , 1998	165	385	243	567	<b>⊢≢</b> ⊣	1.00 [0.79, 1.27]
+ Culic <sup>6</sup> , 2002	427	174	918	477	<b>⊦</b> ∎(	1.14 [0.90, 1.44]
+ Grace <sup>7</sup> , 2003	67	68	150	197		1.17 [0.97, 1.40]
+ Lovlien,Gjengedal <sup>8</sup> , 2006	10	28	17	27	k∎⊣	1.14 [0.95, 1.36]
+ Arslanian-Engoren <sup>10</sup> , 2006	172	511	374	884	⊧ <b>≜</b> ⊣	1.02 [0.81, 1.28]
+ Lovlien,Hole <sup>11</sup> , 2006	78	71	186	197	° <b>⊢∎</b> ⊣	1.04 [0.86, 1.26]
+ Kirchberger <sup>13</sup> , 2011	344	224	941	769	HEH	1.08 [0.91, 1.28]
+ O'Donnell <sup>17</sup> , 2012	185	360	428	974	1984	1.09 [0.95, 1.26]
+ Zevallos <sup>18</sup> , 2012	110	527	220	558	·+ <b>=</b> -1	0.99 [0.80, 1.23]
+ Coventry <sup>19</sup> , 2013	90	531	105	955	н	1.04 [0.84, 1.28]
+ Khan <sup>21</sup> , 2013	150	155	293	417	H <b>a</b> -1	1.07 [0.88, 1.30]
+ An <sup>27</sup> , 2018	<mark>1</mark> 03	380	72	251	<b>H</b> ∎-1	1.06 [0.88, 1.27]
Abbreviations: OR: Odds	ratio. CI: Confider	nce Interval		0.25	1 2 4	i i

■ Odds ratio H 95% Confidence Interval

# 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.

Nausea or vomiting	Wo	omen		Men		
Author(s) and Year	Nausea/vomiting	No nausea/vomiting	Nausea/vomitin	g No nausea/vomiting		Cumulative OR [95% CI]
Meischke <sup>3</sup> , 1998	670	857	1041	1929	<b>H</b>	1.45 [1.28, 1.64]
+ Goldberg <sup>4</sup> , 1998	221	329	239	571	-	1.48 [1.33, 1.66]
+ Milner <sup>5</sup> , 1999	27	63	20	107	Hel	1.50 [1.35, 1.67]
+ Culic <sup>6</sup> , 2002	345	256	571	824	H <b>H</b> H	1.67 [1.40, 1.99]
+ Grace <sup>7</sup> , 2003	57	78	100	247	H#H	1.68 [1.44, 1.96]
+ Lovlien, Gjengedal <sup>8</sup> , 2006	25	13	15	29	HEH	1.73 [1.47, 2.03]
+ Arslanian-Engoren <sup>10</sup> , 2006	201	482	317	941	H#H	1.64 [1.38, 1.94]
+ Lovlien, Hole <sup>11</sup> , 2006	69	80	110	273	H <b>H</b> H	1.69 [1.43, 1.99]
+ Dey <sup>12</sup> , 2009	111	233	154	528	HEH	1.67 [1.45, 1.92]
+ Kirchberger <sup>13</sup> , 2011	269	299	549	1161	<b>H</b>	1.70 [1.49, 1.93]
+ O'Donnell <sup>17</sup> , 2012	152	393	336	1066	HBH	1.64 [1.44, 1.87]
+ Coventry <sup>19</sup> , 2013	46	575	52	1008	18-1	1.63 [1.45, 1.84]
+ Melberg <sup>20</sup> , 2013	22	43	50	129	144	1.62 [1.44, 1.82]
+ Khan <sup>21</sup> , 2013	108	197	162	548	<b>II</b> I	1.64 [1.46, 1.83]
+ Asgar Pour <sup>22</sup> , 2015	52	85	59	124	-	1.62 [1.45, 1.80]
+ DeVon <sup>23</sup> , 2017	56	75	113	230	-	1.61 [1.46, 1.79]
+ Sederholm Lawesson <sup>25</sup> , 2018	62	64	117	289	-	1.64 [1.48, 1.82]
+ Allana <sup>26</sup> , 2018	68	48	48	85	100	1.67 [1.50, 1.85]
+ An <sup>27</sup> , 2018	143	340	80	243	-	1.64 [1.48, 1.82]
Abbreviations: OP: Odds r	atio. CI: Confidenc			C	<del>-  </del>	
■ Odds ratio				0.25	1 2 4	
5% Confidence Interval				Odds	Ratio (log scale)	

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.

Neck pain	Women		I	<b>Nen</b>		
Author(s) and Year	Neck pain	No neck pain	Neck pain	No neck pain		Cumulative OR [95% CI]
Goldberg <sup>4</sup> , 1998	90	460	82	728	<b>1-8-</b> 1	1.74 [1.26, 2.39]
+ Milner <sup>5</sup> , 1999	9	81	11	116	<b>HB</b> -1	1.67 [1.23, 2.26]
+ Culic <sup>6</sup> , 2002	104	497	149	1246	<b>⊢</b> ∎+1	1.71 [1.40, 2.10]
+ Grace <sup>7</sup> , 2003	47	88	71	276	₩	1.77 [1.47, 2.13]
+ Khan <sup>21</sup> , 2013	101	204	134	576	H=1	1.86 [1.59, 2.18]
+ Sederholm Lawesson <sup>25</sup> , 2018	43	83	72	334	HEI	1.91 [1.65, 2.22]
+ An <sup>27</sup> , 2018	117	366	59	264	: <b>18</b> 1	1.83 [1.60, 2.10]
Abbreviations: OR: Odds ratio ■ Odds ratio H 95% Confidence Interval	o. CI: Confiden	ce Interval		0.25 Odds	1 2 4	

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.

shoulder blades	Women		Men			
Author(s) and Year	Pain	No pain	Pain	No pain		Cumulative OR [95% CI]
Goldberg <sup>4</sup> , 1998	84	466	56	754	<b>⊢</b> ∎-1	2.43 [1.70, 3.47]
+ Milner <sup>5</sup> , 1999	12	78	2	125		3.93 [1.08, 14.21]
+ Culic <sup>6</sup> , 2002	64	537	73	1322	H <b>-</b>	2.37 [1.85, 3.04]
+ Lovlien,Gjengedal <sup>8</sup> , 2006	15	23	7	37	+=-1	2.42 [1.90, 3.08]
+ Lovlien,Hole <sup>11</sup> , 2006	39	110	60	323	H∎H	2.30 [1.86, 2.85]
+ Kirchberger <sup>13</sup> , 2011	227	341	383	1327	HB-I	2.30 [1.99, 2.67]
+ O'Donnell <sup>17</sup> , 2012	41	504	67	1335	<b>H</b>	2.21 [1.93, 2.54]
+ Zevallos <sup>18</sup> , 2012	86	551	59	719	H#H	2.17 [1.91, 2.46]
+ Coventry <sup>19</sup> , 2013	28	593	30	1030	HEH	2.13 [1.88, 2.41]
+ Khan <sup>21</sup> , 2013	130	175	190	520	H	2.11 [1.89, 2.37]
+ Asgar Pour <sup>22</sup> , 2015	52	85	59	124	=	2.05 [1.83, 2.30]
+ DeVon <sup>23</sup> , 2017	52	79	62	281	=	2.10 [1.88, 2.34]
+ Sederholm Lawesson <sup>25</sup> , 2018	37	89	48	358	=	2.13 [1.91, 2.38]
+ Allana <sup>26</sup> , 2018	80	36	56	77	<b>H</b>	2.17 [1.94, 2.42]
+ An <sup>27</sup> , 2018	224	259	98	225	-	2.15 [1.95, 2.37]

■ 95% Confidence Interval

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.

Palpitations	Wo	omen	ľ	Nen		
Author(s) and Year	Palpitations	No palpitations	Palpitations	No palpitations	Cu	mulative OR [95% CI]
Milner <sup>5</sup> , 1999	9	81	4	123		3.42 [1.02, 11.47]
+ Lovlien,Hole <sup>11</sup> , 2006	57	92	70	313	<b>⊢</b> ∎-1	2.83 [1.91, 4.21]
+ Dey <sup>12</sup> , 2009	21	323	29	653	<b></b>	2.25 [1.36, 3.71]
+ O'Donnell <sup>17</sup> , 2012	30	515	39	1363	( <b></b> )	2.19 [1.58, 3.02]
+ Asgar Pour <sup>22</sup> , 2015	30	107	48	135		1.76 [1.07, 2.88]
+ DeVon <sup>23</sup> , 2017	34	97	58	285	F	1.74 [1.17, 2.58]
+ Lichtman <sup>24</sup> , 2018	376	1633	122	854	<b>1-8-</b> 1	1.71 [1.26, 2.33]
+ Allana <sup>26</sup> , 2018	76	40	63	70	<b>14</b> -1	1.75 [1.34, 2.29]
+ An <sup>27</sup> , 2018	99	384	44	279	H=-1	1.73 [1.38, 2.18]
+ Plaza-Martin <sup>28</sup> , 2019	18	289	15	734	⊨∎⊣	1.80 [1.44, 2.26]
Abbreviations: OR: Odds ■ Odds ratio H 95% Confidence Interva	s ratio. CI: Confiden	ce Interval		□ 0.2	5 1 2 4 8 Codds Ratio (log scale)	٦ 20

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.

Right arm pain	Women		I	<b>Nen</b>		
Author(s) and Year	Right arm pain	No right arm pain	Right arm pain	No right arm pain		Cumulative OR [95% CI]
Goldberg <sup>4</sup> , 1998	99	451	130	680	₽╧■−−1	1.15 [0.86, 1.53]
+ Culic <sup>6</sup> , 2002	285	316	559	836	<b>i=</b> 1	1.28 [1.09, <mark>1</mark> .51]
+ Arslanian-Engoren <sup>10</sup> , 2006	56	627	113	1145		1.16 [0.92, 1.45]
+ Lovlien,Hole <sup>11</sup> , 2006	51	98	103	280		1.20 [1.00, <mark>1</mark> .44]
+ Kirchberger <sup>13</sup> , 2011	188	380	517	1193	1 <b></b> 1	1.19 [1.05, 1.36]
+ Coventry <sup>19</sup> , 2013	40	581	114	946	H <b>F</b> -1	1.06 [0.83, <mark>1</mark> .35]
+ Khan <sup>21</sup> , 2013	78	227	136	574	H <b>a</b> -i	1.11 [0.89, <mark>1</mark> .38]
+ An <sup>27</sup> , 2018	7	476	7	316	H <b>B</b> -1	1.09 [0.88, 1.35]
Abbreviations: OR: Odds ra ■ Odds ratio H 95% Confidence Interval	ttio. CI: Confiden	ce Interval		0.25 Odd	1 2 4 s Ratio (log scale)	

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.

Shortness of breath	Women		Men			
Author(s) and Year	Present	Absent	Present	Absent		Cumulative OR [95% CI]
Meischke <sup>3</sup> , 1998	791	736	1369	1601	H#H	1.26 [1.11, 1.42]
+ Goldberg <sup>4</sup> , 1998	250	300	324	486	HEH	1.26 [1.13, 1.40]
+ Milner <sup>5</sup> , 1999	45	45	45	82	=	1.27 [1.14, 1.41]
+ Culic <sup>6</sup> , 2002	291	310	478	917	H <b>a</b> H	1.45 [1.17, 1.79]
+ Grace <sup>7</sup> , 2003	67	68	139	208	H <b>-</b>	1.45 [1.21, 1.73]
+ Lovlien,Gjengedal <sup>8</sup> , 2006	20	18	15	29	H#H	1.47 [1.23, 1.75]
+ Arslanian-Engoren <sup>10</sup> , 2006	350	333	607	651	HEH	1.39 [1.18, 1.64]
+ Lovlien, Hole <sup>11</sup> , 2006	70	79	144	239	HEH	1.40 [1.21, 1.62]
+ Dey <sup>12</sup> , 2009	144	200	282	400	HEH	1.35 [1.17, 1.56]
+ Kirchberger <sup>13</sup> , 2011	320	248	787	923	HE-1	1.37 [1.20, 1.55]
+ Pelter <sup>16</sup> , 2012	30	80	43	178	<b>I=</b> -1	1.37 [1.21, 1.55]
+ O'Donnell <sup>17</sup> , 2012	272	273	601	801	I=I	1.36 [1.22, 1.52]
+ Coventry <sup>19</sup> , 2013	176	445	273	787	-	1.34 [1.21, 1.49]
+ Melberg <sup>20</sup> , 2013	12	53	29	150	<b>P</b> I	1.34 [1.21, 1.48]
+ Khan <sup>21</sup> , 2013	136	169	319	391	=	1.31 [1.18, 1.45]
+ Asgar Pour <sup>22</sup> , 2015	100	37	141	42	H	1.29 [1.16, 1.43]
+ DeVon <sup>23</sup> , 2017	72	59	165	178	=	1.29 [1.17, 1.42]
+ Lichtman <sup>24</sup> , 1998	1061	948	465	511	=	1.29 [1.18, 1.40]
+ Sederholm Lawesson <sup>25</sup> , 2018	40	86	131	275	-	1.27 [1.17, 1.39]
+ Allana <sup>26</sup> , 2018	89	27	87	46	<b>F</b> 1	1.28 [1.18, 1.40]
+ An <sup>27</sup> , 2018	308	175	156	167	=	1.31 [1.19, 1.43]
+ Plaza-Martin <sup>28</sup> , 2019	101	206	144	605	<b>PH</b>	1.34 [1.21, 1.48]
Abbreviations: OR: Odds ratio	. CI: Confidenc	e Interval		0.25	1 2 4	

■ Odds ratio H 95% Confidence Interval

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.

### Stomach or epigastric pain

	Wo	omen	I	len		
Author(s) and Year	Pain	No pain	Pain	No pain		Cumulative OR [95% CI]
Meischke <sup>3</sup> , 1998	160	1367	316	2654	14-1	0.98 [0.80, 1.20]
+ Goldberg <sup>4</sup> , 1998	22	528	44	766	H	0.93 [0.75, 1.17]
+ Culic <sup>6</sup> , 2002	80	521	225	1170	<b>⊨</b> ∎-1	0.88 [0.74, 1.06]
+ Grace <sup>7</sup> , 2003	13	122	18	329	H	0.92 [0.76, 1.13]
+ Lovlien,Hole <sup>11</sup> , 2006	27	122	56	327	F#4	0.97 [0.79, 1.20]
+ Kirchberger <sup>13</sup> , 2011	76	492	173	1537	H <b>a</b> -1	1.06 [0.84, 1.34]
+ Pelter <sup>16</sup> , 2012	5	105	6	215	⊢∎-i	1.08 [0.85, 1.36]
+ Zevallos <sup>18</sup> , 2012	62	575	44	734	i <b>¦∎</b> -1	1.17 [0.91, 1.50]
+ Coventry <sup>19</sup> , 2013	19	602	24	1036	<b>k</b> ∎-1	1.18 [0.94, 1.49]
+ Sederholm Lawesson <sup>25</sup> , 2018	6	120	37	369	H <b>#</b> -1	1.13 [0.90, 1.43]
+ Allana <sup>26</sup> , 2018	51	65	36	97	k∎-1	1.20 [0.94, 1.53]
				Г		
Abbreviations: OR: Odds ratio. ■ Odds ratio	CI: Confiden	ce Interval		0.25	5 1 2 4	
H95% Confidence Interval				Od	ds Ratio (log scale)	

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.

Syncope	Women		Men			
Author(s) and Year	Syncope	No syncope	Syncope	No syncope		Cumulative OR [95% CI]
Tunstall-Pedoe <sup>2</sup> , 1996	54	1497	107	3884	<b>⊨</b> =-1	1.31 [0.94, 1.83]
+ Meischke <sup>3</sup> , 1998	47	<mark>14</mark> 80	75	2895	⊨∎⊣	1.27 [0.99, 1.63]
+ Goldberg <sup>4</sup> , 1998	55	495	65	745	₽₩	1.27 [1.03, 1.56]
+ Grace <sup>7</sup> , 2003	8	127	19	328	;+ <b>=</b> -1	1.26 [1.03, 1.54]
+ Lovlien,Hole <sup>11</sup> , 2006	20	129	27	356	⊦æ⊣	1.32 [1.09, 1.60]
+ Dey <sup>12</sup> , 2009	76	268	144	538	H <b>a</b> t	1.25 [1.06, 1.47]
+ Kirchberger <sup>13</sup> , 2011	38	530	83	1627	H <b>a</b> -1	1.27 [1.09, 1.47]
+ Coventry <sup>19</sup> , 2013	54	567	67	993	H <b>H</b> H	1.29 [1.12, 1.48]
+ Melberg <sup>20</sup> , 2013	9	56	26	153	H=1	1.28 [1.11, 1.46]
+ Sederholm Lawesson <sup>25</sup> , 2018	32	94	105	301	i=i	1.25 [1.09, 1.42]
+ Allana <sup>26</sup> , 2018	5	111	6	127	HEH	1.24 [1.09, 1.42]
Abbreviations: OR: Odds ratio	o. Cl: Confiden	ce Interval		0.25	1 2 4	
- 95% Confidence Interval				Odds	Ratio (log scale)	

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