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REVIEW

Erectile Dysfunction and Depression: A Systematic Review and Meta-Analysis

Qian Liu, MPH,[1,2,*] Youpeng Zhang, MD,[1,*] Jin Wang, MD,[1] Sen Li, MD,[1] Yongbiao Cheng, MD,[1] Jialun Guo, BS,[1] Yong Tang, BS,[1] Hanqing Zeng, MD,[1] and Zhaohui Zhu, MD[1]

ABSTRACT

Background: Some studies have reported that exposure to depression increases the risk of erectile dysfunction (ED), whereas others have observed no association. Moreover, additional studies have reported that exposure to ED increases the risk of depression.

Aim: To identify and quantitatively synthesize all studies evaluating the association between ED and depression and to explore factors that may explain differences in the observed association.

Methods: We conducted a systematic review and meta-analysis. We searched Medline, Ovid Embase, and the Cochrane Library through October 2017 for studies that had evaluated the association between ED and depression. Studies were included in accordance with Patient Population or Problem, Intervention, Comparison, Outcomes, and Setting (PICOS) inclusion criteria.

Outcomes: The odds ratio (OR) was regarded as the effect size, and the heterogeneity across studies was assessed using the I^2 statistic.

Results: We identified 49 eligible publications. The pooled OR for studies evaluating depression exposure and risk of ED was 1.39 (95% CI: 1.35−1.42; n = 46 publications with 48 studies). Although we observed large heterogeneity ($I^2 = 93.6\%$), subgroup analysis indicated that it may have been as a result of variations in study design, comorbidities, ED assessment, depression assessment, the source of the original effect size, etc. No significant publication bias was observed ($P = .315$), and the overall effect size did not change by excluding any single study. The pooled OR for studies evaluating ED exposure and risk of depression was 2.92 (95% CI: 2.37−3.60; n = 5 publications with 6 studies). No significant heterogeneity ($P < .257$, $I^2 = 23.5\%$) or publication bias ($P = .260$) was observed.

Clinical Implications: Patients reporting ED should be routinely screened for depression, whereas patients presenting with symptoms of depression should be routinely assessed for ED.

Strengths and Limitations: There are several strengths to this study. First, evaluations of the association between ED and depression are timely and relevant for clinicians, policymakers, and patients. Second, we intentionally conducted 2 meta-analyses on the association, allowing us to include all potentially relevant studies. However, our study also possesses some limitations. First, the OR is a measure of association that only reveals whether an association is present. Thus, this study was unable to determine the direction of causality between ED and depression. Second, the high heterogeneity among studies makes it difficult to generalize the conclusions.

Conclusion: This study demonstrates an association between depression and ED. Policymakers, clinicians and patients should attend to the association between depression and ED. **Liu Q, Zhang Y, Wang J, et al. Erectile dysfunction and depression: A systematic review and meta-analysis. J Sex Med 2018;15:1073−1082.**

Key Words: Depression; Erectile Dysfunction; Review; Meta-Analysis

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[1]Department of Urology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China;

[2]Department of Nosocomial Infection Management, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

*Qian Liu and Youpeng Zhang contributed equally.

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INTRODUCTION

Erectile dysfunction (ED), which is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance,[1] can have a negative effect on quality of life for both patients and their partners because of its effects on both physical and psychosocial health. Epidemiologic studies have revealed that the prevalence and incidence of ED are high among men,[2] with evidence suggesting that ED will affect an estimated 322 million individuals worldwide by the year 2025.[3] However, research has indicated that ED may also be an early predictor of future cardiovascular events and coronary artery disease[4]; 4 meta-analyses have confirmed the relationship between ED and cardiovascular risk.[5–8] Corona et al[9] demonstrated that the impairment of penile Doppler ultrasound is an independent risk factor for cardiovascular disease.[10] A meta-analysis by Gupta et al[11] reported that only-lifestyle modification and pharmacotherapy for cardiovascular risk factors can improve ED. Depression, which may significantly impact quality of life, is common among patients with ED,[12,13] with a reported frequency ranging from 8.7%[14] to 43.1%.[15]

A systematic review and meta-analysis also indicated that there is an association between depression and sexual dysfunction for both men and women; however, the term *sexual dysfunction* encompasses not only ED, but also includes sexual desire, sexual aversion, lack of sexual enjoyment, failure of genital response, and more.[16] Numerous primary studies have focused on the association between ED and depression.[17–22] Although some studies have reported that exposure to depression increases the risk of ED, others observed no association between depressive symptoms and the incidence of ED. Moreover, some studies have reported that ED exposure increases the risk of depression.[23–25] Quantitative syntheses of these studies may provide evidence of the association between ED and depression and help to elucidate factors influencing odds ratios (ORs).

Therefore, this study aims to quantitatively synthesize the findings of all studies that had evaluated the association between ED and depression. We performed 2 meta-analyses: 1 summarizing studies evaluating the risk of ED on the basis of exposure to depression, and the other exploring the risk of depression based on exposure to ED. We also explored factors that may explain the differences in ORs, such as differences in study design or the assessment scales used for ED and depression.

METHODS

Reporting Standards

The present meta-analysis complies with the standards of reporting meta-analyses of observational studies in epidemiology.[26]

Eligibility Criteria

In accordance with the Patient Population or Problem, Intervention, Comparison, Outcomes, and Setting inclusion criteria,[27] studies were included if they (1) were performed among male humans; (2) documented exposure to depression or ED; (3) involved the diagnosis or evaluation of depression and ED; (4) included cross-tabulation analysis or calculation of ORs and 95% CIs between depression and ED; and (5) were cohort, case-control, or cross-sectional studies. Studies in English and of any publication type were included.

Studies were excluded if they were not conducted among male humans; did not document exposure to depression or ED; did not involve the diagnosis of depression and ED; or did not involve cross-tabulation analysis or calculation of ORs and 95% CIs between depression and ED. Commentaries, editorials, meeting abstracts, and review articles lacking original data were excluded. Case series without control groups were also excluded.

Data Sources

We conducted a systematic search in Medline, Ovid Embase, and the Cochrane Library. MeSH terms for the search strategy included *erectile dysfunction* and *depression*. The complete search strategy for each database is presented in eTable 1. The last search was performed on October 15, 2017. Moreover, all references of the included articles were reviewed.

Study Selection

Duplicate references were removed. Independently, 2 reviewers screened all titles and abstracts, and records identified by either reviewer as eligible for inclusion were reviewed in full text. Conflicts were resolved by discussion with a third research member.

Data Extraction

A form was developed in accordance with the data extraction template provided by the Cochrane Consumers and Communication Review Group. This form was then pilot-tested on 10 randomly selected eligible articles and refined accordingly. The form included year of publication, first author's name, country of study, study design, sample size, comorbidities, mean age of patients, ED scale, depression scale, and use of cross-tabulation analysis or ORs and 95% confidence interval (95% CI). Data were independently extracted by the 2 reviewers using the same form, and disagreements were resolved by discussion with another research member. If some required information was not reported in original publications, attempts were made to obtain the data by e-mailing the corresponding authors.

Quality Assessment

The quality of individual studies was assessed using the Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) tool.[28] Based on signaling questions, 7 domains were assessed: bias resulting from confounding, bias in selection of participants into study, bias in classification of interventions, bias as a result of departure from intended interventions, bias because of missing

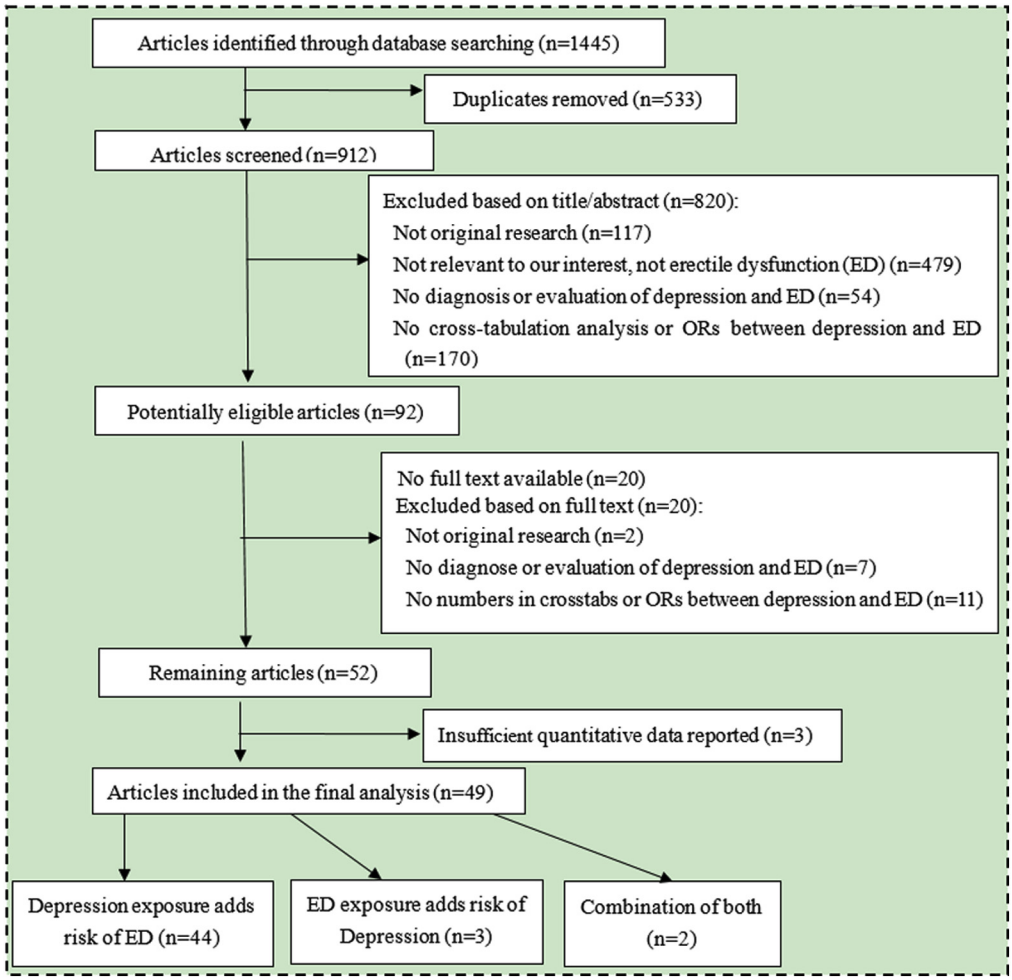

Figure 1. Study selection process. Figure 1 is available in color at www.jsm.jsexmed.org.

data, bias in measurement of outcomes, and bias in selection of the reported results. Depending on the responses to the signaling questions, each domain was classified as follows: low, moderate, serious, or critical risk of bias or no information. An overall risk of bias was defined by combining the results of the 7 domains. If any of the 7 domains was judged as serious or critical risk, the study was classified as exhibiting an overall serious or critical risk, respectively. Risk-of-bias graphs were created based on the results of ROBINS-I ratings. Risk of bias was classified in Review Manager 5.3 as low, high, or unclear risk of bias. Thus, we combined "low" and "moderate" ROBINS-I ratings into "low" category, and "serious" and "critical" ROBINS-I ratings were combined into "high" category. Grading of Recommendations Assessment, Development and Evaluation was used to evaluate the quality of evidence.

Data Synthesis

Data analyses were conducted using Stata Version 12.0 (Stata Corporation, College Station, TX), Review Manager 5.3 and R 3.4.2. The OR was used as the effect size.

The heterogeneity across studies was assessed using the I^2 statistic.[29] Given the clinical heterogeneity observed, a random-effect model was used. Meta-analyses and forest plots were conducted. In addition, we explored publication bias using Begg's tests. To explore potential sources of heterogeneity, multiple meta-regression and subgroup analyses were conducted based on prespecified study-level characteristics (eg, the country in which the study was conducted, study design, comorbidities, ED assessment, depression assessment, source of the effect size, quality scores, etc). Sensitivity analyses were conducted to evaluate the robustness of the results.

RESULTS

Study Selection

The searches identified a total of 1,445 citations, following which 533 duplicate citations were removed. We identified 92 potentially eligible publications following the screening of titles and abstracts. We then attempted to access the full text of each candidate study for further assessment, but the full text was inaccessible for 20 articles. Then 52 publications remained, and an additional 3 contained insufficient quantitative data. Although we attempted to contact the authors of these 23 publications via e-mail, we received no reply. Hence, 49

Table 1. Summary description of included studies

	Is depression a risk factor for ED?		Is ED a risk factor for depression?	
Study characteristics	Studies (N = 48)	Participants (N = 169,927)	Studies (N = 6)	Participants (N = 22,527)
Study design				
Case-control	21 (43.8%)	31,108	2 (33.3%)	5,169
Cross-sectional	24 (50.0%)	113,543	3 (50.0%)	2,196
Cohort	3 (6.3%)	25,276	1 (16.7%)	15,162
Mean age of patients				
≤45	15 (31.3%)	31,308	0	0
> 45	30 (62.5%)	34,324	5 (83.3%)	20,444
Not known	3 (6.3%)	104,295	1 (16.7%)	2,083
Country				
Developed	31 (64.6%)	156,866	5 (83.3%)	18,492
Developing	16 (33.3%)	12,115	1 (16.7%)	4,035
Mixed	1 (2.1%)	946	0	0
With other disease				
Diabetes	6 (12.5%)	4795	0	0
Others	14 (29.2%)	8,557	3 (50.0%)	4,148
None	28 (58.3%)	15,6575	3 (50.0%)	18,379
ED assessment				
IIEF	35 (72.9%)	22,964	3 (50.0%)	4,148
Others	13 (27.1%)	146,963	3 (50.0%)	18,379
Depression assessment				
BDI	13 (27.1%)	8,666	1 (16.7%)	4,035
CES-D	13 (27.1%)	7,708	1 (16.7%)	2,038
HADS	4 (8.3)	1,795	0	0
Others	18 (37.5)	151,758	4 (66%)	16,409
Original effect size				
Cross-tabulation analysis	37 (77.1)	164,007	0	0
ORs and 95% CIs	11 (22.9)	5,920	6 (100.0%)	22,527
ROBINS-I				
Low	15 (31.3)	15,337	2 (33.3%)	6,118
Moderate	20 (41.7)	127,450	3 (50.0%)	1,247
Serious	13 (27.1)	27,140	1 (16.7%)	15,162
Critical	0	0	0	0

BDI = Beck Depression Inventory; CES-D = Center for Epidemiological Studies Depression Scale; ED = erectile dysfunction; HADS = Hospital Anxiety and Depression Scale; IIEF = International Index of Erectile Function; OR = odds ratio; ROBINS-I = the Risk of Bias in Non-randomized Studies—of Interventions.

publications were included, 2 of which provided the data on both the risk of ED based on exposure to depression and the risk of depression based on exposure to ED (Figure 1). No eligible studies were identified from the references of the included publications.

Study Characteristics

Our meta-analysis included 46 publications (representing 48 studies published from 1997 to 2017) evaluating the risk of ED based on exposure to depression. These 48 studies included a total of 169,927 participants,[15,17–22,30–40] and[41–68] the number of participants in each study ranged from 60[34] to 101,685.[14]

We also included 5 publications representing 6 studies evaluating the risk of depression based on exposure to ED. These studies were published between 2006 and 2015 and covered a total of 22,527 participants.[15,17,23–25] The number of participants ranged from 40[23] to 15,162[25] in each study. Table 1 summarizes the key features of the included studies, and eTable 2 provides detailed information regarding each study.

Study Quality

The details of the quality assessment are presented in eTable 3. Because of the study design (observational study), the quality of evidence was low for those studies evaluating the risk of ED based on exposure to depression. However, for those studies evaluating the risk of depression based on exposure to ED, the evidence was of moderate quality. Risk-of-bias graphs were presented in eFigure 1. eTable 4 provides the GRADE evidence profile.

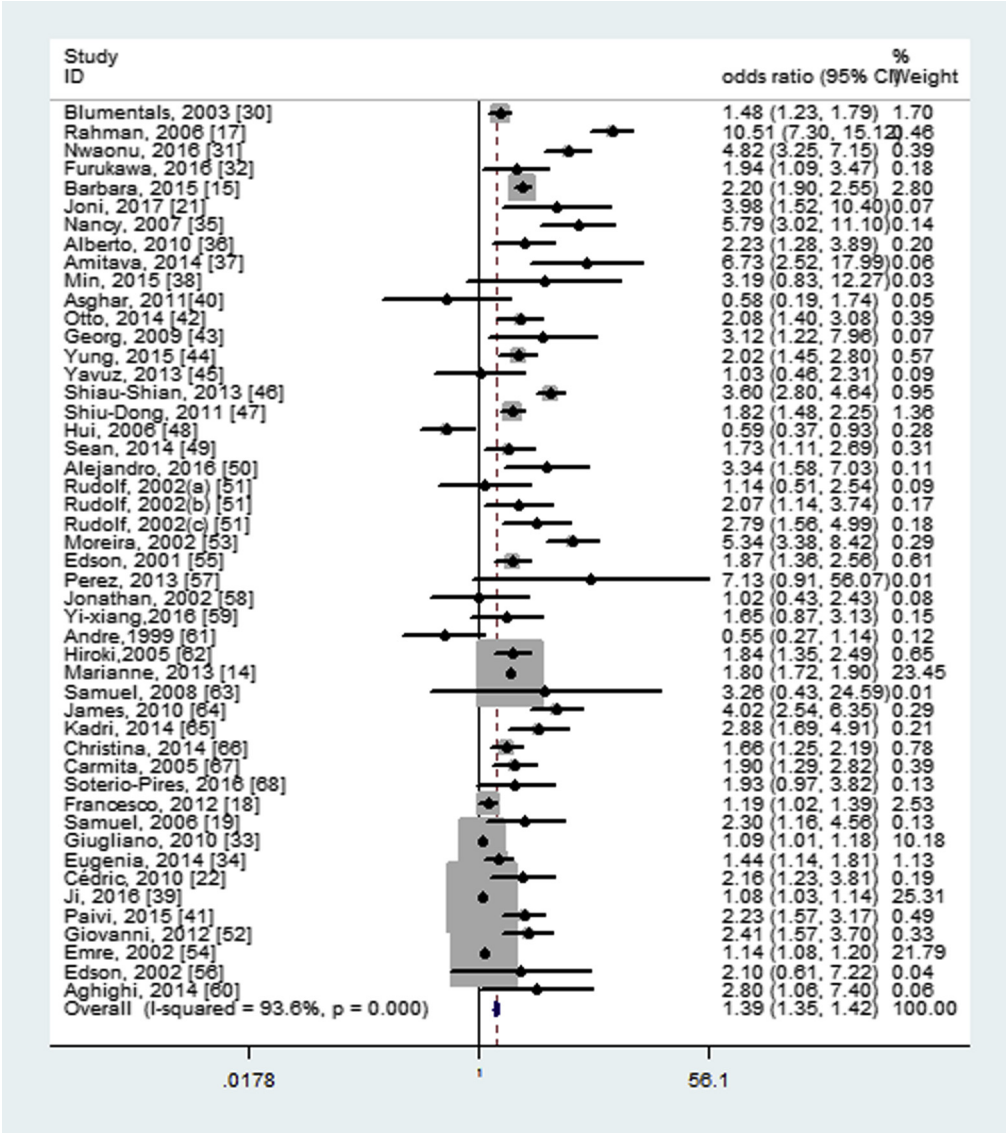

Figure 2. Forest plot on risk of erectile dysfunction based on exposure to depression. Figure 2 is available in color at www.jsm.jsexmed.org.

Evidence Synthesis

Risk of ED Based on Exposure to Depression

Significant heterogeneity was found across studies ($P < .001$, $I^2 = 93.6\%$), and individual effect sizes ranged from 0.55 (0.27−1.14) to 10.51 (7.30−15.12). The overall effect size was 1.39 (1.35−1.42), and Figure 2 presents the detailed results of the meta-analysis. Begg's test revealed no significant publication bias across studies ($P = .315$).

Meta-Regression and Subgroup Analysis

We developed a multiple regression model with each possible source of heterogeneity (I^2_res = 82.42%, adjusted R^2 = 0.07%; I^2_res: residual variation due to heterogeneity). Table 2 shows the detailed results of the subgroup analysis. We observed a statistically significant interaction favoring cohort studies (P for interaction $< .001$), along with larger pooled effect sizes for studies conducted in developed countries (P for interaction $< .001$). Effect sizes were significantly higher for studies in which the mean age of patients was ≤45 (P for interaction $< .001$). Larger effect sizes were also observed for studies involving patients without comorbidities (P for interaction $< .001$) and for those in which ED assessments other than the International Index of Erectile Function (IIEF) were used (P for interaction $< .001$). Statistically significant differences were also found based on depression assessment used (P for interaction = .047). Effect sizes were significantly higher for studies in which the source of original effect size was determined via cross-tabulation analysis (P for interaction $< .001$).

Sensitivity Analyses

The overall effect size, which ranged from 1.28 (95% CI: 1.24−1.32) to 1.51 (95% CI: 1.47−1.55), did not change by excluding any single study.

Table 2. Subgroup analysis: Is depression a risk factor for ED?

Subgroup	Studies, n	Pooled ORs (95% CI)	Heterogeneity (I^2)	*P* for meta-regression	*P* for interaction
All studies	48	1.39 (1.35–1.42)	93.6% ($P < .001$)		
Study design					
Case-control	21	1.24 (1.19–1.29)	92.7% ($P < .001$)	.829	<.001
Cross-sectional	24	1.46 (1.42–1.51)	93.6% ($P < .001$)		
Cohort	3	2.55 (2.12–3.06)	87.8% ($P < .001$)		
Mean age of patients					
≤45	15	1.94 (1.77–2.12)	88.2% ($P < .001$)	.619	<.001
> 45	30	1.27 (1.22–1.31)	92.5% ($P < .001$)		
Not known	3	1.45 (1.40–1.50)	98.7% ($P < .001$)		
Country					
Developed	31	1.64 (1.53–1.70)	91.3% ($P < .001$)	.815	<.001
Developing	16	1.19 (1.15–1.23)	93.3% ($P < .001$)		
Mixed	1	2.42 (1.57–3.71)	0		
With other disease					
Diabetes	6	1.14 (1.06–1.22)	85.2% ($P < .001$)	.210	<.001
Others	14	1.22 (1.17–1.27)	91.5% ($P < .001$)		
None	28	1.58 (1.52–1.63)	93.7% ($P < .001$)		
ED assessment					
IIEF	35	1.26 (1.22–1.31)	89.0% ($P < .001$)	.831	<.001
Others	13	1.52 (1.47–1.57)	96.8% ($P < .001$)		
Depression assessment					
BDI	13	2.19 (1.97–2.44)	52.7% ($P = .053$)	.622	.047
CES-D	13	1.16 (1.16–1.20)	92.6% ($P < .001$)		
HADS	4	1.66 (1.39–1.99)	58.2% ($P = .067$)		
Others	18	1.600 (1.54–1.66)	94.4% ($P < .001$)		
Original effect size source					
Cross-tabulation analysis	37	1.94 (1.87–2.02)	85.7% ($P < .001$)	.168	<.001
ORs and 95% CIs	11	1.13 (1.10–1.17)	79.3% ($P < .001$)		
ROBINS-I					
Low	15	1.20 (1.16–1.24)	0	.322	<.001
Moderate	20	1.59 (1.53 –1.65)	89.3% ($P < .001$)		
Serious	13	2.48 (2.19 –2.80)	95.9% ($P < .001$)		

BDI = Beck Depression Inventory; CES-D = Center for Epidemiological Studies Depression Scale; ED = erectile dysfunction; HADS = Hospital Anxiety and Depression Scale; IIEF = International Index of Erectile Function; OR = odds ratio; ROBINS-I = the Risk of Bias in Non-randomized Studies—of Interventions.

Risk of Depression Based on Exposure to ED

No significant heterogeneity was observed ($P < .257$, $I^2 = 23.5\%$), and individual effect sizes ranged from 1.64 (0.91–2.95) to 3.62 (2.53–5.18). The overall effect size was 2.92 (95% CI: 2.37–3.60), and Figure 3 shows the detailed results of the meta-analysis. No significant publication bias was found across studies with Begg's test ($P = .260$).

Sensitivity Analyses

The overall effect size, which ranged from 2.62 (95% CI: 2.03–3.39) to 3.18 (95% CI: 2.54–3.98), did not change by excluding any single study.

DISCUSSION

Principal Findings

The findings of the present meta-analysis indicate that exposure to depression increases the risk of ED (OR: 1.39, 95% CI: 1.35–1.42). Our results demonstrated that the risk of ED increases by 39% in patients with depression, and that the incidence of ED is 1.39 times higher in patients with depression than in those without depression. Our results also revealed that exposure to ED increases the risk of depression (OR: 2.92, 95% CI: 2.37–3.60) by 192% and that the incidence of depression is 2.92 times higher in patients with ED than in those without ED. To the best of our knowledge, this study is the first meta-analysis to reveal an association between ED and depression.

Although our meta-analysis of depression exposure and the risk of ED was characterized by large heterogeneity, the subgroup analyses can, in part, account for these differences. The large heterogeneity may be as a result of variations in study country, study design, patient age, comorbidities, ED assessment, depression assessment, and the source of the original effect size. In addition, larger effect sizes were observed for studies in which ED assessments other than the IIEF were used. Similarly, significant differences were also observed based on the depression

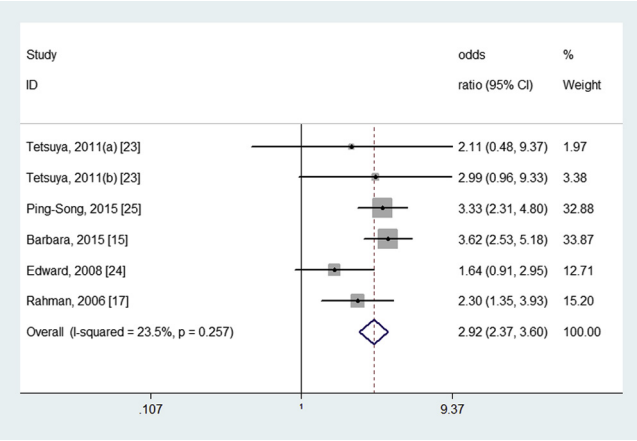

Figure 3. Forest plot on risk of depression based on exposure to erectile dysfunction. Figure 3 is available in color at www.jsm.jsexmed.org.

assessment used, likely because of the unknown reliability and validity of the self-administered ED or depression assessments used in some studies.[14,68] We also observed significantly higher effect sizes for studies in which cross-tabulation analyses represented the original source of the effect size than for those in which effect sizes were determined using ORs and 95% CIs. This may be because ORs in some studies were adjusted according to patient age or other factors, making these results more credible and reliable than those determined via cross-tabulation analyses.[54]

The mechanism underlying the association between ED and depression remains to be established.[46] However, both behavioral and biological models have been proposed to explain the increased risk of ED in patients with depression.[69] The behavioral model postulates that patients with depression tend to engage in negative thought and are less confident, which results in performance anxiety that further reduces erectile function.[69] The biological model postulates that depression affects the hypothalamic pituitary adrenocortical (HPA) axis, leading to excess catecholamine production, which in turn, leads to poor cavernosal muscle relaxation and ED.[70] Moreover, most antidepressant drugs have adverse effects on erectile function.[17] In addition, low testosterone is a possible explanation for the exacerbation of depression by ED.[25] Previous studies have suggested that testosterone plays a key role in ED development and that low testosterone levels are associated with ED.[71] Furthermore, testosterone levels are lower in patients with depression than in those without depression; testosterone replacement therapy has been shown to improve depressive symptoms.[25]

Strengths and Limitations

There are several strengths to this study. First, evaluations of the association between ED and depression are timely and relevant for clinicians, policymakers, and patients. Second, we intentionally conducted 2 meta-analyses regarding the association between ED and depression, allowing us to include all potentially relevant studies and the greatest number of participants. Third, we searched manifold research databases including the Cochrane Library, which involves literature for relevant studies published through October 2017. Moreover, we conducted all aspects of the review process in duplicate, and each of our 2 meta-analyses included a large sample size. Furthermore, we used relative effect estimates to calculate absolute effect estimates, which are remarkably consistent and more useful than absolute effect estimates.

However, the present study also possesses some limitations of note. First, there is a possibility that relevant research papers were missed (eg, those not written in English), resulting in selection bias. Second, although we searched the Cochrane Library, grey literature in other databases may have been missed. Third, although we conducted the review and extraction processes independently and in duplicate, it was still subjective and dependent on the reports of articles, rather than direct assessment of the studies. Fourth, although the ROBINS-I tool is reliable, it is associated with a risk of reviewer bias resulting from reviewer subjectivity. Besides, the methods used for the assessment of ED varied between studies. The IIEF questionnaire has been adopted as the gold standard when assessing the efficacy of treatment for ED, but other methods have a higher likelihood of misclassification bias that could lead to underestimation of the strength of the association. Furthermore, there was limited information regarding the use of medications such as antidepressants, beta-blockers, diuretics, phosphodiesterase inhibitors, testosterone, and antihypertensive agents that may have contributed to ED. In addition, although our subgroup analyses demonstrated the variability in the study design, mean age of patients, country in which the study was conducted, and other factors, the high heterogeneity among studies makes it difficult to generalize the conclusions. Moreover, we did not assess other potential sources of heterogeneity such as study duration or circumstances. Besides, we did not register the analysis on PROSPERO. Finally, the OR is a measure of association that only reveals whether an association is present. Thus, the present study was unable to determine the direction of causality between ED and depression.

Implications

Our study has both research-based and clinical implications for ED, as well as depression. Although our conclusions may be weakened by heterogeneity among studies, the results of our meta-analysis indicate that ED increases the risk of depression and that depression also increases the risk of ED. Therefore, to improve overall patient care, clinicians and policymakers should attend to the interrelationship between depression and ED.

The pooled estimates calculated during our first meta-analysis suggested that exposure to depression increases the risk of ED. However, despite the large sample size and no significant reporting bias, the quality of evidence was low because of the observational design of the included studies. Thus further research is required to determine with confidence whether

exposure to depression indeed increases the risk of ED. Pooled estimates calculated during our second meta-analysis indicated that exposure to ED also increases the risk of depression. The inclusion of observational studies produced a large effect size, resulting in evidence of moderate quality, suggesting that further research is likely to change the estimate. Moreover, only 6 studies were included, necessitating further studies regarding the association between depression and ED.

CONCLUSION

The findings of this study demonstrated an association between depression and ED. Patients reporting ED should be routinely screened for depression, whereas patients presenting with symptoms of depression should be routinely assessed for ED.

Corresponding author: Zhaohui Zhu, MD, Department of Urology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China. Tel: (8627)84309728; Fax: (8627) 84309729; E-mail: zhuzhaohui316@163.com

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STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Zhaohui Zhu, Jin Wang

(b) Acquisition of Data
Qian Liu, Youpeng Zhang, Jin Wang, Sen Li, Yongbiao Cheng

(c) Analysis and Interpretation of Data
Qian Liu, Youpeng Zhang, Jin Wang, Sen Li, Yongbiao Cheng, Jialun Guo, Hanqing Zeng, Yong Tang

Category 2

(a) Drafting the Article
Qian Liu, Youpeng Zhang

(b) Revising It for Intellectual Content
Qian Liu, Youpeng Zhang, Jin Wang, Sen Li, Yongbiao Cheng, Jialun Guo, Hanqing Zeng, Yong Tang

Category 3

(a) Final Approval of the Completed Article
Qian Liu, Youpeng Zhang, Jin Wang, Sen Li, Yongbiao Cheng, Jialun Guo, Yong Tang, Hanqing Zeng, Zhaohui Zhu

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SUPPLEMENTARY DATA

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