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Relationship Between Depression and Medication Adherence in Older Patients With Cardiovascular Disease: A Systematic Review and Meta-Analysis

Mina Berimavandi[1] | Parvin Abbasi[2] | Behnam Khaledi-Paveh[3] | Nader Salari[4]

[1]Student Research Committee, Kermanshah University of Medical Sciences, Kermanshah, Iran | [2]Department of Nursing, School of Nursing and Midwifery, Kermanshah University of Medical Sciences, Kermanshah, Iran | [3]Department of Psychiatric Nursing, School of Nursing and Midwifery, Kermanshah University of Medical Sciences, Kermanshah, Iran | [4]Department of Biostatistics, School of Nursing and Midwifery, Kermanshah University of Medical Sciences, Kermanshah, Iran

Correspondence: Parvin Abbasi (p_abasi2003@yahoo.com)

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ABSTRACT

Background: Depression and cardiovascular disease (CVD) by the end of 2030 will be among the major causes of disability worldwide. Meanwhile, medication adherence is an important factor in predicting clinical outcomes in patients with CVD. Further, lack of medication compliance is affected by depression. Thus, this study aimed to explore the relationship between depression and medication adherence among older patients with CVD.

Materials and Methods: The search was done across eight databases of PubMed/MEDLINE, Google Scholar, Embase, Scopus, APA Psycinfo, CINAHL/ebsco, ProQuest, and Web of Science. For the selection of included studies, there were no constraints regarding publication language. All studies available in each of the databases were searched up to December 9, 2021. Risk of bias assessment was done based on the Joanna Briggs Institute scale. The final result was estimated using a random effects model. The data were analyzed by CMA 2 software.

Results: Seven studies and 10,153 elderly suffering from CVD were identified. Most included studies had reported an inverse association between depression and medication adherence. There was a small effect between depression and medication adherence among these older patients (combined odds ratio 0.603, 95% confidence interval 0.252–1.442). Thus, having depression would reduce medication adherence by 40%.

Conclusion: Depression has a considerable effect on medication adherence among older patients with CVD. Thus, it is suggested that considering the importance of depression and lack of medication adherence in increasing the negative outcomes of this disease in these patients, primary studies be conducted in this regard to achieve conclusive results in subsequent systematic reviews and meta-analyses.

Abbreviations: ACS, acute coronary syndrome; CMA, comprehensive meta-analysis; JBI, Joanna Briggs Institute; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis; PROSPERO, International Prospective Register of Systematic Reviews.

1 | Background

The World Health Organization (WHO) has estimated the elderly population by 2050 as about 2 billion people [1]. Meanwhile, in recent years, ageing has changed into a major challenge worldwide [2, 3]; 80% of elderly suffer from at least one type of chronic disease [4]. Cardiovascular disease (CVD) in older patients, as the most important cause of mortality worldwide, significantly affects the healthcare and economic system of the world [5].

1.1 | Aging and Cardiovascular Disease

The aging process brings about significant physiological changes that have a substantial impact on the physical and psychological well-being of the elderly [6, 7]. These changes, combined with decreased physical activity and increased incidence of obesity, are the leading causes of CVD in older adults [6]. CVD encompass a variety of conditions, such as hypertension, coronary artery diseases, and heart failure, which are prevalent in the elderly population [8, 9]. Furthermore, the physiological changes, retirement, reduced income, spousal loss, changes in sexual activity, decreased social activities, and diminished social communication can significantly affect the elderly [10].

1.2 | Medication Adherence

Possessing healthy and suitable healthcare skills is one of the best solutions for preventing the aggravation of these patients' conditions and reducing their mortality due to cardiac events [11]. Accordingly, one of the important instances of self-care is medication adherence [11]. This adherence is defined as "extent of match between the patient's health behaviors including drug consumption, dietary adherence, and having a healthy lifestyle and the healthcare team recommendations" [12]. Lack of medication adherence in older patients with CVD has become very common due to different reasons such as ageing, the long course of treatment, and polypharmacy [13–16]. In addition, lack of medication adherence is an important predictor of poor treatment outcomes and increased healthcare costs [17–19]. Older patients with CVD, due to reasons such as doubt about definite cure and the necessity of adhering to healthcare recommendations for a longer time, are more susceptible to developing depression, which is the most common psychiatric disorder among the elderly [20–22].

The relationship between depression and medication adherence in older patients with CVD based on various primary studies has had variable outcomes (odds ratio (OR) CI 95% 0.151–3.920) [23–29]. A systematic review and meta-analysis examining the factors that predict lack of medication adherence among patients with acute coronary syndrome (ACS) has reported that lack of medication adherence is twice as common in patients with depression compared to nondepressed counterparts (7 primary studies on the depression and medication inherence association, 5058 patients) [18]. Another systematic review and meta-analysis exploring the factors related to lack of persistence in taking statin drugs among older patients with CVD found that there was a direct relationship between depression and lack of medication adherence among this group of patients (6 studies on the depression and lack of medication adherence association, 165,889 patients) [5].

Considering the importance of medication adherence among CVD patients and the relationship between depression and medication adherence in the elderly, conducting this study has seemed essential for the researchers. To our knowledge, no systematic review and meta-analysis has addressed this issue. Consequently, this review does not provide a detailed analysis of the shortcomings of existing studies. Thus, the primary aim of this study is a systematic review and meta-analysis examining the relationship between depression and medication adherence in older patients with CVD, and the secondary aim is to find the potential sources of statistical heterogeneity in primary studies.

2 | Materials and Methods

To write this systematic review and meta-analysis study, the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist has been used.

2.1 | Protocol and Registration

The protocol of this systematic review and meta-analysis study has been registered as priori in the International System of Prospective Register for Systematic Reviews (PROSPERO) with the code of CRD42021294016.

2.2 | Eligibility Criteria

The inclusion criteria in this study has been determined as classified in the form of PICO-S: P (population): primary studies with the elderly population suffering from CVD (including hypertension, heart failure, coronary acute syndrome, etc.) with age older than 60 years of both genders, I/E (intervention/exposure): all primary studies evaluating the variable of depression with any method or scale, C (comparison): given the nature of this study, this section was not applicable, O (outcome): primary studies reporting the medication adherence with any method or scale, S (study design): all primary studies of cohort, cross-sectional, or case-control type. Further, qualitative studies, trials, case reports, and case series were all excluded. No study whose full test was unavailable or had no statistical data on the depression and medication adherence association was included.

2.3 | Search Strategy

For searching primary studies, the databases of PubMed/MEDLINE, Google Scholar, Embase, Scopus, APA Psycinfo, CINAHL/ebsco, and Web of Science were used. The search was done on dissertations, theses, conference papers, as well as databases including ProQuest, Scopus, and Google Scholar for searching the gray literature. In addition, the reference list search was also done. The search of primary studies for this

study was done with no publication time constraint up to December 9, 2021 and with no publication language constraint either. The keywords were incorporated in the search strategy as PICO-S based on MeSH and Emtree. The search strategy for the PubMed database is as follows:

(depression[tiab] OR "Depressive Symptom"[tiab] OR (depressive [tiab] AND symptom[tiab]) OR "depressive disease"[tiab] OR (depressive[ti] AND disease[ti]) OR "depressive disorder"[tiab] OR (depressive[ti] AND disorder[ti]) OR "depressive episode"[ti] OR (depressive[ti] AND episode[ti]) OR "depressive illness" [tiab] OR (depressive[ti] AND illness[ti]) OR "depressive state"[ti] OR (depressive[ti] AND state[ti]) OR "depressive syndrome"[ti] OR (depressive[ti] AND syndrome[ti])) AND ("Medication adherence"[tiab] OR (Adherence[ti] AND Medication[ti]) OR "Drug Adherence"[tiab] OR (Adherence[ti] AND Drug[ti]) OR "Medication Nonadherence"[tiab] OR (Nonadherence[ti] AND Medication[ti]) OR "Medication Noncompliance"[tiab] OR (Noncompliance[ti] AND Medication[ti]) OR "Medication Non-Adherence"[tiab] OR "Medication Non Adherence"[ti] OR (Non-Adherence[ti] AND Medication[ti]) OR "Medication Persistence"[tiab] OR (Persistence[ti] AND Medication[ti]) OR "Medication Compliance"[tiab] OR (Compliance[ti] AND Medication[ti]) OR "Medication Non-Compliance"[tiab] OR "Medication Non Compliance"[ti] OR (Non-Compliance[ti] AND Medication[ti]) OR "Drug Compliance"[tiab] OR (Compliance[ti] AND Drug[ti]) OR ("Non adherence"[ti] AND medication[ti]) OR (NonCompliance[ti] AND medication[ti]) OR ("Non Compliance"[ti] AND medication[ti]) OR "NonCompliance medication"[tiab] OR "drug intake compliance"[tiab] OR "drug regimen adherence"[tiab] OR "drug regimen compliance"[tiab] OR "medication intake adherence"[tiab]).

Then, this search strategy was also adapted for implementation in other electronic databases, which can be seen in the Supporting file [see Supporting file S1]. It is important to note that the search strategies for other electronic databases were adjusted using https://sr-accelerator.com.

2.4 | Study Selection

First, all references of the searched primary studies were imported into an EndNote library. After screening the duplicated studies, all primary studies were screened based on the title and abstract as well as the inclusion and exclusion criteria by one of the reviewers (M. B.). Next, the screened studies were evaluated based on the full text plus inclusion and exclusion criteria by two reviewers independently (P. A. and M. B.). The reviewer disagreed about two studies, then they were resolved through consensus.

2.5 | Data Extraction

Data extraction form was designed by the research team and according to the inclusion/exclusion criteria. This form included three groups of information: (1) general information: reviewer's name. assessment data, title of study, first author's name, year of publication, and country, (2) study information including: number of subjects, mean age of subjects, percentage and number of men and women, the scale or method of assessing depression as well as the scale or method of assessing the mediation adherence, (3) information on findings including the statistical data required for exploring the relationship between depression and medication adherence in the study population for the meta-analysis as well as the statistical data analysis method. The data extraction was done by two reviewers independently, and cases of disagreement were resolved through consensus (P. A. and M. B.).

2.6 | Assessment of Risk of Bias

The quality assessment for each of the included studies was done to examine the relationship between the outcome of studies and their methodological quality independently by two reviewers using the JBI scale (P. A. and B. K. H.-P.). The reviewers understood the scale and read the usage instructions. Next, the papers were classified into three groups of low, moderate, and high risk of bias based on their methodological quality score (ratio of "yes" response to the total acquired score based on the scale). JBI scale for cross-sectional studies had 8 items and for cohort had 11 items, with each item having 4 options (yes, no, unclear, and not applicable). Response "yes" would acquire a Score 1, and others would receive 0. Cases of disagreement between two reviewers were resolved through consensus.

2.7 | Data Synthesis

Data analysis in this systematic review and meta-analysis study was done by CMA 2 software. Heterogeneity in primary studies was assessed based on I^2 coefficient, Q-Cochrane, and Tau test. Random effects model was used. The interpretation regions of OR have been defined in five groups of ineffective (1), trivial (0.19–1.00 and 1.00–1.21), small (0.55–0.89 and 1.22–1.85), medium (0.34–0.54 and 1.86–2.99), and large effect (≤ 0.33 and ≥ 3.00) [30]. To find the potential sources of heterogeneity in primary studies as well as identifying the factors affecting the pooled effect size, subgroup analysis and meta-regression methods were used. For this purpose, confounding and modifying factors with priority of priori factors were evaluated. Publication bias was first evaluated based on funnel plot and then based on Begg's and Egger's statistical indices to achieve more accurate results. Sensitivity analysis was performed via one-out removed and subgroup analysis based on the methodological quality of the primary studies. For interpreting the significance of all tests utilized in this meta-analysis, a significance coefficient of $p < 0.0.5$ will be used.

3 | Results

3.1 | Study Selection

PRISMA diagram shows the process of selecting the primary studies, which includes descriptive information (Figure 1). Overall, 10,012 studies were searched in the databases. After eliminating the duplicated studies, from among 4891 studies, 159 which met the inclusion criteria were selected based on the

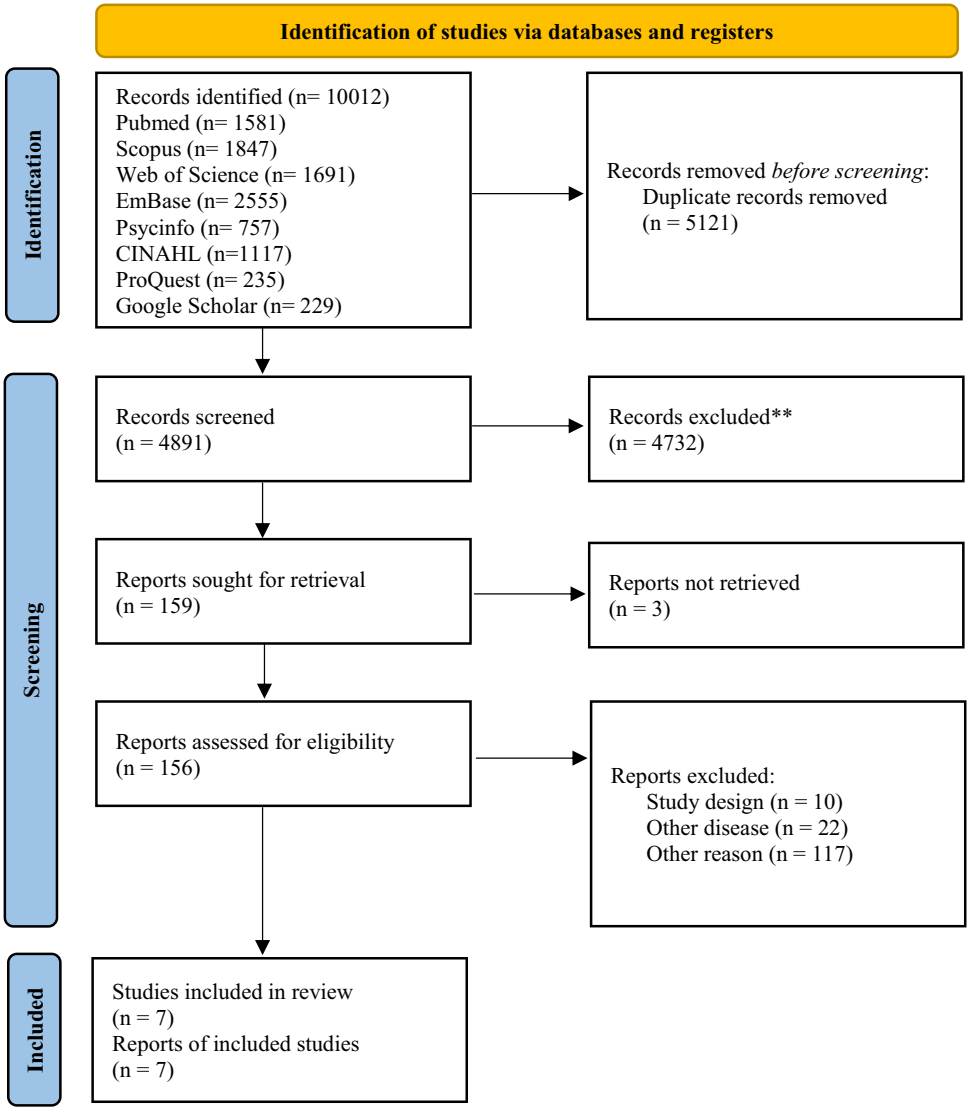

FIGURE 1 | Flow chart showing results of the literature search. **Number of duplicated studies.

title and abstract. After access to their full text, seven studies were chosen to be included in this systematic review and meta-analysis study.

3.2 | Study Characteristics

The characteristics of the studies included are summarized in Table 1. Overall, 7 studies ($n = 10{,}153$) were included to explore the relationship between the effect of depression on medication adherence in older patients with CVD [23–29]. Six studies covered elderly above 65 years, and one dealt with elderly above 60 years. Meanwhile, the participants of five studies consisted of the elderly with hypertension, one study of heart failure, and one study of CVD. Finally, the primary studies came from six countries and three different continents (Asia, Europe, and North America).

3.3 | Risk of Bias Assessment

The results of assessing the methodological quality of the primary studies are reported in Table 2. From seven primary studies, four had high quality [23, 25, 26, 29]. Further, three had moderate quality, all being of cohort type [24, 27, 28]. In these studies, mostly weakness of identifying the confounding variables, expressing ways to handle them, and the strategies related to incomplete follow-ups had resulted in their diminished methodological quality.

3.4 | Data Synthesis

Considering the difference in the sample size and the assumption of methodological heterogeneity of the primary studies, the data related to the depression and medication adherence association were meta-analyzed using random effects model, with its results shown in Figure 2. The results of this meta-analysis indicated that there is a small effect between depression and medication adherence among older patients with CVD, which is inconsiderable based on the CI 95% values (OR = 0.603 95% CI 0.252–1.442, $I^2 = 97.28\%$). Accordingly, it can be stated that the elderly suffering from depression have had 40% lower adherence. Considering severe heterogeneity among the included studies, subgroup analysis and meta-regression were done with

TABLE 1 | Summary of included studies.

First author	Year	Country	Type of study	Age (mean)	Number of participants	Female%	Type of disease	Depression scale	Medication adherence scale	Risk of bias assessment
Demirturk	2018	Turkey	Cross-sectional	71.77	350	52	HTN[a]	GDS[b]	MASES-SF[c]	High
Gentil	2012	Canada	Longitudinal observational	Not reported	926	75.1	HTN	ESA-Q[d]	Number of day supply medication	Moderate
Holvast	2018	Netherlands	Cohort	68	4477	69.3	CVD[e]	Nivel-PCD[f]	Time to nonpersistence (only β-blocker)	High
Krousel-Wood	2011	Louisiana	Cohort	75	1965	59	HTN	CES-D[g]	MMAS-8[h]	Moderate
Krousel-Wood	2010	Louisiana	Cross-sectional	75	2180	58.5	HTN	CES-D	MMAS-8	High
Lin	2019	Iran	Cohort	69.3	468	49.2	HF[i]	HADS[j]	MARS-5[k]	Moderate
Son	2016	South Korea	Cross-sectional	73.89	255	48.2	HTN	GDS	MMAS-8	High

[a]Hypertension.
[b]Geriatric Depression Scale.
[c]Medication Adherence Self-Efficacy Scale-Short Form.
[d]Seniors Health Survey Questionnaire.
[e]Cardiovascular disease.
[f]Nivel Research Primary Care Database.
[g]Center for Epidemiological Studies Depression Scale.
[h]Morisky Medication Adherence Scale.
[i]Heart failure.
[j]Hospital Anxiety and Depression Scale.
[k]Medication Adherence Report Scale.

TABLE 2 | Quality assessment all included studies by JBI scale.

Study design	First author	Year	Total score	Quality	1	2	3	4	5	6	7	8	9	10	11
Cross-sectional	Demirturk	2018	7: yes 1: no	High	☺	☺	☺	☺	☺	☹	☺	☺	—	—	—
	Krousel-Wood	2010	7: yes 1: unclear	High	☹	☺	☺	☺	☺	☺	☺	☺	—	—	—
	Son	2016	8: yes	High	☺	☺	☺	☺	☺	☺	☺	☺	—	—	—
Cohort	Gentil	2012	7: yes 3: no 1: not applicable	Moderate	☺	☺	☺	☹	☹	☹	☺	☺	☺	☹	☺
	Holvast	2018	11: yes	High	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺
	Krousel-Wood	2011	8: yes 3: no	Moderate	☺	☺	☺	☹	☹	☺	☺	☺	☺	☹	☺
	Lin	2019	7: yes 4: no	Moderate	☺	☺	☺	☹	☹	☺	☺	☺	☹	☹	☺

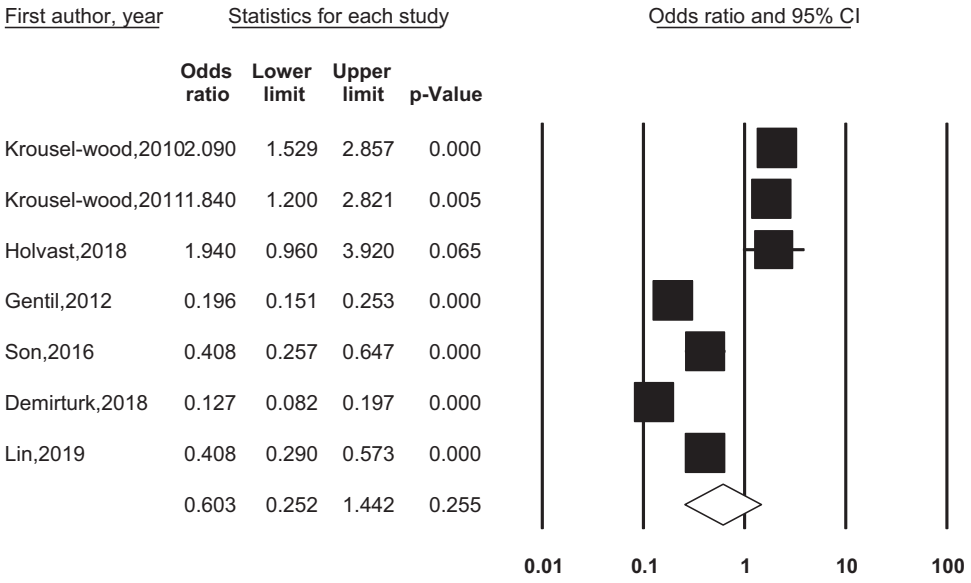

FIGURE 2 | Forrest plot showing overall odds ratio of all studies.

priority of priori variables to find the potential sources of heterogeneity and identify the factors affecting effect size.

3.5 | Subgroup Analysis

From among the priori variables, type of study and type of CVD, and from among post hoc variables, the medication adherence measurement scale, depression measurement scale, and continent were used for subgroup analysis, with its results outlined in Table 3. Regarding the age variable, which had been chosen a priori, there was not sufficient statistical data in some primary studies. The outcome of this analysis based on the variable of depression measurement scale can be seen in Figure 3. The subgroup analysis results revealed that criterion I^2 was 0 in the CES-D subgroup of the depression scale group, which was not observed in any other groups. Therefore, this is the most significant finding from the subgroup analysis.

3.6 | Meta-Regression

To perform meta-regression, the percentage of women participating in the study, which was a priori variable, was used. Also, sample size and year of study initiation were analyzed. The results related to the sample size variable can be seen as a diagram in Figure 4.

3.7 | Sensitivity Analysis

The sensitivity analysis to ensure lack of effect of bias in each primary study on the overall outcome of the meta-analysis was done via the one-out removed method. Based on the results of this analysis, almost none of the primary studies had a considerable change. Further, to ensure this result, subgroup analysis was done based on the methodological quality of the primary studies, which confirmed the above results (Figure 5).

TABLE 3 | Result of subgroup analysis based on each variable.

Variable	Potential	OR 95% CI	Number of study	Heterogeneity	*p*	I^2%
Study design	Cohort	0.717 (0.203–2.532)	4	98.071	0.000	96.94
	Cross-sectional	0.481 (0.112–2.054)	3	110.148	0.000	98.18
	Total	0.604 (0.233–1.565)	7			
Type of disease	HTN	0.523 (0.167–1.638)	5	205.373	0.000	98.05
	Other	0.870 (0.140–5.397)	2	15.311	0.000	93.47
	Total	0.604 (0.229–1.589)	7			
Scale of medication adherence	MMAS-8	1.174 (0.455–3.026)	3	35.319	0.000	94.32
	Other	0.357 (0.156–0.816)	4	52.961	0.000	94.34
	Total	0.597 (0.320–1.004)	7			
Scale of depression	CES-D	1.964 (0.781–4.942)	2	0.222	0.637	00.00
	Other	0.360 (0.198–0.652)	5	56.161	0.000	92.88
	Total	0.592 (0.359–0.976)	7			
Continent	America	0.904 (0.218–3.760)	3	160.319	0.000	98.75
	Other	0.442 (0.127–1.541)	4	44.341	0.000	93.23
	Total	0.603 (0.236–1.543)	7			

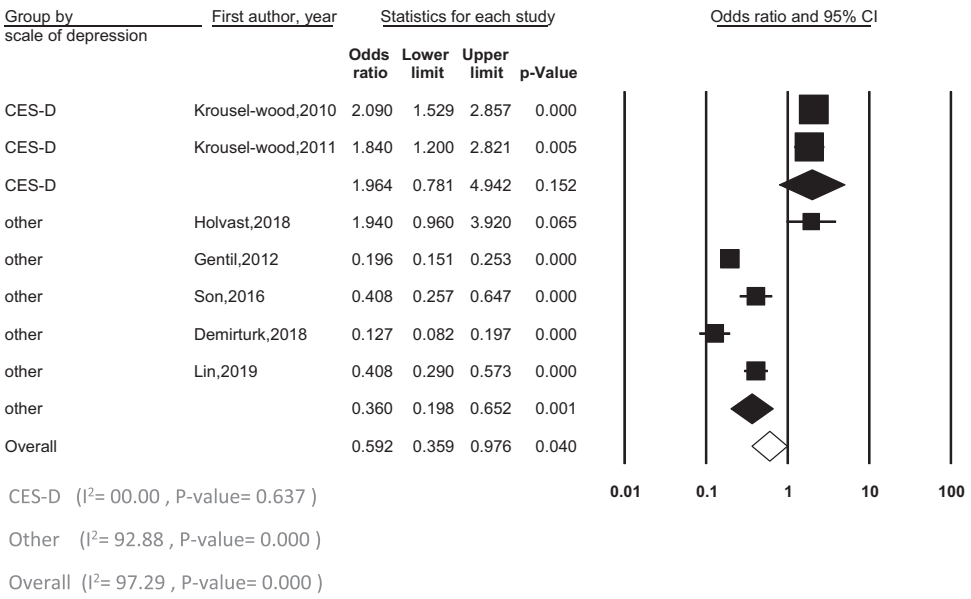

FIGURE 3 | Forrest plot showing overall odds ratio of all studies by scale of depression.

3.8 | Publication Bias

To assess publication bias in this study, a funnel plot was used (Figure 6). Based on the funnel plot, which shows a heterogeneous distribution pattern, it can be concluded that publication bias in this study has been ignorable. However, due to the limited number of studies included as well as the funnel plot limitations in accurate representation of reporting bias, the Begg and Egger method was used for assessing this bias [31]. The interpretation of the Begg test was as $p = 0.76$ and $z = 0.3$. Also, the results of Egger's test revealed that CI 90% for the intercept has been 28.32 to −16.63 with $p = 0.53$. Accordingly, based on the results of Egger's and Begg's tests, the result related to the funnel plot was confirmed and publication bias in this study has been negligible. Thus, it can be concluded that combined OR resulting from this meta-analysis has not been much affected by the various dimensions of publication bias.

4 | Discussion

The present study was a systematic review and meta-analysis for exploring the effect of depression on medication adherence among older patients with CVD.

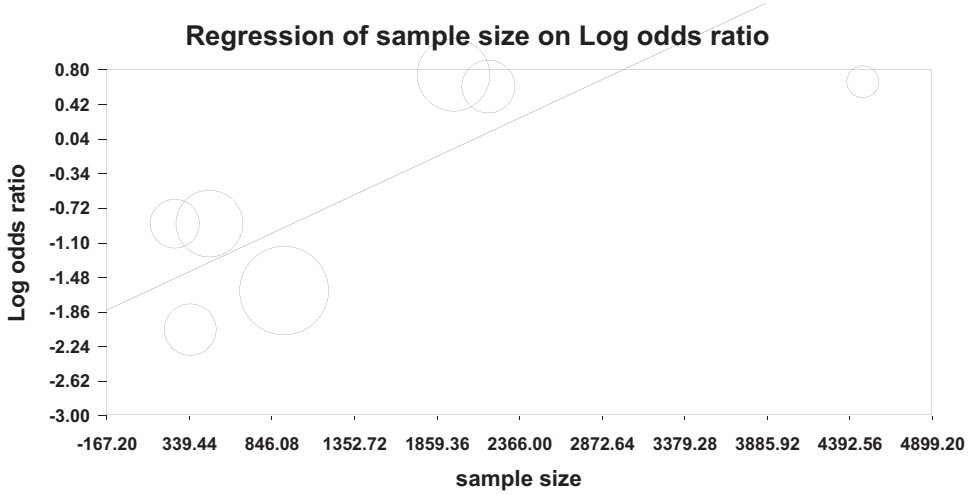

FIGURE 4 | Meta-regression diagram by sample size.

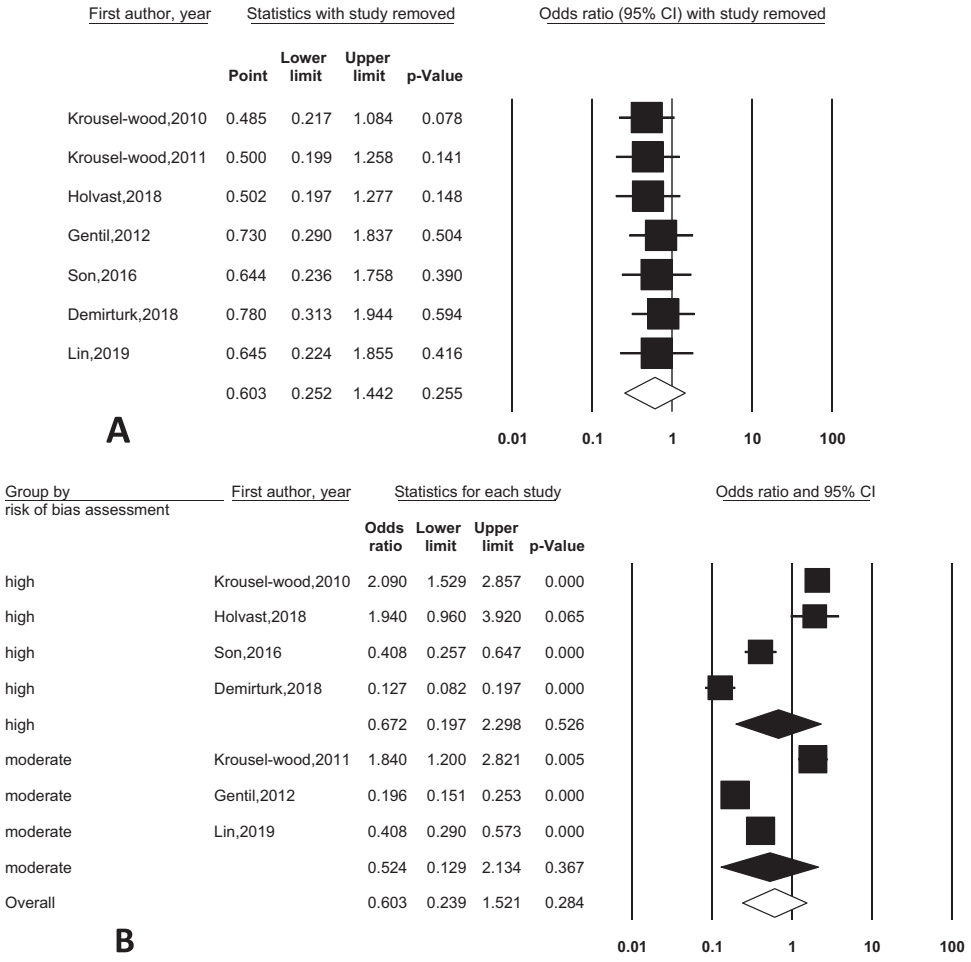

FIGURE 5 | Results of sensitivity analysis: (A) one-out removed method; (B) subgroup analysis by quality assessment.

This study had two main findings, which matched the primary and secondary questions of the research. Based on overall OR, the older patients with CVD who had evidence of concomitant depression reported up to 40% lower medication adherence. This suggests a considerable effect between depression and medication adherence. Also, the obtained result was in line with most included studies. However, due to wide CI, it cannot be a conclusive result. In addition, there was severe heterogeneity among the included studies for the outcomes of this study.

Accordingly, there was a moderate to large effect among the studies that had examined depression using a scale other than CES-D. This would indicate that depression in this group of elderly lowers the medication adherence. It also confirmed the

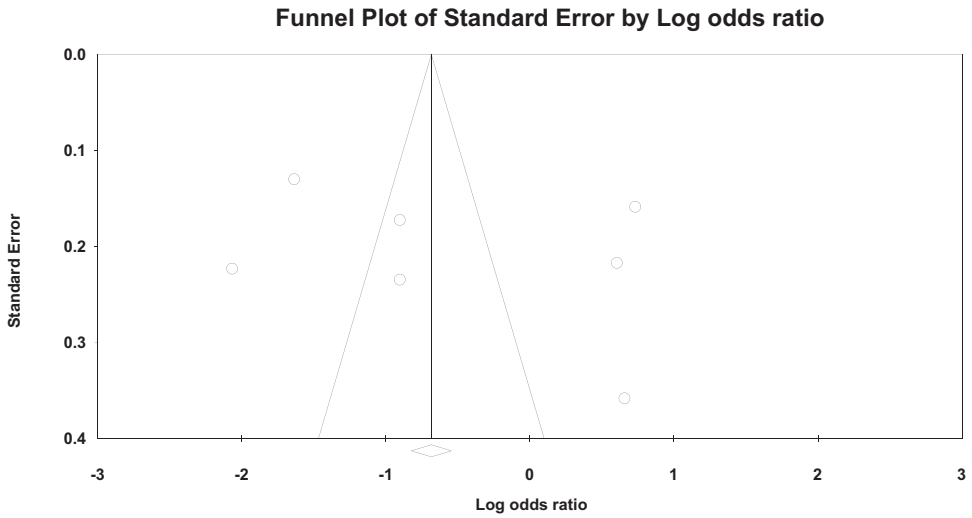

FIGURE 6 | Funnel plot.

overall results of this meta-analysis. Nevertheless, it can be concluded that the scale used for evaluating depression in comparison with other variables is the most important cause of heterogeneity in the primary studies. This variable would reduce the heterogeneity among the included studies by up to 50%. Thus, it can be a reason for the difference in the combined OR in the studies in the meta-analysis.

In addition, the difference in sample size of studies could also be a major cause of different effect size in the included studies, explaining this difference by up to 58%. As the sample size enlarges, the relationship between depression and medication adherence diminishes. In other words, every increase by 1000 participants would lower effect size by 0.8% in log OR scale.

Our overall results have been in accordance with studies of Crawshaw et al., Kessing et al., and Ofori-asenso et al. [5, 11, 18]. The systematic review and meta-analysis study by Ofori-asenso and colleagues has shown a relationship between the factors affecting lack of medication adherence in elderly above 65 years who took statins, known as statins discontinuation. Based on the results of this study, depression has a small to moderate effect on lack of medication adherence, which is a direct but nonsignificant effect (OR = 1.11 CI 95% 1.06–1.26, $p = 0.180$) [5]. Crawshaw and colleagues have reported that depression has a small to large as well as significant effect on lack of medication adherence (OR = 2.00, CI 95% 1.57–3.33, $p = 0.015$) [18]. Kessing and colleagues have also reported that medication adherence is one of the important instances of self-care, and depression is inversely related to medication adherence. Based on the results of this study, depression has a trivial to small effect on medication adherence, though this outcome was not significant ($r = -0.05$, CI 95% −0.177 to −0.078, $p = 0.44$) [11]. The results of these reviews consistently showed a relationship between depression and adherence to medication. However, the differences in results may be attributed to the various tools used in the primary studies, the number of databases used, the time frames of the studies, or the cultural factors influencing medication adherence.

Depression is a common and serious psychiatric condition, negatively affecting a person's performance [13, 32, 33]. However, the elderly, due to personal and social changes they face through the initiation of senescence period, are more at risk of developing depression and chronic diseases [34]. From among these factors, retirement, loss of spouse, and changes in social relations are important [35]. These factors, by lowering the level of dopamine and increasing stress, predispose them to depression [6]. Existence of stress in the elderly, by affecting the hypothalamus–pituitary–adrenal axis, causes elevation of cortisol and blood lipid levels. It eventually increases the risk of developing CVD [34, 35]. Although based on the results of recent studies, the lead–lag relationship of depression and CVD is still unknown [34, 35]. Depression can be one of the most important outcomes of CVD, increasing the risk of mortality by up to 20% in these patients [21]. Another important predictor factor for clinical outcomes in these patients is medication adherence [36, 37]. Medication adherence is affected by various psychological factors, the most important being mood-dependent factors such as depression [18, 38, 39]. Accordingly, concomitant depression and CVD in older patients is associated with diminished self-efficacy and limited social activities and generally decreased quality of life plus lack of medication adherence in these older patients [13, 15, 17, 24, 40, 41]. Hence, lack of medication adherence can be one of the most important barriers against drug effectiveness and control of disease in these older patients [4].

To explore the reporting bias in this systematic review and meta-analysis, funnel plot and Begg's and Egger's tests were used. Based on the distribution pattern of the included studies into the funnel plot, there was low publication bias in this study. Also, the results of Begg's test with a significance level of $p < 0.05$ rejected the hypothesis of homogeneity of the included studies. The results of Egger's test also confirmed the mentioned results, since its CI with 90% interval covers the point of zero. Accordingly, it can be concluded that this study has had an ignorable publication bias.

5 | Strengths and Limitations

There were some limitations in this study. The results of this meta-analysis were based on a limited number of studies (seven

studies) to explore the effect of depression on medication adherence. All of these studies were cohort and cross-sectional. This would reduce the reliability of the conclusions drawn from this meta-analysis. The gray literature search in this systematic review was performed to search for conference reports, dissertations, and theses only in ProQuest, Scopus, and Google Scholar. Although the tables of contents of the included studies were also examined, this can somehow justify the low number of included studies.

The strong point of our systematic review and meta-analysis can be the use of two methods for sensitivity analysis, which enhances the reliability of this analysis. Accordingly, we can confidently report that bias in none of the included studies had any effect on pooled OR. Also, to boost the sensitivity of the statistical tests employed for assessing publication bias and meta-regression, their significance level was considered $p < 0.10$. Nevertheless, all of the mentioned tests showed considerable results with wide differences. In addition, all of the included studies had high and moderate methodological quality.

Despite extensive searches on the characteristics of the included studies, none of them were case-control. Thus, it is suggested to conduct future primary studies of prospective case-control type using valid and specific depression measurement scales such as the Geriatric Depression Scale (GDS). In addition to reducing heterogeneity among primary studies (based on the results of this study), this would also add to the conclusivity of the results in subsequent meta-analyses.

6 | Clinical Implication

The findings of this study can offer valuable insights for healthcare providers responsible for the well-being of elderly individuals affected by CVD. Specifically, the results highlight the importance of conducting regular depression screenings for this particular demographic. Thus, further research using valid scales of depression such as the GDS plus medication adherence measurement on these older patients is recommended.

7 | Conclusion

Based on the studies included into this systematic review and meta-analysis, there is evidence suggesting that depression has a considerable effect on medication adherence among older patients with CVD. The results of this meta-analysis indicated that there is severe heterogeneity among the results of primary studies. Based on the subgroup analysis and meta-regression, the scale used for assessing depression in primary studies can be the most important cause of methodological heterogeneity. Also, the difference in sample size of the included studies considerably justifies the difference in pooled OR. Although after publication bias, sensitivity analysis, risk of bias assessment, and finding notable reasons for methodological heterogeneity, we reached considerable results. Due to the wide-pooled OR confidence interval and its allocation to several interpretation zones, the outcome of this systematic review and meta-analysis is inconclusive. Nevertheless, the results of every single study included concurred with the final result of this meta-analysis. This suggests that depression can effectively reduce medication adherence among older patients with CVD.

Author Contributions

Mina Berimavandi: writing – original draft, writing – review and editing, software, conceptualization, investigation. **Parvin Abbasi:** methodology, investigation, supervision, project administration, writing – original draft, writing – review and editing. **Behnam Khaledi-Paveh:** conceptualization, investigation, writing – original draft, visualization, writing – review and editing. **Nader Salari:** writing – original draft, methodology, validation, writing – review and editing, software.

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Ethics Statement

The code of ethics has been approved by the Ethics Committee of Kermanshah University of Medical Sciences with Code IR.KUMS.REC.1400.651.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data set used and analyzed during the current study are available from the corresponding author on reasonable request.

Transparency Statement

The lead author Parvin Abbasi affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.