Gender Differences in Risk of Adverse Outcomes and Complications Associated With Peripheral Artery Disease: A Systematic Review

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Background

Peripheral artery disease (PAD) is a narrowing of blood vessels in the extremities, depriving the tissues of much-needed oxygenation. PAD typically arises from atherosclerosis, which is a fatty plaque deposition in the arteries. It may affect the legs or arms of an individual. The prevalence of PAD increases with age. Approximately 5% of individuals in their 60's exhibit PAD and more than 20% of individuals 80yo or greater have PAD. African Americans and Hispanics appear to have increased risks for PAD development. Nearly 6.5 million Americans currently suffer from PAD.[1] Patients with PAD typically manifest pain, aches, or cramping with physical activity such as walking. The claudication symptoms can affect patients' walking and dramatically affect their activities of daily living. PAD is also accompanied by weakness, cool skin, and numbness.

Lower extremity PAD can be diagnosed through blood pressure measures using the ankle-brachial index. It can also be assessed with doppler ultrasound, magnetic resonance angiography, and computer tomographic angiography. PAD treatments include antiplatelet agents, lipid-lowering medications, surgery to bypass blocked arteries, and interventional procedures to restore blood flow through stenting and angioplasty.[2] The health care cost for an individual with PAD is approximately $11,553/year compared to only $4219/year for a similar individual without PAD.[3] PAD patients often suffer substantial morbidity with their disease and they have a highly elevated risk of all-cause and cardiovascular mortality.[4] In Virginia House Joint Resolution No. 137 during the 2022 session, the Virginia House of Delegates and the Senate acknowledged that: 1) approximately 200,000 individuals in Virginia including disproportionate numbers of minorities will need amputations as a result of PAD that were not properly diagnosed and treated; 2) that approximately 20% of Virginians age 60+ are affected by PAD; 3) PAD is often unrecognized by individuals and healthcare professionals thereby resulting in negative outcomes that could have been avoided; 4) early diagnosis and treatment of PAD through screening and awareness can "reduce care costs, prevent limb loss, and enhance the overall well-being of countless individuals'."[5]

With the increasing elderly population and diversity in the Commonwealth of Virginia, the prevalence of PAD will likely further increase; approximately 15 to 20 patients are seen daily at UVA Health for PAD. Therefore, this project aims to identify differences in risk of being diagnosed, outcomes, and complications including cardiovascular issues, amputations, or overall death in men vs women undergoing treatment for PAD and to increase awareness, education, and early detection of PAD. The current study entails a systematic review and analysis of the differences in risk outcomes in female vs male patients undergoing treatment for PAD. Disease outcomes are often studied in clinical trials which may not represent female patients equally. We hypothesize female and male patients with PAD are equally at risk for significant disease endpoints.

Methods

Search Strategy

The scoping review was conducted with guidance from the librarians at the University of Virginia's Health and Sciences Library. MeSH terms were identified for a literature review using the PICO framework. Ovid MEDLINE was the platform used to conduct the literature review. The literature review was conducted and data was extracted as detailed below. Articles were be excluded or included based upon the criteria detailed below. Rayyan, an AI powered tool for systematic literature reviews, was be utilized by two reviewers to include or exclude each paper. Disputes between the two reviewers were settled by a third party.

Study selection and data extraction

All studies that reported sex-specific unadjusted numbers, rates, and percentages of the studied outcomes (MI, MALE, MACE, amputation, all-cause mortality) were included. The inclusion and exclusion criterion are listed below.

Inclusion criteria
- Quantitative and Qualitative research question
- Gender data included
- Study population is patients with peripheral artery disease (ABI<0.9)
- Outcomes include death, cardiovascular-related death, and amputation
- Timing: Outcome should occur after surgical intervention

Exclusion criteria
- Published prior to 2000
- Full text not available
- Language other than English
- Systematic Review
- Upper extremity PAD
- Op/ed
- Book Chapters
- Case Reports/Studies

Study Quality Assessment

In compliance with scoping review methodology, no quality assessment of included studies was conducted, as our goal was to rapidly map the literature.[6] A detailed analysis was conducted on the articles which met the inclusion criteria specified above and data was extracted. Statistical assessments were conducted on: risk of being diagnosed with PAD based on gender, complications of PAD (cardiovascular-related death and overall death), and adverse outcomes following surgical interventions.

Statistical analysis

The R language (R version 4.1.0) in R Studio was utilized to perform all statistical analyses; 1,2 the package metafor was used to perform the meta-analysis. 3 Categorical variables were summarized using frequencies and percentages. Based on extracted data, the odds ratios (OR) with their corresponding 95% confidence intervals (CI) were pooled across studies using random-effects models with inverse-variance weighting for each outcome. Tests of heterogeneity were evaluated with Cochran's Q test and I^2 statistic. Publication bias was assessed with the Begg's rank correlation test and its funnel plots. Statistical significance was set at $P < 0.05$.

Results

1252 articles were screened for eligibility. Disease endpoints analyzed were amputation, all-cause mortality, myocardial infarction (MI), major adverse cardiovascular events (MACE), and major adverse limb events (MALE). Female and male patients are equally at risk for these significant PAD endpoints. More attention should be raised for PAD diagnosis and treatments for female patients.

All-cause mortality: Seven studies reported outcomes on sex-specific all-cause death rates. The heterogeneity test results showed an I 2 of 95.6% (P < 0.001), indicating that the between-study heterogeneity was significant; thus, a random-effects model was chosen for meta-analysis. The forest plot showed that all-cause death rates did not differ significantly between the two sexes with the pooled OR between the groups being 1.11 (95% CI: 0.87-1.42).

Amputation: Seven studies reported outcomes on sex-specific amputation rates. The heterogeneity test results showed an I 2 of 87.7% (P < 0.001), indicating that the between-study heterogeneity was significant; thus, a random-effects model was chosen for meta-analysis. The forest plot showed that amputation rates did not differ significantly between the two sexes with the pooled OR between the groups being 1.04 (95% CI: 0.78-1.38).

MACE: Five studies reported outcomes on sex-specific MACE rates. The heterogeneity test results showed an I 2 of 90.3% (P < 0.001), indicating that the between-study heterogeneity was significant; thus, a random-effects model was chosen for meta-analysis. The forest plot showed that MACE rates did not differ significantly between the two sexes with the pooled OR between the groups being 1.11 (95% CI: 0.85-1.44).

MALE: Three studies reported outcomes on sex-specific MALE rates. The heterogeneity test results showed an I 2 of 77.5% (P < 0.001), indicating that the between-study heterogeneity was significant; thus, a random- effects model was chosen for meta-analysis. The forest plot showed that MACE rates did not differ significantly between the two sexes with the pooled OR between the groups being 1.07 (95% CI: 0.77-1.49).

MI: Six studies reported outcomes on sex-specific MI rates. The heterogeneity test results showed an I 2 of 46.8% (P = 0.09), indicating that the between-study heterogeneity was not significant; thus, a fixed-effects model was chosen for meta-analysis. The forest plot showed that MI rates did not differ significantly between the two sexes with the pooled OR between the groups being 0.95 (95% CI: 0.87-1.04).
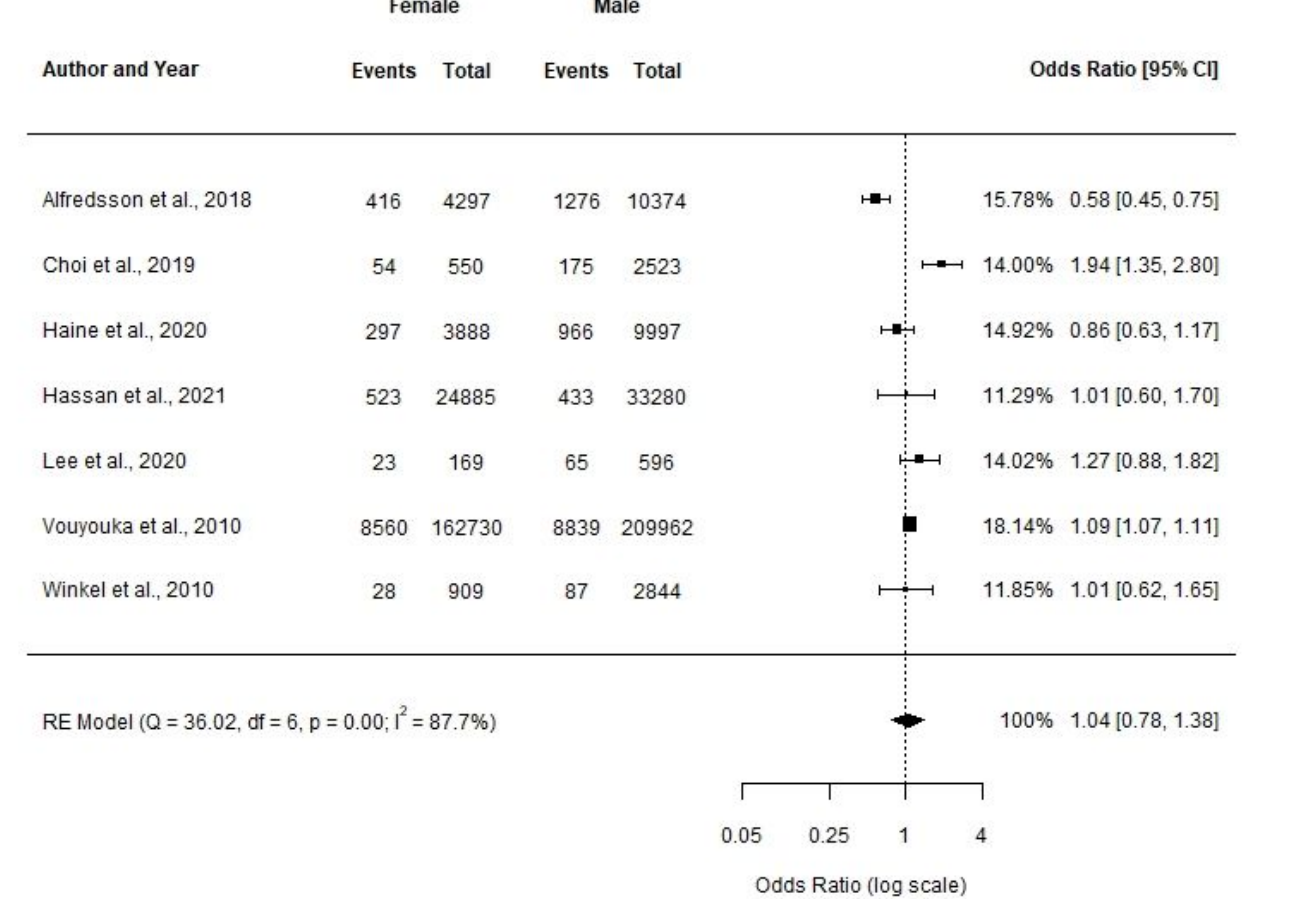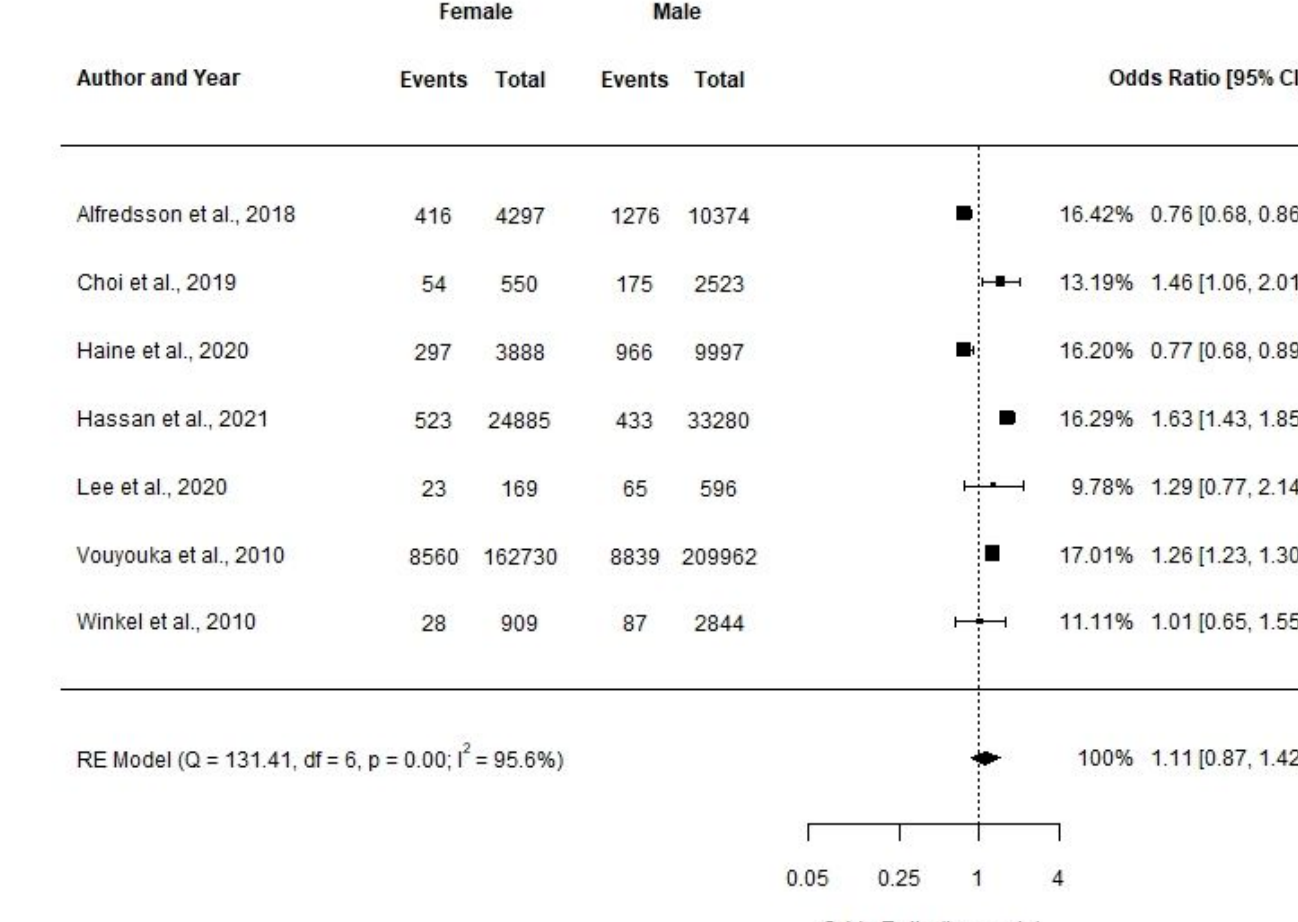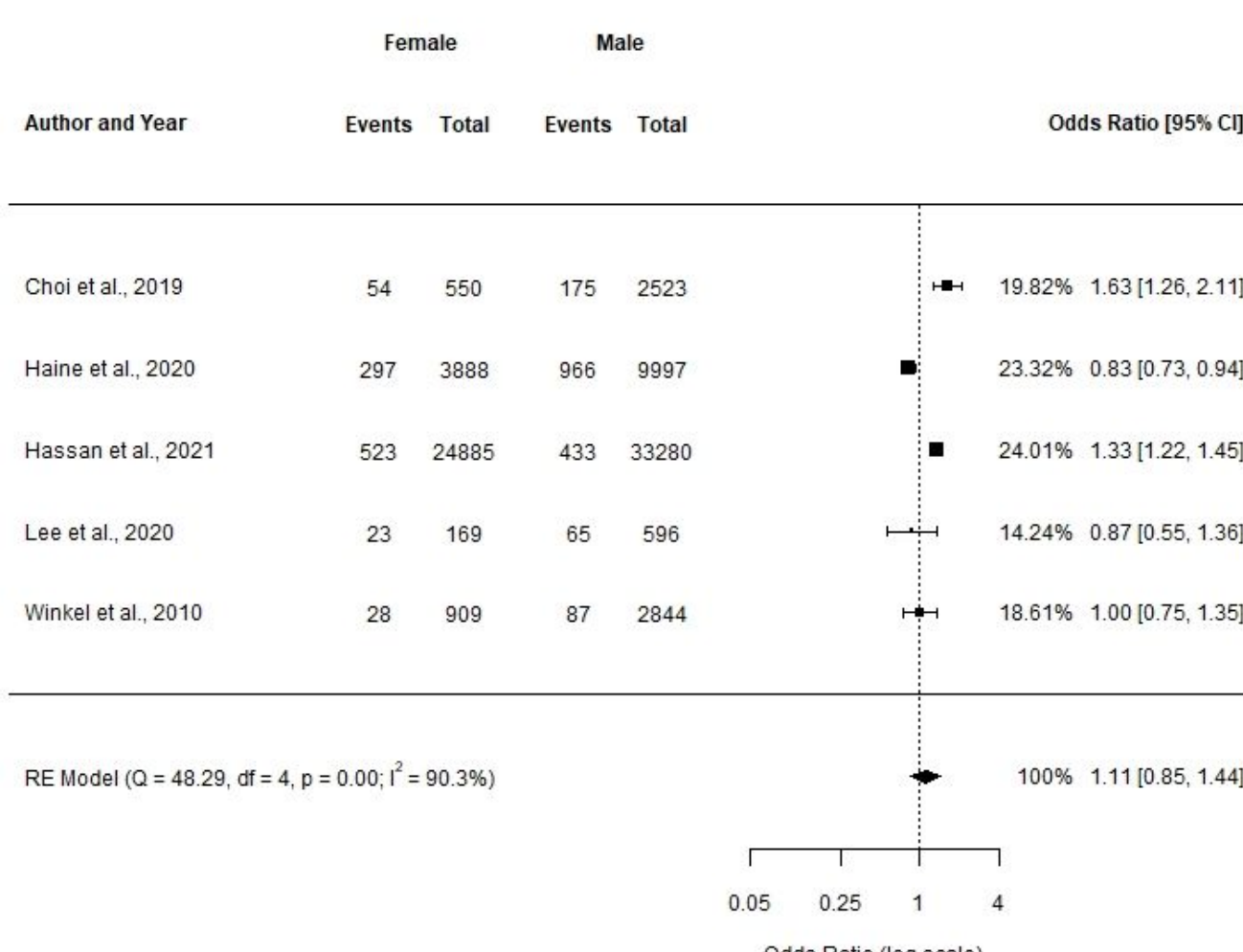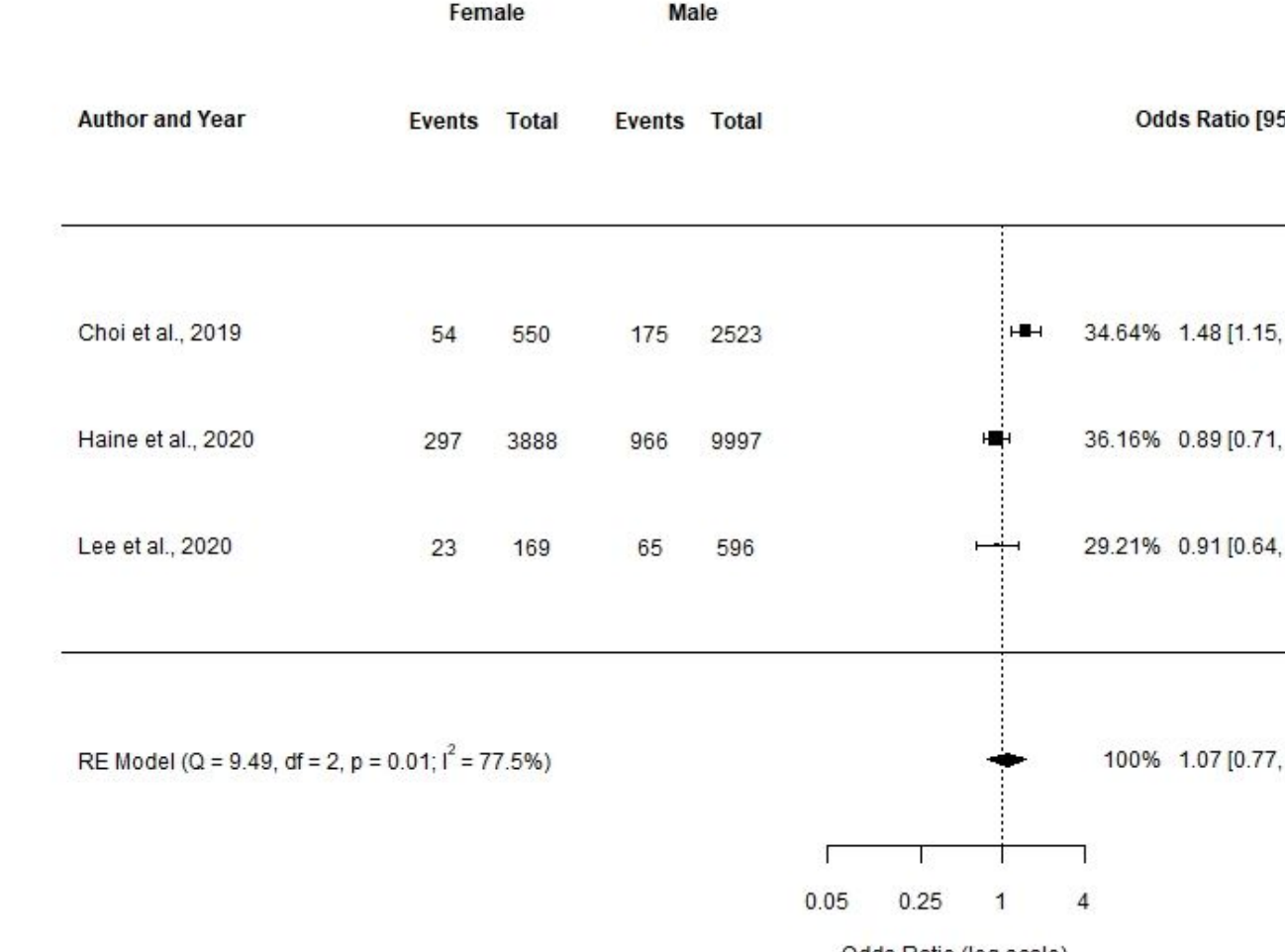
MI Forest Plot
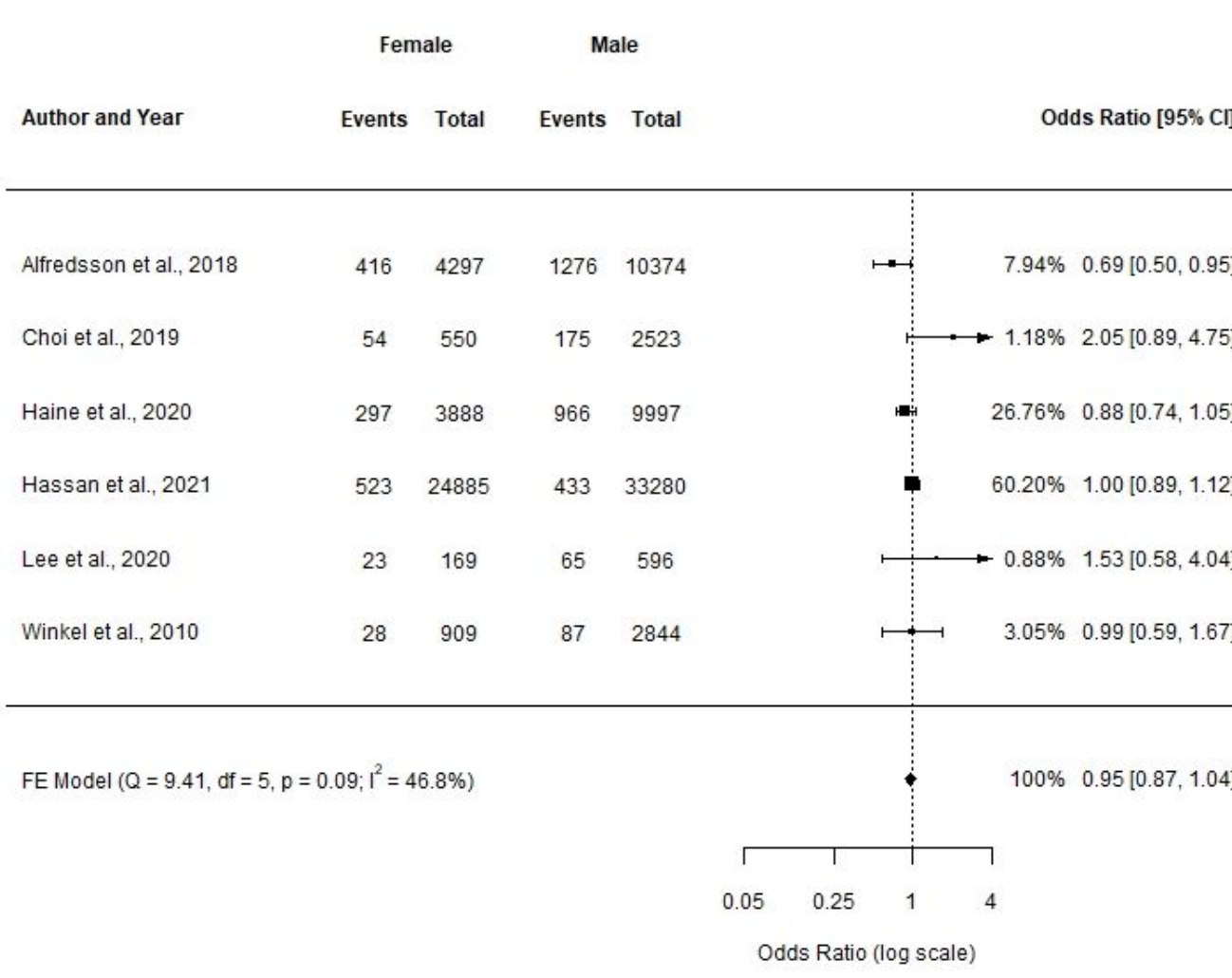
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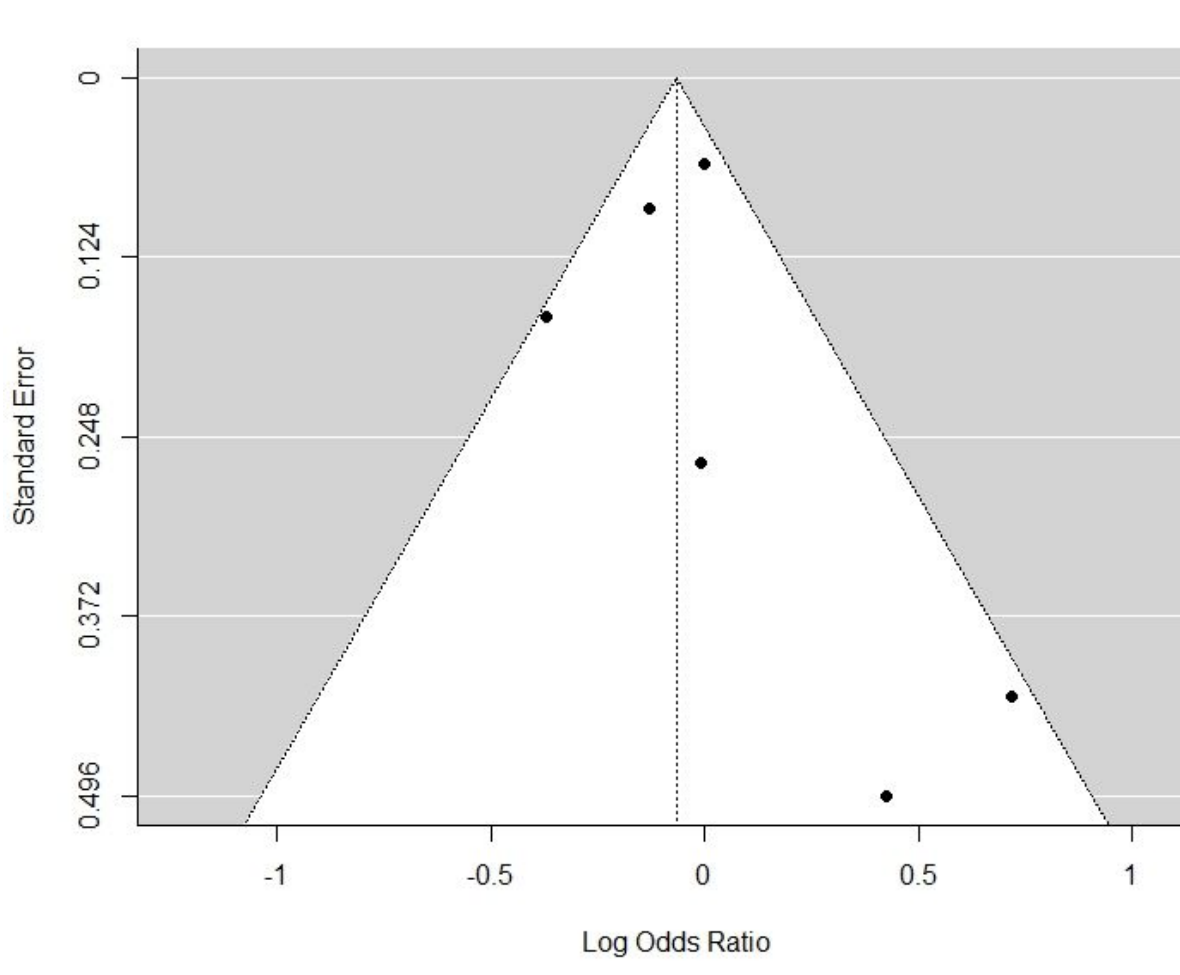
Amputation Forest Plot

All-Cause Mortality Forest Plot

MACE Forest Plot

MALE Forest Plot

Conclusion

Our study serves to update and expand upon mortality and adverse outcome predictors for PAD patients. This study provides the framework for a tool to identify PAD patients that are at risk of adverse effects and mortality and emphasizes the importance of female representation in clinical trials relating to PAD given the similar adverse outcomes for female and male patients with PAD. Female and male patients should be equally screened, examined, and treated for PAD. Equal representation of female patients in clinical trials is essential for PAD treatments. Previous studies have found a higher risk of mortality in males with PAD compared to females.[7] However, the current study found that female and male patients were equally at risk for all-cause mortality as well as several significant disease endpoints including amputation, myocardial infarction, MACE, and MALE. Female patients are often underrepresented in clinical trials studying PAD.[8] This underrepresentation is significant and could have serious consequences on female patient outcomes. Female patients should be equally represented in clinical trials regarding PAD because female and male patients are equally at risk for significant adverse outcomes associated with PAD. In conclusion, female patients with PAD should be equally represented in clinical trials on PAD, and the screening and treatment process should be similar to female and male patients with PAD.

References

1. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. *Circulation*. 2021;143:e254–e743.
2. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in 2017 Mar 21;135(12):e790]. *Circulation*. 2017;135(12):e686-e725.
3. Scully RE, Arnaoutakis DJ, Smith AD, Semel M, Nguyen LL. Estimated annual health care expenditures in individuals with peripheral arterial disease. *J Vasc Surg*. 2018 Feb;67(2):558- 564.
4. Agnelli G, Belch JJF, Baumgartner I, Giovas P, Hoffmann U. Morbidity and mortality associated with atherosclerotic peripheral artery disease: A systematic review. Atherosclerosis. 2020 Jan; 293:94-100.
5. House Joint Resolution No. 137 Designating September 2022 and in each succeeding year as Peripheral Artery Disease Awareness in Virginia. https://lis.virginia.gov/cgi- bin/legp604.exe?221+ful+HJ137ER+pdf. Accessed online on October 7, 2022.
6. Peters MDJ, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil, H. Chapter 11: Scoping Reviews (2020 version). In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis, JBI, 2020. Available from https://synthesismanual.jbi.global. https://doi.org/10.46658/JBIMES-20-12
7. Morrell J, Zeymer U, Baumgartner I, Limbourg T, Röther J, Bhatt DL, Steg PG; REACH Registry Investigators. Differences in management and outcomes between male and female patients with atherothrombotic disease: results from the REACH Registry in Europe. Eur J Cardiovasc Prev Rehabil. 2011; 18:270–277. doi: 10.1097/HJR.0b013e32833cca34
8. Mayor JM, Preventza O, McGinigle K, et al. Persistent under-representation of female patients in United States trials of common vascular diseases from 2008 to 2020. *Journal of Vascular Surgery*. 2022;75(1):30-36. doi:10.1016/j.jvs.2021.06.480
9. R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.
10. RStudio Team (2020). RStudio: Integrated Development Environment for R. RStudio, PBC, Boston, MA. http://www.rstudio.com/.
11. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *Journal of Statistical Software*. 2010;36:1-48. doi:10.18637/jss.v036.i03

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