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Research Article

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Erectile Dysfunction as a Novel Biomarker for the Onset of Cardiometabolic Vascular Disease Risk in the Aging Male: A Systematic Review and Meta-Analysis

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Abstract

Background and Objectives: *Vascular Erectile dysfunction (ED) is considered a sentinel marker for underlying cardiovascular and metabolic disorders. This systematic review and meta-analysis aim to quantify the correlation and the predictive value of ED for cardiometabolic vascular diseases (CVD) in young adults as well as aging males and to explore the temporal relationship between ED onset and the development of these diseases.*

Methods: *A comprehensive search of databases including PubMed, EMBASE, and Cochrane Library was conducted to identify relevant studies. Inclusion criteria were studies assessing the association between ED and CVD, with effect sizes reported as odds ratios (ORs) or hazard ratios (HRs). Data were extracted and pooled using random-effects meta-analysis. Sensitivity analyses, including leave-one-out analysis, and Egger's test for publication bias, were performed.*

Findings: *The pooled analysis of 39 studies revealed a significant association between ED and CVD with an OR of 1.42 (95% CI: 1.28-1.57). The temporal relationship indicates that ED precedes the onset of CVD by approximately 2 to 5 years. Endothelial dysfunction, a common pathway in ED and CVD, was highlighted through biomarkers such as flow-mediated dilation (FMD), nitric oxide (NO) levels, and C-reactive protein (CRP).*

Limitations: *Limitations include heterogeneity among study designs and the potential for residual confounding.*

Conclusions: *ED is a robust predictive biomarker for CVD in aging males, with significant implications for early detection and preventive strategies.*

Clinical Implications: *Clinicians should consider cardiovascular risk assessment in patients presenting with ED to facilitate timely intervention and improve long-term outcomes.*

Keywords: Erectile Dysfunction, Cardiovascular Disease, Coronary Artery Disease, Stroke, Cardiovascular Mortality, Risk Factors, Endothelial Dysfunction

1. Introduction

Erectile dysfunction (ED) is a common condition in aging males, with prevalence increasing from 40% at age 40 to about 70% by age 70 [1]. Beyond its impact on quality of life, ED is increasingly recognized as a harbinger of cardiometabolic vascular diseases (CVD), such as coronary artery disease (CAD), hypertension, and diabetes [2-4]. This systematic review and meta-analysis aim to synthesize the evidence on ED as a predictive biomarker for CVD, examining the underlying pathophysiological mechanisms and the temporal relationship between the onset of ED and the development of cardiometabolic conditions.

Through the systematic review and meta-analysis, the primary objectives are to investigate the role of erectile dysfunction (ED) as a consistent and reliable early biomarker for cardiometabolic vascular diseases. The aim is to explore the existing evidence to determine the strength of the association between ED and cardiometabolic vascular diseases, with a focus on establishing

ED as a potential early indicator of cardiovascular health issues. Furthermore, the study seeks to provide practical recommendations for clinical practice based on the findings. This includes assessing the feasibility and effectiveness of using ED as a screening tool for the early detection of cardiometabolic vascular diseases. By evaluating the potential of ED as a predictive marker for cardiovascular risk, the goal is to contribute valuable insights to enhance screening and management strategies in clinical settings. In summary, the systematic review and meta-analysis aim to shed light on the relationship between ED and cardiometabolic vascular diseases, with the ultimate goal of improving early detection and management of cardiovascular health issues through the utilization of ED as a screening tool in clinical practice.

2. Methods

2.1. Data Search and Selection

A systematic search was conducted in PubMed, EMBASE, and the Cochrane Library databases for studies published up to July 2023. Search terms included "erectile dysfunction," "cardiovascular disease," "coronary artery disease," "hypertension," "diabetes," and "biomarker." Inclusion criteria were observational studies and meta-analyses reporting the association between ED and CVD, with effect sizes as ORs or HRs.

Overall, 3,727 records were identified, with 616 duplicates removed. After screening and assessment, 39 studies were included in the analysis, with 26 from databases and registers and 13 from other methods.

2.2. Data Extraction and Quality Assessment

Data were extracted on study design, sample size, effect sizes, confidence intervals, and follow-up duration. Quality assessment was performed using standardized criteria, focusing on the reliability and validity of reported outcomes.

2.3. Statistical Analysis

The statistical analysis for this study involved several important steps. Firstly, a meta-analysis combined the effect sizes from individual studies. Random-effect models were utilized to account for the variability among the included studies. This approach is particularly useful when there is heterogeneity in the data. The degree of heterogeneity among the studies was quantified using the I^2 statistic. This statistic helps to understand the extent to which the variability in effect sizes is due to true differences between studies rather than random error.

In addition, Egger's test was performed to evaluate the presence of publication bias in the meta-analysis. Publication bias can occur when studies with significant results are more likely to be published, leading to an overestimation of the true effect size. Furthermore, sensitivity analyses were conducted on studies that have consistent reporting standards and methodologies. This ensures that the comparison and assessment of their influence on the pooled effect size are meaningful.

3. Results

3.1. Data Extraction

Thirty-nine studies met the inclusion criteria, encompassing a total of over 450,000 participants. The studies varied in design, including cohort studies, meta-analyses, and systematic reviews.

3.2. Data Analysis

The majority of studies report effect sizes (OR) range from 0.53 to 4.62. were found to be generally consistent, indicating a positive association between ED and CVD, with ORs typically above 1.0, again suggesting a positive association. The 95% confidence interval (CI) for the pooled effect size is (1.28, 1.57). provides consistent and robust evidence supporting the association between erectile dysfunction (ED) and cardiovascular disease (CVD).

3.3. Heterogeneity Analysis

The I^2 statistic indicates significant heterogeneity among the studies, with values ranging from approximately 70.6% to 75.2%. This suggests that a considerable proportion of the variability in effect sizes is due to differences between studies rather than sampling error alone. High I^2 values (>50%) suggest that the studies are not all estimating the same underlying effect and that there are likely differences in study populations, methodologies, or other factors contributing to the variability in results. The moderate to high heterogeneity values observed in this analysis indicate that the association between erectile dysfunction (ED) and cardiovascular disease (CVD) may be influenced by various factors that differ across studies. Despite the heterogeneity, the overall pooled effect size remains robust, indicating a consistent positive association between ED and CVD across the studies.

3.4. Publication Bias

Based on the provided p-value of 0.282, which is greater than the conventional threshold of 0.05, there is no significant evidence of publication bias in this meta-analysis. This indicates that the results are unlikely to be substantially influenced by unpublished studies or selective publication of positive findings.

3.5. Sensitivity Analysis

In conducting a sensitivity analysis, the primary goal was to ensure the robustness and stability of the pooled effect size by examining how the exclusion of individual studies affects the overall results. The consistent positive association, robust statistical significance, large sample sizes, diverse study designs, and lack of significant publication bias strongly support the potential use of ED as an early biomarker for CVD. The overall pooled effect size remains stable with slight changes when excluding each study one by one. This indicates that no single study disproportionately influences the overall results, demonstrating robustness. The sensitivity analysis demonstrates that the association between erectile dysfunction (ED) and cardiovascular disease (CVD) is not overly influenced by any single study, supporting the robustness of the evidence.

3.6. Association Between ED and CVD

The meta-analysis demonstrated a pooled OR of 1.42 (95% CI:

1.28-1.57), indicating a significant association between ED and increased risk of CVD. Sensitivity analyses confirmed the stability of the results, with no single study disproportionately influencing the pooled effect size.

3.7. Temporal Relationship

Longitudinal studies indicated that ED often precedes the diagnosis of CVD by 2 to 5 years, emphasizing its potential role as an early marker for cardiovascular risk [4-6].

3.8. Pathophysiological Mechanisms

Endothelial dysfunction emerged as a central mechanism linking ED with CVD. Key biomarkers such as FMD, NO levels, and CRP were consistently associated with both conditions [7-9]. The shared pathophysiological pathways underscore the relevance of ED in predicting cardiometabolic diseases.

4. Discussion

4.1 Implications for Clinical Practice

The findings underscore the importance of considering ED not merely as a quality-of-life issue but as a significant indicator of underlying endothelial dysfunction and cardiovascular risk. Routine cardiovascular screening in patients presenting with ED could facilitate early detection and intervention, potentially mitigating the progression of CVD and other diseases related to vascular health.

4.2. Strengths and Limitations

The strengths of this systematic review and meta-analysis include a comprehensive search strategy, rigorous inclusion criteria, and robust statistical analysis methods, which collectively enhance the validity and reliability of the findings. Additionally, the large sample size and diversity of included studies strengthen the generalizability of the results.

• **Heterogeneity:** The included studies vary in design, population characteristics, and diagnostic criteria for both ED and CVD, which introduced moderate to high heterogeneity values that were observed in this analysis and indicate that the association between erectile dysfunction (ED) and cardiovascular disease (CVD) may be influenced by multifactorial factors that differ across studies.

• Despite the heterogeneity, the overall pooled effect size remains robust, indicating a consistent positive association between ED and CVD across the studies.

• **Residual Confounding:** While many studies adjusted for confounders, the potential for residual confounding cannot be entirely ruled out. Factors such as lifestyle, comorbid conditions, and medication use may influence the observed associations.

• **Publication Bias:** Although Egger's test and funnel plot analyses did not reveal significant publication bias, the possibility of unpublished studies with null results remains.

• **Temporal Relationship:** The exact temporal relationship between ED onset and CVD development is challenging to establish definitively due to the varying follow-up durations and retrospective nature of some studies.

4.3. Future Directions

Further research should focus on:

• **Prospective Cohort Studies:** Long-term, large-scale prospective cohort studies are needed to confirm the temporal relationship and causality between ED and CVD.

• **Mechanistic Studies:** Investigating the underlying biological mechanisms through which ED contributes to the development of CVD will provide deeper insights and potential therapeutic targets.

• **Integrated Care Models:** Developing and evaluating integrated care models that include routine cardiovascular risk assessment and management in men with ED could improve outcomes.

5. Conclusion

The findings from multiple studies and meta-analyses consistently demonstrate a significant association between erectile dysfunction (ED) and cardiovascular disease (CVD). The effect sizes, represented by odds ratios, support this association, and systematic reviews generally agree on the increased risk of CVD in men with ED. The pooled effect size from the meta-analysis is approximately 1.42 (95% CI: 1.28 to 1.57), indicating a robust association between ED and CVD. This strong effect size underscores the importance of considering ED as a potential early indicator of cardiovascular risk. The large sample sizes in the included studies, particularly in meta-analyses, further strengthen the validity of these findings. Some meta-analyses included sample sizes ranging from 45,000 to over 150,000 participants, providing a solid foundation for the observed associations. The diversity of study designs, including cohort studies, meta-analyses, and reviews, provides longitudinal data that are crucial for establishing temporality and inferring causality. This mix of study designs enhances the robustness of the findings, making the association between ED and CVD more credible.

Funnel plot analysis and Egger's regression test suggest no significant publication bias, indicating that the findings are reliable and not influenced by selective reporting. This adds to the credibility of the evidence. Biological plausibility is supported by shared pathophysiological mechanisms between ED and CVD, such as endothelial dysfunction, atherosclerosis, and inflammation. Biomarkers like flow-mediated dilation (FMD), nitric oxide (NO) levels and C-reactive protein (CRP) are consistently linked with both conditions, providing a plausible explanation for the association. Overall, the evidence supports the use of ED as an early biomarker for CVD. This warrants further research and consideration in clinical practice to facilitate early detection and intervention, ultimately improving cardiovascular outcomes. Given the consistent positive association and the quality of the studies, ED can be considered a potential early biomarker for CVD. However, further meta-analytic techniques and sensitivity analyses are needed to confirm the robustness and consistency of the evidence [10-35].

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