

Systematic Review

Sex-Based Differences in the Presentation and Outcomes of Acute Pulmonary Embolism: A Systematic Review and Meta-Analysis

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Abstract

Background: The study aimed to review differences in the presentation and outcomes of acute pulmonary embolism (PE) between men and women.

Methods: PubMed, CENTRAL, Web of Science, and Embase were searched for studies comparing clinical features or outcomes of PE between men and women. Baseline comorbidities, risk factors, clinical features, and mortality rates were also compared between men and women.

Results: Fourteen studies were included. It was noted that men presented with PE at a statistically significantly younger age than women ($P < .001$). Smoking history ($P < .001$), lung disease ($P = .004$), malignancy ($P = .02$), and unprovoked PE ($P = .004$) were significantly more frequent among men than among women. There was no difference between the sexes for hypertension, diabetes, and a history of recent immobilization. A significantly higher proportion of men presented with chest pain ($P = .02$) and hemoptysis ($P < .001$), whereas syncope ($P = .005$) was more frequent in women. Compared with men, women had a higher proportion of high-risk PE ($P = .003$). There was no difference in the use of thrombolytic therapy or inferior vena cava filter. Neither crude nor adjusted mortality rates were significantly different between men and women.

Conclusion: This review found that the age at presentation, comorbidities, and symptoms of PE differed between men and women. Limited data also suggest that women more frequently had high-risk PE compared with men, but the use of thrombolytic therapy did not differ between the 2 sexes. Importantly, both crude and adjusted data show that the mortality rate did not differ between men and women.

Keywords: Venous thromboembolism; sex; mortality; lung; pulmonary disease; male; female

Introduction

Acute pulmonary embolism (PE) is a common thromboembolic disorder and the third-most common cause of cardiovascular mortality in the United States. Data indicate that the incidence of PE has increased from 3 per 100 people to more than 6.5 per 100 people in the past 2 decades.¹ Clinically, a PE that is large enough to cause significant hemodynamic compromise can result in remarkable morbidity and mortality.² Because much of the research on cardiovascular diseases (CVDs) has been conducted in male-dominated cohorts, however, there is a scarcity of knowledge on how sex influences the morbidity and mortality rates of these diseases.³

It is now well known that sex differences exist in the risk and outcomes of CVDs. Men are more prone to such illnesses, especially coronary artery disease and stroke, along with an increased risk of mortality with CVDs.^{4,5} Men and women have similar risk factors for CVDs, but the relative risk of each factor varies by sex.³ Sex-based differences in presentation and treatment have been shown in patients with acute coronary syndrome.⁶ Similar differences exist for stroke, with sex-based differences in risk, treatment, and outcomes after the event.⁷ In this context,

Citation: Zhang Y, Qiu Y, Luo J, Zhang J, Yan Q. Sex-based differences in the presentation and outcomes of acute pulmonary embolism: a systematic review and meta-analysis. *Tex Heart Inst J*. 2023;50(4):e238113. doi:10.14503/THIJ-23-8113

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the American Heart Association and the World Heart Federation have recommended that more research be conducted to obtain evidence on sex-specific differences in various CVDs.⁸

Over the past 2 decades, numerous studies have compared the clinical presentation and outcomes of PE between men and women,⁹⁻¹² but results have been variable and limited by the small sample sizes of most studies. A thorough systematic review and meta-analysis are needed to comprehensively evaluate the sex-based difference in PE. Because no such analysis has been conducted to date, the current study pooled data from studies published in the year 2000 or later to compare the comorbidities, risk factors, clinical presentation, and mortality rates of PE between men and women.

Methods

The PROSPERO registration (No. CRD42022366268) of the review was initiated before beginning the study. The standard guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement were taken into account during the conduct of the review.¹³

Literature Search

The search strategy involved 2 independent reviewers examining the databases of PubMed, CENTRAL, Web of Science, and Embase electronically. The search was conducted without any language restrictions. To obtain only current and relevant evidence, the databases were searched for studies published between January 1, 2000, and October 13, 2022. To identify relevant publications, combinations of the following keywords were used: *gender, sex, men, women, male, female, and pulmonary embolism*. A detailed description of the search is shown in [Supplementary Table I](#). The search results from every database were combined for screening by the 2 reviewers. When deduplication was complete, the articles were sorted by their titles and abstracts. Full texts of relevant articles were obtained, and they were read by both reviewers against the eligibility criteria. All discrepancies between the reviewers were solved by discussion with a third reviewer.

Eligibility Criteria

The population, exposure, comparison, outcomes, and study type inclusion criteria of the review were as follows:

Key Points

- Women present with PE at a much younger age and frequently with high-risk disease.
- Comorbidities and symptoms at presentation differ between the 2 sexes.
- Mortality rates of PE do not differ between men and women.

Abbreviations and Acronyms

| | |
|-------|--|
| CVD | cardiovascular disease |
| OR | odds ratio |
| PE | pulmonary embolism |
| PESI | Pulmonary Embolism Severity Index |
| sPESI | simplified Pulmonary Embolism Severity Index |

- Population: patients with PE
- Exposure: male
- Comparison: female
- Outcomes: clinical features or outcomes, including mortality and recurrence
- Study type: all types

Single-arm studies, studies not reporting separate data for PE, studies with overlapping or duplicate data, unpublished data, and review articles were excluded. For studies with duplicate data, the study reporting the maximum outcomes and with the maximum sample size was included. Studies with a sample size of at least 50 patients per group were included to avoid small sample size bias.

Data Extraction and Quality Assessment

Two reviewers were independently involved in data collection. Details of authors; study location; study type; sample size; age; smoking status; obesity; hypertension; diabetes; lung disease; recent immobilization; coronary artery disease; malignancy; unprovoked PE; symptoms such as dyspnea, chest pain, hemoptysis, and syncope; treatment modalities such as thrombolytic therapy and inferior vena cava filter; high-risk PE; and outcomes such as death and PE recurrence were collected.

Quality assessment was conducted using the Newcastle-Ottawa Scale.¹⁴ Every study was examined for study population selection, comparability, and outcomes. These components were given a maximum of 4, 2, and 3 points, respectively. Two reviewers were involved in the quality assessment, and any disagreements were solved by discussion with a third reviewer.

Statistical Analysis

The meta-analysis was performed using Review Manager (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration]). Meta-analysis was conducted for all demographic, clinical, and outcome variables if data were available from at least 5 studies. Dichotomous data were combined using the DerSimonian and Laird random-effects model to calculate pooled odds ratios (ORs) with 95% CIs. Continuous variables were pooled to obtain the mean difference. Adjusted data on mortality were also extracted where available and pooled to ORs. The I^2 statistic was used to assess interstudy heterogeneity. Funnel plots were generated, and the Egger test was used to test for publication bias. A sensitivity analysis was conducted to judge the effect of each study

on the meta-analysis results. We excluded 1 study at a time in the meta-analysis software to check whether there was any change in the significance of the results. $P < .05$ was considered statistically significant.

Results

The total number of results after the literature search was 9,495, of which 5,811 were duplicates and hence removed. The remaining 3,684 articles were screened, and 26 were selected for full-text review. Finally, a total of 14 studies were included in the analysis^{9-12,15-24} (Fig. 1). The inter-reviewer agreement for study selection was high ($\kappa = 0.9$).

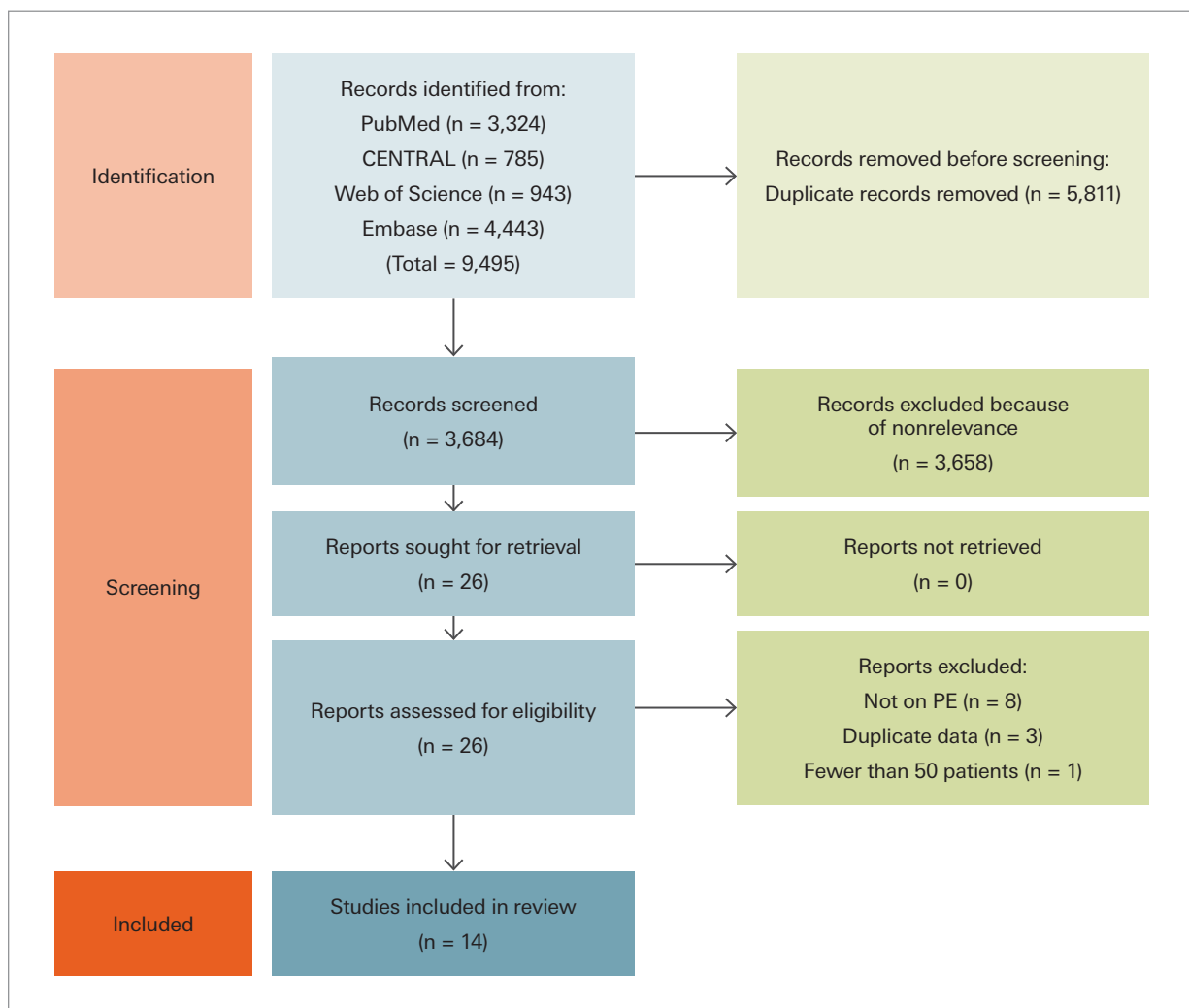


Fig. 1 Study flowchart

CENTRAL, Cochrane Central Register of Controlled Trials; PE, pulmonary embolism.

Data extracted from the studies are presented in Table I^{9-12,15-24} and Table II.^{9-12,15-24} All studies were observational and conducted in different countries. The sample size of the studies ranged from 72 to 146,174 patients per group. On meta-analysis of age in years, it was noted that men presented with PE at a statistically significantly younger age than women (mean difference, -4.01 years; 95% CI, -5.07 to -2.94; $I^2 = 74\%$; $P < .00001$) (Fig. 2). The number of smokers among men was significantly higher than among women (OR, 2.34; 95% CI, 1.55-3.55; $I^2 = 91\%$; $P < .0001$) (Fig. 3). The frequency of hypertension was not significantly different between men and women (OR, 0.83; 95% CI, 0.69-1.00 $I^2 = 80\%$; $P = .05$) (Fig. 4). On the exclusion of Pribish et al¹⁰ from the analysis, the results indicated a significantly lower frequency of hypertension among men (OR, 0.76; 95% CI, 0.61-0.94; $I^2 = 78\%$; $P = .01$). There was no difference in the number of patients with diabetes between groups (OR, 1.04; 95% CI, 0.92-1.17; $I^2 = 35\%$; $P = .57$) (Fig. 5). Lung disease was significantly more frequent among men than among women (OR, 1.68; 95% CI, 1.18-2.40; $I^2 = 98\%$; $P = .004$) (Supplementary Fig. 1). There was no statistically significant difference in the history of recent immobilization between men and women (OR, 0.79; 95% CI, 0.61-1.03; $I^2 = 88\%$; $P = .08$) (Supplementary Fig. 2). On the exclusion of McHugh et al¹⁹ from the analysis, a significantly lower number of men had a history of recent immobilization (OR, 0.72; 95% CI, 0.63-0.82; $I^2 = 36\%$; $P < .00001$). The incidence of coexisting malignancy was significantly higher among men than among women (OR, 1.14; 95% CI, 1.02-1.27; $I^2 = 72\%$; $P = .02$) (Supplementary Fig. 3); however, these results were not stable on sensitivity analysis and turned nonsignificant on exclusion of Borrero et al²⁰ (OR, 1.11; 95% CI, 0.96-1.28; $I^2 = 69\%$; $P = .17$), Agarwal et al²⁴ (OR, 1.12; 95% CI, 0.95-1.32; $I^2 = 73\%$; $P = .18$), and Barrios et al¹⁷ (OR, 1.12; 95% CI, 0.99-1.25; $I^2 = 74\%$; $P = .07$). It was also noted that men had a significantly higher incidence of unprovoked PE than women (OR, 1.29; 95% CI, 1.08-1.53; $I^2 = 50\%$; $P = .004$) (Supplementary Fig. 4).

On analysis of symptoms, there was no significant difference between men and women for dyspnea (OR, 0.84; 95% CI, 0.70-1.01; $I^2 = 67\%$; $P = .06$) (Supplementary Fig. 5). On exclusion of Deng et al²³ (OR, 0.80; 95% CI, 0.69-0.93; $I^2 = 51\%$; $P = .003$) and Barrios et al¹⁷ (OR, 0.79; 95% CI, 0.66-0.94; $I^2 = 49\%$; $P = .007$), the results indicated significantly lower presentation of dyspnea among men. Also, a significantly higher proportion of men presented with chest pain (OR, 1.27;

95% CI, 1.05-1.54; $I^2 = 69\%$; $P = .02$) (Supplementary Fig. 6) and hemoptysis (OR, 2.12; 95% CI, 1.67-2.69; $I^2 = 0\%$; $P < .00001$) (Supplementary Fig. 7) compared with women. The presentation of syncope, however, was significantly lower among men than among women (OR, 0.83; 95% CI, 0.72-0.94; $I^2 = 0\%$; $P = .005$) (Supplementary Fig. 8). These results turned nonsignificant on exclusion of Barrios et al¹⁷ (OR, 0.86; 95% CI, 0.74-1.01; $I^2 = 0\%$; $P = .06$). Comparing the 2 groups, women had a higher proportion of high-risk PE (OR, 0.83; 95% CI, 0.74-0.94; $I^2 = 0\%$; $P = .003$) (Supplementary Fig. 9).

With respect to treatment, there was no difference in the use of thrombolytic therapy between men and women (OR, 1.08; 95% CI, 0.80-1.24; $I^2 = 82\%$; $P = .98$) (Supplementary Fig. 10). Similarly, there was no difference in inferior vena cava filter use between men and women (OR, 1.09; 95% CI, 1.00-1.20; $I^2 = 32\%$; $P = .06$) (Supplementary Fig. 11).

For outcomes, the majority of studies reported data on mortality. A combined analysis of 12 studies showed no statistically significant difference in the risk of mortality between men and women (OR, 0.93; 95% CI, 0.82-1.06; $I^2 = 62\%$; $P = .30$) (Supplementary Fig. 12). The results did not change on the exclusion of any study during sensitivity analysis. Also, there was no evidence of publication bias ($P = .85$ for Egger test) (Supplementary Fig. 13). On pooled analysis of adjusted data from 6 studies, we noted similar results, with no difference in mortality between men and women (OR, 0.94; 95% CI, 0.75-1.17; $I^2 = 85\%$; $P = .57$) (Supplementary Fig. 14). These results also did not change in significance during sensitivity analysis. The Newcastle-Ottawa Scale score of the studies ranged from 5 to 8 (Table II). The inter-reviewer agreement for quality assessment was high ($\kappa = 0.9$).

Discussion

Several anatomic and physiologic differences exist between men and women that can modulate the pathophysiology, morbidity, and mortality rates of several diseases. Such differences have already been well elucidated for cardiovascular, lung, autoimmune, and neurologic disorders.^{8,25-28} Another major difference between the 2 sexes is neurohormonal modulation, especially by estrogen-related compounds; importantly, exogenous estrogens are an accepted risk factor for PE.²⁹ Therefore, biological sex could play an important role in the patho-

TABLE I. Details of Included Studies

| Study | Country | Diagnosis of PE | Sex | Sample size, No. | Age, mean (SD), y | Smoking, No. | Obesity, No. | HT, No. | DM, No. | Lung disease, No. | Recent immobilization, No. | CAD, No. | Malignancy, No. | Unprovoked PE, No. |
|---|----------|------------------------------|-------|------------------|--------------------------|--------------|--------------|---------|---------|-------------------|----------------------------|----------|-----------------|--------------------|
| McHugh, et al ¹⁹ (2002) | US | CTPA or V/Q scan or autopsy | Men | 1,095 | 60.7 (15.5) | NR | NR | NR | NR | 175 | 296 | NR | 252 | NR |
| | | | Women | 1,359 | 63.5 (17.4) | NR | NR | NR | NR | 136 | 294 | NR | 299 | NR |
| Borrero, et al ²⁰ (2007) | US | NR | Men | 6,227 | NR | NR | NR | NR | NR | 1,261 | NR | NR | 1,366 | NR |
| | | | Women | 9,304 | NR | NR | NR | NR | NR | 1,607 | NR | NR | 1,680 | NR |
| Geibel, et al ²¹ (2007) | Germany | NR | Men | 291 | NR | NR | NR | NR | NR | 38 | 97 | NR | 32 | NR |
| | | | Women | 428 | NR | NR | NR | NR | NR | 32 | 150 | NR | 53 | NR |
| Blanco-Molina, et al ²² (2014) | MC | Multinational | Men | 10,979 | 66 (16) | NR | NR | NR | NR | 2,052 | 2,173 | NR | NR | 5,286 |
| | | | Women | 12,838 | 69 (17) | NR | NR | NR | NR | 1,318 | 3,167 | NR | NR | 5,517 |
| Agarwal, et al ²⁴ (2015) | US | ICD codes | Men | 120,272 | 61.1 (16.2) ^a | 31,906 | 14,213 | 59,877 | 22,952 | 28,680 | NR | NR | 16,976 | NR |
| | | | Women | 146,174 | 63.1 (18.6) ^a | 24,731 | 23,855 | 76,445 | 27,990 | 36,636 | NR | NR | 18,460 | NR |
| Deng, et al ²³ (2015) | China | CTPA or clinical | Men | 73 | 72.6 (14.7) | NR | NR | NR | NR | 23 | 24 | NR | NR | NR |
| | | | Women | 76 | 75 (15.1) | NR | NR | NR | NR | 11 | 38 | NR | NR | NR |
| Obradović, et al ¹⁵ (2016) | Serbia | CTPA | Men | 72 | 56 (17) | 20 | 10 | NR | NR | NR | NR | 10 | 5 | 39 |
| | | | Women | 72 | 64 (15) | 6 | 23 | NR | NR | NR | NR | 3 | 11 | 33 |
| Panigada ¹⁶ (2016) | Italy | CTPA or V/Q scan or clinical | Men | 180 | 73.5 (12.4) | NR | NR | NR | NR | 36 | 64 | NR | 71 | 43 |
| | | | Women | 272 | 77.6 (12) | NR | NR | NR | NR | 27 | 126 | NR | 65 | 70 |
| Barrios, et al ¹⁷ (2017) | Spain | CTPA or V/Q scan | Men | 1,004 | 66.6 (16.2) | NR | NR | NR | NR | 136 | 160 | NR | 232 | NR |
| | | | Women | 1,092 | 70.6 (16.8) | NR | NR | NR | NR | 33 | 252 | NR | 200 | NR |
| Tanabe, et al ¹⁸ (2018) | Japan | CTPA or V/Q scan or autopsy | Men | 633 | 60.9 (15.6) | 186 | NR | 231 | 90 | NR | NR | 29 | 30 | NR |
| | | | Women | 795 | 68 (16.1) | 70 | NR | 317 | 90 | NR | NR | 31 | 46 | NR |
| Keller, et al ⁹ (2019) | Germany | NR | Men | 251 | NR | NR | NR | NR | 39 | 38 | NR | 63 | 52 | 153 |
| | | | Women | 318 | NR | NR | NR | NR | 58 | 43 | NR | 43 | 43 | 151 |
| Dzudovic, et al ¹¹ (2020) | Serbia | European guidelines | Men | 294 | 60 (14) | 58 | 54 | 141 | 44 | 34 | NR | NR | 29 | 165 |
| | | | Women | 294 | 65.5 (16) | 26 | 91 | 175 | 55 | 29 | NR | NR | 43 | 129 |
| Oliveira, et al ¹² (2020) | Portugal | CTPA or V/Q scan | Men | 213 | 62 (19) | NR | NR | 97 | 43 | NR | NR | NR | NR | 139 |
| | | | Women | 364 | 67 (18) | NR | NR | 221 | 71 | NR | NR | NR | NR | 237 |
| Pribish, et al ¹⁰ (2020) | US | ICD codes | Men | 950 | 62.3 (15) | 131 | 17 | 510 | 195 | 84 | NR | 92 | 284 | NR |
| | | | Women | 1,081 | 63.8 (17.4) | 122 | 34 | 545 | 191 | 107 | NR | 71 | 333 | NR |

^aMean (SE).CAD, coronary artery disease; CTPA, computed tomography pulmonary angiography; DM, diabetes mellitus; HT, hypertension; ICD, *International Classification of Diseases*; MC, multicentric; NR, not reported; PE, pulmonary embolism; V/Q, ventilation-perfusion.

TABLE II. Symptoms and Outcomes Reported, by Included Studies

| Study | Groups | Sample size, No. | Dyspnea, No. | Chest pain, No. | Hemoptysis, No. | Syncope, No. | Thrombolytic therapy, No. | IVC filter, No. | High-risk PE, No. | Death, No. | Recurrent PE, No. | NOS score |
|---|--------|------------------|--------------|-----------------|-----------------|--------------|---------------------------|-----------------|-------------------|------------|-------------------|-----------|
| McHugh, et al ¹⁹ (2002) | Men | 1,095 | 865 | 559 | 99 | 142 | NR | NR | NR | 186 | 81 | 5 |
| | Women | 1,359 | 1,142 | 639 | 68 | 190 | NR | NR | NR | 255 | 109 | |
| Borrero, et al ²⁰ (2007) | Men | 6,227 | NR | NR | NR | NR | NR | NR | NR | 609 | NR | 8 |
| | Women | 9,304 | NR | NR | NR | NR | NR | NR | NR | 830 | NR | |
| Geibel, et al ²¹ (2007) | Men | 291 | NR | NR | NR | 60 | 73 | NR | 0 | 26 | 53 | 6 |
| | Women | 428 | NR | NR | NR | 120 | 96 | NR | 0 | 43 | 64 | |
| Blanco-Molina, et al ²² (2014) | Men | 10,979 | NR | NR | NR | NR | 117 | 341 | NR | NR | NR | 8 |
| | Women | 12,838 | NR | NR | NR | NR | 111 | 360 | NR | NR | NR | |
| Agarwal, et al ²⁴ (2015) | Men | 120,272 | NR | NR | NR | NR | 26,400 | 15,852 | NR | 3,837 | NR | 8 |
| | Women | 146,174 | NR | NR | NR | NR | 39,087 | 17,892 | NR | 5,116 | NR | |
| Deng, et al ²³ (2015) | Men | 73 | 57 | 16 | NR | 6 | NR | NR | NR | 6 | NR | 6 |
| | Women | 76 | 45 | 7 | NR | 12 | NR | NR | NR | 5 | NR | |
| Obradović, et al ¹⁵ (2016) | Men | 72 | 62 | 32 | 13 | 11 | 42 | NR | 10 | 11 | NR | 7 |
| | Women | 72 | 65 | 14 | 4 | 13 | 44 | NR | 18 | 19 | NR | |
| Panigada ¹⁶ (2016) | Men | 180 | NR | NR | NR | NR | 7 | 0 | 31 | 22 | NR | 6 |
| | Women | 272 | NR | NR | NR | NR | 15 | 5 | 50 | 21 | NR | |
| Barrios, et al ¹⁷ (2017) | Men | 1,004 | 454 | 717 | NR | 125 | 54 | 18 | 686 | NR | NR | 8 |
| | Women | 1,092 | 482 | 797 | NR | 175 | 37 | 31 | 772 | NR | NR | |
| Tanabe, et al ¹⁸ (2018) | Men | 633 | 354 | 111 | NR | NR | 209 | 235 | 205 | 27 | NR | 8 |
| | Women | 795 | 487 | 107 | NR | NR | 219 | 254 | 296 | 49 | NR | |
| Keller, et al ⁹ (2019) | Men | 251 | 207 | 133 | 13 | 55 | NR | 0 | 30 | 18 | 6 | 6 |
| | Women | 318 | 280 | 161 | 6 | 65 | NR | 0 | 38 | 253 | 3 | |
| Dzudovic, et al ¹¹ (2020) | Men | 294 | 247 | 111 | 37 | NR | 97 | NR | 33 | 34 | NR | 6 |
| | Women | 294 | 254 | 91 | 16 | NR | 102 | NR | 47 | 48 | NR | |
| Oliveira, et al ¹² (2020) | Men | 213 | NR | NR | NR | NR | 22 | NR | NR | 100 | NR | 8 |
| | Women | 364 | NR | NR | NR | NR | 45 | NR | NR | 140 | NR | |
| Pribish, et al ¹⁰ (2020) | Men | 950 | 494 | 299 | 38 | 41 | 20 | 82 | 34 | 50 | 9 | 8 |
| | Women | 1081 | 646 | 326 | 21 | 53 | 37 | 92 | 52 | 82 | 20 | |

IVC, inferior vena cava; NOS, Newcastle-Ottawa Scale; NR, not reported.

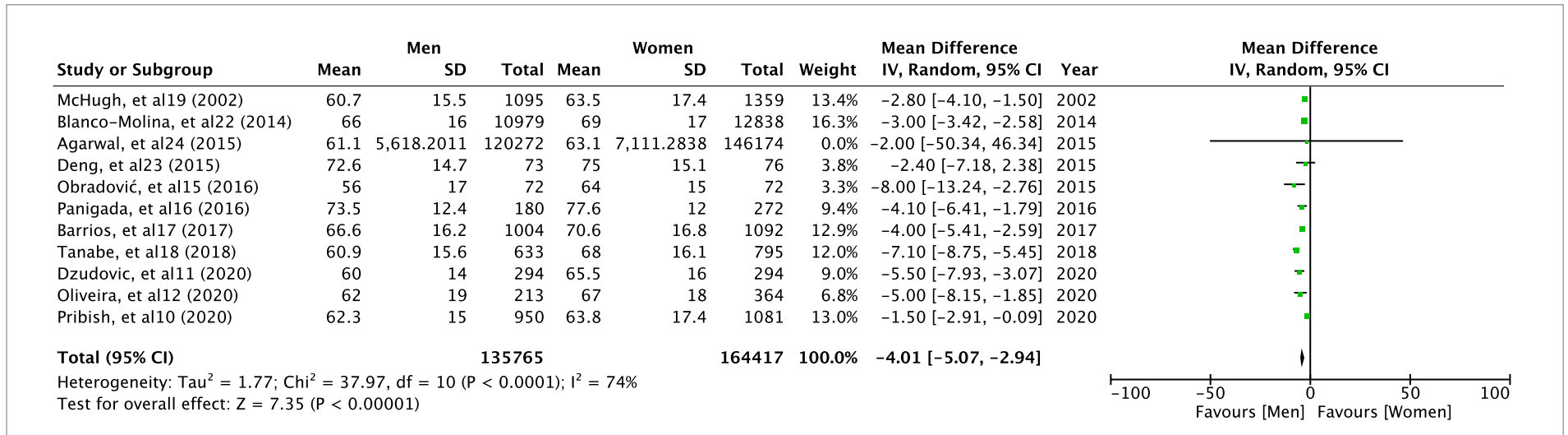


Fig. 2 Meta-analysis of age between men and women with pulmonary embolism

IV, inverse variance.

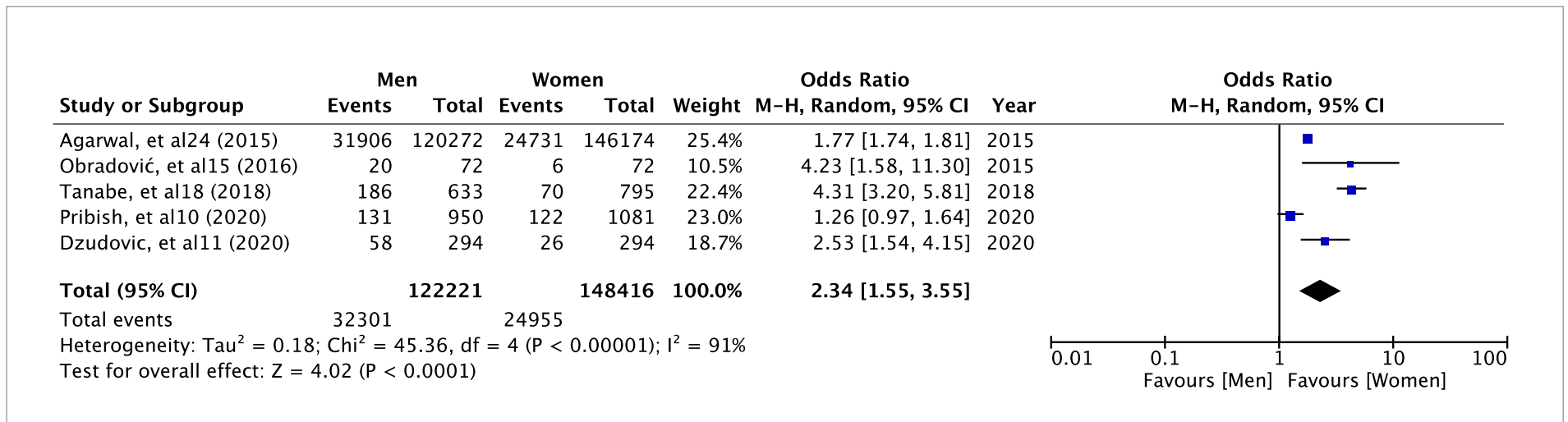


Fig. 3 Meta-analysis of smoking between men and women with pulmonary embolism

M-H, Mantel-Haenszel; IV, inverse variance.

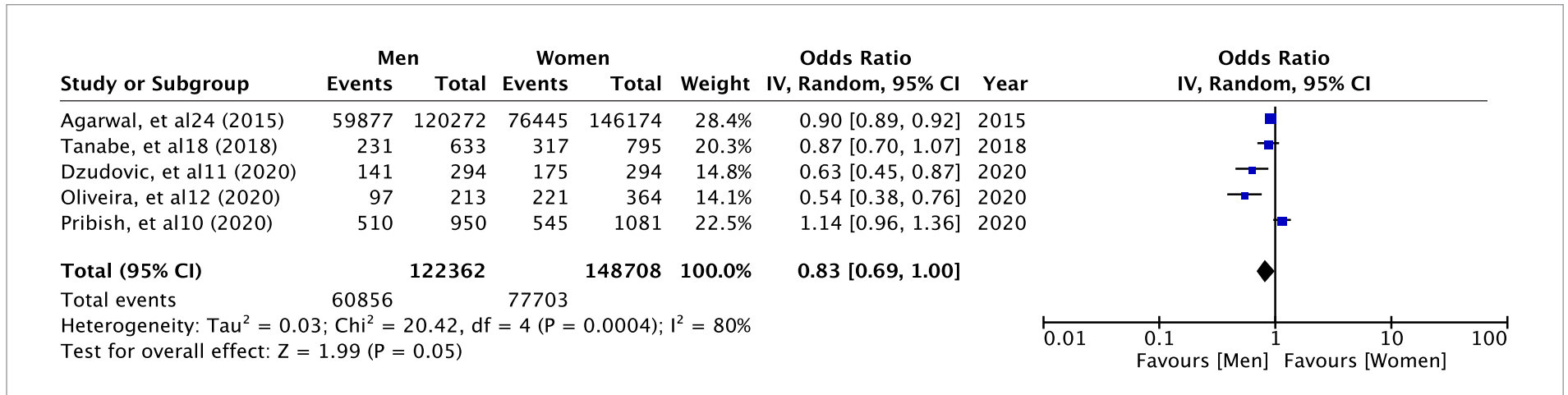


Fig. 4 Meta-analysis of hypertension between men and women with pulmonary embolism
IV, inverse variance.

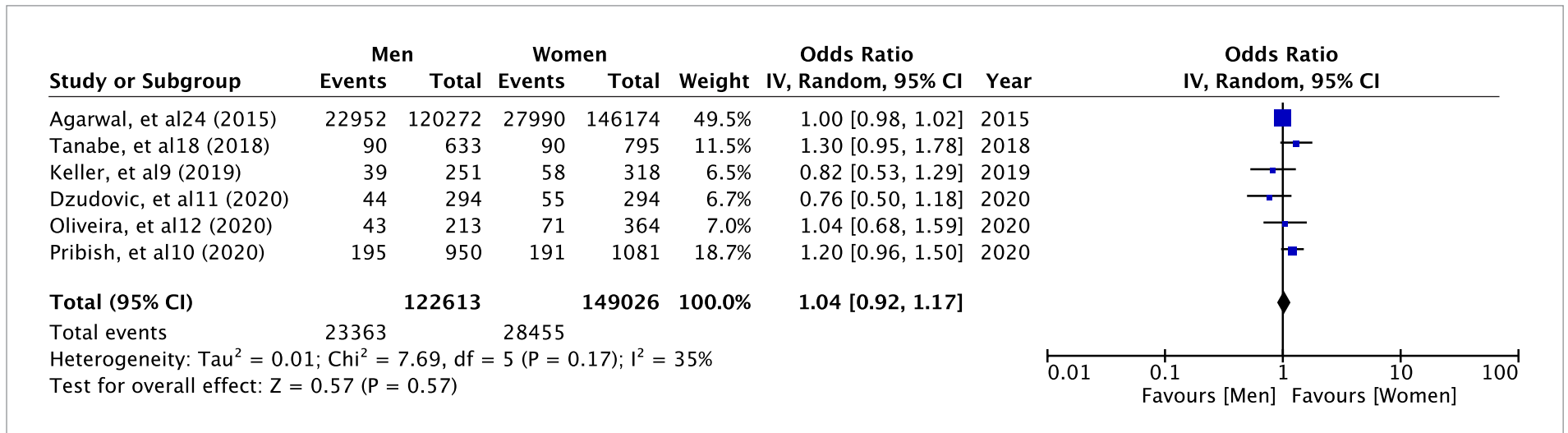


Fig. 5 Meta-analysis of diabetes between men and women with pulmonary embolism
IV, inverse variance.

physiology and outcome of PE.³⁰ To this point, there has been no pooled evidence in the literature to elucidate the influence of sex on PE. This meta-analysis compared the age at presentation, baseline comorbidities, risk factors, symptoms, treatment, and outcomes of PE between men and women. It should be stated at the outset that the data pooled in the meta-analysis were primarily limited by the reporting of the included studies. Many of the baseline comorbidities, risk factors, clinical features, and outcomes could not be compared because they were not reported by all included studies. Also, to avoid small sample size bias, a meta-analysis was conducted only if there were at least 5 studies reporting similar data.

Pulmonary embolism is primarily seen in older individuals, and its incidence increases 2-fold every decade after 40 years of age.³¹ In the present analysis, it was noted that the mean age at presentation with PE for both men and women was 60 years. There was a statistically significant difference between the 2 groups, with the mean age for men being 4 years lower, although such a minuscule difference would likely have negligible clinical significance. The age of the study population also depends on geographical variations and study methods, factors reflected in the high heterogeneity of the meta-analysis. The review found that men were more often smokers and more often had lung disease, malignancy, and unprovoked PE, whereas there were no differences in the history of diabetes or hypertension. These differences reflect the general behavioral pattern of men who smoke more frequently and consequently have lung diseases.³² The malignancy rate may also reflect global cancer incidence rates. The recent GLOBOCAN estimates have shown that the worldwide cancer incidence rate is 19% higher in men than in women.³³

Several risk factors have been identified for PE, including prior thromboembolism, major trauma, recent surgery, immobilization, and exogenous estrogen administration. Many of these factors could not be analyzed in the meta-analysis owing to a lack of data. It was noted that the history of recent immobilization did not differ between women and men, but it has been reported previously that women are more prone to immobilization after surgery, which could lead to a higher incidence of thromboembolism in female patients.³⁴ Another factor is external hormonal therapy, which is a well-established risk factor for women. Estrogen-based oral contraceptive pills and estrogen hormone replacement therapy have been shown to increase the risk of venous thromboembolism among women.³⁵ The relative risk is different based on the type of estrogen, however,

and endogenous sex hormones are not associated with an increased risk.³⁰ Furthermore, many other demographic variables, such as diet and physical activity, can influence PE risk, all of which could not be assessed in the current review.

A few differences were noted in the presentation of PE between men and women. Although the incidence of dyspnea was not significantly different between the 2 groups, a significantly higher proportion of men presented with chest pain and hemoptysis. Also, syncope was more frequently seen in women than in men. Such differences in presentation have been noted in other diseases, as well, although without any clear explanation.⁶ Further in the analysis, it was noted that women presented more frequently with high-risk PE. Risk assessment for PE is conducted using the Pulmonary Embolism Severity Index (PESI) or the simplified PESI (sPESI), which classify individuals into low-, intermediate-, and high-risk categories. Although sex was a factor in the PESI score, the sPESI in 2010 did not find sex to be a predictor of mortality.³⁶ Research suggests that sPESI may predict fatal outcomes more precisely in women, although it has good performance in both sexes.³⁷ Future research on sex-based prognostic indicators should provide better evidence of such differences.

With respect to treatment, there was no difference in the use of thrombolytic therapy or inferior vena cava filter between men and women. Also, no difference was noted in mortality rates after PE between sexes. With respect to mortality, maximum studies were included in the meta-analysis with data from 291,088 patients, thereby increasing the statistical power of the results. The lack of publication bias and no change in the effect size on sensitivity analysis also strengthen the results of the review. Importantly, because this analysis was of crude mortality rates, it can be confounded by several variables. In addition, mortality after PE can be affected by factors such as patient age, comorbidities, risk factors, location of PE, severity, and the treatment protocol.² In an attempt to generate more robust results, we also extracted multivariable adjusted ratios and pooled them in a meta-analysis. Although only 6 studies were available for this analysis, the results confirmed that there was no difference in the risk of mortality after PE between the 2 sexes. Outcomes of PE also include the risk of recurrence, quality of life, and exercise tolerance in the long term. One prospective study from Canada has shown that compared with men, women had diminished exercise tolerance and worse quality of life after PE after adjustment for confounding factors.³⁸ At this point,

however, this review could not quantitatively analyze these outcomes.

Limitations

Several limitations exist with this review. Many of the outcomes had moderate to high heterogeneity; therefore, the results should be interpreted with caution. The heterogeneity can be explained by different inclusion criteria, heterogeneous study populations, variable data-collection methods, and several sources of bias. Because of limited data and several differences among the studies, however, a subgroup analysis for such variables was not possible. Second, outcome data were limited to mortality, which varied from in-hospital mortality to early mortality (within 6 months). No long-term results were available, and most studies did not adjust for confounders. Third, the review was unable to quantitatively analyze PE characteristics such as its location, cardiac function, and laboratory values. This information would have provided further insight into differences by sex.

The strengths of the review lie in the large number of studies in the analysis. A sensitivity analysis was conducted to check the stability of the results. Only contemporary data from after 2000 were included to present this meta-analysis on sex differences for PE.

Conclusion

This review showed that the age at presentation, comorbidities, and symptoms of PE differ between men and women. Limited data also suggest that women more frequently have high-risk PE than men, but the use of thrombolytic therapy does not differ between the sexes. Importantly, both crude and adjusted data showed that the mortality rate does not differ between men and women. Results should be interpreted with caution owing to high interstudy heterogeneity in several analyses. Further research should be conducted to provide insight into differences in other characteristics and outcomes of PE between the 2 sexes.

Published: 14 August 2023

Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Yu Zhang, Yu Qiu, Jinming Luo, and Jian Zhang. The manuscript was written by Qingqing Yan, and all authors read and approved the final manuscript.

Conflict of Interest/Disclosure: None

Funding/Support: None

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